PREDICTORS OF MORTALITY AMONG HUMAN IMMUNODEFICIENCY VIRUS INFECTED PATIENTS’ RECORDS IN GONDAR UNIVERSITY HOSPITAL – ETHIOPIA

by

DEME ERGETE GURMU

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SUPERVISOR: DR B L DOLAMO

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DECLARATION

I declare that PREDICTORS OF MORTALITY AMONG HUMAN IMMUNODEFICIENCY VIRUS INFECTED PATIENTS’ RECORDS IN GONDAR UNIVERSITY HOSPITAL – ETHIOPIA is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references and that this work has not been submitted before for any other degree at any other institution.

Dr Deme Ergete Gurmu

November, 2011
ACKNOWLEDGEMENTS

I am heartily thankful to GOD for supporting me to understand and complete this study. I am also blessed in having my first daughter, Sophie, during the study period. She has become my purpose in life. Furthermore I would like to extend my sincere and heartfelt appreciation to my wife, Lydia Tsegaye (Sweety), who has been considerate, patient and supportive when I was much too busy with my career to provide enough family time. I want to thank the following persons for their respective contributions to this dissertation.

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ABSTRACT

Purpose of the study - Identify predictors of mortality and develop a related care plan for patients who are on antiretroviral therapy (ART) in Gondar, Ethiopia.

Design - A quantitative, retrospective cohort study was conducted analysing medical records of HIV patients who presented to Gondar University Hospital (GUH), Gondar, and started ART between 1 January 2007 and 30 June 2010.

Results - In defining the predictors of mortality, the findings in bivariate analysis revealed: female sex, CD4 cell count ≤ 50/µl, CD4 cell count 51-199/µl, a haemoglobin concentration ≤8g/dl, a history of oral candidiasis, tuberculosis and Cryptococcus meningitis were all statistically significant. A female sex, CD4 cell count ≤ 50/µl and CD4 cell count 51-199/µl maintain their significance level in the multivariate analysis.

Conclusions - The study therefore recommends that clinicians and case managers be vigilant of these predictors of mortality while managing HIV patients who are on ART.

Key Concepts- ART, AIDS, HIV, predictors of mortality
TABLE OF CONTENTS

LIST OF FIGURES .................................................................................................................. x
LIST OF TABLES .................................................................................................................. xi
LIST OF ABBREVIATIONS .................................................................................................... xii
LIST OF ANNEXURES .......................................................................................................... xiii

CHAPTER 1 ORIENTATION TO THE STUDY ........................................................................ 1

1.1 INTRODUCTION ............................................................................................................. 1

1.2 BACKGROUND OF THE PROBLEM ............................................................................ 2

1.2.1 Statement of the research problem ........................................................................ 3

1.3 AIM OF THE STUDY .................................................................................................... 3

1.3.1 Research purpose .................................................................................................. 3

1.3.2 Research objectives ................................................................................................ 3

1.4 SIGNIFICANCE OF THE STUDY ............................................................................... 4

1.5 DEFINITIONS OF KEY CONCEPTS ............................................................................ 4

1.6 RESEARCH DESIGN .................................................................................................... 5

1.6.1 Quantitative ............................................................................................................ 5

1.6.2 Analytical ............................................................................................................... 5

1.6.3 Retrospective cohort ............................................................................................ 5

1.7 RESEARCH METHODS ............................................................................................... 6

1.7.1 Patients’ records and sample ................................................................................ 6

1.7.1.1 Study groups .................................................................................................. 6

1.7.1.2 Sampling method ............................................................................................ 6

1.7.1.3 Criteria for eligibility / exclusion .................................................................... 7

1.7.2 Data collection ........................................................................................................ 8

1.7.3 Data analysis .......................................................................................................... 8

1.8 DESIGN VALIDITIES AND RELIABILITIES .......................................................... 8

1.8.1 Validity .................................................................................................................. 8
1.8.2 Reliability ............................................................................................................. 9
1.9 ETHICAL CONSIDERATIONS .................................................................................. 9
1.10 CONCLUSIONS ..................................................................................................... 9

CHAPTER 2 LITERATURE REVIEW ........................................................................... 10

2.1 INTRODUCTION ..................................................................................................... 10
2.2 PURPOSE OF THE LITERATURE REVIEW ............................................................. 10
2.3 OVERVIEW OF HIV ............................................................................................... 10
   2.3.1 Global HIV burden ......................................................................................... 11
   2.3.2 HIV burden in Sub-Saharan Africa ................................................................. 11
   2.3.3 HIV burden in Ethiopia .................................................................................. 12
2.4 ANTI RETROVIRAL TREATMENT ......................................................................... 12
   2.4.1 Millennium Development Goals ..................................................................... 13
   2.4.2 Progress made in Ethiopia .............................................................................. 14
2.5 DEATH IN PEOPLE LIVING WITH HIV ................................................................. 15
   2.5.1 Death while on Pre ART .................................................................................. 15
   2.5.2 Death while on ART ....................................................................................... 16
2.6 ADHERENCE TO ANTIRETROVIRAL TREATMENT .............................................. 17
   2.6.1 Reasons for non-adherence ........................................................................... 18
      2.6.1.1 Difficulties related to social factors and life styles .................................. 18
      2.6.1.2 Difficulties related to negative beliefs about the use of ART ................. 18
      2.6.1.3 Difficulties directly related to the use of medication ............................... 19
   2.6.2 Barriers for optimal ART-adherence ............................................................... 19
   2.6.3 Virologic Failure ............................................................................................ 19
2.7 IMMUNO RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) .................... 20
2.8 PREDICTORS OF HIV/AIDS ASSOCIATED MORTALITIES ....................... 21
   2.8.1 Poor resource settings .................................................................................... 21
   2.8.2 Malnutrition .................................................................................................. 22
   2.8.3 Opportunistic infections .................................................................................. 22
2.9 COMMON LIFE-THREATENING OPPORTUNISTIC INFECTIONS .......................... 22
  2.9.1 Pulmonary Tuberculosis ........................................................................ 23
  2.9.2 Toxoplasmosis .................................................................................... 24
  2.9.3 Pneumocystis Jirovecii Pneumonia ....................................................... 24
  2.9.4 Cryptococcus Meningitis ...................................................................... 24

2.10 SUMMARY ............................................................................................... 25

CHAPTER 3 RESEARCH DESIGN AND METHOD ........................................... 26

3.1 INTRODUCTION ......................................................................................... 26

3.2 RESEARCH DESIGN ................................................................................. 26
  3.2.1 Quantitative study .............................................................................. 26
  3.2.2 Analytical study .................................................................................. 27
  3.2.3 Cohort study ....................................................................................... 27
    3.2.3.1 Prospective cohort study ............................................................... 27
    3.2.3.2 Retrospective cohort study .......................................................... 28
    3.2.3.3 Strength of a cohort study ........................................................... 28
    3.2.3.4 Limitations of a cohort study ....................................................... 28

3.3 RESEARCH METHOD ............................................................................... 29
  3.3.1 Study population ................................................................................. 29
  3.3.2 Screening tool ..................................................................................... 29
  3.3.3 Sampling ............................................................................................. 30
  3.3.4 Sampling error .................................................................................... 31
  3.3.5 Research assistant .............................................................................. 32
  3.3.6 Data collection approach and method .................................................. 32
  3.3.7 Data collection instrument ................................................................... 32
  3.3.8 Data analysis ....................................................................................... 33

3.4 RELIABILITY AND VALIDITY ................................................................. 34
  3.4.1 Reliability ........................................................................................... 34
  3.4.2 Validity ................................................................................................ 34
5.7 LIMITATIONS OF THE STUDY .................................................................60
5.8 CONCLUDING REMARKS .................................................................61
REFERENCES ..........................................................................................62
ANNEXURES .........................................................................................70
LIST OF FIGURES

Figure 4.1: Sex distribution in the dead and alive HIV patients; GUH ART clinic patients chart review .................................................................39

Figure 4.2: Age distribution in the dead and alive HIV patients; GUH ART clinic patients chart review .................................................................41

Figure 4.3: CD4 group distribution in the dead and alive HIV patients; GUH ART clinic patients chart review .................................................................44

Figure 4.4: Haemoglobin group distribution in the dead and alive HIV patients; GUH ART clinic patients chart review .................................................................47

Figure 4.5: History of Oral Candidiasis distribution in the dead and alive HIV patients; GUH ART clinic patients chart review .................................................................49

Figure 4.6: History of Tuberculosis distribution in the dead and alive HIV patients; GUH ART clinic patients chart review .................................................................51

Figure 4.7: History of Cryptococcus Meningitis distribution in the dead and alive HIV patients; GUH ART clinic patients chart review .................................................................53
LIST OF TABLES

Table 2.1: Adherence to ARV drugs

Table 2.2: Correlation between adherence and virologic response to ART

Table 4.1: Sex distribution in the chart review of HIV patients who were on ART follow-up at GUH from 1 January 2007 – 30 June 2010

Table 4.2: Age group distributions from the chart review of HIV patients who were on ART follow-up from 1 January 2007 - 30 June 2010 at GUH.

Table 4.3: CD4 groups distribution from the chart review of HIV patients who were on ART follow-up from 1 January 2007 to 30 June 2010 at GUH.

Table 4.4: Bivariate analysis of CD4 count and Bio-status of the patients

Table 4.5: Haemoglobin count groups distribution from the chart review of HIV patients who were on ART follow-up from 1 January 2007 to 30 June 2010 at GUH.

Table 4.6: Bivariate analysis of Haemoglobin count and Bio-status of the patients

Table 4.7: The distribution of Oral Candidiasis in the reviewed HIV patients’ charts who had ART follow-up at GUH from 1 January 2007 - 30 June 2010 at GUH.

Table 4.1: Bivariate analysis of History of Oral Candidiasis and Bio-status of the patients

Table 4.9: The distribution of Tuberculosis in the reviewed HIV patients’ charts who had ART follow-up at GUH from 1 January 2007 - 30 June 2010 at GUH.

Table 4.10: Bivariate analysis of History of TB and Bio-status of the patients

Table 4.11: The distribution of Cryptococcus Meningitis in the reviewed HIV patients’ charts who had ART follow-up at GUH from 1 January 2007 - 30 June 2010 at GUH.

Table 4.2: Bivariate analysis of History of Cryptococcus Meningitis and Bio-status of the patients

Table 5.1: Care plan for PLWHIV who are on ART and has mortality predictor indicators
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACM</td>
<td>Adherence Case Manager</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Virus</td>
</tr>
<tr>
<td>ARC</td>
<td>AIDS Resource Centre</td>
</tr>
<tr>
<td>ART</td>
<td>Anti Retroviral Therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Anti Retroviral</td>
</tr>
<tr>
<td>CDC</td>
<td>Centre for Disease Control and prevention</td>
</tr>
<tr>
<td>ECA</td>
<td>Economic Commission for Africa</td>
</tr>
<tr>
<td>GUH</td>
<td>Gondar University Hospital</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Treatment</td>
</tr>
<tr>
<td>HAPCO</td>
<td>HIV/AIDS Prevention and Control Office</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>I-TECH</td>
<td>International Training and Education Centre for Health</td>
</tr>
<tr>
<td>LTFU</td>
<td>Lost To Follow-UP</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goal</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
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<tr>
<td>NGO</td>
<td>Non Governmental Organization</td>
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<tr>
<td>OI</td>
<td>Opportunistic Infection</td>
</tr>
<tr>
<td>PCP</td>
<td>Pneumocystis Jirovecii Pneumonia</td>
</tr>
<tr>
<td>PEPFAR</td>
<td>Presidential Emergency Plan For AIDS Relief</td>
</tr>
<tr>
<td>PLWHIV</td>
<td>People Living with HIV</td>
</tr>
<tr>
<td>PMTCT</td>
<td>Prevention of Mother-to-Child-Transmission</td>
</tr>
<tr>
<td>SNNPR</td>
<td>Southern Nation and Nationality People Region</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Science</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TI</td>
<td>Transferred In</td>
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<tr>
<td>TO</td>
<td>Transferred Out</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<tr>
<td>UNAIDS</td>
<td>United Nations Programme on HIV/AIDS</td>
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<tr>
<td>UNISA</td>
<td>University of South Africa</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
LIST OF ANNEXURES

Annexure A: Time frame

Annexure B: Budget

Annexure C: Data collection instrument

Annexure D: Federal Ministry of Health, Ethiopia HIV care/ART follow-up form

Annexure E: Letter asking for permission to conduct the research at GUH

Annexure F: Approval from Gondar University Hospital

Annexure G: Ethical clearance from UNISA

Annexure H: Ethical clearance from Gondar University
CHAPTER 1
ORIENTATION TO THE STUDY

1.1 INTRODUCTION

According to the World Health Organization (WHO), there are 33.4 million people living with Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS) worldwide (WHO 2010c). In Sub Saharan Africa, where HIV/AIDS is a leading cause of morbidity and mortality, there resides 22 million people living with Human Immunodeficiency Virus (PLWHIV), making 67% of the global total. According to Ethiopian calibrated single point estimate sentinel surveillance 2007, the prevalence of adult infection was 2.4 (urban 7.7%, rural 0.9%), adult HIV incidence was 0.29% (urban 2.04%, rural 0.2%) with a total HIV positive population of 1,216,908 (urban 760,475, rural 456,432) (Ethiopia AIDS resource centre 2010b).

To curtain such a huge health problem, the Ethiopian government in collaboration with Presidential Emergency Plan For AIDS Relief (PEPFAR) has engaged in tackling the HIV / AIDS epidemic using divers interventions; the major action being availing free access to drugs for Antiretroviral therapy (ART) and Opportunistic Infections (OI). This action was launched in January 2005 (Ethiopia AIDS resource centre 2010a). With this major action in place it has been possible to significantly decrease HIV associated mortalities on a large scale. Compared to the pre ART era where AIDS related mortality was very high in Ethiopia, 134,450 (Federal Ministry of Health 2006), free and easy access to ART and OI treatment has been showing an improvement in the general morbidity and mortality of PLWHIV. The current 2010 Ethiopian national data showed that AIDS related death has declined to 28,073 (Ethiopia AIDS resource centre 2010b).

According to the Ethiopian administrative structure, the country is organized in two federal cities (Addis Ababa, Dire Dawa) and nine regional states (Harari, Amhara, Tigray, Gambella, Afar, Benishangule Gumuz, Oromia, Southern Nations and Nationalities People Region (SNNPR), Somali) (WHO 2010b; Federal Ministry of Health 2006). These regions have their own different geographical topography, language, culture and socioeconomic strata. Moreover, different disease entities have different epidemiological distributions. By the same token, HIV / AIDS show a typical distribution pattern
among the regions. Amhara, Oromia, Addis Ababa and SNNPR accounted for 86.6% of all PLWHIV and 88.2% of AIDS deaths that occurred in Ethiopia in 2005; the regions large population size and high HIV prevalence played the major role (WHO 2010b; Federal Ministry of Health 2006).

