

ATTRITION OF WOMEN INITIATING ANTIRETROVIRAL
THERAPY UNDER OPTION B+: COX PROPORTIONAL
HAZARDS, COMPETING RISKS AND MULTISTATE SURVIVAL
MODELS

MSc.(BIOSTATISTICS) Thesis

By

Andrew Mganga

BSc (Demography and Statistics)-University of Malawi

Submitted to Faculty of Science in partial fulfilment of the
requirements for the degree of Master of Science
(Biostatistics)

UNIVERSITY OF MALAWI
CHANCELLOR COLLEGE

August, 2016

DECLARATION

I, the undersigned, hereby declare that this dissertation is my own original work which has not been submitted to any other institution for similar purposes. Where other people's work has been used acknowledgements have been made.

Andrew Mganga

Name

Signed

Date

Certificate of Approval

The undersigned certify that this thesis represents the students own work and effort and has been submitted with our approval.

Signature: _____ Date _____

L. Kazembe, PhD (Senior Lecturer)

Supervisor

Signature: _____ Date _____

B. Ngwira, PhD (Senior Lecturer)

Supervisor

Signature: _____ Date _____

T. Kaombe, MSc (Lecturer)

Programme Coordinator

ACKNOWLEDGEMENT

My ultimate gratitude goes to the Almighty God, my Father who did not disappoint me but constantly fought my fierce battles.

I am very grateful for the supervision and assistance I got from Prof. L. Kazembe and Dr. B. Ngwira throughout the entire process of writing this thesis. Your time, resources and constructive criticism have made this work a success.

Special thanks should go to Management Sciences for Health (MSH) for allowing me to use their HIV/AIDS dataset.

Thanks should also be extended to the coordinator of the programme, Mr T. Kaombe and all members staff of Mathematical Sciences Department, Chancellor College, for their support during my studies.

Lastly, I am indebted to all my classmates, friends, and my brothers and sisters who have made this study bearable.

ABSTRACT

Prevention of Mother to Child Transmission (PMTCT) remains critical to decreasing the number of exposed children infected with HIV. However women need to remain on ART in order for PMTCT to be effective in preventing HIV transmission. In 2011, the Malawi program changed the clinical guidelines for the provision of PMTCT to option B+. However, Option B+ intervention was implemented without any trials to assess effectiveness. To-date, few studies have evaluated outcomes of women on option B+. Therefore, knowledge on effectiveness of option B+ is limited. This study explores the ART outcomes of women who initiated under option B+ in Malawi. This is in order to inform effective and efficient implementation of the interventions.

This study explored facility level and individual level factors that affect attrition among Option B plus (Option B+) women in Malawi. Secondary data from PMTCT Retention of Option B+ Evaluation (PROBE) study collected by Management Sciences for Health (MSH) was used in the study. Three models were used, Cox proportional hazards model, competing risks model and multi-state models. The main outcome variable was attrition from ART.

The findings suggest that management authority, facility level, status at initiation, age group, ART education and clinical condition are significantly associated with

attrition from ART. The association of the predictors and attrition, however, varies from ART registration to ART treatment follow-up and follow-up outcomes. On the other hand, location of residence did not have an effect on attrition from ART. The association of predictors and attrition however varies from ART registration to ART treatment follow-up and follow-up outcomes.

Contents

Abstract	i
Table of Contents	vi
List of Tables	vii
List of Figures	ix
List of Abbreviations	x
Chapter 1 Introduction	1
Background	1
Problem Statement	4
Thesis Statement	4
General Objectives	5
1.4.1 Specific Objectives	5
1.5 Significance of the Study	5
1.6 Organisation of the Study	6
Chapter 2 Literature Review	7
Debate on Option B+	7
Attrition and Retention in Care	11
Overview of Models	16

2.3.1	Survival Data	16
2.3.2	Types of Censoring	16
2.4	Proportional Hazards Model	17
2.4.1	Cox proportional Hazards Model	17
2.4.2	Competing Risks Survival Model	18
2.4.3	Multi-state Survival Model	19
2.5	Parametric Proportional Hazards model	20
2.5.1	Exponential	20
2.5.2	Weibull	21
2.5.3	Gompertz	22
2.6	Accelerated Failure Time Models	23
2.6.0.1	Log-logistic	23
2.6.1	Log-normal	24
2.7	Shared frailty survival Model	24
Chapter 3 Study Methodology		26
	Data Sources and Description	26
3.1.1	PROBE Study	26
3.1.2	PROBE Study Sampling	27
3.1.3	Inclusion Criteria	29
3.1.4	Data collection	29
3.2	Study Variables	29
3.2.1	Dependent Variable	30
3.2.2	Independent Variables	31

3.3	Model Description	32
3.3.1	Formulation of the Cox Proportion Hazards Model	32
3.3.2	Formulation of Competing Risks Survival Model	32
3.3.3	Formulation of Multi-state Survival Model	33
3.4	Model Fitting	35
3.4.1	Parameter Estimation	35
3.5	Summary	36
Chapter 4	Results and Discussions	37
	Descriptive	37
	Model Building	48
4.2.1	Bootstrapping	50
4.3	Cox Proportional Hazards Model	51
4.3.1	Test of PH Assumptions	55
4.3.2	Model Assessment	58
4.4	Competing Risks Model	60
4.4.1	Competing Risk Model Test of PH Assumptions	65
4.4.2	Stratified Competing Risks Model	66
4.5	Multi-state Models	69
4.6	Summary	77
Chapter 5	Conclusions and Recommendations	78
	Conclusion	78
	Study Limitations	82

Recommendations	83
References	85
Appendices	90
Appendix A: PROBE Study Sampling	91

List of Tables

4.1	Characteristics, Log Rank Test Results and Trend Test Results. . .	39
4.2	Bayesian Information Criteria Results	49
4.3	Cox Proportional Hazards Model	52
4.4	Cox Model Assessment of Assumption	56
4.5	Competing Risks Model	62
4.6	Competing Risk Model Assessment of Assumption	65
4.7	Competing Risk Model Stratified by Facility Level	67
4.8	Multi-state Model from Registration to Failed Initiation or ART .	71
4.9	Multi-state Model from ART to Default or Transfer Out	72

List of Figures

4.1	Kaplan-Meier curves showing retention of women on ART under Option B+ by location of facility.	40
4.2	Kaplan-Meier curves showing retention of women on ART under Option B+ by managing authority of the facility.	42
4.3	Kaplan-Meier curves showing retention of women on ART under Option B+ by facility level of service provision.	43
4.4	Kaplan-Meier curves showing retention of women on ART under Option B+ by status at initiation.	44
4.5	Kaplan-Meier curves showing retention of women on ART under Option B+ by age group.	45
4.6	Kaplan-Meier curves showing retention of women on ART under Option B+ by patient education status.	46
4.7	Kaplan-Meier curves showing retention of women on ART under Option B+ by clinical stage.	47
4.8	Graph of the scaled Schoenfeld residuals and their lowess smooth for management authority and facility level.	57
4.9	Graph of the scaled Schoenfeld residuals and their lowess smooth for status at registration and age group.	57
4.10	Graph of the scaled Schoenfeld residuals and their lowess smooth for ART education and clinical condition.	58
4.11	Cox-Snell residuals	59
4.12	Cumulative Incidence of TO and Default	61

4.13 A flow diagram Showing states and transitions	69
--	----

LIST OF ABBREVIATIONS

AFT	Accelerated Failure Time Model
ART	Antiretroviral Therapy
ARV	Antiretroviral
BIC	Bayesian Information Criteria
CHAM	Christian Health Association of Malawi
CIF	Cumulative Incidence Function
HIV	Human Immunodeficiency Virus
HTC	HIV Testing Counselling
IQR	Interquartile Range
LTFU	Lost-to-Follow-Up
MSPA	Malawi Service Provision Assessment
M&E	Monitoring and Evaluation
MoH	Ministry of Health
MSH	Management Sciences for Health
NVP	Neverapine
Option B+	Option B plus

PH	Proportion Hazards
PMTCT	Prevention of Mother-to-Child Transmission
PROBE	PMTCT Retention of Option B+ Evaluation
STI	Sexually Transmitted Infection
TFR	Total Fertility Rate
TO	Transfer Out
WHO	World Health Organisation

CHAPTER 1

Introduction

1.1 Background

Prevention of Mother-to-Child Transmission (PMTCT) remains critical to decreasing the number of exposed children infected with HIV. PMTCT interventions considerably reduce vertical transmission of HIV through the provision of Antiretroviral Therapy (ART) to infected mothers and Antiretroviral (ARV) prophylaxis to infants born to infected mothers (Schouten et al., 2011). The World Health Organisation (WHO) notes that in the absence of any intervention a substantial proportion of children born to women living with HIV acquire the virus during pregnancy, labour, delivery and breastfeeding. The risk of transmission without intervention is 15-30% in non-breastfeeding populations and 20-45% in breastfeeding populations. However, the transmission rate can be reduced to below 5% with effective interventions during the periods of pregnancy, labour, delivery and breastfeeding (World Health Organization, 2010).

The WHO currently recommends three PMTCT approaches (World Health Organization, 2013):

- Option A; recommends maternal AZT for mothers with low CD4 count and ARV prophylaxis for infants.
- Option B; recommends maternal triple ARV prophylaxis for low CD4 count women through breastfeeding.
- Option B plus (Option B+); recommends triple ARVs starting as soon as a mother is diagnosed regardless of CD4 count, and continues this treatment for life.

In 2011, the Malawi program changed the clinical guidelines for the provision of PMTCT to Option B+. Specifically, all women attending antenatal clinic are offered HIV Testing Counselling (HTC) services in Option B+. All consenting HIV positive women are then put on lifelong ART. Furthermore, initiation on ART treatment continues at maternity and during post-natal period (these are classified as having initiated treatment during breastfeeding).

Neverapine (NVP) prophylaxis/preventive is provided to all babies born to Human Immunodeficiency Virus (HIV) infected mothers. This is in order to slow disease progression, increase survival and reduce HIV transmission to the baby.

The main outcomes of the program are retention of mother on ART, retention in exposed child follow-up and HIV free survival of the new born baby at 24 months of age or more precisely; a confirmed HIV negative result at least 6 weeks after weaning.

Children born to infected mothers are tested for HIV at 6 weeks, 12 months and 24 months (Ministry of Health, 2011).

There are several possible challenges that may affect the realisation of Option B+ objectives. Ideally, women are supposed to remain in care for life i.e. retention-in-care. Retention-in-care is commonly used as a proxy for treatment adherence and viral suppression. It is assumed that patients who are retained-in-care receive appropriate care at relevant time points whereas those Lost-to-Follow-Up (LTFU) have stopped taking their treatment (Rollins et al., 2014). Furthermore, women who are retained-in-care are assumed to be virally suppressed and therefore at a low risk of transmitting HIV. PMTCT interventions are therefore considered effective if women are virally suppressed with low risk of transmission. Some women however default from treatment, transfer to another health facility, die, and stop treatment. These are considered to be adverse outcomes. The fourth quarter 2014 Ministry of Health (MoH) integrated HIV program report indicates that retention on Option B+ was 78%, 72% and 68% retained on ART at 6, 12 and 24 months after initiation, respectively (Ministry of Health, 2014). These retention rates are among the women who had not transferred out as of end June 2014.

Retention of Option B+ women data is an example of censored survival data that is routinely collected. Censored survival data is common in health, therefore survival analysis methods are used in the analysis of such data. A widely used survival analysis method is Cox Proportion Hazards Model. Competing risks and Multi-state survival models are extensions of the basic survival models to context with multiple events of interest and across a continuum. However, there are other approaches to modelling survival data that have been put forward.

1.2 Problem Statement

In Malawi, women have been initiating ART under Option B+ since July 2011. However, limited evaluation has been done to determine the outcomes of women initiated under Option B+. Furthermore, Option B+ was implemented without any trials to assess effectiveness as a PMTCT intervention (Coutsoudis et al., 2013). To-date, few studies have evaluated outcomes of women on Option B+. Therefore, knowledge on effectiveness of Option B+ is limited. There is a need to study the outcomes and characteristics of women who initiate ART on Option B+. In a viewpoint, Schouten et al agreed that there is indeed a strong case for expanding research on Option B+ but not for impeding countries that implement Option B+ on the basis of available evidence and programmatic experience (Schouten et al., 2013). Outcomes of the intervention strategy are therefore not comprehensively understood. Subsequently, effectiveness of the intervention is not comprehensively understood.

1.3 Thesis Statement

Adolescents, pregnant women and/or women access ART in government hospitals require additional focused interventions in order to improve their ART outcomes.

1.4 General Objectives

This study explores the ART outcomes of women who initiated treatment under Option B+ in Malawi. This is in order to inform effective and efficient implementation of the interventions.

1.4.1 Specific Objectives

Specifically the study will look at the following objectives:

- To assess characteristics affecting ART treatment outcomes among women on Option B+.
- To compare cause-specific hazard and sub-hazards ratios in evaluating retention on ART treatment.
- To describe the change in retention rate within the first 21 months of ART registration among Option B+ women.

