COST EFFECTIVENESS AND SURVIVAL ANALYSIS OF HIV AND AIDS TREATMENT IN KENYA

Elizabeth Anyango Owiti

A thesis submitted in partial fulfillment for the Degree of Doctor of Philosophy in Economics in the University of Nairobi

2013

DECLARATION

DECLARATION

This thesis is my original work and has not been presented for a degree in any other university.

.....
Elizabeth Anyango Owiti

19th July 2013.
Date

This thesis has been submitted for examination with our approval as university supervisors

.....
Professor Germano M. Mwabu

19/7/2013
Date

.....
Dr. Mercy Mugo

19th JULY 2013
Date

ii

ABSTRACT

HIV and AIDS is a major cause of premature death and imposes a large disease burden in Kenya. An estimated 1.5 million people are infected with human immune-deficiency virus (HIV), while 1.5 million have died since the HIV virus was first detected in Kenya in 1984. Economic studies on the cost and health effects of ART/HAART are very scarce in developing countries, Kenya included. There is also limited understanding of the life time cost and benefits associated with HIV and AIDS treatment, and about survival rate conditional on treatment. Also equally poorly understood are impacts of socioeconomic factors on survival of HIV positive patients and on treatment follow-up.

The aim of this thesis is to enhance understanding of the interaction between patient treatment outcomes and economic dynamics given the existing HIV and AIDS trends in Kenya. To achieve its aim, the study collected data from two hospitals in Kenya – Mbagathi Hospital in Nairobi and Moi National Referral Hospital in Eldoret. A micro-costing method was used to cost all the treatment inputs, including laboratory services, human resources for health, prescriptive dugs and ARVs. Using Markov modelling methods the study carried out cost-effectiveness analysis involving a static and dynamic comparison of HIV and AIDS treatments in the two hospitals and estimated the lifetime costs and benefits of ARTs and Non-ARTs. The thesis also employed survival analysis to estimate the survival rate of the patients on treatment follow up from the two different treatment sites controlling for potential confounders.

The study found that ART treatment is the most cost effective treatment method. It also shows that those patients using ARVs and are on treatment follow up in AMPATH (Moi Hospital) treatment site survived for a significantly longer duration of time compared to the patients who were on follow up in Mbagathi Hospital. In addition, the study found that the patients who were on ARVs and were employed at the time of treatment debut had a lower risk of dying compared to the patients who were on ARVs and were unemployed at the time of enrolment for treatment. The study confirmed that ARVs is beneficial and increasingly beneficial the lower the CD4 count values. The study found that condom use not only prevents new HIV infection, but also reduces the mortality risk for the patients on treatment follow up. Finally, in terms of gender, the study found that men who were on treatment follow up had a higher risk of dying than the women.

The study findings support the policy of universal access to treatment for AIDS patients that the government is currently implementing. However, for this policy to achieve the desired results the government not only needs to increase employment but also to ensure that

employees are not retrenched based on their HIV positive status. The study concludes that ART treatment is a highly cost-effective intervention.

ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisors Prof. Germano Mwabu and Dr. Mercy Mugo. I particularly would like to thank Prof. Mwabu for his mentorship, friendship and scholarly advice. Thank you so much for your patience, guidance and encouragement throughout this study period.

I am also extremely grateful to the African Economic Research Consortium (AERC) for the various training grants and scholarships that enabled me to participate in numerous technical workshops and successfully complete both the course work and the thesis. I am indebted to the former AERC Executive Director Prof. William Lyakurwa for his mentorship and guidance.

It was a privilege to access the AMPATH and Mbagathi District Hospital (MDH) data without which this study could not have been possible. I am grateful to the entire AMPATH team including Dr Sylvester Kimaiyo, Dr William M. Tierney, Dr Samson Ndege, Dr. John Sidle, Daniel Murgor, Jepchirchir Kiplagat, Gilbert Simiyu, Asha Owuor, Agnes Sigilai, the Accounts department and the team of research assistants. My appreciation also goes to the staff of Mbagathi Hospital, particularly Dr Andrew J. Sule, Dr. Josephine Mwagiru, Juliana Kimwele, Consolata Ndege, the HIV clinic records staff and the team of research assistants.

Numerous friends and colleagues encouraged and supported me in various ways during the many years of my studies and thesis writing, I can't forget to thank Prof Damiano Manda, Maurice Awiti, Japheth Awiti, Dr. Martin Oleche, Jaqueline Odula, Roberta Muli, Lydiah Auma, Franscisca Omunga, Judith Odhiambo and Yvonne Arogo. I also thank the entire AERC family.

To the CPP class of 2006, especially the graduate students who were studying at the University of Dar-es-Salaam, thank you for the class discussions, encouragements and support. To the graduate students who were studying at Cape Town University (UCT), thank you for your support and visits to the UCT Environmentally Protected Cancer Treatment Centre and Lyle Suits. To the staff of University of Dar-es-Salaam, Department of Economics and School of Economics University of Nairobi, I say thank you.

To my family, I wish to thank my parents Julius Owiti and Linet Owiti for the virtues that they inculcated in me, Mama and Baba you taught me to work hard, to be steadfast, to be honest and above all to worship God. Thank you. To all my siblings, thank you for your support and encouragement throughout the many tiresome and gruelling years of studying. To my husband Dr. John Wasonga, thank you for your support and encouragement.

Lastly but not least, to my only child, the love of my life the late Ivy Josephine Wasonga, I thank you Mamana for being the central part of my journey to this level. I joined the University of Nairobi when you were only two months old. Mamana, today mummy has finished her studies, you could have been 19 years old and yet you are no more. As you always said, God has provided and our dreams have come true. I only wish you were here to see this. Thank you my love, I really miss you today. Finally, I glorify and thank God for granting me the unique opportunity and privilege to reach this far.

DEDICATION

To my love, my only child, my study partner, my comforter, my source of inspiration, well my everything! For the loneliness you endured as Mummy was studying as you used to say at the 'Umivesity'. For all the love and support you gave Mummy during your time here,

The Late Ivy Josephine Wasonga

"My heart and my flesh may fail, but God is the strength of my heart and my portion forever" *Psalm 73:26*

"Lord you are all that I have; and you give me all I *need. My future is in your hands*" *Psalm 16:5*

TABLE OF CONTENTS

DECLARATION ..... **II**

ABSTRACT ..... **II**

ACKNOWLEDGEMENTS ..... **V**

DEDICATION ..... **VII**

TABLE OF CONTENTS ..... **VIII**

LIST OF FIGURES ..... **XIII**

ABBREVIATIONS AND ACRONYMS ..... **XVI**

CHAPTER ONE: INTRODUCTION **1**

1.1 Global situation and Commitments **1**

1.2 Global Response to HIV and AIDS **3**

1.3 The HIV and AIDS Consequences **4**

1.3.1 Trends and Prevalence 4

1.3.2 Government Response and Policy Issues 6

1.4 Socio-economic impact of HIV and AIDS **9**

1.4.1 Demographic trends and population changes 10

1.4.2 Household Impacts and Implications 10

1.4.3 Economic growth and per-capita income 11

1.4.4 HIV/AIDS and poverty 12

1.5 Economics of HIV and AIDS in Kenya **12**

1.5.1 The medical costs of HIV and AIDS 13

1.5.2 The short-run cost of HIV and AIDS illness – morbidity and mortality 14

1.5.3 The long-run cost of HIV and AIDS 15

CHAPTER TWO: THE ANTIRETROVIRAL THERAPY (ART) **18**

2.1 Study settings **24**

2.1.1 The Academic Model for the Prevention and Treatment of HIV/AIDS (AMPATH) 24

2.1.2 Mbagathi District Hospital 25

2.2 Statement of Research Problems **26**

2.3 The objectives: **27**

2.4 Study Justification **27**

CHAPTER THREE: THEORETICAL LITERATURE REVIEW **30**

3.1 Introduction **30**

3.2 Techniques of economic evaluation **31**
3.2.1 Cost-effectiveness analysis 31
3.2.2 Cost benefit analysis 33
3.2.3 Cost-utility analysis 34

3.3 Theoretical Foundations for Cost Effectiveness Analysis **35**
3.3.1 Welfare Economics as a theoretical foundation for CEA 35
3.3.2 The Cost-Effectiveness Ratio 36
3.3.3 Cost-Effectiveness Analysis and Cost-Benefit Analysis 37
3.3.4 Future costs in cost effectiveness analysis 38

3.4 Economic evaluation using decision analytic modelling **38**
3.4.1 The role of decision analytic models for economic evaluation 39
3.4.2 The decision tree 40
3.4.3 The Markov decision analysis model 41

3.5 Adjustments to the Cost and Outcome Quantities **45**
3.5.1 Discounting 45
3.5.2 The Half-Cycle Corrections 46
3.5.3 Use of Markov model in medical decision-making 46

CHAPTER FOUR: EMPIRICAL LITERATURE REVIEW **47**

CHAPTER FIVE: METHODOLOGY **55**

5.1 Study design **55**

5.2 Costing Analysis **55**
5.2.1 Capital Costs 56

5.3 Cost-effectiveness analysis **56**

5.4 Cost benefit analysis **57**

5.5 Cost-utility analysis **57**

5.6 Markov Model Conceptual Framework **58**

5.7 Data 60

5.8 Site and patient selection criteria 61

5.9 Perspective of the study 62

5.10 Ethical Approval 62

CHAPTER SIX: MARKOV MODELLING RESULTS 63

6.1 Costs 63
6.1.1 Laboratory tests and imaging Services utilization and costs 63
6.1.2 Outpatient service utilization and costs 66
6.1.3 Cost per inpatient day 67

6.2 Distributions of resource costs and effects 70

6.3 The Cost effectiveness analysis results 71
6.3.1 The cost effectiveness results 71
6.3.2 Sensitivity 74
6.3.3 The Monte Carlo probabilistic sensitivity analysis results 74
6.3.4 The Cost effectiveness Acceptability Curves 75

CHAPTER SEVEN: SURVIVAL ANALYSIS 77

7.1 Introduction 77
7.1.1 Nonparametric models 78
7.1.2 Semi-parametric models 78
7.1.3 Parametric models 79

7.2 Survival analysis theoretical literature 79
7.2.1 Hazard Functions 80
7.2.2 Hazard Functions Conditional on Covariates 81
7.2.3 Survivor Function 81
7.2.4 Proportional Hazard Models 82

7.3 Cox Regression Model 83
7.3.1 Introduction 83
7.3.2 Cox PH model Hazard Ratio 84
7.3.3 Cox Regression Model with time dependent variables 85
7.3.4 Stratified Cox PH Model 86
7.3.5 Adjusted Survival Curves using the Cox PH Model 86
7.3.6 Fitting the Proportional Hazard Regression Model 87
7.3.7 Fitting the PH model with tied survival 88
7.3.8 Cox Proportional Hazard Model Diagnostics 88

7.4 Parametric model 93
7.4.1 The Proportional Hazard Models 94
7.4.2 Accelerated failure time model 94
7.4.3 Parametric proportional hazards model 95

7.5 Exponential Distribution 95

7.6 Weibull PH Distribution 96

7.7 The Log-Logistic Hazard Function 97

7.8 The Log-logistic Distribution 97

CHAPTER EIGHT: APPLICATION OF SURVIVAL ANALYSIS TO HIV DATA 98

8.1 The Data 98

8.2 Variable selection Method: purposeful covariate selection 98

8.3 Cox PH Model Diagnostics Results 101
8.3.1 Testing the scale of the continuous covariates: 101
8.3.2 Testing for Influencial Variables 106
8.3.3 Assessing the Proportional Hazard Assumption 107
8.3.4 Assessing the Goodness of Fit 112
8.3.5 The Predictive power of the Cox Model 113

CHAPTER NINE: SURVIVAL ANALYSIS RESULTS 115

9.1 Univariate Analysis Results 115
9.1.1 Univariate Analysis: Kaplan-Meier Survival Curves 116
9.1.2 Univariate Analysis Results: Nelson –Aalen Cumulative Hazard Curves 119

9.2 Multivariate Analysis Results: Stratified Cox PH Regression Model 121
9.2.1 Interpretation of the Cox regression results 122

9.3 Multivariate Analysis Results: Stratified Weibull Regression Model 126
9.3.1 Interpretation of the Weibull PH regression results 127

9.4 Discussion 128
9.4.1 CEA study discussion 128
9.4.2 Survival Analysis discussion 130

9.5 Study Limitations 131
9.5.1 CEA Study Limitations 131
9.5.2 Survival analysis Study Limitations 131

CHAPTER TEN: CONCLUSION 132

REFERENCES 135

APPENDICES 146

APPENDIX 1: MARKOV MODELS FOR NO ART AND ART USE 146

APPENDIX 2: THE MARKOV DECISION TREE 147

APPENDIX 3: LIST OF DOCUMENTS REVIEWED 148

APPENDIX 4: ADULT INITIAL VISIT QUESTIONNAIRE 162

APPENDIX 5: RETURN VISIT QUESTIONNAIRE 167

APPENDIX 6: LABORATORY COSTING FORM 172

APPENDIX 7: ETHICAL APPROVAL 174

LIST OF FIGURES

Figure 1: Health States and Transition Probabilities 59

Figure 2: The Isocontours 73

Figure 3 AMPATH acceptability curve 76

Figure 4: Residual-based Methods for Selecting the Scale of the Continuous Variables 104

Figure 5: Deviance Residuals and a running mean Smoother for Continuous Variables 105

Figure 6: Deviance Residuals and a running mean Smoother for Adjusted Number of Dependants.....105

Figure 7 Graph of score residuals for Continuous Variables.....106

Figure 8 Scatterplot of scaled Schoenfield residuals for the discrete variables.....111

Figure 9 Scatterplot of scaled Schoenfield residuals for the continuous variables ...112

Figure 10 Cumulative hazard for Cox-Snell residual for the Models.....113

Figure 11: Survival duration: Kaplan-Meier estimate of Survival function 117

Figure 12: Nelson –Aalen Cumulative Hazard Curves for overall data 120

LIST OF TABLES

Table 1 The 10 leading causes of death in East SSA in 1990 and 2010 2

Table 2: Estimated national prevalence among 15-49 year olds 4

Table 3: Leading causes of Deaths and Disabilities in Kenya 5

Table 4: Estimated prevalence per province among 15-49 year olds 5

Table 5: Estimated Prevalence among 15-24 year olds 6

Table 6: Estimated number of orphans by type 11

Table 7: Key Registered Health personnel in Kenya 13

Table 8: CD4 count distribution among adults with HIV not on ART 19

Table 9: Multi-state transition Matrix 58

Table 10: Multi-state transition Matrix 59

Table 11: Exchange Rates 63

Table 12: The Laboratory Costs/Test 64

Table 13: Laboratory test and imaging procedures per Markov Cycle 64

Table 14: Laboratory and Imaging Costs and Utilization per Markov Cycle 65

Table 15: The ARV prices 66

Table 16: The average cost of ART per Markov cycle (KSh) 66

Table 17: Average number of visits per Markov Cycle 67

Table 18: The outpatient costs for MDH and AMPATH 67

Table 19: HRH cost per inpatient day 68

Table 20: Average number of admissions per cycle 69

Table 21: Patient specific cost per inpatient day 69

Table 22: Transition costs and on-going hospitalisation costs in Markov states 70

Table 23: Cost of food support per person per cycle 70

Table 24: Means and standard errors of input costs per quarter and their associated distribution parameters 71

Table 25: AMPATH cost effectiveness analysis results 72

Table 26: Mbagathi District Hospital cost effectiveness analysis results 73

Table 27: Table AMPATH Sensitivity Analysis 74

Table 28: Table Mbagathi District Hospital Sensitivity Analysis 74

Table 29: Second Monte Carlo simulation results for AMPATH (r=10%) 75

Table 30: Second Monte Carlo Simulation Results for MDH (r=10%) 75

Table 31: Significant interaction terms 99

Table 32: Description of Variables: 100

Table 33: Fractional polynomial model comparisons for Age (n =701) 101

Table 34: Fractional polynomial model comparisons for CD4 count values (n =701) 102

Table 35: Fractional polynomial model comparisons for dependants (n =701) 102

Table 36: The Stratified Cox PH Model 108

Table 37: The Stratified Cox Time Interaction Model 109

Table 38: Test of proportional hazards assumption 110

Table 39 Harrell's C concordance statistic 113

Table 40: Demographic and clinical information of HIV patients (n=701) 116

Table 41: Survival Duration: Kaplan-Meier Survival and Nelson-Aalen Cummulative Hazard Function 118

Table 42: Stratified Cox Analysis Results; n = 701 121

Table 43: Stratified Cox Analysis Showing Hazard Ratios; n = 701 122

Table 44: Estimated HR and 95% CI; $\boldsymbol{ever\_arv = 1}$ and $\boldsymbol{employ\_state = 1}$ ... 123

Table 45: Estimated HR and 95% CI; when $\boldsymbol{ever\_arv = 1}$ and $\boldsymbol{employ\_state = 0}$ 124

Table 46: Estimated HR and 95% CI; when $\boldsymbol{ever\_arv = 0}$ and $\boldsymbol{employ\_state = 1}$ 124

Table 47: Weibull regression log relative hazard Regression Model 127

ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
APS	AIDS Programme Secretariat
AMPATH	Academic Model for the Prevention and Treatment of HIV/AIDS
ART	Anti-Retroviral Therapy
ARV	Anti-Retroviral Drugs
BCC	Behaviour Change Communication
CCC	Comprehensive Care Centre
CSW	Commercial Sex workers
FBO	Faith-Based Organisation
FPI	Family Preservation Initiative
GFATM	The Global Fund to fight AIDS, Tuberculosis and Malaria
GoK	Government of Kenya
HCW	Health Care Worker
HIV	Human Immuno-deficiency Virus
IDU	Intravenous drug users
IEC	Information, Education, and Communication
KAIS	Kenya AIDS Indicator Survey
KDHS	Kenya Demographic and Health Survey
KEMSA	Kenya Medical Supplies Agency
KNASP	Kenya National AIDS Strategic Plan
MAP	Multi-country AIDS Project
MDG	Millennium Development Goal
MDH	Mbagathi District Hospital
MoH	Ministry of Health
MSF	Médecins Sans Frontières
MSM	Men having Sex with Men
MTRH	Moi Teaching and Referral Hospital
MUSM	Moi University School of Medicine
NACC	National AIDS Control Council
NASCOP	National AIDS & STI Control Programme
NGO	Non-Governmental Organisation
OIs	Opportunistic Infections

OVC	Orphans and Vulnerable Children
PEP	Post-Exposure Prophylaxis
PEPFAR	President's Emergency Plan for AIDS Relief
PLHIV	People Living with HIV
PMTCT	Prevention of Mother to Child Transmission
PwP	Prevention with Positives
STIs	Sexually Transmitted Infections
TAC	Treatment Action Group
TB	Tuberculosis
ToT	Training of Trainers
TOWA	Total War against HIV and AIDS
UNAIDS	Joint United Nations Programme on AIDS
UNGASS	United Nations General Assembly Special Session on HIV and AIDS
VCT	Voluntary Counselling and Testing
VMMC	Voluntary Medically-Assisted, Adult Male Circumcision
WHO	World Health Organization

1 CHAPTER ONE: INTRODUCTION

1.1 Global situation and Commitments

Human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) has posed the greatest global public health challenges over the last quarter century (Strauss and Thomas, 2008). Although global commitment to control the HIV and AIDS pandemic has increased significantly in recent years, some evidence suggest that the virus continues to spread and much remains to be done to reverse these trends (Bertozzi, et al., 2006). By the end of 2010, an estimated 34 million people worldwide were living with HIV infection or disease. In 2010, close to 2.7 million new HIV infections including 390,000 among children and 1.8 million AIDS deaths occurred (UNAIDS, 2010). The lack of an imminent vaccine or cure means that many more deaths are inevitable (WHO, 2001).

Sub-Saharan Africa (SSA) remains the region most affected by HIV and AIDS; however, the virus is now spreading rapidly in other parts of the developing world (e.g., Asia and The Caribbean) and in the newly emerging economies (e.g., Russia and Eastern Europe but also in the Middle East) (Bertozzi, et al., 2006). With only 12% of the world's population, Sub-Saharan Africa (SSA) accounted for 68% of all HIV infections worldwide and 76% of all AIDS-related deaths in 2010 (UNAIDS, 2010). In addition SSA also accounted for 70% of new HIV infections in 2010. This makes AIDS the leading cause of loss of lives, productivity and hardship in SSA (Kumaranayake & Watts, 2001; Mathers et al., 2006) Table 1 shows that HIV mean rank moved from the fifth major cause of mortality in 1990 to the first major cause major cause of disability and mortality. However, a total of 2.5 million deaths have been averted in low- and middle-income countries since 1995 due to introduction of antiretroviral therapy (UNAIDS, 2011).

Despite this global image, the scale of HIV and AIDS related problems and trends varies considerably within different parts of SSA. This is mainly due to the diversity in cultural practices and actions taken by governments and health related agencies in the past. For example, countries like Uganda that reacted soon enough with information campaigns are experiencing single digit HIV-prevalence. However, in

South Africa where information campaigns started as late as 2005, the HIV-prevalence is close to 32% while an estimated 1.8 million South Africans have already died of AIDS-related diseases since the epidemic begun (UNAIDS and WHO, 2008).

Countries in East Africa (e.g., Kenya, Uganda and Tanzania) have been experiencing a decline in HIV incidence rates and a steadiness in terms of HIV-prevalence. For example, Kenya's HIV-prevalence declined to between 6-8% from approximately 15% in the 1990s. Latest reports from Ethiopia and Tanzania indicates HIV-prevalence rates of 1.4% and 6.5%, respectively. However, despite Uganda and Kenya being among the countries that first experienced a decline in HIV-prevalence, recent estimates shows a re-emergence of the epidemic (UNAIDS and WHO, 2008 and NASCOP and MoH, 2008). This can partly be explained by people's belief about the impact of highly active antiretroviral therapy (HAART) in HIV and AIDS treatment (Crepaz et al., 2004).

Table 1 The 10 leading causes of death in East SSA in 1990 and 2010

1990 Mean Rank	2010 Mean Rank
1. Lower Respiratory	1. HIV and AIDS
2. Diarrhoeal diseases	2. Lower Respiratory
3. Material	3. Malaria
4. Malnutrition	4. Diarrhoeal diseases
5. HIV and AIDS	5. Stroke
6. TB	6. TB
7. Measles	7. Malnutrition
8. Stroke	8. Birth complications
9. Meningitis	9. Road Injury
10. Birth complications	10. Ischemic heart

Source: Institute for Health Metrics and Evaluation

Compared to other parts of SSA, Eastern Africa has done well at effectively controlling the spread of the HIV virus. Nevertheless, there is need to compare the HIV and AIDS problem in Eastern Africa to that in the developed countries in order to understand that it remains a 'high HIV-prevalence zone'. In the developed economies - e.g., Western Europe - the HIV-prevalence rates is below 0.1% and almost always confined to very specific social groups (e.g., intravenous drug users,

(IDU), and man-that-have-sex-with-man, MSM). Clearly, it is not just a difference with regards to the prevalence rates but the nature of how the virus spreads that determines the prevalence rates. Studies have shown that high concurrent heterosexual partnerships in SSA countries explains the significant difference in the HIV and AIDS infection rates between SSA countries and Western Europe (Morris and Kretzschmar, 2000). In Kenya, adults in polygamous marriages are more likely to be HIV positive than those in monogamous marriages (NASCOP and MoH, 2008).

In Eastern Africa, HIV and AIDS is yet to be effectively controlled. This is explained by the steady HIV prevalence which significantly affects all socio-economic groups and not just women working in the sex industry, intravenous drug users (IDU) or man who have sex with man (MSM). This implies that adults (15-64 years old), as well as children, are at risk of this infection. HIV prevalence of adults ages 15-64 is 7.4% (NASCOP and MoH, 2008). In fact, it is exactly such spread or risk among all groups in society that makes a difference between the rate of transfer and thus the HIV prevalence rates in Eastern Africa and the developed world.

There is a need to understand precisely what the effect of different treatments - including information campaigns treatments is - among society and how such treatments may help Kenya find effective ways of reducing HIV-prevalence in the country. Secondly, we need to understand the survival rates of HIV positive patients on treatment follow up. Finally, it is important to use cost effective treatments thus, there is need to understand the effect of the different treatments, the cost and ultimately the economic benefit to society of controlling the epidemic.

1.2 Global Response to HIV and AIDS

There have been global commitments to the fight against HIV and AIDS. This has been through the formation of Joint United Nations Programme on HIV/AIDS (UNAIDS), United Nations General Assembly Special Session on AIDS (UNGASS), the Abuja Declaration, and the Millennium Development Goals. These commitments have led to increased resources and international support, including the World Bank Multi-country AIDS Project (MAP), the Global Fund for AIDS, Tuberculosis and Malaria (GFATM), the US President's Emergency Plan for AIDS Relief (PEPFAR), and other substantial bilateral, multilateral and charitable efforts. The World Health

organization (WHO) 3 by 5 Initiative—to place 3 million people on antiretroviral therapy (ART) by the end of 2005—played a significant role in bringing Africa and other developing countries around the world into the treatment era for HIV and AIDS.

1.3 The HIV and AIDS Consequences

1.3.1 Trends and Prevalence

Kenya still bears the burden of a relatively high HIV prevalence, approximately 1.5 million people are infected with HIV, while 1.5 million have died since the HIV virus was first detected in Kenya in 1984 (NASCOP, 2007). However, the national HIV prevalence rate among adults has been declining and was 6.0% in 2009 (KDHS, 2010). This reduction has been attributed to greater awareness and the resulting behaviour change, a lower incidence of new infections, better medical practices and higher death rates (NACC, 2008). In spite of the decline, current trends are showing an increase in prevalence as shown in Table 2.

Table 2: Estimated national prevalence among 15-49 year olds

	Prevalence (%)									
Year	1998	2000	2001	2002	2003	2004	2005	2006	2007	2009
Male					4.6	4.3			5.8	4
Female					8.7	8.3			9.2	8
Total	**25**	**13.5**	**15**	**8.3**	**6.7**	**6.4**	**6.6**	**6.1**	**7.8**	**6.0**

Source: Kenya HIV/AIDS Data Booklet, NACC 2005; AIDS in Kenya, 7th ed. Nairobi: NASCOP; 2005; NASCOP & MoH, 2008; CBS, MoH and ORC Macro. (2004);CBS, MoH and ORC Macro. (2008-9).

HIV remains the greatest cause of morbidity and mortality in Kenya accounting for 29% of mortality while unsafe sex is the greatest risk of mortality (WHO, 2010). Table 3 shows ten leading causes of disabilities and mortality in Kenya.

Table 3: Leading causes of Deaths and Disabilities in Kenya

Rank	Cause of Death	Percentage of total deaths
1.	HIV & AIDS	29.3
2.	Prenatal conditions	9.0
3.	Lower Respiratory Infections	8.1
4.	Tuberculosis	6.3
5.	Diarrhoeal Diseases	6.0
6.	Malaria	5.8
7.	Cerebrovascular Disease	3.3
8.	Ischemic Heart Disease	2.8
9.	Road Traffic Accidents	1.9
10.	Violence	1.6

Source: WHO 2010 World Health Statistics

It is noteworthy that wide variations in HIV prevalence exist between different geographic regions and even within sub-populations e.g., there is a higher prevalence in the very poor sectors of society, Nyanza Province, the females, urbanized areas and among high risk groups in large cities such as intravenous drug users (IDU) (see Table 4 and Table 5). However, latest studies are now showing new trend where the HIV infection rate is increasing in stable marriages and discordant couples (couples with one spouse HIV positive and the other HIV negative) compared to other population segments (NASCOP and MoH, 2008). Moreover, the epidemiological nature of the virus suggest that women are more vulnerable to the infection than men (Markus, 2002) (as shown in Table 5), while children are not completely risk free unless medical practices are effective at reducing the risk of transmission at birth

Table 4: Estimated prevalence per province among 15-49 year olds

	Prevalence (%)				
Year	2000	2003	2004	2007	2009
Nyanza	22	15.1	13.1	15.3	13.9
Nairobi	16	9.9	9.0	9.0	7
Coast	10	5.8	5.7	7.9	4.2
Rift Valley	11	5.3	5.0	7.0	4.6
Western	12	4.9	4.5	5.1	6.6
Central	13	4.9	5.6	3.8	4.6
Eastern	16	4.0	3.7	4.7	3.5
North Eastern	3	0.0	3.0	1.0	0.9

Source: Kenya HIV/AIDS Data Booklet, NACC 2005; AIDS in Kenya, 7th ed. Nairobi: NASCOP; 2005; NASCOP & MoH, 2008; CBS, MoH and ORC Macro. (2004); CBS, MoH and ORC Macro. (2010).

Table 5: Estimated Prevalence among 15-24 year olds

	Prevalence (%)					
Year	2003	2004	2005	2006	2007	2009
Male	1.2	0.9	0.8	0.8	1.5	1.4
Female	5.8	4.9	4.5	4.4	6.1	5.6
Total	**3.5**	**2.9**	**2.6**	**2.6**	**3.8**	**3.8**

Source: Kenya HIV/AIDS Data Booklet, NACC 2005; CBS, MoH and ORC Macro. (2010); NASCOP, 2009.

1.3.2 Government Response and Policy Issues

Recognizing the seriousness of AIDS, the government of Kenya came up with various policy initiatives to stem the scourge (Nyaga et. al., 2004). In 1985, the government established AIDS Programme Secretariat (APS), this later became the Kenya National AIDS Control Programme (NASCOP) in 1987. In the same year, the government developed the first 5-year strategic plan for AIDS control (National Medium Term Plan 1987-1991) which emphasized the need for AIDS awareness creation, blood safety, capacity building and clinical management of AIDS, (NASCOP, 2005). The second medium term plan (1992-1996), highlighted the need to mobilize a nationwide response involving all sectors in the fight against AIDS. In 1994, the government developed the Health Policy Framework highlighting the need to fight against HIV and AIDS (GoK, 1994).

The *Sessional Paper No.4 of 1997 on AIDS in Kenya* (GoK, 1997) marked an important change on the political front and outlined a new institutional framework. This paper recognized the main response measures by the government as the establishment of the National AIDS committee and the development of strategic plans to deal with the pandemic. The government went further to recognize AIDS as a development issue (Nyaga, et al. 2004) and hence, incorporated HIV and AIDS into the Fifth District Development Plans, Seventh National Development plan, and other succeeding policy documents. However, it was in 1999 that the government of Kenya declared HIV and AIDS a national disaster. This allowed more government spending and involvement in the fight against HIV and AIDS and at the same time created an opportunity for greater AIDS related donor funding (Nyaga, et al. 2004).

In emphasising the need to increase prevention of HIV infection, the government published two main policies in 2001. *The National Condom Policy and Strategy* and the *National Guidelines for Voluntary Counselling and Testing*. The goals of these guidelines were to improve access to affordable quality condoms and to standardize the delivery of VCT services and to assure its high quality and confidentiality (GoK, 2001a & GoK 2001b). To address the gender aspects of the HIV and AIDS epidemic, the government published a *Strategic Plan on Mainstreaming Gender into the Kenya National HIV and AIDS Strategic Plan, 2000-2005*. This strategic plan took into account most concerns that were gender specific in the exposure to HIV and AIDS and response mechanisms. This approach was to empower women and remove gender inequality at all levels of anti-AIDS programmes (NACC, 2002).

Recognizing that hospital-based care was too expensive and not sustainable for people with AIDS, the government came up with the *National Home-Based Care Policy Guidelines* in 2002. These guidelines ensures that those in the final stages of HIV are given quality and adequate medical, psychological, physical, spiritual support and care in their homes. The home-based care reduces the health care cost to the family members and at the same time reduces the demand on the health care facilities, (GoK, 2002).

The government developed the *National Programme Guidelines on Orphans and Other Children Made Vulnerable (OVC) by HIV/AIDS* in 2003 to address the plight of these children. This guideline provides programmers with information and direction for formulating and implementing effective interventions for OVCS (GoK, 2003).

To ensure that the progress made in the fight against HIV and AIDS is tracked, the government came up with the *National HIV/AIDS Monitoring and Evaluation Framework* in 2005. This framework was to guide collection, analysis, use and dissemination of information that enabled tracking of progress made in response to HIV and AIDS and enhanced informed decision-making (GoK, 2005).

Kenya has continuously played a key role in the research and development of HIV and AIDS vaccines. To facilitate this, Kenya AIDS Vaccine Initiative (KAVI) was established in 1999. In enacting an important part of HIV research, the government in 2005 developed guidelines to facilitate and support research in this field. The *Kenya*

National Guidelines for Research and Development of HIV/AIDS Vaccines spell out a number of policy issues affecting vaccine research: the roles of government, regional and sub-regional intergovernmental organizations, the African AIDS Vaccine Programme, WHO, UNAIDS, vaccine manufacturers, funding organizations, investigators, and collaborating institutions (GoK, 2005).

Kenya developed and implemented the first multisectoral strategic plan, *Kenya National HIV and AIDS Strategic Plan (KNASP 2000-2005)*. The emphasis for this multisectoral response to HIV and AIDS were; prevention and advocacy; treatment, continuum of care and support; mitigation of the socio-economic impact; monitoring, evaluation, and research and management and coordination. The KNASP 2000-2005 also emphasized greater involvement of the civil and private sector organizations. The second Strategic Plan (KNASP 2005/6 to 2009/10) was also developed to guide Kenya's national response to HIV and AIDS. Its goal is to reduce the spread of HIV, improve the quality of life of those infected and affected, and mitigate the socio-economic impact of the epidemic.

The share of the Kenyan population under 15 years of age is 45% and that of the youth between the ages of 15 and 29 years is 26% (KDHS, 2010). Statistics shows the youth to have early sexual debut with 70% of women and 80% of men engaging in sex by the age of 20, with a median age at first sexual intercourse of 17 years (KDHS, 2003; KDHS, 2010). The youth consequently face many risks that come with early sex debut. At the same time, 10% of adolescents aged 15-19 years reported experiencing sexual violence and one in five is coerced or forced into their first sexual encounter (CBS and ORC Macro, 2004). The KDHS 2003 report also shows that more than 75% of AIDS cases occur between the ages of 20-45, and approximately 33% of all AIDS cases reported are among the ages of 15-30, CBS and ORC Macro (2004). Muga et al (2004) indicated that over half of all new HIV infections occurred among young people aged 15-24. Given the high HIV infection risks among the youth, the government of Kenya developed the *"Kenya National HIV and AIDS Communication Strategy for Youth 2007".* This Communication Strategy provides a broad framework that guides communication on youth and HIV and AIDS in Kenya from 2007 to 2010. It addresses the needs and gaps in communication programming in the areas of knowledge, skills and self-efficacy, capacity, coordination, policy

support and utilization of services. Its broad objective is to improve knowledge and access to information for rural, urban and low literate youth on ways to prevent and mitigate HIV and AIDS and ensure delay in sexual debut.

In January 2007, the government published the HIV and AIDS Prevention and Control Act, 2006 (GoK, 2007). However, several years later, this act is yet to be passed in law. This act seeks to:

- Regulate HIV and AIDS education and information;
- Ensure safe clinical practices and procedures;
- Regulate testing, screening and access to healthcare services;
- Regulate confidentiality such as on privacy and disclosure of information and penalty on breach of confidentiality;
- Regulate prevention of transmission;
- Regulate equity tribunal;
- Stem discrimination in the workplace, schools and in the provision of healthcare services;
- Regulate HIV and AIDS research.

Studies have shown that male circumcision reduces the probability of female to male transmission of HIV and AIDS by approximately 60% (Auvert et al., 2005; Bailey et al., 2007 and Gray et al., 2007). In line with its policy of preventing HIV infection, the government of Kenya developed the *Policy on Male Circumcision in Kenya*, in January 2008. This policy document provides a broad framework for the integration of male circumcision into existing HIV prevention programmes. It also ensures safe, accessible, and sustainable male circumcision done on voluntary basis and provides appropriate information on the role of male circumcision in reducing the risk of HIV infection.

1.4 Socio-economic impact of HIV and AIDS

Kenya is a low-income country with a per capita gross domestic product (GDP) of USD 21,186 million in 2006, (World Bank, 2007). Approximately 80% of its 37.2 million people (CBS, 2006) live in rural areas and subsist almost entirely on agricultural production. HIV epidemic in Africa manifests itself both as an immediate crisis – in need of an urgent response - and a systemic condition – that requires

strategic planning. HIV is a crisis due to its high infection rates and is a systemic condition because it mainly targets prime-aged adults. Thus, HIV and AIDS deprive these economies of scarce human resource skills, children of their parents, and a continent of a generation in the prime of their working lives.

1.4.1 Demographic trends and population changes

New evidence shows that HIV prevalence in Kenya is rising. Although ART has reduced HIV related morbidity and mortality, only 54% of those people in need of ART have access to them. This epidemic has a negative effect on life expectancy, infant mortality, adult mortality and dependency ratios and is fast eroding the health benefits, which Kenya gained in the first two decades after independence (Were and Nafula, 2003). The national under-5 mortality rate was 97 per 1000 in 1990. This had risen to 121 per 1000 by 2006 (UNICEF 2007). HIV/AIDS affects the per capita income through increase in the dependency ratio.

According to World Bank, (2007), life expectancy at birth in SSA declined from 49.2 years to 47.1 between 1990 and 2005. HIV and AIDS, malaria and armed conflict have contributed to the decline in life expectancies. However, the life expectancy of Kenya decreased to 46 years in 2006 from 62 years in 1991 with some regions like Nyanza being much lower (Ministry of Health, 2007). This is expected to continue decreasing as AIDS has now reached the death stage and with low access to HAART. Moreover, many people are facing a day-to-day experience of declining standards of living, reduced capacities for personal and social achievement, and an increasingly uncertain future.

1.4.2 Household Impacts and Implications

It is at the level of the family and community that the fullest impacts of the HIV pandemic are unravelling. There is AIDS related poverty and rising number of orphans in Kenya. In June 2007 it was estimated that there were 2.4 million orphans in Kenya. Half were orphans caused by the AIDS pandemic (Table 6).

Table 6: Estimated number of orphans by type

Maternal orphans	**1,282,000**
AIDS	692,000
Non-AIDS	590,000
Paternal orphans	**1,591,000**
AIDS	750,000
Non-AIDS	841,000
Double orphans	**443,000**
AIDS	349,000
Non-AIDS	94,000
Total orphans	**2,430,000**
All AIDS orphans	**1,149,000**

Source: NACC & NASCOP, epidemic review report, Nairobi, Kenya, June 2007

AIDS selectively destroys human capital, that is, peoples' accumulated life experiences, their human and job skills, and their knowledge and insights built up over a period of years. It also weakens the mechanisms that generate human capital formation. Lastly, the chance that the children themselves might contract the disease in adulthood makes investment in their education less attractive, even when both parents themselves remain uninfected (Bell, Devarajan and Gersbach, 2003, 2006).

Social customs of adoption and fostering, however well established, may not be able to cope with the scale of the problem generated by a sharp increase in adult mortality, thereby shifting the onus onto the government. The government itself, however, is likely to experience increasing fiscal problems and so be unable to fully finance this additional task. While the costs of AIDS in terms of human suffering and lives lost are undeniably large, estimates of the associated macroeconomic costs have tended to be more modest. For example, studies that focus on Africa – the continent where the epidemic has hit the hardest – calculate the annual loss of GDP to be around 1%. These estimates all stem from a particular view of how the economy functions (Bell, Devarajan and Gersbach, 2003).

1.4.3 Economic growth and per-capita income

HIV and AIDS may affect economic growth and income per capita through various channels. Disruptions to the production process caused by sickness and death of employees have adverse impact on productivity, and the decline in the rate of growth of the labour force results in a fall in the rate of growth of GDP (Markus, 2002). HIV and AIDS also have direct effects on output, as well as future economic development.

(Were and Nafula, 2003). The impact of HIV and AIDS on economic growth can be seen though it's impact on determinants of growth such as impact on physical, human and social capital. The majority of Kenyans rely on the agricultural sector for their livelihood, from subsistence farmers through to cash crop foreign exchange earners. This sector has been affected by loss of labour, low productivity due to long illness and the prime-age male death.

1.4.4 HIV/AIDS and poverty

HIV and AIDS reduce growth by increasing depreciation of health capital and therefore reducing life expectancy (Grossman, 1972). This foreshortening of life expectancy undermines individual's incentives to accumulate education human capital. Thus, HIV and AIDS may cause poverty by reducing health and education human capital, the two key determinants of income. However, the positive relationship from poverty to HIV and AIDS is not causal, because a virus is the reason for the disease. The positive relationship from poverty to AIDS reflects the correlation between poverty and a cluster of behavioural patterns that put individuals at high risks of infection by HIV (Mwabu, 2008). The dynamics of HIV and AIDS and poverty are best comprehended at the micro level. There is increased healthcare expenditure and reduction in income. This depletes family savings and may result to debts, sale of family assets and reduction in current consumption. The low demand for goods and services implies low production and investment (Were and Nafula, 2003).

1.5 Economics of HIV and AIDS in Kenya

HIV and AIDS is not a primarily an economic issue. This epidemic has attained a scale that makes it a major (if not the major) factor that will continue to affect the economic development in the region over the next decades (Markus, 2002). This infection has characteristics that distinguish it from many other diseases. It is pandemic, chronic, fatal and highly stigmatized (Mwabu, 2008). It threatens the viability of Health infrastructure, social systems and economic growth in Kenya.

There are many mechanisms through which AIDS may have potential impact on the economy (WHO, 2001), unlike other deadly illnesses, HIV's prime target is people of working age**.** However, the macro evidence from the early phases of the pandemic

failed to substantiate the hypothesis that AIDS would have detrimental effect on the growth rates per capita income. The pandemic has since grown rapidly and has begun to have significant effect on life expectancy and other human development indicators (WHO, 2001).

The economic impact of HIV and AIDS can be classified into three different categories; the burden in the health sector of providing care and treatment, the actual cost of illness in the short-run – morbidity and mortality and finally the long run cost of illness.

1.5.1 The medical costs of HIV and AIDS

The HIV and AIDS epidemic has an immediate effect on the health sector, increasing the demand for public and private health services and, at the same time taking its toll on health sector personnel (Markus, 2002).

In June 2008, there were an estimated 190,000 patients on antiretroviral therapy (ART) in Kenya, with an increase of 5000 new patients monthly (MoH, 2008). The cost of treating these 190,000 patients for one year was estimated to be 3.42 billion shillings and this was anticipated to rise to 3.8 billion shillings in 2009 to cater for 250,000 clients. Kenya faces acute shortage of trained health workers, especially in rural area**s** (Table 7).