1.2 BACKGROUND OF THE PROBLEM

Amhara national regional state, with the population size of 17.2 million which is predominantly 87.3% of rural residence, is located in the mid-northern part of Ethiopia. There are 17 government hospitals (including one university hospital: Gondar University Hospital (GUH)), 199 health centres, 2621 health posts, two regional public health research laboratories, and 765 private health facilities (Amhara National Regional State Health Bureau 2009).

GUH is a tertiary referral teaching hospital with 350 beds giving service to more than 5 million people living in the vicinity areas. The hospital started to provide HIV/AIDS related services in 2003 with limited scope for shortage of trained man power and fee based Antiretroviral (ARV) drugs. In March 2005, the hospital scaled up its HIV/AIDS related care with the introduction of free ART service. Currently, the hospital is fully staffed with highly trained HIV/AIDS health care providers and is greatly supported by a PEPFAR funded international Non Governmental Organization (NGO), International Training and Education Centre for Health (I-TECH), in the area of capacity building with technical and financial support. According to GUH June 2010 hospital HIV/AIDS report, there has been a total of 8377 patients enrolled to the HIV care program, out of which 5566 patients started ART. Around 858 patients have been transferred out (TO) to other ART centres and 397 patients were transferred in (TI) to the hospital. In the same report, there are a cumulative 855 patients who were dropped out and 152 lost from follow-up patients making the overall active patients on ART to 3370 (Gondar University Hospital 2010).

The researcher was working in the capacity of physician mentor in one of the major international NGOs. This NGO gives technical and capacity building support for hospitals in Amhara region in the area of HIV/AIDS. This was a great privilege and a great opportunity to further look in-depth at the challenges of the hospital’s ART clinic. From all the hospitals under I-TECH’s scope of work, GUH has one of the most crowded and over-
loaded ART clinics. In this clinic, there is a huge mortality report in PLWHIV who were on ART service. Therefore the source of the research problem arises from the clinical experience.

1.2.1 Statement of the research problem

Although increased access to ART is likely to reduce mortality, under the prevailing conditions, the cumulative deaths in the hospital are 732 making AIDS deaths among PLWHIV who have been on HIV/AIDS care 14.3% according to the June 2010 GUH monthly report (GUH 2010). The predictors of mortality in accordance to clinical and laboratory findings in adult PLWHIV who are currently on ART are not well studied and understood in Ethiopia at large and GUH in particular.

1.3 AIM OF THE STUDY

The aim of the study is to describe predictors of mortality among PLWHIV at GUH ART clinic.

1.3.1 Research purpose

The purpose of this study is to develop a simple medical care plan to assist clinicians and adherence case managers prioritise defined predictors of mortality among HIV positive patients on ART at GUH ART clinic, Gondar, Ethiopia

1.3.2 Research objectives

The following objectives guided this study:

- To determine the predictors of mortality among PLWHIV who were on follow-up at GUH ART clinic by analysing their records.
- To develop a care plan for PLWHIV based on the mortality predictors at GUH ART clinic.
1.4 SIGNIFICANCE OF THE STUDY

This study will benefit PLWHIV, currently on ART care, an intensified review of documents will probably detect clinical or laboratory disorders which were overlooked in the previous times.

Adherence Case Managers (ACMs) will also be assisted in the development of care plan, which can further extend to secure funds from local and international NGOs working with GUH to strengthen patient support programs by presenting evidence based problems.

1.5 DEFINITIONS OF KEY CONCEPTS

These concepts are regularly referred to in this study:

Active patients on ART: Attended the last scheduled visit at the ART clinic at Gondar University Hospital (GUH protocol).

Adherence Case Managers: Lay health workers who are trained to give adherence counselling support for PLWHIV (GUH protocol).

Adherence: Extent to which patients take medications as prescribed by their health care provider (Osterberg and Blaschke 2005).

Mortality: Death from all causes which happened at any time after the patient started ART; deaths registered from hospital records or reported through out-reach workers (GUH protocol).

Predictors of mortality: Clinical or laboratory values which help to forecast death before happening for PLWHIV who are on ART.

Weight loss: A decrease in body weight resulting from involuntary (illness) circumstances. (Med term 2010)
1.6 RESEARCH DESIGN

The research design in this study was quantitative, analytical, retrospective cohort study (chapter three discusses in detail).

1.6.1 Quantitative

Quantitative studies require the researcher to measure variables, express associations and relationships among variables using statistics; may also be used to examine and determine causality (Burns and Groove 2005:747).

Stommel and Wills (2004:442) describes a quantitative research as a method that enables one to measure and describe phenomena’s in standardized numerical scales which are analyzed statistically. This research will analyse patients’ clinical and laboratory chart/records with the mortality outcome.

1.6.2 Analytical

To address the aim and objective of this study, it was better to use an analytical technique; according to Joubert and Ehrlich (2007:78) an analytical study look details of factor associations (chapter 3 discusses in detail).

1.6.3 Retrospective cohort

An analytical cohort study aim at examining the possible relationship between an exposure and an outcome (Joubert and Ehrlich 2007:79). The same authors also describe the existence of two types of cohort studies: prospective and retrospective. A prospective cohort is a study which the researcher studies and observes a population for a certain duration of time in a forward direction while a retrospective cohort study “shortens the time needed to conduct a cohort study as it makes use of historically or previously compiled data” (Joubert and Ehrlich 2007:81). The research is a retrospective cohort study design looking at the factors (clinical, laboratory, and treatment adherence) in re-
lation to predictors of AIDS death retrospectively from patients’ records analysis. Odds ratio was calculated to indicate the strength of an association.

1.7 RESEARCH METHODS

The study was conducted in Gondar, Ethiopia; after ethical review approval was granted by the University of South Africa and Gondar University Hospital.

1.7.1 Patients’ records and sample

Data were drawn from all ART patients’ paper based medical records who have been on follow-up in GUH from 1 January 2007 to 30 June 2010.

1.7.1.1 Study groups


Record #2: Survivors, ART patients’ records those who were alive during 1 January 2007 – 30 June 2010 and had follow-up at GUH ART clinic.

1.7.1.2 Sampling method

A systematic random sampling method was implemented for the survivor PLWHIV records. “In systematic sampling, individuals are selected at a fixed intervals from some list of ordering” (Joubert and Ehrlich 2007:100). In GUH, the ART registration log book has all the tracks of PLWHIV who have got service in the HIV clinic. To the end of June 2010, the log book accounts for 8377 PLWHIV records to have ever been enrolled in the care; out of which 3370 were actively on regular follow-up. There were 2 information technicians who had been working in GUH I-TECH data room for assuring the completeness of the records before feeding the data to an electronic copy. For the purpose of this study therefore, the total confirmed clean records of 2622 PLWHIV charts indicated as an active status with complete record documentation were enrolled. The paper charts corresponding to the records were extracted from the GUH main chart room us-
ing their unique ART number and later all labelled with new serial numbers. In this case for the sample size of 800, the sampling interval was 3; therefore to determine the random starting point one had to draw a random number within the first sampling intervals, then after every third record was selected to the study group. While revising GUH ART clinic I-TECH database, the total number of death records of PLWHIV while on ART follow-up between 1 January 2007 to 30 June 2010 were 360 (GUH 2010) out of which 324 were adults with age greater than 18. Out of 324 charts, only 200 had complete documentation of both ART intake and follow-up sheets. Moreover, hospital causes of deaths were appropriately documented by then treating physician. Therefore with a statistician recommendation from GUH, the total 200 death charts were considered for the study by further assigning four survivors PLWHIV charts for every death record from the same sampling frame. The sample size was determined as follows.

*Record # 1: N= 200*
*Record # 2: N= 800*

### 1.7.1.3 Criteria for eligibility / exclusion

#### Inclusion criteria

*Record #1 and Record #2*: Those with CD4 T lymphocyte counts < 200 cells/mm3 or those with WHO stage 3 and CD4 < 350 or WHO stage 4 were included.

*Record #1*: ART patients’ records, for those who had follow-up at GUH ART clinic and died during 1 January 2007 – 30 June 2010, and the cause of death documented in the patients’ charts.

*Record #2*: ART patients’ records, for those who had regular follow-up at GUH ART clinic during 1 January 2007 – 30 June 2010.

#### Exclusion criteria

*Record #1*: < 18 years of age, patients’ records on Pre-ART follow-up, ART patients’ records that had no documented cause of death, and women patients’ records that died while on short course ART for the purpose of prevention of mother-to-child-transmission (PMTCT) of HIV were excluded.
Record #2: < 18 years of age, patients’ records on Pre-ART follow-up, lost to follow-up (LTFU) patients’ records; drop out from follow-up patients’ records; and women patients’ records that started short course of ART for the purpose of PMTCT of HIV were all excluded.

1.7.2 Data collection

Ethiopian Ministry of Health (MOH), ART intake and follow-up format was used after modification and exclusion of the unnecessary variables for this study; then the data collection format was pretested before implementation (Federal Ministry of Health 2010). Paper based patients’ charts (including intake and follow-up documents) and the I-TECH ART database were assessed for a retrospective case record analysis of clinical and laboratory findings.

The variables included in the data collection instrument were: sex, age, date of HIV diagnosis, date of ART initiation, types of ART regimens; CD4 cell count, weight, haemoglobin value, adherence to ART and OIs. For non survivors (dead patients) the cause of death was also included (Annexure C). Data was collected by the researcher.

1.7.3 Data analysis

Data analysis was done with the assistance of a bio-statistician from CDC; the statistician was also actively involved in sample size determination and data collection tool modification. Data was coded and entered in to Statistical Package for Social Science (SPSS) Version 16; Predictive Analytics Software, (PASW). Bivariate and multivariate analyses, odds ratio and P-test were used.

1.8 DESIGN VALIDITIES AND RELIABILITIES

1.8.1 Validity

To ensure the research validity, the source population for both groups were all drawn from GUH ART clinic record pool. The survivor records were selected with systematic random sampling technique while the total cleaned records of deaths were enrolled.
Follow-up time frame for both groups was similar, moreover there was not be any record bias, because the data collection method was a full document retrospective case record analysis.

1.8.2 Reliability

In this research the death records were limited in number therefore to ensure the research reliability, all PLWHIV death records who had complete chart documentation in their hospital records were considered; additionally four survivor patients’ records were selected for every death record (Joubert and Ehrlich 2007: 83) and CDC statistician recommendation. Fifty more charts were reviewed from the survivor patients’ records as a contingency plan to complete the sample size in case of any lost paper based patient charts occur. Data was collected using a modified Ethiopian national Ministry of Health HIV patients follow-up charts which was standardized, and the researcher collected the data. The collected data was crossed checked with I-TECH patient follow-up database. The cleaned data then entered in to a password protected Microsoft excel file, which later was fed into SPSS.

1.9 ETHICAL CONSIDERATIONS

Ethical clearance from both University of South Africa (UNISA) and Gondar University was secured before rolling out any part of the research activity (Annexure G and Annexure H). Moreover a support letter was also issued from the hospital’s medical director to facilitate an easy access to patients’ medical records (Annexure F) (chapter three discusses in detail).

1.10 CONCLUSIONS

Chapter one gave orientation to the study. Background of the problem, aim of the study, significance of the study and definitions of key concepts were all addressed in detail. The chapter also highlighted the research design, methods and ethical considerations.
CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

The aim of this study was to define predictors of mortality among people living with human immunodeficiency virus (PLWHIV) at Gondar University Hospital (GUH) anti retroviral treatment (ART) clinic. According to the findings, the purpose was to develop a care plan. This chapter reviews relevant literatures from previous studies on factors associated with acquired immunodeficiency syndrome (AIDS) deaths. The scope of this literature review therefore was to synthesize evidence from text books, published researches, scientific reports and other credible sources of scientific work done globally mainly on HIV/AIDS and ART issues.

2.2 PURPOSE OF THE LITERATURE REVIEW

Literature review is to ‘re-view’ or ‘further look’ at what has already been studied and published on a particular subject (Joubert & Ehrlich 2007:66). The purpose is to inform the researcher of what is already known about that specific subject of interest in making knowledge based choices about policy, practice, research direction and resource allocation (Chalmers 2003:575).

In this review several sources were consulted including medical and research text-books, latest publications of scientific journals, World Health Organization (WHO) publications and guidelines, United Nation (UN) agencies reports, the internet and several Ministry of Health (MOH) publications.

2.3 OVERVIEW OF HIV

HIV is a lenti virus from the member of retrovirus family incremented as a cause of AIDS (Weiss 1993:1273; Douek, Roederer and Koup 2009:471), which leads to a failure of the immune system and predisposes to different life-threatening opportunistic infections and malignancies. There are four means of HIV transmissions which are; unprotected sex, mother-to-child-transmission (perinatal transmission) including breast milk, contaminated body fluids, blood, blood products and organ donation, and contaminated needles.
HIV infects CD₄⁺T cells from the human immune system which are macrophages, T-helper cells and dendritic cells (Cunningham, Donaghy, Harman, Kim and Turville 2010:524). There are two species of HIV: HIV-1 and HIV-2. HIV-1 is more virulent and infective (Gilbert, Mckeague, Eisen, Mulins, Guéye-Ndiaye, Mboup and Knaki 2003:573), and it is the dominant cause of HIV infection globally. HIV-2 has low infectivity and is mainly distributed in West Africa (Reeves & Doms 2002:1253). There are different rate for different individuals progression of HIV to AIDS. Most will progress within an average of 10 years of HIV infection, though some progress much sooner and some will stay much longer (Buchbinder, Katz, Hessol, O’Malley and Holmberg 1994:1123; Time from HIV-1 2000:1131). To date there is no publicly available vaccine or cure for HIV or AIDS (Fighting the world’s 2010; Robb 2008:1857).

### 2.3.1 Global HIV burden

According to World Health Organization (WHO) 2009 global HIV/AIDS report for year 2009; the number of people living with HIV in total was 33.3 million [31.4 million – 35.3 million] out of which adults account for 30.8 million [29.2 million – 32.6 million]. Even though the trend for people newly infected with HIV decreased from 2001 to 2009, there were around 2.6 million people newly infected in 2009, with adults contributed 2.2 million and children (<15 years) 370000 (WHO 2009). The report from Joint United Nations Programme on HIV/AIDS (UNAIDS) indicate annual AIDS related deaths worldwide is decreasing from 2.1 million [1.9 million – 2.3 million] in 2004 to 1.8 million [1.6 million – 2.1 million] in 2009 (UNAIDS 2010).