1.5 Significance of the Study

Evaluation and testing of public health intervention is fundamental to effective and efficient implementation of the interventions. Understanding of the effectiveness of the intervention is central to achieving PMTCT program objectives. Specifically, understanding of Option B+ effectiveness in reducing the risk of HIV transmission from a woman living with HIV to the child will support programming, planning

and implementation of Option B+ intervention. This study will therefore generate evidence for PMTCT programming and subsequently enhance evidence-based programming.

The Option B+ intervention was implemented without trials on its effectiveness (Coutsoudis et al., 2013). It is, therefore, ethical to evaluate effectiveness of Option B+ intervention.

1.6 Organisation of the Study

This report is presented in 4 broad chapters. Chapter 2 presents methodology of the study. Study data and model description is presented in this chapter. Routine health facility data was used in the survival analysis models fitted. The variables used in the analysis are also presented in chapter 2. Chapter 3 presents the results and discussions. The results of fitting Cox proportional hazards, competing risks, and multi-state Models are provided. Management, status at registration, age group, ART education and clinical condition were found to be associated with attrition. There was no association between facility level and location with attrition from ART. Finally chapter 4 presents the synthesis of the major findings, draw conclusion and make policy and programme recommendations. The results with the exception of location are noted to be similar to findings from other studies. Changes to PMTCT programming is also recommended in this chapter.

CHAPTER 2

Literature Review

2.1 Debate on Option B+

The Option B+ intervention has a number of possible outcomes. The programme outcomes are affected by several factors that include facility level and individual level characteristics.

The Option B+ was proposed as a simplified and subsequently easy to implement PMTCT intervention. Schouten et al proposed the Option B+ intervention strategy in 2011 (Schouten et al., 2011). They argued for universal initiation of lifelong ART treatment among HIV positive pregnant women regardless of CD4 count. They noted that WHO guidelines specify that a CD4 cell count is crucial to decisions on the eligibility of HIV-infected pregnant women for lifelong ART. Further, they noted that access to CD4 cell count analysis is minimal in Malawi and was unlikely to improve any time soon. Thus, making CD4 test a prerequisite for increasing the coverage of PMTCT services and early access to ART would hinder rapid expansion in countries with heavily constrained health systems.

In the same viewpoint, Schouten et al noted that the expansion of the PMTCT

programme in Malawi through implementation of option B+ would have various other benefits. Following are the main benefits they noted: first, due to a high Total Fertility Rate (TFR) in Malawi stopping and then re-starting ART recommended in the then WHO guidelines was almost redundant. Second, many women present for antenatal care late in pregnancy, continuing prophylaxis with ART drugs would mean that the next pregnancy could be protected from conception. Thirdly, the stopping of ART after cessation of breastfeeding might lead to viral rebound, with the risk of transmission to a sexual partner or fetus being notably raised. Lastly, scheduled stopping is also difficult to implement, as it requires tapering of doses to prevent drug resistance owing to the different half-lives of the ART drugs. Additionally, the risks of opportunistic disease or death might be raised.

Opponents of Option B+ argued that there was no evidence on the purported benefits of Option B+ (Coutsoudis et al., 2013). Further, the business case, which supports use of Option B+ in resource-limited settings, does not fully address four critical considerations of ethics, medical safety and benefits, programme feasibility, and economic concerns. They further note that options A, B, and B+ have similar protective benefits with respect to prevention of HIV transmission from mother to child. Furthermore, data suggest that triple ART therapy may provide maternal health benefits even up to CD4 cell counts of 600 cells per μL and reduces transmission between discordant couples. However, these data alone do not justify favouring pregnant women for treatment over men and non-pregnant women.

Coutsoudis et al note further that, if Option B+ is used because it might decrease mortality and disease progression in HIV-infected mothers with CD4 cell counts more than 350 cells per μL , then the justification should extend to the pregnant women's families, partners, friends, community, and the whole HIV-infected population (Coutsoudis et al., 2013). They argued that the application of different treatment thresholds in different sub-populations could create tension between people with and those without access to treatment. In addition, if Option B+ is a phase-in of a universal test-and-treat goal, then this should be made explicit, and the ethics of early treatment initiation in the context of unmet need would need to be discussed.

Coutsoudis et al added that Option B+ is being considered only in resource-limited countries with high HIV burden, where it would target pregnant women for non-pregnancy-related interventions such as treatment-as-prevention and early treatment initiation (Coutsoudis et al., 2013). They noted that there was no data that suggested that pregnant women have above average involvement in discordant relationships or that pregnant women contribute disproportionately to the horizontal transmission of HIV.

The medical benefits and safety of long-term ART, including adherence and resistance, in sub-populations of mothers and infants who do not need the treatment for their own health need to be considered (Coutsoudis et al., 2013). They further argued that, Option B+ is expensive because of additional drugs, laboratory tests, human resource, and other health system expenditures.

Furthermore, experience of Option B+ is restricted to Malawi and Rwanda, which

is insufficient to measure universal feasibility (Coutsoudis et al., 2013). The success of Option B+ depends on the retention of women in treatment programmes, which increases pressure on already strained health systems. The public health implications (including resistance and potential for future treatment) of reduced adherence in Options B and especially Option B+ are unknown and likely to be concerning. Finally, although higher treatment thresholds might be necessary, particularly in regions with high fertility rates, it is unclear whether universal provision of ART treatment for pregnant women only is appropriate.

The pioneers of the Option B+ replied to Coutsooudis and colleagues concerns (Schouten et al., 2013). Schouten et al noted that lack of CD4 testing impeded effective roll-out of WHO options A or B in Malawi. Without timely CD4 results, both WHO regimens risk withholding therapy from women who need it. In addition, other countries share this limitation. They, however, note that even in countries where all three regimens are feasible, Option B+ might be best.

Schouten and colleagues noted that, option A involves a relatively complex drug regimen compared with daily fixed-dose ART and has been operationally difficult to implement in many low-resource settings, according to WHO. Option B requires women to stop and restart ART with each pregnancy, risking increased morbidity and mortality, especially where fertility is high. On the other hand, Option B+ prioritises maternal health by providing ART for life irrespective of CD4. It follows the worldwide trend towards earlier treatment initiation and offers multiple collateral benefits, including decreased horizontal transmission. They note that, Coutsooudis and colleagues suggest that an early start for pregnant women is unfair,

especially where WHO-eligible patients await treatment. Schouten and colleagues believe that although treatment access is rarely zero-sum, the women are a legitimate priority, and leaders have resolved to eliminate paediatric HIV by 2015 while keeping mothers alive. The pioneers noted that a strong case exists for expanding research on **option B+!** (**option B+!**), but not for impeding countries that pursue it on the basis of available evidence and programmatic experience.

2.2 Attrition and Retention in Care

Retention on ART is defined as proportion of patients with HIV known to be on treatment months after initiation of ART. On the other hand, attrition is the proportion of patients with HIV lost from treatment months after initiation of ART. The specific definition of attrition varies across studies.

Tenthani et al studied 6 months retention among Option B+ women in Malawi (Tenthani et al., 2014). Their objective was to explore the levels and determinants of LTFU under universal lifelong ART for pregnant and breastfeeding women (Option B+) in Malawi. They found that on average, 17% of the women were lost to follow-up 6 months after ART initiation. During pregnancy, women who initiated ART for PMTCT were five times more likely never to return to the clinic after treatment initiation compared to women who initiated ART for their own health. Women who began ART while breastfeeding were twice as likely to not return compared to those who started for their own health. Further, more than

one third of all pregnant Option B+ patients initiated ART on the day of diagnosis, and members of this group were almost twice as likely never to return to the facilities after the initial visit as pregnant Option B+ patients who started later. There was extensive variation in the level of LTFU between clinics, ranging from 0 % to 58% at 6 months after ART initiation. Notably, the risk of LTFU was highest in facilities where the patient cohort contained a large proportion of Option B+ patients.

Tweya et al in 2012 studied retention in a general cohort of ART patients (Tweya et al., 2013). The objective of the study was to describe the extent to which patients considered LTFU are misclassified as true disengagement from care. They described reasons for ART discontinuation using an active tracing program. This was to further improve ART retention programs and policies. They used a log-binomial regression to compare categories of tracing outcomes with baseline characteristics of patients considered LTFU. Tweya et al found that 25% of patients suspected to be LTFU were actually found alive and on ART when traced. Of those, 61% had transferred to another ART clinic, 15% reported uninterrupted therapy using ARVs from other sources and 24% reported treatment gaps. About one fifth of traced patients reported stopping ART. Further; they found that even though most patients had stopped by themselves, some patients (3%) were stopped by a clinician and had erroneous patient records. Among the 18% of traced patients who stopped ART at some time, travel and financial constraints were the primary causes of discontinuation. These findings suggest both significant patient misclassification error and an underestimation of overall ART program retention.

Boyles et al conducted a prospective cohort analysis of outcome measures in adults from a rural HIV care programme in South Africa (Boyles et al., 2011) . Boyles and colleagues used frequency distribution and median with Interquartile Range (IQR) to describe the variables because the distribution of the continuous variables were found to be non-normal. Multiple Cox proportional hazard regression analysis, adjusted for competing risks, was used to identify variables associated with a likelihood of being LTFU or dying. At the end of the study, 82.4% were retained in care within the study facilities or had transferred out, 11.1% had died and 6.5% were LTFU. In the study, independent predictors associated with an increased risk of LTFU were CD4 >200, initiating ART as an inpatient or while pregnant, and younger age, while being in care for >6 months before initiating ART was associated with a reduced risk.

Du Toit et al studied retention in pre-ART care in South Africa (Du Toit et al., 2014). They evaluated the proportion of People Living with HIV in pre-ART and ART care and factors associated with retention in pre-ART and ART care from a community cohort. Data was from a cross sectional survey. They used logistic regression with robust standard errors to control parameter estimates for clustering at a community level. Logistic regression was used to explore factors associated with retention in HIV care in the pre-ART group. Univariate regression was used to explore the effect of factors on the likelihood of retention in pre-ART. The study found that retention was at 94%. None of the factors included in the analysis were significantly associated with retention in pre-ART.

Yehia et al studied the interaction of retention with viral suppression across the

continuum of HIV care in United States of America (Yehia et al., 2015). Patients were classified into one of five categories: (1) retained/suppressed, (2) retained/not-suppressed, (3) not-retained/suppressed, (4) not-retained/not-suppressed, and (5) lost to follow-up. They used standard descriptive analysis of demographic and clinical characteristics of the sample. Multinomial logistic regression was used to determine the probability of patients transitioning between the retention/suppression categories. They calculated marginal predicted probabilities for transitioning from one retention/suppression category to another over 1-year and 2-year periods based on the regression results. Overall, the study reported that 65.8% of patients were retained/suppressed, 17.4% retained/not-suppressed, 10.0% not-retained/suppressed, and 6.8% not-retained/not-suppressed. They concluded that not counting patients not-retained/suppressed as virally suppressed, as is commonly done in the HIV care continuum, underestimated the proportion suppressed by 13%. Applying the care continuum in a longitudinal manner will enhance its utility.

Odafe et al evaluated the rates and factors associated with attrition of patients receiving ART in tertiary and secondary hospitals in Nigeria (Odafe et al., 2012). Attrition rates were calculated as a proportion of patients lost from care through death, LTFU and those who stopped treatment at 12 and 24 months observation periods. The Wilcoxon sign rank test was used to compare median changes in CD4 counts between patients in secondary and tertiary hospitals. The Chi-square test was used to test the differences in proportions. The probability of retention in care was estimated using Kaplan-Meier product-limit method. Potential explanatory variables of attrition were checked with the Breslow-Gehan test. A multivariable

analysis for attrition was conducted using the Cox proportional hazard model. Finally, the incidence rates of subcategories of attrition (dead, LTFU and treatment stopped) were expressed as the number of patients with at least one occurrence of the given event per 100 person years. They found that patients LTFU accounted for 62.7% of all attrition followed by treatment stops (25.3%) and deaths (12.0%). Attrition was 14.1 (N=624) and 15.1% (N=300) in secondary and tertiary hospitals respectively ($p=0.169$) in the first 12 months on follow-up. During the 13 to 24 months follow-up period, attrition was 10.7% (N=407) and 19.6% (N=332) in secondary and tertiary facilities respectively. Median time to LTFU was 11.1 (IQR: 6.1 to 18.5) months in secondary compared with 13.6 (IQR: 9.9 to 17.0) months in tertiary sites ($p=0.002$). At 24 months follow-up, male gender [AHR 1.18, 95% CI: 1.011.37, $P=0.038$]; WHO clinical stage III [AHR 1.30, 95%CI: 1.031.66, $P=0.03$] and clinical stage IV [AHR 1.90, 95%CI: 1.203.02, $p=0.007$] and care in a tertiary hospital [AHR 2.21, 95% CI: 1.832.67, $p<0.001$], were associated with attrition. Attrition could potentially be reduced by decentralizing patients on ART after the first 12 months on therapy to lower level facilities, earlier initiation on treatment and strengthening adherence counseling amongst males.

Lamb et al examined the effect of availability of adherence support and active patient outreach services on patient attrition following ART initiation (Lamb et al., 2012). Log-linear models were used to estimate cumulative attrition, LTFU, and death rate ratios comparing clinics with and without availability of each adherence support and outreach service. Cumulative attrition, LTFU, and death rates were 14.2, 9.2, and 4.9 per 100 person-years on ART, respectively.