Table 7: Key Registered Health personnel in Kenya

Health Personnel	**2007**	**2008**	**2010**	**2011**	**No. per 100,000 population**
Doctors	6,271	6,623	7,129	7,549	19
Dentists	931	974	898	930	3
Pharmacists	2,775	2,860	3,097	3,205	8
Pharmaceutical Technologist	1,680	1,818	2,233	2,409	6
Nursing officers	12,198	14,073	29,678	34,071	86
Enrolled Nurses	31,917	31,917	34,282	34,576	87
Clinical Officers	5,797	5,035	8,598	9,793	25

Source: Economic Survey, 2012

Kenya has inadequate health system infrastructure and lacks the resources to improve it. Table 7 shows the total number of registered key health care workers and their ratios to the patients. Therefore, HIV and AIDS treatment competes with the

resources that could be used to improve health systems and the country's development in general. At the same time, increased health spending could mean cuts in investment in other growth-enhancing areas such as education and infrastructure (WHO, 2001). It is for this reason that the burden of HIV and AIDS is complex and high.

The burden of HIV and AIDS is direct as result of the cost implied by the treatment, but also indirect for two main reasons: first, as result of the loss in productivity given its effect on morbidity and mortality and secondly because the existence of the illness draws scarce resources away from alternative socio-economic needs (e.g., the treatment of other acute conditions such as Malaria, tuberculosis or malnutrition but also the needs to invest in other economic sectors such as education, infrastructure, health care facilities and the diversification of human capital - e.g., nurses, doctors - that would have been productive elsewhere).

1.5.2 The short-run cost of HIV and AIDS illness – morbidity and mortality

According to Grossman model (Grossman, 1972; 2000), education and health play an interrelated role at determining the productive capacity of individuals, an individual's good health (or 'healthy time') determines the individual's capacity to produce conditional on some start up level of education. In countries where the burden of disease due to risk factors such as unsafe sex, malnutrition, malaria or Tuberculosis is significantly high, the implications from Grossman's model is one of economic decay for two reasons, induced morbidity and accelerated mortality (Vazquez-Alvarez and Adam, 2008).

HIV and AIDS morbidity and premature mortality therefore imply reduction in human capital stock, level of productivity and production, income, current level of consumption resulting into low levels of investment in human capital (Fox et al. 2004; Chapoto and Jayne 2008). This lowered domestic productivity reduces exports and increases imports especially of expensive healthcare products (Dixon et. al., 2002). The premature mortality implies that new staff must be trained and recruited, a cost that would not otherwise have been borne. AIDS is also debilitating, particularly in the final 2 years before death (Arndt and Lewis, 2000) and absenteeism for both those infected and those caring for them may have impact on business and other work

organizations. The impact of HIV and AIDS on productivity may also decrease an economy's attractiveness to foreign investors and diminish tax revenue (WHO, 2001).

1.5.3 The long-run cost of HIV and AIDS

Bell, Devarajan and Gersbach (2003, 2006) using an overlapping generations framework shows that, AIDS can severely retard economic growth, even to the point of leading to an economic collapse. In this model, orphans' education hence human capital development is affected through three main channels:

First, AIDS destroys existing human capital in a selective way. It is primarily a disease of young adults. After transmission, infected individuals enter a clinical latent stage during which health status declines gradually without signs of disease symptoms, (Mwabu, 2008). A few years later, it reduces their productivity by making them sick and weak, and then it kills them in their prime, thereby destroying the human capital progressively built up in them through child-rearing, formal education, and learning on the job, (Bell, Devarajan and Gersbach, 2003, 2006).

Second, AIDS weakens the mechanisms that generate human capital formation. In the household, the quality of child-rearing depends heavily on the parents' human capital. If one or both parents die while their offspring are still children, the transmission of knowledge and potential productive capacity across the two generations would be weakened. At the same time, the loss of income due to disability and early death reduces the lifetime resources available to the family, which may well result in the children spending much less time (if any at all) at school. Finally, the chance that the children themselves will contract the disease in adulthood makes investment in their education less attractive, even when both parents themselves remain uninfected. The weakening of these transmission processes is insidious; for its effects are felt only over the longer run, as the poor education of children today translates into low productivity of adults a generation hence (Bell, Devarajan and Gersbach, 2003, 2006).

Third, as the children of AIDS victims become adults with little education and limited knowledge received from their parents, they are in turn less able to raise their own children and to invest in their education. A vicious cycle ensues. If nothing is done,

the outbreak of the disease will eventually precipitate a collapse of economic productivity (Bell, Devarajan and Gersbach, 2003, 2006).

The functional consequences of malnutrition and illnesses during childhood are felt throughout the lifecycle (Strauss and Thomas, 2008). Thus, prevention of childhood diseases and malnutrition would substantially increase health and economic growth in low-income countries (Mwabu, 2008). HIV and AIDS therefore has the potential to increase poverty, as orphans of AIDS are more likely to experience malnutrition, childhood diseases and are endowed with less human capital and will eventually face lower returns from their inherited lower productive capacity. With lower transfers of productive capacity, children in households that suffer the consequence of HIV and AIDS end up in sub-optimal conditions when compared to similar children brought up in households where HIV and AIDS has not had an effect. Bell, Devarajan and Gersbach (2003, 2006) conclude that HIV and AIDS has the added feature of inducing a burden that persists over incoming generations. Together with the fact that HIV and AIDS remains very much a behaviour illness, it is its feature as a long-run effect that distinguishes HIV and AIDS from other adverse health conditions.

Parental deaths have negative impacts on child schooling, and this occurs through three channels: firstly, financial losses caused by medical and funeral payments after parental deaths reduce family income and may reduce investment in schooling (Yamano and Jayne 2004; Yamano, 2006). Secondly, the opportunity costs of children's time may increase because of the time required to take care of sick parents and to replace the labour of the sick parents (Evans and Miguel, 2004; Yamano and Jayne, 2005). Thirdly, changes in parental preference after the loss of one parent may affect the schooling of orphans (Beegle et. al., 2006).

Ueyama and Yamauchi, (2008) shows that excess mortality arising from AIDS observed in recent years decreased women's age for their first marriage in Malawi. The findings have some implications on human capital formation among women and for the next generations. Firstly, early marriage means less schooling among young women, which may weaken their bargaining power in the household and consequently have negative outcomes on children. Secondly, a longer period of marriage may also imply an increase in fertility, which also has a negative outcome on child schooling through so-called quantity-quality trade-offs. Therefore, it is possible that AIDS-

related excess mortality has negative effects on human capital formation among women and the next generations through changes in women's marriage behaviour.

2 CHAPTER TWO: THE ANTIRETROVIRAL THERAPY (ART)

Antiretroviral therapy (ART) is the treatment that slows down the reproduction of HIV in the body. The drugs that form the treatment are often referred as antiretroviral drugs (ARVs), anti-HIV drugs and HIV antiviral drugs. Highly active antiretroviral therapy (HAART) is a combination of three or more antiretroviral drugs (TAC, 2006). In Kenya the ART is a triple drug therapy and hence ART implies HAART. The natural history of HIV infection in an average patient without ant-retroviral therapy from the time of HIV transmission to death is between 9 to 11 years, (Bartlett and Gallant, 2001; Thirumurthy et al., 2005).

World Health Organization (WHO) recommends that ARV therapy should be started when the damage caused by the HIV to the immune system reaches a certain threshold. This is based on clinical condition and/or laboratory tests particularly CD4 cell counts. When CD4 testing is not available, simpler laboratory tests such as lymphocyte counts can be used (WHO, 2003; Wasonga, 2005). ART can be initiated in a person without AIDS (WHO stages I, II, or III) or a person with AIDS (WHO stage IV). Nevertheless, initiating antiretroviral therapy has a proven benefit for patients with a CD4 count less than 350 cells/μL (Palella et. al., 2003). In patients with a higher CD4 count, the benefits of antiretroviral therapy are believed to be outweighed by the toxicities that may accrue from continued drug exposure (Mallal and others 2000). Due to the side effects, toxicities and costs, HAART is only given to pregnant women as they approach delivery, or those who have already passed into full AIDS with the hope to go back to a low CD4 count.

The public sector provision of ART was initiated in five pilot sites in 2001. In 2003, 11000 people were on ART in Kenya with only 1000 receiving ARV drugs from the public sector, while the remaining 10,000 received ART from non-government organizations (NGOs) facilities, faith based facilities (FBOs) and the private sector. The HIV treatment scale up was however, rolled out after the government received financial aid from bilateral and multilateral partners including the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM), the United States President's Emergency Plan for AIDS Relief (PEPFAR), the William J. Clinton Foundation and United Nations agencies (WHO/UNAIDS, 2006). Kenya is also a beneficiary of the

World Bank Multi-Country HIV and AIDS Program for Africa and Bill and Melinda Gates Foundations funding.

Although the government of Kenya (GoK) increased its allocation for HIV and AIDS programmes, it's important to note that ART is mainly funded by external donors. In 2003, the WHO launched global target to provide three million people living with HIV and AIDS in 50 low- and middle-income countries with life-prolonging antiretroviral treatment (ART) by the end of 2005 ("3 by 5" initiative). Though this target was not achieved worldwide, it provided the necessary impetus for treatment scale up. Kenya's "3 by 5" target was to put 95000 HIV positive people on treatment by the end of 2005. However, by the end of 2005, only about 55000 people were receiving ART. Thus, it is obvious that Kenya failed to achieve the expected target.

Current guidelines from the Ministries of Health recommend ART for all HIV-infected adults with CD4 cell counts less than 250 cells/μL, and for adults with WHO Stage 3 disease with CD4 cell counts less than 350 cells/μL or WHO Stage 4 disease regardless of CD4 cell count (see Table 8 for CD4 count distribution). It is estimated that out of 1.5 million HIV infected Kenyans 392,000, are in need of ART. Of these only 212,000 were on ART as at the end of June 2008 (NASCOP & MoH, 2008).

Table 8: CD4 count distribution among adults with HIV not on ART

CD4 Counts	Unweighted n	Weighted %	Projected population estimate
<200	123	13.1	189,000
200-249	49	4.9	71,000
250-349	104	10.7	155,000
350-499	147	15.6	225,000
≥500	513	55.7	805,000

Source: NASCOP &MoH, 2008.

Table 8 shows that among adult Kenyans with HIV who are not taking ART, 18% have a CD4 cell count below 250 cells/mL indicating a clear need for antiretroviral therapy according to current guidelines, an additional 10.7% have a CD4 cell count below 350, indicating they may need therapy now, depending on their clinical status, or will need therapy in the near future. The remaining 71.3% have CD4 cell counts greater than 350.

The distribution of ART varies both regionally and within the sub-population. There are more women accessing ARV drugs than men and higher access to these medications in urban as compared to rural areas. Although progress has been made in extending coverage and Kenya is likely to surpass the 2010 target of putting 250,000 people on ART, the United Nations General Assembly target of universal access to antiretroviral treatment (ART) by 2010 for all in need presents a formidable challenge. This is because Kenya's target is way below the total number of those in need of treatment.

There are four different avenues that a developing economy can take in the presence of HIV and AIDS: (1) no treatment; (2) prevention only (i.e., informing the population about the risks associated with HIV and AIDS and how to avoid infection); (3) treatment of opportunistic infections only; (4) HAART treatment. The following provides a more detail explanations of these four avenues:

No treatment: That is, the patient has to guarantee own treatment while there is no intervention from the government. The government plays no role in facilitating the treatment access to those infected. This was the position of most governments in developing countries at the onset of this pandemic. The government of Uganda was the first to acknowledge HIV and AIDS and organized a quick response (de Walque, 2007). However, in other countries like South Africa this position was maintained until the mid-2000s when HIV and AIDS prevalence rate was 30%. It is clear that this first stance would lead to economic collapse (Bell et al., 2006).

Treatment with low technology (prevention): Prevention measures to limit the transmission of AIDS include mass media campaigns; condom distribution; peer education of commercial sex workers (CSWs); the prevention of mother-to-child transmission (pMTCT); voluntary counselling and testing (VCT); male circumcision and diagnosis and treatment of other sexually transmitted diseases (STDs) (since the symptoms of these diseases can make it easier for the HIV virus to spread, i.e., sometime it is the case that other virus or bacteria acts as a riding horse for the HIV virus to penetrate the system as result of unsafe sex, etc., WHO 2008).

Prevention has been advocated for by developed countries and economists who argue that; (i) poor countries lack the adequate medical infrastructure to provide ART safely

and effectively; (ii) adherence to complicated medication regimens would be impossible hence providing ARVs will promote and spread drug resistance; (iii) antiretroviral drugs are too expensive (Harvard University Consensus, 2001). However, Mills, et. al. (2006) found favourable levels of adherence in sub-Saharan African settings and noted that adherence was still a major concern in North America.

At the same time, studies have shown that prevention initiatives are important though they may only be effective if combined with treatment (Wasonga, 2005; Montaner, 2006). The study by Frölich and Vazquez-Alvarez (2008), shows that, information campaigns effectively equipped the adult population in Kenya with the required knowledge to avoid becoming HIV-positive. However, these campaigns only benefited younger females whose sexual debut happened after the implementation campaigns became widespread in Kenya. The campaigns statistically reduced the probability of these females from becoming HIV-positive. For males there was not impact.

Treatment of opportunistic infections (OIs) and other HIV-related conditions:
OI is an infection or cancer that occurs especially or exclusively in persons with weak immune systems due to AIDS, cancer or immunosuppressive drugs. Appropriate diagnosis and management of opportunistic infections is one of the most important aspects of the care of patients with HIV disease. OIs include tuberculosis (TB), cryptococcal meningitis, toxoplasma encephalopathy, infectious diarrhoea, Kaposis's sarcoma and nonspecific wasting (slim disease) and are the main cause of morbidity and mortality in people living with HIV and AIDS (PLWHIV). Treating OIs do not reduce the viral load nor increase the CD4 counts. This is mainly used to treat PLWHIV who do not have access to ART or used in combination with ART.

HAART treatment: although the triple therapy is more expensive, studies have shown that HAART is not only cost-effective but also cost saving. It's effective in reducing viral load to almost undetectable levels and partially enabling immune restoration, thereby preventing the onset and recurrence of opportunistic infections while significantly reducing the probability of infection to others (Montaner, 2006). Scientific research has shown that if adhered to (i.e. taken strictly according to directions); antiretroviral therapy can induce a sustained recovery of CD4 cell

reactivity against opportunistic pathogens in severely immune-suppressed patients (Bertozzi et al, 2006; Detels, 1998).

In the western world the use of HAART has turned HIV and AIDS from a life-threatening illness into a chronic condition that requires treatment but nevertheless implies that individuals are likely to survive their full-expected life span. Nevertheless, the effectiveness of antiretroviral therapy is determined by two combined factors: the individual's ability to adhere to the drug and the ability of the drug at reducing the patient's viral load. To a large extent the ability of the patient to adhere to the drug depends on the level of toxicity the individual patient's metabolism can withstand. On the other hand, the ability of the drug to reduce viral load also depends on how fast the virus learns to mutate thus reacting against HAART. In general, HAART offers the best treatment for HIV and AIDS by ensuring that patients can live relatively normal lives. However, the drug is not equally effective for all.

There are at least 4 compelling reasons for providing HAART in Kenya. First, ART is essential to the 1.5 million Kenyans infected with HIV, most of whom will die without it. This is an immediate humanitarian rationale for ART treatment.

Second, treatment is necessary to optimize prevention efforts (Montaner, 2006; Wasonga, 2005, Harvard University Consensus, 2001). ART encourages voluntary counselling and testing (VCT) and lowers the viral load within PLWHIV, hence reducing the likelihood that they will transmit HIV infection to others. HAART drastically reduces mother-to-child transmission. Montaner (2006) also shows that the effect of HAART is similar to that of a vaccine. Third, treatment is necessary to save the children and fabric of societies. Without treatment, the number of adult deaths expected from AIDS could be very high; hence AIDS orphans would greatly increase from the current 1.2 million to a socially devastating wave in future. Without family support, these children are unlikely to go attend school, suffer from extreme and malnutrition, and become victims of violent and sexual crimes (Harvard University Consensus, 2001). This is the main justification for treatment as a necessity for continuing economic development and reduction in poverty. Bell, Devarajan and Gersbach (2003, 2006) shows that premature parental mortality lowers the orphans' capacity of dealing as economic agents in future periods ahead.

Lastly, treatment is necessary for continuing economic development. Without treatment, millions of adults in the prime of their working lives will die of AIDS and take with them the skills and knowledge base that are necessary for human and economic development. To avoid the economic burden of the epidemic it is necessary to assess both the economic and the human benefits of ensuring universal access to all effective treatments, including studying the consequence of universal HAART treatment as its applied in the developed world.

In Kenya most of the studies on the effectiveness of HAART are epidemiological. Wools et al. (2006) carried out an epidemiology study to determine the clinical and immunological outcomes of a cohort of HIV infected patients receiving antiretroviral therapy in Kenya. The study showed that ART treatment resulted in significant and persistent clinical and immunological benefit. Hence, viability and effectiveness of large-scale HIV treatment initiatives in resource limited settings. A study by Song et al., (2007) investigated the efficacy of antiretroviral therapy among HIV-infected children in Kenya and concluded that there was excellent efficacy among treatment-naïve-HIV-infected children in a resource-limited country. Clinical and immunologic improvement occurred in all patients.

Whereas epidemiologically there has been some coverage, the durational analysis studies looking at survival rates and controlling for confounding factors are scarce. In addition no studies have been done that compares the economic impact of ART versus No ART treatment scenarios in more than one treatment model. Based on these information gaps, this thesis carried out cost effectiveness and durational regression analysis using treatment costs, health care utilization, patient outcome and socioeconomic data to provide a better understanding of the implication of ART versus no ART treatment scenarios. In addition, the thesis also carried out a comparative analysis of costs and patient treatment outcomes in AMPATH and MDH treatment models. The thesis further analysed the direct and indirect net economic benefits of two treatment methods allowing for both long run (e.g., simulation studies that take the initial micro-economic parameters to lead towards understanding of the effect of alternative treatments with regards to life-expectancy and cost) and short run effects (e.g., micro-economic studies on the determinants of survival given treatment type).

The study was drawn from micro-economic program evaluation as a way to measure the micro-economic implications of the ARV use and no ARV treatment methods. The study carried out survival analysis to determine the survival rate of the patients on ARV and those not on ARVs controlling for the covariates. It also uses Markov processes to provide a better understanding the economic implications of the HIV and AIDS epidemic in Kenya. Traditional use of Markov process take care of the dynamic implication of the illness allowing for deterministic models without taking into account for heterogeneous behaviour in the population.

2.1 Study settings

This study was conducted in two hospitals in Kenya and Markov modelling and Survival analyses were utilized to simulate lifetime costs and benefits of ART use and no ART use.

2.1.1 The Academic Model for the Prevention and Treatment of HIV/AIDS (AMPATH)

This is a comprehensive model of HIV and AIDS control in western Kenya. It grew out of a long-standing partnership between Indiana University School of Medicine, Moi University School of Medicine (MUSM), and Moi Teaching and Referral Hospital (MTRH). AMPATH was initiated in 2001 and uses a systems-based approach to prevention and treatment that closely links clinical care, research, and training. At the time of this study, AMPATH was caring for more than 55,000 HIV infected adults and children, with nearly one-half of all patients on anti-retroviral drugs, and enrolling into the program 2,000 patients per month. Its prevention activities were impacting the lives of an estimated 1.5 million people in western Kenya. AMPATH was working in 19 healthcare facilities within government of Kenya facilities, non-governmental facilities, and at the grassroots level in multiple communities. Almost all its workers are employees of government of Kenya. It has a strong referral system starting from the grassroots level to the tertiary hospital (MTRH). In addition to HIV prevention and treatment it also provides other services that improve the quality of life of people infected and affected by HIV and AIDS, and mitigates the social and economic impact of HIV and AIDS and tuberculosis (TB). These services include: nutritional and economic, patient transport Support, VCT,

PMTCT, human resources capacity building, orphans and vulnerable children support among others.

2.1.1.1 Nutrition and Food Production Program

Apart from clinical care, AMPATH also runs nutritional and sustainable income generating programmes. The goal of the nutrition program is to improve the nutritional status of clients accessing care at AMPATH. They strive to correct and treat severe malnutrition related to HIV and AIDS and to alleviate food insecurity in the households of clients accessing care at AMPATH. Nutritional programme activities includes: Nutrition assessment, education and counselling; providing therapeutic feeding for the severely malnourished; provision of supplementary feeding for the moderately malnourished and the vulnerable groups and food support for the food insecure households. AMPATH operates three production farms covering a total of 10 acres, which produce approximately 6 tons of vegetables per week. The food is from World Food Programme and AMPATH's production farms. At the time of this study, 31,000 individuals were receiving nutritional support.

2.1.1.2 Family Preservation Initiative (FPI)

The Family Preservation Initiative (FPI) provides income-generating programs to help HIV positive patients and their families get back on their feet. The goal of this programme is to give assistance without encouraging dependency by offering income-generating programs. FPI provides services in two major forms capacity building and enterprise development. Capacity building is in the form of business and agricultural training, access to loans and savings. While enterprise development is in the form of fruit processing business, handicrafts, restaurant and fruit tree seedling business.

2.1.2 Mbagathi District Hospital

Mbagathi District Hospital (MDH) is situated in Kenyatta Golf Course Location, Dagoretti District of Nairobi County in Kenya. MDH is a public hospital located in Nairobi on the outskirts of the Kibera informal settlement and has been considered as a hospital of the poor (MoH and MSF, 2008). This hospital was built to in the 1950s to serve as the infectious disease department of the then “King George VI Hospital”,

currently Kenyatta National Hospital. In the year 1995, IDH was curved from Kenyatta National Hospital and transformed into an autonomous District Hospital for Nairobi, though with very poor and dilapidated facilities.

The Médecins Sans Frontières (MSF) Belgium collaboration and support to this district hospital started in 1997 when the facility was overwhelmed by moribund HIV positive patients. Then, MDH was considered the hospital of the last resort where the rich and the middle class Kenyans were admitted to after they had exploited all their resources managing HIV and AIDS in the more expensive private hospitals. The hospital therefore posted very high HIV and AIDS related mortality. MSF built a clinic on the hospital grounds, allowing integration of the comprehensive MSF and MoH HIV/AIDS activities. However, it was in 2003 that MSF started providing ARVs and introduced the a comprehensive care package, with the objective of increasing access to quality medical and psycho-social services to people living with HIV and AIDS free of charge (MoH and MSF, 2008).

The Government of Kenya (GoK) initiated its own ART service in Mbagathi hospital soon afterwards, and integration of the two programmes into one Comprehensive Care Centre (CCC) under a single management system began in 2005. By the time of this study, MSF had successfully handed over the Comprehensive Care and Clinic to the government and a total of fifteen thousand HIV positive patients were on treatment follow up. MDH also acts as a HIV training centre for government staff, a centre for complicated ART clients, a specialist centre in paediatric and adolescent HIV care, an information centre and a spring-board for PLHIV groups.

2.2 Statement of Research Problems

HIV and AIDS have caused major economic and health impacts in Kenya. To address these impacts several interventions has been put in place including comprehensive care and treatment in which eligible patients are put of ARVs and treatment of opportunistic infections only without ART use. Although, there have been various clinical studies on the impact of ART use in Kenya, economic studies linking patient health outcomes and the cost of managing HIV and AIDS in Kenya have been very limited. In addition, no study in Kenya has assessed the socioeconomic factors determining the survival for the people living with HIV who are using ARVs. Studies

addressing these issues will significantly contribute towards strengthening both policy and implementation of ART.

In this research efforts have been made to answer the following questions:

- What are the lifetime costs and benefits of ART and no ART use for the patients in Mbagathi and Moi Referral hospitals?
- What are the factors determining survival of HIV positive adults on ART and those not on ART in these two hospitals?
- Which treatment type or hospital is more cost effective?

2.3 The objectives:

General Objectives

The main objective of this study is to estimate the cost effectiveness of ART use and no ART use and the determine factors influencing survival of people living with HIV on treatment follow up using data from Mbagathi hospital and AMPATH treatment centre.

Specific objectives

i. To estimate the cost of alternative HIV treatment scenarios in Kenya
ii. To compute the effectiveness of alternative HIV treatment scenarios in Kenya in terms of life years (LYs) gained
iii. To compute the cost-effectiveness of ART under different treatment starting conditions
iv. To determine the factors influencing survival of HIV positive patients on treatment follow up.

2.4 Study Justification

This thesis aims at providing sound economic policy advice regarding the use of scares resources in public health. In Kenya as in other developing countries, there is a constant need for a better understanding of the interaction between public health interventions and economic outcomes. Clearly, HIV and AIDS epidemic remains a major health and development issue in such economies. However, only sound quantitative evidence can bring about sound policy advice.

Major programs that combine antiretroviral therapy distribution are being planned and are becoming operational as drug prices plummet and resources increase (Yazdanpanah, 2004). Given the scale of treatment envisaged, the paucity of data estimating the lifetime costs and efficiency of HIV treatment is a serious hindrance to effective planning. In the absence of data local and global policy advice have been based on normative modelling exercises and in publishing simulation estimates that may not accurately represent the complex dynamics associated with HIV and AIDS.

Studies have recommended primary research into the costs and cost-effectiveness of ART to address these gaps (Cleary et al., 2006). More refined cost-effectiveness analyses are needed to evaluate available HIV and AIDS prevention, treatment, and care, and to identify the interventions that provide the best value for money (Yazdanpanah, 2004). However, to implement such models and come up with sound policy advice there is need to assess the availability of data. Therefore, a complementary aim of this thesis was to assess the available epidemiological and economic data and also collect more data.

As more effective HIV therapies have become available, resource constraints and cost-effectiveness have increasingly been at the centre of the debate on HIV care. Economic analysis is an important methodological approach to the understanding and establishment of priorities for health interventions designed to combat HIV in both high-income and low-income countries (Yazdanpanah, 2004). In Kenya, the cost of antiretroviral therapy has dramatically decreased over the past few years, from US$ 4128 per patient-year in January 2001 to about US$ 180 per patient-year for branded ART. In addition, generic formulations have also decreased from US$ 288 in November 2003 to about US$ 100 per patient-year for generic ART (Wasonga, 2005; Wasonga, personal communication, April 2008). However, this therapy remains expensive compared to the per capita national health expenditures of Kenya.

Given demands for care and constrained resources, this thesis enhances the understanding and prioritizing of HIV health interventions in Kenya. Combining the epidemiological and economic data helps us understand the lifetime costs and effects of ART, in addition survival regression analysis enabled us to estimate the impact of ART on reducing the risk of death for patients on treatment follow up.

Treatment for HIV infection is not widely accessible to many PLWHIV in need of it, although there is increasing evidence of its feasibility and efficacy. In addition to the cost of making antiretroviral drugs available, the provision of treatment to patients living with HIV in Kenya involves other major expenses, such as those of developing and sustaining health care structures, laboratory facilities, health care technologies, and distribution channels. Kenyan government recognizes the need for comprehensive national reforms and comprehensive prevention, treatment, and care and support initiatives to reduce future transmission and meet the growing demand for HIV services. Hence, better monitoring and evaluation of those who may benefit from treatment as well as monitoring and evaluating those that are already under treatment would provide the governmental authorities with a better understanding of the situation of HIV and AIDS, the need for better practices and the requirements with regards to investment in the health sector.

To achieve Vision 2030, that is moving Kenya to a middle income country by 2030, the Government of Kenya must efficiently use its resource. This thesis not only evaluates the impact and cost-effectiveness of ART use and no ART use, but it also offers insight into efficient resource utilization. Among other things, the thesis aims at pinpointing with clarity the cost effectiveness of different treatment scenarios. Clearly, HIV and AIDS may be one illness that needs treatment, but it is our hope that the cost-effectiveness lessons drawn from this thesis may also help researchers to better understand the cost-effectiveness of public health related treatments that often have a significant economic impact. By ensuring that such clinical economic evaluations are available, health planners and policy makers will be in a position to allocate resources better. In general, the aim is that such findings can enable the policymakers and implementers of public health interventions to allocate scare resources more effectively among alternative health uses.

3 CHAPTER THREE: THEORETICAL LITERATURE REVIEW

3.1 Introduction

Economics is a study of decision making in the face of scarcity. The resources used to provide health care including, money, staff, time, facilities, equipment, knowledge, technology are scarce (Drummond et al. 2005; Hoch and Smith, 2006; Gafni, 2006; Brazier et al. 2007). Decisions about what health services to provide, to whom, where and when, more often than not have resource and choice implications (Drummond et al. 2005; Brazier et al. 2007). At the same time provision of one intervention usually implies opportunity cost of providing other services. Economic evaluation is a comparative analysis of costs and consequences of alternative options (Coyle and Davies, 1993; Drummond et al. 2005; Hoch and Smith, 2006; Edlin et al. 2008). It provides much more useful information for policy decisions than analyses based solely on costs or outcomes (Hoch and Smith, 2006). Since economic evaluation addresses only one dimension of healthcare programme decisions, it is most useful and appropriate when preceded by efficacy, effectiveness and resource availability evaluations (Drummond et al. 2005).

The overall aim of economic evaluation is to aid decision makers to make efficient and equitable decisions by comparing the costs and benefits of different health care interventions (Coyle and Davies, 1993; Drummond et al. 2005). It enables the researchers and policy makers to identify the relevant alternative interventions, evaluate the view point assumed during implementation and measure the opportunity cost of given alternatives (Drummond et al. 2005). Over the past several years, the use of economic evaluation to inform policy making has increased (Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007).

A full economic evaluation should consider all costs and benefits of health care interventions to the society (Coyle and Davies, 1993; Gold et al. 1996; Drummond et al. 2005). The resource/inputs costs evaluated should include direct and indirect treatment costs as well as direct and indirect non-treatment costs (Coyle and Davies, 1993; Gold et al. 1996; Drummond et al. 2005). The disciplinary origins of economic evaluation of health care can be traced in several directions (Gold et al. 1996; Briggs

et al. 2006). One direction relates to welfare economic theory and the other operations research and management science (Briggs et al. 2006).

3.2 Techniques of economic evaluation

There are five major techniques of economic evaluation namely; cost analysis/ cost minimization analysis – methodology which estimates costs of a particular type of care or a specific illness and are used primarily for budgeting and planning purposes; cost effectiveness analysis –in which costs and consequences of programmes are examined; cost-benefit analysis – in which impacts of the intervention are translated into monetary terms, in order to obtain a ratio; cost-utility analysis – a methodology in which the impact is measured in terms of gains in the quality-adjusted life-years (QALYs) of an individual. Lastly, cost-consequences analysis- in which the costs and outcomes of different interventions are computed separately and the results presented in a table (Coyle and Davies, 1993; Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007). These different techniques of economic evaluations are distinguished mainly by the unit for measuring the benefits of health care (Coyle and Davies, 1993; Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007).

3.2.1 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is a form of full economic evaluation where both costs and consequences of health programmes or treatment are examined (Gold et al. 1996; Drummond et al. 2005). The results of CEA are usually summarized in a series of cost-effectiveness ratios showing the cost of achieving one unit of health outcome for different kinds of patients and interventions (Coyle and Davies, 1993; Gold et al. 1996). In addition, the added costs and health outcomes associated with a programme are used to calculate the incremental cost –effectiveness ratio (Gold et al. 1996; Drummond et al. 2005).

The numerator, depending on the study and on the viewpoint taken, may be total cost, net health care cost or net economic cost to society while the denominator is the measure of health effect most relevant to the program under study (Torrance, 1986). The health outcomes can be disease prevented, life saved, life-years gained, quality adjusted life years (QALYs) etc. (Gold et al. 1996; Drummond et al. 2005; Brazier et

al. 2007). Thus, the results of a CEA can be expressed in terms of shillings per case of disease prevented, or shillings per life saved, or shillings per life-year gained. The particular type of CEA that uses quality adjusted life-years (QALYs) is usually referred to as cost-utility analysis (CUA) (Gold et al. 1996; Drummond et al. 2005).

CEA is useful in comparing alternative programmes whose effects are measured in the same units (Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007). However CEA is incapable of assessing a single programme and hence unable to address the issue of opportunity cost of funding a new programme; it cannot be used to make comparison across abroad set of interventions, in addition, it is not suitable for analyzing programmes with several types of clinical effects - for example, reductions in both morbidity and mortality and lastly, CEA cannot rank outcomes of varying value (Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007). Furthermore this economic evaluation method is more narrowly client focused and addresses mainly questions of production efficiency with outcomes restricted to health benefits (Drummond et al. 2005).

The underlying premise of cost–effectiveness analysis in health problems is that for any given level of resources available, society (or the decision-making jurisdiction involved), wishes to maximize the total aggregate health benefit conferred (Weinstein and Stason 1977). Originally, CEA was not related to a welfare theory and was presented as a solution to an optimization problem, however, there has been several attempts by economists to ground the methodology of CEA of medical interventions in economic welfare theory or the welfarist approach (e.g., Garber et al. 1996; Garber and Phelps 1997; Meltzer 1997; Gafni, 2006).

CEA is the most straightforward technique of economic evaluation and can be undertaken from a number of different perspectives (Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007). The perspective can be the employers' perspective where only the costs and outcomes directly affecting the employer are evaluated, the patients' perspective, the health providers' perspective, the government's perspective and the societal perspective. Though the CEA conducted from the societal perspective is preferred by analysts, it's normally difficult to measure (Gold et al. 1996).

There are two decision rules employed to determine how cost effective an intervention is: the league table approach and the threshold approach (Gold et al. 1996; Drummond et al. 2005; Gafni, 2006). Under league table, the decision maker is only concerned with the relative value of the ICER and programmes are adopted in a descending order of cost–effectiveness until all available resources are exhausted. In the threshold approach the decision-maker focuses on the absolute value of the ICER and if the programme's ICER is lower than the threshold value, it should be adopted (Gafni, 2006).

It's worth noting that although, CEA provides valuable information regarding the trade-offs in broad allocation of health resources, other factors including fairness, justice, negative and positive externalities and feasibilities of interventions should be considered in decision making and therefore CEA is only an aid but not a complete decision making process (Gold et al. 1996; Brazier et al. 2007).

3.2.2 Cost benefit analysis

Cost-benefit analysis (CBA) is a form of economic evaluation that requires programme consequences to be valued in monetary units, hence direct comparison between programme costs and consequences (Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007). It compares discounted future streams of incremental programme benefits with the incremental programme costs and the difference between these two streams is the net social benefit (NSB) of the programme (Drummond et al. 2005; Brazier et al. 2007). The CBA decision rule is straightforward, if the NSB is greater than zero (NSB>O), then the project is cost-beneficial and it should be implemented (Torrance, 1986; Drummond et al. 2005; Brazier et al. 2007).

CBA holds significant conceptual appeal for economists because of its theoretical foundation in welfare economics, specifically the Kaldor–Hicks criterion (Gold et al. 1996; Drummond et al. 2005; Gafni, 2006; Brazier et al. 2007). In addition, its principle of net benefit is applicable to various sectors (e.g., environment, transport, education etc.), so that intersectoral comparisons of resource use can be considered (Gafni, 2006). Hence, cost-benefit analysis is broader in scope than CEA and

overcomes the disadvantages of CEA and CUA; a decision can be made on a single programme, and disparate effects in the same or different programmes can be compared, at the same time CBA is able to capture programme externalities (Torrance, 1986; Gafni, 2006; Drummond, 2005; Brazier et al. 2007).

Cost–benefit analysis (CBA) is the most commonly used method of economic evaluation in all other areas (e.g., transportation, education and agriculture) besides health-care (Gafni, 2006). It's able to inform questions of allocative efficiency and using techniques of willingness to pay (WTP), it can quantify a broad range of effects (Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007). CEA and CUA are by far the most common types of analyses in health-care applications (Gafni, 2006).

However, the major issue for use of cost-benefit analysis in health care is the evaluation of outcomes in money and the argument that it is insensitive to income inequality (Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007).

3.2.3 Cost-utility analysis

Cost-utility analysis (CUA) is like CEA because it compares interventions in terms of their costs per unit of effect (Gold et al. 1996; Brazier et al. 2007). It's a special form of CEA in which the measure of effect is quality-adjusted life-years (QALYs) gained (Torrance, 1986; Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007). CUA is a form of economic evaluation that focuses particular attention on the quality of health outcome produced or forgone by health programmes (Drummond et al. 2005).

CUA has several advantages over CEA (Brazier et al. 2005). First, interventions with more than one kind of health outcome including side effects can be analyzed. Second, interventions of the same condition with different health outcomes can be compared against each other. Third, interventions for different kinds of health problems with different health outcomes can be compared (Brazier et al. 2005). The results of CUA are reported in terms of monetary costs per QALYs and the healthcare interventions can be compared in terms of their incremental costs per QALY (Torrance, 1986; Gold et al. 1996; Drummond et al. 2005; Brazier et al. 2007).

3.3 Theoretical Foundations for Cost Effectiveness Analysis

Cost-effectiveness analysis is an economic evaluation designed to evaluate the outcomes and costs of different health interventions (Garber et al. 1996; Garber and Phelps, 1997; Meltzer, 1997; Drummond et al. 2005; Lee 2008). It can be used to make optimal decisions regarding the allocation of medical resources, under specific circumstances (Garber and Phelps, 1997; Meltzer, 1997; Lee 2008). CEA is an essential tool for increasing the efficiency of health expenditures and informs resource allocation decisions in health and medicine (Garber et al. 1996; Garber and Phelps 1997; Garber and Phelps 2008). How well it does so depends on comparability and consistency of analyses of diverse interventions (Garber and Phelps 2008).

Historically there is no single theoretical foundation for CEA (Garber et al. 1996). Its roots can be traced to a variety of sources including decision analysis and operations research (Meltzer 1997). However, in recent times, economists have sought to graft CEA to theoretical roots in welfare economics (Garber et al. 1996; Garber and Phelps 1997; Meltzer 1997).

3.3.1 Welfare Economics as a theoretical foundation for CEA

There is no theoretical foundation that can address all the questions that arise in the process of setting policies for the allocation of resources for health care (Garber et al. 1996). Cost-effectiveness analysis is a tool for improving the general welfare of the society and can be justified within a welfare theoretic framework (Garber et el. 1996; Garber and Phelps, 1997; Meltzer, 1997). The welfare-economic framework facilitates derivation of the cost-effectiveness approach from fundamental principles that social welfare is a function of individual preferences, and that individuals are expected utility maximizers (Garber et al. 1996; Garber and Phelps 1997; Meltzer 1997; Drummond et al. 2005). Welfarist economists also assume that individual utilities can be aggregated by appeal to the Kaldor-Hicks criterion (Garber et al. 1996; Garber and Phelps 1997; Meltzer 1997). Based on the above assumptions, cost-effectiveness ratio (C/E ratio) is derived (i.e., cost per quality-adjusted life year) as a criterion for ranking health investments (Weinstein and Manning 1997).

Although, welfare economics has been emphasized as the theoretical foundation for CEA, some CEA principles can be based outside of this school of thought (Garber et al. 1996). The welfare theoretic framework can inform specific issues in the application of CEA from the societal perspective.

It's worth noting that the values implicit in the welfare economics are not shared by all decision makers even those working from societal perspective hence the need to accommodate alternative formulations of social goals regarding health and health care (Garber et al. 1996).

3.3.2 The Cost-Effectiveness Ratio

The central measure used in CEA is the cost-per-unit-outcome, or cost-effectiveness ratio. The cost-effectiveness ratio is a comparison between alternatives i.e. alternative one is the intervention under study and another intervention or no intervention (Gold et. al., 1996).

The cost-effectiveness ratio for comparing the two or more alternatives is the difference in their costs (net costs) divided by the difference in their effectiveness (net effects) (Garber et al. 1996; Drummond et al. 2005; Briggs et al. 2006). C/E ratio is the incremental price of obtaining a unit health effect from a given health intervention when compared with an alternative (Garber et al. 1996; Drummond et al. 2005; Gafni, 2006).

Interventions that have a relatively low C/E are "good buys" and would have high priority for resources (Garber et al. 1996). A decision rule based on adopting all interventions with C/E ratios less than or equal to a "threshold" will be optimal if the resulting set of interventions will maximize the aggregate heath effect achievable by the resources used and the resulting aggregate health effect will have been achieved at the lowest possible cost (Garber et al. 1996; Drummond et al. 2005; Briggs et al. 2006).

3.3.3 Cost-Effectiveness Analysis and Cost-Benefit Analysis

There are two schools of thought linking cost-benefit analysis and cost per QALY analysis (Garber et al. 1996; Drummond et al. 2005; Brazier et al. 2007). One is the welfarist approach, which argues that CBA is the theoretically correct method for economic evaluation and cost per QALY (CEA using QALY) is only used because it avoids monetary evaluation of health outcomes (Brazier et al. 2007). The second school of thought is the 'extra-welfarist', 'non-welfarist' or 'decision makers' approach which argues that CEA using QALY is preferred because it's more relevant to policy makers (Brazier et al. 2007).

There in need to note that, those who identify the theoretical foundation of CEA as the welfarist approach also realize that this logically leads to the use of CBA. However, the broad use of CEA/CUA instead of CBA is that it is broadly accepted within the health-care field (Garber et al. 1996; Gafni, 2006). CEA and QALY are viewed as income free and use of CEA avoids the distributional problem that underlies CBA's willingness-to-pay method of valuation (Garber et al. 1996; Drummond et al. 2005; Gafni, 2006; Brazier et al. 2007). However, the measure of health consequences in CEA is only one component of the analysis, while the other aspects like costs are not income free. Hence, the CEA cannot be seen as a tool that is free of the income distribution problem (Gafni, 2006).

According to Brazier et al. 2007, there are also welfarist CEA with QALY and non-welfarist. Welfarist CEAs builds on a literature that places the concept of the QALY upon the utility theory (Brazier et al. 2007). It's worth noting that it is the non-welfarist or `social decision making view that has implicitly or explicitly provided the methodological foundation for CEA in health (Briggs et al. 2006).

Two important and contentious issues still remain in CEA: these includes the question of which future costs to include in the analysis and the other is the role of economic welfare theory as a foundation of CEA and, therefore, as a guide to methodological standards (Garber and Phelps, 1997; Meltzer, 1997; Gold et al. 1996; Weinstein and Manning 1997; Gafni, 2006; Lee 2008).

3.3.4 Future costs in cost effectiveness analysis

There is a general agreement that CEA should account for related costs however, the treatment of unrelated future costs has been controversial (Garber and Phelps, 1997; Meltzer, 1997; Gold et. al., 1996; Lee 2008). Researchers using Conditional budget constraints show that unrelated future costs need not be considered, while those using Annuity budget constraint argue that they should be included (Garber and Phelps, 1997; Meltzer, 1997; Lee 2008).