### 2.3.2 HIV burden in Sub-Saharan Africa

UNAIDS in 2009 reported that, Sub-Saharan Africa embraced 22.5 million [20.9 – 24.2 million] people living with HIV in making the adult (15 – 49 years) HIV prevalence to 5.0% [4.7% - 5.2%]. Annually, 1.8 million [1.6 – 2.0 million] adults and children became newly infected with HIV. Moreover, there were 1.3 million [1.1 – 1.5 million] AIDS related deaths among adults and children (UNAIDS 2010). According to the same report the major means of HIV transmission was unprotected heterosexual intercourse (including paid sex) and vertical transmission of HIV to newborns and breast fed babies. From all the countries with HIV pandemic in the world, South Africa remains the largest in the
world with an estimate of 5.6 million [5.4 million – 5.8 million] people living with HIV in 2009 (UNAIDS 2010). Epidemic in East Africa used to be very high but since 2000 it has been declining and stabilizing, whereas in West Africa the HIV prevalence has been relatively low with an estimate at ≤ 2% (UNAIDS 2010).

2.3.3 HIV burden in Ethiopia

In 2009 Ethiopia had a total of 1,216,908 people living with HIV out of which 79,871 were children (Ethiopia AIDS resource centre 2010a). According to the same report, national fact sheet 2010, new HIV infections per year in 2009 was 137,494 from which 14,276 were children. Ethiopian adult (15 – 49 yrs) HIV prevalence in 2009 was 2.4% and incidence of HIV was 0.29%. These numbers add up to a significantly high mortality figure; in year 2009 the total AIDS deaths were recorded to be 28,073 of which 3,537 were children.

2.4 ANTI RETROVIRAL TREATMENT

Although HIV infection cannot be cured, the advent of highly active antiretroviral therapy (HAART) has transformed HIV into a chronic controllable condition. Management of PLWHIV include not only antiretroviral drugs, but also social and psychological care, prevention of opportunistic infections and prevention of transmission of HIV. There are five goals of therapy. First, the improvement of quality and expectancy of life related to the clinical goal of the treatment. Second, the greatest possible reduction in viral load for as long as possible; which is the virologic goal of ART. Third, the immunological goal expects both qualitative and quantitative improvement in immune reconstitution. The remaining two are therapeutic and epidemiologic goals. The former describe a rational sequencing of drugs in achieving the clinical, virologic and immunologic goals in maintaining treatment options, limiting drug toxicity and facilitate adherence; which the later aimed to reduce HIV transmission (Bartlett, Gallant & Pham 2009 – 2010:71).

Treatment regimens for HIV infection are complicated and require a long term commitment to high levels of adherence. A combination of clinical assessment and laboratory marker data, including viral load and CD4 counts together with individual circumstances, should guide therapeutic decision making. Therefore, based on these facts many countries developed their own national ART guideline according to their particular circum-
stances. There are few other internationally acknowledged ART guidelines which are currently in wide use all over the world; Department of Health and Human Service (DHHS) and Centre for Disease Control and prevention (CDC) ART guidelines from United States and World Health Organization (WHO) ART guideline, which uses different assessment and criteria for initiation and lifelong provision of ART in different socio-economic and geographic setups. So far the main determinants for initiating antiretroviral therapy in most patients are patient readiness and CD4 count, even though the cut off point is different for different setups (Bartlett et al 2009-2010:71).

Treatment is initiated with a combination of drugs started simultaneously. The preferred regimen is two nucleoside reverse transcriptase inhibitors in combination with either a non-nucleoside reverse transcriptase or protease inhibitors. Patients may need to change therapy because of virological failure or drug side effect (WHO 2010a:22).

2.4.1 Millennium Development Goals

The Millennium Development Goals (MDGs) and targets came from the Millennium Declaration signed by 189 countries, including 147 head of states, in September 2000 in order for the goals to be met within 15 years, making the final year of achievement being 2015 (UN 2000). They were designed in a principle to strengthen partnership between developed and developing nations, as it is clearly put in the declaration “To create an environment at the national and global levels alike which is conducive to development and the elimination of poverty” (UN 2000). The MDGs are eight in number and each goal has its own targets and indicators for monitoring progress; it is worth mentioning the goals:

Goal 1: Eradicate extreme poverty and hunger
Goal 2: Achieve Universal primary education
Goal 3: Promote gender equality and empower women
Goal 4: Reduce child mortality
Goal 5: Improve maternal health
Goal 6: Combat HIV/AIDS, malaria and other disease
Goal 7: Ensure environmental sustainability
Goal 8: Develop a global partnership for development
According to the above MDGs, three out of eight are directly related to health issues and the rest five goals also have major indirect influence in public and global health.

In the context of this dissertation; activities undertaken in goal number six (combat HIV/AIDS, malaria and other diseases), has a paramount significance. One of the indicators for this goal is: the number of children orphaned by HIV/AIDS (UN 2000) which is directly related to the total HIV/AIDS associated adult deaths in PLWHIV. Similarly, the rest of the goals and targets are also interrelated and should be seen as a whole.

2.4.2 Progress made in Ethiopia

Ethiopia, after committing to the Millennium declaration with the MDGs in 2000, has begun working toward the 2015 set goals. The ‘Millennium AIDS campaign’ designed by the federal government has been the centre piece of efforts to scale up prevention and treatment program. Moreover, Ethiopia joined the United Nations (UN) general assembly in issuing the political declaration of HIV/AIDS in 2006 (Ethiopia MDGs 2010). In cooperation with multiple stake holders, quality HIV/AIDS services have been delivered at the community level and in a context of task shifting approach from high level health professionals (General practitioners and Specialist doctors) to mid level health professionals (Nurses and Health officers), various standardized guidelines and trainings were developed, distributed and carried out (Ethiopia MDGs 2010).

According to the 2010 Ethiopia MDGs report, with the above efforts in place, Ethiopia has been able to provide free ART for 206,907 PLWHIV in 2008 / 2009. Additionally, a trend analysis of HIV/AIDS prevalence rate shows that the urban epidemic appears to have levelled off at a higher prevalence in the past years while the rural epidemic hasn’t shown significant change (Ethiopia MDGs 2010). In the same report, there are an estimated 1.1 million PLWHIV in Ethiopia with adult HIV prevalence in 2009/10 estimated to be 2.4% but HIV/AIDS incidence rate has remained below 0.3 percent.

Overall the Ethiopia Ministry of Health focused its national response strategy in alleviating the HIV/AIDS burden in accordance to MDG 6 which is towards achieving a universal access focusing on three key approaches: the health extension program targeting in prevention and awareness creation support, health facility expansion in ensuring easy access to health facilities, and human resource capacity development. In the 2010
MDGs report, the Ethiopian Ministry of Health was enthusiastic about the progress on HIV/AIDS and malaria and the progress made is commendable. It is thus highly probable that the MDGs target will be met in 2015.

2.5 DEATH IN PEOPLE LIVING WITH HIV

Globally, there has been a huge number of HIV/AIDS associated deaths and hence HIV/AIDS has remained one of the major health burdens in the world today. Developed versus developing countries differ significantly in the rank of the cause of death therefore a global summary are not adequately descriptive. However, to merely indicate some of the global facts: in 1998 HIV/AIDS ranked the fourth, as a major cause of death worldwide with a global total of 2,285,229 people (Cause of death 1998). In another report from WHO in 2002, HIV/AIDS was incriminated as the number one cause of death in developing countries with the total death of 2,678,000 (List of causes 2002). Although both reports cited above are outdated due to the lack of recent data on these issues, one can learn the significance of the problem from the reports. HIV/AIDS associated deaths occur in both groups of PLWHIV, patients who have never been exposed to antiretroviral drugs, the so called ART naive and those patients who are on ART. In one study done in India, it is found that mortality was high among those not on HAART (81%) while it is significantly reduced (28%) among those on HAART (P < 0.001) (Rajagopalan, Suchitra, Shet, Khan, Garcia, Nonnemacher, Jacobson and Wigdahl 2009:219).

2.5.1 Death while on Pre ART

Symptom free ART naive or Pre ART PLWHIV are categorized in to two groups based on their CD4 count, high CD4 count and low CD4 count, according to WHO 2010 ART guideline which makes the cut-off CD4 level for the two groups to be at 350 cells/mm\(^3\) (WHO 2010a:24). One recent study noted that ART naive patients with high CD4 cell counts death rates were raised compared with the general population, even though the finding was not in a strong statistical significance and can be due to confounding factors (Death rate in HIV-positive 2010:340). On the other hand, mortality rate is very high for those groups with CD4 counts of less than 350 cells / mm\(^3\), it has been indicated in different studies and therefore 350 cells/mm\(^3\) CD4 count is taken as a cut-off point for initiation of ART (WHO 2010a:24).
When one discusses mortality, it is also sound to look-up an overview about the causes of death. In one study, recurrent diarrhoea followed by pulmonary tuberculosis (TB) at first hospital admission of PLWHIV was found to be the major causes of death. In the same study, Pneumocystis Jiroveci Pneumonia (PCP), Cryptococcus meningitis and Toxoplasmosis were also found to negatively affect survival, even though the findings were not statistically significant (Rajagopalan et al 2009:219). From another study the leading cause of death appear to be tuberculosis, acute sepsis, cryptococcal meningitis, malignancy and wasting syndrome (Lawn, Harries, Anglaret, Myer and Wood 2008:1897).

Globally Mycobacterium tuberculosis is the leading cause of morbidity and mortality among PLWHIV. In Ethiopia there is a huge burden of co-infection rate of symptomatic HIV infection and tuberculosis which is reaching 20 – 50% (FHAPCO 2008:10). Accordingly one can extrapolate tuberculosis as a major cause of death in the country. Therefore from all of the cases above, one can clearly note that the causes of mortalities correspond mainly to AIDS defining opportunistic infections.

2.5.2 Death while on ART

Following the introduction of HAART, the mortality rate among PLWHIV significantly decreased (Rajagopalan et al 2009:219; WHO 2010a:26). Despite this improvement, Sub-Saharan Africa is still staggering with a very high mortality rate of between 8 and 25% of PLWHIV in the first years of initiation of ART (Lawn et al 2008:1897). From all global deaths that have occurred during ART, the highest death rate occurs in the first month of treatment, “Mortality declined by 9 fold after the 8th week of follow-up” (Jerene, Endale, Hailu and Lindtjorn 2006:136). Furthermore, a study mentions that the excess mortality in PLWHIV is moderated by the treatment and reaching the mortality rate of the healthy general population by the second year of ART (Brinkhof, Boulle, Weigel, Messou, Mathers, Orrell, Dabis, Pascoe and Egger 2009:e1000066). Similarly, a study from a rural hospital in Tanzania described that the majority of deaths occurred in PLWHIV who were initiated ART to be within the first three months of the therapy (Johannessen, Naman, Ngowi, Sandvik, Matee, Aglen, Gundersen and Bruun 2008:52).
The cause specific mortality of PLWHIV who were on ART is found to be mainly linked to an advanced HIV disease at treatment initiation (as reflected by low CD4 cell count) and immune reconstitution inflammatory syndrome (IRIS) (Journal watch 2009).

2.6 ADHERENCE TO ANTIRETROVIRAL TREATMENT

Adherence means a “faithful attachment”; “devotion” (THE FREE DICTIONARY 2011) therefore adherence to ART is devotion in proper taking of the antiretroviral drugs as prescribed by the health care providers. Federal Ministry of Health (2010) in Ethiopia described adherence in three distinct stages as good, fair or poor (Table 2.1). For HAART to be effective patients need to take > 95% of their prescribed tablets of antiretroviral drugs (Table 2.2).

Table 2.1: Adherence to ARV drugs

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>(of 30 doses)</th>
<th>(of 60 doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G (good)</td>
<td>&gt; 95 %</td>
<td>&lt;= 2 doses</td>
<td>&lt; 3 doses</td>
</tr>
<tr>
<td>F (fair)</td>
<td>85 – 94 %</td>
<td>3 – 5 doses</td>
<td>3 – 9 doses</td>
</tr>
<tr>
<td>P (poor)</td>
<td>&lt; 85 %</td>
<td>&gt;= 6 doses</td>
<td>&gt; 9 doses</td>
</tr>
</tbody>
</table>

Adopted: (Federal Ministry of Health 2010)

Table 2.2: Correlation between adherence and virologic response to ART

<table>
<thead>
<tr>
<th>Adherence to ART</th>
<th>Viral load &lt; 400 copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 95% adherence</td>
<td>78%</td>
</tr>
<tr>
<td>90 – 95% adherence</td>
<td>45%</td>
</tr>
<tr>
<td>80 – 90% adherence</td>
<td>33%</td>
</tr>
<tr>
<td>70 – 80% adherence</td>
<td>29%</td>
</tr>
<tr>
<td>&lt; 70% adherence</td>
<td>18%</td>
</tr>
</tbody>
</table>

Adopted: (FHAPCO 2008:103)

Multiple studies have confirmed the importance of adherence but in the real world it is a very difficult issue for PLWHIV to have adequate adhere all the time to the ART medications which are supposed to be taken life-long. In one secondary analysis of prospective clinical trial data in USA, differential adherence to ART drugs combination was reported at least once by 29% of participants over 60 months median follow-up time (Gardner, Sharma, Peng, Hullsick, Burman, MacArthur, Chesney, Teizak, Friedland and Mann-
heimer 2008:75). Similarly in another retrospective data analysis of 4476 PLWHIV who are on ART in South Africa, 65% missed no visits, while 26% missed one visit, 7% missed two and 1.6% missed three or more visits during the first six months on treatment (Brennan, Maskew, Sanne and Fox 2010:49).

2.6.1 Reasons for non-adherence

A qualitative study from Brazil describes different challenges to ART adherence by classifying them into three categories; difficulties related to social factors and life style of the population, difficulties which are directly related to the use of medication, and difficulties related to negative beliefs about the use of ART (Melchior, Nemes, Alencar and Buchalla 2007:41). There are other multiple reasons stated in different countries but all directly or indirectly line up to the above categories.

2.6.1.1 Difficulties related to social factors and life styles

According to Melchior, stigma to live with HIV/AIDS is an important barrier for adherence to ART for many PLWHIV who relate strong need to hide the disease and use of medication. Other social factors such as the consumption of alcoholic beverages and use of drugs were incriminated as major barriers to adherence. Social drinking is a frequent mentioned obstacle for adherence (Melchior et al 2007:42). Missing a scheduled visit and lack of disclosure of HIV status were associated with non-adherence from a retrospective review in South Western Uganda (Bajunirwe, Arts, Tisch, King, Debanne and Sethi 2009:139).

2.6.1.2 Difficulties related to negative beliefs about the use of ART

Perceptions and opinions about medications such as “medicine is what kills”, “AZT is for cancer”, “too much medicine is bad for health”, “you need to take a break from the medicine”, and “medicine makes you drowsy and slow” are all reasons which pull back PLWHIV from properly adhering to their medications (Melchior et al 2007:42).
2.6.1.3 Difficulties directly related to the use of medication

Drug side effects such as nausea, vomiting, headaches and diarrhoea are reasons directly related to non adherence moreover intolerance to the smell or taste of medications. Difficulty to dissolve or swallow and confusion about the interval between doses also contribute to poor adherence (Melchior et al 2007:42-45).