2.3 Overview of Models

2.3.1 Survival Data

Survival data can be defined as data in the form of times from a well defined time of origin until the occurrence of some particular event (Collett, 2003). Censoring of observations is the main feature of survival data. An individual is said to be censored when the end point of interest has not been observed for that individual. An individual is censored when the event of interest has not been observed. This is either because the event has not occurred at the end of study, the individual has been LTFU or the individual experiences another event that is not of interest (Collett, 2003).

2.3.2 Types of Censoring

Liu discusses there are three main types of censoring, right censoring, left censoring and interval censoring (Liu, 2012). Further; censoring can be informative or non-informative. Right censoring is when an individual enters a study but is LTFU and the actual event time is somewhere to the right of the censored time along the time axis. Left censoring, on the other hand, is when an event is known to have occurred before a certain date but the exact location is unknown. Interval censoring is when the exact event time is unknown, however, it is only known to be located between two known time points. In non-informative censoring; it is assumed that censoring is random. That is, censored data is independent of survival times. In informative censoring, however, there is dependency between

censored data and survival times.

2.4 Proportional Hazards Model

2.4.1 Cox proportional Hazards Model

The Cox hazard function is defined by:

$$h_i(t) = h_0(t)e^{\beta x_i} \quad (2.1)$$

where $i = 1, 2, \dots, n$ are individuals in the study. $h_0(t)$ is the baseline hazard function. The baseline hazard characterises how the hazard function changes as a function of time. While $e^{\beta x_i}$ characterises hazard function of subject covariates (Hosmer & Lemeshow, 1999). The hazard function is equal to $h_0(t)$ when all the variables included in the model are zero. That is when $e^{\beta x_i} = 1$.

The ratio of hazard functions of two subjects with a dichotomous covariates values denoted as x_1 and x_0 is given by:

$$HR(t, x_1, x_0) = e^{\beta(x_1 - x_0)} \quad (2.2)$$

Where HR is the Cox proportional hazards model. When $x_1 = 1$ and $x_0 = 0$, the Cox model is defined by the following:

$$HR(t, x_1, x_0) = e^\beta \quad (2.3)$$

In the Cox proportional hazard model, the hazard ratio is only dependant on e^β . The description of the baseline function is therefore avoided in fitting proportion hazards model. The hazard function therefore is not restricted to a particular functional form and the model has flexible and widespread applicability. The hazard function is therefore sometimes referred to as semi-parametric.

The survival function is defined by:

$$S(t, x, B) = [S_0(t)]e^{\beta x} \quad (2.4)$$

where $S_0(t)$ is the baseline survivorship function. The survival function $S(t, x, B)$ is always between zero and one.

2.4.2 Competing Risks Survival Model

In competing risks survival model, the main interest is in the time until a first event and also the type of the event that occurs. Subjects are at risk of several different types of events during the follow-up period. Unlike censoring, which merely obstructs one from viewing the event, a competing event prevents the event of interest from occurring altogether, and analysis is adjusted accordingly. In Cox regression, you focus on the survivor function, which indicates the probability of surviving beyond a given time. In competing-risks regression, you instead focus on the cumulative incidence function, which indicates the probability of the event of interest happening before a given time. The hazard function is specific to a

particular event in competing risks (Kleinbaum & Klein, 2012). The hazard is therefore known as cause-specific hazard. The cause specific hazard is defined by:

$$h_{ij}(t, x_i) = \lim_{\Delta t \rightarrow 0} \frac{t < T \leq t + \Delta t, J = j \mid T \geq x_i}{\Delta t} \quad (2.5)$$

It is the instantaneous risk of event of cause j . In other words, it is the conditional probability that a subject with covariates x has an event in the interval $[t, t + dt)$ from the $J - th$ cause, given that the subject had not experienced any other just before time t . Dividing by dt and then taking the limit as $dt \rightarrow 0$ converts to probability. The overall hazard is given by law of total probability as follows:

$$h(t, x_i) = \sum_{j=1}^m h_{ij}(t, x_i) \quad (2.6)$$

where $j = 1, 2, \dots, m$ are competing events and x_i are covariates. The overall survivorship is therefore defined by:

$$S(t, x_i) = e^{-H(t, x_i)} \quad (2.7)$$

where $H(t, x_i)$ is the cumulative risk obtained by integrating the overall hazard.

$$H(t, x_i) = \int_0^t h(u, x_i) du \quad (2.8)$$

2.4.3 Multi-state Survival Model

In multi-state survival models, the main interest is in the occurrence of different types of events and the subsequent events. The subsequent events are also usually

of several different types. This is in contrast to competing risks where the main interest is the first event and event type. Multi-state models are therefore a generalisation of basic survival data analysis to a case where several competing events occur successively over time. The occurrence of successive events constitutes the transitions from an initial state to a final state.

The multi-state hazard function is specific to a particular transition from one competing risk set to another nested competing risks set. This transition is also referred to as transition from one state to another. The multi-state transition hazard is therefore given by:

$$h_{ij}(t) = P(X_{(t+dt)} \mid X_t = i) \quad (2.9)$$

where $i, j = 0, 1, 2, \dots, J$ and $i \neq j$. It is the instantaneous risk of transitioning. In other words; it is the probability of making $i \rightarrow j$ transition in the interval dt .

2.5 Parametric Proportional Hazards model

A proportional hazard model can be parametrized by a full specification of the hazard function (Collett, 2003).

2.5.1 Exponential

The simplest form of the hazard function is when a hazard is constant over time. This form is given by an exponential distribution. The hazard function for an exponential distribution is defined by:

$$h(t) = \lambda \tag{2.10}$$

where λ is a hazard of failure event and t is time taken to failure limited to $0 \leq t < \infty$.

The hazard function does not depend on the time. It is therefore constant over time Collett (2003). λ is estimated by fitted model to observed data. Therefore the ratio of hazard functions of two subjects with dichotomous covariates values denoted as x_1 and x_0 is defined by:

$$HR(x = 1, x = 0) = e^{-\beta_1} \tag{2.11}$$

The exponential survivorship function is then defined by:

$$S(t) = e^{-\lambda t} \tag{2.12}$$

2.5.2 Weibull

The assumption of constant hazard function is rarely attained. There are other parametric models that allow for non-constant hazard function such as the Weibull function. The Weibull hazard function allows for a monotonically decreasing or increasing hazard function, however, it does not change direction. The Weibull hazard function depends on time. The hazard function for a Weibull distribution is defined by:

$$h(t, x_i, \beta, \lambda) = \lambda \gamma t^{\lambda-1} e^{-\lambda \beta x_i} \quad (2.13)$$

where x_i are the model covariates with $\beta x_i \neq \beta x_i$, β fitted model coefficient, t is time taken to failure limited to $0 \leq t < \infty$, $\lambda \gamma t^{\lambda-1}$ is the baseline hazard function, $\lambda = \frac{1}{\sigma}$ the shape parameter and γ is the scale parameter. When $\gamma = 1$ the hazard function is constant and therefore the survivor time is exponentially distributed. While when $\gamma \neq 1$ the hazard function increases or decreases monotonically (Hosmer & Lemeshow, 1999). The survival function for the Weibull model is defined by:

$$S(t, x, \beta, \lambda) = \exp(-t^\lambda \exp[(\frac{-1}{\sigma})(\beta_0 + \beta_1 x)]) \quad (2.14)$$

2.5.3 Gompertz

The hazard function for a gompertz model is defined by:

$$h(t) = \theta e^{\lambda t} \quad (2.15)$$

where θ determines the shape of the hazard function with positive values leading to a hazard function that increases with time, $0 \leq t < \infty$ and $\lambda > 0$ and is the shape parameter. The hazard has a constant hazard when $\lambda = 0$ and the survivor time has an exponential distribution. Similar to the Weibull, the hazard function increases or decreases monotonically (Collett, 2003).

The survivorship function is defined by:

$$S(t) = e^{(\frac{\theta}{\lambda}(1-e^{\lambda t}))} \quad (2.16)$$

2.6 Accelerated Failure Time Models

An Accelerated Failure Time Model (AFT) is a parametric model that provides an alternative to the commonly used proportional hazards models. There are some situations where the Proportion Hazards (PH) requirement cannot be satisfied. AFT models might fit the data better. AFT therefore have wider applicability relative to PH models. Furthermore, the widely used distributions of Weibull and Gompertz have hazards functions that are either monotonically increasing or decreasing (Collett, 2003).

2.6.0.1 Log-logistic

The uni-modal form of the hazard function is defined by a log-logistic. It is given by:

$$h(t) = \frac{e^{\theta} k t^{k-1}}{1 + e^{\theta} t^k} \quad (2.17)$$

where $0 \leq t < \infty$ and $k > 0$. The hazard function above decreases monotonically if $k \leq 1$ but when $k > 1$ has a single mode (Collett, 2003). The corresponding survivorship function is defined by:

$$S(t) = [1 + e^{\theta t^k}]^{-1} \quad (2.18)$$

2.6.1 Log-normal

The survivorship function is defined by a log-normal (Collett, 2003). It is:

$$S(t) = 1 - \Phi\left(\frac{\log t - \mu}{\sigma}\right) \quad (2.19)$$

where μ and σ are unknown parameters and $\Phi(\cdot)$ is a standard normal distribution function, defined by:

$$\Phi(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^x \frac{-u^2}{2} du \quad (2.20)$$

2.7 Shared frailty survival Model

Survival analysis models presented this far require that the survival times be independent. There are however situations when survival times are dependent. Dependant survival time data arise when the individuals have some feature in common. For instance, there is some characteristic that is shared by more than one observed event time. Account can be taken of effects of this characteristic by introducing a corresponding term into the model (Collett, 2003). The hazard function of a shared frailty survival model is defined by:

$$h_{ij}(t) = h_0(t)e^{(\beta x_{ij} + \zeta_i)} \quad (2.21)$$

Where $h_0(t)$ is baseline hazard; ζ_j is the frailty term and it is unobservable. $e^{(\beta x_{ij} + \zeta_i)}$ is the covariate term. $i = 1, \dots, n$ are groups with $j = 1, \dots, n_i$ observation in group i . A frailty survivorship function is defined by:

$$S_{ij}(t_{ij}) = e^{[-e^{(\beta x_{ij} + \zeta_j)} H_0(t_{ij})]} \quad (2.22)$$

Where $H_0(t_{ij})$ is the cumulative hazard function evaluated at time t_{ij} .

CHAPTER 3

Study Methodology

3.1 Data Sources and Description

This study used secondary data from PMTCT Retention of Option B+ Evaluation (PROBE) study collected by Management Sciences for Health (MSH).

3.1.1 PROBE Study

The goal of the PROBE study was to evaluate the extent to which HIV-infected pregnant women initiating ART under Option B+ are retained in care both during pregnancy and beyond. The results of the study was to inform additional analysis and project design for future research. The results would further assist in examining adherence to other care and support strategies among HIV positive pregnant women, including tuberculosis prophylaxis, malaria prevention, and Sexually Transmitted Infection (STI) diagnosis and treatment. Data for PROBE was consolidate from routinely collected information from clinic records. The outcome measure obtained from selected clinic registries and other sources is documentation of repeat clinic visits for medication renewals during pregnancy and

following delivery. Data collected include information on initial presentation at antenatal clinic, date of HIV diagnosis, date of ART initiation under Option B+, other clinical prophylaxis and tracking additional presentation at clinics to refill prescriptions for ART according to the prescribed ART regimen.

Specifically, probe study focused on analysing attrition of mothers from ART care and treatment in relation to gestational age/age of infant. Identify the step(s) of the PMTCT cascade (including the breastfeeding period) at which attrition from the ART regimen is most likely to occur. Analyse adherence of mothers to medication based on documentation of pill count, missed doses, and attendance at follow up appointments. Determine age related adherence and attrition. Analyse adverse outcomes of mothers initiating ART under Option B+. Collect and analyse information on care and support services provided by the clinics to pregnant, HIV-infected women, such as client initiation on Cotrimoxazole Prophylaxis, TB status and treatment, treatment of STI, and malaria prevention.

3.1.2 PROBE Study Sampling

PROBE study uses a stratified multi-stage sampling.

To ensure that the sample is representative, the country was stratified into 4 geographical areas. This was for the first stage in the multi-stage sampling. The geographical areas are rural health facilities from north & central, rural districts of the southern region, Blantyre urban and Lilongwe urban. The geographical areas were divided based on the epidemiological characteristics of the area (HIV

prevalence and rural & urban facilities).

In the second stage of sampling, facilities were sampled from each of these strata through systematic random sampling. The sample frame was limited to facilities that had more than 100 exposed infants ever enrolled. These were 76 % of the 600 total ART facility. To achieve a total sample of 30 facilities, every 15th facility was selected from the sample frame. The first facility was randomly selected from the first 15 facilities. An additional 5 facilities were sampled as spare. The spare sites were selected to ensure that data is collected from 30 sites and would be replacement in case the PROBE study failed to collect from initial selected 30 facilities. The number of facilities sampled in each area was based on the number of women on ART in the area. Appendix A contains a list of the selected facilities.