3.4 Economic evaluation using decision analytic modelling

Decision analysis describes a series of computational methods that have been developed to address problems of identifying optimal solutions to problems with multiple alternatives (Tom and Schulman, 1997). It is a systematic approach for assessing the relative costs and consequences for one or more treatment options (Lang et al. 2003). In the context of economic evaluation, a decision analytic model uses mathematical relationships to define a series of possible consequences that would flow from a set of options being evaluated (Briggs et al. 2007). These models are particularly appropriate where a problem involves chance events that occur over a short time horizon or 'on-off' intervention (Lang et al. 2003). Decision analytic modelling provides a framework for decision-making under conditions of uncertainty using sensitivity and threshold analysis (Briggs and Sculpher, 1998; Drummond et al. 2005).

Decision analytic tools are useful for several purposes, including assessing clinical problems that have not been studied previously, assessing degrees of uncertainty in clinical decision making, assessing sensitivity of clinical and economic analyses to critical assumptions in the analysis, and projecting the results of clinical trials into subsequent time periods (Tom and Schulman, 1997; Briggs and Sculpher, 1998; Drummond et al. 2005).

Economic evaluation for decision-making requires data drawn on evidence from a variety of sources including a range of trial, observational and epidemiological data. These data are then synthesized using the decision analysis models (Briggs and

Sculpher, 1998; Drummond et al. 2005). Decision-analytical models play important roles in the economic evaluation process (Briggs and Sculpher, 1998).

In cases where economic evaluations are concerned with lifetime costs and effectiveness, modelling techniques are used to extrapolate the observed results (Briggs and Sculpher, 1998). The major purpose of decision analysis is to quantify each option in terms of expected value and economists assume that a rational decision maker would choose the option that provides the greatest expected value.

The decision models are being used increasingly to address clinical issues in health policy planning, to develop computer algorithms for clinical information and decision-support systems, to evaluate clinical pathways, to establish practice guidelines or utilization review criteria, and to conduct epidemiologic research (Tom and Schulman, 1997; Drummond et al. 2005). As a set of methods, decision analysis satisfies almost all the important objectives of any economic evaluation and it has been widely used outside health care e.g. in business and engineering (Drummond et al. 2005). The key elements to decision analysis are probabilities and expected values.

3.4.1 The role of decision analytic models for economic evaluation

Decision analysis has a controversial role in economic evaluation in health care (Buxton et al. 1997). They complement the randomized controlled trials and are used in each and every stage of economic evaluation (Drummond et al. 2005; Briggs et al. 2007). Health care evaluation in general and economic evaluation in particular involves measurement and decision-making (Drummond et al. 2005). And decision analysis is used in synthesizing of the measured data.

The following are requirements for an economic evaluation: need for comparison of all relevant options, need to reflect all appropriate evidence, need to link intermediate to final endpoints, need to extrapolate over the appropriate time horizon of the evaluation, need to make results applicable to the decision-making context (Drummond et al. 2005). Decision modelling is used in all these conditions (Drummond et al. 2005). The structure of decision models can be in the form of a series of equations and schematically (Tom and Schulman, 1997; Drummond et al.

2005). The two model structures that predominate in the economic evaluation literature are decision trees and Markov models (Tom and Schulman, 1997; Briggs et al. 2007; Drummond et al. 2005).

3.4.2 The decision tree

This is probably the most common structure for decision model in economic evaluation. It represents individual's possible prognosis following some sort of intervention by a series of pathways. Decision trees provide a simple visual tool for the clinician and health care professionals to identify treatment options and the expected risks, costs, and benefits of these options for the patient (Tom and Schulman, 1997). It therefore permits the health care problem to be separated in discrete, manageable units. The overall structure of the problem forms the central portion of the decision tree, which includes: decision nodes, chance nodes, branch probabilities, pathways and expected values (Beck and Pauker, 1983; Drummond et al. 2005).

The decision analytic formalization works well for problems involving chance events that occur once over a short time horizon with a limited number of "downstream" chance and decision nodes (Beck and Pauker, 1983; Tom and Schulman, 1997). When the natural history of disease involves either events that occur repeatedly or over prolonged time, the decision tree becomes "bushy" and the approach becomes cumbersome (Beck and Pauker, 1983; Tom and Schulman, 1997; Briggs and Sculpher, 1998; Drummond et al. 2005; Brazier et al. 2007; Sun and Faunce, 2007). The utility structure also becomes unmanageable because utility must depend on when each good and each deleterious clinical event occurs (Beck and Pauker, 1983).

Decision trees often underlie many of the models used to evaluate medical technologies, therapeutic and diagnostic procedures, pharmaceutical products, and disease management techniques. However, there are several limitations of using simple decision trees in economic evaluations including the assumption that events occur over an instantaneous discrete period and there is no time variable in a decision tree. Decision trees would therefore be very complicated when used to model treatment for patients with chronic diseases that experiences given events more than

once (Lang et al. 2003; Drummond et al. 2005; Briggs et al. 2007). In addition, the decision trees are not able to specify when a given event occurs.

3.4.3 The Markov decision analysis model

The Markov process is a special case of a more general category of processes called stochastic processes (Mullins and Weisman, 1996). Markov models are often employed to represent stochastic and dynamic processes, that is, random processes that evolve over time (Sonnenberg, 1993; Briggs and Sculpher, 1998; Hunink et.al., 2001; Schaefer et al. 2003; Sun and Faunce 2007).

Markov models have a long history of use in health service decision-making, including clinical and epidemiological applications, however, health economists are also beginning to use Markov models widely in economic-evaluation studies (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Buxton, Drummond, & van Hout B.A., 1997; Briggs and Sculpher, 1998). These models are more appealing to use due to their simplicity, computational ease, accuracy and broad applicability in presentation of clinical problems (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Tom and Schulman, 1997). These models use a dynamic programming technique that doesn't restrict their analysis to continuous differentiable decision variables like calculus-based techniques (Mullins and Weisman, 1996). Markov models have traditionally been used to evaluate the cost-effectiveness of competing health care technologies that require the description of patient pathways over extended time horizons, (Karnon, 2003).

These models are most powerful when a decision problem involves risk that is continuous over time, when the timing of events is important and when events may happen more than once (Sonnenberg and Beck, 1993; Hunink and Glasziou, 2001; Gray et. al, 2011). Representing such clinical settings with conventional decision trees is difficult as the tree will be too "bushy" and may require unrealistic simplifying assumptions (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Tom and Schulman, 1997; Briggs and Sculpher, 1998; Drummond et al. 2005). Hence, in a healthcare context, Markov decision models are particularly suited to modelling the progression of chronic disease or situations where events are likely to recur over time

(Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Drummond et al. 2005; Brazier et al. 2007; Sun and Faunce, 2007). As such Markov models incorporate a multi-stage decision process (Mullins and Weisman, 1996).

Markov decision model is an alternative to standard decision-analytic formulation and addresses the limitations of decision trees hence widely used in economic evaluations (Beck and Pauker, 1983; Tom and Schulman, 1997; Drummond et al. 2005; Sun and Faunce, 2007; Schaefer et al. 2003). These models can replace the decision tree completely or can be grafted onto standard decision analysis as an equivalent to the utility structure (Beck and Pauker, 1983).

Whereas the decision trees characterize possible prognosis in terms of alternative brunches, Markov models are based on a series of states that a patient occupies at a given point in time (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Drummond et al. 2005). The model assumes that the patient is always in one of a finite number of states of health referred to as Markov states (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Tom and Schulman, 1997; Briggs and Sculpher, 1998; Hunink et. al., 2001; Drummond et al. 2005; Brazier et al. 2007; Sun and Faunce, 2007). In each case, the states are defined with reference to clinical characteristics such as stages of disease severity, HIV and AIDs clinical stages etc. and economically important events that occur to patients over time (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Deltour, et. al. 1999; Drummond et al. 2005; Brazier et al. 2007; Sun and Faunce, 2007). The states are mutually exclusive and a patient is assumed to be in a single state during a cycle.

The probability of a patient occupying a given state expressed over a series of discrete time periods is called Markov cycles (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Drummond et al. 2005; Sun and Faunce, 2007). The cycle length is chosen to represent a clinically meaningful time interval and varies depending on the disease and the intervention being evaluated, it may be one week, one month, one year etc. (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Drummond et al. 2005).

All events are represented as transitions from one state to another (Sonnenberg and Beck, 1993; Hunink et. al., 2001). The likelihood of moving from one health state to another is called a transition probability (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Hunink et. al., 2001). Transitions are assumed to take place for each cycle of the model. The transition probabilities may be constant or vary within a model (Beck and Pauker, 1983; Briggs and Pauker, 1993; Tom and Schulman, 1997; Lang et al, 2003).

The Markov process is completely defined by the probability distribution among the starting states and the probabilities for the individual allowed transitions (Sonnenberg and Beck, 1993). In a model comprising k states, all possible transitions between those states will be k^2. If these probabilities are constant over time, they can be represented by a $k \times k$ transition matrix; however, probabilities representing disallowed transitions will be zero hence, reducing the number of transition probabilities to be estimated (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998). These probabilities are calculated from transition rates – i.e. the number of occurrences of an event for a given number of patients per unit of time.

States of Markov models from which it is impossible to leave are known as 'absorbing states'; the most common example of an absorbing state in medical decision-making is death (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Drummond et al. 2005; Sun and Faunce, 2007). In addition to transition and absorbing states, Markov models have two other less applied but useful states: temporary and tunnel states (Sun and Faunce, 2007).

The major difference between economic and other applications of Markov modelling in medical decision-making is that economists are interested in both the resource and health outcome consequences of healthcare interventions (Briggs and Sculpher, 1998). Markov models provide a way of handling both costs and outcomes simultaneously in a simple and intuitive manner.

A Markov model may be evaluated using matrix algebra, as a cohort simulation, or as a Monte Carlo simulation (Beck and Pauker, 1983; Sonnenberg and Beck, 1993;

Briggs and Sculpher, 1998). Another representation of Markov models, the Markov-cycle tree, uses a tree representation of clinical events and may be evaluated either as a cohort simulation or as a Monte Carlo simulation (Sonnenberg and Beck, 1993).

3.4.3.1 The Markovian Property

The choice of a Markov model implies two overall assumptions. First, is the called Markov property and second, is the stationarity assumption. The first assumption states the Markov models have no intrinsic property to memorize the history of the previous events to determine transitions and therefore, the probability of moving out of a state is not dependent on the states a patient may have experienced before entering that state (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Drummond et al. 2005; Sun and Faunce, 2007). This is the 'memoryless' feature of Markov models, which is often referred to as the 'Markovian assumption' (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Drummond et al. 2005; Sun and Faunce, 2007). This implies that individuals starting in a given state can be modelled in the same manner and that the route to arriving in a state or the time spent in a state has no influence on subsequent parameters. The Markovian assumption is not followed strictly in medical problems (Sonnenberg and Beck, 1993). It may be possible to address it by characterizing the progressive part of the disease as tunnel states and use time dependent probabilities (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Drummond et al. 2005; Sun and Faunce, 2007). The stationarity assumption states that parameters are time homogeneous and do not vary from one cycle to another.

3.4.3.2 Attaching Weights to the Markov Model

In economic evaluation, utilities and costs are attached separately to the model and each state in the model has a cost associated with it and for cost-utility analysis, a utility value (Drummond et al. 2005; Sun and Faunce, 2007). The time duration over which the average patient occupies the various states in the model is normally weighted by relevant costs or utility and used to calculate expected costs and outcomes (Beck and Pauker, 1983; Drummond et al. 2005). By running the model over a large number of cycles, it is possible to estimate the long-term costs and

outcomes associated with a disease and a particular healthcare intervention (Beck and Pauker, 1983; Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998).

3.4.3.3 Types of Markov Processes

Markov processes are categorized according to whether the state-transition probabilities are constant over time or not (Beck and Pauker, 1983; Briggs and Pauker, 1993; Sonnenberg and Beck, 1993; Drummond et al. 2005; Briggs et al. 2007; Sun and Faunce, 2007). The first category is the most general type of Markov processes in which transition probabilities are time-dependent whereas the second is Markov chains in which the state transition probabilities are constant (Beck and Pauker, 1983; Briggs and Pauker, 1993; Sonnenberg and Beck, 1993; Drummond et al. 2005; Briggs et al. 2007; Sun and Faunce, 2007). The Markov chains are a subset of the more general Markov processes (Beck and Pauker, 1983; Briggs and Pauker, 1993). The Markov Chains are easier to use compared to Markov process; however, the latter is more flexible with regard to modelling chronic diseases (Beck and Pauker, 1983; Briggs and Pauker, 1993; Drummond et al. 2005; Briggs et al. 2007; Sun and Faunce, 2007).

3.5 Adjustments to the Cost and Outcome Quantities

There are two types of adjustments to costs and outcomes that analysts frequently consider when constructing a Markov model. The first involves discounting adjustments for differential timing and the second is the principle of half-cycle correction (Briggs and Sculpher, 1998).

3.5.1 Discounting

It is standard practice in economic evaluation to adjust costs and outcomes for differential timing correction by applying a rate of discount which allows comparison of costs and outcomes in terms of a net present value (NPV) (Briggs and Sculpher, 1998). This is based on the fact that costs or benefits occurring immediately are valued more highly than those occurring in the future (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998). The standard discounting formula is given by:

$$v_0 = \frac{v_t}{(1+r)^t}$$

where v_0 is the equivalent current value at time zero (or NPV), v_0 is the value at time *t* and *r* is the rate of discount (Briggs and Sculpher, 1998; Drummond et al. 2005). The discount rate can either be based on the rate of risk free investment such as government bonds, rate used by Finance Ministry of a given country or rates based on economic guidelines like 3% or 5% (Drummond et al. 2005). For this study the discount rate used was 10% per annum based on real interest rates of the government bonds.

3.5.2 The Half-Cycle Corrections

In the Markov modelling, we assume that transition can only occur once in each cycle and the transition from state to state is instantaneous. However, in reality, transitions occur continuously throughout each cycle and patients move between the different phases of their disease continuously, not at discrete points in time (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998). Therefore, assuming that patients move between states at the beginning or the end of a cycle will lead to errors (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Hunink et. al., 2001).

To more accurately reflect the continuous nature of the state transitions, a half-cycle correction is employed, which is equivalent to an assumption that, state transitions occur, on average, halfway through each cycle (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998). Such half-cycle corrections will be most important for the health outcome predictions of the model, particularly life expectancy, since without a half-cycle correction Markov models will either consistently overestimate or underestimate life expectancy (Briggs and Sculpher, 1998). TreeAge Software Data Pro was used for half cycle correction.

3.5.3 Use of Markov model in medical decision-making

Markov models yield risk and quality adjusted life expectancies. The Markov process can be the entire analysis or may provide utilities for "tree-based" clinical analyses (Beck and Pauker, 1983). The choice between a Markov analysis, a standard decision tree and a combined analysis is made on the basis of ease of representation and requirement for relevant sensitivity analysis (Beck and Pauker, 1983).

4 CHAPTER FOUR: EMPIRICAL LITERATURE REVIEW

In a study to assess the cost-effectiveness of ART for routine clinical practice in a district hospital setting in Ethiopia, Bikilla et al. (2009) used Markov model to estimate the lifetime costs, health benefits and cost-effectiveness of ART. The unit cost, HIV-related health care service utilization and health effects were estimated and compared for HIV infected patients on ART and those not on ART using a health care provider perspective. The health effect was measured in terms of life years gained (LYG).

Bikilla et al. (2009) found that ART yielded an undiscounted 9.4 years expected survival, and resulted in 7.1 extra LYG compared to patients not receiving ART. The lifetime incremental cost was US$2,215 and the undiscounted incremental cost per LYG was US$314. In addition, the undiscounted and discounted incremental costs per LYG from introducing ART were less than the per capita GDP threshold at the base year. Thus, ART could be regarded as cost-effective in a district hospital setting in Ethiopia.

Bachmann (2008) compared the effectiveness and cost effectiveness of different treatment options for South African adults, using a Markov Monte Carlo simulation model. This study was based on published estimates of disease progression, treatment effectiveness and health care costs. The outcome measure was QALY and both the cost and health outcome values were discounted. Bachman used acceptability curves to summarize uncertainties and sensitivity analysis was also carried out. This study showed that triple ARV plus antibiotics would prolong life by 6.7 undiscounted years if provided 'late' (i.e. CD4=200 cells/ml) and by 9.8 years if provided 'early' (CD4=350 cells/ml). The incremental undiscounted costs per year of life gained, compared to no preventive therapy, were $17 for isoniazid plus cotrimoxazole started late, $244 for both antibiotics started early, $2454 for ARV plus antibiotics started late and $2784 for ARV plus both antibiotics started early.

The discounted incremental costs per QALY gained were, respectively, $29 saving, $254, $4937 and $3057. His conclusion was that late ARV plus both antibiotics was

the strategy most likely to be cost effective if society was willing to pay more than $2000 per life year gained.

Hogan et al. (2008) assessed the costs and health effects of a range of interventions for preventing the spread of HIV and for treating people with HIV/AIDS in the context of the millennium development goal for combating HIV/AIDS. The study was undertaken using cost effectiveness analysis based on an epidemiological model for countries in SSA and in South East Asia with very high adult and child mortality. Hogan et al. found that a reduction of HIV transmission could be achieved most efficiently through mass media campaigns, interventions for sex workers and treatment of sexually transmitted infections. In addition, pMTCT, VCT, and school based education were also found to be highly cost effective based on standard international benchmarks. They concluded that antiretroviral therapy was at least as cost-effective in improving population health as some of the interventions studied.

Vijayaraghavan et al. (2007) developed lifetime Markov model incorporating costs, quality of life, survival, and transmission through sexual contacts to determine the cost-effectiveness of initiating and monitoring highly active antiretroviral therapy (HAART) in developing countries. Incorporating transmission to partners (excluding indirect costs) and treating patients according to developed versus developing world guidelines increased costs and life expectancy by US $11,867 and 3 QALYs respectively giving an incremental cost-effectiveness of $3956 per QALY. When the indirect costs were included over the duration of the model, there were net cost savings to the economy of $39.4 billion. The increase in direct medical costs of $60.5 billion was offset by indirect cost savings of $99.9 billion. This study concluded that, treating patients with HIV according to developed versus developing world guidelines is highly cost-effective and may result in substantial long-term savings.

Hubben et al. (2007) compared the lifetime costs and effects of two theoretical groups of 1000 HIV infected patients that were not ARVs naïve in the Netherlands. One group was receiving a standard of care regimen with ritonavir-boosted tipranavir (TPV/r) and the other receiving a standard of care comparator protease inhibitor regimen boosted with ritonavir (CPI/r). This study used a 3-stage Markov model with 12 health states to simulate HIV disease progression. The cost and health effects were

discounted at varying rates and the analysis conducted from the Dutch healthcare perspective using 2006 unit cost prices.

An accumulated discounted cost to the Dutch healthcare system was €167,200 and €145,400 per patient receiving the TPV/r and CPI/r regimens respectively, hence an incremental cost of €21,800 per patient. In addition, the accumulated discounted effect was 7.43 life years (6.31 QALYs) and 6.91 life years (5.80 QALYs) per patient receiving TPV/r and CPI/r respectively. The corresponding iCERs were €41,600 per LYG and €42,500 per QALY. Hubben et al. estimated the iCER for TPV/r compared to CPI/r at approximately €40,000 in treatment experienced HIV-1 infected patients in the Netherlands. This iCER was within the threshold therefore, TPV/r regimen cost effective.

Cleary et al. (2006) analyzed the cost-effectiveness of antiretroviral treatment in Khayelitsha, South Africa using primary. They used Markov modelling process to estimate HIV healthcare utilization, unit costs of HIV services, cost per life year (LY) and quality adjusted life year (QALY) gained of HIV treatment interventions from a provider's perspective. Data on healthcare utilization was estimated from 1,729 patients in the Khayelitsha cohort (1,146 No-ART patient-years, 2,229 ART patient-years) using a before and after study design. Probabilistic sensitivity analysis was used to assess uncertainty. The discounted lifetime costs for No-ART and ART were US$2,743 and US$9,435 over 2 and 8 QALYs respectively. The incremental cost-effectiveness ratio (ICER) through the use of ART versus No-ART was US$1,102 (95% CI 1,043-1,210) per QALY and US$984 (95% CI 913-1,078) per life year gained.

This study enhanced the standard Markov modelling approaches by use of tunnels states to capture the rapidly diminishing utilization and mortality through the first years on ART, used transition costs to capture the cost of in-patient care which was incurred during patients' transition from a Markov state to death. The multi-way sensitivity analysis, used also revealed that the main findings on the ICER were robust when the assumptions were simultaneously varied.

In a study to assess the cost-effectiveness of HIV treatment in resource-poor settings, Goldie et al. (2006) used a computer-based simulation model that incorporated the CD4 cell count and HIV RNA level as predictors of disease progression and compared the long-term clinical and economic outcomes associated with no treatment, trimethoprim-sulfamethoxazole prophylaxis alone, ART alone, and prophylaxis with ART. Goldie et al. found that strategies involving both ART and trimethoprim–sulfamethoxazole prophylaxis were consistently more effective and more cost-effective than those involving ART alone. In addition, strategies based on CD4 measurements and clinical criteria for initiating and discontinuing ART were always more effective than strategies based on clinical criteria alone. Hence, strategies of prophylaxis and ART, with the use of clinical criteria alone or in combination with CD4 testing to guide the timing of treatment, were economically attractive health investment in settings with limited resources.

Cleary et al. (2004) used both cost-utility Analysis (CUA) and CEA to establish the costs and effectiveness of ART for HIV positive adults in a resource-constrained public-sector setting. This study also used a Markov process to model and compare the healthcare benefits and the costs of HIV-positive adults receiving ART relative to the same outcomes when patients alternatively receive treatment for opportunistic and HIV-related infections in the absence of ART: the study, data and patients outcomes were based on the three HIV-dedicated clinics in Cape Town in South Africa. They noted that ARVs drugs accounted for 50% of the lifetime costs of the ART option. Patients reported higher Health Related Quality of Life (HRQoL) on ART than off ART. This study concluded that ART was efficient in economic terms, and ought to be pursued if economically feasible and desirable to society.

A study on cost-effectiveness of HAART in South Africa by Badri et al. (2006) calculated the use and cost of services for 265 HIV-infected adults without AIDS (WHO stage 1, 2, or 3) and 27 with AIDS (WHO stage 4) receiving HAART between 1995 and 2000 in Cape Town and compared with HIV-infected controls matched for baseline WHO stage, CD4 count, age, and socioeconomic status, who did not receive antiretroviral therapy (ART; No-ART group). The clinical outcome, was estimated in terms of disease progression or life year gained (LYG) by clinical stage of HIV infection, between ART and no-ART groups of patients.

Costs of service provision included local unit costs, and two scenarios for HAART prices for WHO recommended first-line regimens: scenario 1 used current South African public-sector ART drug prices of $730 per patient-year (PPY), whereas scenario 2 was based on the anticipated public-sector price for locally manufactured drug of $181 PPY. These were calculated from a public health-care system perspective.

The study findings showed that, for patients without AIDS, the mean number of inpatient days PPY was 1.08 (95% CI: 0.97–1.19) for the HAART group versus 3.73 (95% CI: 3.55–3.97) for the No-ART group, and 8.71 (95% CI: 8.40–9.03) versus 4.35 (95% CI: 4.12–5.61), respectively, for mean number of outpatient visits PPY. Average service provision PPY was $950 for the No-ART group versus $1,342 and $793 PPY for the HAART group for scenario 1 and 2, respectively, whereas the incremental cost per life-year gained (LYG) was $1,622 for scenario 1 and $675 for scenario 2. For patients with AIDS, mean inpatients days PPY was 2.04 (95% CI: 1.63–2.52) for the HAART versus 15.36 (95% CI: 13.97–16.85) for the No-ART group. Mean outpatient visits PPY was 7.62 (95% CI: 6.81–8.49) compared with 6.60 (95% CI: 5.69–7.62) respectively. Average service provision PPY was $3,520 for the No-ART group versus $1,513 and $964 for the HAART group for scenario 1 and 2, respectively, whereas the incremental cost per LYG was cost saving for both scenarios

This study confirmed that the use of HAART was associated with decreased disease progression, AIDS, and death. The HAART group used fewer inpatient services than the No-ART group. The cost per LYG showed HAART to be a very cost-effective intervention. Badri et al. (2006) concluded that, HAART was a cost-effective intervention in South Africa, and cost saving when HAART prices were further reduced.

Masaki et al. (2003) used data from African countries to compare the cost-effectiveness of both HIV prevention and treatment interventions using cost per life-year saved as the outcome measure. They examined five prevention interventions: VCT, pMTCT, sexually transmitted disease (STD) mass treatment for general population, STD management for sex workers; and blood screening – and four drug

price scenarios for antiretroviral treatment for HIV+ patients. This study revealed that both the cost-effectiveness analysis and the budgetary analysis suggest that HIV prevention interventions were much more cost-effective than ARV treatment. Furthermore, both blood screening and STD control among sex workers were the most cost-effective preventative interventions. Hence HIV prevention interventions should be prioritized if poor countries hope to maximize the scarce resources available for reducing the impact of the AIDS epidemic.

In a study to determine direct medical costs, overhead costs, societal costs, and personnel requirements for the provision of antiretroviral therapy to patients with AIDS in Haiti, Koenig et al. (2008) examined data from 218 treatment-naïve adults who were consecutively initiated on ART at a centre in Port-au-Prince, Haiti between December 2003 and May 2004. The study measured service utilization and cost from the societal perspective and calculated costs and personnel requirements for the first year of ART. Koenig et al (2008). found out that the mean total cost of treatment per patient was approximately $US 1,000 per patient per year. The study further noted that for patients who were on generic first-line antiretroviral drugs, only 36% of the cost was for medications.

Freedberg et al. (2001) developed a mathematical simulation model of HIV disease to estimate the clinical benefits and cost effectiveness of three-drug antiretroviral regimens in the United States. They used the CD4 cell count and HIV RNA level as predictors of the progression of disease. While the outcome measures included life expectancy, life expectancy adjusted for the quality of life, lifetime direct medical costs, and cost effectiveness in dollars per QALY gained. The study found the initial CD4 cell count and drug costs to be the most important determinants of costs, clinical benefits, and cost effectiveness. Freedberg et al. concluded that treatment of HIV infection with a combination of three antiretroviral drugs is a cost-effective use of resources.

Cook et al. (1999) developed a Markov model to estimate the potential clinical and economic impact of antiretroviral therapy for HIV-infected patients. They used observed HIV RNA levels and CD4 cell counts to estimate the probability of disease progression and estimated the total net cost of care and long-term cost-effectiveness

of ART. Cook et al. applied the model to patients in a clinical trial (Merck protocol 035) that compared the surrogate marker response to triple therapy with indinavir (IDV) plus zidovudine (ZDV) plus lamivudine (3TC) to double therapy with ZDV + 3TC.

The model projected that for an individual without AIDS who received triple therapy the progression to AIDS and death would be delayed more than for a patient who received double therapy with ZDV+3TC if no other treatment options were offered. The total discounted cost over the initial 5-year period was projected to be $5100 lower for patients who received triple therapy compared with double therapy if suppression with triple therapy lasts up to 3 years.

Sweat et al. (2001) assessed the impact, cost, and cost-effectiveness of HIV-1 VCT for a hypothetical cohort of 10 000 people seeking VCT in urban East Africa. They modelled outcomes based on results from a randomized controlled trial of HIV-1 VCT in Tanzania and Kenya. Sweat et al. concluded that HIV-1 VCT is highly cost-effective in urban East African settings, but slightly less so than interventions such as improvement of sexually transmitted disease services and universal provision of nevirapine to pregnant women in high prevalence settings. However, with the targeting of VCT to populations with high HIV-1 prevalence and couples, the cost-effectiveness of VCT is improved significantly.

Rosen and Long (2006) provides a survey using both published and gray sources to understand the cost of providing ART in service delivery (non-research) settings in SSA. Estimates based on primary local data for input prices were used. They found 17 eligible cost estimates, of these, 10 were from South Africa. The cost per patient per year ranged from $396 to $2,761. Antiretroviral drugs comprised an average of one third of the cost of treatment in South Africa and one half to three quarters of the cost in other countries. This study concluded that there was very little empirical information available about the cost of providing antiretroviral therapy in non-research settings in Africa. Furthermore, Rosen and Long (2006) recommended that cost analysis should be a routine part of operational research on the treatment rollout in Africa.

However, in Kenya most of the studies on the effectiveness of HAART are epidemiological. Wools et al. (AIDS, 2006, 41-48) carried out an epidemiology study to determine the clinical and immunological outcomes of a cohort of HIV infected patients receiving antiretroviral therapy in Kenya. The study showed that ART treatment resulted in significant and persistent clinical and immunological benefit. Hence, viability and effectiveness of large-scale HIV treatment initiatives in resource limited settings. A study by Song et al. (2007) investigated the efficacy of antiretroviral therapy among HIV-infected children in Kenya and concluded that there was excellent efficacy among treatment-naïve-HIV-infected children in a resource-limited country. Clinical and immunologic improvement occurred in all patients.

Based on these, this thesis uses epidemiological and cost data to estimate the cost and health implications of HIV treatment with a view to provide an in depth understanding of lifetime costs and benefits of ART use and the determinants of survival for the patients on ARVs. The study reinforces the need for the government of Kenya to continue increasing access to HIV related care and treatment and also the need for planning for sustainable financing of HIV if the success gained in the treatment process is to be maintained in the long run. The study employs durational analysis to understand the survival level and rate for the patients on treatment controlling for confounding factors including education, income, sex etc. In addition the study also estimates the lifetime costs and benefits of both treatment types in the two treatment sites.

5 CHAPTER FIVE: METHODOLOGY

5.1 Study design

To achieve study objectives and test hypothesis that ART use lengthens life more than no ART use, several economic evaluation methods of measuring the costs and consequences of alternative programmes will be used. These methodologies are discussed in this section. There are four major techniques of economic evaluation namely; Cost analysis - methodology which estimates costs of, a particular type of care or a specific illness and are used primarily for budgeting and planning purposes; cost effectiveness analysis - costs and consequences of programmes are examined; cost-benefit analysis - impacts of the intervention are translated into monetary terms, in order to obtain a ratio; cost-utility analysis - impact is measured in terms of life years gained by an individual. This study will use economics costs. Markov modelling approach will be used to calculate lifetime costs, LYs, and incremental cost-effectiveness ratios (ICERs).

5.2 Costing Analysis

One of the objectives of this study was to estimate the life time cost of treatment of HIV positive patients both on ARVs and those not on ARVs. Since, costing involves identifying, measuring and valuing all resources changes that occur in a certain health care intervention (Brouwer, et. al. 2001), it was important to collect data and value all the resources that were used in the care and treatment of these patients.

The individual patient cost data was collected for an average period of two years while the survival data was collected for the entire period of follow up of each patient that is from the time of initial hospital visit to either the time the patient was lost to follow up, died or was censored at the time of our data collection.

In costing the outpatient and inpatient services we employed both micro-costing and gross-costing methods. Micro-costing entails the determination of a production function with all the arguments of the function identified, measured and valued while in gross-costing the production function is estimated on a more general cost items

such as hospital days or doctors' visits, that is the composite intermediate products are valued without being broken down further into their underlying components.

5.2.1 Capital Costs

In costing furniture, medical and electronic equipment, staff training, vehicles and HIV Clinic building, we computed the equivalent annual costs (EAC) based of WHO regional recommendations. This is the best economic costing method for capital goods since it embodies both the opportunity cost and depreciation (Drummond, et al, 2005). To calculate the annual economic cost, we used the 2005 replacement values (WHO website) and annuitized using the real interest rate in 2010. This was divided by the average number of visits to get a capital cost per visit.

5.3 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is one form of full economic evaluation where both costs and consequences of health programmes or treatment are examined (Drummond, 2005). CEA determines a cost/effectiveness ratio. The numerator, depending on the study and on the viewpoint taken, may be total cost, net health care cost or net economic cost to society. The denominator is the measure of health effect most relevant to the program under study (Torrance, 1986). Thus, the results of a CEA are expressed in terms such as shillings per case of disease prevented, or shillings per life saved, or shillings per life-year gained.

CEA is useful in comparing alternative programmes whose effects are measured in the same units. However, CEA is not very helpful in assessing a single program, because there is nothing to which one can compare the C/E ratio. Moreover, CEA cannot be used to compare disparate alternatives, since the denominators of the C/E ratios will be in different units (Drummond, 2005). CEA/CUA addresses mainly questions of production efficiency with outcomes restricted to health benefits (Drummond, 2005). CEA/CUA is more narrowly client focused (Drummond, 2005). Finally, CEA is not suited to the analysis of programmes that have several types of clinical effects - for example, reductions in both morbidity and mortality.

CEA was not related initially to a welfare theory (Gafni, 2006). It was presented as a solution to an optimization problem. ‘‘The underlying premise of cost–effectiveness

analysis in health problems is that for any given level of resources available, society (or the decision-making jurisdiction involved), wishes to maximize the total aggregate health benefit conferred'' (Weinstein and Stason, 1977). There were several attempts to ground the methodology of CEA of medical interventions in economic welfare theory or the welfarist approach (e.g., Garber et al. 1996; Garber and Phelps, 1997; Meltzer, 1997).

5.4 Cost benefit analysis

Cost-benefit analysis (CBA) determines the net social benefit (NSB) of the programme. The CBA decision rule is straightforward, if NSB>O, the project is cost-beneficial and it should be implemented (Torrance, 1986; Drummond, 2005). CBA holds significant conceptual appeal for economists because of its theoretical foundation in welfare economics, specifically the Kaldor–Hicks criterion as a hypothetical compensation test between the value of utility gains (to gainers) from a programme compared to the utility losses (to losers) (Gafni, 2006).

CBA overcomes the disadvantages of CEA; a decision can be made on a single programme, and disparate effects in the same or different programmes can be compared (Torrance, 1986; Gafni, 2006; Drummond, 2005). CBA is broader in perspective and able to inform questions of allocative efficiency and using techniques of willingness to pay (WTP), the CBA framework can quantify a broad range of effects (Drummond, 2005). However, the major issue for health care CBA is the evaluation of health care outcomes in money (Drummond, 2005).

5.5 Cost-utility analysis

Cost-utility analysis (CUA) is a special form of cost-effectiveness analysis in which the measure of effect is quality-adjusted life-years (QALY's) gained (Torrance, 1986). The advantage of CUA over CEA is that it uses a common unit of measure, QALY'S gained, for all programmes and thus allows comparisons across all programmes. However, CUA is more compatible with the decision making style of planners and managers in the health care field (Drummond, 2006; Torrance, 1986). Moreover, CUA explicitly incorporates the quality and quantity of life associated with the health outcomes.

This study undertook cost-effectiveness analysis from a providers' perspective. Cost-utility analysis takes both the quantity and quality of life of patients into account and its outcome measure will be cost per life year gained. The cost-effectiveness analysis result will be expressed as costs per life year gained (LY). The cost-effectiveness analysis is an important tool in the priority setting process of strategic planning. CEA is one of a number of economic evaluation tools used to measure efficiency of service delivery. Here, efficiency implies that a given output is achieved at least cost or that the output is maximized at a given cost.

5.6 Markov Model Conceptual Framework

The objective of this study is to estimate lifetime costs and benefits of ART and no ART use. Since, ART treatment has only been used in Kenya for around ten years, the data available is not adequate for lifetime analysis and at the same time both the consumers of treatment and the providers need to understand the implication of ART and no ART use. It's therefore impossible to wait for all the patients on treatment follow up to die so as to use real data to estimate the life time gains and costs. The study therefore used the Markov modelling methodology to project the data up to a time when all the patients on treatment were expected to have died. In addition, the Markov modelling also allowed the integration of clinical inputs and costs into a logical framework, which permitted the projection of lifetime costs and benefits.

Table 9: Multi-state transition Matrix

Current period	**Next Period**		
	$\boldsymbol{CD4 < 51}$	$\boldsymbol{51 \leq CD4 \leq 250}$	**Death**
$\boldsymbol{CD4 < 51}$	$p_{11}(t)$	$p_{12}(t)$	$p_{13}(t)$
$\boldsymbol{51 \leq CD4 \leq 250}$	$p_{21}(t)$	$p_{22}(t)$	$p_{23}(t)$
Death	*0*	*0*	*1*

Table 9 provides an illustrative model where we have three states resulting into nine transitions. The row $(p_{i1}, p_{i2}, \ldots \ldots p_{ik})$ represents all the transitional probabilities out of state *i.* Hence probabilities in the row must sum to 1. Given that $p_{ij}(t)$ is the probability of moving from state *i* to *j,* the associated transitional intensity is given by

$$\lambda_{ij}(t) = \lim_{\Delta t \to 0} \frac{p_{ij}(t, t + \Delta t)}{\Delta t}$$

$\lambda_{ij}(t)$ is therefore the probability that a patient moves out of a particular state *i* to *j* during one standard time interval that is within a duration of 3 months in our model. Therefore, λ_i is a three months progression rates i.e. the probability that over the course of 3 months, the patient exits state *i* by the end of 3 months. As shown in Table 10 the transitional probability of remaining in the initial state at the beginning of a cycle is given by one minus the probabilities of leaving the state.

Table 10: Multi-state transition Matrix

Current period	**Next Period**		
	$\boldsymbol{CD4 < 51}$	$\boldsymbol{51 \leq CD4 \leq 250}$	**Death**
$\boldsymbol{CD4 < 51}$	*1-(tpA+tpB)*	*tpA*	*tpB*
$\boldsymbol{51 \leq CD4 \leq 250}$	*tpC*	*1-(tpC+tpD)*	*tpD*
Death	*0*	*0*	*1*

tp = transition probability

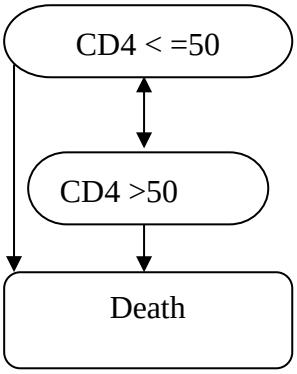


Figure 1: Health states (ovals) and transition probabilities (arrows) contained in the Markov model (arrows indicate direction of potential transitions).

To achieve our objectives, two separate three-stage probabilistic conceptual frameworks were developed for each of the two hospitals. The basic model structure for the two treatment centres has two arms one for ART use and another for no ART use. Although the MDH and AMPATH conceptual frameworks have two arms each, the transitional probabilities, costs and survival length varies. See Appendix 2 for the full Markov conceptual framework used in this study. In addition, the transitional probabilities in this study are a function of time and hence vary over the follow up period. These models consist of three mutually exclusive Markov states in which the health outcomes and associated costs of healthcare are similar:

(a) CD4 <51 cells/µl

(b) $CD4 \geq 51$ cells/µl

(c) Death - the absorbing state

The model has been developed so that one cycle of the model represents 3 months to coincide with important clinical events and costs changes. This cycle is subject to change based on the epidemiological data and clinical findings in the field. This is mainly because on average, patients on treatment follow up are ask to visit the hospital on a three monthly period to up their medication. However, the patients may report back to hospital earlier than three months if they are unwell or develop a complication. At the same time the patients may report back to hospital later than three months if they've defaulted. These clinical data was also used to determine the probability of PLWHIV on ARV drugs changing their treatment regimen from first line to second line regimen, adherence and probabilities of discontinuing ART treatment.

5.7 Data

This study used both primary and secondary data. The individual patient cost data was collected from the electronic medical records and the patient charts. A total of 750 patients were randomly sampled and their data collected. The outpatient follow up data was collected from 300 and 400 patients from MDH and AMPATH MTRH module respectively for HIV positive patients on treatment follow up including patients on ART and those not on ART. While the inpatient data was collected from 50 patients from MDH, however, to estimate the transitional probabilities using the Dirichlet distribution, 5000 patient counts were used.

The inpatient data was collected from HIV positive patients who were not necessarily on treatment follow up. This is because the inpatient and outpatient record keeping was totally independent and patient identification systems totally different. Hence tracing the patients on follow up who were admitted would involve too much time and resources, therefore was beyond this study. The inpatient data was collected from only one treatment site (MDH) because most inpatient services were expected to cost the same in the two treatment sites.

The data collected included types of health care services provided, the quantities of resources used in the process of health care service provision and the cost of these resources. Number of outpatient visits per Markov cycle, laboratory tests, radiology procedures, prescriptive drugs, opportunistic infections and the drugs, psychological support, nutritional support, number of outpatient visits and treatment outcome were captured. The inpatient data collected included length of hospital stay, hotel and non-hotel components of treatment.

Data on the quantities and costs of recurrent and capital overhead goods were obtained from hospitals' supplies and purchase records, accounts and human resource departments, Kenya Medical Supplies Agency (KEMSA) and the Missions for Essential Drugs (MEDS). As recommended (Luce, et. al. 1996; Brouwer et al. 2001; Drummond, et. al. 2005), the overhead costs were allocated using the allocation method, with the floor size being the key for allocation and interviews with service providers. All costs are presented in Kenya Shillings. The service utilization and costs were estimated from the providers' perspective.

All the medicines prescribed to the individual patients were extracted from 750 patient charts and electronic medical records. The prices for medicines were sourced from the 2009 and 2010 Kenya Medical Supplies Agency (KEMSA) and Missions for Essential Drugs (MEDS) tender price lists. The medicine costs per consultation were then allocated to visits, stratified by ART and non-ART.

During this study, data was combined from several sources including the Central Bank of Kenya statistics to estimate exchange rates and discount rates, AMPATH and MDH sources, WHO website data and Demographic and Health Surveys (KDHS, 2004 and KDHS, 2009).

5.8 Site and patient selection criteria

The two sites are selected because they were the first and main treatment programmes in Kenya. At the time of data collection, MDH and AMPATH had been providing care and treatment for PLWHIV in Kenya for at least 10 and 7 years respectively. The sites meet the criteria in terms of data availability and for have been providing ARVs adult patients for at least 4years. They also have patient records computerized or well-

maintained hard copy files. On the other hand, for the patient to be included in the study they must be 18years and above at they were enrolled for treatment, must have started their ART treatment in that site and therefore must have not transferred from that site. Random sampling was used to identify eligible patients.