2.6.2 Barriers for optimal ART adherence

An article from Uganda’s experience mention barriers for optimal ART-adherence in relation to long waiting times in the HIV clinic, the lack of privacy during counselling and medical check-ups in the HIV clinic, stigmatisation, inadequate treatment by support staffs, lack of sufficient social support, food shortage in households of PLWHIV and inability financing transportation to come to visit the HIV clinic (Cornet & Koster 2008). Additionally, key informant interviews in South Africa report that mere denial of the existence of HIV or of one’s own positive status, use of traditional medicines, speaking a different local languages from health service providers, being away from home, perceived severity of side effects, and feeling better on treatment (Dahab, Charalambous, Hamilton, Fielding, Kielmann, Churchyard and Grant 2008:63) were identified as a prohibiting factors from adherence to treatment in different studies. As one can note from the cited evidence above, multiple social, cultural, economical, communication and religious factors play different roles in negatively affecting optimal adherence in PLWHIV who are on ART.

2.6.3 Virologic Failure

In Ethiopian ART guideline virological failure is a plasma viral load above 10000 copies/ml in duplicates after six months on ART (FHAPCO 2008:77), but in the new 2010 WHO’s guideline a virological failure is defined as a persistent viral load above 5000 copies/ml (WHO 2010a:48). Poor adherence or non adherence predicts virologic failure but not necessarily resistance (Bajunirwe et al 2009:139). From the previously mentioned study in USA, of those patients with differential adherence 30% reported it before initial virologic failure, which made them in an increased risk of initial virologic failure plus with antiretroviral resistance compared with participants without differential adherence before initial virologic failure (Gardner et al 2008:75). Similarly from the study in
South Africa, patients who missed two and three or more medical visits had an increased risk of death (Brennan et al 2010:49). Moreover, one retrospective cohort study from Uganda indicates that non-adherence to ART was significantly associated with mortality in two mechanisms. The first is non-adherence leading to failure to suppress viral replications which increase HIV mutation resulting in drug resistance HIV strains. The second is non-adherence make HAART to lose capacity to prevent viral destruction of the cellular immune system which progress to a decline in CD4 cell count which in turn leads to a predisposition to opportunistic infections (Abaasa, Todd, Ekoru, Kalyango, Levin, Odeke and Karamagi 2008:241).

2.7 IMMUNO RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

IRIS only occurs in a subset of PLWHIV after initiation of ART. The name is self explanatory constituting two core components, immune reconstitution and inflammatory condition. The immune reconstitution is associated with the effect of HAART in killing the HIV which in many cases stimulate the redistribution of memory T cells and rapid restoration of pathogen specific immune response (Agmon-Levin, Elbirt and Sthoeger 2008:439,476; Kestens, Seddiki and Bohjanen 2008:419). This is then followed by poor homeostatic control that promote exaggerated immunopathological response, especially if viable pathogen or pathogen debris are present at high concentration (Kestens et al 2008:419) although the precise mechanism of IRIS is not well understood. This pathological inflammatory response can present in a wide scale of clinical spectrums, from mimicking a mild acute inflammation to a severe opportunistic infections, malignancy, or even autoimmune disease (Agmon-Levin et al 2008:439,476). In one published literature review, it was indicated that IRIS resulted in paradoxical short term morbidity and even mortality (Shelburne, Montes and Hamill 2006:1094). On the contrary another cohort study from Uganda shows the contribution of IRIS to mortality was limited and insignificant (Casteinuovo, Manabe, Kiragga, Kamya, Easterbrook and Kambugu 2009:973). The commonest forms of IRIS are associated with mycobacterium infections, fungi, and herpes virus (Dhasmana, Dheda, Ravn, Wilkinson and Meinties 2008:191).

There are no laboratory tests or acceptable criteria’s for diagnosis of IRIS, which remains a diagnosis of exclusion (Agmon-Levin et al 2008:439,476). Therefore in resource poor settings where the primary goal is to initiate HAART, IRIS may go unrecog-
nised and have fatal consequence. To curtain such conditions there is a need for controlled clinical trials regarding the prevention or treatment of IRIS to guide clinicians in their approach to this series common clinical condition.

2.8 PREDICTORS OF HIV/AIDS ASSOCIATED MORTALITIES

HAART resulted in 65% decline in mortality (Jerene, Næss and Lindtjorn 2006:10). However, still many more HIV/AIDS associated preventable deaths have continued to occur in the post ART era; especially the highest death rate being recorded in the first months of initiation of treatment (Jerene et al 2006:136).

2.8.1 Poor resource settings

Patients starting HAART in resource poor settings have an increased risk of mortality rate in the first months of therapy when compared with those in developed countries (ART-LINC 2006:817). Despite the immunologic and virologic response to ART, the numbers are similar for both high and low income countries (Lawn et al 2008:1897). Therefore, one can see that HAART alone without proper OI management and nutritional support does not prevent mortality among PLWHIV (Rajagopalan et al 2009:219). There have been many efforts to predict HIV/AIDS associated mortalities before happening. As one cohort study from Ethiopia indicates, advanced clinical stage of HIV while starting ART, anaemia, low body weight and lack of cotrimoxazole preventive therapy are incriminated as independent predictors of mortality (Alemu & Sebastián 2010: 5398). Similarly another cohort from Ethiopia also pointed out those HIV patients with WHO clinical stage 4 status and total lymphocyte count (TLC) <= 750/mcl are as independent predictors of death (Jerene et al 2006:136). With similar intension to predict mortality among PLWHIV who are on ART, many more studies tried to pin point a wide spectrum of clinical and laboratory findings; for the scope of this literature review it is worth mentioning the most vivid.

There are two retrospective cohort studies from South Africa and Singapore which tried to predict mortality. The South African study indicates that the strongest predictors of mortality related to CD4 cell count < 50/µl, a haemoglobin concentration <= 8 g/dl, a history of oral candidiasis and a history of cryptococcal meningitis (Ojikutu, Zheng, Walensky, Lu, Losina, Giddy and Freedberg 2008:204).
2.8.2 Malnutrition

According to a study in Singapore, malnutrition at the time of starting ART is significantly associated with decreased survival but the effect appeared not to be mediated by impaired immune reconstitution (Paton, Sangeetha, Earnest and Bellamy 2006:323). There are also three prospective cohort studies from Tanzania, Zambia and Senegal, each with their own version of mortality predictors. According to the Tanzanian’s cohort, anaemia, thrombocytopenia and severe malnutrition were strong independent predictors of mortality (Johannessen et al 2008:52), while from Zambia’s cohort, low serum phosphate at ART initiation was an independent predictor of early mortality among HIV patients starting ART with severe malnutrition or advanced immune-suppression (Heimburger, Koethe, Nyirenda, Bosire, Chiasera, Blevins, Munoz, Shepherd, Potter, Zulu, Taylor, Chi, Stringer and Kabagambe 2010:e10687).

2.8.3 Opportunistic infections

A cohort from Senegal indicated mycobacterium infections, neurotropic infections and septicaemia as the most frequent likely cause of death (Etard, Ndiaye, Mieg, Guéye, Guéye, Laniéce, Dieng, Diouf, Laurent, Mboup, Sow and Delaporte 2006:1181). There is also one case control study from India, which likewise came up with a finding that recurrent diarrhoea as a significant risk factor for mortality, followed by the diagnosis of pulmonary tuberculosis (TB) at first admission while TB in general also negatively impact survival. In the same study WHO stage 4 AIDS defining clinical findings like Pneumocystis jiroveci pneumonia, cryptococcal meningitis and toxoplasmosis also found to negatively affect survival, though the findings were not statistically significant (Rajagopalan et al 2009:219). Furthermore according to Lawn (2008:1897), tuberculosis, acute sepsis, cryptococcal meningitis, malignancy and wasting syndrome were indicated as the leading causes of death (Lawn et al 2008:1897). In many of the above studies TB is depicted as one of the major mortality predictors, but in one of the retrospective cohort study it is found that a history of TB in the contrary is not found to be a significant predictor of mortality (Ojikutu et al 2008:204).

2.9 COMMON LIFE-THREATENING OPPORTUNISTIC INFECTIONS

According to one retrospective study from Ethiopia, when ART is started for PLWHIV, immune restoration is paralleled with different opportunistic infections diagnosis, which
are tuberculosis (TB) (66.5%), toxoplasmosis (12.9%), herpes zoster rash (12.9%), Pneumocystis jiroveci pneumonia (4.1%) and cryptococcosis (3.5%) are all noted as immune restorative diseases (Huruy, Kassu, Mulu and Wondie 2010:46). In general, from opportunistic infections, milder infections occur early whereas series life-threatening infections occur later with severe immunity failure. These lives threatening opportunistic infections are alternatively named as AIDS defining opportunistic infections (WHO 2010a:28). TB may occur early as well as later in HIV disease natural history but when TB occurs in a later advanced stage of AIDS, it is atypically more disseminated and more extra pulmonary.

2.9.1 Pulmonary Tuberculosis

Mycobacterium tuberculosis is a causative agent for all kinds of tuberculosis infections (Bartlett et al 2009-2010:434). An estimated 1.37 million new cases of HIV-TB occurred in 2007, representing 15% of the total global burden of TB, 79% of TB-HIV diseases is in Sub-Saharan Africa, 29% of all cases in South Africa alone, TB is the main OI with 23% of global HIV/AIDS mortality (Lawn and Churchyard 2009:325). According to the latest estimate, Ethiopia stands 7th in the list of high burden countries for TB, and half of the individuals who have active tuberculosis also have HIV co-infection (Federal Ministry of Health 2008:4). In the same report, the incidences of TB of all forms and smear positive TB stands at 378 and 163 per 100000 populations respectively. The prevalence and mortality of tuberculosis of all forms are estimated to be 546 and 73 per 100000 populations respectively: in the year 2006/07 Ethiopia registered 129,743 cases of TB.

At individual patient level HIV increases rate of TB reactivation by 100 fold (Chaisson and Martinson 2008:1089). HIV-TB co-infection alters clinical manifestation of TB, creates diagnostic challenges and complicates treatment. On the other hand TB also has an impact on HIV natural history. TB infection activates T-cells which indirectly supports HIV replication. Therefore active TB is associated with increased HIV-1 viral load, rate of progression to AIDS and mortality. Additionally TB therapy when combined with ART drugs has potential for serious drug-drug interaction and side effects. Tuberculosis can cause pulmonary and or extra pulmonary symptoms depending on the degree of immune suppression. In patients with CD4 count below 200 cells / µl, tuberculosis is often atypical, with lower zone infiltration of the lung and tends to be extra pulmonary. According to a cohort study from Malawi, HIV increases the rate of recurrent tuberculosis by increasing the rate of re infection with mycobacterium tuberculosis bacteria, not as
cases of relapse from the previous TB disease (Crampin, Mwaungulu, Mwaungulu, Mwafulirwa, Munthali, Floyd, Fine and Glynn 2010:417).

2.9.2 Toxoplasmosis

CNS toxoplasmosis is caused by the protozoan parasite called Toxoplasma gondii (Bartlett et al 2009-2010:457). According to a cross sectional study in Ethiopia, the overall sero-prevalence of latent Toxo infection among the study subjects in Addis Ababa was 90.0%. Moreover, toxoplasma infection was observed with retrospective prevalence of 93.3% and 86.7% among HIV infected and HIV uninfected people (Shimelis, Tebeje, Tadesse, Tegbaru and Terefe 2009:213). The greatest risk is among patients with a CD4+T lymphocyte count < 50 cells / µl and almost exclusively related to reactivation of latent infection (FHAPCO 2008: 27).

2.9.3 Pneumocystis Jirovecii Pneumonia

The cause of pneumocystosis is a Pneumocystis Jirovecii fungal agent (Bartlett et al 2009-2010:447). Pneumocystis jiroveci pneumonia (PCP) used to be considered as a reactive from a latent infection which was acquired in childhood but now it is believed to result from new infection from an exogenous source, and it causes fatal pneumonia in immune compromised individuals especially in AIDS patients (Herrag, Elfassy Fihry and Alaoul Yazidl 2010:342). Before the advent of HIV/AIDS, this disease used to be common in North America but it was less heard of in Africa including Ethiopia which is partially associated with difficulty of definitive diagnosis or under reporting. In Ethiopia because of the definitive diagnosis difficulty, PCP among PLWHIV is diagnosed empirically for treatment (FHAPCO 2008:9). PCP has a huge seasonal variation in the incidence and mortality rate, the highest mortality is in autumn (21.2%) and lowest in spring (9.7%), however the overall mortality rate is 13.5% (Miller, Evans, Copas, Huggett, Edwards and Walzer 2010:497).

2.9.4 Cryptococcus Meningitis

HIV associated Cryptococcus infections mainly Cryptococcus meningitis is caused by Cryptococcus neoformans which is a fungal infection (Bartlett et al 2009-2010:404). One descriptive study from Ethiopia indicated, Cryptococcus meningitis is common among patients with immune suppression and with highest case fatality rate (Seboxa, Alemu, Assefa, Asefa and Diro 2010:237). Similarly another longitudinal study from
Cambodia also described cryptococcal meningitis as an important cause of morbidity and mortality in Cambodian HIV-infected patients (Espié, Pinoges, Balkan, Chanchhaya, Molitino, Narom and Puiades-Rodriguez 2010:1375).

2.10 SUMMARY

Based on the evidence presented so far, one can easily note that there are long lists of mortality predictors in different countries. Accordingly, it is necessary to validate the studies with the countries real context before endorsing the raw evidence from different clinical setups. Additionally in Ethiopia, especially in North West part, where Gondar University Hospital accommodates the highest PLWHIV in its ART clinic; a recent and sufficiently exclusive data is in scares related to mortality predictors in PLWHIV who are on ART. Therefore, identifying and short listing strong mortality predictors will help to improve the survival of many HIV patients in evidence based clinical practice approach.
CHAPTER 3
RESEARCH DESIGN AND METHOD

3.1 INTRODUCTION

Chapter two dealt with literature review related to previous research works and published documents in the context of the topic under discussion. Here in chapter three the details of the research design, research methods, reliability, validity and ethical consideration will be discussed.

3.2 RESEARCH DESIGN

Research design is a systematic general plan enabling the researcher to provide a solution to the research problem being studied, with minimum bias and scientifically sound result while addressing some research problems encountered during execution phase. In a broad sense “the research design is the architectural back bone of the study” (Polit and Beck 2008:66). A wide variety of research designs are available. For this research a quantitative, analytical, retrospective cohort study is used to address the research objectives by focusing on the research problem. The study took place in northwest Ethiopia, Amhara regional state, Gondar University Hospital ART clinic, Gondar.

3.2.1 Quantitative study

The theme of a quantitative study is finding a connection between concepts by defining relationships (cause and effect) among variables using different numeric statistical methods (Burns and Groove 2005: 747). Similarly another authors Stommel and Wills (2004:442) describe the use of numeric scales to measure the association between multitude of variables and outcome of interest, which can further be analyzed statistically and produce scientifically sound relationships.