Finally, the study subjects were selected through systematic random sampling. The 30 selected facilities based on Monitoring and Evaluation (M&E) data from MoH had a total of 3,574 women initiated on Option B+. The project aimed at collecting information up of to 150 mother-infant pairs from each selected facility. In facilities with less than 150 pregnant or breastfeeding women started on ART, data was collected from all potential subjects. In facilities with 151 to 300 eligible patients, data was collected from every second potential subject. In clinics with 301 to 450 eligible patients, data was collected from every third potential subject. Total sample size that was to be collect was approximately 3000.

3.1.3 Inclusion Criteria

The inclusion criteria of the study was all women who were initiated on ART while pregnant or breastfeeding in 2012. The Option B+ program started in July 2011 in Malawi. In the first 6 months, the program was not fully established. Finally, women starting ART in 2013 could not be followed up long enough.

3.1.4 Data collection

The study used Ministry of Health data collection teams to collect data from the following health facility source documents:

- ART patient card/ARV Formulations card for mother
- ANC register
- ART register
- HIV Care Patient Card for Exposed Child Under 24 Months

This study used data from ART patient cards only. The data collection teams collected data on a number of variables from the above source documents.

3.2 Study Variables

Data collected routinely in health facilities was used. Variables that are clinically significant are documented on patient cards and patient registers within health

facilities. Variables were therefore selected purposively from the PROBE data set.

3.2.1 Dependent Variable

Attrition from ART treatment was the outcome variable in this study. Women in ART care are at risk several events that results in attrition. Women can be removed from care through either default from treatment, transfer out, die or stopping of treatment altogether (Ministry of Health, 2011).

Attrition was a nominal variable indicating whether a woman was still in care, had defaulted, transfer out, died or stopped. In this study however attrition was defined as either a default or a transfer out. Deaths and stops were censored.

Cornell et al recommends separately studying events rates among transfer outs, defaulters and patients retained (Cornell et al., 2014). Mortality among transfer outs, defaulters and patients who were retained was explored. Mortality risk was 3 times higher among transfer out patients and 20 times higher among defaulters.

In another study, Krentz and colleagues examined the characteristics and outcomes of patients who move away and then return. This was to assess the impact of moving on disease progression when compared with patients remaining continuously at the same site. They suspected that despite forward planning, a move may result in potential serious interruptions and/or disengagements of care. The potential harmful health effects can in some be equivalent becoming LTFU. They finally noted that recognising and addressing the potential disruption in care from a planned move may be of value in improving outcomes (Krentz et al., 2011).

In Canada, the cascade of care differs among patients that remain and transfer. Krentz et al notes that there is a need to study Transfer Out (TO) separately in measuring performance within the cascade of care. Performance analysis of cascade of care without accounting for TO could therefore lead to imprecise information for public health initiatives and program metrics (Krentz et al., 2015).

Joseph et al found that TO had similar treatment outcomes to patients that remain in one facility. They studied patients in Mzuzu Central Hospital (Kwong-Leung Yu et al., 2008).

The above, emphasizes the importance of studying ART treatment outcomes of TO separately. The assumption that TO have similar outcomes therefore requires further verification through studies.

3.2.2 Independent Variables

Age at ART registration of the woman. In this study, women registering for ART at 24 years or younger were considered adolescents while women registering at 25 years or above were considered adults. Whether the woman was pregnant or lactating at ART registration was another independent variable as well as whether she received patient education at ART registration or not. Clinical condition was also an independent variable in the study.

Facility characteristics were also included as covariates in this study. The health facility characteristics that were included in the study were managing authority (public or CHAM), level of service provision (health centre, hospital and referral

hospital) and, finally, location of the facility (urban, semi-urban and rural).

All the independent variables in this study were categorical. Age was transformed from a continuous variable to 2 categories of clinical relevance.

3.3 Model Description

This section provides a description of the statistical models used in the study.

3.3.1 Formulation of the Cox Proportion Hazards Model

In the Cox proportion hazards model, the event of interest was default from treatment. The ministry of health considers patients defaulted if they have not returned to the clinic and are not known to have transferred-out, stopped or died (Ministry of Health, 2011).

The date of entry into follow-up in Cox model was the date of ART registration. This study was censored on 1 October, 2013. Subjects were also censored if they had died, stopped treatment or transferred-out of the facility.

3.3.2 Formulation of Competing Risks Survival Model

Outcomes for patients on ART are the possible competing risks events that occurs. The outcomes were modelled from the date they initiate ART. The competing risks for patients on ART are the following:

1. Default
2. Transfer-Out
3. Dead
4. Stopped

This study focuses on default and transfer out as the competing events.

Similar to the Cox model, date of entry into follow-up in the competing risks model was date of ART registration. This study was censored on 1 October, 2013. Subjects were also censored if they had died or stopped. Transfer-outs were censored in modelling the sub-hazard of default while default was censored in modelling the sub-hazards of default.

3.3.3 Formulation of Multi-state Survival Model

Two nested competing risks will constitute multi-state survival model in this study. The first competing risks set in the multi-state was modelled from the date the woman initiates ART. The three possible risks are presented below:

1. Failed registration
2. ART
3. Transferred out

In this study, failed registration refers to patients who missed their first follow up visit after the first visit and did not return to care for at least 60 days. This is similar to the definition used by Tenthani and colleagues in their study on option B+ in Malawi (Tenthani et al., 2014). This was also noted by Rollins and colleagues in their article on defining retention-in-care. They noted that women who did not have a first follow-up visit were never in care. Including these women in definition retention-in-care distorts the understanding of retention-in-care (Rollins et al., 2014). Transition probabilities were estimated for failed registration and ART, transfer out were censored.

The second competing risk set was nested within the state of ART. ART state therefore is a transient state. Failed registration was an absorbing state.

Below are the states that can be reached from the state of ART:

1. Default
2. Transfer Out
3. Dead
4. Stop

Transition probabilities were estimated for defaults and transfers-outs, stops and deaths were censored. Default and transfer out were absorbing.

3.4 Model Fitting

Model fitting and data analysis were done in STATA (version 13; Stata Corporation, College station, Texas, USA) and R statistical software. Cox proportion hazards and competing risks survival model were fitted in STATA. In R, mstate package was used in fitting the multi-state models.

3.4.1 Parameter Estimation

Partial likelihood was used in estimation of parameters for Cox proportional hazards model. Klein and Moeschberger (Klein & Moeschberger, 2003) discusses the Cox parameter estimation. The partial likelihood divides the data into risk sets and within each risk set the likelihood of an event is modelled. Subjects with censored times enter into the likelihood through being in the risk set until they are censored. Breslow approximation method was used in dealing with tied event times.

Cause-specific and transition-specific partial likelihood estimation was used in parameter estimation for competing risks and multi-state models respectively. Similar to Cox model, Breslow method was used to adjust for tied event times (Beyersmann et al., 2012).

3.5 Summary

The Cox Proportional Hazards model, competing risks model and multi-state survival models were used in the analysis of attrition from ART. Routine facility data from the PROBE survey was used in the analysis. The analysis of data was performed in Stata and R statistical packages.

CHAPTER 4

Results and Discussions

This chapter presents the results from the analysis. Section 3.1 presents the descriptive data analysis. This includes a tabulation by independent variables, log-rank test results and Kaplan-Meier survival graphs. Section 3.2 presents model building that includes variable selection and bootstrapping procedure. The Cox Proportion Hazards Model and diagnostics are presented in section 3.3. Section 3.4 presents the fitted Competing Risks Model, model diagnostics and the stratified competing risks model. Finally, section 3.5 presents the fitted Multi-State Model. Results of fitting the multi-state for all the 4 states are presented. All tests in this study were done at 95 % significance level.

4.1 Descriptive

PROBE study collected data on 2,979 Option B+ women. These women had a total of 20,960 observations. 2,739 women with a total of 17,769 observations had complete information on all the studied variables and hence their data was analysed in this study. The incomplete data was dropped based on the assumption that the data was missing at random. Dropped data points therefore could

produce similar results if analysed separately. The 2,739 patients accumulated 2,033 person years. At the end of follow-up, 410 had defaulted, 39 transferred out, 14 died and 4 stopped ART.

Descriptive statistics were used to give the distribution of the variables. K-M methods were used to describe the survival time distribution and log-rank test was used to test equality of variable strata. This provided insight into the shape of the survival function for each group and gave an idea of whether or not the groups are proportional, that is, if the survival functions are approximately parallel. To explore whether or not to include the variable in the final model, test of equality across strata was done. Log-rank test of equality across strata was used for categorical variables. This is a non-parametric test. A predictor was included in the model if the test had a p-value of 0.2 or less. In variable selection, a less stringent significance level is recommended in order to avoid rejecting potentially important variables (Machin et al., 2006). Table 4.1, presents results from the log-rank tests, trend test and frequencies of the independent variables.

Table 4.1: Characteristics, Log Rank Test Results and Trend Test Results.

Variable	Category	n (%)	Log-rank P-Value	Trend test P-values
Location	Urban	1631 (60)	0.531	0.297
	Semi-urban	566 (21)		
	Rural	542 (19)		
Management	CHAM	731 (27)	0.008	
	MoH	2008 (73)		
Facility Level	Health Centre	1984 (72)	0.055	
	Hospital	755 (28)		
Status at Registration	Lactating	672 (25)	< 0.001	
	Pregnant	2067 (75)		
Age Group	Adolescent	642 (23)	0.038	
	Adult	2097 (77)		
ART Education	No	837 (31)	< 0.001	
	Yes	1902 (69)		
Clinical condition	Asymptomatic	2565 (94)	0.064	
	Symptomatic	174 (6)		

The results presented show that most of the studied women were from urban (60%), were in MoH facilities (73%), access services in health centres (72%), were pregnant (75%), adults (77%), had patient education (69%) and finally were asymptomatic (94%).

The results of the log-rank test of equality across strata shows that there were no

differences in defaulting across the strata of location. Location was not significant with a p-value of 0.531. The default rate among women registered in rural, semi-urban and urban facilities was similar. Location was therefore excluded in the fitted models. Figure 4.1, is a Kaplan Meier curve describing survival time distribution by location.

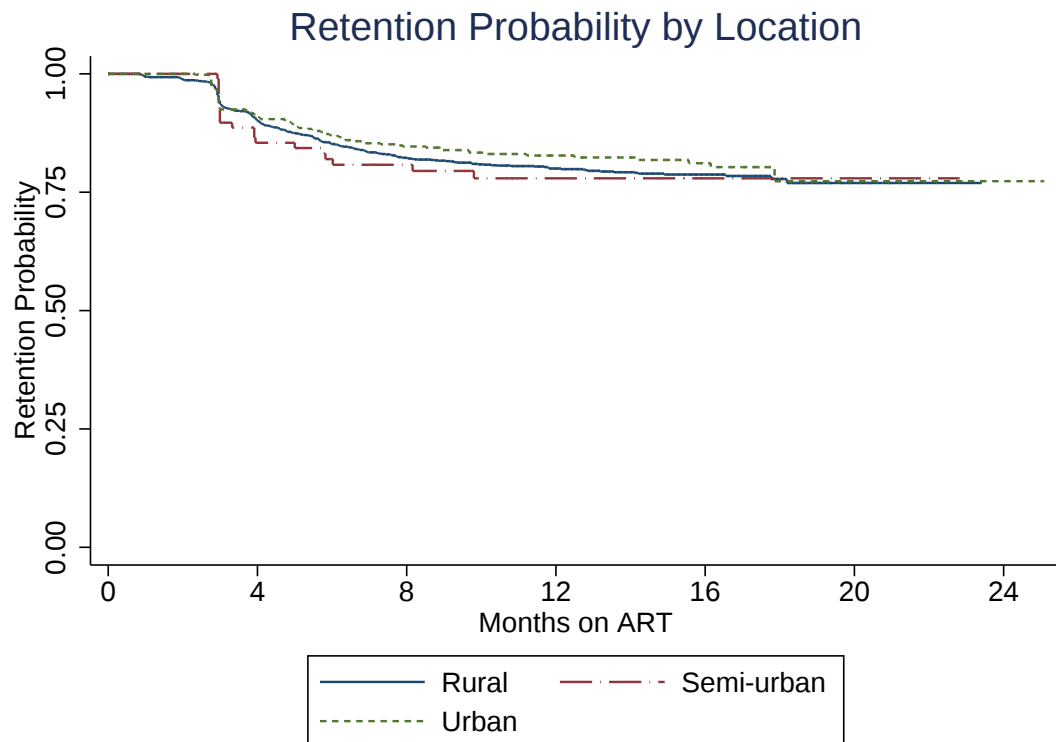


Figure 4.1: Kaplan-Meier curves showing retention of women on ART under Option B+ by location of facility.

Figure 4.1, is the K-M graph on location shows that rural, semi-urban and urban residents survivor experiences were approximately proportional. Women registered in urban health facilities had a slightly better survival experience; followed by women registered in rural and finally semi-urban. Overall, the survival probability appears very similar across categories of location. This is consistent with the log-

rank test results that shows that rate of default is not different across strata of location. The Malawi Service Provision Assessment reports that, all elements of HIV services are available within health facilities across strata of location (Ministry of Health and ICF International, 2015). The similarities in the services provided explains the equality of rates of default.

Managing authority was significant in the log-rank test of equality across strata. There were therefore significant differences in defaulting from ART among women across strata. Women accessing ART through MoH facilities had different default rates relative to women accessing ART through Christian Health Association of Malawi (CHAM) facilities. Managing authority with a p-value of 0.008 was therefore included in the model. Figure 4.2, is a Kaplan Meier curve describing survival time distribution by managing authority of the facility.