5.9 Perspective of the study

Even though most health economic evaluation literature (Luce, et. al. 1996; Brouwer et al. 2001; Drummond, et. al. 2005) recommend the use of societal perspective in economic evaluations in order to capture all changes in resources use regardless of whose budget is affected, and all changes in health outcome, regardless of who gains, we adopted the health providers' perspective. Due to time and other resource constraints we were unable to cost all the patients' and families' resources used in the treatment process including travel and waiting time, lost productivity due to ill health and time of care givers. The costs estimated therefore included the individual patient services like laboratory tests, drugs, health care workers costs, outpatient visits, and inpatient costs while in costing some of the radiology services like CT-scan and MRI we used the prices set by Kenya Medical Research Institute (KEMRI).

5.10 Ethical Approval

The study involved access to confidential medical records of the patients and hence received ethical approval by Moi Treatment and Referral and Moi University Ethical Committee. In addition, we also received approval from the Medical Superintendent of Mbagathi District Hospital and Ministry of Higher Education, Science and Technology.

6 CHAPTER SIX: MARKOV MODELLING RESULTS

In this section, the cost effectiveness analysis results are presented and discussed.

6.1 Costs

The US dollar denominated accounts were converted to Kenya shillings using the average interbank rate for the last 5 years that is from September 2006 to August 2011. This was to control for the high volatility of the Kenya shillings, Table 11 provides the details.

Table 11: Exchange Rates

	US$: KSh
Average (60 months)	74.85
High	92.79
Low	61.90

Author's own calculation using Data from the Central Bank of Kenya

6.1.1 Laboratory tests and imaging Services utilization and costs

In order to cost the treatment services provided to the patients, all the laboratory tests that were done for the sampled patients were valued irrespective of whether they were HIV related or not. In total 37 different types of clinical laboratory tests were done for the sampled patients during their treatment follow-up period.

The ingredients method of costing was used and all the inputs measured and valued with assistance from The University Nairobi Microbiology Unit, for each of the tests carried out, costs based on consumables, equipment, machinery, reagents, labour etc. were measured and valued. The various tests and their estimated costs are shown inTable 11. The imaging costs were based on the Kenyatta National Hospital's own patient fee. Micro-costing of these services needed more time and other resources which were beyond this study. The number of tests and imaging done per patient was collected from the patient charts.

Table 12: The Laboratory Costs/Test

Laboratory Test	Cost per test	Laboratory Test	Cost per test
CD4	770.70	FNA Lymph node	760.00
Viral load	3273.00	CSF	864.00
SGPT/ALT	223.40	Protein plasma	161.50
SGOT/AST	225.40	Albumin	146.00
Creatine	192.18	Urea	146.30
LFTS	640.98	Therapeutic Tap*	700.00
VDRL	309.30	Serum crag	864.00
FHG/ESR	300.00	Rectal swab	237.38
HIV Eliza test	260.80	U/E/C	645.38
HIV DNA	2185.35	Urinalysis	121.97
Sodium (NA+)	356.30	MCV	300.00
Potassium (K+)	238.30	PDT (Pregnancy test)	78.38
Chloride (cl)	292.30	Biopsy-histology	900.00
Electrolytes	550.00	Blood Grouping	386.03
Platelets	300.00	BS (malaria test)	197.08
AFB	450.00	Widal	192.60
Asatic Cytology + Zn stain	1,003.00	Lactic acid levels	210.40
RBS (Random blood sugar)	64.30	HBs ag	356.47
Stool o/c (microscopy)	276.37	FNA Lymph node	760.00

Note: Therapeutic tap is a procedure

In terms of demand for health care services, Tables 12 and 13 shows the service utilization of various laboratory and imaging services per cycle and their costs respectively.

Table 13: Laboratory test and imaging procedures per Markov Cycle

Test	Average tests per Markov Cycles								
	0	1	2	3	4	5	6	7	8
CD4	0.774	0.398	0.467	0.389	0.530	0.402	0.501	0.352	0.484
ALT/SGPT	0.687	0.300	0.341	0.277	0.353	0.238	0.317	0.199	0.236
FBC	0.818	0.331	0.370	0.243	0.330	0.215	0.265	0.175	0.211
AST/SGOT	0.014	0.004	0.006	0.002	0.002	0.000	0.004	0.001	0.000
Creatinine	0.774	0.398	0.467	0.389	0.530	0.402	0.501	0.352	0.484
VDRL	0.545	0.027	0.014	0.011	0.013	0.005	0.001	0.002	0.003
Viral Load	0.000	0.000	0.005	0.006	0.021	0.023	0.032	0.027	0.032
AFB	0.554	0.140	0.065	0.030	0.026	0.015	0.008	0.005	0.005
ALC	0.572	0.152	0.224	0.115	0.146	0.077	0.080	0.041	0.038
X-ray	0.260	0.027	0.017	0.010	0.008	0.007	0.002	0.001	0.000

Table 14: Laboratory and Imaging Costs and Utilization per Markov Cycle

Test		**Markov Cycles**											
		0-3 months		3-6 months		6-9 months		9-12 months		12-15months		15-18 months	
	Price	Q	Total	Q	Total	Q	Total	Q	Total	Q	Total	Q	Total
CD4	771	0.774	596	0.398	307	0.467	360	0.389	300	0.53	409	0.402	310
SGPT/ALT	223	0.687	153	0.3	231	0.341	263	0.277	214	0.353	272	0.238	183
FBC	300	0.818	245	0.331	255	0.37	285	0.243	187	0.33	254	0.215	165
SGOT/AST	225	0.014	3	0.004	3	0.006	5	0.002	2	0.002	2	0	0
Creatinine	192	0.774	149	0.398	307	0.467	360	0.389	300	0.53	409	0.402	310
VDRL	309	0.545	169	0.027	21	0.014	11	0.011	9	0.013	10	0.005	4
Viral Load	3273	0.0003	1	0	-	0.005	4	0.006	5	0.021	17	0.023	18
AFB	450	0.554	249	0.14	108	0.065	50	0.03	23	0.026	20	0.015	12
ALC	771	0.572	441	0.152	117	0.224	173	0.115	89	0.146	113	0.077	59
X-ray	500	0.26	130	0.027	21	0.017	13	0.01	8	0.008	6	0.007	6
Cost per quarter			**2136**		**1369**		**1523**		**1135**		**1510**		**1067**

Table 15 gives the ART prices that were used in costing the ARV drugs. In Table 16 the average cost of ART per patient per Markov cycle are presented.

Table 15: The ARV prices

ARV combinations	Price/ Quarter (US$)	Price/Quarter (KSh) $1=Ksh74.85	ARV combinations	Price /Quarter (US$)	Price/Quarter (KSh) $1=Ksh74.85
3TC+ABC+NVP	21.90	1,639.22	3TC+D4T+NVP	22.51	1,684.87
3TC+AZT+EFV600	64.85	4,854.02	3TC+EFV600+TDF	152.90	11,444.57
3TC+AZT+LPV/r	153.82	11,513.43	3TC+LPV/r + NVP	139.13	10,413.88
3TC+AZT+NVP	42.58	3,187.11	3TC+LPV/r+TDF	65.76	4,922.14
3TC+D4T+EFV600	47.94	3,588.31	3TC+NVP+TDF	37.78	2,827.83
3TC+D4T+LPV/r	136.91	10,247.71	ABC+DDI400+LPV/r	130.14	9,740.98
			ABC+LPV/r+TDF	219.15	16,403.38

Source: MEDS and KNASP III, 2009

Table 16: The average cost of ART per Markov cycle (KSh)

Cycles	Cost of first line ART per cycle	Cost of second line ART per cycle
0	2,298.47	9,496.39
1	2,297.08	10,593.86
2	2,453.18	10,597.46
3	2,297.92	10,601.07
4	2,297.86	10,604.67
5	2,297.80	10,608.27
6	2,338.23	10,594.78
7	2,297.80	10,594.78
8	2,297.80	10,594.78

6.1.2 Outpatient service utilization and costs

Patients initiating ARVs had an average of 4.37 visits in the first three months of treatment while those not on ARVs had 2.26 outpatient visits.Table 17 gives these averages for the first 2 years of treatment. In addition Table 18 provides the average outpatient costs per patient per visit for Mbagathi District Hospital and AMPATH treatment site.

Table 17: Average number of visits per Markov Cycle

	Patients on ARVs					Patients not on ARVs				
Cycle	**Obs**	**Mean**	**Std. Dev.**	**Min**	**Max**	**Obs**	**Mean**	**Std. Dev.**	**Min**	**Max**
0	2222	4.37	1.744	1	11	1798	2.26	1.405	1	10
1	1991	3.08	1.123	1	8	245	1.94	1.003	1	7
2	2013	2.91	1.060	1	11	159	1.96	0.977	1	5
3	2022	2.79	1.103	1	12	108	1.96	0.937	1	5
4	2048	2.74	1.078	1	8	90	1.89	0.880	1	4
5	2065	2.58	1.068	1	8	73	1.96	0.920	1	4
6	2054	2.46	1.038	1	10	58	1.91	0.864	1	4
7	2061	2.33	1.038	1	10	55	1.84	0.877	1	4
8	2090	2.26	1.030	1	7	53	1.92	0.997	1	6

Table 18: The outpatient costs for MDH and AMPATH

Average Cost per Outpatient Visit	**MDH KSh**	**AMPATH KSh**
Recurrent Expenditures		
HRH	438.45	978.69
Recurrent overhead	128.82	172.73
Supplies	26.43	39.17
IGA & OVC support		26.11
Nutritional support		1,193.48
Capital Costs		
Building, furniture & equipment*	84.98	131.14
Total	679.97	2,541.32

*Discount rate (r=10%) & varying life years for different goods obtained from WHO

6.1.3 Cost per inpatient day

The patient specific costing for health care and non-healthcare workers in the hospital was done using micro-costing for Mbagathi District Hospital. Doctors and nurses were interviewed and asked how much time they spent with each patient per day. The data for costing of healthcare workers time was based on focus group discussion involving the key informants. Two doctors, four nurses and four clinical officers were part of this group and each one of them gave an indication of how much time they spent with each patient. On average, they agreed that during the daily clinical rounds, each clinical provider spent on average 20 minutes with each patient. The rest of the day's contact time was based on severity of patient illness and recommended procedures. The remaining contact time was allocated based on the number of

personnel working in each ward per day that is over a period of 24 hours and the average occupied beds, per day.

The average occupied beds per day were 24 per ward, hence 576 inpatient hours per day. On average, there are normally seven nurses, four medical officers (two being on internship) and ten clinical officers (2 being on internship) working in each ward per day. In addition, two consultants visit the ward once a week and when there is need. On average the daily contact time per patient was ranging between 22 minutes to 27 minutes. This was used to cost the patient specific human resource for health time. The time for laboratory tests, imaging and other procedures were based on specific tests and procedures that were done for each patient.

The cost of each health personnel was based on the Government of Kenya's Ministry of Health salary scale. Due to ethical issues we were unable to get the exact income level of each employee; hence we used the lowest rate within each scale. However, we also carried out sensitivity analysis using the highest and the average incomes within each grade. Table 19 gives the details of the costs human resource for health (HRH). The laboratory and radiology employees costs already included in specific tests hence not included here. We assumed that nutritional consultation is once per admission. Table 20 shows the average number of admissions per Markov cycle.

Table 19: HRH cost per inpatient day

Employee	**KSh**
Consultant	55.21
Nurses	95.85
CO	74.42
MO	121.56
MO Intern	108.26
CO Intern	49.06
Pharmacist	55.40
Nutritionist*	4.93
Others	9.91
Total HRH cost	574.60

Source: Author's own calculations

Table 20: Average number of admissions per cycle

Markov Cycle	ART	No ART
0	0.234	0.14
1	0.018	0.05
2	0.007	0.00
3	0.002	0.01
4	0.005	0.02
5	0.002	0.03
6	0.003	0.00
7	0.001	0.02
8	0.001	0.00

The overhead costs were based on hotel costs and the costs of capital good. The patient specific costs for inpatient were only collected for HIV positive patients admitted in Mbagathi district hospital. 44% of the patients were diagnosed with TB and costing of TB medications were done and distributed to all the admission days. TB treatment accounted for 29.31% cost of medication per inpatient day. As shown in Table 21 the total cost per inpatient day was estimated at KSh1,691.

Table 21: Patient specific cost per inpatient day

Item	Inpatient cost/day
Personnel (HRH)	575
Hotel costs	374
Recurrent overhead	309
Medication	157
Laboratory tests	126
Imaging procedures	85
Capital Costs	18
Counselling	13
Consumables	33
Total	**1,691**

The transition costs were calculated based on the data of on-going inpatient days adopted from Clearly et al 2004. This was due to difficulty in estimating transitions probability given the data constraints. These cost estimates are presented in Table 22. The costs of food items provided by AMPATH treatment centre to the eligible PLWHIV households are presented in Table 21.

Table 22: Transition costs and on-going hospitalisation costs in Markov states

Markov State	On-going Inpatient days		Inpatient days prior to death	
	No./cycle	cost/cycle	No./cycle	cost/cycle
No ART, CD4 < 50, all quarters	0.66	1,116	7.13	12,053
No ART, CD4 50-199, all quarters	0.46	778	5.28	8,926
0 - 3 months on ART, CD4 < 50	0.52	879	4	6,762
3 - 6 months on ART, CD4 < 50	0.44	744	4	6,762
0 - 3 months on ART, CD4 50 - 199	0.19	321	4	6,762
3 - 6 months on ART, CD4 50 - 199	0.09	152	4	6,762
6 - 12 months on ART	0.28	473	4	6,762
Beyond 12 months on ART	0.11	186	3/4 @ 4.00, 1/4 @ 7.13	8,085

Source: Number of inpatient days per cycle (Cleary et. al. 2004) and costs are author's own calculation

Table 23: Cost of food support per person per cycle

	Quantity Per Visit	**Quantity Per Cycle**	**Cost per Kg**	**Total Cost**	**Percentage Costs (%)**
Maize	6.00	18.00	21.07	379.20	16.52
Beans	1.80	5.40	60.17	324.94	14.16
Cooking oil	0.45	1.35	200.00	270.00	11.76
Corn soy blend (CSB)	9.00	27.00	85.00	2,295.00	100.00

Source: Kenya National Bureau of Statistics, 2011

6.2 Distributions of resource costs and effects

An empirical examination showed that the sample distribution of the cost data was positively skewed and the uncerainity of these data was modelled using a Gamma distribution (Gray et. al., 2011). We applied the method of moments to obtain the mean (α) and the variance (β) parameters for the gamma distributions (Gray et. al., 2011). The transitional probabilities with more that two tree branches were represented with the Dirichlet distribution (Briggs et. al., 2003). In addition the transitional probability for patients with between zero and fifty CD4 counts and are not on ARVs were represented as beta distribution. The mean of some of the costs used and their distribution parameters are presented in

Table 24: Means and standard errors of input costs per quarter and their associated distribution parameters

Mbagathi District Hospital				
	ART Scenario		**No ART Scenario**	
Resource Item	***Mean (SE)***	***Distribution parameters***	***Mean (SE)***	***Distribution parameters***
Prescriptive drugs	126.99 (18)	Gamma(49.78,0.392)	109.93 (27)	Gamma(16.60,0.151)
Laboratory & Imaging	1343.04 (121)	Gamma(123.56,0.092)	785.47 (11)	Gamma(50.27,0.064)
Overhead	1840.77 (137)	Gamma(180.58,0.098)	1272.57 (26)	Gamma(2395.46,1.882)
AMPATH				
	ART Scenario		**No ART Scenario**	
Resource Item	***Mean (SE)***	***Distribution parameters***	***Mean (SE)***	***Distribution parameters***
Prescriptive drugs	127.07 (24)	Gamma(153.76,1.21)	111.69 (10)	Gamma(21.78,0.195)
Laboratory & Imaging	1344.50 (11)	Gamma(123.56,0.092)	779.53 (121)	Gamma(49.89,0.064)
Overhead	2591.58 (53)	Gamma(179.08,0.048)	2591.58 (280)	Gamma(2390.73,0.923)

6.3 The Cost effectiveness analysis results

In order to complete the Markov model, weights were attached to the model for the cost and health outcome quantities that were estimated. To estimate life expectancy, a weight of 1 was attached to each state of the model in which the patient is alive and a weight of 0 was attached to the dead state. Running the model over a total of 25 cycles and summing the weights across these cycles gave an estimate of the average life expectancy of the patient in terms of the model cycle length. This can then was multiplied by the length of the cycle in years to give life expectancy in years. The results for Markov modelling of cost effectiveness analysis are given below.

6.3.1 The cost effectiveness results

The lifetime costs and benefits of putting HIV positive patients on ARV treatment and no ARV treatment in the two treatment sites are shown in Tables 24 and 25. The undiscounted lifetime costs for the No-ART scenario in Mbagathi District Hospital (MDH) and AMPATH were, KSh169,123 ($2,260) and KSh184,415 ($2,464) respectively, while the undiscounted life years gained for both the treatment sites was 2.68 years. However, for the ART Scenario, the total undiscounted lifetime costs of

treating HIV patients on follow up in MDH and AMPATH were KSh932,071 ($1,245) and KSh1,608,496 ($21,490) respectively. The undiscounted lifetime benefits were 15.85 and 25.56 years for MDH and AMPATH respectively.

The cost effectiveness analysis showed that putting patients on ART is both more costly and more effective compared to treating patients without ART. ART prolonged the life of patients in MDH and AMPATH by an average 13.3 and 23 years with an additional lifetime costs of KSh762,948 ($10193) and KSh1,424,081 ($19,026), respectively resulting to undiscounted incremental cost effectiveness ratio (ICER) of KSh57,405 ($767) and KSh61,911 ($827) per life year gained (LYG) for MDH and AMPATH respectively. However, it is important to note that the impact of nutritional and income generating support received by the patients followed up in AMPATH has not been controlled for and hence could account for the significant variation in expected life years of ART patients followed up in the two treatment sites. The ICER represents the additional costs needed over the cost of No-ART to extend the life expectancy by one more year.

The Markov model also predicted that when both the lifetime costs and life effects for No ART Scenario were discounted at a rate of 10%, the average life years gained for patients followed up in MDH and AMPATH sites decreased to 2.1 years and costs decreased to KSh153,807 ($2,055) and KSh166,377 ($2,223) respectively. In addition, the lifetime discounted cost of initiating ARV in MDH and AMPATH decreased to KSh423,959 ($5,664) and KSh563,647 ($7,530) respectively, while the discounted life time effects decreases to 7.73 years and 6.52 years respectively. The average incremental cost per additional life year gained for MDH was KSh61,133 ($817) and that of AMPATH was KSh70,535 ($942).

Table 25: AMPATH cost effectiveness analysis results

Discount rate (r)	*Strategy*	*Cost (KSh)*	*Incr. Cost (KSh)*	*Eff (Years)*	*Incr. Eff (Years)*	*C/E (KSh)*	*Incr. C/E (ICER) (KSh)*
10%	No ART	166,377		2.10		79,137	
	ART	563,647	397,270	7.73	5.63	72,873	70,535
None (0%)	No ART	184,415		2.56		72,093	
	ART	1,608,496	1,424,081	25.56	23.00	62,930	61,911

Table 26: Mbagathi District Hospital cost effectiveness analysis results

Discount rate (r)	*Strategy*	*Cost (KSh)*	*Incr. Cost (KSh)*	*Eff (Years)*	*Incr. Eff (Years)*	*C/E (KSh)*	*Incr. C/E (ICER) (KSh)*
10%	No ART	153,807		2.10		73,150	
	ART	423,959	270,152	6.52	4.42	65,007	61,133
None (0%)	No ART	169,123		2.56		66,106	
	ART	932,071	762,948	15.85	13.29	58,809	57,405

6.3.1.1 The Increasing Cost Effectiveness Density Plot: Isocontours

The isocontour plots of the joint distribution of the mean incremental costs and mean incremental effects for the 10,000 patient cohorts are shown in

Figure 2. The different bands of the isocontours within the plot represent regions with different frequencies. The plot falls in quadrant II of the cost effectiveness plane suggesting that ART scenario is generally more costly and more effective than No ART scenario; this is for both MDH and AMPATH.

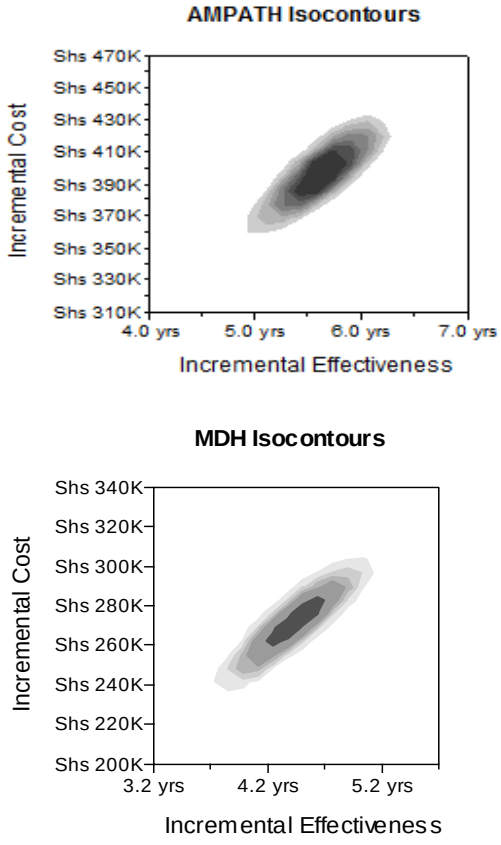


Figure 2: The isocontours

6.3.2 Sensitivity

One way sensitivity analysis was used to test the significant of the discount rates in the cost and effectiveness of different treatment scenarios, and as shown in Table 28 and Table 28 the results are sensitive to the discount rates.

Table 27: Table AMPATH Sensitivity Analysis

Discount rate (r)	*Strategy*	*Cost (KSh)*	*Incr. Cost (KSh)*	*Eff (Years)*	*Incr. Eff (Years)*	*C/E (KSh)*	*Incr. C/E (ICER) (KSh)*
3%	No ART	177,697		2.40		73,977	
	ART	1,037,925	860,229	15.28	12.88	67,939	66,812
5%	No ART	174,222		2.31		75,483	
	ART	830,467	656,245	11.98	9.67	69,348	67,883

Table 28: Table Mbagathi District Hospital Sensitivity Analysis

Discount rate (r)	*Strategy*	*Cost (KSh)*	*Incr. Cost (KSh)*	*Eff (Years)*	*Incr. Eff (Years)*	*C/E (KSh)*	*Incr. C/E (ICER) (KSh)*
3%	No ART	164,440		2.40		68,450	
	ART	680,240	515,800	11.17	8.77	60,881	58,808
5%	No ART	160,865		2.31		69,687	
	ART	575,476	414,611	9.30	6.99	61,857	59,273

6.3.3 The Monte Carlo probabilistic sensitivity analysis results

Model estimates of mean costs and mean effects are given as well as estimates of their SEs at 95% confidence interval (CIs). The 95% CIs presented in Table 30 and Table 30 suggests that the mean costs and effects for each treatment scenario as estimated by the model are significantly different from zero. In addition, these tables also show the estimates for incremental health benefits (INHB), their estimated standard errors and their associated 95% confidence intervals. The results suggests that the incremental net health benefit of ART treatment scenario to No ART treatment scenario is statistically significantly different from zero regardless of the amount the patients are willing to pay per life year gained. Hence the ART scenario is more effective than No ART scenario and we are 95% confidence of the results.

Table 29: Second Monte Carlo simulation results for AMPATH (r=10%)

			95% CI (Nonparametric)	
Statistic	**Model estimate**	**Estimated SE**	**Lower limit**	**Upper limit**
Mean cost (No ART)	KSh168,139	KSh9,532	KSh152,476	KSh189,046
Mean cost (ART)	KSh564,566	KSh18,033	KSh527,923	KSh598,523
Mean effect (No ART)	2.15	0.24	1.75	2.68
Mean effect (ART)	7.75	0.29	7.17	8.30
INHB -0.1m	-2.31	0.0007	-2.311	-2.309
INHB -0.2m	3.62	0.0009	3.618	3.622
INHB -0.3m	4.28	0.0010	4.278	4.282
INHB -0.4m	4.61	0.0010	4.608	4.612
INHB -0.5m	4.82	0.0011	4.818	4.822
INHB -0.6m	4.94	0.0011	4.938	4.942
INHB -0.7m	5.04	0.0011	5.038	5.042
INHB -0.8m	5.11	0.0011	5.108	5.112
INHB -0.9M	5.17	0.0011	5.168	5.172
INHB -1m	5.21	0.0011	5.208	5.212

Table 30: Second Monte Carlo Simulation Results for MDH (r=10%)

			95% CI (Nonparametric)	
Statistic	**Model estimate**	**Estimated SE**	**Lower limit**	**Upper limit**
Mean cost (No ART)	KSh154,064	KSh3,302	KSh147,714	KSh160,689
Mean cost (ART)	KSh425,165	KSh15,512	KSh393,929	KSh454,876
Mean effect (No ART)	2.11	0.09	1.93	2.30
Mean effect (ART)	6.55	0.31	5.94	7.15
INHB -0.1m	1.73	0.0006	1.729	1.731
INHB -0.2m	3.08	0.0008	3.078	3.082
INHB -0.3m	3.53	0.0009	3.528	3.532
INHB -0.4m	3.75	0.0009	3.748	3.752
INHB -0.5m	3.89	0.0009	3.888	3.892
INHB -0.6m	3.99	0.0010	3.988	3.992
INHB -0.7m	4.05	0.0010	4.048	4.052
INHB -0.8m	4.09	0.0010	4.088	4.092
INHB -0.9M	4.13	0.0010	4.128	4.132
INHB -1m	4.16	0.0010	4.158	4.162

6.3.4 The Cost effectiveness Acceptability Curves

We used the acceptability curve approach to evaluate the level of uncertainty within the different levels of willingness to pay per life year gained. The willingness to pay values were varied from Ksh0 to KSh0.5m and the probability that the change in net health benefit would be positive was calculated at various levels of willingness to pay

to obtain the acceptability curve for both treatment sites. The acceptability curves for ART scenarios as compared to No ART Scenarios are presented in Figure 3.

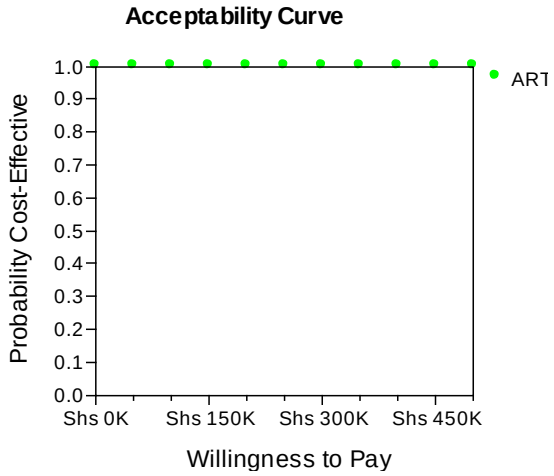


Figure 3 AMPATH acceptability curve

As shown, the probability that ART scenario is cost effectives is 1 at all the values of willingness to pay per life year gained. Hence based on the existing information, there is 100% chance that ART use is an optimal treatment intervention for people living with HIV in Kenya. This finding supports the policy of universal access to HIV and AIDS treatment and ARV use currently being implemented by the Government of Kenya.

7 CHAPTER SEVEN: SURVIVAL ANALYSIS

7.1 Introduction

Survival analysis is a statistical method for data analysis where the outcome variable of interest is the time to the occurrence of an event (Hosmer et. al., 2008). Survival analysis is also referred to as "time to event analysis", “durational analysis”, “transition data analysis” or “event history analysis”. It is the analysis of the duration for the occurrence or non-occurrence of an event during the risk period and an individual can only be eligible to experience an event if there was a period during which they were at ‘risk’ of experiencing the event e.g. in order for an individual to be at risk of getting divorced they have to be married. In this regression analysis the dependent variable measures the time to the occurrence of an event of interest and examines how covariates affect the length of time between consecutive events (Hosmer, et.al., 2008). In survival analysis, the interest is therefore on how various treatments or demographic characteristics affect survival times (Wooldridge, 2001; Collett, 1993).

Survival analysis is applied in a various fields such as medicine, international relations, social science, and engineering. In medical science, time to event can be time until recurrence in a cancer study, time until change in drug regimens, time to death, or time until infection. In the social sciences, time to events may be divorce after being in marriage, getting a job after being unemployed. However, some respondents may not experience a transition before the end of the observation period. These respondents are treated as right-censored observations. Censoring and truncation mechanisms can lead to incomplete observation of time. A censored observation is one whose value is incomplete due to factors that are random for each subject. A truncated observation is incomplete due to a selection process inherent in the study (Hosmer, et.al., 2008).

Duration data present special challenges for statistical models thus the classical theory of linear and ordinary least of squares (OLS) are not applicable (Marubini and Valsecchi, 2004). Survival data are generally positively skewed and hence most of the time the response variable will exhibit considerable asymmetry, particularly if some

observations have exceptionally long duration times (Collett, 1993; Marubini and Valsecchi, 2004).

Secondly, survival times are frequently censored, i.e. the end point of interest is not observed for the individual (Collett, 1993; Hosmer and Lemeshow, 1999; Marubini and Valsecchi, 2004). Since in OLS, we estimate the mean response on *yi* as a function of covariates, inferences regarding the mean response may be misleading if the response variable is heavily skewed. Predicting negative durations, which are impossibility, may occur. One common method of addressing this problem is to transform the response variable, for example, by taking the natural log, and then applying OLS (Collett, 1993; Hosmer and Lemeshow, 1999; Marubini and Valsecchi, 2004). This mitigates the skewness problem, but does not avoid other, more serious problems like dealing censored data. Hence, estimating durational models by OLS may result into some complications. In analysing censored survival data, we assumed non-informative censoring i.e. actual survival time of an individual , t, is independent of any mechanism that causes that individual's time to be censored at time c, c<t (Collett, 1993). Survival analysis models fall in three main categories:

7.1.1 Nonparametric models

These models make no assumption about the shape of the hazard function or about how the covariates affect the hazard function. The hazard function is instead estimated based on the empirical data, showing change over time. The effect of covariate variables is shown only by stratifying the data into groups (by gender) to plot and contrast separate hazard functions for each group. Nonparametric models are neither able to handle continuous data nor multivariate analysis and control for other explanatory variables. Kaplan-Meier survival analysis is the primary example of the nonparametric approach to event history analysis.

7.1.2 Semi-parametric models

These models also make no assumption about the shape of the hazard function in relation to time but do make strong assumptions about how covariates affect the hazard function. Specifically, they assume that hazard rates are proportional between groups over time. While estimates of the shape of the hazard function may be derived

empirically, these estimates are data-driven and may be considered overfitted, with the result that semi-parametric models are not considered appropriate for testing hypotheses about time dependence (about the shape of the hazard function in relation to time).

Semiparametric analysis is a combination of separate binary-outcome analysis, one per failure time while the parametric analysis is a combination of several analyses at all possible failure times (Cleves et. al., 2010). These models are able to support multivariate analysis and when no covariates are considered semiparametric analysis such as Cox regression and non-parametric analysis produce identical estimates (Cleves et. al., 2010). Hence, semi-parametric models are often the method of choice in event history analysis. However, if no failures occur over a particular interval, such periods are considered informative and non-informative in parametric and semiparametric analysis respectively. Cox regression, is the primary example of the semi-parametric approach to event history analysis and is discussed in detail in this section.

7.1.3 Parametric models

The parametric models require two key assumptions about the how the covariates affect the hazard rate in the duration models: First, the researcher must identify in advance the shape of the base line hazard function. Different parametric models make different assumptions about the shape of the baseline hazard function. By selecting inappropriate parametric models, the researcher may provide false or misleading interpretation of the estimated coefficients. Second, the researcher must hypothesize in advance how the covariates affect the hazard rate. This may be in two ways: proportional hazards (PH) or accelerated failure time (AFT). However, not every choice of the baseline hazard function is compatible with both PH and AFT. These are covered in detail in the next sections.

7.2 Survival analysis theoretical literature

Survival analysis concerns data on times T to some event. Depending on the nature of the study the event may be death, relapse into active disease after a period of remission, failure of a machine component, or time to secure a job after a period of

unemployment (Oakes, 2000). Survival analysis data may be right censored, left censored or truncated. The data is said to be right if the actual survival time $T_i = t_i$ for the ith subject is observed only if $t_i < c_i$ for some potential censoring time c_i. Otherwise, the fact that if $\{T_i \geq c_i\}$ is observed, but the actual value of T_i is not (Oakes, 2000).

7.2.1 Hazard Functions

Let $T \geq 0$ be a random variable denoting the time to a failure event; t denotes a particular value of T. In survival analysis, T is the length of time a subject lives. In this study, T is the length of time an HIV positive patient lives after being enrolled on treatment and its measured on three months basis (quarterly basis).

The cumulative distribution function (cdf) of T specifying the probability that the duration or spell length is less than or equal to some value t is defined as

$$F(t) = \int_0^t f(u)d(u) = P(T \leq t), \quad t \geq 0 \quad \text{.....} \quad (1)$$

For all the points that $F(t)$ is differentiable, a probability density function is defined and can be expressed as;

$$f(t) = \lim_{\Delta t \to 0} \frac{F(t+\Delta t) - F(t)}{\Delta t} = \lim_{\Delta t \to 0} \frac{P(t \leq T \leq t+\Delta t)}{\Delta t} \quad \text{.....} \quad (2)$$

Equation (2) is the unconditional failure rate in an infinitesimally small differentiable area. However, the hazard rate, $h(t)$,, which is also referred to at the conditional failure rate is defined as;

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T \leq t+\Delta t | T \geq t)}{\Delta t} \quad \text{.....} \quad (3)$$

Hazard rate is the instantaneous probability of leaving a state conditional on survival to time t. It is the limiting probability that the failure event occurs in a given interval, conditional upon the subject having survived to the beginning of that interval, divided by the width of the interval (Cleves et al. 2010).

7.2.2 Hazard Functions Conditional on Covariates

In economics we are usually interested in hazard functions conditional on a set of covariates or regressors (Wooldridge, 2001). However, these covariates may be time invariant or may vary with time. Thus, following Hosmer & Lemeshow (1999) and Lancaster, (1992) we specify the conditional hazard for time invariant covariates as $h(t;\boldsymbol{x}) = \lim_{\Delta t\to 0} \frac{P(t\leq T\leq t+\Delta t|T\geq t;\boldsymbol{x})}{\Delta t}$ and for time variant covariates as $h[t;\boldsymbol{X}(t)] = \lim_{\Delta t\to 0} \frac{P[t\leq T\leq t+\Delta t|T\geq t;\boldsymbol{X}(t+\Delta t)]}{\Delta t}$, where $\boldsymbol{x}$ is a vector of explanatory variables. The time varying covariates are assumed to be constant over a given time interval.

The shape of the hazard function is of primary interest in many empirical applications and it may exhibit increasing $\left(\frac{dh(t)}{dt} > 0\right)$, decreasing $\left(\frac{dh(t)}{dt} < 0\right)$, or constant $\left(\frac{dh(t)}{dt} = 0\right)$ duration dependence.

7.2.3 Survivor Function

A complementary concept to the cdf in equation (1) is the probability that duration equals or exceeds t, and this is the survivor function which is defined as;

$$S(t) \equiv 1 - \int_0^t f(u)d(u) = 1 - F(t) = P(T > t) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

The survivor function shows the probability of surviving beyond time t (Cleves, Gould and Gutierrez,(2010); Hosmer and Lemeshow,1999). The survival function is a monotone, non-increasing function of time (Cleves et al., 2010). In survival analysis, we observe events at discrete time points and hence $S(t)$ is a step-function. In addition, due censored observations, $S(t)$ never reaches zero.

Equation (4) can be expressed as;

$$h(t) = \frac{\lim_{\Delta t\to 0}\frac{P(t\leq T\leq t+\Delta t)}{\Delta t}}{P(T\geq t)} = \frac{f(t)}{S(t)} = -\frac{S'(t)}{S(t)} = -\frac{d\log S(t)}{dt} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Using $S(0) = 1$, we can integrate both sides of equation (5) to get

$$H(t) = \int_0^t h(s)ds = -\log(S(t)),\ t \geq 0 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

Where $H(t)$ is referred to as the cumulative hazard function. Hence;

$$S(t) = exp\left[-\int_0^t h(s)ds\right] = \exp\left(-H(t)\right),$$

and

$$F(t) = 1 - \exp\left[-\int_0^t h(s)ds\right], \quad t \geq 0 \text{……...……(7)}$$

The probability density function of T is given as;

$$f(t) = h(t)\exp\left[-\int_0^t h(s)ds\right] \text{ ……..……..……..…… (8)}$$

Thus the hazard function can be expressed in terms of the density and cdf and used to approximate a conditional probability (Woodridge, 2001). There is a one-to-one relationship between the hazard rate $h(t)$ and the survival function $S(t)$ as shown by the formula above.

The hazard rate is not a probability but rather a probability rate and it may exceed one just like the density function may also exceed one

7.2.4 Proportional Hazard Models

Proportional hazards models assume that the hazard functions of all individuals differ only by a factor of proportionality. Proportional hazard assumption may be violated for example in biomedical research for HIV treatment because the treatment effect increases with duration of treatment and then may start decreasing. That is immediately patients are put on ARVs, their hazard of dying may be high, after sometime the patients get better and stay well, however after some years patients may develop resistance to ARVs hence increased risk of death for patients on ARVs.

The PH model consists of time-invariant regressors and can be defined as;

$$h(t; \boldsymbol{x}) = k(\boldsymbol{x})h_0(t) \text{ …...……..…… (9)}$$

where $k(\boldsymbol{x}) > 0$ is a nonnegative function of $\boldsymbol{x}$ **,** characterizing how hazard function changes as a function of subjects' covariates and $h_0(t) > 0$ is the baseline hazard, characterizing how hazard function changes as a function of survival time.

The baseline hazard is common to all units in the population while the individual hazard functions differ proportionately based on a function $k(\boldsymbol{x})$ of observed covariates.

If $k(\cdot)$ is parameterized as $k(\boldsymbol{x}) = \exp(\boldsymbol{x\beta})$ where $\boldsymbol{\beta}$ a vector of parameters. Then

$$\ln h(t, \boldsymbol{x}, \boldsymbol{\beta}) = \ln [h_0(t)] + \boldsymbol{x}'\boldsymbol{\beta} \text{ …....……} \quad (10)$$

Where β_j measures the semi- elasticity of the hazard with respect to x_j. If x_j is the log of an underlying variable i.e. $x_j = ln\ (z_j)$, then β_j is the elasticity of the hazard with respect z_j.

However, when dealing with time varying covariates there is not, strictly speaking, such a thing as a proportional hazard model (Wooldridge, 2001). Nevertheless, it has become common in econometrics to call a hazard of the form $h[t, x(t)] = k[x(t)]\, h_0(t)$ a proportional hazard with time-varying covariates. The function multiplying the baseline hazard is usually $k[x(t)] = \exp[x(t)\beta]$.

In this section we discuss the various PH models including Cox regression model, Weibull model, exponential models etc.

7.3 Cox Regression Model

7.3.1 Introduction

The non-parametric methods are useful in the analysis of a single sample of survival data or in comparing one or more groups of survival time. However, these methods do not control for covariates. In clinical analysis several prognostic (explanatory) variables usually influence the survival experience of the patients. The non-parametric models are unable to estimate the survival experience of the patients controlling for the explanatory variables and hence, the need to use parametric models when carrying of survival analysis in the presence of covariates.

Cox proportional hazards (PH) model is one of the mathematical models designed for analysis of time until an event or time between events. It shows the hazard at time t of an individual given the covariates. The hazard at time t is a product of baseline hazard function $h_0(t)$ which is only a function of time and exponential to the linear sum of

$\beta_i x_i$ which is a function of time independent covariates (Hosmer and Lemeshow, 1999; Collett, 1993; Marubini and Valsecchi, 2004).

Definition: The Cox Proportional Hazard model is given by;

$$h(t, \boldsymbol{X}, \boldsymbol{\beta}) = h_0(t) \exp[\sum_{i=1}^{n} \beta_i x_i] = h_0(t) \exp[\boldsymbol{\beta}' x_i] \quad \ldots\ldots\ldots\ldots\ldots\ldots (11)$$

Where $h(t, \boldsymbol{X}, \boldsymbol{\beta})$ is the hazard function at time t for a subject with covariate values $x_1, \ldots x_n$ and the estimated coefficients of the covariates of $\beta_1, \ldots \beta_n$. $h_0(t)$ is the baseline hazard function, which is the hazard function for an individual for whom all the variables included in the model are zero, $\boldsymbol{X} = (x_1, x_2, \ldots\ldots, x_n)$ is the value of the vectors of the explanatory/predictor variables for a particular individual, $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots\ldots, \beta_n)$ is a vector of the estimated coefficients of explanatory/predictor variables and exp is the exponential function $exp(x) = e^x$.

Although Cox regression is semi-parametric, it is a "robust" model, hence its results always closely approximate the results for the correct parametric model (Kleinbaum and Klein, 2005). Cox PH model is therefore preferred over parametric event history analysis models when there is no clear theoretical reason for positing a particular baseline hazard ratio (Hosmer and Lemeshow, 1999; Kleinbaum and Klein, 2005). The exponential part of the Cox PH model ensures that the fitted model will always give a non-negative hazard and by definition a hazard function is between zero and plus infinity i.e. $0 \leq h(t, x, \beta) \leq \infty$.

7.3.2 Cox PH model Hazard Ratio

The hazard ratio (HR) is the hazard of one individual divided by the hazard of a different individual. The two individuals being compared can be distinguished by the values of their covariates.

$$\widehat{HR}(t, \boldsymbol{X}, \boldsymbol{\beta}) = \frac{\hat{h}(t, \boldsymbol{X}^*, \hat{\boldsymbol{\beta}})}{\hat{h}(t, \boldsymbol{X}, \hat{\boldsymbol{\beta}})} = \frac{\hat{h}_0(t) \exp[\sum_{i=1}^{n} \hat{\beta}_i x^*{}_i]}{\hat{h}_0(t) \exp[\sum_{i=1}^{n} \hat{\beta}_i x_i]} = \exp\left[\sum_{i=1}^{n} \hat{\beta}_i (x_i{}^* - x_i)\right] \ldots (12)$$

Where $\boldsymbol{X}^* = x_1{}^*, x_2{}^*, x_3{}^*, \ldots\ldots, x_n{}^*$ and $\boldsymbol{X} = x_1, x_2, x_3, \ldots\ldots, x_n$ denote sets of explanatory variables for two individuals.