This research revised selected laboratory and clinical histories of the study population using the data collection tool in reaching to an important association between the different variables and the cause of death to predict the occurrence of mortality ahead of time in PLWHIV who were on ART.
3.2.2 Analytical study

According to Joubert and Ehrlich (2007:78), an analytical study will address to find the factors that predict an outcome of interest by looking deep into associations and relations of factors rather than simply describing how much the outcome of interest present.

This study analyzed the different variables independently by grouping and sub-grouping to come up with predictors of mortality from the observed variables. Using analytical method for this research brought to light overlooked factors which have statistical or clinical significance in predicting mortality for PLWHIV who were on ART.

3.2.3 Cohort study

A study design also needs to include the number of times in which data will be collected. A study involving the collection of data more than one point in time over an extended period is a longitudinal design, whereas a study in which data are collected once in order to capture the phenomena under study is a cross sectional design (Polit and Beck 2008:208).

A cohort study also known as a follow-up or longitudinal study encompasses three main points: a group of people, certain common characteristic and follow-up time. Therefore the relationship between an exposure and an outcome in the followed groups of people over a certain given time can be examined (Joubert and Ehrlich 2007:79). The same authors also describe the existence of two types of cohort studies: prospective and retrospective cohort. Time is an important factor for either retrospective or prospective designs, timing refers to the occurrence sequence of independent and dependent variables but not timing of data collection (Polit and Beck 2008:210).

3.2.3.1 Prospective cohort study

A prospective cohort is a study which the researcher selects the study population at the beginning of the study period and follows them in a forward direction through the calendar time and eventually record whether the outcome of interest develop or not (Joubert and Ehrlich 2007:81). A prospective longitudinal cohort study is important for studying
the dynamics of phenomena over time in which data are collected at more than one point in time with an extended follow-up of the cohort groups (Polit and Beck 2008:210).

3.2.3.2 Retrospective cohort study

Retrospective cohort, the name is self descriptive; the study has a backward direction and the acquisition of data is retrospectively from past records (Kirkwood 1994:156). It “shortens the time needed to conduct a cohort study as it makes use of historically or previously compiled data” (Joubert and Ehrlich 2007:81). Retrospective studies are typically cross-sectional in nature, data inferred all about the variables and events occurred in the past are collected at a single point in time (Polit and Beck 2008:210).

In this research data from antecedents or determinants occurring in the past were collected at a fixed point in time with a cross-sectional fashion, from a cohort of HIV patients who started ART at GUH during January 01, 2007 and June 30, 2010. These cohorts of HIV patients’ charts farther subdivided in to two groups: survivor PLWHIV charts and dead HIV patients’ charts. In-sum the study helped to look at the variables (clinical, laboratory and treatment adherence) in relation to AIDS associated deaths retrospectively from the corresponding GUH paper based patients’ records.

3.2.3.3 Strength of a cohort study

In cohort studies one can certainly know that the exposure precedes the outcome of interest, which is one of the criteria helping to claim a causal relationship between a factor and an outcome. Additionally, the researcher can assess a range of outcomes in relation to the variables being studied (Joubert and Ehrlich 2007:81). Therefore if one conducts a research, the strength of evidence collected by a cohort study is stronger than the rest of the observational studies.

3.2.3.4 Limitations of a cohort study

In cohort studies, after data collection, the analysis is complicated. Sometimes in a very long prospective cohort studies adjustments need to be considered for the possible aging of the study groups. In addition cohort studies bear different logistic problems and become costly (Kirkwood 1994:156). Cohort studies are also vulnerable to biases; in a
prospective cohort: loss to follow-up of participants and reporting of outcome by the participants; in retrospective cohort: incomplete or lost documentations, may contribute in introducing information bias to the studies (Joubert and Ehrlich 2007:82).

3.3 RESEARCH METHOD

According to Polit and Beck (2008:765) research method is “the technique used to structure a study and to gather and analyze information in a systematic fashion”. In the methodology portion of a research, one can look at details of the study population, sampling techniques, data collection instruments, data collection approaches and methods.

3.3.1 Study population

The study population is a group whose members have certain common attributes about which the researcher wants to gather information and draw conclusion. The population do not always have to be people, rather events, places, objects and animals can make up a study group; additionally study population should have clear description in respect to place, time and other factors relevant to the study (Joubert and Ehrlich 2007:94). According to Stommel and Wills (2004:297) in conducting a research, population are described as, target population and accessible population. Target population are the ideal full set of population with a character of interest in which the researcher wants to project the study findings for generalization. In this study the target population were all PLWHIV in Ethiopia who were on ART. Whereas the accessible population are subsets of the target population from which a representative sample or the whole population are actually subjected to the research. In this study the accessible population were all PLWHIV in Ethiopia who were on ART and more specifically whose ART initiation and subsequent follow-up was located in GUH ART clinic. Inclusion and exclusion criteria’s are considered as very important components of the study population which will help to screen those who will participate in the study (Joubert and Ehrlich 2007:94).

3.3.2 Screening tool

The clinical factors for the accessible population were those patients’ charts with initial ‘CD4 T lymphocyte count < 200 cells/mm$^3$’ or those with ‘WHO stage 3 and CD4 < 350
cells/mm$^3$ or ‘WHO stage 4’, because these are the eligible PLWHIV who can start ART in Ethiopia. The other important factor here was that the charts need to have full and proper documentations including in-hospital documentation of the cause of death for the dead patients’ charts. The exclusion criteria’s for this study were age less than 18 years, patients’ records for those on pre-ART follow-up and women patients’ records who died while on short course ART for the purpose of prevention of mother-to-child-transmission (PMTCT) of HIV.

### 3.3.3 Sampling

Sampling is the process of selecting individuals from a population who will be studied (Burns and Groove 2005:341). A sample needs to be representative of the study population so that a researcher can generate the necessary information cost effectively (Joubert and Ehrlich 2007:94). There are two major types of sampling methods: random/probability sampling and non probability sampling. The former was of the principle that whether or not an individual is selected depends upon chance, whereas the later sampling technique depends on the researcher role in determining for an individual selection (Joubert and Ehrlich 2007:95). Similarly Polit and Beck (2008:762,764) define probability sampling as “the selection of sampling units (e.g., participants) from a population using random procedures (e.g., simple random sampling or cluster sampling)” and random sampling as “the selection of a sample such that each member of a population has an equal probability of being included”. Probability sampling ensures representativeness of the probability sample, hence it is the most preferred and respected method of the two approaches (Polit and Beck 2008:340). To perform random sampling, a sampling frame is needed which is a full list of members of the population from which the study participants (sampling unites) will be selected (De Vos, Strydom, Fouche and Delport 2007:194).

There are different types of random sampling techniques: simple random sampling, stratified random sampling, cluster sampling and systematic sampling (Polit and Beck 2008:344-348); from those “systematic random sampling is particularly useful if a sample of patient records has to be selected” (Joubert and Ehrlich 2007:100). To perform systematic random sampling, the study frame need to be listed down orderly and with the first participant chosen at random, the rest will be selected at a fixed sampling interval.
In this research a systematic random sampling method was implemented for all survivor PLWHIV chart records. In GUH, the ART registration log book had all the tracks of PLWHIV who have got services in the ART clinic. According to the ART clinic log book, up to the end of June 2010 there were 8377 PLWHIV records that have ever enrolled in care; out of which 3370 were actively on regular follow-up. Out of the 3370 active PLWHIV only 2622 had a follow-up period between January 01, 2007 to June 30, 2010 with clean and complete paper based chart records; and their clinical information were also fully transferred to an electronic database. Therefore, the 2622 paper based PLWHIV chart records were taken as a study frame. The charts were extracted from GUH main chart room using their unique ART numbers and later all were labelled with a new serial numbers. According to a statistician’s recommendation a sample size was determined to be 800. Therefore, to come-up with the 800 sample size of survivor PLWHIV charts, one needs to divide 2622 by 800 to reach for the sampling interval: which is 3.28 (approximate to a whole number ‘3’). Thereafter to determine the random starting point, the research had drawn a random number within the first sampling interval so that every third record was selected to the study group.

While revising GUH ART clinic I-TECH database, the total number of death records of patients who once had ART follow-up at the hospital’s ART clinic between January 01, 2007 to June 30, 2010 were 360 (GUH 2010); out of which 324 were adults with age greater than 18. From the 324 charts only 200 had complete documentations of ART intake sheets, follow-up sheet and hospital cause of death. Therefore, again at the statistician’s recommendation, the total 200 dead patients’ paper based charts with a complete documentation were included in this study.

### 3.3.4 Sampling error

Polit and Beck (2008:765) defines sampling error as “the fluctuation of the value of a statistic from one sample to another drawn from the same population”; which in other words indicate the discrepancy between a true population result and a sample result. There is always a big concern among researchers over whether a sample value reliably estimate true population parameter; in this respect probability sampling allows researchers to estimate the magnitude of sampling error (Polit and Beck 2008:348).
3.3.5 Research assistant

Data collection was done by the researcher, who is a medical doctor and has worked as HIV physician for more than 4 years, specially the recent 2 years at GUH as a physician mentor in the ART clinic where the research took place.

In GUH there were two full time information technicians who were employed by I-TECH as a technical assistance in supporting the ART clinic data room for assuring the completeness of the paper based patients’ records before feeding the data into an electronic database. They were requested to be involved in this research to help list down and order the paper based charts unique ART number during their off duty hours. Following, a porter from GUH ART clinic was also requested to assist in collecting the paper based charts from the main chart room similarly on his off duty hours. Special training about the research was not considered for the assistances, as they were not involved in anyways with the technical aspects of the research apart from an extra work load in their routine activities. For all the assistants’ stipend was paid as individual mutual agreement.

3.3.6 Data collection approach and method

The format and variables of the data collection instrument had two sections, demographic and clinical follow-up characteristics that correspond to the regular GUH ART clinic patient intake and follow-up form. Therefore it was simply be the transferring of information with the corresponding variables. In case of information’s were misplaced or written in different parts of the chart, the data collector dug the information from the chart review and transferred the findings to the correct variable locations in the data collection instrument. Overall meticulous chart review was performed for inclusion of all the necessary variables. For ambiguous and illegible handwriting, GUH I-TECH ART electronic database was consulted.

3.3.7 Data collection instrument

The Federal Ministry of Health, Ethiopia, HIV care/ART follow-up form has been used universally throughout the country as a paper based chart for HIV clinic clients to docu-
ment all issues related to HIV/AIDS, opportunistic infections and ART (Annexure D). Therefore, for the purpose of this research only selective variables of high interest were incorporated from the follow-up form in to the data collection tool to address the research problem and objectives. The items directly transferred in the data collection tool were (Facility name, Age, Sex, Date confirmed HIV +, Eligible date, Eligible and ready date, Follow-up date, Opportunistic infections, Weight in kilogram, Functional status, WHO stage, ARV drugs, Adherence, Side effect, Reason for change of drug, CD4/mm³ and Haemoglobin count). There were two modified items (Number and Patients’ residence); “Number” was allocated by the researcher sequentially corresponding to their unique ART numbers in the client’s follow-up form whereas “patients’ residence” was broadly categorised as “Gondar town” residence or “outside of Gondar” residence referring to the clients’ complete address from their follow-up form. There were two items added by the researcher: the current status of patients “alive” or “dead” and for the dead groups “the cause of death”. The values for all these variables were easily found during the chart review data collection period either directly from the ART follow-up form or from the paper based client’s general hospital chart. The data collection tool was designed by the researcher in collaboration with a statistician. The tool has two portions; the upper most part which concentrates on demographic data including HIV confirmed date, eligibility and readiness date for the initiation of ART.

The second and lower portion incorporated the patients’ follow-up status, encounters of opportunistic infections, weight, functional status, ART adherence, ART drug types, ART drug side effect, and reasons for changing ART drugs; finally the laboratory investigation values which have a direct relationship with HIV treatment outcome and side effect: CD4⁺ cell count and haemoglobin (Annexure C). The data collection instrument was pretested in a randomly selected 50 charts from GUH ART clinic before implementation.

3.3.8 Data analysis

Data analysis is a process carried out at the completion of the data collection; which will categorize, put in order, manipulate and summarize the data in order to be able to answer the research problem, in the mean time addressing the aim of the research (De Vos et al 2007:218). For this research, the statistician assistance was paramount in
analyzing the collected data. Moreover proper cleaning procedures were performed before coding and entry of the data into SPSS version 16 statistical software for analysis.

Using SPSS, bivariate and multivariate analysis were performed for association between variables and mortality. Odds ratios (ORs) were derived from the bivariate and multivariate analysis. Finally a two sided statistical significance test were carried out with a probability cut-off value of 0.05.

3.4 RELIABILITY AND VALIDITY

Reliability, precision and repeatability can interchangeably be used to describe the same character. Likewise validity and accuracy can also be used interchangeably; but it is important to give attention to the fact that reliability and validity (or their inverse, imprecision and bias) are different phenomena, therefore they need to be discussed separately (Joubert and Ehrlich 2007:156).

3.4.1 Reliability

Reliability or precision refers to stability, consistency, repeatability or reproducibility of the measurements; if the measurements were taken over and over again, it provides an indication of the random error in the measurement (Burns and Groove 2005:374; Joubert and Ehrlich 2007:155). In this study all complete charts of the dead and almost one out of three alive PLWHIV charts were enrolled in the study making the total study population to be 1000. Therefore the larger the sample size in this study contributed to an increase in the precision of the study result.

3.4.2 Validity

Validity or accuracy is the proximity of a measurement to the truth (Joubert and Ehrlich 2007:156). The same author in another context describe validity as “the extent to which a measurement instrument actually measures what it is meant to measure” (Joubert and Ehrlich 2007:117). According to Burns and Groove (2005:214) validity is a “measure of the truth or accuracy of a claim".
In this research to ensure the research validity, the source population for the dead and alive HIV patients was all drawn from GUH ART clinic record pool that had similar criteria of treatment initiation with the same enrolment study duration. The survivor PLWHIV medical records were selected with a systematic random sampling technique while the total cleaned and completed records of the dead HIV patients’ charts were all enrolled in this study. There was no record bias, because the data collection method was a full document retrospective case record review and analysis. In a broad context, clinical attendees were not representative of the general population since those who attend the clinic in some way differ from other community members who did not. However, in this particular study, the all the study population need to visit the ART clinic to have ART exposure; therefore this possible bias had no place to interfere with this research.

3.5 ETHICAL CONSIDERATION

According to the American heritage dictionary (2000) ‘ethics’ is defined as “a theory of a system of moral values”, “the study of the general nature of morals and of the specific moral choices to be made by a person” and “the rules or standards governing the conduct of a person or the members of a profession”.

Respecting to the above ethical values, there were many considerations taken while conducting this research. Initially the research proposal was submitted to UNISA Health Studies Research and Ethics Committee College of Human Sciences, from where a clearance certificate was granted for this project number: 4323-288-4.