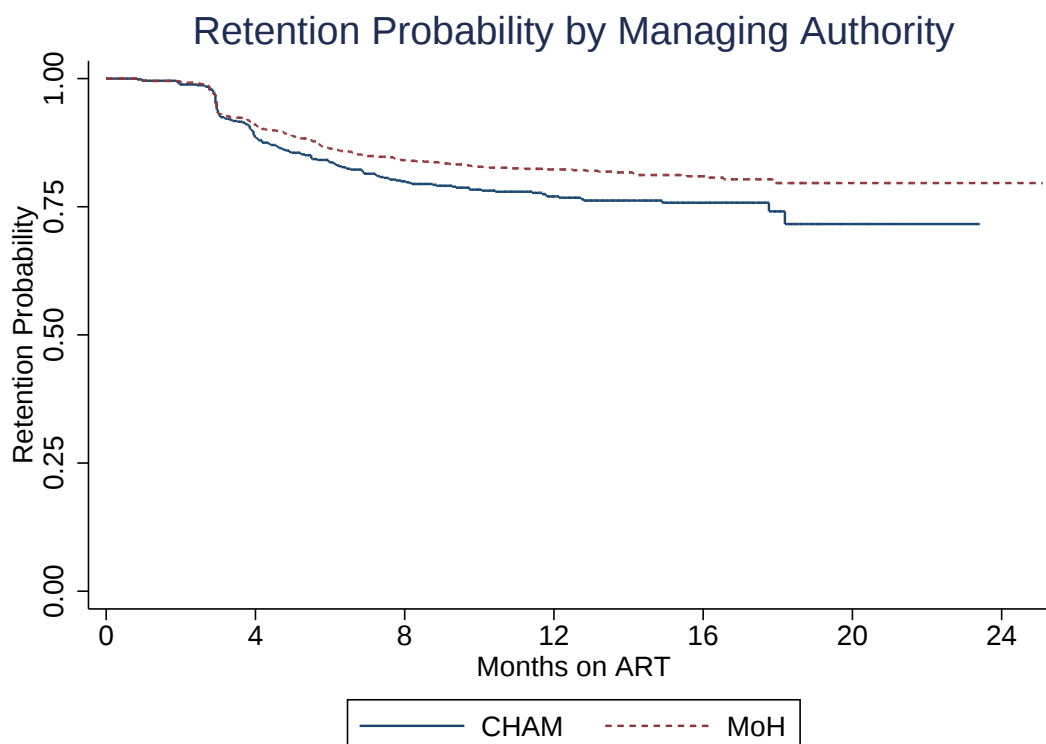


Figure 4.2: Kaplan-Meier curves showing retention of women on ART under Option B+ by managing authority of the facility.

Figure 4.2, is the K-M graph by managing authority of the facilities. Across the strata of managing authority, the survivor experience was proportional. Again, the survival experience was similar in the first 3 months. The survival probability of women accessing ART in MoH was higher from 3 months onwards.

Facility level of service provision was significant in the log-rank test of equality across strata. There were therefore significant differences among women in different strata of health service provision. Women accessing ART through health centres and hospitals had different rates of defaulting. Facility level of accessing ART with a p-value of 0.014 was therefore included in the model. Figure 4.3, is a Kaplan Meier curve describing survival time distribution by level of service

provision.

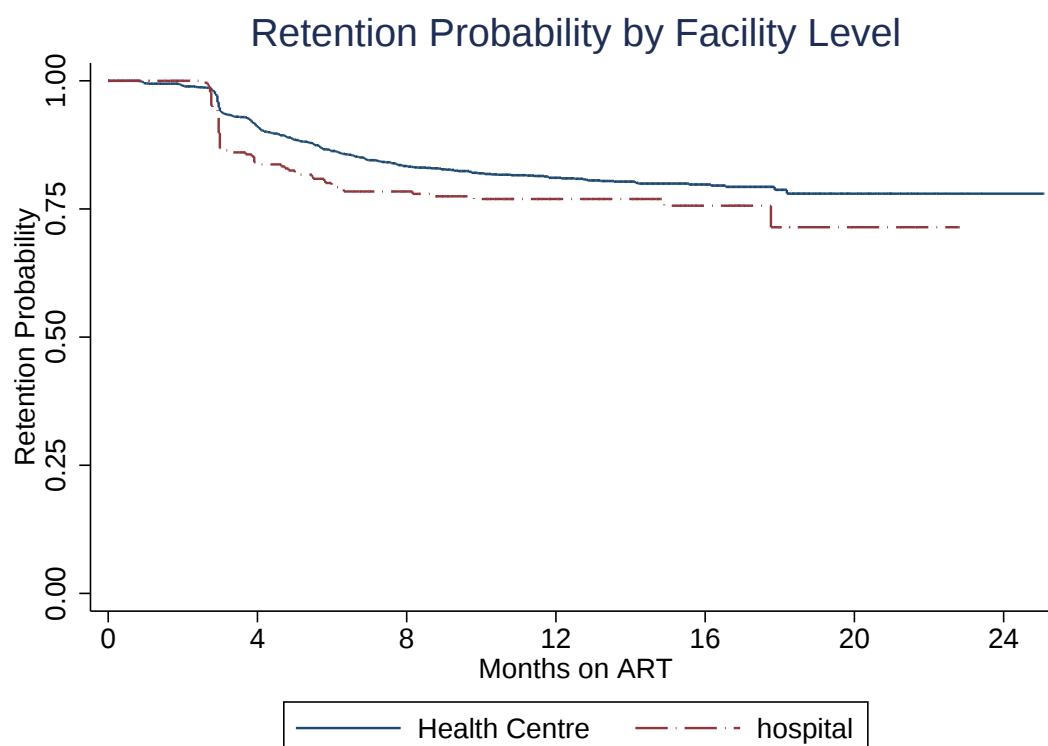


Figure 4.3: Kaplan-Meier curves showing retention of women on ART under Option B+ by facility level of service provision.

Figure 4.3, is the K-M graph on level of service provision ART was accessed. Across the level of service provision, the survivor experiences of women was proportional. Similar to other predictors, the survival experience was similar in the first 3 months. Women accessing ART through health centres had a higher survival probability.

Status at ART registration was significant in the log-rank test of equality across strata. There were therefore significant differences across the strata of status at registration. Among women initiated on ART while lactating or pregnant, there were differences in defaulting from ART treatment. Status at initiation with a

p-value of < 0.001 was therefore included in the model. Figure 4.4, is a Kaplan Meier curve describing survival time distribution by status at registration.

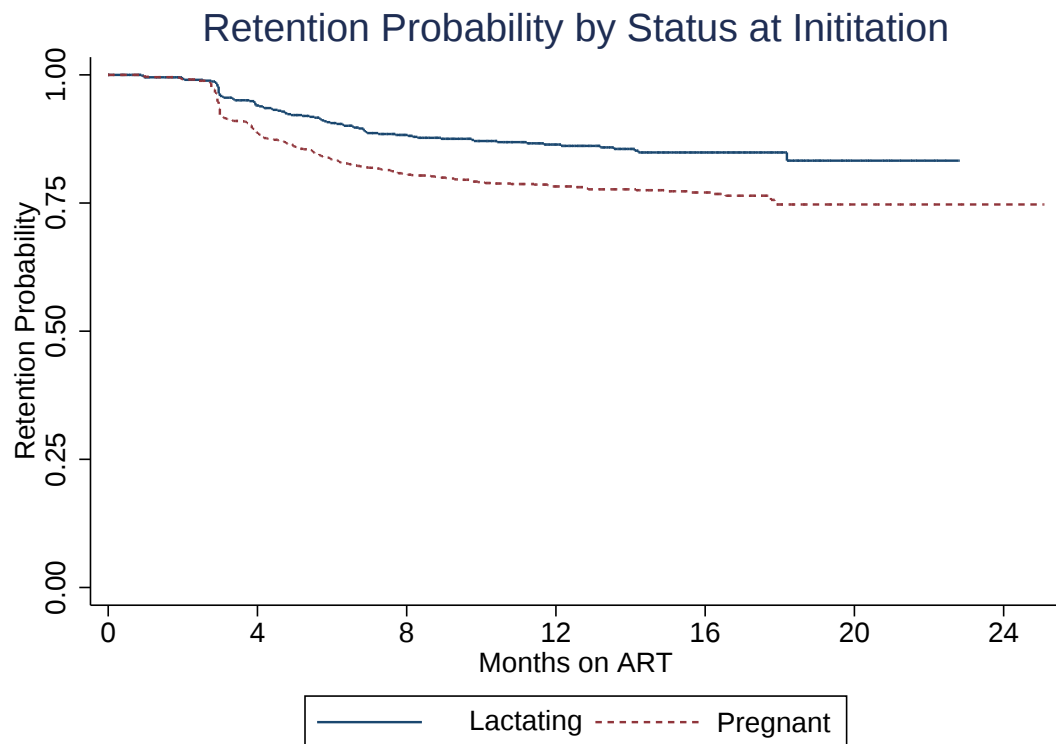


Figure 4.4: Kaplan-Meier curves showing retention of women on ART under Option B+ by status at initiation.

Figure 4.4, is the K-M graph on status at registration of women shows that the survivor experiences of lactating and pregnant women were proportional. The survival experience was very similar in the first 3 months. Lactating relative to pregnant women had a higher retention probability from 3 months onwards.

Age group was significant in the log-rank test of equality across strata. There were therefore significant differences among women in the strata of age group. There were differences in defaulting from ART treatment among young women relative to older women. Age group with a p-value of 0.038 was therefore included in the

model. Figure 4.5, is a Kaplan Meier curve describing survival time distribution by age group.

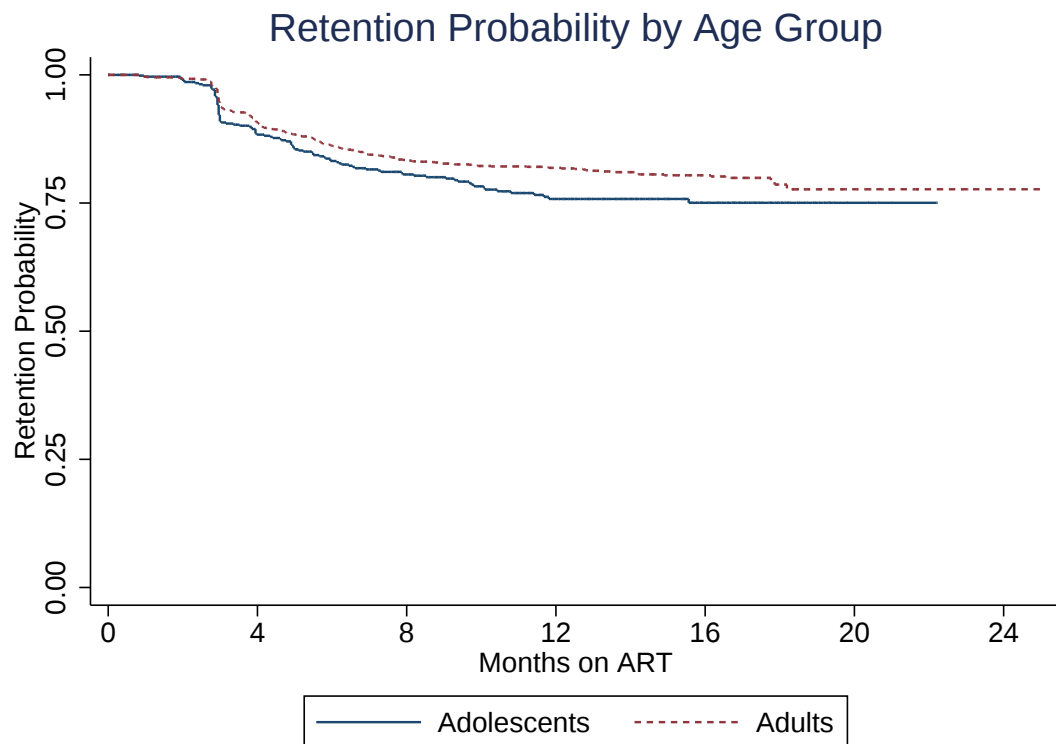


Figure 4.5: Kaplan-Meier curves showing retention of women on ART under Option B+ by age group.

Figure 4.5, is the K-M graph age group. Across the levels of age group, the survivor experiences of women was proportional. Like the other predictors, the survival experience was similar in the first 3 months. There were a few defaulters in both age groups in the first 3 months. The survival probability of adults was higher from 3 months onwards.

Patient ART education was significant in the log-rank test of equality across strata. There were therefore significant differences across the strata of ART education. There were differences in defaulting from ART treatment among women who had

ART education relative women who did not had patient ART education. ART education with a p-value of < 0.001 was therefore included in the model. Figure 4.6, is a Kaplan Meier curve describing survival time distribution by ART education.