The hazard ratio in equation (12) is interpreted as a "relative risk"-type ratio (Hosmer and Lemeshow, 1999). Given dichotomous covariate e.g. sex, with value of $x_1^* = 1$ for males and $x_1 = 0$ for females, the hazard ratio in equation (12) becomes $e^{\hat{\beta}}$. If the value of the coefficient is $\hat{\beta} = \ln(2)$ then males are "dying" at twice the rate of females. If x_1 is a $(0, 1)$ exposure variable adjusted for other variables then, the $\widehat{HR}(t, \boldsymbol{X}, \beta) = e^{\hat{\beta}_1}$, provided there is no interaction terms involving the primary exposure variable in the model (Kleinbaum and Klein, 2005). However, if the Cox model contains interaction terms between the primary exposure variable and other covariates then, their hazard ratio is;

$$\widehat{HR}(t, \boldsymbol{X}, \boldsymbol{\beta}) = \exp\left[\hat{\beta} + \sum_{j=1}^{n} \hat{\delta}_j W_j\right] \quad \text{.....(13)}$$

Where $\hat{\beta}$ is the estimated coefficient of the exposure variable, $\hat{\delta}_j$ is the estimated coefficient of the interaction terms, W_j is the covariates interacting with exposure variable and $j = 1, 2, 3, \ldots, n$

7.3.3 Cox Regression Model with time dependent variables

Model (11) gives a Cox PH model with time independent covariates. However, we may have situations in which the values of the covariate change over time and in which the value of the hazard function depends more on the current value of the covariate than on the value at time zero. In all instances, inclusion of time varying covariates should be based on strong clinical evidence (Hosmer and Lemeshow, 1999). When covariates are time dependent, then the PH assumption is violated and extended Cox model is estimated (Marubini and Valsecchi, 2004; Hosmer and Lemeshow, 1999; Collett, 1993; Wooldridge). The extended Cox PH model including both time dependent and time independent covariates as given by Hosmer and Lemeshow, (1999) is;

$$h(t, \boldsymbol{X}(t), \boldsymbol{\beta}) = h_0(t) \exp\left[\sum_{i=1}^{n1} \beta_i x_i + \sum_{i=1}^{n2} \alpha_j x_j\,(t)\right] \quad \text{.....(14)}$$

Where $\boldsymbol{X}(t) = (x_1,\ x_2, \ldots, x_{n1}, x_1(t),\ x_2(t), \ldots, x_{n2}(t))$ and x_i and $x_j(t)$ are the time independent and time dependent predictors respectively.

The general hazard ratio formula for extended Cox model is;

$$\widehat{HR}(t, \boldsymbol{X}, \boldsymbol{\beta}) = \frac{\hat{h}(t,\boldsymbol{X}^*,\boldsymbol{\beta})}{\hat{h}(t,\boldsymbol{X},\boldsymbol{\beta})} = \exp\left[\sum_{i=1}^{n1} \hat{\beta}_i [x_i{}^* - x_i] + \sum_{i=1}^{n2} \hat{\alpha}_i \left[x_j{}^*(t) - x_j(t)\right]\right] \ldots\ldots. (15)$$

Where $\boldsymbol{X}^*(t) = (x^*{}_i,\ x^*{}_j(t))$ and $\boldsymbol{X}(t) = (x_i,\ x_j(t))$ are the two sets of predictors and x_i and $x_j(t)$ are time independent and time dependent predictors respectively.

In this model the hazard ratio is a function of time and the PH assumption is violated if any α_i is not equal to zero (Kleinbaum and Klein, 2005). The hazard ratio increases or decreases with time if $\alpha_i < 0$ and $\alpha_i > 0$ respectively. The hazard is assumed to be a function of the value of $x_j(t)$ at time t (Kleinbaum and Klein, 2005). According to Kleinbaum and Klein (2005), if the Cox model contains interaction terms between the primary exposure variable and time then, their hazard ratio is expressed as;

$$\widehat{HR}(t, \boldsymbol{X}, \boldsymbol{\beta}) = \exp\left[\hat{\beta}_1 + \hat{\delta}t\right] \ldots\ldots(16)$$

Where $\hat{\beta}_1$ is the estimated coefficient of the exposure variable, $\hat{\delta}$ is the estimated coefficient of the interaction terms and t is time expressed in days, weeks, months, years etc.

7.3.4 Stratified Cox PH Model

The Cox PH model can be stratified to correct for violation of the proportional hazard assumption and the model is stratified on the variable that violets the PH assumption. The general stratified Cox model is given by $h_g(t, x) = h_{0g}(t) \exp\left[\sum_{i=1}^{p} \beta_i x_i\right]$ where $g = 1, 2, \ldots., k$ strata defined from z^* and z^* is not included in the model while $x_1, x_2, \ldots, x_p$ are included.

7.3.5 Adjusted Survival Curves using the Cox PH Model

When a Cox PH model is used to fit survival data, survival curves obtained are adjusted for the covariates used as predictors hence the term adjusted survival curves. To convert the hazard function for Cox PH model to corresponding survival function gives;

$$S(t, \boldsymbol{X}, \boldsymbol{\beta}) = [S_0(t)]^{\exp \sum_{i=1}^{n} \beta_i x_i} \ldots\ldots (17)$$

And the estimated survival function is given by

$$\hat{S}(t, \boldsymbol{X}, \boldsymbol{\beta}) = [S_0(t)]^{\exp \sum_{i=1}^{n} \hat{\beta}_i x_i} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (18)$$

Hence the adjusted survival curve comparing two groups for exposed and unexposed subjects are $\hat{S}(t, \boldsymbol{X}, \boldsymbol{\beta}) = \left[\hat{S}_0(t)\right]^{exp\hat{\beta}_1(1)+\sum_{i\neq 1}\hat{\beta}_i\bar{x}_i}$ and

$\hat{S}(t, \boldsymbol{X}, \boldsymbol{\beta}) = \left[\hat{S}_0(t)\right]^{exp\hat{\beta}_1(0)+\sum_{i\neq 1}\hat{\beta}_i\bar{x}_i}$ respectively. The adjusted survival curve which adjusts for all the covariates in the model is therefore given by;

$$\hat{S}(t, \overline{\boldsymbol{X}}, \boldsymbol{\beta}) = \left[\hat{S}_0(t)\right]^{exp\sum\hat{\beta}_i\bar{x}_i} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (19)$$

7.3.6 Fitting the Proportional Hazard Regression Model

To fit the Cox proportional hazards model, we need to estimate $h_0(t)$ and β. One approach is to attempt to maximize the likelihood function for the observed data simultaneously with respect to $h_0(t)$ and β. However, since $h_0(t)$ is not specified in Cox regression, maximum likelihood estimation is not possible hence the partial likelihood approach that was proposed by Cox (1972) is used. This partial likelihood for Cox model is given by;

$$l_p(\beta) = \prod_{i=1}^{n}\left[\frac{e^{x_i\beta}}{\sum_{j\in R(t_i)} e^{x_j\beta}}\right]^{c_i} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (20)$$

The equation assumes that there is no tied times i.e. no two subjects have the same events and is usually modified to exclude terms when $c_i = 0$ giving;

$$l_p(\beta) = \prod_{i=1}^{m}\frac{e^{x_i\beta}}{\sum_{j\in R(t_i)} e^{x_j\beta}} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (21)$$

Where the product is over the m distinct ordered survival times and x_i denotes the value of the covariate for subject with ordered survival time (t_i). The log partial likelihood is;

$$L_p(\beta) = \sum_{i=1}^{n}\left\{x_i\beta - \ln\left[\sum_{j\in R(t_i)} e^{x_j\beta}\right]\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (22)$$

For more details see (Hosmer and Lemeshow, 1999).

7.3.7 Fitting the PH model with tied survival

However, when there are tied survival functions Hosmer and Lemeshow (1999), the Breslow approximation uses as partial likelihood

$$l_{p1}(\beta) = \prod_{i=1}^{m} \frac{e^{x_i+\beta}}{\left[\sum_{j\in R(t_{(i)})} e^{x_j\beta}\right]^{d_i}} \text{...} (23)$$

Where d_i is the number of subjects with survival time $t_{(i)}$, x_i is the sum of the covariates over the d_i subjects *i.e.* $x_i = \sum_{j\in D(t_{(i)})} x_j$, and $D\left(t_{(i)}\right)$ is the subjects with survival times equal to $t_{(i)}$

7.3.8 Cox Proportional Hazard Model Diagnostics

Model-based inferences depend completely on the fitted statistical model and for these inferences to be "valid", the model fitted must provide adequate summary of the data upon which it is based (Hosmer and Lemeshow, 1999). Central to the evaluation of model adequacy in any setting is an appropriate definition of a residual (Hosmer and Lemeshow, 1999). The fact that the outcome variable is time to some event and the observed variables may be censored is what differentiates regression analysis of survival time from other regression models (Hosmer and Lemeshow, 1999). The definition of a residual is much more complicated in survival regression analysis compared to other regression models due to data, PH modelling and partial likelihood (Hosmer and Lemeshow, 1999). The absence of an obviuos residual led to development of several different residuals each playing different roles in examining some aspect of the PH model.

7.3.8.1 Schoenfeld and Scaled Schoenfeld Residual

These residuals were proposed by Schoenfeld (1982) and are used for checking and testing the proportional hazard assumption, examining leverage points, and identifying outliers (Cleves, et. al., 2008). They are essentially, observed minus the expected values of the covariate at each failure time (Hosmer et al 2008). The Schoenfeld residual plot reveals whether a particular coefficient from a covariate is time dependent (Mills, 2011). Although a residual is produced for each independent

variable fitted in the model, their non-zero values only a rise for uncensored observation (Collett, 1993).

Given p covariates and n independent observations time, covariate and censoring indicator are denoted in triplet $(t_i, x_i, c_i),\ i = 1, 2, \ldots, n,$ where $c_i = 1$ for uncensored observation and zero otherwise. According to Schoenfeld (1982) the estimator of Schoenfeld residual for the i^{th} subject on the kth covariate is;

$$\hat{r}_{ik} = c_i\left(x_i - \hat{\bar{x}}_{w_i}\right) \quad \text{(24)}$$

And $\hat{\bar{x}}_{w_i}$ is the estimator of the risk set conditional mean of the covariate. Grambsch and Therneau (1994) proposed a scaled Schoenfeld residual which has a greater diagnostic power than the unscaled residuals. The scaled Schoenfeld residual is;

$$\hat{r}_{ik} = m\widehat{\text{Var}}\left(\hat{\beta}\right)\hat{r}_{i.} \quad \text{(25)}$$

7.3.8.2 Martingale Residual

The Martingale-based residuals and/or their transformations are useful for investigating the functional form of a covariate, the proportional hazards assumption, the leverage of each subject upon the estimates of β, and the lack of model fit to a given subject (Therneau et al., 1990). These residuals include; Martingale residual, Cox-Snell residual, score residual and deviance residual.

The Martingale residuals are useful in determining the functional form or the scale of the continuous variables included in the model (Cleves, et. al., 2008; Hosmer and Lemeshow, 1999). These residuals can be interpreted, at each t, as the difference over $[0, t]$ between the observed number of failures in the data and the number of failures predicted by the model (Therneau et al., 1990; Collett, 1993; Cleves, et. al., 2008; Hosmer and Lemeshow, 1999). The residuals have some properties reminiscent of linear models: $\sum \widehat{M}_i(t) = 0$ for any t, and $\text{E}\left(\widehat{M}_i\right) = \text{cov}\left(\widehat{M}_i, \widehat{M}_i\right) = 0$ asymptotically (Therneau et al., 1990; Collett, 1993; Cleves, et. al., 2008; Hosmer and Lemeshow, 1999; Mills, 2011). According to Hosmer and Lemeshow (1999), the martingale residual for the ith subject is;

$$M(t_i) = N(t_i) - H(t_i, \boldsymbol{x}, \boldsymbol{\beta}) \quad \text{(26)}$$

Since $N(t_i)$ is the count that represents the observed part of the model and is always equal to the value of censoring indicator while $H(t_i, \boldsymbol{x}, \boldsymbol{\beta})$ is the systematic component of the model, equation (50) can be re-written as;

$$M(t_i) = c_i - H(t_i, \boldsymbol{x}, \boldsymbol{\beta}) \quad \text{(26b)}$$

And for a Cox model with no time-dependent covariates, this residual reduces to

$$\widehat{M}_i = c_i - h_0(t_i)e^{\beta_i x_i} \quad \text{(26c)}$$

To check the functional form, martingale residuals are plotted against covariates and are used to form component-plus-residual (partial residual) plots. The residual is plotted on the Y-axis and the covariate on the X-axis (Mills, 2011). If the currently specified functional form is acceptable, then the regression line will have a slope and intercept of zero. If the martingale residuals on Y are plotted against a linear predictor on X then there should be no pattern of correlation if the PH assumption is met (Mills, 2011).

7.3.8.3 Cox-Snell residual: Assessing PH Model Fit

Cox-Snell residual is transformed from martingale residual (Collett, 1993; Hosmer & Lemeshow, 1999; Cleves, et. al., 2008). They are usually plotted to assess model fit. Substituting the value of the partial likelihood estimator of the coefficient, $\widehat{\boldsymbol{\beta}}$ in martingale residual in equation (26b) gives us the Cox-Snell or modified Cox-Snell residual;

$$\widehat{M}(t_i) = c_i - H(t_i, \boldsymbol{x}, \widehat{\boldsymbol{\beta}}) \quad \text{(27)}$$

If model fits the data well, graph of integrated (cumulative) hazard conditional on Cox-Snell residuals vs. Cox-Snell residuals will fall on a line (Cleves, et. al., 2008). And for a Cox model with no time-dependent covariates, the Cox-Snell or modified Cox-Snell residual is

$$\widehat{M}_i = c_i - \hat{h}_0(t_i)e^{\widehat{\beta}_i x_i} \quad \text{(27b)}$$

Where;

$\hat{\mathrm{h}}_0(\mathrm{t_i}) =$ the estimate of the cumulative hazard based on model results

$\hat{\beta}_i =$ estimates from the model

$x_i =$ values for each case in your data

Interpretation: "The expected number of events in a given time-interval"

7.3.8.4 Score Residual: Assessing the Individual's Leverage

The score residuals also falls into a class of martingale transformed residuals and are useful in diagnosis of each subject's leverage on parameter estimates and in assessing model assumptions such as proportional hazards (Therneau et al., 1990). These residuals are covariate specific with score residual for each observation for each covariate (Mills, 2011). A high absolute score residuals means that the observation has a strong influence on the regression coefficient for the covariate (Mills, 2011).

It shows by how much each coefficient would change if a single observation was removed (Mills, 2011). Following Hosmer and Lemeshow (1999), the score residual for the ith subject on the kth covariate is;

$$\frac{\partial L_p(\boldsymbol{\beta})}{\partial \beta_k} = \sum_{i=1}^{n} L_{ik} \quad \ldots\ldots (28)$$

Where $L_{ik} = \sum_{j=1}^{n} \left(x_{ik} - \bar{x}_{w_j k} \right) dM_i(t)$ and for Cox model $\bar{x}_{w_i} = \frac{\sum_{j \in R(t_i)} e^{x_j \beta} x_j}{\sum_{j \in R(t_i)} e^{x_i \beta}}$

7.3.8.5 Deviance residuals: Assessing Model Accuracy for Individual Subjects

An important use of residuals is in graphical assessment of poor prediction by a model for individual subjects. The size of the individual's martingale residual $\widehat{M}_i$ indicates model accuracy, with a large positive value for a subject who has more events than predicted by the model, i.e. dies 'too soon', and a large negative residual for fewer events than predicted by the model, i.e. lives 'too long' (Therneau et al., 1990). One deficiency of the martingale residual $\widehat{M}_i$, particularly in the single event setting of Cox's model, is its skewness i.e. it has a maximum value of $+1$ and a minimum value of -∞ (Therneau et al., 1990; Collett, 1993).

This skewness distorts the appearance of a standard residual plot making it difficult to interpret (Therneau et al., 1990; Collett, 1993). In addition, the long right-hand tail of

the martingale residuals may also produce spurious outliers among those who 'live too long' (Therneau et al., 1990). The deviance residual, introduced by Therneau et al., (1990) are normalized transform of the martingale residual and are symetrically distributed about zero. This residual helps to alleviate problem of martingale residual. When censoring is minimal, <25% or so, the distribution of the deviance residuals is very close to a normal distribution (Therneau et al., 1990).

According to Therneau et al. (1990), the deviance residuals for the Cox PH model is given by $d = \text{sgn}\left(\widehat{M}_i\right)\left[-2\left\{\widehat{M}_i + c_i \ln(c_i - \widehat{M}_i)\right\}\right]^{\frac{1}{2}}$ ……..……(29)

Where;

$\widehat{M}_i$ = the martingale residual for the i^{th} individual

sgn = is a sign function, it takes the value +1 if the argument is positive and -1 if negative.

The log function inflates the martingale residuals close to one, while the square root contacts the large negative values (Therneau et al., 1990). The deviance is a static used to summarize the extent to which the fit of a model of current interest deviates from that of a model which is a perfect fit to the data (Collett, 1993). Observations with large deviance residuals are poorly predicted by the model.

7.3.8.6 Assessing the Proportional Hazard Assumption

This is one of the major assumptions underlying the proportional hazards models such as Cox and Weibull regression models. PH assumption characterizes the model as a function of time and not of the covariate per se (Hosmer and Lemeshow, 1999). This assumption is vital to the interpretation and use in fitted proportional hazard models (Hosmer and Lemeshow, 1999). Non proportional hazard can arise if some covariates only affect survival up until sometime or if the size of its effect changes over time (Hosmer and Lemeshow, 1999; Collett, 1993).

The proportional hazards model makes two major assumptions: the hazard ratio is constant over time, and the relationship between the hazard and continuous covariates is log-linear (Sasieni and Winnett, 2003). From equation (10), the poportional Hazard Function model has a log-hazard function of the form;

$$ln\, h(t, \boldsymbol{x}, \boldsymbol{\beta}) = ln\, [h_0(t)] + \boldsymbol{x}'\boldsymbol{\beta}$$

To assess proportional hazard assumption, Grambsch and Therneau (1994) considered an alternative proportional hazard model with a specific form of time-varying coefficient

$$\beta_j(t) \equiv \beta_j + \gamma_j g_j(t) \quad \text{.......} \quad (30)$$

Where $g_j(t)$ is a specified function of time and proved that the scaled Schoenfeld residual and its approximation have for the jth covariate, a mean at time t of approximately;

$$\mathrm{E}\left[r^*{}_j(t)\right] \cong \gamma_j g_j(t) \quad \text{.......} \quad (31)$$

Hence, a plot of the scaled Schoenfeld residuals over time may be used to assess whether coefficient γ_j is equal to zero and if not the nature of time dependence that $g_j(t)$ maybe. If $g_j(t) = \ln(t)$ then, equation (30) becomes $\beta_j(t) \equiv \beta_j + \gamma_j \ln(t)$ and the linear predictor portion of the model is;

$$\beta_j x_j + \gamma_j\, x_j \ln(t) \quad \text{.......} \quad (32)$$

and the hypothesis that $\gamma_j = 0$ can be tested via partial likelihood ratio test, score test or Wald test when the interaction $x_j \ln(t)$ is added to proportional hazard model.

7.4 Parametric model

The Cox PH model described in Section is the most common regression analysis used in analysing explanatory variables in clinical data. This because it is a semi parametric model that allows researchers to estimate and make inference about the parameters without assuming any distribution for the survival time. However, when the proportional hazards assumption is not tenable or when the distribution of the survival time is known, these models will not be suitable. In this section, we present parametric survival models and their assumptions.

The parametric models require the researcher to make two key assumptions about the how the covariates affect the hazard rate in the duration models: First, the researcher must posit in advance the shape of the base line hazard function. Different parametric

models make different assumptions about the shape of the baseline hazard function. By selecting inappropriate parametric models, the researcher may provide false or misleading interpretation of the estimated coefficients. Second, the researcher must posit in advance how the covariates affect the hazard rate. This may be in two ways: proportional hazards (PH) or accelerated failure time (AFT). However, not every choice of the baseline hazard function is compatible with both PH and AFT. The parametric models support multivariate analysis of discrete and continuous explanatory variables and yields precise parameter estimates, provided the correct model assumptions are made. Estimates are derived using maximum likelihood methods. If the wrong shape of the hazard function is specified, parameter estimates can be seriously biased. Parametric models are preferred when time is itself considered a meaningful independent variable and the researcher wants to be able to describe the nature of time dependence. Also, because parametric models specify the shape of the baseline hazard function, that function can be extrapolated into the future, making it useful for predictive modelling.

7.4.1 The Proportional Hazard Models

The Proportional hazard models exist in parametric survival analysis and semi-parametric Cox regression models. In these models, the covariates are assumed to raise or lower the hazard function in a multiplicative manner. The covariate effects are effects compared to the baseline hazard function. The PH parameterization is available for exponential, Weibull and Gompertz models. The proportional hazard assumption is that all groups of observations have the same shape of hazard function, but that function is moved up or down in parallel with the others according to the influence of the covariates. For example, in our study, the patients not on ART may have a higher risk of death than those on ARVs, but for both groups the shape of the hazard function is assumed to be the same.

7.4.2 Accelerated failure time model

These models assume that covariates multiply the time scale. In an AFT model the dependent variable is event time and covariate effects are interpreted in terms of time ratios. The AFR parameterization is available for exponential, Weibull, gamma, log-normal and log-logistic models. The AFT assumption is that all the observations have

the same shape hazard function but the time axis varies such that some groups of observations pass through the stages of the hazard curve faster than others. The parameter estimates in AFT models have the opposite sign from corresponding estimates in the PH models. This is because the PH models predict the hazard rate while the AFT models predict the time, however, when the hazard rate is high in PH models, time to event is low in AFT models. In addition, the significance of the parameter estimates for the same covariates must not be the same in PH and AFT models.

7.4.3 Parametric proportional hazards model

The parametric proportional hazards model is the parametric versions of the Cox proportional hazards model. It is given with the similar form to the Cox PH models (equation 11). The hazard function at time t for the particular patient with a set of n covariates $(x_1, x_2, \dots, x_n)$ is given as follows;

$$h(t|\boldsymbol{X}) = h_0(t)\exp[\textstyle\sum_{i=1}^{n}\beta_i x_i] = h_0(t)\exp[\boldsymbol{\beta}' x_i] \quad \text{.....(33)}$$

The major difference between semi-parametric and parametric models is that when a fully parametric PH model is fitted to the data, the base line hazard function is assumed to follow a specific distribution. Secondly, the coefficients of the parametric models are estimated by the maximum likelihood while in the Cox model they are estimated by partial likelihood. Other than this, the two types of models are equivalent. Hazard ratios have the same interpretation and proportionality of hazards is still assumed. A number of different parametric PH models may be derived by choosing different hazard functions. The commonly applied models are exponential, Weibull, Log-logistic, lognormal Generalized gamma or Gompertz models.

7.5 Exponential Distribution

In the simplest case, the hazard function is constant and $h(t) = h,$ all $t \geq 0$. This function means that the process driving T is memoryless, implying that the probability of exit in the next interval does not depend on how much time has been spent in the initial state. The cdf of the exponential distribution is $F(t) = 1 - \exp(-ht)$. The

hazard and survivor functions for the exponential distribution is a constant and is given by

$$h(t) = \frac{f(t)}{S(t)} = \lambda \text{ and } S(t) = \exp(-\lambda t) \; and \; h = \lambda. \quad \text{.....(34)}$$

The hazard function of a particular patient under this model a set of n covariates $(x_1, x_2, \dots, x_n)$ is given by;

$$h(t|\boldsymbol{X}) = \lambda \exp[\sum_{i=1}^{n} \beta_i x_i] = \lambda \exp[\boldsymbol{\beta}' x_i] \quad \text{.....(35)}$$

7.6 Weibull PH Distribution

According to Hosmer and Lemeshow (1999), if T has a Weibull distribution, its cdf is given by $F(t) = 1 - \exp(-\lambda t^p)$ and the density is $f(t) = \lambda p t^{p-1} \exp(-\lambda t^p)$. By equation (5), the hazard and survivor function are;

$$h(t) = \frac{f(t)}{S(t)} = \lambda p t^{p-1} \quad and \; S(t) = \exp(-\lambda t^p) \quad \text{..... (36)}$$

with $p, \lambda \geq 0$. When $p = 1$, the Weibull distribution reduces to the exponential with $h = \lambda$. If $p > 1$, the hazard is monotonically increasing and exhibits positive duration dependence however, if $p < 1$, the hazard is monotonically decreasing and exhibits negative duration dependence.

Under the Weibull PH model, the hazard function of a particular patient is given by

$$h(t|\boldsymbol{X}) = \lambda p(t)^{p-1} \exp[\sum_{i=1}^{n} \beta_i x_i] = \lambda p(t)^{p-1} \exp[\boldsymbol{\beta}' x_i] \quad \text{.....(37)}$$

The survival time of this patient has a Weibull distribution with a scale parameter $\lambda \exp[\boldsymbol{\beta}' x_i]$ and a shape parameter p. The Weibull models with fixed p possesses the PH property. Hence the effects of the explanatory variables in the model alter the scale parameter of the distribution, while the shape parameter remains constant.

From equation (7), the corresponding survival function is given by;

$$S(t|\boldsymbol{X}) = \exp\{-\exp(\boldsymbol{\beta}' x_i) \lambda t^p\} \quad \text{.....(38)}$$

7.7 The Log-Logistic Hazard Function

This model is not a proportional hazard model but accellared failure time model. Following Hosmer and Lemeshow (1999), we specify the log-logistic hazard function as;

$$h(t) = \frac{\lambda p t^{p-1}}{1+\lambda t^p} \qquad p, \gamma \geq 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (39)$$

When $p = 1$, the hazard is monotonically decreasing from λ at $t = 0$ to zero as $t \to \infty$; when $p < 1$, the hazard is also monotonically decreasing to zero as $t \to \infty$, but the hazard is unbounded as t approaches zero. When $p < 1$, the hazard is increasing until $t = [(p-1)/\lambda]^{1-p}$ and then it decreases to zero.

Straightforward integration gives

$$\int_0^t h(s)ds = \log(1 + \lambda t^p) = -log\,[(1 + \lambda t^p)^{-1}] \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (40)$$

by equation (10),

$$F(t) = 1 - (1 + \lambda t^p)^{-1}, \qquad t \geq 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (41)$$

Differentiating with respect to t gives

$$f(t) = \lambda t^{p-1}(1 + \lambda t^p)^{-2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (42)$$

Using the above density function, it can be shown that $Y \equiv \log(T)$ and has a density $g(y) = \frac{\exp[p(y-\mu)]}{\{1+\exp[p(y-\mu]\}^2}$, where $\mu = -p^{-1}\log(\gamma)$ is the mean of Y. In other words, log (T) has a logistic distribution with mean μ and variance $\pi^2/3p^2$ (hence the name "log-logistic").

7.8 The Log-logistic Distribution

For notational reasons; we show this depending only on $x(t)$ and not on past covariates. The log-logistic hazard can be modified by including time-varying covariates parametrically

$$h[t, x(t)] = \frac{\exp[x(t)\beta]pt^{p-1}}{1+\exp[x(t)\beta]t^p} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (43)$$

8 CHAPTER EIGHT: APPLICATION OF SURVIVAL ANALYSIS TO HIV DATA

This chapter presents the detailed methodology of how the non-parametric methods, Cox PH regression model and Weibull models were used to determine the survival rates and determinants of survival for the patients on treatment follow up. The same data from the two hospitals are used. The first section provides a summary of the data use, the second section, presents an analysis of how significant covariates were selected for model analysis and the last section gives a description of the Cox PH diagnostic tests were carried out to test the scale of the continuous variables, identify leverage and outliers, test for the PH assumption and model fit.

8.1 The Data

This study calculated survival time from the date the people living with HIV were enrolled in the HIV and AIDS clinic to the date of death or, if alive, at the time of data collection – March 2010 and June 2010 for Mbagathi hospital and Moi hospital respectively. Cox stratified model and Weibull stratified model were used in the regression analysis.

8.2 Variable selection Method: purposeful covariate selection

In selecting the covariates for analysis, several statistical procedures were carried out including descriptive, univariate, and multivariate analysis. The objectives of the univariate analysis were assess whether the groups of variables were proportional or not and to test equality across each of the strata. Firstly Kaplan-Meier curves were plotted for all the categorical variables to evaluate whether these groups of variables were proportional or not. Then we considered the tests of equality across strata to explore whether or not to include the predictor in the final data. For the categorical variables we used the log-rank test of equality across strata which are a non-parametric test. For the continuous variables we used a univariate Cox proportional hazard regression which is a semi-parametric model.

The study used the purposeful selection of covariates for the final multivariate analysis and included variables that were tested to be significant at $P \leq 0.25$ in

univariate analyses or which were predetermined to be clinically significant. *P*-values were two-sided and those ≤0.05 were considered to be statistically significant. We also allowed for interaction of the covariates to capture the interaction effects of the variable. Table 31 shows the interactions which were significant and hence included in the preliminary model. These interactions included; ART use and CD4 count values, ARV use and employment state, CD4 strata and income and finally, income and education level. However, only four interaction terms were significant in the multivariate model and hence maintained in the final model for analysis. Data from both Mbagathi District Hospital and AMPATH were pooled for these analyses. Table 32 gives the description of all the variables that were included in the model for analysis.

Table 31: Significant interaction terms

Interaction	**Variable**	**df**	**p-value**
Ever_arv			
	cd4_value	1	0.0178
	employ_state	1	0.0092
cd4_strata			
	income	2	0.0016
income			
	educ_level	3	0.0246

Table 32: Description of Variables:

Variable	Description	Code/Values
_id	Patient identification code	1-700
age	Age at enrolment	Years
alcohol	Drinking alcohol during enrolment	0 = No
		1 = Yes
bmi	Body Mass Index	10.60 – 35.26
censor	Death	0 = No
		1 = Yes
cd4_strata	CD4 strata at enrolment	0 = 0-50
		1 = 51-250
cd4_value	CD4 value at enrolment	1 - 250
condom	Condoms use at enrolment	0 = No
		1 = Yes
cycle	Length of follow-up – 91 days	91 days
dependants	Number of dependants	0 - 13
educ-level	Highest level of education	1 = None
		2 = Primary
		3 = Secondary & above
employ_state	If the patient was employed at enrolment	0 = No
		1 = Yes
ever_arv	If the patient is on ARVs or not	0 = No
		1 = Yes
income	Patient's level of income at enrolment	1 = 0 – 2,500
		2 = 2,501-10,000
		3 = 10,001-50,000
married	If married or not	0 = No
		1 = Yes
pipwater	If piped water available in the house	0 = No
		1 = Yes
sex	Sex of patient	0 = Female
		1 = Male
txmodel	Treatment Hospital	0 = Mbagathi District
		1 = AMPATH

8.3 Cox PH Model Diagnostics Results

Model-based inferences depend completely on the fitted statistical model and for these inferences to be "valid", the model fitted must provide adequate summary of the data upon which it is based (Hosmer and Lemeshow, 1999). The following diagnostic tests were carried out to test the scale of the continuous variables, identify leverage and outliers, test for the PH assumption and model fit. The results of these diagnostic tests are also presented.

8.3.1 Testing the scale of the continuous covariates:

We examined the scale of the three continuous variables in the model, age, cd4_value and dependants using the fractional polynomials method, Martingale and deviance residuals. We used both the graphical and fractional polynomial methods to assess the scale of the continuous covariates.

8.3.1.1 Fractional polynomials method

Table 33 to Table 35 presents the results for fractional polynomial results. The tables contain four rows and each row corresponds to a particular parameterization of the continuous variable (i.e. age, cd4_value and dependants). The first row presents a model containing all the covariates except the covariate of interest, that is the coefficients are set equal to zero (β_{age} = 0, β_{cd4_value} = 0 and $\beta_{dependants}$ = 0). The model presented in the second row is our preliminary model in which the continuous covariates enter as linear terms as shown by the power of 1 (i.e. $p = 1$) in the last column. The significance levels are reported in third column, these are the partial likelihood ratio test of the continuous variables entering the models in different scales.

Table 33: Fractional polynomial model comparisons for Age (n =701)

	Age	-2xlog_like (Deviance)	G for Model vs Linear (Dev. dif.)	Approximate P-value P (*)	Powers
Model 1	Not in model	1853.416			
Model 2	Linear	1850.471	3.757	0.440	1
Model 3	m = 1 (2 df)	1850.005	0.813	0.846	3
Model 4	m = 2 (4 df)	1849.659	0.347	0.841	0.5 0.5

(*) P-value from deviance difference comparing reported model with m = 2 model

Table 34: Fractional polynomial model comparisons for CD4 count values (n =701)

	cd4_value	-2xlog_like (Deviance)	G for Model vs Linear (Dev. dif.)	Approximate P-value P (*)	Powers
Model 1	Not in model	1854.933			
Model 2	Linear	1850.471	7.962	0.093	1
Model 3	m = 1(2 df)	1850.331	3.499	0.321	0.5
Model 4	m = 2(4 df)	1846.972	3.360	0.186	3 3

(*) P-value from deviance difference comparing reported model with m = 2 model

Table 35: Fractional polynomial model comparisons for dependants (n =701)

	dependants	-2xlog_like (Deviance)	G for Model vs. Linear (Dev. dif.)	Approximate P-value P (*)	Powers
Model 1	Not in model	1852.790			
Model 2	Linear	1850.471	2.629	0.622	1
Model 3	m = 1(2 df)	1850.439	0.310	0.958	2
Model 4	m = 2(4 df)	1850.161	0.278	0.870	-0.5 3

(*) P-value from deviance difference comparing reported model with m = 2 model

From Table 33 Model 1 contains all covariates except age, hence β_{age} = 0. Model 2 is our preliminary model with age entering as a linear term. $G = 7.962$ and the p-value $p = 0.440$. The best power when age enters the model as a single,$J = 1$, term is $p_1 = 3$ that is age cubed. The partial likelihood ratio test comparing the use of $p_1 = 1$ to $p_1 = 3$ is $G = 0.39$ while reported p-value is $\Pr(\chi^2(1) \geq 0.39) = 0.823$. The likelihood ratio is chi square with 1 degree-of- freedom under the null hypothesis that age is a linear function of log hazard. We accept the null hypothesis since $0.39 < p < 0.823$. Hence this confirms our presentation of age as a linear term.

Note that the p-value of all the parameterization of age is not significant, implying that we accept the null hypothesis that age is linear. The same is true for CD4 values and for number of dependants. Hence CD4 count value and for number of dependants also fits the model as a linear function of log hazard ratio. These results confirms that an assumption of linearity in the log hazard is reasonable for the three variables; age, CD4 count values and number of dependants.

8.3.1.2 Martingale residuals

We used the martingale residuals obtained from fitting the model without the covariates to determine the functional form of the covariates. These residuals were plotted against each of the continuous variables in the model. We then superimposed the smoothed curves for ease of interpretation. It has been shown by Therneau et al. (1990) that this plot should display the functional form required for the covariate and a straight line plot indicates that a linear term is needed.

Figure 4 presents the results. The top three graphs are martingale residuals and their lowess residuals plotted from the model that excludes the covariates of interest while the bottom three plots are log of the ratio of smoothed censor to smoothed cumulative hazard. The bottom plots tend to over emphasize the shape (Hosmer and Lemeshow, 1999).

The scatter plot for martingale residual and their lowess smooth are assessing whether age, CD4 count values at first visit and number of dependents effects are linear to our Cox regression model. The residual and the smoothed curve for age is positively slopped showing the hazard ratio slightly increases with that age. CD4 count values and number of dependents are linear variables, except for the extreme numbers of dependants. The smoothed curve for CD4 count values at debut of treatment is horizontal with a slope of zero, while that of dependants is roughly horizontal with slight curve at the extreme numbers of dependants. If we drop two outliers with 13 dependants, then the curve is horizontal with a zero slope. However, dropping these subjects does not increase the explanatory value of the model. Hence the final model is unadjusted for number of dependants and this variable is treated as linear.

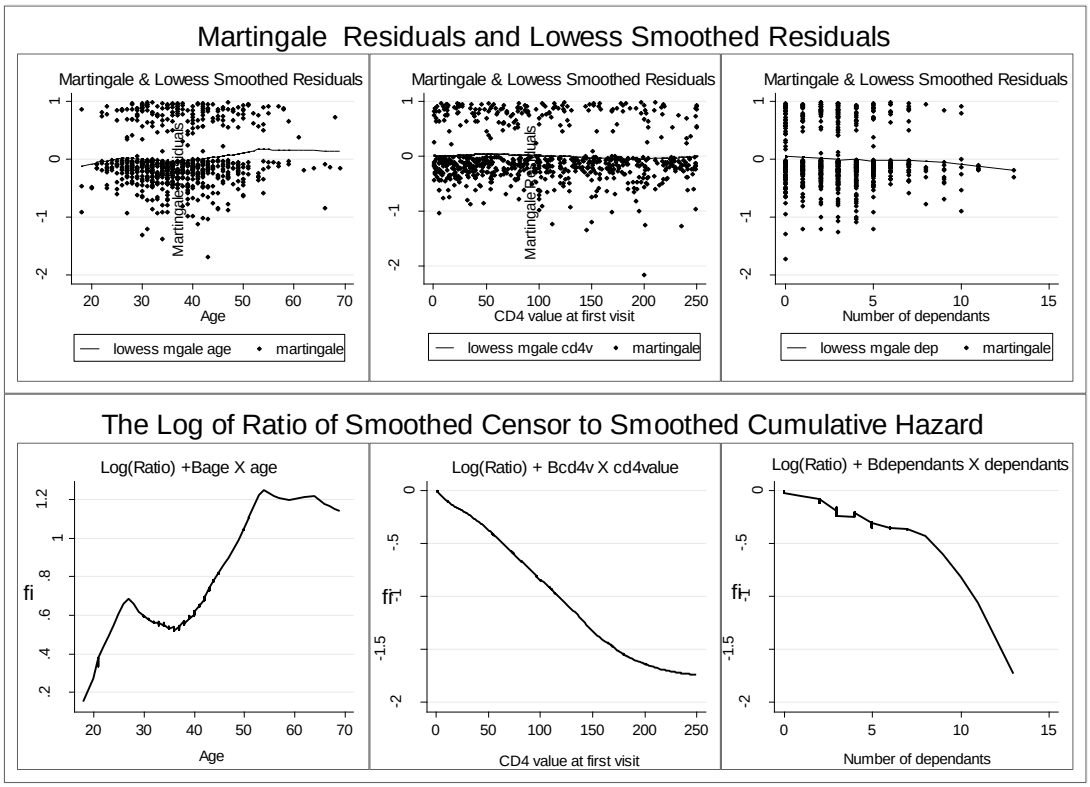


Figure 4: Plots of two residual-based methods for selecting the scale of the continuous variables

8.3.1.3 Deviance residuals

This is also transformed martingale residual and it shows that all the continuous covariates are linear. The slopes of the deviance residuals and their smoothed lowess are shown in Figure 5 and Figure 6. The deviance residual and the smoothed lowess for age is roughly horizontal with a slope approximately zero. This contradicts the martingale residual which showed that the hazard ratio increases with age. The deviance residual shows that the observations in martingale residual that showed age as outliers are not really outliers. The deviance residuals for CD4 count at first visit and ART and CD4 counts interaction confirms the martingale residual, confirming that there are no outliers in the observations.

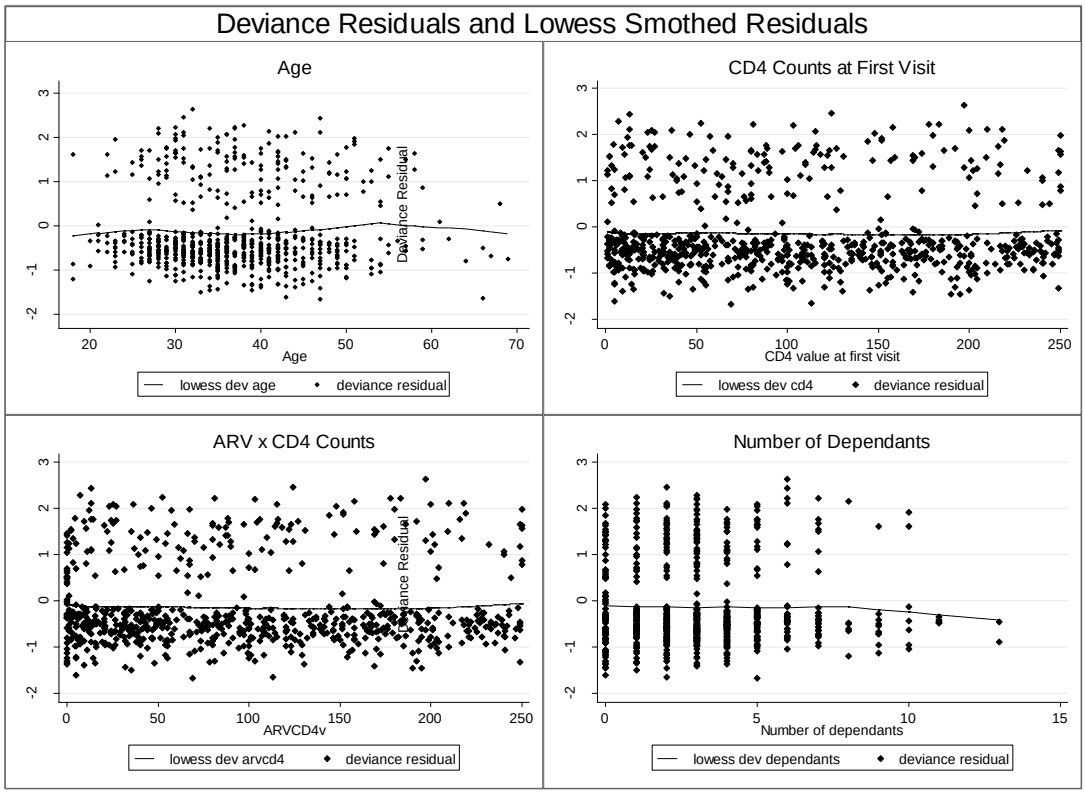


Figure 5: Deviance Residuals and a running mean smoother for (1) age (2) CD4 Counts at first visit (3) ARV x CD4 count interaction (4) Number of dependants.