The clearance from UNISA, the research proposal, a request for waiver of consent and support letter from GUH Medical Director was then presented to Gondar University ethical review board for permission to conduct the study. A one year ethical clearance certificate was granted. The request for waiver of consent to conduct the study, letter of support from GUH Medical Director, ethical clearance certificate from UNISA and Gondar University are all annexed as annexure E, F, G and H respectively.

Risk: There was no psychological or physiological risk with respect to this study. As there was no patient encounter or contact, the only approach was retrospective chart reviews which bear negligible risk.
Confidentiality: The subjects’ “unique ART number” was not collected in the process. Data was stored in an electronic copy in a password protected file on the investigator’s personal computer and backed-up in hard copy which was stored in a locked cabinet in a locked room. After completion of the study, the stored data won’t include any personal identifiers, and was not shared with government agencies or NGOs.

3.6 CONCLUSION

The chapter addressed the study design and method. The rationales for the selection of these specific study design and method were guided by different factors. These factors were: addressing the research problem efficiently, availability of data, ethical values, ability to control likely biases and the cost to conduct the study. The next chapter deals with the study results.
CHAPTER 4
ANALYSIS, PRESENTATION AND DESCRIPTION OF
THE RESEARCH FINDING

4.1 INTRODUCTION

Chapter 3 described the research design and method, which is quantitative, analytical, retrospective cohort study on predictors of mortality among human immunodeficiency virus infected patients’ records in Gondar University Hospital-Ethiopia. The aim of the study was to define predictors of mortality among PLWHIV at GUH ART clinic. In this chapter; analysis, presentation and description of the research findings are discussed.

4.2 DATA MANAGEMENT AND ANALYSIS

The data collection tool was structured in two sections as follows:

- Demographic characteristics
- Patient follow-up history

Data from the data collection instrument was coded on the summary sheets by the researcher. The data was then analysed and interpreted with the great help of a biostatistician using the Statistical Package for Social Scientists (SPSS) and Microsoft Excel computer programs. The study findings were then presented in a narrative format, tables and diagrams to further clarify the relationships of the different variables and findings.

4.3 RESEARCH RESULTS

The following is the presentation of the research results.

4.3.1 Sample characteristics (N=1000)

The sample frame for the study consisted of charts of PLWHIV who were on ART and had a regular follow-up at GUH ART clinic from 1 January 2007 to 30 June 2010. These charts were further categorised in two groups: dead and alive (Alive N=800 and Dead N=200). The study analysed both sexes of age 18 and above years. Charts of Women who started ART for the purpose of Prevention of Mother-to-Child-Transmission (PMTCT) of HIV were not enrolled in the sample.
### 4.3.1.1 Sex

From the total of 1000 reviewed HIV patients' charts n=536 (53.6%) were females [(41.4%) were alive and the rest (12.2%) were dead]. Similarly there were n=464 (46.4%) male patients' charts reviewed; [(38.6%) were alive and n=78 (7.8%) were dead] by the end of June 2010. Table 4.1 and Figure 4.1 show the details of their sex distribution. In a bivariate analysis there was a correlation between mortality and Female sex, from the dead HIV patients n=122 (61%) were females, whereas n=78 (39%) of the dead patients were males therefore having a female sex was one of the predictors of mortality (OR 1.458, 95% CI 1.063 – 2.001, P = 0.019); similarly in multivariate analysis female sex was also found to be one of the predictors of mortality (OR 1.748, 95% CI 1.127 – 2.71, P= 0.013).

**Table 4.1**: Sex distribution in the chart review of HIV patients who were on ART follow-up at GUH from 1 January 2007 – 30 June 2010

<table>
<thead>
<tr>
<th>Sex of the patient</th>
<th>Bio status of the patients</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>alive</td>
<td>Dead</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>386</td>
<td>78</td>
<td>464</td>
<td></td>
</tr>
<tr>
<td></td>
<td>83.2%</td>
<td>16.8%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>414</td>
<td>122</td>
<td>536</td>
<td></td>
</tr>
<tr>
<td></td>
<td>77.2%</td>
<td>22.8%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>51.8%</td>
<td>61.0%</td>
<td>53.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41.4%</td>
<td>12.2%</td>
<td>53.6%</td>
<td></td>
</tr>
</tbody>
</table>
4.3.1.2 Age

The mode of the patients’ age from the chart review was 23 years, but when one groups the age in such a way as age range: 18 – 25 years, 26 – 49 years and ≥50 years, the mode become the age range between 26 – 49 years. The mean age of the patients’ was 33.5 years and the median age was 32 years. According to the reviewed charts, the minimum age of the patient was 19 years and the maximum age of the patient was 78 years old. From the total reviewed charts, n=248 (24.8%) alive and n=21 (2.1%) dead patients were in an age range of 18 – 25 years. The majority n=512 (51.2%) alive and n=151 (15.1%) dead patients’ charts fall in the age range between 26 – 49 years. Similarly in the age range above 50 years, there were only n=40 (4%) alive and n=28 (2.8%) dead patients. Table 4.2 and Figure 4.2 show the detail of their age categories. None of the age group categories were significant indicators of mortality in the bivariate analysis.
Table 4.2: Age group distributions from the chart review of HIV patients who were on ART follow-up from 1 January 2007 - 30 June 2010 at GUH.

<table>
<thead>
<tr>
<th>Age of the patient &lt;=25</th>
<th>Count</th>
<th>% within age of the patient grouped</th>
<th>% within Bio status of the patients</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>alive</td>
<td>dead</td>
<td>total</td>
</tr>
<tr>
<td></td>
<td>248</td>
<td>21</td>
<td>269</td>
<td></td>
</tr>
<tr>
<td></td>
<td>92.2%</td>
<td>7.8%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31.0%</td>
<td>10.5%</td>
<td>26.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.8%</td>
<td>2.1%</td>
<td>26.9%</td>
<td></td>
</tr>
<tr>
<td>26-49</td>
<td>512</td>
<td>151</td>
<td>663</td>
<td></td>
</tr>
<tr>
<td></td>
<td>77.2%</td>
<td>22.8%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>64.0%</td>
<td>75.5%</td>
<td>66.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>51.2%</td>
<td>15.1%</td>
<td>66.3%</td>
<td></td>
</tr>
<tr>
<td>&gt;=50</td>
<td>40</td>
<td>28</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>58.8%</td>
<td>41.2%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.0%</td>
<td>14.0%</td>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.0%</td>
<td>2.8%</td>
<td>6.8%</td>
<td></td>
</tr>
</tbody>
</table>
4.3.1.3 Status of the patient

Out of the reviewed 1000 charts, n=800 (80%) of them were charts of patients who were on ART follow-up at GUH between 1 January 2007 and 30 June 2010, and they were alive at the end of June 2010. The rest n=200 (20%) of them were charts of HIV patients who had follow-up at GUH between 1 January 2007 and 30 June 2010, but they were dead before the end of June 2010 while on treatment.

4.3.2 Follow-up history

During the chart review, patients’ ART follow-up history was given major emphasis. There were two laboratory and three clinical characteristics considered to be the area of interest in this study. The laboratory history noted the latest values of the patients’ CD4
cells and haemoglobin counts, whereas the clinical history focused on the history of Tuberculosis (TB), Oral Candidiasis and Cryptococcus Meningitis. For the clinical history, only the confirmed diagnoses were included in the study.

4.3.2.1 CD4 count

In Gondar University Hospital ART laboratory, HIV patients CD4 cell count had been determined every six months. The machine which determined the CD4 cell count was Fluorescent Activated Cell Sorter – Count (FACS-Count) from Becton Dickinson Company. The result from the chart review showed that the mean CD4 count was 152.65 (153/µl) (standard deviation (SD) 78.9) and the median CD4 cell count was 172/µl (25th – 75th quartile = 91 – 209/µl). One hundred seventy four (17.4%) had the latest CD4 cell count ≤ 50/µl, five hundred fourteen (51.4%) a CD4 cell count of 51 – 199/µl and three hundred twelve (31.2%) a count of ≥ 200/µl; the detail can be seen in Table 4.3 and Figure 4.3.

Out of the reviewed 200 dead HIV patient charts, n=134 (77%) had CD4 ≤ 50/µl; the rest n=60 (11.7%) had CD4 range 51 – 199/µl and n=6 (1.9%) had CD4 ≥ 200/µl. Bivariate analysis revealed that the most recent CD4 count ≤ 50/µl was a significant predictor of mortality (OR 170.85, 95% CI 70.74 – 412.63, P < 0.0001) (Table 4.4). Patients who died while on ART had a mean recent CD4 count of 57/µl compared with 176/µl for those who were alive at the end on the study (June 2010). In multivariate analysis, patients with a CD4 count ≤ 50/µl had higher risk of mortality (OR 155.8, 95% CI 53.57 – 453.16, P<0.0001).

The latest CD4 cell count range of 51 – 199/µl was also found to be one of the mortality predictors in the bivariate analysis (OR 6.74, 95% CI 2.876 – 15.795, P < 0.0001); taking this result in to the multivariate analysis similar result was also found with (OR 7.07, 95% CI 2.975 – 16.8, P < 0.0001).
Table 4.3: CD4 groups distribution from the chart review of HIV patients who were on ART follow-up from 1 January 2007 to 30 June 2010 at GUH.

<table>
<thead>
<tr>
<th>CD4 count grouped</th>
<th>Count</th>
<th>Bio status of the patients</th>
<th>% within CD4 count grouped</th>
<th>% within Bio status of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=50</td>
<td>40</td>
<td>alive</td>
<td>23.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td>134</td>
<td>Dead</td>
<td>77.0%</td>
<td>67.0%</td>
</tr>
<tr>
<td></td>
<td>174</td>
<td>Total</td>
<td>100.0%</td>
<td>17.4%</td>
</tr>
<tr>
<td>51-199</td>
<td>454</td>
<td>alive</td>
<td>88.3%</td>
<td>56.8%</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>Dead</td>
<td>11.7%</td>
<td>30.0%</td>
</tr>
<tr>
<td></td>
<td>514</td>
<td>Total</td>
<td>100.0%</td>
<td>51.4%</td>
</tr>
<tr>
<td>&gt;=200</td>
<td>306</td>
<td>alive</td>
<td>98.1%</td>
<td>38.2%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Dead</td>
<td>1.9%</td>
<td>3.0%</td>
</tr>
<tr>
<td></td>
<td>312</td>
<td>Total</td>
<td>100.0%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Total</td>
<td>800</td>
<td>alive</td>
<td>80.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>Dead</td>
<td>20.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>Total</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Table 4.4: Bivariate analysis of CD4 count and Bio-status of the patients

<table>
<thead>
<tr>
<th>Step 1&lt;sup&gt;a&lt;/sup&gt; cd4_grp</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>cd4_grp(1)</td>
<td>5.141</td>
<td>.450</td>
<td>130.573</td>
<td>1</td>
<td>.000</td>
<td>170.850</td>
<td>70.741</td>
</tr>
<tr>
<td>cd4_grp(2)</td>
<td>1.908</td>
<td>.435</td>
<td>19.283</td>
<td>1</td>
<td>.000</td>
<td>6.740</td>
<td>2.876</td>
</tr>
<tr>
<td>Constant</td>
<td>-3.932</td>
<td>.412</td>
<td>90.972</td>
<td>1</td>
<td>.000</td>
<td>.020</td>
<td></td>
</tr>
</tbody>
</table>

Bar Chart

Figure 4.3: CD4 group distribution in the dead and alive HIV patients; GUH ART clinic patients chart review
4.3.2.2 Haemoglobin count

In Gondar University Hospital ART laboratory, HIV patients’ haemoglobin count had been determined every six month together with their CD4 cell count. For patients who took Zidovudine (AZT) based regimen, which is a nucleoside analogue reverse transcriptase inhibitors (NRTI), one of the drug found in the first line regimen of highly active antiretroviral treatment (HAART) combinations; haemoglobin count had been mandatorily determined every month for the first six months then after every six months similar to the rest of the drugs. The exception here is because, AZT is associated with anaemia. The machine which determined the haemoglobin count was Cell-Dyn 1800 from Abbott Company.

The result from the chart review showed the mean haemoglobin count was 11.068 g/dl (Standard error of the mean (SE) 0.0587) and the median haemoglobin count was 11.9 g/dl (25th – 75th quartile= 10.1 – 12.3). Out of the reviewed 1000 charts the minimum haemoglobin value was 4.6 g/dl and the maximum was 14.0 g/dl. 109 (10.9%) had the latest haemoglobin determined value of ≤ 8 g/dl, 891 (89.1%) a haemoglobin count of >8 g/dl: the detailed can be seen in Table 4.5 and Figure 4.4.

Out of the reviewed 200 dead HIV patients’ charts, n=76 (38%) had haemoglobin count ≤ 8 g/dl; the rest n=124 (62%) had haemoglobin > 8 g/dl. Bivariate analysis revealed that a recently determined haemoglobin count of ≤ 8 g/dl was found to be predictive of mortality (OR 14.245, 95% CI 9.079 – 22.352, P < 0.0001) (Table 4.5, 4.6 and Figure 4.4). Patients who died while on ART had a mean recent haemoglobin count of 9.43 g/dl compared with 11.48 g/dl for those who were alive at the end of the study (June 2010). In multivariate analysis haemoglobin count was not significant.
Table 4.5: Haemoglobin count groups distribution from the chart review of HIV patients who were on ART follow-up from 1 January 2007 to 30 June 2010 at GUH.

<table>
<thead>
<tr>
<th>HG grouped</th>
<th>Count</th>
<th>Bio status of the patients</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=8</td>
<td></td>
<td>alive</td>
<td>33</td>
<td>76</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% within HG grouped</td>
<td>30.3%</td>
<td>69.7%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% within Bio status of the patients</td>
<td>4.1%</td>
<td>38.0%</td>
<td>10.9%</td>
</tr>
<tr>
<td>&gt;8</td>
<td>767</td>
<td>alive</td>
<td>124</td>
<td></td>
<td>891</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% within HG grouped</td>
<td>86.1%</td>
<td>13.9%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% within Bio status of the patients</td>
<td>95.9%</td>
<td>62.0%</td>
<td>89.1%</td>
</tr>
<tr>
<td>Total</td>
<td>800</td>
<td>alive</td>
<td>200</td>
<td></td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% within HG grouped</td>
<td>80.0%</td>
<td>20.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% within Bio status of the patients</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Table 4.6: Bivariate analysis of Haemoglobin count and Bio-status of the patients

Hg = haemoglobin, grp = group

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Step 1a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hg_grp(1)</td>
<td>2.656</td>
<td>.230</td>
<td>133.574</td>
<td>1</td>
<td>.000</td>
<td>14.245</td>
<td>9.079</td>
</tr>
<tr>
<td>Constant</td>
<td>-1.822</td>
<td>.097</td>
<td>354.433</td>
<td>1</td>
<td>.000</td>
<td>.162</td>
<td></td>
</tr>
</tbody>
</table>

a. Variable(s) entered on step 1: hg_grp.
History of Oral Candidiasis

There were a total of n=183 HIV patients (18.3%) who had a history of Oral Candidiasis. In a bivariate analysis there is a correlation between mortality and history of Oral Candidiasis, from the dead HIV patients n=112 (56%) had a history of Oral Candidiasis, whereas n=71 (8.9%) of the alive patients had history of Oral Candidiasis: (OR 13.068, 95% CI 9.021 – 18.930, P < 0.0001) therefore having a history of Oral Candidiasis was one of the predictors of death in HIV patients who were on ART; the details are shown in Table 4.7, 4.8 and Figure 4.5; but with the multivariate analysis history of Oral Candidiasis was not a predictor of mortality (OR 1.243, 95% CI 0.612 – 2.524, P= 0.548).