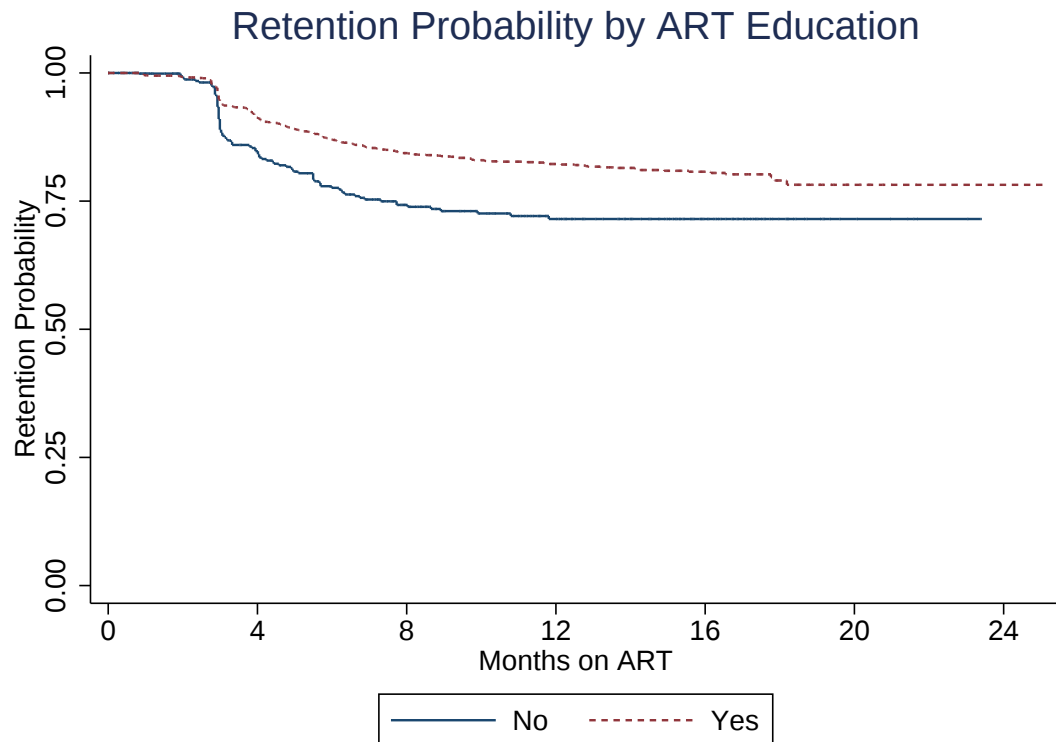


Figure 4.6: Kaplan-Meier curves showing retention of women on ART under Option B+ by patient education status.

Figure 4.6, is the K-M graph on patient ART education. Across strata of ART education, the survivor experiences of women was proportional. Like the other predictors, the survival experience was similar in the first 3 months. There were a few defaulters in both groups during the first 3 months. The survival probability of women with ART education was higher from 3 months onwards.

WHO HIV clinical condition was significant in the log-rank test of equality across strata. There were therefore significant differences among women in the strata

of clinical condition. Clinical condition with a p-value of 0.031 was therefore included in the model. Figure 4.7, is a Kaplan Meier curve describing survival time distribution by age group.

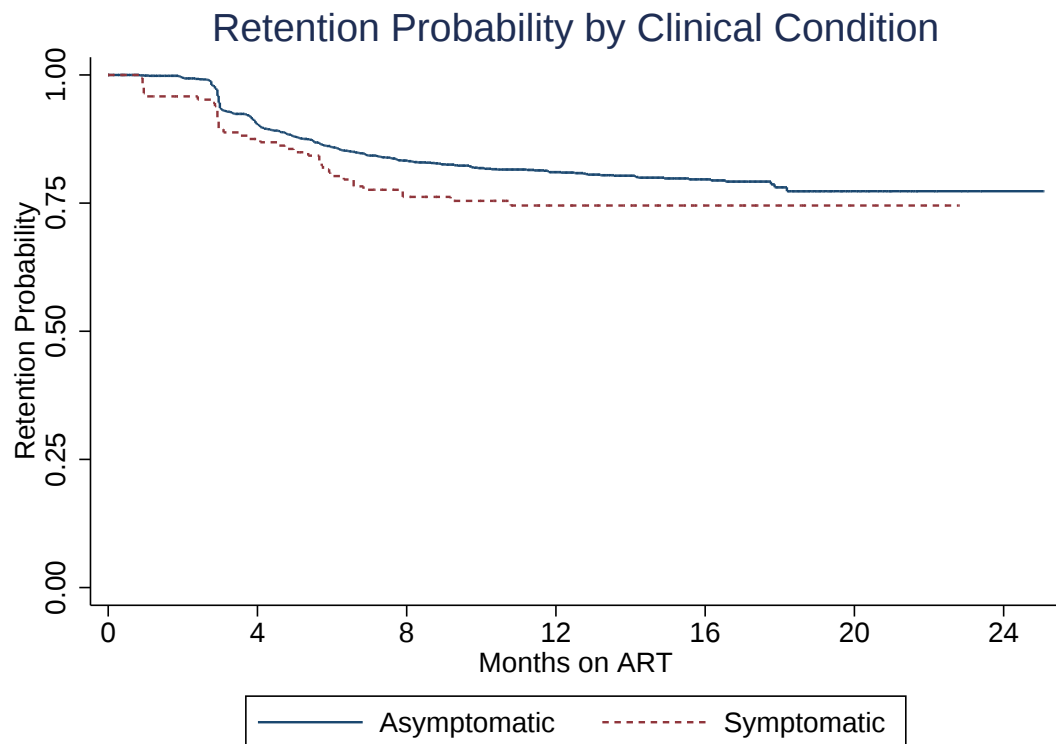


Figure 4.7: Kaplan-Meier curves showing retention of women on ART under Option B+ by clinical stage.

Figure 4.7, is the K-M graph on clinical condition. Across strata of clinical conditions; the survivor experiences of women was proportional. The proportionality of the survival curves was evident after 3 month. There were a few defaulters in both groups in the first 3 months.

Overall, Kaplan Meier graphs presented indicates that there were very few defaulters and the survival rate remained at almost 100% until about 3 months on ART. There is a steep drop in survival probability soon after the third month

until around the sixth month. The survival probability then stabilises at around 75%. This is likely a result of the definition of defaulter in the clinical guidelines. According to the guidelines (Ministry of Health, 2011), an ART patient is considered a defaulter 2 months after the patient run outs of ARVs. On the other hand, newly registered ART patients are given one-month worth of drugs in order to necessitate clinical reviews. This therefore means that most cases can only be considered as defaulters at least 3 months after registering. The women indicated as defaulters at third month might never have started ART or they stopped ART during the first month, however, considering the guidelines and the monthly drug dispersion at ART registration, they can only be considered defaulters after 3 months.

4.2 Model Building

In multivariate Cox proportional hazards model, predictors that had a p-value of 0.2 or less in univariate analysis were first included in the model. The p-values from the wald test were then used to check if the coefficients of the fitted model were different from zero (Hosmer & Lemeshow, 1999). In the initial multivariate model, all the coefficient were significantly different from zero. Finally, all possible interactions of the predictors were then considered. The p-value from the wald test of the interaction terms was used to select significant interactions. The two factor interactions of pregnancy & ART education, age group & manage and age group & pregnancy were significant. A model with all the interaction terms was then compared with the nested models using the Bayesian Information Criteria

(BIC) test. Lawl (Lawal, 2003) discusses model selection criteria. They note that parsimony is one of the basic characteristics in model selection. Specifically, the balance between complexity of the model and easiness of the model to interpret. BIC takes account of not only the model complexity, but also of the sample size. This is unlike the other penalised criterion. The main effects model had the lowest BIC and therefore the most parsimonious model. Table 4.2 presents results from the BIC test.

Table 4.2: Bayesian Information Criteria Results

Model	Nested Model	LL	df	BIC
m1		-3026.15	9	6140.37
	m2	-3027.63	8	6133.55
	m3	-3028.97	8	6136.23
	m4	-3028.87	8	6136.02
m2				
	m5	-3030.96	7	6130.42
	m6	-3030.50	7	6129.50
m6				
	m7	-3033.93	6	6126.56

Where,

- LL Log likelihood
- m1 Pregnancy & ART education, age group & manage and age group & pregnancy

- m2 Pregnancy & ART education and age group & manage
- m3 Pregnancy & ART education and age group & pregnancy
- m4 age group & pregnancy and age group & manage
- m5 Pregnancy & ART education
- m6 age group & manage
- m7 main effects only model

4.2.1 Bootstrapping

Vittinghoff et al discusses bootstrapping. They note that bootstrap procedures approximate the sampling distribution of statistics of interest by a re-sampling procedure. The sample is treated as if it were the source population, and bootstrap samples are repeatedly drawn from it. Bootstrap samples of the same size as the actual sample a key determinant of precision are obtained by re-sampling with replacement. The sampled observations represents the population and hence re-sampling from this sample mimics drawing repeated samples from the source population. Then, from each of a large number of bootstrap samples, the statistics of interest are computed. Vittinghoff and colleagues further notes that, standard errors and confidence intervals reflect the sampling distribution of statistics of interest, such as regression coefficient estimates: that is, their relative frequency if independent samples of the same size are repeatedly drawn from the source population, and recalculate the statistics in each new sample (Vittinghoff et al., 2005).

Normal approximation confidence intervals were used in the fitted models. The distribution of the bootstrap estimates was assumed to be reasonably normal, confidence intervals centered on the observed statistic were therefore calculated using the bootstrap standard deviation. Vittinghoff et al notes that, the bootstrap standard deviation is a relatively stable estimate of the standard error, since it is based on the complete set of bootstrap samples, so a relatively small number of bootstrap samples may suffice (Vittinghoff et al., 2005).

Harrel (Harrell, 2001) discusses the number of bootstrap samples. A guide of number of bootstrap is provided. Starting from small number of replications and then increasing the number of replications until the estimates converge. In this study, 50 replications were initially used with 2 seed values. The differences in standard errors of the same estimates in the 2 sets of bootstrap were noted. The number of bootstrap replications were adjusted upwards 50 until the changes in standard errors were small. At least 450 replications provided stable standard errors. 1000 replications were however were used after consideration of the computer power, that is, time taken for 1000 replications was bearable.

4.3 Cox Proportional Hazards Model

Table 4.3 presents results from fitting the final model.

Table 4.3: Cox Proportional Hazards Model

Predictor	Observed	Bootstrap			Normal based
	HR	Std. Error	Z	P-Value	95% CI
Management					
CHAM	Ref				
MoH	0.70	0.08	-3.27	0.001	0.56, 0.87
Facility Level					
Health centre	Ref				
Hospital	1.32	0.20	1.88	0.060	0.99, 1.77
Status at Reg.					
Lactating	Ref				
Pregnant	1.64	0.20	4.09	< 0.001	1.29, 2.07
Age Group					
Adolescent	Ref				
Adult	0.79	0.09	-2.01	0.045	0.62, 0.99
ART Education					
No	Ref				
Yes	0.60	0.07	-4.13	< 0.001	0.47, 0.77
Clinical Condition					
Asymptomatic	Ref				
Symptomatic	1.61	0.35	2.17	0.030	1.05, 2.48

Note: Ref is the reference category

From the fitted Cox model above, all the covariates included in the model with

the exception of facility level were significantly associated with defaulting from ART treatment.

Women in MoH facilities were at a 30% lower risk defaulting relative to women in CHAM facilities ($HR = 0.70$; $CI = 0.56, 0.87$). The hazard ratio of women in hospitals relative to women health centres was not significantly different. Women in hospitals were more likely to default relative to women in health centres. Women in hospitals had a hazard ratio of $HR = 1.32$; $CI = 0.99, 1.77$. Women who initiated ART while pregnant had 64% higher risk of defaulting relative to women who initiated while lactating. The hazard ratio among pregnant relative to breastfeeding women was $HR = 1.64$; $CI = 1.29, 2.07$. Adult women were 21% less likely to default compared to adolescent women with a hazard ratio of $HR = 0.79$; $CI = 0.62, 0.99$. Women who had ART patient education had much lower rate of default relative to women who did not have patient education at registration. Women with ART education have a 40% lower risk of default with a hazard ratio of $HR = 0.60$; $CI = 0.47, 0.77$. Similarly, symptomatic women at ART registering had a higher default rate relative to asymptomatic women. Symptomatic had a hazard ratio of $HR = 1.61$, $CI = 1.05, 2.48$. The ratio of the hazards rates of symptomatic women to asymptomatic women were significantly different.

Management and facility level are facility characteristic in predicting ART treatment default. These results suggest that there are important variations in the provided services by management. MoH relative to CHAM facilities provide a better ART service. Malawi Service Provision Assessment (MSPA) reported a

higher proportion of MoH compared to CHAM facilities with at least one trained ART provider (Ministry of Health and ICF International, 2015). These findings are therefore consistent with the MSPA findings. The same 2015 MSPA assessment reported a higher proportion of hospitals compared to health centres with at least one trained ART provider. However, hospitals are most likely to have a high burden of patients and further distant from most of the catchment population.

The higher default rate among pregnant compared to breastfeeding women suggest that pregnant women are relatively unprepared for ART. This could be due to poor counselling of pregnant women in the antenatal clinic leading to low spousal and family disclosure.

Adult women, expectedly had better retention rates. These women might have better spousal and family support, making it easier for them to remain on treatment. Secondly, older women are comparably likely to remain on treatment solely for PMTCT. Specifically, the desire to protect the child from infection might be higher among adult women.