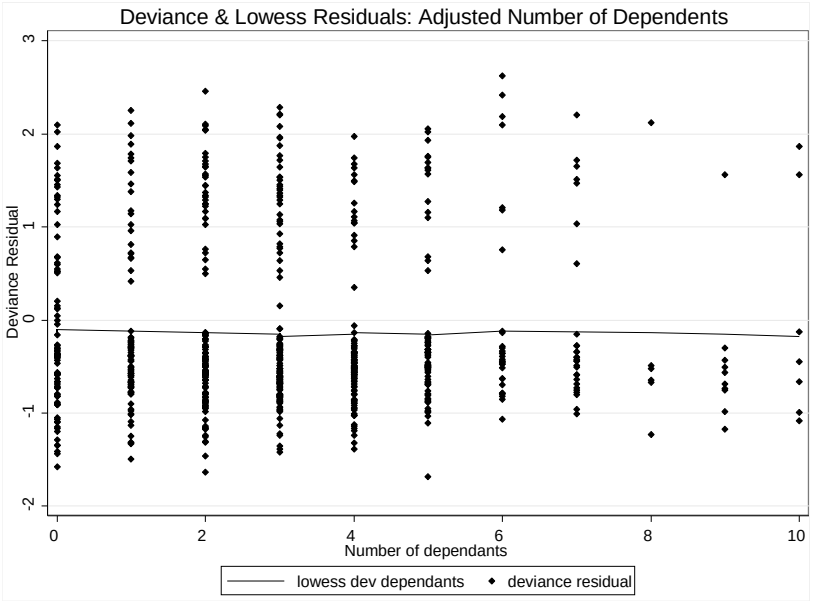


Figure 6: Deviance Residuals and a running mean smoother for adjusted Number of Dependants

8.3.2 Testing for Influencial Variables

In assessing model adequacy, the study also determined whether any particular variable had undue impact on the inferences made the basis of the Cox PH regression model. To do this we use Score Residuals.

8.3.2.1 Score Residual: Testing for influential variables

Score residuals can be thought of as a three-way array with dimensions of subject, covariate and time. These residuals are useful for assessing individual influence and for robust variance estimation. According to Hosmer & Lemeshow (1999), for continuous covariates, the score residuals have the linear regression leverage property that the further the value is from the mean, the larger the score residual. The score residuals for age, CD4 count, number of dependants and ARV x CD4 count interaction variables were plotted. This is because only the score residuals for continuous variables can be examined graphically (Hosmer and Lemeshow, 1999).

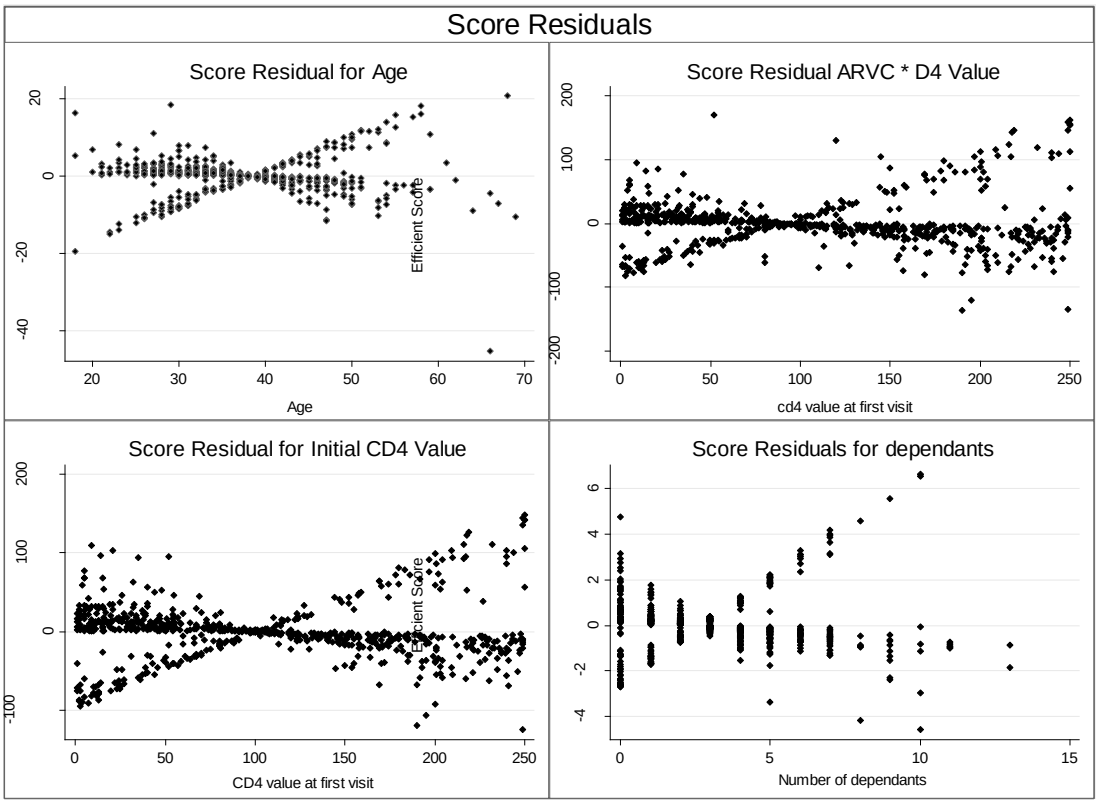


Figure 7 Graph of score residuals for (a) age (b) ARV x CD4 counts (c) CD4 counts (d) Number of dependants

Figure 7 shows the plots for all the score residuals. All the score residuals display a fun shape as expected. The score residual for age is smallest near the mean age of 37 years and increasing in absolute values for ages increasingly older than 37. The purpose of this graph is to see if there are ages that yield unexpectedly large values and this would be a point lying well away from the others in the plot. From our graph there are two points that fall a bit far away from the rest of the points. However, the distance between these points and the others are not striking. The two oldest subjects are 68 and 69 years old, have the score residuals that are well within the observed range of value. Hence, we conclude that there are no high leverage values for age.

The score residual for dependants is smallest near its mean which is three dependants and increasing in absolute values for number of dependants increasingly more than three. As with age, the fun shape of the graph is expected and although two extreme points are noted to the right of the graph shows the largest number of dependants i.e. 13, the distance between these points and others are not striking and hence no high leverage for number of dependants. The score residual for CD4 counts at treatment debut and the ARV and CD4 counts interaction are as expected; the graphs are fun shaped and are smallest around the mean of the two variables. There are no extreme points and hence no high leverage for CD4 counts and ARV and CD4 counts interaction.

8.3.3 Assessing the Proportional Hazard Assumption

We used two statistical methods the time interactions and residual based tests as well as a graphical presentation to test the proportional hazard assumption (PH assumption) of the Cox regression model.

8.3.3.1 Time Interactions

We considered the model in equation (31) which involved explicit tests of the coefficients for interactions of covariate and time. We checked the proportionality by including time-dependent covariates (i.e. age, CD4 count value, CD4 strata and ARV use and CD4 count value interaction) in the model. If a time-dependent covariate is significant this indicates a violation of the proportionality assumption for that specific predictor. The Tables 35 and 36 show the results of fitting the main effects model and

the model with interactions with log-time. The main effects model shows that CD4 counts and ARV use and CD4 counts interaction covariates are significant, while age and CD4 strata covariates are not significant. The p-values for the Wald statistics for all the four interactions are not significant suggesting that the hazard function may be proportional in all the four covariates. The value of partial likelihood ratio test for addition of the four interaction variables is $G = 2.06$, and with four degrees of freedom the p-value is 0.724.

Table 36: The Stratified Cox PH Model

_t	Coef.	Std. Err.	z	P>z	[95% Conf. Interval]	
ever_arv	-2.1736	0.5178	-4.20	0.0000	-3.1883	-1.1588
age	0.0170	0.0093	1.83	0.0670	-0.0012	0.0352
cd4_strata	0.0240	0.2597	0.09	0.9260	-0.4850	0.5330
cd4_value	-0.0082	0.0032	-2.54	0.0110	-0.0146	-0.0019
condom	-0.7508	0.1951	-3.85	0.0000	-1.1332	-0.3684
dependants	-0.0674	0.0361	-1.87	0.0620	-0.1382	0.0034
employ_state	0.9876	0.4836	2.04	0.0410	0.0398	1.9355
pipwater	0.3952	0.1786	2.21	0.0270	0.0450	0.7453
sex	0.6433	0.1715	3.75	0.0000	0.3071	0.9794
income2	-0.4346	0.2251	-1.93	0.0540	-0.8758	0.0066
income3	-3.6998	1.2074	-3.06	0.0020	-6.0664	-1.3333
married	-0.1844	0.1626	-1.13	0.2570	-0.5031	0.1344
educ_level2	-0.2044	0.3418	-0.60	0.5500	-0.8743	0.4655
educ_level3	-0.6939	0.3587	-1.93	0.0530	-1.3970	0.0092
arvcd4va	0.0071	0.0034	2.06	0.0390	0.0004	0.0139
arvemploy	-1.2456	0.4888	-2.55	0.0110	-2.2036	-0.2875
cd4strinco~3	2.7925	1.0433	2.68	0.0070	0.7477	4.8372
income3_ed~3	1.4912	0.6554	2.28	0.0230	0.2067	2.7757

Table 37: The Stratified Cox Time Interaction Model

_t	Coef.	Std. Err.	z	P>z	[95% Conf. Interval]	
rh						
ever_arv	-2.1619	0.5156	-4.19	0.0000	-3.1725	-1.1513
age	0.0223	0.0211	1.06	0.2890	-0.0190	0.0636
cd4_strata	-0.5812	0.5747	-1.01	0.3120	-1.7075	0.5452
cd4_value	-0.0074	0.0061	-1.21	0.2260	-0.0194	0.0046
condom	-0.7561	0.1968	-3.84	0.0000	-1.1418	-0.3703
dependants	-0.0663	0.0362	-1.83	0.0670	-0.1373	0.0046
employ_state	1.1062	0.4985	2.22	0.0260	0.1291	2.0833
pipwater	0.3869	0.1787	2.16	0.0300	0.0366	0.7372
sex	0.6525	0.1723	3.79	0.0000	0.3147	0.9902
income2	-0.4236	0.2258	-1.88	0.0610	-0.8662	0.0190
income3	-3.6659	1.2097	-3.03	0.0020	-6.0368	-1.2949
married	-0.1975	0.1638	-1.21	0.2280	-0.5185	0.1235
educ_level2	-0.1831	0.3423	-0.53	0.5930	-0.8540	0.4878
educ_level3	-0.6671	0.3594	-1.86	0.0630	-1.3715	0.0372
arvcd4va	0.0076	0.0056	1.35	0.1760	-0.0034	0.0186
arvemploy	-1.3707	0.5044	-2.72	0.0070	-2.3593	-0.3821
cd4strinco~3	2.7417	1.0439	2.63	0.0090	0.6956	4.7878
income3_ed~3	1.5155	0.6589	2.30	0.0210	0.2240	2.8070
t						
age	-0.0026	0.0099	-0.26	0.7950	-0.0220	0.0168
cd4_strata	0.3190	0.2640	1.21	0.2270	-0.1984	0.8363
cd4_value	-0.0004	0.0026	-0.16	0.8690	-0.0055	0.0047
arvcd4va	-0.0003	0.0021	-0.14	0.8920	-0.0044	0.0038

8.3.3.2 Schoenfeld Residuals

The second method used was the residual based tests using Schoenfeld residuals. We calculate the correlation between the Schoenfeld residuals for each of the covariates and the rank of the survival time; we then tested the proportionality for each predictor and that of the model as a whole. The statistical test as shown in Table 38 are not significant since no covariate has a p-value less than 0.05, we therefore can't reject the proportionality and we assume that we do not have a violation of the proportional hazard assumption. Both individual predictor and global tests shows that the Cox PH model does not violate the PH assumption.

Table 38: Test of proportional hazards assumption

Time: Rank(t)

	rho*	chi2	df	Prob>chi2
ever_arv	-0.0097	0.02	1	0.8854
age	0.0071	0.01	1	0.9188
cd4_strata	0.0660	0.81	1	0.3689
cd4_value	-0.0135	0.04	1	0.8513
condom	0.1105	2.23	1	0.1352
dependants	-0.0548	0.55	1	0.4595
employ_state	-0.0331	0.21	1	0.6476
pipwater	0.0501	0.41	1	0.5235
sex	0.0258	0.12	1	0.7251
income2	0.1071	2.04	1	0.1535
income3	0.0432	0.33	1	0.5637
married	-0.0250	0.13	1	0.7218
educ_level2	-0.0456	0.37	1	0.5409
educ_level3	-0.0484	0.44	1	0.5066
arvcd4va	0.0102	0.02	1	0.8868
arvemploy	-0.0138	0.04	1	0.8500
cd4strinco~3	-0.0381	0.27	1	0.6052
income3_ed~3	-0.0118	0.03	1	0.8738
Global test		9.79	18	**0.9387**

rho is correlation between residuals and time.

8.3.3.3 Scaled Schoenfeld Residual

We then plotted the scaled Schoenfeld graphs for both dichotomous and continuous covariates against time. The rationale behind the Schoenfeld residual is that the effect of a covariate may change over the follow up period. If the PH assumption holds, the Schoenfeld residuals should be a random walk over the range of survival times; that is, there should be no relationship between an observation's residual for that covariate and the length of its survival time. The plots for our scaled Schoenfeld and their smooth show no trend over time (see Figure 8 and Figure 9). The smoothed residuals of all the covariates except condom use have essentially slopes of zero. This further indicates that there is no violation of the proportionality assumption. However, the slope condom use coefficient only changes slightly and the statistical test does not show that it violates the PH assumption.

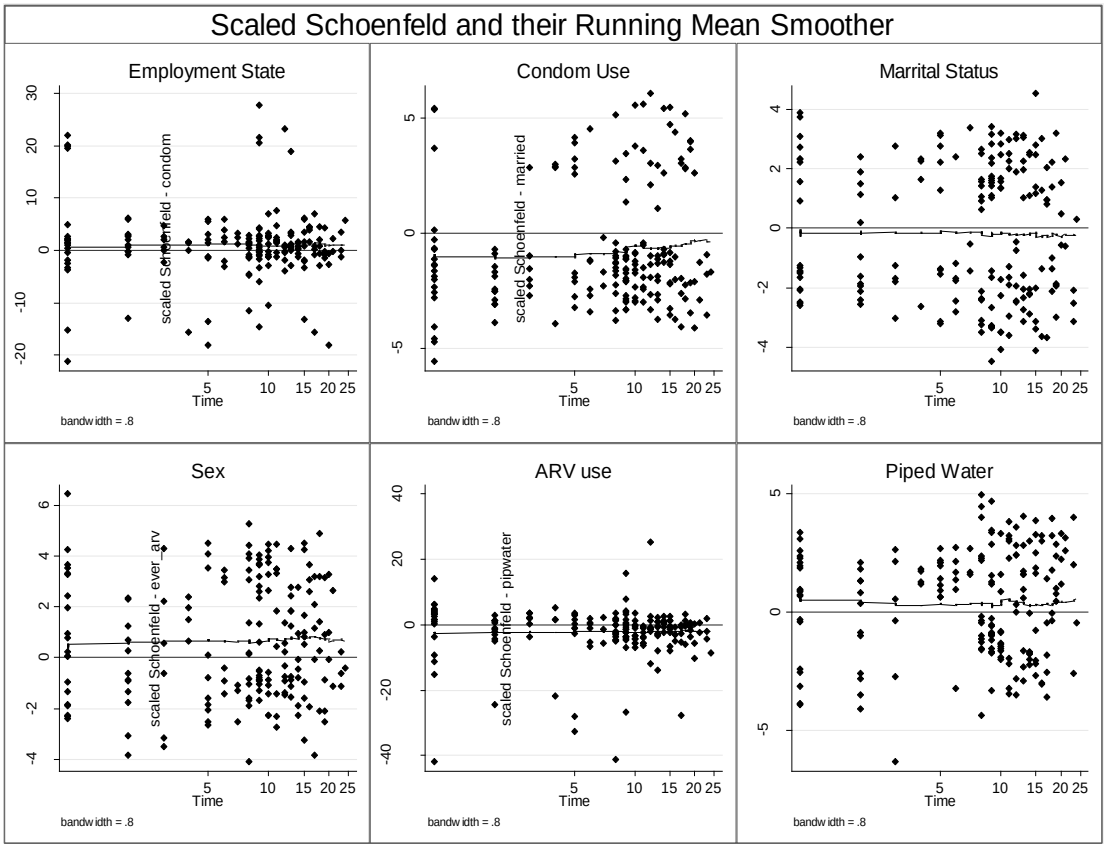


Figure 8 Scatterplot of scaled Schoenfeld residuals for the discrete variables employment status, condom use, marital status, sex, ARV use and use of piped water and their lowess smooth versus the follow up time in years.

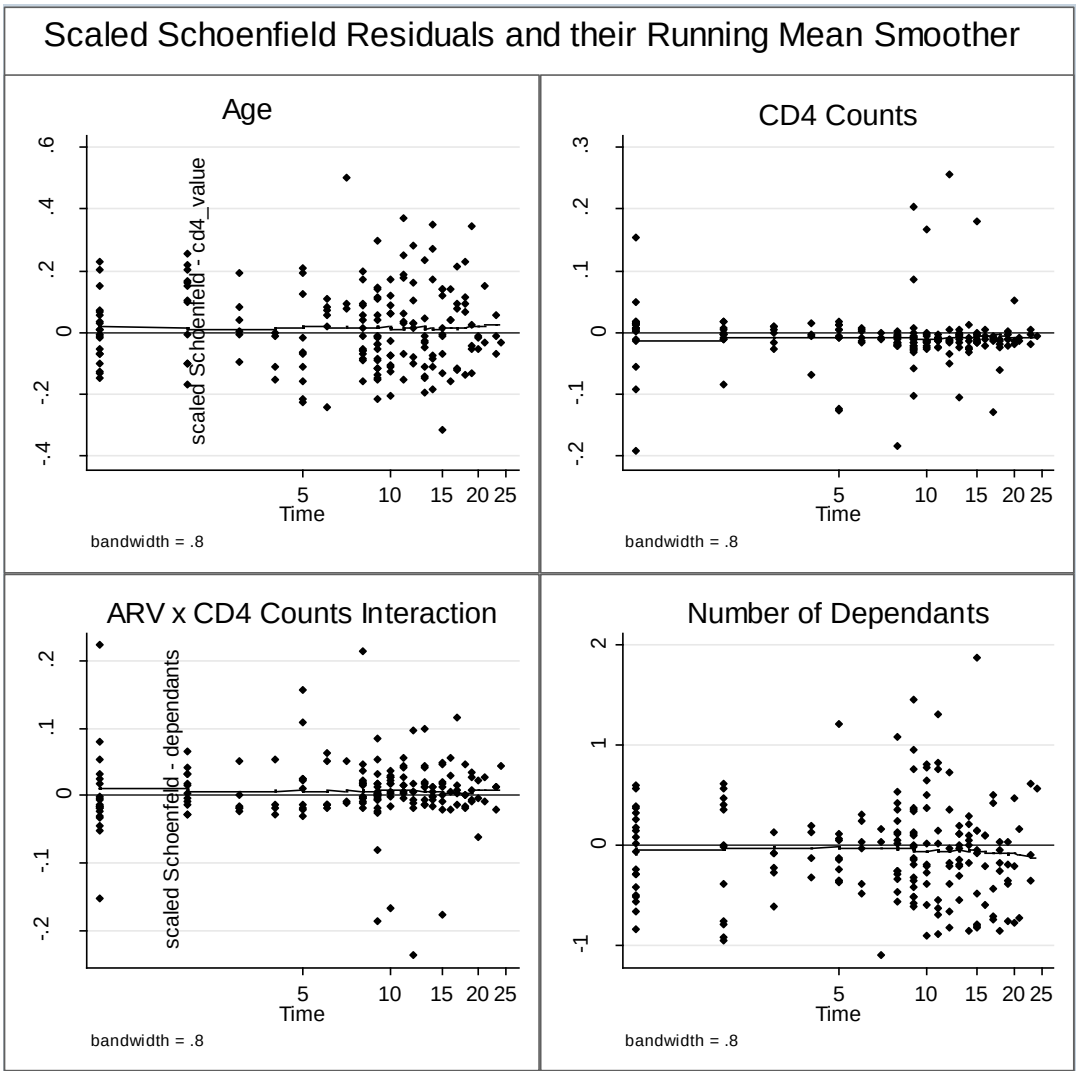


Figure 9 Scatterplot of scaled Schoenfield residuals for the continuous variables age, CD4 count values, ARV use and CD4 count interaction and number of dependants and their lowess smooth versus the follow up time in years

8.3.4 Assessing the Goodness of Fit

Overall fit of the model was assessed by the Cox–Snell residuals. In a well-fitting model, these residuals will follow a standard exponential distribution with a hazard ratio of one. A unit exponential distribution is demonstrated in a plot of Cox-Snell residuals against an estimate of the integrated hazard rate based on Cox-Snell residuals. This plot should form a 45-degree straight line through the origin if the model fit is correct. A plot of the Cox-Snell residuals against the cumulative hazard of Cox-Snell residuals is presented (Figure 10). There is some evidence of a systematic deviation from the straight line, which gives us some concern about the adequacy of

the fitted Cox PH model. However, the model-fit is satisfactory for the Weibull and Log-logistic models as shown in Figure 10.

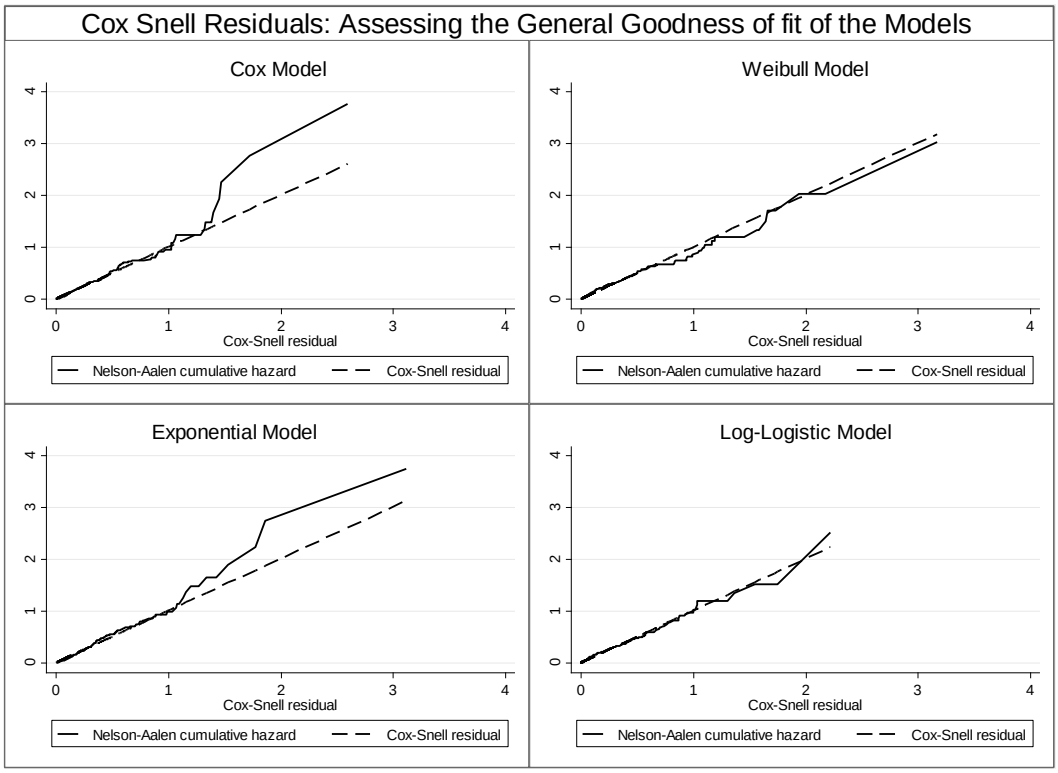


Figure 10 cumulative hazard for Cox-Snell residual for Cox, Weibull, Exponential and Log-logistic models

8.3.5 The Predictive power of the Cox Model

We evaluated the predictive power of the Cox Model by computing the Harrell's C concordance statistic. This statistic is defined as the proportion of all usable subjects pairs in which predictions and outcomes are concordant and measures the agreement of predictions with observed failure order (Cleves et al, 2008).

Table 39 Harrell's C concordance statistic

Number of subjects (N)	701
Number of comparison pairs (P)	87103
Number of orderings as expected (E)	62228
Number of tied predictions (T)	0
Harrell's C = (E + T/2) / P	0.7144
Somers' D	0.4288

The value of C ranges between 0 and 1, and is 0.714 indicating that by using all the predictors in the model, we correctly identify the order of the survival times of pairs of patients 71.4% of the time. Since the value of Somers' D is greater than zero, it also confirms that the Cox model has predictive powers.

9 CHAPTER NINE: SURVIVAL ANALYSIS RESULTS

9.1 Univariate Analysis Results

The study sample size was 701 patients out of whom 688 were on ARVs while 33 were not on ARVs. It's important to note that there was constraint in accessing data of patients who were only on opportunistic infection and prophylactic treatment. The imbalance is therefore due to data constraints. Table 40 summarizes the demographic characteristics of the cohort studied. Of all the patients sampled, 57% were from Moi Referral and Teaching Hospital (AMPATH) while the remaining 43% were from Mbagathi District Hospital (MDH). The median age of patients at the start of the treatment was 37 years (range 18–69). In both treatment models, the majority of the patients were women 57.1% and 64.2%, of the patients were female in MDH and AMPATH respectively. In each of the treatment models, slightly over 30% of the patients had CD4 count 50 and below at the treatment onset. 35% and 26% of the patients in MDH and AMPATH were using condoms respectively.

Table 40: Demographic and clinical information of HIV patients (n=701)

Demographic variable	Mbagathi District Hospital N=301(43%)	AMPATH N=400 (57%)	*P*-value
Sex			
Male	129 (42.9%)	143 (35.8%)	0.124*
Female	172 (57.1%)	257 (64.2%)	
Dead			
Yes	106 (35.2%)	74 (18.5%)	
No	195 (64.8%)	326 (81.5%)	
Baseline CD4 strata			
0-50	100 (33.2%)	124 (31%)	0.000*
51-250	201 (66.8%)	276 (69%)	
Condom use			
Yes	105 (34.9%)	105 (26.2%)	0.000*
No	196 (65.1%)	295 (73.8%)	
Income Level (KSh)			
0-2,500	131 (43.5%)	309 (77.2%)	0.544*
2,501-10,000	126 (41.9%)	36 (9.0%)	
>=10,001	44 (14.6%)	55(13.8%)	
Highest level of educational			
None	6 (2%)	29 (7.3%)	0.247*
Primary	126 (41.9%)	207 (51.7%)	
Secondary or above	169 (56.1%)	164 (41.0%)	
Employment state			
Yes	157 (52.2%)	152 (38%)	0.054*
No	144 (47.8%)	248 (62%)	
Marital status			
Married	143 (47.5%)	233 (58.3%)	0.292*
Not Married	158 (52.5%)	167 (41.7%)	
Baseline CD4 counts (mean)	98.8	108.1	0.004**
Number of dependants	3	4	0.004**
Piped water			
Yes	223 (74.1%)	144 (36%)	0.075*
No	78 (25.9%)	256 (64%)	
Age -Median age (years)	37.6	36.8	0.032**
Total time at risk (quarters)	4350	5048	
Median follow up duration (months)	15	11	
Ever_ARV			
Yes	280 (93%)	388 (97%)	0.000*
No	21 (7%)	12 (3%)	

Note * Logrank **Univariate Cox regression

9.1.1 Univariate Analysis: Kaplan-Meier Survival Curves

The survival durations were measured in 3 monthly interval. The Kaplan-Meier curve is shown in Figure 11 window 1 by the dark line.the grey are around the estimated Kaplan-Meier curve represent 95% confidence interval. The estimeted survival curve

declines slowly overtime. At the end of the 26 spells that is 78 months (6.5 years), the survival probability is above 50% indicating that some of the patients were still a live at the time of data collection. In Figure 11 window 2 we plot the survival function by ARV use, that is whether the patients on treatment follow up were ever put on ARVs or not. As expected, the curve shows that the patients on ARVs were likely to survive longer than the patients who were not put on ARVs. In Figure 11 window 4 we plot the survival function by sex, that is whether the patients on treatment follow up were male or female. The curves shows that the female patients were likely to survive longer than their male counterparts. The survival curve for marital status in Figure 11 window 3 shows that married patients on treatment follow up are likely to live longer than those not married.

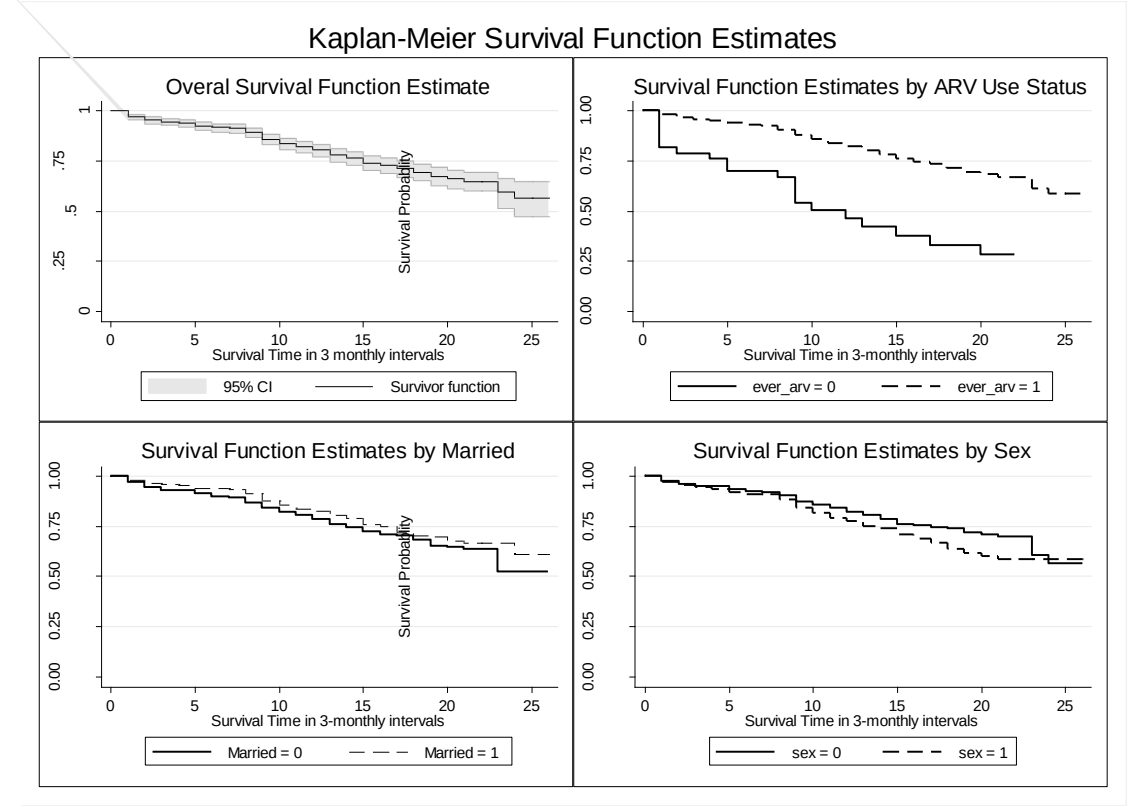


Figure 11: Survival duration: Kaplan-Meier estimate of Survival function – overall, by ARV use, by marital status and by sex

Table 41: Survival Duration: Kaplan-Meier Survival and Nelson-Aalen Cummulative Hazard Function

Time	Survivor Function	Cumulative Hazard
1	0.9715	0.0285
2	0.9544	0.0462
3	0.9458	0.0551
4	0.9401	0.0612
5	0.9258	0.0763
6	0.9173	0.0856
7	0.913	0.0902
8	0.8914	0.1138
9	0.8594	0.1497
10	0.8381	0.1745
11	0.8207	0.1953
12	0.8041	0.2156
13	0.7819	0.2431
14	0.7649	0.2648
15	0.7403	0.2971
16	0.7281	0.3136
17	0.7121	0.3355
18	0.6940	0.3610
19	0.6743	0.3892
20	0.6612	0.4087
21	0.6493	0.4267
22	0.6493	0.4267
23	0.5936	0.5125
24	0.5654	0.5601
25	0.5654	0.5601
26	0.5654	0.5601

Table 41 shows that after the first period, the survival probability is 0.97, indicating that roughly 3% of the HIV positive enroled on treatment had died within the first three months of treatment follow-up and at the time of the study, at the end of 26 spell (78 months) 57% of the patients were still a live and on follow up.

9.1.2 Univariate Analysis Results: Nelson –Aalen Cumulative Hazard Curves

The Nelson –Aalen cumulative hazard in Figure 12, window 1 shows little variaton in the hazard rate, which translates into an approximately linear hazard. If the crude hazard varies a lot then the cumulative hazard would appear non linear. The cummulative hazard function by ARV use in window 2, shows that the hazard rate increases at a higher rate for those patients who were not using ARVs than it does for the patients on ARVs. The cummulative hazard function by marital status in window 3, shows that the hazard rate increases at a higher rate for the patients who are not married than it does for those married on treatment follow up. The cummulative hazard function by sex in window 4, shows that the hazard rate increases at a higher rate for male patients than it does for female patients on treatment follow up. The curves cross at the end, but this is due to very few subjects remaining on follow up.

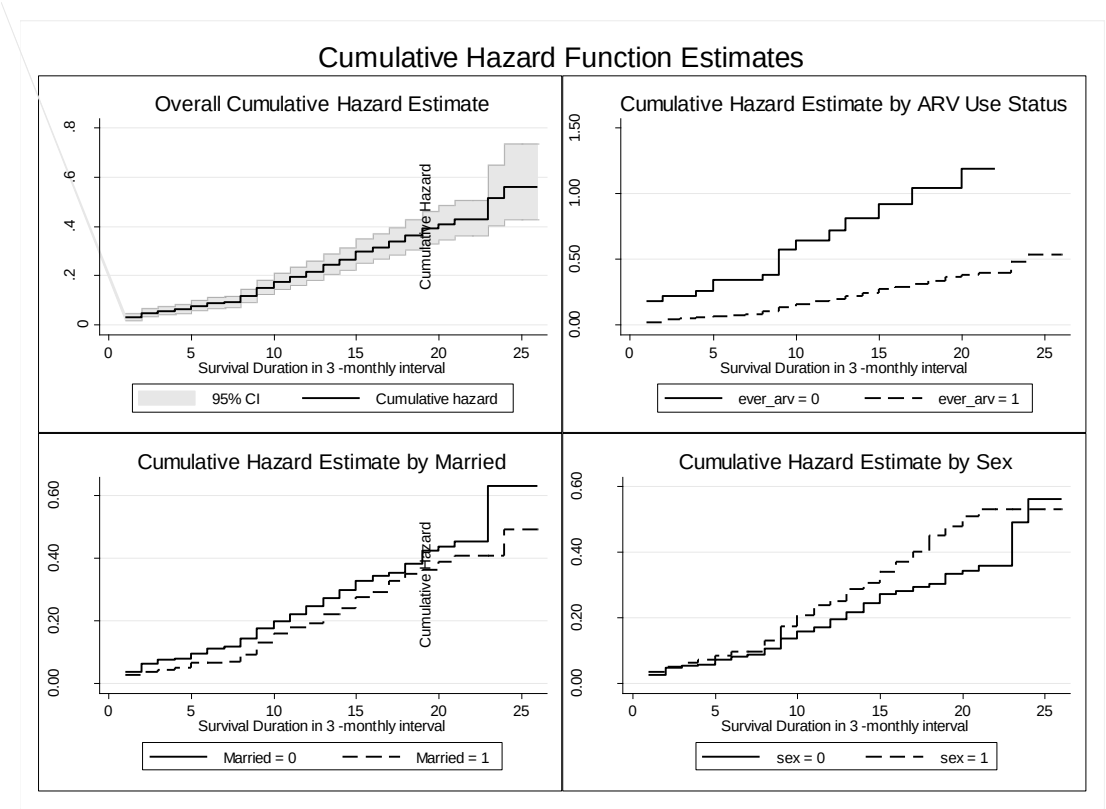


Figure 12: Nelson –Aalen Cumulative Hazard Curves for overall data, by ARV use, by marital status and by sex

9.2 Multivariate Analysis Results: Stratified Cox PH Regression Model

The results for stratified Cox PH model are presented and discussed in this section. This model is stratified by the type of hospital where the people living with HIV sought treatment. This is because the dummy variable "txmodel" that describes the hospital type violated the proportional hazard assumption. The explanatory variable that satisfied the proportional hazard assumption are included in the model, whereas the variable for the hospital type is not included in the model. The stratified Cox model therefore controls for the hospital type by stratification while all the other variables are controlled for by inclusion in the model.

However, since the hospital type variable is excluded from the model, we are unable to estimate its hazard ratio controlled for the covariates. This is the limitation of stratification on the hospital type. Stratification allows the baseline for Mbagathi hospital and Moi referral hospital to vary while the coefficients for the covariates are the same for the two hospitals. The results of this analysis are presented in Table 42 and Table 43.

Table 42: Stratified Cox Analysis Results; n = 701

_t	Coef.	Std. Err.	z	P>z	[95% Conf. Interval]	
ever_arv	-2.1357	0.5196	-4.11	0.0000	-3.1541	-1.1172
age	0.0219	0.0109	2.01	0.0450	0.0005	0.0433
cd4_strata	0.0643	0.2604	0.25	0.8050	-0.4462	0.5747
cd4_value	-0.0084	0.0033	-2.59	0.0100	-0.0148	-0.0021
condom	-0.7542	0.1953	-3.86	0.0000	-1.1369	-0.3715
dependants	-0.0679	0.0369	-1.84	0.0660	-0.1402	0.0044
employ_state	0.9836	0.4836	2.03	0.0420	0.0358	1.9315
pipwater	0.3997	0.1790	2.23	0.0260	0.0489	0.7506
sex	0.6540	0.1751	3.74	0.0000	0.3109	0.9972
income2	-0.4319	0.2259	-1.91	0.0560	-0.8747	0.0109
income3	-3.6277	1.2075	-3.00	0.0030	-5.9944	-1.2610
married	-0.1796	0.1637	-1.10	0.2730	-0.5004	0.1412
educ_level2	-0.1743	0.3437	-0.51	0.6120	-0.8481	0.4994
educ_level3	-0.6780	0.3589	-1.89	0.0590	-1.3814	0.0253
arvcd4va	0.0069	0.0035	1.99	0.0470	0.0001	0.0137
arvemploy	-1.2969	0.4896	-2.65	0.0080	-2.2565	-0.3374
cd4strinco~3	2.7359	1.0430	2.62	0.0090	0.6916	4.7801
income3_ed~3	1.4839	0.6555	2.26	0.0240	0.1992	2.7686

Log likelihood = -909.987

Table 43: Stratified Cox Analysis Showing Hazard Ratios; n = 701

_t	Haz. Ratio	Std. Err.	z	P>z	[95% Conf. Interval]	
ever_arv	0.1138	0.0589	-4.20	0.0000	95.88	68.61
age	1.0172	0.0094	1.83	0.0670	0.12	-3.59
cd4_strata	1.0243	0.2660	0.09	0.9260	38.43	-70.40
cd4_value	0.9918	0.0032	-2.54	0.0110	1.45	0.19
condom	0.4720	0.0921	-3.85	0.0000	67.80	30.82
dependants	0.9348	0.0338	-1.87	0.0620	12.91	-0.34
employ_state	2.6849	1.2984	2.04	0.0410	-4.06	-592.75
pipwater	1.4846	0.2652	2.21	0.0270	-4.61	-110.71
sex	1.9027	0.3263	3.75	0.0000	-35.95	-166.29
income2	0.6475	0.1458	-1.93	0.0540	58.35	-0.66
income3	0.0247	0.0299	-3.06	0.0020	99.77	73.64
married	0.8316	0.1352	-1.13	0.2570	39.53	-14.38
educ_level2	0.8152	0.2786	-0.60	0.5500	58.28	-59.29
educ_level3	0.4996	0.1792	-1.93	0.0530	75.27	-0.92
arvcd4va	1.0071	0.0035	2.06	0.0390	-0.04	-1.40
arvemploy	0.2878	0.1407	-2.55	0.0110	88.96	24.99
cd4strinco~3	16.3216	17.0276	2.68	0.0070	-111.22	-12511.98
income3_ed~3	4.4424	2.9114	2.28	0.0230	-22.96	-1504.95

Log likelihood = -909.987

9.2.1 Interpretation of the Cox regression results

The stratified Cox PH model reports no intercept since it is subsumed into the baseline hazard $h_0(t)$and is unidentifiable from the data. The primary variable of interest in this study is ARV use. Our major objective is to compare survival of patients on ARV drugs and those not on ARV drugs, adjusting for possible confounding or interaction effects of other covariates such as age, CD4 count values, CD4 strata, condom use etc. Ever-ARV is the exposure variable of primary interest. Since the CD4 count value variable and ART use variables interact, the hazard ratio for effect of ARV use is given by:

$$\widehat{HR} = e^{\widehat{\beta}_E + \sum_{0=j}^{J} \widehat{\delta}_j W_j}$$

Where;

$\hat{\beta}_E$ is the estimated coefficient of the exposure variable ($E = ever_{arv}$)

$$E = \begin{cases} 1 & \text{if patient is on ARVs drugs} \\ 0 & \text{if patient is not on ARVs drugs} \end{cases}$$

$$\hat{\beta}_{Ever_{ARV}} = -2.1357 \; if \; E = 1$$

$\hat{\delta}_j$ = the estimated coefficient of the interaction terms; and $j = 1,2$

$$\hat{\delta}_1 = \beta_{ARVCD4value} = 0.0069$$

$$\hat{\delta}_2 = \beta_{ARV_{Employ}} = -1.2969$$

W_j = the covariates interacting with exposure variable; and $j = 1, 2$;

$$W_1 = CD4\ count\ values\ at\ enrolment;\ W_1 = 1, 2, \ldots, 250$$

$$W_2 = Employment\ state\ at\ enrolment;\ W_2 = \begin{cases} 1 & \text{if employed} \\ 0 & \text{if unemployed} \end{cases}$$

The Estimated hazard ratio for ARV use (Ever-ARV=1)

$$\widehat{HR} = e^{\hat{\beta}_E + \hat{\delta}_1 W_1 + \hat{\delta}_2 W_2}$$

The estimated hazard ratio for ARV use is given by:

$$\widehat{HR}(everavr = 1; cd4\ val;\ employ = 1) = e^{-2.1357 + 0.0069 * CD4value + -1.2969}$$

$$\widehat{HR} = e^{-3.4326 + 0.0069 * CD4value}$$

The magnitude of the estimated hazard ratio depends on the value of CD4 counts of the patients. We present a table containing point and interval estimates of treatment effect for key values of CD4 count.