Figure 4.4: Haemoglobin group distribution in the dead and alive HIV patients; GUH ART clinic patients chart review
Table 4.7: The distribution of Oral Candidiasis in the reviewed HIV patients’ charts who had ART follow-up at GUH from 1 January 2007 - 30 June 2010 at GUH.

<table>
<thead>
<tr>
<th>history of Oral Can-yes</th>
<th>Count</th>
<th>% within history of Oral Candidiasis</th>
<th>% within Bio status of the patients</th>
<th>Bio status of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>alive</td>
<td>71</td>
<td>38.8%</td>
<td>8.9%</td>
<td></td>
</tr>
<tr>
<td>dead</td>
<td>112</td>
<td>61.2%</td>
<td>56.0%</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>183</td>
<td>100.0%</td>
<td>18.3%</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>729</td>
<td>89.2%</td>
<td>91.1%</td>
<td></td>
</tr>
<tr>
<td>% within history of Oral Candidiasis</td>
<td>10.8%</td>
<td>44.0%</td>
<td>81.7%</td>
<td></td>
</tr>
<tr>
<td>% within Bio status of the patients</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>817</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1: Bivariate analysis of History of Oral Candidiasis and Bio-status of the patients

<table>
<thead>
<tr>
<th>Step 1&lt;sup&gt;a&lt;/sup&gt; Oral C</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Oral C</td>
<td>2.570</td>
<td>.189</td>
<td>184.783</td>
<td>1</td>
<td>.000</td>
<td>13.068</td>
<td>9.021</td>
</tr>
<tr>
<td>Constant</td>
<td>-4.684</td>
<td>.272</td>
<td>296.729</td>
<td>1</td>
<td>.000</td>
<td>.009</td>
<td></td>
</tr>
</tbody>
</table>

a. Variable(s) entered on step 1: Oral C.
4.3.2.4 History of Tuberculosis

The chart review result showed that there were a total of n=215 HIV patients (21.5%) who had a history of TB. In a bivariate analysis there was a correlation between mortality and history of TB, from the dead HIV patient charts n=55 (27.5%) had a history TB whereas n=160 (20%) of the alive patients had similar history, (OR 1.517, 95% CI 1.063 – 2.165, P = 0.022) therefore having a history of TB predicts death; the details are shown in Table 4.9, 4.10 and Figure 4.6, but in a multivariate analysis history of TB was not a significant predictor of mortality (OR 1.303, 95% CI 0.802 – 2.118, P=0.286).
**Table 4.9:** The distribution of Tuberculosis in the reviewed HIV patients’ charts who had ART follow-up at GUH from 1 January 2007 - 30 June 2010 at GUH.

<table>
<thead>
<tr>
<th>History of TB</th>
<th>Count</th>
<th>Alive</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>160</td>
<td>74.4%</td>
<td>25.6%</td>
<td>215</td>
</tr>
<tr>
<td>No</td>
<td>640</td>
<td>81.5%</td>
<td>18.5%</td>
<td>785</td>
</tr>
<tr>
<td>Total</td>
<td>800</td>
<td>80.0%</td>
<td>20.0%</td>
<td>1000</td>
</tr>
</tbody>
</table>

**Table 4.10:** Bivariate analysis of History of TB and Bio-status of the patients

<table>
<thead>
<tr>
<th>Step 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>.417</td>
<td>.181</td>
<td>5.284</td>
<td>1</td>
<td>.022</td>
<td>1.517</td>
<td>1.063 - 2.165</td>
</tr>
<tr>
<td>Constant</td>
<td>-1.902</td>
<td>.241</td>
<td>62.061</td>
<td>1</td>
<td>.000</td>
<td>.149</td>
<td></td>
</tr>
</tbody>
</table>

a. Variable(s) entered on step 1: TB
4.3.2.5 History of Cryptococcus Meningitis

There was a total of n=36 HIV patients (3.6%) who had a history of Cryptococcus Meningitis. In a bivariate analysis there was a correlation between mortality and history of Cryptococcus Meningitis, from the dead HIV patients’ n=32 (16%) had a history of Cryptococcus Meningitis, whereas only n=4 (0.5%) of the alive patients had similar history (OR 37.905, 95% CI 13.229 – 108.608, P < 0.0001). Therefore having a history of Cryptococcus Meningitis was one of the significant predictors of death in HIV patients who were on ART, the details are shown in Table 4.11, 4.12 and Figure 4.7. There were only 36 cases of Cryptococcus Meningitis in the total reviewed HIV patients’ charts, therefore history of Cryptococcus Meningitis was not included in the multivariate analysis.

**Figure 4.6:** History of Tuberculosis distribution in the dead and alive HIV patients; GUH ART clinic patients chart review
Table 4.11: The distribution of Cryptococcus Meningitis in the reviewed HIV patients’ charts who had ART follow-up at GUH from 1 January 2007 - 30 June 2010 at GUH.

<table>
<thead>
<tr>
<th>history of crypt. men- yes</th>
<th>Count</th>
<th>Bio status of the patients</th>
<th>% within history of crypt. meningitis</th>
<th>% within Bio status of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>alive</td>
<td>11.1%</td>
<td>.5%</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>Dead</td>
<td>88.9%</td>
<td>16.0%</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Total</td>
<td>100.0%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>history of crypt. men- no</th>
<th>Count</th>
<th>Bio status of the patients</th>
<th>% within history of crypt. meningitis</th>
<th>% within Bio status of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>796</td>
<td>alive</td>
<td>82.6%</td>
<td>99.5%</td>
</tr>
<tr>
<td></td>
<td>168</td>
<td>Dead</td>
<td>17.4%</td>
<td>84.0%</td>
</tr>
<tr>
<td></td>
<td>964</td>
<td>Total</td>
<td>100.0%</td>
<td>96.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total</th>
<th>Count</th>
<th>Bio status of the patients</th>
<th>% within history of crypt. meningitis</th>
<th>% within Bio status of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>800</td>
<td>alive</td>
<td>80.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>Dead</td>
<td>20.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>Total</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Table 4.2: Bivariate analysis of History of Cryptococcus Meningitis and Bio-status of the patients

<table>
<thead>
<tr>
<th>Step 1a</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Crypto M</td>
<td>3.635</td>
<td>.537</td>
<td>45.808</td>
<td>1</td>
<td>.000</td>
<td>37.905</td>
<td>13.229</td>
</tr>
<tr>
<td>Constant</td>
<td>-5.191</td>
<td>.557</td>
<td>86.891</td>
<td>1</td>
<td>.000</td>
<td>.006</td>
<td></td>
</tr>
</tbody>
</table>
4.4 OVERVIEW OF THE RESEARCH FINDING

A total of 1000 patients’ charts over the age of 18 years who started ART and had continued their follow-up at Gondar University Hospital during the study period were reviewed; 80% of them were alive and 20% of them were dead at the end June 2010.

Mean age at the last visit was 33.5 years (range 19 – 78 years). 53.6% were female and 46.4% were male. The median CD4 cell count was 172/µl (25th – 75th quartile = 91 – 209/µl) and the mean CD4 cell count was 152.65 (153/µl) (Standard deviation (SD) 78.9).

Bivariate analysis revealed that a last CD4 cell count ≤ 50/µl was a significant predictor of mortality (OR 170.85, 95% CI 70.74 – 412.63, P < 0.0001) followed by another CD4 cell count range of 51 – 199/µl (OR 6.74, 95% CI 2.876 – 15.795, P < 0.0001). Patients

Figure 4.7: History of Cryptococcus Meningitis distribution in the dead and alive HIV patients; GUH ART clinic patients chart review
who died had a mean last CD4 cell count of 57/µl compared with 176/µl for those who were alive at the end of the study. Similarly haemoglobin concentration ≤ 8 g/dl was also one of the significant predictors of mortality (OR 14.245, 95% CI 9.079 – 22.352, P < 0.0001). A history of TB, Oral Candidiasis and Cryptococcus Meningitis were also found to be correlated with an increased mortality risk of HIV patients who were on ART, similarly in bivariate analysis having a history of these opportunistic infections inclined to predict death, (OR 1.517, 95% CI 1.063 – 2.165, P = 0.022; OR 13.068, 95% CI 9.021 – 18.93, P < 0.0001 and OR 37.905, 95% CI 13.229 – 108.608, P < 0.0001).

In multivariate analysis, HIV patients with a latest CD4 cell count ≤ 50/µl had the highest risk of mortality (OR 155.8, 95% CI 53.57 – 453.16, P < 0.0001) followed by last CD4 cell count of 51 – 199/µl (OR 7.070, 95% CI 2.975 – 16.8, P < 0.0001) and Female sex (OR 1.748, 95% CI 1.127 – 2.710, P = 0.013). Age, History of TB and History of Oral Candidiasis were not predictors of mortality. Because there were only 36 cases of Cryptococcus Meningitis, the multivariate analysis didn’t incorporate the history of Cryptococcus Meningitis as a predictor of mortality.

4.5 CONCLUSION

This chapter has addressed how the data was analysed during the study. The research findings are also presented in detail. The findings described in this study have also been in harmony with the other similar studies that were referred in the literature review part.
CHAPTER 5
CONCLUSIONS AND RECOMMENDATIONS

5.1 INTRODUCTION

Chapter 4 described the research data analysis, presentation and description of the research findings. This chapter summarises the study, provides the research overview, conclusions, and limitations. The chapter also provides a care plan as a contribution of the study and recommendations on the research findings.

5.2 RESEARCH DESIGN AND METHOD

The researcher conducted a retrospective cohort study using a medical chart review for all HIV patients who were on ART at Gondar University Hospital (GUH) ART clinic from 01 January 2007 to 30 June 2010. Exclusion criteria were: (i) Age of < 18 years old, (ii) ART patients’ records who had no documented cause of death and (iii) women patients’ records who died while on short course ART for the purpose of prevention of mother-to-child-transmission of HIV.

A total of 1000 charts were studied which included 200 charts of dead patients and 800 charts of alive people living with HIV (PLWHIV) who were on ART. With the aim to define predictors of mortality among PLWHIV at GUH ART clinic, data from the patients’ medical records were collected using a data collection instrument. The data collection instrument was modified from the Federal Ministry of Health (FMOH)/ HIV AIDS Prevention and Control Office ART patient intake and follow-up chart which facilitated a transfer of identical information from the patients’ medical documents into the data collection instrument. All chart reviews were conducted by the researcher. A random sample of 100 charts were re-reviewed by a physician working at GUH ART clinic to confirm inter-rater reliability. Inter-rater reliability was 1.00. Data was then summarized on a master sheet and double-entered to an electronic system which helped to correct any errors. A biostatistician helped the researcher to analyze and interpret the data.
5.3 SUMMARY AND INTERPRETATION OF THE RESEARCH FINDINGS

There were several research findings which go in line with the objectives of the study. More or less all the findings were similar to earlier studies as evidenced by literatures that related to the study and mentioned in the review part. The findings and interpretations are summarized in the further discussion.

5.3.1 Demographic information

Sex was very important in predicting mortality. From the reviewed charts 53.6% were females. From the dead patients’ charts N=122 (61%) were also females. In another approach, out of all reviewed female patients’ charts 22.8% were dead whereas only 16.8% of all reviewed male patients were dead at the completion of the study. When taking this descriptive result into a bivariate analysis, it was found to be significant in predicting mortality; further analysis of the result in multivariate test similarly showed a significant prediction potential while controlling all cofounder factors.

Age was not found to be a good predictor of mortality for patients who were on ART. The mode for the age falls in a range 26 – 49 years old, but 23 years was the mode age for the individuals when one disaggregating the cluster. The mean age was 33.5 years and the median was 32 years. The age range for the reviewed patients’ medical record extends from 19 – 78 years.

5.3.2 Follow-up history

Two factors were found to be the strongest predictors of mortality in patients who were under the study from their medical records: last CD4 cell count ≤ 50/µl and last CD4 cell count of 51 – 199/µl. Though both predictors came from the patients CD4 cell count, the former one was incriminated as the most significant predictor with a very high odds ratio and confidence interval value. The median CD4 cell count was 172/µl (25th – 75th quartile= 91 – 209/µl) and the mean was 152.65 (153/µl). The most recent CD4 cell determination of ≤ 50/µl contributed 77% of those dead patients at the completion of the study.

Both haemoglobin concentration ≤ 8 g/dl and the history of opportunistic infections (OIs) were also correlated with mortality in the bivariate analysis, but neither haemoglobin
concentration nor any of the OIs history was a significant predictor when computed in a multivariate analysis.

From all the reviewed HIV patients’ medical records, haemoglobin concentration ranged from 4.6 g/dl to 14 g/dl with only 10.9% of the patients had a haemoglobin concentration ≤ 8 g/dl. The median haemoglobin concentration was 11.9 g/dl (25th – 75th quartile= 10.1 – 12.3).

In a bivariate analysis, a history of TB, Oral Candidiasis and Cryptococcus Meningitis conferred an increased mortality risk. When one brought these findings in to multivariate analysis none was able to predict mortality. Cryptococcus Meningitis was not included in the multivariate analysis because there were only 36 cases found from the reviewed documents.

There were multiple presumptive OI diagnosis’s documented in patients’ medical records such as Pneumocystis Jirovecii Pneumonia (PCP), Toxoplasmosis, Herpes Zoster, Kaposi’s sarcoma, Non-Hodgkin’s lymphoma and Primary Central Nervous System (CNS) lymphoma. However, none of the diagnoses were based on evidences for confirmation. Therefore, even though there were multiple OIs documented in the charts, only the confirmed were taken for the interest of this study.

5.4 CONCLUSIONS OF THE STUDY

Simple clinical and laboratory data had a huge potential to independently predict mortality in HIV patients who were on ART in Gondar, Ethiopia. These same data further helped to stratify risks. According to this study a female sex, CD4 cell count ≤ 50/µl and CD4 cell count 51 – 199/µl were found to be significant predictors of mortality. Likewise a history of Cryptococcus Meningitis was also a strong predictor of mortality in bivariate analysis even if it was not computed in multivariate analysis. Using these mortality predictors a care plan was drawn which assist adherence case managers to systematically reduce the prevailing death risk of PLWHIV who are on ART.
A medical care plan:

Simple mortality predictors check boxes that will attach to medical follow-up charts of PLWHIV who are on ART can help to intensify medical care provision. From the check boxes either of female sex, CD4 cell count ≤ 50/µl, CD4 cell count 51 – 199/µl or a history of Cryptococcus meningitis is ticked, then the patient will be said to be under mortality risk. Therefore these patients are expected to get a special attention with full package clinical and non clinical palliative care services by adherence case managers (Table 5.1).