These finding stresses the importance of ART education. ART education prepares the women in mitigating challenges faced when on ART treatment and emphasizes the importance of remaining on treatment. It is therefore not surprising that women with ART education had better retention rates.

The findings above suggest that symptomatic women have a higher default rate. These women are clinically unwell and therefore anticipated to have better retention rates. 135(78 %) of the symptomatic women in this study had mild symptoms in WHO clinical stage 2, therefore, were clinically unwell but not feeling ill. The

women therefore were on ART primarily for PMTCT but not for their own health. This is even though they were symptomatic.

4.3.1 Test of PH Assumptions

Cox proportional Hazard assumptions were then assessed. Cox model assumptions are that; all the covariates included in the model are proportional and time independent.

Hosmer and Lemeshow recommends using a two-step procedure for assessing the proportional hazards assumptions. First, add the interaction term of time and covariates to the model. Assess the significance of the interaction terms using partial likelihood ratio test, score test or Wald test. Second, plot the scaled and smoothed scaled residuals obtained from model without the interaction terms. The assumptions are met if the results of the two step procedure should be consistent (Hosmer & Lemeshow, 1999). Table 4.4, presents the Cox model with time-dependent covariates.

(Quantin et al., 1996) and (Ng'andu, 1997) discusses the function form of the interaction term in assessing proportional hazards assumptions. They found that the log-time form of the time interaction term performs equally well or better than other commonly used tests. (Hess, 1995) on the other hand discusses graphical approaches in assessing the Cox assumptions. Hess recommends smoothed plots of the scaled Schoenfeld residuals because they provide precise usable information about the time dependence of the covariate effects. Therefore, the log-time form and the scaled Schoenfeld residuals was used in the assessment of the assumptions.

Table 4.4: Cox Model Assessment of Assumption

Predictor	HR	Std. Error	Z	P-Value	95% CI
Time-dependent					
Management	0.91	0.18	-0.49	0.625	0.62, 1.34
Facility level	0.70	0.18	-1.37	0.171	0.42, 1.17
Status at registration	0.84	0.19	-0.74	0.462	0.54, 1.32
Age group	0.95	0.20	-0.25	0.806	0.63, 1.43
ART education	1.21	0.27	0.83	0.405	0.78, 1.88
Clinical condition	0.36	0.12	-3.02	0.003	0.19, 0.70

The interaction of log time and clinical condition was significant with a p-value of 0.003. However, the interaction terms of log-time and the other covariates fitted in the model were all non-significant.

The in the second step of the two-step assessment process of proportionality assumption, scaled Schoenfeld residuals were plotted. A plot of scaled Schoenfeld residuals should have a slope of zero if the proportional hazards assumption is met. Figures 4.8 to 4.10, presents graphs of Schoenfeld residuals and their lowess smooths.

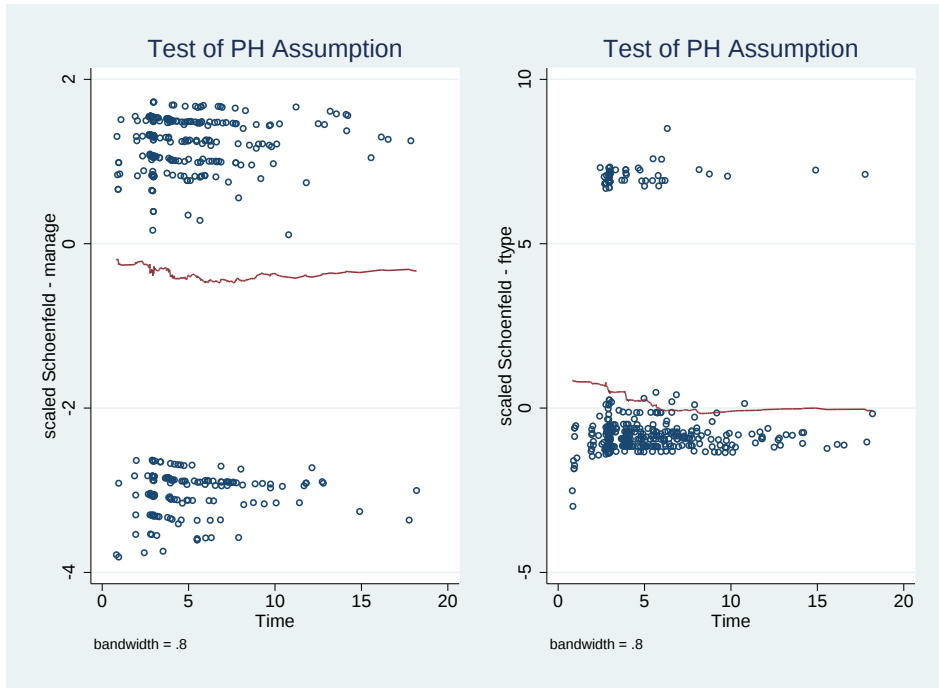


Figure 4.8: Graph of the scaled Schoenfeld residuals and their lowess smooth for management authority and facility level.

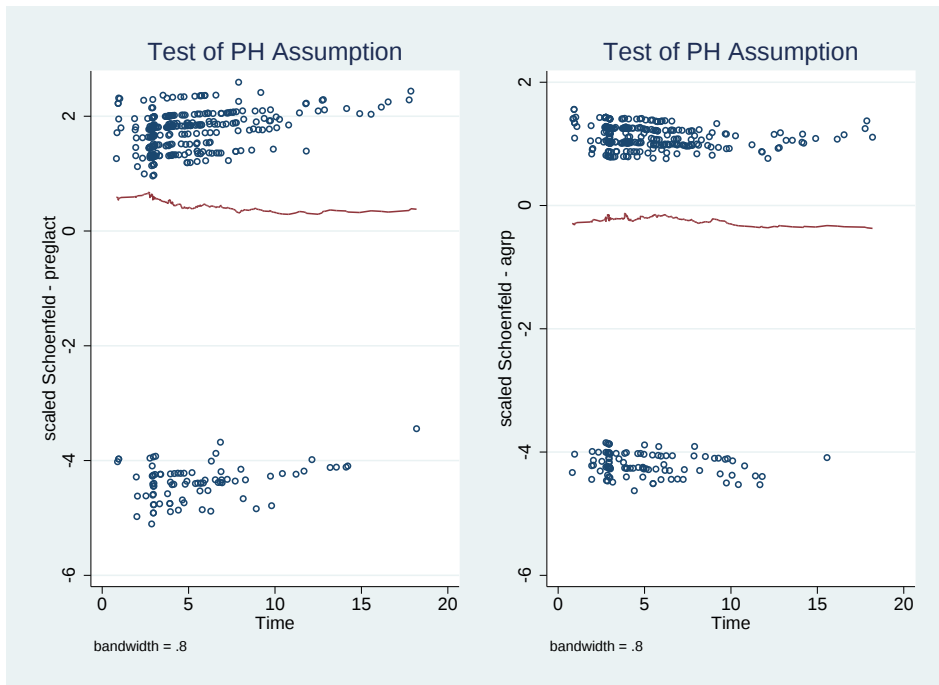


Figure 4.9: Graph of the scaled Schoenfeld residuals and their lowess smooth for status at registration and age group.

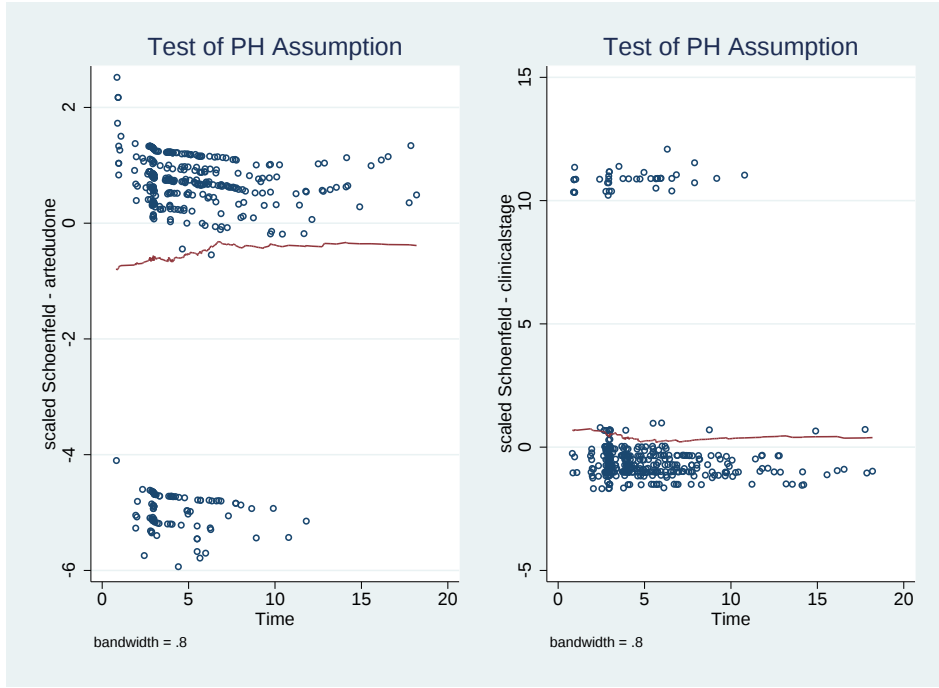


Figure 4.10: Graph of the scaled Schoenfeld residuals and their lowess smooth for ART education and clinical condition.

Plots of scaled Schoenfeld residuals and the lowess smooths. In summary, only facility level and ART education do not have a zero slope over time.

Overall, results for facility level, clinical condition and ART education were inconsistent over the two-steps of the assessment process. Therefore, all the covariates included met the proportional hazards assumption of Cox model.

4.3.2 Model Assessment

The model fit was assessed by using the Cox-Snell residuals. These residuals were used to assess the model through evaluating whether the residuals were indeed a plausible sample from a unit exponential distribution. This is based on

the fact that if a random variable T has an exponential distribution with unit mean, the survival function of T is e^{-t} . A plot of the cumulative hazard function $H(t) = -\log S(t)$ against t will have a straight line through the origin with unit slope. Graphing the Nelson-Aalen cumulative hazard function and the Cox-Snell variable to compare the hazard function to the diagonal line. If the hazard function follows the 45 degree line then we know that it approximately has an exponential distribution with a hazard rate of one and that the model fits the data well. Figure 4.11, presents a plot of Cox-Snell residuals.

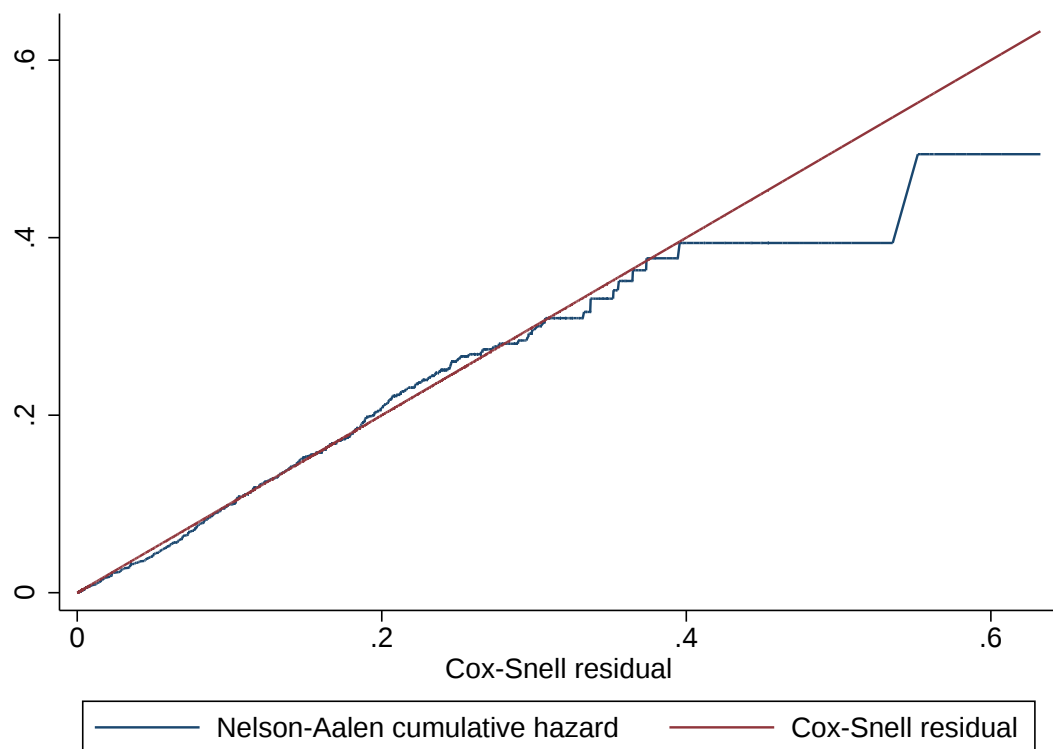


Figure 4.11: Cox-Snell residuals

The hazard function follows the 45 degree line very closely except for very large values of time. Overall, we conclude that the final model fits the data well.

4.4 Competing Risks Model

Cumulative incidence are used to describe the survival experience when there are competing events. Kaplan-Meier estimate ignores events of all types other than the one of interest and the probability is calculated whenever the event of interest occurs.