Table 44: Estimated HR and 95% CI; *ever_arv* = 1 and *employ_state* = 1

CD4 count	Hazard Ratio	95% Conf. Interval	
10	0.035	0.007	0.178
50	0.046	0.008	0.269
100	0.065	0.009	0.467
250	0.182	0.012	2.881

The estimated hazard ratios in Table 44 are all less than one and increase with the size of CD4 count values, indicating that for the patients employed ($employ\_state = 1$), being on ARVs (ever_arv =1), is beneficial or reduces the rate of death and its increasingly beneficial the lower the value of CD4 count values. The confidence intervals support significant effects of ARV treatment for patients with CD4 counts 10, 50 and 100. Table 44 shows that for patients with CD4 count value of 10 and are employed, the estimated hazard ratio is 0.035, this implies that, being on ARVs reduces their rate of death by 96.5 percent compared to patients with same CD4 count value who are not on ARVs. At the same time, the patient with CD4 count value of 250 have an estimated hazard ratio of 0.182, indicating that being on ARVs for those employed reduces the risk of death by 81.8 percent compared to those not on ARVs.

Estimated Hazard Ratios (HR) and 95% confidence intervals for ARV use effect $\underline{ever\ arv = 1}$ **and** $\underline{employ\ state = 0}$

However for the patients on ART and unemployed, the hazard ratio of ART treatment is given by: $\widehat{HR} = e^{\hat{a}_E + \hat{a}_1 W_1}$ since $W_2 = 0$. Hence the estimated hazard ratio is

$$\widehat{HR} = e^{-2.1357 + 0.0069 * CD4value}$$

Table 45: Estimated HR and 95% CI; when *ever_arv* = 1 and *employ_state* = 0

CD4 count	Hazard Ratio	95% Conf. Interval	
10	0.127	0.044	0.365
50	0.167	0.048	0.587
100	0.236	0.051	1.096
250	0.667	0.057	7.820

The estimated hazard ratios for unemployed patient who are on ARV treatment are given in Table 45. These ratios are also less than one and significantly increase with increase in CD4 count values. These ratios show that being on ARV when unemployed decreases the rate of death and its more beneficial for patients with very low values of CD4. The confidence interval for patients with CD4 counts 10 and 50 supports the significance effect of ARV treatment. The hazard ratio for the unemployed patients with CD4 counts of 10 is 0.127, indicating that, being on ARV reduces their death rate by 87.3 percent compared to those not on ARVs. Comparing this percentage by that of the same category of patients who are employed, we see that employment reduces the rate of death by close to 10 percent.

The hazard ratio for patients not on ART and are employed

$\widehat{HR} = e^{\hat{a}_1 W_1 + \hat{a}_2 W_2}$ since $\hat{a}_E = 0$

Table 46: Estimated HR and 95% CI; when *ever_arv* = 0 and *employ_state* = 1

CD4 count	Hazard Ratio	95% Conf. Interval	
10	1.072	0.081	1.059
50	1.414	0.090	1.651
100	1.998	0.100	2.988
250	5.644	0.118	20.099

Note: Care needs to be taken when interpreting these results as the sample with no ARVs was very small and inference may result into errors.

The hazard ratio for condom use of 0.472 implies that patients using condoms face 52.8 percent lower risk of death compared to patients not using condoms. The 95

percent confidence interval suggests that the rate could be as much as 68 percent lower to 31 percent lower. The p-value is equal to 0 and the confidence interval excludes the null of 1, hence, condom use is a significant predictor of better survival.

The partial likelihood ratio test for the overall significance of the educational level coefficients is 4.31 and the p-value computed using a chi-square distribution with two degrees of freedom is 0.116, suggesting that neither secondary school leavers nor people with more than secondary school education have a hazard rate that is significantly different from people with no education. The p-value of the individual Wald statistics indicates that the hazard rate in each of the two groups is not significantly different from that of reference group.

The hazard ratio comparing primary education to no education

The estimated hazard ratio comparing primary education and no education ($\widehat{HR}(2,1) = e^{\hat{\hat{a}}_{Educ\_level\_2}}$) is 0.815. And the hazard ratio comparing secondary or above level of education to no education ($\widehat{HR}(2,1) = e^{\hat{\hat{a}}_{Educ\_level\_3}}$) is 0.5. These hazard ratios imply that, HIV positive patients on follow up with primary levels of education and those with secondary or higher levels of education are dying at a rate that is 18 percent and 50 percent lower than patients with no education at all. The p-values and the confidence intervals show that the education coefficients are not significant determinants of survival.

The hazard ratio for sex is 1.903, implying that holding all other factors constant, men on HIV treatment follow up die at 90.3 percent rate higher than women on follow-up. The estimated p-value = 0 and the confidence interval excludes the null of one both showing that sex has a significant impact on survival.

The hazard ratio of age is 1.017; this means that holding all other factors constant, for each year's increase in age, there is 1.7% increase in the patient risk of death, 95% CI (0% increase to 4% increase). As shown by the p-value and 95% confidence interval age is not a significant determinant of survival.

The hazard ratio of dependants is 0.935; this means that an increase in number of dependants by one reduce the patient risk of death by 6.5 percent. As shown by the p-

value and 95% confidence interval, number of dependants is not a significant determinant of survival.

The hazard ratio for marriage is 0.832, this means that, holding all other factors constant, those who are married and on HIV treatment follow up die at a lower rate than those not married. However married is not a significant determinant of survival.

The hazard ratio for piped water is 1.485, implying that, holding all the other variables constant, patients with piped water within their households, die at 48.5 percent rate higher than those without piped water. Piped water is a significant determinant of survival.

9.3 Multivariate Analysis Results: Stratified Weibull Regression Model

This thesis also estimated the stratified Weibull model. This is because the model fit test indicated that the Weibull regression model fit the data better. This model was also stratified on the hospital type because the treatment site where the patients sought care was fixed by design and the dummy variable "txmodel" describing hospital types violate proportional hazard assumption. Stratification allowed the shape and scale of the Weibull PH model to vary with the hospital type holding all the other covariates constant. Since the variable "txmodel" is a dummy variable, STATA introduces this variable in the model and puts it in two places, in the main equation to capture the variation in the scale and in the ancillary equation to capture the variation in the shape of the hazard function. STATA then labels the variable created as _Stxmodel_1, the prefix _S denotes the variable created in STATA (Cleves et. al., 2008). The findings of this analysis are shown in Table 47.

Table 47: Weibull regression log relative hazard Regression Model

_t	Coef.	Hazard Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
ever_arv	-2.4242	0.0885	0.5246	-4.62	0.0000	-3.4523	-1.3960
age	0.0180	1.0182	0.0094	1.90	0.0570	-0.0005	0.0365
cd4_strata	-0.0166	0.9835	0.2606	-0.06	0.9490	-0.5275	0.4942
cd4_value	-0.0093	0.9907	0.0032	-2.87	0.0040	-0.0157	-0.0030
condom	-0.7982	0.4501	0.1976	-4.04	0.0000	-1.1855	-0.4110
dependants	-0.0661	0.9360	0.0358	-1.85	0.0640	-0.1363	0.0040
employ_state	1.1372	3.1180	0.4876	2.33	0.0200	0.1816	2.0928
pipwater	0.3716	1.4501	0.1776	2.09	0.0360	0.0235	0.7198
sex	0.6500	1.9155	0.1727	3.76	0.0000	0.3116	0.9884
income2	-0.4895	0.6129	0.2235	-2.19	0.0290	-0.9275	-0.0514
income3	-3.7631	0.0232	1.2053	-3.12	0.0020	-6.1254	-1.4009
married	-0.1979	0.8205	0.1633	-1.21	0.2250	-0.5179	0.1221
educ_level2	-0.2916	0.7471	0.3415	-0.85	0.3930	-0.9609	0.3777
educ_level3	-0.8083	0.4456	0.3584	-2.26	0.0240	-1.5108	-0.1059
arvcd4va	0.0084	1.0084	0.0034	2.44	0.0150	0.0017	0.0152
arvemploy	-1.3757	0.2527	0.4917	-2.80	0.0050	-2.3395	-0.4120
cd4strinco~3	2.8611	17.4807	1.0435	2.74	0.0060	0.8159	4.9063
income3_ed~3	1.4924	4.4478	0.6517	2.29	0.0220	0.2152	2.7696
_Stxmodel_1	-6.0449	0.0024	0.7775	-7.77	0.0000	-7.5688	-4.5209
_cons	-1.0761	0.3409	0.7312	-1.47	0.1410	-2.5093	0.3571
ln_p							
_Stxmodel_1	1.1718	3.2278	0.1211	9.68	0.0000	0.9344	1.4091
_cons	-0.0606	0.9412	0.0857	-0.71	0.4790	-0.2286	0.1074

Log likelihood = -434.843

9.3.1 Interpretation of the Weibull PH regression results

The Wald test results for txmodel $z = 9.68$ with a significance level of 0.000. This shows that the hospital where the patients sought care has an effect on their mortality risk. In addition, the Wald test for scale parameter $z = -7.77$ with the $p = 0.000$, this also shows that the effect of the scale parameter is significant.

From Table 47, since txmodel ==1 for AMPATH and txmodel==0 for Mbagathi,

$ln\hat{p} = -0.0606$ for Mbagathi hospital (txmodel 2) and

$ln\hat{p} = 1.1112$ for AMPATH treatment centre (txmodel 1)

Hence,

$\hat{p} = \exp(-0.0606) = 0.941$ for Mbagathi hospital (txmodel 2) and

$\hat{p} = \exp(1.1112) = 3.038$ for AMPATH treatment centre (txmodel 1)

The estimate hazards are given by

$$\hat{h}(t_j|\boldsymbol{x}_j)\begin{cases} exp\begin{pmatrix} -1.08 - 2.42ever_{arv_j} + 0.018age_j - 0.02cd4_{strata_j} \\ -0.01cd4_{value_j} + \cdots + 1.50income\_educ3_j \end{pmatrix} 0.94t_j^{-0.06}, \text{if Mbagathi} \\ exp\begin{pmatrix} -7.11 - 2.42ever_{arv_j} + 0.018age_j - 0.02cd4_{strata_j} \\ -0.01cd4_{value_j} + \cdots + 1.50income\_educ3_j \end{pmatrix} 3.04t_j^{2.04}, \text{if AMPATH} \end{cases}$$

The results show that the hazard for Mbagathi hospital given the covariates is almost constant. The results also show that ART use is interacted with CD4 count values and employment status, while CD4 strata and income as well as income and education levels are also interacted. The p-values for all these interaction terms are less than 0.05 and hence they are significant determinants of survival for the patients on treatment follow up. These are interpreted just like in the Cox model. In addition, the CD4 count value, condom use, employment state, availability of piped water, patients sex, income and educational levels are significant determinants of survival for the patient on ARV compared to those not on ART.

9.4 Discussion

9.4.1 CEA study discussion

The cost effectiveness results confirm the findings by other studies (Clearly et. al., 2004) that even though ART treatment scenario is more costly, it remains the most cost effective intervention compared to No ART treatment scenario. Evaluating these results based on the WHO willingness to pay threshold for the East African region, the ICER for MDH and AMPATH are Ksh61,133 and Ksh70,535 respectively are significantly lower, hence cost effective. These are significantly lower than the WTP and hence highly cost effective.

There is significant difference in the effectiveness of ART treatment scenario in the two treatment sites with AMPATH reporting 26 undiscounted life years gained and MDH 13 undiscounted life years gained. This significant variation may be accounted for the by extra care and support services that is provided to patients on ARVs by the

AMPATH treatment modules. These extra services include structured and consistent nutritional support, in which patients with a given threshold of CD4 counts and are on ART are not only given the medical, support but are also given nutritional support. AMPATH treatment centre also provides income generating activities (IGAs) support to their patients. These IGAs acts as avenues for community counselling, treatment support and source of income to the members.

The food support and IGA support also enhances adherence to treatment and clinic visits, since group members provide group support to the patients. AMPATH also tracks the patients adherence and has stronger mechanisms in place for tracing the patients, studies have shown that adherence to ART is positively correlated to survival. In addition, Mbagathi hospital has been considered as a hospital of last resort where most middle income level patients report to very late when all other interventions has failed. The late presentation could also have contributed to higher mortality of Mbagathi hospital patients and hence lower life expectancy.

The study also reported the life expectancy for HIV positive patients on treatment follow up but not on ARVs to be 2.68 years. This is significantly lower and is not comparable to other studies that have reported the average survival for no ART to be between 9 and 11years (Johansson et. al 2010). However, it should be noted that in adequate data for no ART patients caused major constraints in this study. Records of data before on set of ART were not available and in addition, most of the mortality data are not stored in accessible format in Mbagathi hospital. The study therefore relied on limited data for no ART and mortality data for patients not on ART, most of which were for patients who died too soon most of the time before they are ready to be put on ART especially due to late presentation. The life expectancy of 2.68 years therefore only represents the life expectancy of the patients who presented late to the hospital and some who came early but were lost to follow up and only to resurface when very ill.

Comparing the increasing cost effectiveness ratio (ICER) values for Mbagathi hospital and AMPATH treatment centre, Mbagathi hospital is more cost saving than AMPATH and hence a more cost effective treatment site.

9.4.2 Survival Analysis discussion

As expected, the survival analysis findings show that the risk of mortality for patients on ART is less than for the patients who are not on ART. The survival rate is also found to be higher for the female than for male on treatment follow up. The lower survival rate of men may be partly explained by the health care seeking behaviour of men. Generally men tend to seek care late and have difficulty with follow up, especially given the need to visit hospitals on a regular basis. Secondly for most families, the men are bread winners and they may not have freedom to miss work frequently to go to hospital. Given the long-term follow up in ART treatment, these challenges may contribute to increase in treatment default and hence increased mortality risk for men.

On the other hand, the females seek health care more frequently than men and are generally more willing to seer additional support like counselling, nutritional support and health education. The women also have more avenues for accessing ART care than their male counterparts. For example during clinic visit for prevention of mother to child transmission, when the women take their sick and sometime HIV positive children to hospital, they too are likely to seek care. These opportunities are likely to increase women's access and adherence to treatment and hence increased survival rate.

The study also found out that condom use not only prevents HIV infection but also determines the survival of the people using ART. The risk of mortality for the patients on ART and using condoms were found to be lower than their counterparts who were on ART but not using condoms. Condom use proved to be a significant determinant of survival. This finding confirm the epidemiological studies that have been done and show that condom use reduces the chances of HIV positive people to acquire new and sometimes more resistant strains of HIV that recuses the effectiveness of ART and hence increased the risk of mortality for PLWHI and even for those on ART.
In addition, employment significantly increases survival for the people living with HIV on treatment follow up. Employment, age, marital status, dependants were also found to influences the survival rate of those using ART.

9.5 Study Limitations

9.5.1 CEA Study Limitations

The economic externalities such as the impact of treatment on income and productivity were beyond the scope of this study. In addition, ARV adherence and resistance was not factored into the model. These were basically due to data constraints as we used patient chart to collect the patient information yet the socioeconomic and demographic data was collected once at treatment debut. However, if the productivity costs associated with AIDS were included in the analysis the ART scenario could have been much more effective. The study employed the providers' perspective and was unable to measure all the individual costs including waiting time and the social costs of the HIV and AIDS infection.

The record for outpatient and inpatients were not synchronised and hence it was not possible to estimate the accurate inpatient care need for patients on treatment follow up, the inpatient health care needs and costs were therefore based on the general inpatient care need for HIV positive patients in Mbagathi hospital. Hence is likely to include the needs for HIV positive patients who were not on treatment follow up.

9.5.2 Survival analysis Study Limitations

This study was not able to control for some of the important determinants of patient survival including the body mass index (BMI) and adherence to medication for the patients on treatment although clinically, these are key indicators to patient survival. This was due to data constraints as the patient weights were missing for several patients and adherence indicator was not captured at all in Mbagathi hospital patient record. In addition, the socioeconomic and demographic data were only capture at treatment debut and hence in was not possible to capture impact of long term ART use of employment, income etc.

10 CHAPTER TEN: CONCLUSION

HIV and AIDS is a major cause of premature death and has resulted into a large economic loss in the country. There has been both local and global response to not only prevent the new infections but also to provide treatment, care and support the population that are already infected with the HIV virus. ART treatment has been introduced to treat eligible patients.

The cost effectiveness analysis of ART shows that putting patients on ART is costly but more effective compared to treating patients without ART. ART was found to prolong the life of patients in the treatment sites. In Mbagathi Hospital and Moi Referral Hospital, life expectancy increased by an average 13.3 and 23 years, respectively, with an additional lifetime costs of KSh762,948 ($10,193) and KSh1,424,081 ($19,026), respectively resulting to undiscounted incremental cost effectiveness ratio (ICER) of KSh57,405 ($767) and KSh61,911 ($827) per life year gained (LYG) for Mbagathi Hospital and Moi Hospital, respectively. However, it is important to note that the impact of nutritional and income generating support received by the patients followed up in Moi Hospital has not been controlled for and hence could account for the significant variation in expected life years between the study sites.

The study therefore not only provides relevant findings for policy implementation but also provides a unique avenue for other researchers to build on the Markov modelling and survival analysis methodology in studying patient outcomes and economic impact of health care interventions. The finding that unemployment lowers the survival rate of HIV positive patients on ARVs by 10% is a unique contribution. The study finding that condom use not only prevents HIV infection but increases the survival of people living with HIV and AIDS is also important.

The Government of Kenya committed itself to the UNAIDS declaration of Universal Access to HIV and AIDS care, treatment and support. In addition, the government signed a commitment to achieve millennium development goals (MDGs) by 2015. The MDG 6 is to combat HIV and AIDS, malaria and other diseases, with the target that by 2015, the government will have halted and begun to reverse the spread of HIV and AIDS. This study provides insights into the survival duration of patients on

treatment follow-up ranging from 13 to 26 additional years. Given these benefits, study findings support the Government of Kenya policy of universal access HIV and AIDS care and treatment.

The study found that even though education level had a positive impact on individual survival rate, this impact was not statistically significant. This may imply that the treatment education received by the patients on treatment follow up was more relevant for their survival than their general level of education. This study recommends that the Government applies the lessons learnt in HIV and AIDS care and treatment and develop relevant treatment education policies targeting other health care conditions that will empower and include the patients in their treatment process including early testing, treatment follow up and adherence to treatment recommendations. The Kenyan institutions for higher learning need to embrace this change and modify their curriculum especially on communication and empowering the patients to actively play their roles as they seek care and treatment. This will be very relevant for both communicable and non-communicable diseases treatment.

Economic and persistent financial challenges in both developed and developing countries putting unprecedented downward pressure on funding sources, internally and internationally. The international funding for HIV and AIDS care, treatment and support has been declining for the last three years. In response to this, the Government of Kenya is in the process of developing a sustainable HIV and AIDS financing strategy. This policy document will guide domestic resource mobilization for HIV and AIDS. The microeconomic analysis embraced by this study provides a clear understanding of individual costs and benefits of ART both in the short term and long term, including the determinants of survival length after treatment as well as after treatment follow-up.

The Government of Kenya is in the process of developing the Second Medium Term Plan (MTP II) for its Vision 2030 in which a special thematic group, The HIV and AIDS Thematic Group was set up to assess the achievements and challenges of implementation of HIV and AIDS related activity in MTP I. In addition, this thematic group is to ensure that all the sectors substantially include HIV and AIDS in each of the sector plans and activities. This study can be used to facilitate the work HIV and AIDS thematic group by making it understand the impact of ART treatment, the

impact of employment on survival of HIV and AIDS patients and the need to increase abilities of people on follow-up care to generate income at least for consumption purposes. The fact that the people living with HIV and AIDS who are employed and are on treatment survive longer than the group on treatment but not employed is important in guiding the thematic group to not only focus on treatment provision but also to ensure that each sector addresses macroeconomic stability issues that have a bearing on employment creation, inflation control and poverty reduction. These measures will improve the survival rates of patients on ART. The findings reported in the thesis support the Government's position on HIV and AIDS treatments, and gender mainstreaming of employment opportunities. The findings show the importance of addressing different socio-economic issues in efforts to improve rates of survival of AIDS patients.

The thesis recommends the need for research policy nexus between the institutions of higher learning and also with health care providing institutions. This will enhance continuous longitudinal data collection on clinical, demographic and socioeconomic indicators. This will facilitate multidisciplinary research and enable us understand the combined effects of medical treatment and socio-economic outcomes. In collecting this data, our health care and research institutions will be emulating the data collection techniques implanted in developed economies where HIV and AIDS patients are monitored epidemiologically while they are also asked to constantly provide information on their socio-economic conditions (e.g., family changes, educational changes, employment changes, motivation, believes, etc.) This will enhance research and development in our institutions, ensure the standard of research and service provisions is improved and in addition enable continuous monitoring and evaluation. The Government and our institutions of higher learning need to embrace the partnership and research approach employed by the AMPATH treatment at the Moi Referral Hospital.

REFERENCES

Ainsworth, M., K. Beegle, and G. Koda. (2005). The impact of adult mortality and parental deaths on primary schooling in northwestern Tanzania. Journal of Development Studies 41 (3): 412-439.

Arora, S. (2001). Health, Human Productivity, and Long-Term Economic Growth. The Journal of Economic History, 61(3), 699-749.

Asfaw, D B., Degu, J., Bjarne, R. and L. Bernt. (2009). Cost-effectiveness of anti-retroviral therapy at a district hospital in southern Ethiopia. Cost Effectiveness and Resource Allocation, 7 (13): 1-11

Auvert, B., Taljaard, D., Lagard, E., Sobingwi-Tambekou, J., Sitta, R., and A. Paren. (2005): Randomized controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med 2005:e298.

Bachmann, M. O. (2006). Effectiveness and Cost Effectiveness of Early and Late Prevention of HIV/AIDS Progression with Antiretrovirals or Antibiotics in Southern Africa. AIDS Care, 18(2), 109-120.

Badri, M., Maartens, G., Mandalia, S., Bekker, L., and Penrod, J. (2006). Cost-effectiveness of Highly Active Antiretroviral Therapy in South Africa. PLoS Med, 3 (1. e4).

Bailey, R., Moses, S., Parker, C., Agot, K., and MacLean, I. (n.d.). Male circumcision for HIV prevention in young men in Kisumu, Kenya: A randomized controlled trial. Lancet, 369(9562), 643–656.

Bartlett, J.G. and J.E. Gallant. (2001). Medical management of HIV infection. Johns Hopkins University, Division of Infectious Diseases. 2001-2002 Edition.

Beegle, K. De Weerdt, J. and S. Dercon. (2006). Orphan hood and the long-run impact on children. Am J Agric Econ 88:1266–1272.

Bell, C. S. Devarajan and H. Gersbach. (2006). Economic Growth, Education, and AIDS in Kenya: A Long-run Analysis, The World Bank Policy Research, Working Paper 4025, October 2006.

Bell, C., Devarajan, S., and Gersbach, H. (2003). The Long Run Economic Cost of AIDS: A Model with an Application to South Africa. The World Bank Economic Review, vol.20,(1), 55-89.

Bertozzi, S., Padua, N. S., Wegbreit, J., DeMaria, L., Feldman, B., Gayle, H., et al. (2006). HIV/AIDS Prevention and Treatment. In D. Jamison, J. Breman, A. Measham, G. Alleyne, M. Claeson, D. Evans, et al., Disease Control Priorities in Developing Countries (pp. 331-369). Geneva: World Health Organization.

Briggs, A., Ades, A. E., and J., M. (2003). Price Probabilistic Sensitivity Analysis for Decision foe Decision Trees with Multiple Branches: Use of the Dirichlet Disribution in a Bayesian Framework. Medical Decision Making, 23, 341.

Briggs, A., and Sculpher, M. (1998). An Introduction to Markov Modelling for Economic Evaluation. Pharmacoeconomics , 13 (4).

Briggs, A., Campbell, H., Clarke, P., and Sculpher, M. (2004). Parametric survival models and decision models: relating continuous hazards to discrete-time transition probabilities. Health Economists' Study Group Conference (pp. -). Glasgow: Unpublished.

Briggs, A., Sculpher, M., and Claxton, K. (2006). Decision Modelling for Health Economic Evaluation. New York: Oxford University Press.

Brouwer, W., Rutten, F., and Koopmanschap, M. (2001). Costing in Economic Evaluations. In M. Drummond, and A. McGuire, Economic Evaluation in Health Care: Merging Theory with Practice (pp. 68-93). New York: Oxford University Press.

Central Bank of Kenya (CBK) (2011). Retrieved September 20, 2011, from http://www.centralbank.go.ke/Publications/default.aspx

Central Bank of Kenya (CBK) (2011). Statistics http://www.centralbank.go.ke/downloads/publications/statistics/bulletin/dec10.pdf

Central Bank of Kenya. (2011). Central Bank of Kenya. Retrieved September 20, 2011, from http://www.centralbank.go.ke/Publications/default.aspx

Chapoto, A. and Jayne. T.S. (2008). Impact of HIV/AIDS-related deaths on rural farm household's welfare in Zambia: implications for poverty reduction strategies. Econ Dev Cul Change 2008; 56: 327–374.

Cleary, S. M., Boulle, A., McIntyre, D., and Coetzee, D. (2004). Cost-Effectiveness of Antiretroviral Treatment for HIV-Positive Adults in a South African Township. Health Trust MSF and University of Cape Town.

Cleary, S., McIntyre, D., and Boulle, A. M. (2006). The cost-effectiveness of Antiretroviral Treatment in Khayelitsha, South Africa – a Primary Data Analysis. Cost Effectiveness and Resource Allocation, 4(20).

Cleves, M., Gould, W., and Gutierrez, R. (2010). An Introduction to Survival Analysis Using STATA (3rd ed.). Texas: STATA Press.

Collett, D. (1993). Modelling Survival Data in Medical Research. Chapman and Hall/CRC.

Cook, J., E. Dasbach, P. Coplan et al.1999. Modelling the long-term outcomes and costs of HIV Antiretroviral therapy using HIV RNA levels: Application to a clinical trial. AIDS Research and Human Retroviruses Vol. 15, No.6, 1999, pp. 499± 508

Creese A., K. Floyd, A. Alban. et al. (2002). Cost-effectiveness of HIV/AIDS interventions in Africa: A systematic review of the evidence. The Lancet • Vol 359 May 11, 2002 www.thelancet.com

Crepaz, N., Hart, T., and Marks, G. (2004). Highly Active Antiretroviral Therapy and Sexual Risk Behavior: A Meta-analytic Review JAMA 2004;. Journal of American Medical Association, 292(2), 223-236. http://jama.ama-assn.org/cgi/content/full/292/2/224. Accessed on 24 July 2008.

De Walque, D. (2007), "How does the impact of an HIV/AIDS information campaign, vary with educational attainment? Evidence from rural Uganda", Journal of Development Economics, 84, 686-714.

Deltour, S., Richardson, S., and Jean-Yves Le Hesran. (1999). Stochastic algorithms for Markov models estimation with intermittent missing data. Biometrics Vol. 55, No. 2, pp. 565-573. International Biometric Society. http://www.jstor.org/stable/2533807. Accessed on 24 July 2008.

Detels, R., Muñoz, A., McFarlane, G. et al. (1998). Effectiveness of potent antiretroviral therapy on time to aids and death in men with known HIV infection duration. JAMA. 1998;280(17):1497-1503.

Dixon, S. McDonald, and J. Roberts (2002). The impact of HIV and AIDS on Africa's economic development. BMJ2002;324;232-234. doi:10.1136/bmj.324.7331.232. http://bmj.com/cgi/content/full/324/7331/232. Accessed on 11 August 2008.

Drummond, M. F., Sculpher, M. J., Torrance, G. W., O'Brien, J. B., and Stoddard, G. L. (2005). Methods for the Economic Evaluation of Health Care Programmes (3rd ed.). New York: Oxford University Publishers.

Economic Commission for Africa. Africa: The Socio-Economic Impact of HIV/AIDS. CHG Commission on HIV/AIDS and Governance in Africa

Fox, M. S. Rosen, W. MacLeod, M. Wasunna, M. Bii, G. Foglia, and J. Simon. (2004). The Impact of HIV/AIDS on Labor Productivity in Kenya. Tropical Medicine and International Health volume 9 no 3 pp 318–324 march 2004.

Freedberg, K.A. E .Losina, MC. Weinstein et al. (2001). The cost effectiveness of combination antiretroviral therapy for HIV disease. N Engl J Med 2001; 344:824-831. Accessed on April 12, 2008

Freedberg, K.A., Scharfstein, J.A., Seage III, G.R., et al. (1998). The cost-effectiveness of preventing AIDS-related opportunistic infections. JAMA. 1998; 279(2):130-136. http://jama.ama-assn.org/cgi/content/full/279/2/130. Accessed on July 10 , 2008.

Froelich, M. and R. Vazquez-Alvarez (2007). HIV/AIDS and HIV-knowledge: Can information campaigns reduce the HIV infection? The case of Kenya, forthcoming. African Development Review, June 2008.

Gafni A. (2006). Economic Evaluation of Health-care Programmes: Is CEA Better than CBA? Environmental and Resource Economics (2006) 34: 407–418. Springer. DOI 10.1007/s10640-006-0008-x

Garber, A.M. and Phelps, C.E., 1997. Economic Foundations of Cost-Effectiveness Analysis. Journal of Health Economics 16, 1–31.

Garber, A.M., Weistein, M.C., Torrance, G. W., and Kamlet M.S. (1996). Theoretical Foundations of Cost-Effectiveness Analysis. In M. Gold, J. Siegel, L. Russell, and M. Weinstein, Cost-Effectiveness in Health and Medicine (pp. 25-53). New York: Oxford University Press.

Gijs AA, G.A.A. Hubben, J.M. Bos, C.A.Veltman-Starkenburg, et al.(2007). Cost-effectiveness of tipranavir versus comparator protease inhibitor regimens in HIV infected patients previously exposed to antiretroviral therapy in the Netherlands. Cost effectiveness and Resource Allocation.

Gold, M., Siegel J.E., Russell L.B., Weinstein M.C., (Ed) (1996). Cost-Effectiveness in Health and Medicine New York, Oxford: Oxford University Press.

Goldie, S. J., Kuntz, K. M., Weinstein, M. C., et al. (1999). The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. JAMA. 1999; 281(19):1822-1829. http://jama.ama-assn.org/cgi/content/full/281/19/1822. Accessed on 10 July 2008.

Goldie, S. J., Y.Yazdanpanah, E. Losina, et al., (2006).Cost-Effectiveness of HIV Treatment in Resource-Poor Settings — The Case of Côte d'Ivoire. N Engl J Med 2006; 355:1141-53. http//www.nejm.org. Accessed on April 12, 2008.

Government of Kenya (2007). Kenya Gazette Supplement No. 98 (Acts No.14). The HIV/AIDS Prevention and Control Act, (2006). Nairobi: Government Printer; 2007.

Gray R.H., et al. (2007). Male circumcision for HIV prevention in young men in Rakai, Uganda: a randomized trial. Lancet, 369:657-666.

Gray, M. A. (2011). Applied Methods of Cost-effectiveness Analysis in Health Care. New York: Oxford University Press.

Grossman, M. (1972). On the Concept of Health Capital and the Demand for Health. The Journal of Political Economy, 80(2), 223-255.

Grossman, M. (1972). The Demand for Health: A Theoretical and Empirical Investigation. NBER.

Grossman, M. (2000). "The human capital model". In: Culyer, A.J., J. Newhouse, (Eds.), Handbook of Health Economics, vols. 1A and 1B. North-Holland, Amsterdam, pp 347-408.

Hawkins C et al. Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. J. Acquir Immune Defic Syndr 45: 304-310, 2007.

Hogan, D. R. et al. (2008). Cost effectiveness analysis of strategies to combat HIV/AIDS in developing countries. BMJ. http://bmj.com/cgi/content/full/331/7530/1431. Accessed on 7 April 2008.

Hosmer, D., and Lemeshow, S. (1999). Applied Survival Analysis: Regression Modelling of Time to Event Data. New York.

Hosmer, W., Lameshow, S., and May, S. (2008). Applied Survival Analysis: Regression Modelling of Time to Event Data (2nd ed.). New Jersey: John Wiley and Sons. http://www.centralbank.go.ke/downloads/publications/statistics/bulletin/Jun10b.pdf

Hunink, M., and Glasziou, P. e. (2001). Decision Making in Health and Medicine. New York: Cambridge University.

Individual Members of the Faculty of Harvard University (2001). Consensus statement on antiretroviral treatment for AIDS in poor countries. http://www.cid.harvard.edu/cidinthenews/pr/consensus_aids_therapy.pdf. Accessed April 20, 2008.

Kleinbaum, D. G., and Klein, M. (2005). Survival Analysis: A Self-Learning Text (2 ed.). New York: Springer.

Koenig, S.P., C. Riviere, P. Leger, et al. (2008). The cost of antiretroviral therapy in Haiti. Cost Effectiveness and Resource Allocation. http://www.resource-allocation.com/content/6/1/3. Accessed on 14 April 2008.

Kumaranayake, L., and Watts, C. (2001). Resource Allocation and Priority Setting of HIV/AIDS Interventions: Addressing the Generalized Epidemic in Sub-Saharan Africa. Journal of International Development, 451-466.

Kuntz K, Weinstain MC: Modelling in Economic Evaluation. In Economic Evaluation in Health Care: Merging theory with practice Edited by: Drummond M, McGuire A. Oxford: Oxford University Press;2001.

Lancaster, T. (1992). The Econometric Analysis of Transition Data. Econometric Society Monographs, 17 .

Lang, D. L., R. Lopert and S. R. Hill. (2003). Use of pharmacoeconomics in prescribing research. Part 5: Modelling – beyond clinical trials. Journal of Clinical Pharmacy and Therapeutics 2003, 28, 433–439.

Luce, B., Manning, W., Siegel, J., and Lipscomb, J. (1996). Estimating Costs in Cost-Effectiveness Analysis. In M. Gold, J. Siegel, L. Russell, and M. Weinstein, Cost-Effectiveness in Health and Medicine (pp. 176-213). New York: Oxford University Press.

Maathers, D.C., A.D. Lopez, and C.J.L. Murray (2006). "The burden of disease and mortality by condition: data, methods and results for 201". In Lopez, A.D., D.C.Maathers, M. Ezzati, D.T.Jaminson, and C.J.L., Murray (Eds.), Oxford University Press and World Bank.

Markus H. (2002). The Economic consequences of HIV/AIDS in Southern Africa. IMF Working Paper. WP/02/38. International Moneraty Fund.

Marubini, E., and Valsecchi, M. G. (2004). Analysing Survival Data from Clinical Trials and Observational Studies. England: John Wiley and Sons.

Masaki, E., R.Green, F.Greig, et al. (2003). Cost-Effectiveness of HIV Interventions for Resource Scarce Countries: Setting Priorities for HIV/AIDS. Bay Area International Group (University of California, Berkeley).

Meltzer, D. (1997). Accounting for future costs in medical cost-effectiveness analysis. Journal of Health Economics 16 (1997) 33-64.

Mills, E.J., Nachega, J. B., Buchan I. et al. (2006). Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA. 2006; 296(6):679-690. http://jama.ama-assn.org/cgi/content/full/296/6/679.

Mills, M. (2011). Introducing Survival and Event History Analysis.Unpublished Chapter 1.

Miners, A.H. C.A.Sabin, P.Trueman, et al. (2001). Assessing the cost-effectiveness of highly active antiretroviral therapy for adults with HIV in England. HIV Medicine 2001. 2, 52-58.

Ministry of Health (2005). Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines.

Ministry of Health (2007). Facts and figures at glance: Health and health related indicators 2006. Ministry of Health.

Ministry of Health and NACC (2002): National Home-Based Care Policy Guidelines. Nairobi: MOH; 2002

Ministry of Health. (1999) National health sector strategic plan 1999–2004. Nairobi: MOH.

Ministry of Health. (2001) National guidelines: prevention of mother-to-child HIV/AIDS transmission (PMCT), 2nd ed. Nairobi: MOH; 2002.

Ministry of Health. (2001) Policy guidelines on blood transfusion in Kenya. Nairobi: National Blood Transfusion Services of Kenya.

Ministry of Health. (2001). National condom policy and strategy 2001–2005. Nairobi: MOH in collaboration with the National AIDS Control Council.

Ministry of Health. (2001). National guidelines for voluntary counseling and testing. Nairobi: MOH and the National AIDS Control Council.

Ministry of Health. (2002). National home-based care programmer and service guidelines. Nairobi: MOH.

Ministry of Health. (2003). National prevention of mother to child transmission strategic management plan, year 2003–2008. Nairobi: MOH.

Ministry of Health. (2005) National health accounts 2001/02. Nairobi: MOH.

Ministry of Health. (2005b). Kenya health sector strategic plan 2005–2010. Nairobi: MOH.

Ministry of Health. (2005c). Kenya national strategy for VCT scale-up. Nairobi: NASCOP.

Ministry of Health (1997). Sessional Paper No. 4 of 1997 on AIDS in Kenya. Nairobi: MOH; 1997.

Ministry of Health.(2001). Guidelines to anti-retroviral drug therapy in Kenya. Nairobi: MOH.

Ministry of Home Affairs and NACC (2003). National Programme Guidelines on Orphans and Other Children Made Vulnerable by HIV/AIDS.

Montaner,J.S.G., Hogg, R., Wood, E., Kerr T., et al. (2006). The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. The Lancet August 5, 368:531-536

Morris, M., and Kretzschmar, M. (2000). A Microsimulation Study of the Effect of Concurrent Partnerships on the Spread of HIV in Uganda. Mathematical Population Studies , 8(2), 109-133.

Muga, R., Kichamu, G., Ntekerei, F., et al. (2004). The Center for Adolescent Health and Development, the National Council for Population and Development (NCPD), Adolescence in Kenya: The Facts. Nairobi, 3rd Edition.

Murray, C. J., D. B. Evans, A. Acharya, et al. (2000). Development of WHO guidelines on generalized cost-effectiveness analysis. Health Economics 9, 235–51.

Musau, S., C. Chanfreau, and L. B. Kyomuhangi. (2005). Field-Testing Home-Based Care Costing Guidelines: The Case of Uganda. Bethesda, MD: The Partners for Health Reformplus Project, Abt Associates Inc.

Mwabu, G. (2008). "Health Economics for low-income countries". In: Schultz, T.P., Strauss, J. (Eds.), Handbook of Development Economics, vol. 4. Elsevier/North-Holand, Amsterdam.

Naimark, D., et al. 1997. Primer on Medical Decision Analysis: Part 5-Working with Markov Processes. Med Decis Making 1997; 17:152-159. http://www.ppge.ufrgs.br/ats/disciplinas/10/naimark-krahn-naglie-1997.pdf. Accessed on 19th February 2009

National AIDS and STD Control Programme (2001). National guidelines for voluntary counseling and testing. Nairobi: NASCOP.

National AIDS and STI Control Programme, Ministry of Health, Kenya. (2005). AIDS in Kenya, 7th ed. Nairobi: NASCOP.

National AIDS and STI Control Programme, Ministry of Health, Kenya. (2001). AIDS in Kenya, 6th ed. Nairobi: NASCOP.

National AIDS and STI Control Programme, Ministry of Health, Kenya. (2008). Kenya AIDS Indicator Survey 2007: Preliminary Report. Nairobi, Kenya.

National AIDS Control Council (2005). Kenya National HIV/AIDS Strategic Plan (KNASP) 2005/6-2009/10. NASCOP.

National AIDS Control Council, Office of the President, Kenya (2008). UNGASS 2008 Country Report for Kenya. NACC, Nairobi.

National AIDS/STD Control Programme (2008). Policy on Male Circumcision in Kenya. Ministry of Health, Republic of Kenya.

Nyaga, R. K., Kimani D.N, Mwabu G and Kimenyi S.M (2004): HIV/AIDS in Kenya: review of Research and Policy Issues. Nairobi: KIPPRA.

Oakes, D. (2000). Survival Analysis. Journal of the American Statistical Association, 95(449), 282-285.

Ono, S., T. Kurotaki, T. Nakasone, et al. (2006). Cost effectiveness analysis of antiretroviral drug treatment and HIV-1 vaccination in Thailand. Jpn. J. Infect. Dis., 59, 168-173.

Palella, F.J.J., Delaney K.M., Moorman A.C., et al. (1998). Declining morbidity and mortalityamong patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998, 338(13):853-860.

Republic of Kenya, (2012). Economic Survey 2012. Nairobi: Government Printer.

Republic of Kenya (2009). Kenya AIDS Indicator Survey: Final Report. Nairobi: NASCOP Government Printer.

Republic of Kenya (2003). Kenya Demographic and Health Survey. National Government Printer, Nairobi Kenya.

Republic of Kenya (1999). Ministry of Finance and Planning. Kenya Population and Housing Census. Projections. Government Printer. Nairobi.

Rosen, S. and L. Long (2006). How much does it cost to provide antiretroviral therapy for HIV/AIDS in Africa? Health and Development Discussion Paper No. 9 October 2006. Center for International Health and Development. Boston University School of Public Health.

Sanders, G.D, A.M. Bayoumi, V.Sundaram, et al. (2005) Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. N Engl J Med 2005; 352:570-85. http://www.nejm.org. Accessed on May 18, 2008.

Schoenfeld, D. (1982). Residuals for the Proportional Hazards Regresssion Model. Biometrika,, 69(1), 239-241.

Song, R., et al., (2007). Efficacy of highly active antiretroviral therapy in HIV-1–Infected children in Kenya. Pediatrics Vol. 120 No. 4 October 2007, pp. e856-e861

Sonnenberg, F.A. and J. R. Beck 1993. Markov Models in Medical Decision Making: a Practical Guide. Reprinted from Medical Decision Making. ttp://umg.umdnj.edu/smdm/pdf/13-04-322.pdf. Accessed on 14 April 2008.

Strauss, J., and Thomas, D. (2008). Health over the Life Course. In T. Schultz, and J. Strauss, Handbook of Development Economics (Vol. 4, pp. 3374-3474). Amsterdam: Elsevier/North-Holand.

Sweat, M., S.Gregorich, G.Sangiwa et al. (2000). Cost-effectiveness of voluntary HIV-1 counseling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania. The Lancet • Vol 356 July 8, 2000

Tantivess, S. and G. Walt (2006). Using cost-effectiveness analyses to inform policy: the case of antiretroviral therapy in Thailand. Cost Effectiveness and Resource Allocation, http://www.resource-allocation.com/content/4/1/21. Accessed on 8 April 2008.

Thirumurthy, H, J.Graff Zivin, M.Goldstein (2005). The economic impact of AIDS treatment: labor supply in western Kenya. NBER working paper series working paper 11871. Cambridge: National Bureau of Economic Research.

Tom, E., and Schulman, K. (1997, January). Mathematical Models in Decision Analysis. Infection control and Hospital Epidemiology, 18(1), 65-73.