Table 5.1: Care plan for PLWHIV who are on ART and has mortality predictor indicators

<table>
<thead>
<tr>
<th>Mortality predictors check box</th>
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</thead>
<tbody>
<tr>
<td>SEX</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>CD4 cell count</td>
</tr>
<tr>
<td>0 – 50/µl</td>
</tr>
<tr>
<td>51 – 199/µl</td>
</tr>
<tr>
<td>≥ 200/µl</td>
</tr>
<tr>
<td>History of Cryptococcus meningitis</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Non-Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain management</td>
<td>Psychological counselling and support</td>
</tr>
<tr>
<td>Nursing care for bed ridden</td>
<td>Spiritual counselling and support</td>
</tr>
<tr>
<td>Safe water, hygiene and</td>
<td>Social support</td>
</tr>
<tr>
<td>sanitation counselling</td>
<td>End of life care</td>
</tr>
<tr>
<td>Nutritional counselling</td>
<td></td>
</tr>
<tr>
<td>OIs screening</td>
<td></td>
</tr>
<tr>
<td>ART and Cotrimoxazole adherence counselling</td>
<td></td>
</tr>
</tbody>
</table>
5.5 RECOMMENDATIONS

The following recommendations are helpful to improve the quality of HIV care and treatment service provision to GUH ART clinic in specific and to Ethiopia ART centres at large. The recommendations also provide an insight to FMOH, HAPCO, National and International Non Governmental Organizations (NGOs) working in the areas of HIV care and support to design an evidence based and targeted planning for HIV treatment, care and support policy formulation. The recommendations will also serve as bases for further studies.

Recommendations to clinicians and adherence case managers

It is recommended that:

- Clinicians to be more vigilant for HIV patients who are on ART with the mortality predictor clinical and laboratory biomarkers. The treatment should be aggressive and the clinicians should preferably make their follow-up more frequent.
- Adherence case managers give priority to support the HIV patients who are on ART with mortality predictors. Their adherence counselling session should be longer and more frequent. They also need to develop a special problem specific targeted care plan.
- Adherence case managers give priority to HIV patients who are on ART with mortality predictor biomarkers by linking those to local NGOs who provide HIV patients with care and support service based on their need assessment.

Recommendations to service providers and stakeholders

It is recommended that:

- Efforts need to be made by the ART clinics to link PLWHIV with mortality predictors to Regional Civil Society Organizations which provide home based palliative care and economic strengthening supports.
FMOH, HAPCO and the hospital management need to focus in ensuring that free OI drugs are available and further facilitation for priority in getting hospital admission beds for HIV patients who are on ART with the mortality predictors.

5.6 CONTRIBUTIONS OF THE STUDY

Following the result of this study, GUH Adherence Case Managers were assisted to revise their care plan, to give more emphasis for HIV patients who are on ART with mortality predictors. According to the developed medical care plan (table 5.1), the hospital’s adherence case managers are expected to provide a holistic palliative care service provision to their patients. The above medical care plan can also be implemented at the patients’ home using the town health extension workers and voluntary providers from the civil society organizations.

5.7 LIMITATIONS OF THE STUDY

The study was successfully conducted and concluded, nevertheless there were many limitations which hamper to generalize the findings in all geographic areas and clinical setups. They include the following:

- There were many opportunistic infections documented in the patients’ medical charts, but many of them were presumptive diagnoses. For the purpose of this study, only definitive evidence based diagnoses were taken. Therefore, lack of definitive investigation modalities for many OIs affected the clinical history for OIs in considering them as mortality predictors.
- All the reviewed charts were paper based medical documents, therefore poor documentations and illegible handwritings limit the number of variables for analysis. For example, poor documentation of sequential date for patients on ART and patients residential location affected the scope of the analysis.
- The retrospective study design has limited ability to collect some core factors that contributed to mortality of HIV patients who were on ART such as poor adherence and lack of social support and real time quality of clinical service provided. These factors might have a significant implication in predicting mortality for HIV patients who are on ART.
- HIV RNA viral load was not available for all the patients; this value would have given a deep insight in predicting mortality together with CD4 cell count.

5.8 CONCLUDING REMARKS

Regardless of all cited limitations, the result contributed to generate information and knowledge for the decision support system to HIV health care providers in ensuring the quality of service. This study indicates that a simple clinical and laboratory data during the course of ART treatment can predict patients with an increased risk of death. Aggressive interventions to curb these clinical and laboratory biomarkers will help ensure to decrease unprecedented death and maximize survival to fulfil the goal of ART. Comparison of the research outcomes with the situations in other ART sites in Ethiopia or elsewhere will enhance understanding of predictors of HIV associated mortalities in PLWHIV who are on ART.
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FMOH.


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ney, M, Teizak, EE, Friedland, G and Mannheimer, SB. 2008. Differential adherence to 
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## ANNEXURES

### Annexure A: Time frame

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<tr>
<td>Prepare research proposal, conduct literature review, gather background data from GUH ART clinic Pre-test and validation of data collection instrument</td>
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<tr>
<td>Week #3&amp;4: Conduct chart review, and finalizing data collection</td>
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<td>Submit and defend thesis</td>
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* After ethical clearance is assured form UNISA

** Will plan to submit and defend thesis no later than November, 2011: (This time line may have to be changed depending up on the time it takes to receive ethical review approval both from UNISA and GUH board).
Annexure B: Budget

In order to complete this study, costs for consumable materials, per diem, transportation to Gondar, lodging, food and supplies, UNISA annual registration fees, as well as costs of all professional technical supports were all covered by the researcher. The budget break down is presented below.

<table>
<thead>
<tr>
<th>Expense</th>
<th>Source*</th>
<th>Total (Calculated at an exchange rate of ≈ 17 Birr / 1USD and ≈ 2.5 Birr / 1 Rand)</th>
</tr>
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<tbody>
<tr>
<td>The annual UNISA registration fees for dissertation</td>
<td>Self-funded</td>
<td>5000 rand / 12500 birr / $735 USD</td>
</tr>
<tr>
<td>Typing and printing of dissertation</td>
<td>Self-funded</td>
<td>300 rand / 750 birr / $44 USD</td>
</tr>
<tr>
<td>Preparation and photocopying of the research data collection tool</td>
<td>Self-funded</td>
<td>800 rand / 2000 birr / $118 USD</td>
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<td>Expenses while staying in Gondar</td>
<td>Self-funded</td>
<td>500 rand / 1250 birr / $74 USD</td>
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<td>Postage, telephone calls, Internet time</td>
<td>Self-funded</td>
<td>250 rand / 625 birr / $37 USD</td>
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<tr>
<td>In country travel expenses for PI to / from Gondar and Addis Ababa</td>
<td>Self-funded</td>
<td>1500 rand / 3750 birr / $221 USD</td>
</tr>
<tr>
<td>Editing of the dissertation by a professional editor</td>
<td>Self-funded</td>
<td>1000 rand / 2500 birr / $147 USD</td>
</tr>
<tr>
<td>Statistician Service</td>
<td>Self-funded</td>
<td>3000 rand / 7500 birr / $441 USD</td>
</tr>
<tr>
<td>Photocopying and binding of 4 examination copies</td>
<td>Self-funded</td>
<td>100 rand / 250 birr / $15 USD</td>
</tr>
<tr>
<td>The service of a professional typist to finalize the examination copies</td>
<td>Self-funded</td>
<td>3500 rand / 8750 birr / $515 USD</td>
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<td>Photocopies of final copies after the examiners’ comments have been imple-</td>
<td>Self-funded</td>
<td>75 rand / 187 birr / $11 USD</td>
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<td>Funding Type</td>
<td>Costs</td>
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<td>---------------------------</td>
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<td>Binding of two final copies, plus one unbound copy and one CD-Rom copy</td>
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<td>250 rand / 625 birr / $37 USD</td>
</tr>
<tr>
<td>Lodging while in Gondar for PI</td>
<td>Self-funded</td>
<td>3750 rand / 9375 birr / $551 USD (assuming PI spend one month in Gondar)</td>
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<td>Other expenses while staying in Gondar</td>
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<td>1500 rand / 3750 birr / $221 USD</td>
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<td>Grand total</td>
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<td>21525 rand / 53812 birr / $3165 USD</td>
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* All expenses are covered from the PI own pocket.
Annexure C: Data collection instrument

*** Adopted from Ethiopian national HIV CARE / ART FOLLOW-UP FORM

| Facility name: ___________________________ | Number: ________ |
| Patient residences: □ Gondar town  □ Outside of Gondar |
| Age: ______ years  Sex: □ M □ F |
| Date confirmed HIV +: ___ / ___ / ____ (dd/mm/yy) |
| Eligible (date): __ / __ / __ (dd/mm/yy)  Elg. & Ready (date): __ / __ / ____ (dd/mm/yy) |
| Current status of patient □ alive  □ dead |
| if dead Cause of death______________________________________________________________ |

<table>
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<tr>
<th>Follow-up date (dd/mm/yy)</th>
<th>OI (Opportunistic infection)</th>
<th>Weight in Kg</th>
<th>Functional Status (W,A,B)</th>
<th>WHO stage 1 - 4</th>
<th>ARV drugs</th>
<th>Adh (G,F,P)</th>
<th>Side effect</th>
<th>Reason for change</th>
<th>CD4 /µl</th>
<th>Hgb</th>
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<td>ARV drugs</td>
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</table>

**Key:**  
W = Working  A = Ambulatory  B = Bed ridden  
G = Good  F = Fair  P = Poor
Annexure D: Federal Ministry of Health, Ethiopia HIV care/ART follow-up form

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<tr>
<th>HIV CARE/ART FOLLOW-UP FORM</th>
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<th>Date of Diagnosis</th>
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<th>Age</th>
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<th>CD4 Count</th>
<th>Viral Load</th>
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<tr>
<td>Viral Load</td>
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<table>
<thead>
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<th>CD4 Count</th>
<th>Viral Load</th>
<th>Action</th>
</tr>
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<tbody>
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<td>TDF/FTC/3TC</td>
<td>500</td>
<td>100</td>
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<th>Viral Load</th>
<th>ART Regimen</th>
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<tr>
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<td>100</td>
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<td>100</td>
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<th>CD4 Count</th>
<th>Viral Load</th>
<th>Action</th>
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<tbody>
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Date: 14 February, 2011

Subject: Request for waiver of consent to conduct research at Gondar University Hospital

Dear Sir/Madam,

My name is Dr. Deme Ergeto. I am a Health Informatics MPH student at University of South Africa (UNISA). After working with International Training and Education Centre for Health (I-TECH) supporting Gondar University Hospital internal medicine department and HIV clinic in Gondar for more than two years as a clinical team lead and clinical physician mentor, I have become quite interested in the predictors of mortality for people living with HIV (PLWHIV) who are on antiretroviral treatment (ART). I have found that a great deal of PLWHIV who are on ART still continue to die despite all advances in tackling the problem by governmental and non-governmental bodies and have also found there to be a paucity of quantitative research looking at reasons and predictors of mortality.

I am required to conduct my MPH dissertation anywhere in the country as part of my program requirement and would like to have the opportunity to conduct a quantitative study based at Gondar University Hospital where I know the HIV clinic health burden in depth and breadth. I am also grateful to extend my contribution by sharing the result of the study with all stakeholders to benefit the clinic.

I am providing you with my research proposal and believe this research to be minimal risk, because it involves only chart review of dead and alive people living with HIV paper charts. There will neither be patient interview nor sample collection.

Therefore I hereby kindly request waiver of consent form to be able to conduct my chart review at Gondar University Hospital at earliest possible time.

Sincerely,

Deme Ergeto, MD, MPHc
Annexure F: Approval from Gondar University Hospital

To Whom It May Concern

I am writing this letter on behalf of Gondar University Hospital in the capacity of Medical Director. I have known Dr. Deme Ergelo while he was working with I-TECH as a clinical team lead and physician clinical mentor supporting the internal medicine department and ART clinic. I believe his proposed research study which is intended to be conducted in Gondar University Hospital, ‘PREDICTORS OF MORTALITY AMONG HUMAN IMMUNODEFICIENCY VIRUS INFECTED PATIENTS’ RECORDS IN GONDAR UNIVERSITY HOSPITAL-ETHIOPIA: a quantitative study’ will help to strengthen the evidence-based clinical care delivery practice. Therefore I enthusiastically support this research.

Dr. Deme’s study has the potential to provide useful information for supporting people living with HIV/AIDS and for helping to improve ART care delivery in this hospital. I am writing this letter in support of his conducting this research at Gondar University Hospital. Provided that the appropriate ethical committees at the University of South Africa and in Gondar University Institutional review board approve the proposal, I have no objection to the research and will facilitate it by assuring that Dr. Deme has the necessary access to data and information.

Respectfully,

Kassahun D Bikela, MD;
Clinical Director,
Gondar University Hospital.
Date of meeting: 2 December 2010                Project No: 4323-288-4

Project Title: Predictors of mortality among human immunodeficiency virus infected patient’s records in Gondar University Hospital - Ethiopia

Researcher: Deme Ergete Gurmu

Supervisor/Promoter: Dr BL Dolamo

Joint Supervisor/Joint Promoter: N/A

Department: Health Studies

Degree: Masters in Public Health

DECISION OF COMMITTEE

Approved √    Conditionally Approved

Prof TR Mavundla
RESEARCH COORDINATOR

Prof MC Bezuidenhout
ACADEMIC CHAIRPERSON: DEPARTMENT OF HEALTH STUDIES

PLEASE QUOTE THE PROJECT NUMBER IN ALL ENQUIRES
Annexure H: Ethical clearance from Gondar University

To: Dr. Demi Ergete
College of Medicine and Health Science
University of Gondar

Subject: Ethical Clearance

Your research project proposal titled "Predictors of mortality among human immunodeficiency virus infected patients' records in Gondar University Hospital, Ethiopia" has been reviewed and it is found to be ethically acceptable. Thus, the Institutional Ethical Review Board of the University of Gondar has awarded this ethical clearance for the aforementioned study to be carried out only for one year by Dr. Demi Ergete as a principal investigator as of February 16, 2011.

The investigator is highly expected to present every quarter their research progress report to the Research and Community Service Core Process Office of the University of Gondar.

Co-
College of Medicine and Health Science
University of Gondar

With regards,

[Signature]

Dr. Shiferaw Alemu
Institutional Ethical Review Board Chairperson

P.O. Box 156
Gondar, Ethiopia

Telephone PBX 088 114 1305
Fax - 088 114 1303

In Replying please quote our Ref. No.