Torrance, G.W. 1986. Measurement of health state utilities for economic appraisal: A review. Journal of Health Economics 5 (1986) l-30. North-Holland

Ueyama, M. and F. Yamauchi. (2008). Marriage behavior response to prime-age adult mortality evidence from Malawi. IFPRI Discussion Paper 00764, April, 2008. International Food Policy Research.

Vazquez-Alvarez, R. and T. Adam. (2008). A Life-cycle model of human capital formation and educational choices in developing economies. Preliminary copy. Unpublished

Vijayaraghavan, A., Efrusy, M. B., Mazonson, P. D., et al.(2007). Cost-effectiveness of alternative strategies for initiating and monitoring highly active antiretroviral therapy in the developing world. J Acquir Immune Defic Syndr. 2007 Sep 1; 46(1):91-100. Abstract.

Wasonga, J.G., C.N. Morris, Y. Kombe, and J.M. Chakaya. (2005). Barriers to Antiretroviral Therapy: A case study of persons living with HIV/AIDS in Nairobi, Kenya. MPH Dissertation. Unpublished

Were, M. and N. N. Nafula. (2003). "An Assessment of the impact of HIV/AIDS on economic growth: the Case of Kenya". CESIFO Working Paper No. 1034. Category 5: Fiscal Policy, Macroeconomics and Growth.

WHO and UNAIDS (2006). Towards universal access: assessment by the Joint United Nations Programme on HIV/AIDS on scaling up HIV prevention, treatment, care and support. Geneva, United Nations General Assembly; 2006:1-21.

WHO. (1994). Cost Analysis in Primary Health Care: A Manual for Programme Managers. In C. A., and P. D. Geneva: World Health Organization.

WHO. (2001). Macroeconomics and Health: Investing in Health for Economic Development. Commission on Macroeconomics and Health. Geneva: World Health Organization.

WHO/UNAIDS (2006). Progress on global Access to HIV antiretroviral therapy: A report on "3 by 5" and beyond, March 2006. Geneva.

Wooldridge, J. M. (2001). Econometric Analysis of Cross Section and Panel Data. London: The MIT Press, Cambridge, Massachusetts.

Wools-Kaloustiana, K., S. Kimaiyod, L. Dierod, et al. (2006). Viability and effectiveness of large-scale HIV treatment initiatives in sub-Saharan Africa: Experience from western Kenya. AIDS 2006. 20: 41-48

World Bank. (2007). Spreading and sustaining growth in Africa: Africa development indicators 2007. The World Bank.

World Health Organisation (1994). Cost analysis in primary health care: a manual for programme managers. Edited by: Creese A. WHO.

World Health Organization: Regional Data. http://www.who.int/choice/costs/en/ - accessed October 6,

Yamano, T. (2006). "The Long-term Impacts of Orphanhood on Education Attainment and Land Inheritance among Adults in Rural Kenya." Mimeo. Foundation for Advanced Studies on International Development, Japan. Paper presented at the International Association of Agricultural Economists Conference, Gold Coast, Australia August 12-18, 2006.

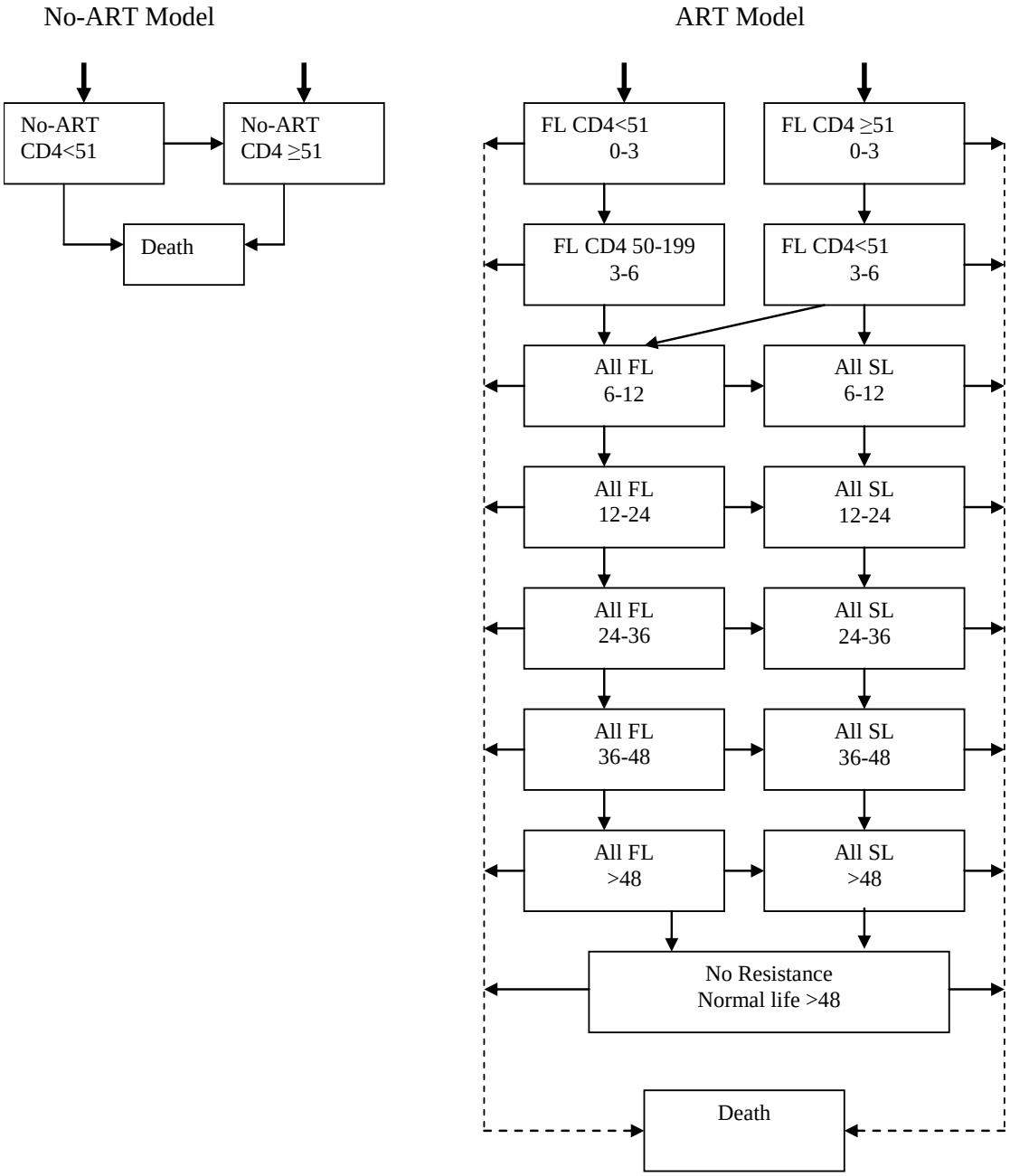
Yamano, T., and T.S. Jayne, (2004). Measuring the Impacts of Working-Age Adult Mortality on Small-Scale Farm Households in Kenya. World Development 32.1: 91-119.

Yamano, T., and T.S. Jayne, (2005). Working-age adult mortality and primary school attendance in rural Kenya. Economic Development and Cultural Change 53 (3): 619-654.

Yazdanpanah ,Y. (2004). Costs associated with combination antiretroviral therapy in HIV-infected patients. Journal of Antimicrobial Chemotherapy 53, 558–561.

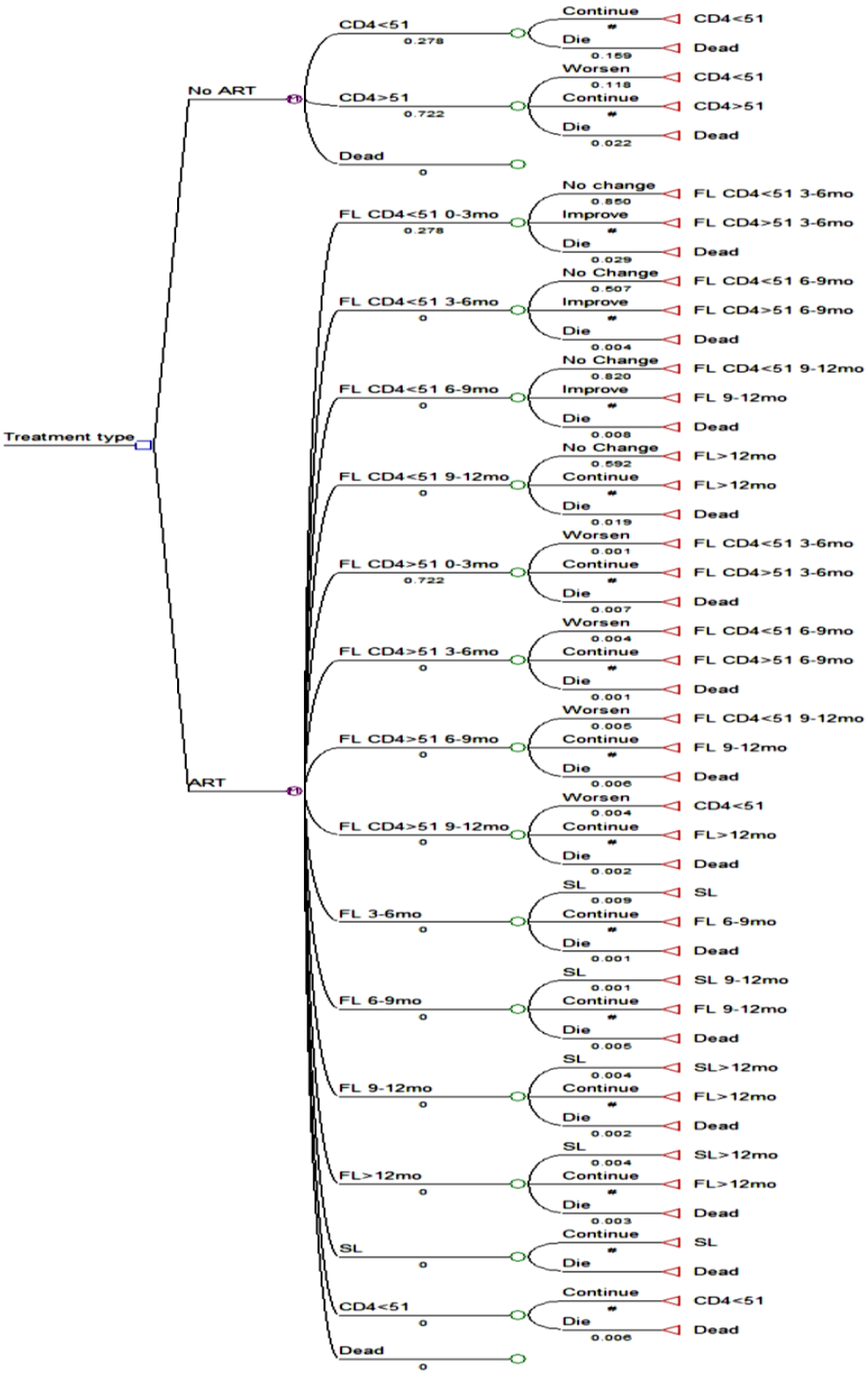
APPENDICES

Appendix 1: Markov Models for No ART and ART Use



Markov models for No-ART and ART. All: All patients. FL: First-line ART regimen; SL: Second-line ART regimen; TL: third line regimen *0–3*; *3–6*; *6–12*; *12–24; 24–36; 36–48;* and *>48* refer to months since the initiation of ART. Adapted from Cleary et al. 2006

Appendix 2: The Markov Decision Tree



Appendix 3: List of Documents Reviewed

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
Badri et al. (2006)	Cost-effectiveness of HAART in South Africa	South Africa 292 patients on HAART & 292 matched No-ART patients	To compare use & cost of HIV-1–related service provision between patients on HAART & a comparison group not on ART, & assess the cost effectiveness of HAART.	Patients on HAART & a matched comparison group not on ART	Life years gained (LYG)	The product-limit Kaplan-Meier survival method & maximum likelihood least squares method.	For patients without AIDS, the mean number of inpatient days PPY = 1.08 & 3.73 for the HAART & No-ART group, while mean number of outpatient visits PPY = 8.71 & 4.35, respectively. The incremental cost /LYG = $1,622 & $675 for scenario 1 & 2. For patients with AIDS, mean inpatients days PPY = 2.04 & 15.36 for the HAART & No-ART group, while mean number of outpatient visits PPY was 7.62 & 6.60 respectively	Excellent paper. For further reference
Sanders et al.	Cost-	USA	To evaluate the	Screening for HIV	LYG &	Markov	Screening ↑ life	

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
(2005)	Effectiveness of screening for HIV in the Era of HAART	Cohort of 43years old HIV+ & HIV-	cost effectiveness of screening for HIV.	infection & not screening	quality-adjusted life-years (QALYs),	transition	expectancy by 5.48 days, (4.70 quality-adjusted days) CE ratio = $15,078/QALY	
Ono et al. (2006)	CEA of ART & HIV-1 Vaccination	Thailand	To evaluate the cost-effectiveness of recombinant Bacillus Calmette Guerin (rBCG) vaccine & recombinant vaccinia virus DIs (rDIs) vaccine	Vaccination, HAART & combination of the two	Disability adjusted life years (DALY)	Markov transition	Incremental CE ratio (iCERs) of vaccination, HAART & combination =$75, $610 & $267 respectively	Excellent paper. For further reference
Hubben et al. (2007)	Cost effectiveness of TPV/r versus CPI/r in HIV infected patients previously exposed to ART.	Netherlands 2 theoretical groups of 1000 HIV-1 + people	To assess life-time costs & effects of a ritonavir (TPV/r) based regimen compared to comparator protease inhibitor (CPI/r)	Two theoretical groups of patients one on ART with TPV/r as a component & the other receiving a standard of care regimen with CPI/r.	LYG & QALYs	Markov transition	Incremental CE ratios (iCERs) = €41,600/LYG & €42,500/QALY.	Good study
Masaki et al.	Cost	Hypothetical	Compare the CE	• VCT	LYG & # of	Static budgetary	HIV prevention	

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
(2003)	effectiveness of HIV interventions for resource scarce countries: setting priorities for HIV/AIDS management	country 1 million people	of HIV prevention & treatment interventions	• pMTCT • STD mass treatment for general population • STD management for sex workers • Blood screening • 4 drug price scenarios for ART for HIV+ patients	HIV infections prevented	simulation	interventions are more cost-effective than ART. Blood screening & STD control among sex workers are the most cost-effective preventative interventions at the costs of $3.35 & $3.95/life-year saved (LYS), ART is the least cost-effective, costing $1,317.20/LYS at generic drug prices	
Miners et al. (2001)	Assessing the Cost effectiveness of HAART for adults with HIV in England	United Kingdom (UK) Hypothetical cohorts of 1000 individuals infected with HIV	To assess the cost effectiveness of HAART compared with two nucleoside reverse transcriptase inhibitors (NRTIs) for	HAART - dual NRTI therapy plus a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor - vs. dual NRTI therapy	LYS & QALYs	Markov simulation	Incremental CE ratios (iCERs) of £14 602/LYS & £17698 /QALY saved.	Excellent study look for appendix

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
			HIV+ individuals					
Sweat et al. (2000)	Cost effectiveness of HIV-1 VCT in reducing sexual transmission of HIV-1 in Kenya & Tanzania	East Africa (Tanzania & Kenya). 10 000 people seeking VCT in urban centres	To assess the impact, cost, and cost-effectiveness of HIV-1 voluntary counselling and testing (VCT) in less-developed country settings	HIV-1 VCT compared with no intervention by use of the effects before & after the intervention.	HIV-1 infection averted & DALYs		1104 & 895 HIV-1 infections were averted in Kenya & Tanzania respectively during the subsequent year at the cost of US$249 & $346, respectively. Cost/DALY saved was $12.77 & $17.78	
Clearly et al. (2006)	Cost effectiveness of ART in Khayelitsha, South Africa – a primary data analysis	South Africa 1,729 patients in the Khayelitsha cohort (1,146 No-ART patient-years, 2,229 ART patient-years) using a before and after study design.	To estimate HIV healthcare utilisation; the unit costs of HIV services & the cost per LY & QALY gained of HIV treatment interventions from a provider's perspective	Patients on ART & a group on treatment of OIs without ART (i.e. ART & No ART group)	LYs, QALYs	Markov modelling	Discounted lifetime costs for No-ART & ART = US$2,743 & US$9,435 over 2 & 8 QALYs respectively. The ICER of ART & No-ART = US$1,102 per QALY and US$984 per life year gained	Excellent paper & necessary for future review
Clearly et al.	Cost-	South Africa	To establish the	Patients on ART & a	LYs &	Markov	ART & No-ART	Relevant

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
(2004)	effectiveness of antiretroviral treatment for HIV+ adults in a South African township		costs & effectiveness of ART for HIV + adults in a resource-constrained public-sector setting & to describe the life time costs of ART & no ART.	group on treatment of OIs without ART (i.e. ART & No ART group)	QALYs	modelling	patients costs R13754/QALY & R14189/QALY respectively. The incremental cost/QALY gained on ART = R13 621. The average life expectancy for ART & No-ART groups = 8.33 & 2.27 respectively. ART leads to an average gain in life expectancy of 6.06 years. Hence 6.79 QALYs on ART or 1.59 QALYs for no ART.	methodology
Koenig et al. (2008)	The cost of ART in Haiti	Haiti 218 treatment-naïve adults who were consecutively initiated on ART	To determine direct medical costs, overhead costs, societal costs & personnel requirements for providing ART to patients with	None comparative	Outcome measure was cost. Effectiveness was not measured.	Observational study & Micro-costing approach	Initial ART treatment costs approximately $US 1,000 per patient per year.	Important study for the costing aspect.

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
			AIDS in Haiti					
Goldie et al., (2006).	Cost effectiveness of HIV treatment in resource-poor settings: the case of Côte d'Ivoire.	Côte d'Ivoire 1million HIV+ adults mean age, 33 years; CD4 = 331 cells/mm^3; HIV RNA level, 5.3 log copies/ml	To assess the cost-effectiveness of treatment strategies for a cohort of adults in Côte d'Ivoire who were infected with the HIV	No treatment, trimethoprim–sulfamethoxazole prophylaxis alone, ART only & prophylaxis with ART	Year of life gained	Monte Carlo simulation	Strategies involving both ART and prophylaxis were more effective & more cost-effective than those involving only ART	Relevant for future use
Goldie et al. (1999).	The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men.	Hypothetical cohort of homosexual and bisexual HIV positive men living in the United States.	To estimate the clinical benefits & cost-effectiveness of screening HIV+ Homosexual & bisexual men for anal squamous intraepithelial lesions (ASIL) & anal SCC.	No screening vs several screening strategies for ASIL & anal SCC using anal Papanicolaou (Pap) testing at different intervals	Life expectancy, quality-adjusted life expectancy, QALYs saved,	Markov transition model	Screening for ASIL increased quality-adjusted life expectancy at all stages of HIV disease. Screening with anal Pap tests every 2 years, beginning in early HIV disease (CD4 cell count. 0.503109/L), resulted in a 2.7-month gain in quality-adjusted life expectancy for an iCER of $13 000 per QALY saved	

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
Freedberg et al (2001)	The cost effectiveness of combination antiretroviral therapy for HIV disease	USA 1 million hypothetical patients were individually modeled	To estimate the clinical benefits and cost effectiveness of three-drug antiretroviral regimens	ART versus No ART	Life expectancy, life expectancy adjusted for the quality of life & QALYs gained	Mathematical simulation (Monte Carlo simulation) model of HIV disease, using the CD4 cell count & HIV RNA level as predictors of the progression of disease	For patients with mean CD4 cell count of 87/μL life expectancy adjusted for the quality of life increased from 1.53 to 2.91 years, & per-person lifetime costs increased from $45,460 to $77,300 with triple therapy versus no therapy. The incremental cost per QALY as compared with no therapy was $23,000.	Necessary for further reference
Freedberg et al. (1998).	The cost-effectiveness of preventing AIDS-related opportunistic infections.	USA	To determine the clinical impact, cost, and cost-effectiveness of strategies for preventing OIs in patients with advanced HIV disease.	Different strategies for prophylaxis of Pneumocystis carinii pneumonia (PCP), toxoplasmosis, Mycobacterium avium complex (MAC) infection, fungal infections, and	Projected life expectancy, quality-adjusted life expectancy & QALYs	Markov simulation model	CD4 cell = 200-300/μL patients not on prophylaxis, quality-adjusted life expectancy = 39.08 months & average total lifetime costs = $40 288. CD4 cell < or = 200/μL less patients on prophylaxis	

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
				cytomegalovirus (CMV) disease in HIV-infected patients.			for PCP & toxoplasmosis with trimethoprim-sulfamethoxazole increased quality-adjusted life expectancy to 42.56 months, implying an incremental cost of $16 000/QALY saved. Prophylaxis for MAC for patients with CD4 cell counts of 50/μL or less produced smaller gains in quality-adjusted life expectancy; iCER = $35 000/QALY saved for azithromycin & $74 000/QALY saved for rifabutin. Oral ganciclovir for the prevention of CMV infection was the least	

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
							cost-effective prophylaxis ($314 000/QALY saved).	
Anis et al. (2000).	The cost effectiveness of antiretroviral regimens for the treatment of HIV/AIDS.	• Canada All HIV+ adults aged ≥18 years with CD4+ counts ≤350 cells/μL enrolled in the province-wide drug treatment programme.	To estimate survival, the number of life-years gained and cost effectiveness of ART regimens	ART regimens, denoted as ERA-I [zidovudine + (didanosine or zalcitabine)]; ERA-II [stavudine + (didanosine or zalcitabine) or lamivudine + (zidovudine or didanosine or zalcitabine or stavudine)]; & ERA-III [2 nucleoside reverse transcriptase inhibitors + (1 protease inhibitor or 1 non-nucleoside reverse transcriptase inhibitor)].	Survival & Life year gained.	Actuarial methods used to estimate the annual mortality rates Kaplan-Meier methods used to estimate cumulative mortality Cox proportional hazard model estimated to calculate CD4+ cell count–adjusted mortality rates.	Total costs at 12 months under ERA-I, -II & -III = $Can4897, $Can6620 & $Can11 914, respectively. Survival at 12 months under ERA-I, -II &-III = 89.6%, 91.0% & 97.6%, respectively. The annual incremental cost between ERA-II &ERA-I = $Can1723. iCER between ERA-III & ERA-I, & between ERA-III & ERA-II =$Can58 806 & $Can46 971 per life-year gained, respectively	
Cook et al., (1999)	Modelling the long-term outcomes &	USA	To understand the potential clinical & economic	HIV RNA & CD4 cell counts response to triple therapy with	Life year gained	Health state transitional model. & Semi-	Progression to AIDS & death of a person without AIDS on triple	Good paper

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
	costs of HIV ART using HIV RNA levels: Application to a clinical trial		impact of ART for HIV-infected patients	indinavir (IDV) + zidovudine (ZDV) + lamivudine (3TC) to double therapy with ZDV+ 3TC.		Markov	therapy was slower than for a patient on double therapy (ZDV+ 3TC) if no other treatment options were offered. The total discounted cost over the initial 5-year period was $5100 lower for patients on triple therapy if suppression lasts up to 3 years. At 20 years, the incremental cost per life-year gained of IDV + ZDV+ 3TC regimen was estimated at $13,229.	
Bachmann, (2006)	Effectiveness & cost effectiveness of early & late prevention of HIV/AIDS progression	South Africa	To estimate the health effects, service costs & iCER of earlier or later use of antibiotics & ARV, alone & in	Earlier & late use of antibiotics only, ART only & early &late use of both antibiotics &ART	QALY	Markov Monte Carlo simulation	Triple ARV + antibiotics would prolong life by 6.7 undiscounted years if provided 'late' (CD4 = 200 cells/ml) & by 9.8 years if provided	An important paper for future reference

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
	with ART or antibiotics in Southern African adults		combination, in HIV+ adults. To examine the cost-effectiveness of treatment options in relation to society's willingness to pay to prevent death & illness.				'early' (CD4 = 350 cells/ml). The incremental undiscounted costs per year of life gained, compared to no preventive therapy, were $17 & $244 for isoniazid + cotrimoxazole started late & early respectively, $2454 & $2784 for ARV + antibiotics started late & early respectively.	
Hornberger (2006)	Cost-effectiveness of enfuvirtide in HIV therapy for treatment-experienced patients in the United States	United States	To project the impact of virological & immunological response biomarkers found in the analyses of the TORO trials on long-term	Enfuvirtide (ENF) & optimized background (OB) therapy on patients infected with HIV-1 who are highly ARV experienced	Life year gained and QALY	Markov transition	Mean life expectancy of patients on ENF + OB was 7.4 years from initiation of therapy, and that of patients on OB alone was 5.6 years. The incremental cost-effectiveness of ENF + OB = $24,604/QALY.	Good study

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
			clinical prognosis; To estimate the cost-effectiveness of ENF + OB versus OB alone as measured in cost per life year & cost per QALY saved.					
Hogan et al (2005)	Cost effectiveness analysis of strategies to combat HIV/AIDS in developing countries	Countries in SSA & South East Asia with very high adult and high child mortality	To assess the costs & health effects of a range of interventions for preventing the spread of HIV & for treating people with HIV/AIDS in the context of the MDG* for combating HIV/AIDS.	Mass media; VCT; Peer education for sex workers; Peer education & treatment of sexually transmitted infections for sex workers; School based education; Treatment of STIs* (general population); PMTCT*; HAART* & no intervention	Disability adjusted life year (DALY)	A mathematical model of HIV/AIDS	In both regions interventions focused on mass media, education & treatment of STIs for female sex workers, & treatment of STIs in the general population cost < $Int150 /DALY averted. VCT costs < $Int350/DALY averted in both regions, while pMTCT costs < $Int50/DALY	For future review

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
							$Int850/DALY averted in Afr-E & Sead-D respectively. School based education strategies & various ART strategies cost between $Int500 & $Int5000/DALY averted.	
Vijayaraghavan, et al. 2007.	Cost-effectiveness of alternative strategies for initiating & monitoring HAART in the developing world	South Africa	To determine the cost-effectiveness of initiating & monitoring HAART in developing countries according to developing world versus developed world guidelines	Treating HIV + patients in SA according to WHO "3 by 5" guidelines (treat CD4 counts <or=200 cells/mm or patients with AIDS & monitor CD4 cell counts every 6 months) versus modified WHO guidelines i.e. developed world guidelines: treat CD4 counts <or=350 cells/mm or viral loads	QALY	Lifetime Markov model incorporating costs, quality of life, survival, & transmission to sexual contacts	Incorporating transmission to partners (excluding indirect costs), treating patients according to developed versus developing world guidelines increased costs by US $11,867 & increased life expectancy by 3.00 QALYs, for an incremental cost-effectiveness of $3956 per QALY.	Paper relevant to current study

Author	Study	Country & sample size	Objectives of study	Compared strategies	Measure of effectiveness	Methodology	Findings	My comments
				>100,000 copies/mL, & monitor CD4 cell counts and viral load every 3 months				

MDG* is millennium development goal; STIs* - sexually transmitted infections; pMTCT* - Prevention of mother to child transmission; HAART*- Highly active antiretroviral therapy

Appendix 4: Adult Initial Visit Questionnaire

(1) Ampath site **(2) Mbagathi District Hospital site**

(2) Ampath site **(2) Mbagathi District Hospital site**

Patient No.		**Date**			
Date of birth		**Age**	**Sex**	□ M	□ F
Tribe	**Location**		**Sub-Location**		
Clinic Location					
Point of HIV testing					
□ pMTCT		□ DTC/PITC (AMPATH)			
□ VCT		□ TB clinic			
□ Mobile VCT		□ In patient			
□ MCH		□ Other:			
Social History					

1a. Time taken to reach the hospital/clinic
- □ Less than 30 minutes
- □ Between 30 and 60 minutes
- □ Between 1 and 2 hours
- □ More than 2 hours

1b. Transport cost to the hospital (return)
- □ 0 (No cost)
- □ Less than 50 Shillings
- □ Between 50 and 100 shillings
- □ Between 100 and 300 shillings
- □ More than 300 shillings

2a. If the client ever attended school?
□ Yes □ No

2b. Client's number of completed school years _____ Years

2c. client's highest level of completed educational
- □ None
- □ Primary school
- □ Secondary school
- □ Vocational training
- □ University/ post graduate/

3a. Client's employment status outside his/her home □ Yes □ No

3b. Client's kind of work
- □ Not working
- □ Self employed (any type)
- □ Professional (Specify)
- □ Unskilled labourer (specify)

3c. Client's net monthly income
- □ Between 50,000-100,000
- □ More than 100,000

4. Access to electricity by the client inside his/her home
□ Yes □ No

5. Access of piped water by the client inside in his/her home □ Yes □ No

6a. Number of people living in client's household _____

6b. Gender of household head
- □ Male
- □ Female

6c. Number of direct dependants of the clients_____

6d. Number of client's children under 5 years of age? _____

7a. Client's disclosure of HIV status to anyone
□ Yes □ No

7b. If yes, person disclosed to
- □ Partner/spouse
- □ Other family member
- □ Friend
- □ Other household member
- □ Health care provider
- □ Other (specify): _____

7c. Client's membership to an AIDS care and support group, or PLWHA Association

□ Yes

□ None □ Less than 2,500 □ Between 2,500-10,000 □ Between 10,000-50,000	□ No
Women Only: **8a.** Number of times the client has been pregnant _____ **8b.** Number of children client has given birth to _____ **8c.** Number of own children currently living with the client _____ **8d.** Number of own children< 5yrs currently living with client: _____ **8e.** No. of own children less < 18 months old _____	**10e**. How the client thinks was exposed to HIV (Check all that apply) □ Patient knows spouse or partner is HIV+ □ Suspected exposure in prior relationship □ Blood Transfusion (Year of Transfusion) □ History of Intravenous Drug Use □ Contaminated Needle Stick □ Unknown □ Other (specify) _____
Men Only: **9.** Client's number of children ___ _____	**11a.** If the client currently pregnant □ Yes □ No If yes: _____Weeks If Yes: Enrolled in ANC? □ Yes □ No
10a. Client's current relationship/marital status? □ Never married and not living with a partner □ Legally married: Number of wives _____ □ Living with a partner □ Separated □ Divorced □ Widowed --- **10b.** If widowed, suspicion of HIV as cause of death of spouse? □ Yes □ No No of Years since death of spouse ____ --- **10c.** Discordant couple □ Yes □ No □ Unknown --- **10d.** Client's Sexual Activity: □ Yes □ No - Spouse or partner suspected of sex partner outside of marriage/relationship □ Yes □ No - Patient has sex partners outside □ Yes □ No - Sexually active last 6 months Number of different partners: _____ marriage or current relationship	**11b.** If the client currently Breast Feeding □ Yes □ No **12.** If the client or their partner currently using any form of family planning? □ Yes □ No □ Condoms *(check all that apply)* □ Oral Contraceptive Pill □ Intrauterine Device □ Sterilization / Hysterectomy □ Natural Family Planning / Rhythm □ Diaphragm / Cervical Cap □ Injectable Hormones (Depo-Provera/ Norplant) □ Other:
13a. If the client smokes cigarettes? □ Yes □ No □ Stopped Smoking cigarettes. How long ago?	**13b.** Current or Past Cigarette Use: # Sticks per day: ____ # Years of Use: ____

___wks ___mos ___yrs	
13c. If the client drinks alcohol? □ Yes □ No □ Stopped How long ago? ___wks ___mos ___yrs	**13d.** Client's current or past drink of alcohol *(tick all that apply)* □ Beer □ Spirits/Liquor □ Wine □ Chang'aa □ Busaa

13e. Client's frequency of alcoholic drinks in the last year? □ Never □ Monthly or less □ 2 to 4 times a month □ 2 to 3 times a week □ 4 to 5 times a week □ 6 or more times a week	**13f.** Client's frequency of alcoholic drink in a typical day or during the period currently or in the previous year? □ 0 drinks □ 1 to 2 drinks □ 3 to 4 drinks □ 5 to 6 drinks □ 7 to 9 drinks □ 10 or more drinks	**13g.** Number of times client had six or more drinks on one occasion in the past year? □ Never □ Less than monthly □ Monthly □ Weekly □ Daily or almost daily

Review of Systems:	
14. Indicate chief complaint: □ Feeling well □ Having symptoms	
15. List general complaints: □ No complaint □ Fever □ Chills □ Weight loss □ Night Sweats □ Rash □ Fatigue □ Weight gain	
TB: □ Currently on treatment □ Defaulted _____(year)	□ Treatment completed _____ (year) □ Known exposure to household contact with TB
16. Hospitalizations	
17a. If the client had been hospitalized in the previous year? □ Yes □ No	**18b.** If yes, number of hospitalizations of the client in the past year? _____
19a. Is the client <u>currently</u> taking any antiretroviral medications? □ Yes □ No ***If yes drop***	
19b. Has the client used any antiretroviral medications in the past? □Yes □ No ***If yes drop***	
20. Other Current Medications:	
PCP Prophylaxis: □ Yes □ No ***If yes drop***	TB Treatment: □ Yes □ No ***If yes drop***
TB Prophylaxis: □ Yes □ No ***If yes drop***	Cryptococcus Tx: □ Yes □ No ***If yes drop***
Other Drugs: □ Yes □ No ***If yes drop***	

PHYSICAL EXAMINATION

21. Vitals:
Wt _____kg Height_____ cm Karnofsky Score _____%

22. General Exam: □ Temporal wasting Comments

23. List Patient Complaints

24. Tests

Test	Date	Cost	Test	Date	Cost
1. WBC / mm3			10. CD4		

2. Hgb g / dL			11. CD8		
3. MCV			12. CD4 %		
4. Platelets / µ L			13. VDRL		
5. ALC / mm3			14. HIV Test (Rapid)		
6. SGPT			15. HIV Test (Long ELISA)		
7. Creatinine mmol / L			16. Viral Load		
8. Chest X-ray (CXR)			17. other		
9. Other:					

25. HIV-related Diagnoses/Problems	
1.	2.
3.	4.
5.	6.

26. Plan:		
ARVs	□ None	□ Start ARVs
Reason to start ARVs:	□ Treatment	□ Total pMTCT
Eligible for ARVs but not started:		
□ Due to cap (limits set by donor) □ Adherence Concerns	□ OI/TB tx □ Other_____	□ Patient Refused
*If **start** tick regimen:*		
Combination: □ Combivir	□ Triomune-30	□ Triomune-40 □ Truvada
Individual:		
□ Nevirapine (NVP)	□ Stavudine-40(D4T-40)	□ Didanosine-125(DDI)
□ Lamivudine (3TC)	□ Efavirenz(EFV)	□ Didanosine-200(DDI)
□ Zidovudine (AZT)	□ Abacavir(ABC)	□ Tenofovir(TDF)
□ Stavudine-30(D4T-30)	□ Aluvia/(Kaletra)	□ Indinavir(IDV)
□ Other		
PCP Prophylaxis:	□ None	□ Start
Drugs:	□ Septrin ____tabs/day	□ Dapsone_____ mg/day
TB Prophylaxis:	□ None	□ Start INH
TB Treatment:	□ None	□ Start Induction

Drugs :	
□ Rifater (RHZ) _____tabs/day	□ INH_____mg/day
□ Rifafour (RZHE) _____tabs/day	□ Pyrazinamide_____mg/day
□ Ethizide (EH) _____tabs/day	□ Ethambutol_____mg/day
□ Rifinah (RH)_____tabs/day	□ Streptomycin_____mg/day
□ Rifampicin_____mg/day	□ Other:

27. Additional Drugs (ordered at the time of the initial visit)		
Drug	**Dose (# of tabs)**	**Cost**
i.		
ii.		
iii.		
iv.		
v.		

28. Test ordered for the client **□ None**		
• Complete Blood Count	• CD4 Count Assay	• VDRL
• ALT	• Creatinine	• Electrolytes
• AST	• HIV ELISA	• HIV Viral load
• Chest X-ray (CXR)	• Sputum for AFB	• Pregnancy Test
• Radiology Test (specify):		
• Other (specify)		

29. Referrals made for the client		
• None	• Social Support Services	• Psychosocial counseling
• Disclosure counseling	• Family Planning services	• Reproductive Health
• TB treatment/DOT program	• Nutritional support	• Adherence Counseling
• Alcohol counseling/ support groups	• Mental Health Services	•
• Other referral (specify)		
• Inpatient care/Hospitalization: □ MTRH □ Mbagathi District		
30. The client's next appointment • None • Between 1 and 3 days • Between 5 and 5 days • More than 5 days *Fill in appropriate box:* □ 1 week □ 2 weeks □ 1 month □ 3 months □ 6 months □ Other (specify):		
Return to clinic: Days _____ weeks _____ Months _____Date _____		

Appendix 5: Return Visit Questionnaire

(1) Moi Teaching & Referral Hospital (MTRH) **(2) Mbagathi District Hospital**

1 Patient Number

2 **Clinic Location**

		Return 1	Return 2	Return 3	Return 4	Return 5	Return 6	Return 7	Return 8
3	**Weight**								
4	**Client is Discordant Couple**								
	□Yes □No □ unknown								
5	**Visit type**								
	□ Scheduled visit								
	□ Unscheduled visit early								
	□ Unscheduled visit late								
6	**Does the patient have any interval complaints?**								
	□Yes □No								
	Comments:								
7	**Client has any children less than 18 months?**								
	□ Yes □No								
8	**Male and Female Patients:**								
8a	**Family Planning:**								
	□ Yes □No								
	If Yes, Method:								
8b	**Condom Use:**								
	□Yes, always								
	□Yes, sometimes								
	□No								
9	**If client has been Hospitalized since last visit?**								

	□ Yes □No								
10	**Physical Exam:**								
	Comments:								
11	**Diagnoses/Problems**								
	1								
	2								
	3								
	4								
	5								
12	**Test done**								
	WBC/mm^3								
	Hgb g/dL								
	MCV								
	Platelets/ mm3								
	ALC/ mm^3								
	SGPT								
	Creatinine mmol/L								
	CXR								
	CD4								
	CD8								
	CD4%								
	VDRL								
	Viral Load								
	HIV Elisa								
	HIV DNA PCR								

	CD4 Panel (specify):								
	CXR								
	Radiology test (Specify):								
	Other								
13	**Treatment plan:**								
13a	**ARVs:**								
	□ None								
	□ ARVs								
	If **start or change**, tick new regimen:								
	Combination:								
	□ Combivir								
	□ Triomune-30								
	□ Triomune-40								
	□ Truvada								
	Individual:								
	□ Nevirapine (NVP)								
	□ Lamivudine (3TC)								
	□ Zidovudine(AZT)								
	□ Stavudine-30(D4T-30)								
	□ Stavudine-40(D4t-40)								
	□ Efavirenz (EFV)								
	□ Abacavir(ABC)								
	□Aluvia/(Kaletra)								
	□ Didanosine-125(DDI)								
	□ Didanosine-200(DDI)								
	□Tenofovir (TDF)								
	□ Indinavir(IDV)								
	□Other:								

13b	**PCP Prophylaxis:**								
	□ None								
	□ Yes								
13c	**TB Prophylaxis:**								
	□ None								
	□ INH								
13d	**TB Treatment:**								
	□None								
	□Yes								
	New Drugs:								
	□ Rifater (RHZ) tabs/day								
	□ Rifafour (RZHE) tabs/day								
	□ Ethizide (EH) tabs/day								
	□ Rifinah (RH) tabs/day								
	□ Rifampicin mg/day								
	□ INH mg/day								
	□ Pyrazinamide mg/day								
	□ Ethambutol mg/day								
	□Streptomycin mg/day								
	□ Other:								
13e	**Cryptococcus Tx:**								
	□ None								
	□ Start Diflucan								

	□ Continue Diflucan								
	□ Stop Diflucan								
14f	**Additional Drugs Started This Visit:**								
	Drug	Dose (# Tabs)	Dose (# Tabs)	Dose (# Tabs)	Dose (# Tabs)	Dose (# Tabs)	Dose (# Tabs)	Dose (# Tabs)	Dose (# Tabs)
	1								
	2								
	3								
	4								
	5								
	6								
15	**Referrals:**								
	□ None								
	□ Counselling								
	□ TB /DOT program								
	□ Nutritional support								
	□ Income generating activity support								
	□ Other referral (specify):								
	Comments:								
16	**Hospitalization:**								
	□ MTRH								
	□ Mbagathi District								
	□ Other:								
	Reason for Admission:								
	Date of Return to Clinic								

Appendix 6: Laboratory Costing Form

1	**Direct costs**	**Quantity**	**Cost (KSh)**	**Unit cost (KSh)**	**Total cost (KSh)**
	Specimen collection				
	Consumables.				
	A. Gloves (50 pairs)				
	B. Syringe (50)				
	C. Needle (100)				
	D. Swab/spirit				
	E. Vacutain tubes (100)				
	F. Dustin bin				
2	**Processing specimen**				
	Consumables.				
	A. Gloves (50 pairs)				
	B. Tips (yellow/ blue)1000				
	C. Pipettes (10-100ul)				
	D. Thermal paper				
	F. Jik				
	G. Racks				
3	**Reagents**				
	A calibrators				
	B. Controls				
	C. Reagents				
	A. Albumin reagents				
	i.				
	ii.				
4	Analytical consumables				
	A. Cuvettes				
	B. Tips				
	C. Gloves				
5	Proficiency testing mats.				
	A.				
	B.				
	C.				
6	Labour				
	A. Collection				
	B. Accessioning				
	C. Analysis				
	D. Quality Control				
	E. Reporting				

	Direct costs	**Quantity**	**Cost (KSh)**	**Unit cost (KSh)**	**Total cost (KSh)**
7	Equipment costs				
	A. Depreciation				
	B. Maintenance				
	C. Service contracts				
8	Office supplies				
	A. Reporting cost				
	i. Paper				
	ii. Printing				
	iii. Fax/telephone.				

Appendix 7: Ethical Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2009/55
Approval Number: 000455

30th October, 2009

Elizabeth Anyango Owiti,
School of Economics,
University of Nairobi,
P.O. Box 1967- 00100,
NAIROBI.

Dear Ms. Owiti,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:

"Cost Effectiveness of Alternative HIV Treatment Scenarios in Kenya".

Your proposal has been granted a Formal Approval Number: **FAN: IREC 000455** on 30th October, 2009. You are therefore permitted to continue with your study.

Note that this approval is for 1 year; it will thus expire on 29th October, 2010. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Yours Sincerely,

PROF. D. NGARE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
APPROVED
30 OCT 2009
P.O. Box 4606 ELDORET

cc: Director - MTRH
Dean - SOM
Dean - SPH
Dean - SOD