The Cumulative Incidence Function (CIF) estimator for a particular event depends not only on the number of individuals who have experienced the event of interest, but also on the number of individuals who have not experienced any other type of event. The CIF represents the probability that an individual will experience an event of the particular type given that the individual has not experienced any event.

In the fitted competing risks model, the main event of interest were default from treatment and transfer out. Figure 4.12, presents a plot of cumulative incidence of defaulting and transferring out.

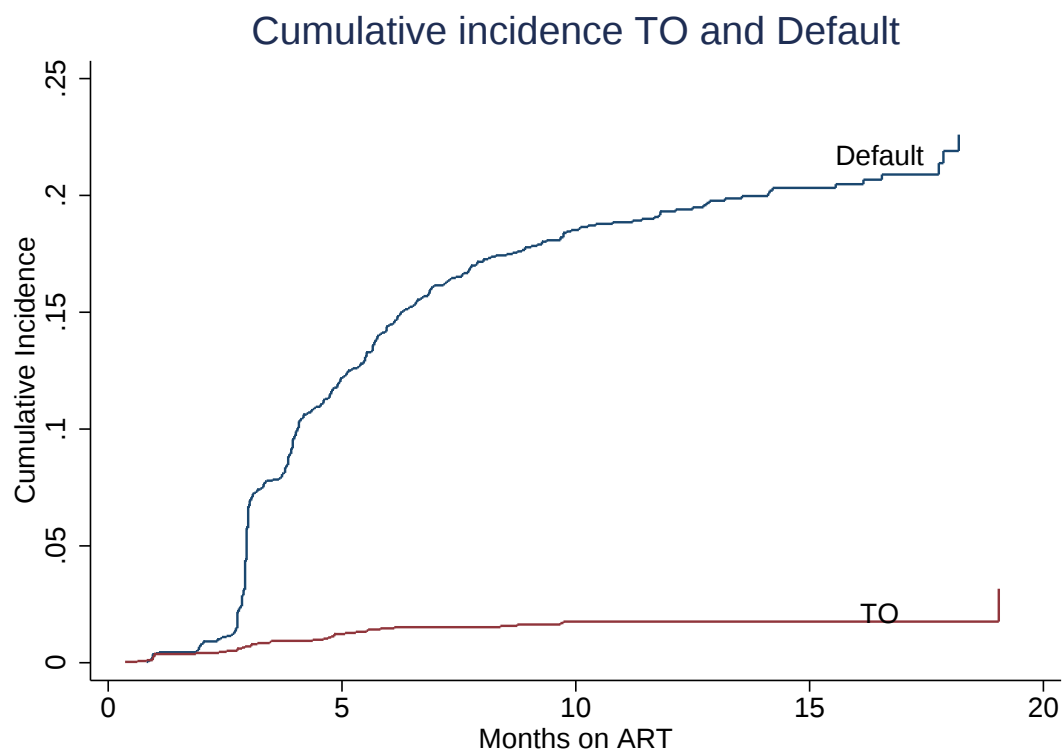


Figure 4.12: Cumulative Incidence of TO and Default

The estimated probability that an individual will experience the event of default is higher over the whole follow-up period. There were a few incidences of both events in the first 3 months of ART treatment. The chance of a woman experiencing either event was therefore very small. The probability of defaulting increases steeply from 3 months then the increase is slower from around 10 months. The probability of transfer-outs, however, remains relatively low over the entire follow-up period. This is very likely because of the few incidences of transfer out over the entire follow-up period.

A competing risks model was then fitted. This was to further study the distribution of hazards among Option B+ patients in the context of competing events. Table 4.5, presents the fitted model of which the results are discussed.

Table 4.5: Competing Risks Model

Predictor	Default			Transfer out		
	Obs.		Norm. based	Obs.		Norm. based
	SHR	P-Value	95% CI	SHR	P-Value	95% CI
Management						
CHAM	Ref					
MoH	0.70	0.001	0.57, 0.87	1.32	0.523	0.56, 3.09
Facility level						
Health centre	Ref					
Hospital	1.29	0.083	0.97, 1.73	1.64	0.242	0.72, 3.74
Status at reg.						
Lactating	Ref					
Pregnant	1.63	< 0.001	1.28, 2.09	0.67	0.263	0.33, 1.35
Age group						
Adolescent	Ref					
Adult	0.79	0.036	0.63, 0.98	0.71	0.368	0.33, 1.50
ART education						
No	Ref					
Yes	0.61	< 0.001	0.48, 0.77	1.83	0.730	0.06, 55.98
Clinical condition						
Asymptomatic	Ref					
Symptomatic	1.56	0.012	1.10, 2.22	0.67	0.935	0.00, 8834.66

Note: Ref is the reference category

Default

In the fitted competing risks model of default, the estimated sub-hazard ratios take into account the possibility that transfer-out can also occur. The sub-hazard ratios of categories of MoH, pregnant, adult, women that had ART education and symptomatic women were significantly associated with the risk of default from ART treatment. There was a 30% decrease in the risk of defaulting among women in MoH facilities relative to women in CHAM facilities ($SHR = 0.70$; $CI = 0.57, 0.87$). Women who initiated ART while pregnant 63% more likely to default from ART care relative to women who initiated while lactating. The sub-hazard ratio among pregnant women to lactating women was $SHR = 1.63$ with a CI of 1.28, 2.09. Adult women were 21% less likely to default compared to adolescent women ($SHR = 0.79$; $CI = 0.63, 0.98$). ART education at registration reduced the risk of a default by 39% ($SHR = 0.61$; $CI = 0.48, 0.77$). Women registering ART whilst symptomatic had a higher default rate relative to women whilst asymptomatic. Symptomatic women had a significant sub-hazard ratio of $SHR = 1.56$, $CI = 1.10, 2.22$.

Similar to the Cox proportional hazards model, above, hospital was non-significantly different from health centre. Women in hospitals had a higher risk of default relative to women in health centres. The sub-hazard of default in hospitals was 29% higher compared to the sub-hazard of default among women in health centres. The sub-hazard of default among women accessing in hospitals was not significant ($SHR = 1.29$; $CI = 0.97, 1.73$).

The sub-hazards of default were similar to the cause specific hazards. The tests

of statistical significance are largely in agreement in the cause-specific and sub-hazards of default. This similarity is likely due to low incidence of transfer-out. Figure 4.12 above show that the incidence of transfer-out remained relatively low over the entire follow-up period. The estimated sub-hazard ratios of default were affected but low incidence. This considering that the estimates take into account the possibility that transfer-out can also occur

Transfer-out

In the fitted competing risks model of transfer-out, above, the estimated sub-hazard ratios take into account the possibility that patients can also default. All the hazard ratios were non-significant. A 32% increase in the risk of transferring-out among women in MoH facilities relative to women in CHAM facilities ($SHR = 1.32$; $CI = 0.56, 3.09$). Women in hospitals were 64% more likely to transfer-out relative to women in health centres. The sub-hazard ratio of transfer-out in hospital to health centres was $SHR = 1.64$ with a CI of $0.72, 3.74$. Women who initiated ART while pregnant 33% less likely to transfer-out relative to women who initiated while lactating. The sub-hazard ratio among pregnant women to lactating women was $SHR = 0.67$ with a CI of $0.33, 1.35$. Adult women were 29% less likely to transfer-out compared to adolescent women ($SHR = 0.71$; $CI = 0.33, 1.50$). Women with ART education were more likely to transfer relative to women with no patient education ($SHR = 1.83$; $CI = 0.06, 55.98$). The sub-hazard of symptomatic relative to asymptomatic was $SHR = 0.67$ with $CI = 0.00, 8834.66$.

The sub hazards of transfer out had no corresponding cause specific hazards. The discussion of the changes in the predictor effect were therefore not carried out.

4.4.1 Competing Risk Model Test of PH Assumptions

Cox proportional hazard assumptions were then assessed in the competing risks model. Similar to Cox proportion hazards model, proportionality was checked by including time-varying covariates in the model. Time dependent covariates are interactions of the predictors and time. If a time-dependent covariate is significant, it is an indication a violation of the proportionality assumption for that specific predictor. Table 4.6 presents the competing risks model of default and transfer-out with time-dependent covariates.

Table 4.6: Competing Risk Model Assessment of Assumption

Predictor	Default			Transfer out		
	SHR	P-Value	95% CI	SHR	P-Value	95% CI
Time-dependent						
Management	0.94	0.745	0.63, 1.40	1.70	0.284	0.65, 4.46
Facility level	0.60	0.031	0.38, 0.95	1.00	0.996	0.40, 2.48
Status at registration	0.85	0.508	0.52, 1.38	1.18	0.693	0.53, 2.62
Age group	0.92	0.692	0.60, 1.40	1.38	0.469	0.57, 3.33
ART education	1.18	0.432	0.78, 1.78	1.52	0.418	0.55, 4.14
Clinical condition	0.36	0.013	0.16, 0.80	0.55	0.385	0.14, 2.14

In the competing risk model of default, the log-time interactions with management,

status at registration, age group and ART education were all non-significant. The interactions of log-time with facility level and clinical condition were significant. This indicates that facility level and clinical condition violates the Cox model assumption of proportional hazards. The Cox proportional hazards assumptions, therefore, are valid only in the 4 of the 6 covariates included in the model.

In the competing risks model of transfer-out, all the log-time interaction terms of management, facility level, status at registration, age group, ART education and clinical condition were all non-significant individually. The Cox proportional hazards assumptions therefore were valid for all the covariates included in the model.

4.4.2 Stratified Competing Risks Model

Stratified competing risks model was fitted to in-order to adjust for violation Cox model assumptions. Facility level and clinical condition violated the Cox model assumptions. However, among the sampled women 174 (6%) were symptomatic and 2,565 (94%) were asymptomatic. Stratifying by clinical condition produced inestimable results. Results from stratifying by clinical condition have not been presented and subsequently have not been included interpretation of results. On the other hand, facility level had large enough sample to produce estimates. A Competing risks model with the sub-hazard of default was fitted. The model was stratified on facility level. Table 4.7 presents the stratified Competing risks model.

Table 4.7: Competing Risk Model Stratified by Facility Level

Predictor	Hospital			Health Centre		
	Obs.		Norm. based	Obs.		Norm. based
	SHR	P-Value	95% CI	SHR	P-Value	95% CI
Management						
CHAM	Ref					
MoH	1.03	0.924	0.56, 1.91	0.66	< 0.001	0.53, 0.82
Status at Reg.						
Lactating	Ref					
Pregnant	1.03	0.924	0.54, 1.96	1.74	< 0.001	1.33, 2.27
Age group						
Adolescent	Ref					
Adult	1.26	0.512	0.63, 2.49	0.74	0.016	0.58, 0.95
ART Education						
No	Ref					
Yes	1.07	0.968	0.43, 2.68	0.55	< 0.001	0.43, 0.71
Clinical condition						
Asymptomatic	Ref					
Symptomatic	0.83	0.979	0.14, 4.92	1.60	0.008	1.13, 2.26

Note: Ref is the reference category

All sub-hazards for covariates included in the stratified competing risks for hospital were not significant. The sub-hazard default in hospitals was 3% higher in MoH relative to CHAM facilities ($SHR = 1.03$; $CI = 0.56, 1.91$). Pregnant women had

also a 3% higher sub-hazard of default compared to lactating women ($SHR = 1.03$; $CI = 0.54, 1.96$). Adults had a 26% higher risk of default ($SHR = 1.26$; $CI = 0.63, 2.49$). Similar to the estimates of management, status at registration and age group, the sub-hazard ratio of default among women with patient education at registration was non-significant in hospitals ($SHR = 1.07$; $CI = 0.43, 2.68$). Finally, symptomatic women had lower rates of default in hospitals ($SHR = 0.83$; $CI = 0.14, 4.92$).

In the stratified competing risks model for health centre, all the sub-hazards for covariates included were significant. Women in MoH facilities had a 34% lower sub-hazard relative to women in CHAM facilities ($SHR = 0.66$; $CI = 0.53, 0.82$). The sub-hazard of default among pregnant women in health centres was 74% higher ($HR = 1.74$; $CI = 1.33, 2.27$). The sub-hazard for adults was lower relative to adolescents ($SHR = 0.74$; $CI = 0.58, 0.95$). Women with patient education were at 45% lower risk of default in health centres ($HR = 0.55$; $CI = 0.43, 0.71$). Symptomatic women in health centres were 60% more likely to default ($HR = 1.60$; $CI = 1.13, 2.26$).

Models fitted above, all the sub-hazard ratios are non-significant at hospital level and significant at health centre level. This further indicates that facility level did not satisfy the proportionality assumption. These results suggest that management, status at registration, age group, ART education and clinical condition are important factors in predicting default rate in health centres but not hospitals. However, the estimates of hospital level had wider confidence intervals relative to estimates of health centre. The 755 (28%) in hospitals presented in table 4.1 is

however a large enough sample to provide estimates with reasonable confidence intervals.

4.5 Multi-state Models

A multi-state model was fitted to further study the effects of the covariates. Specifically, whether the effect of a covariates change over time. Transition-specific covariates were used to estimate the covariate effects across transitions. A stratified baseline hazards models was fitted. In total, the model had 4 transitions. All women started in the registration state. Figure 4.13, presents a diagram showing the states and transitions.

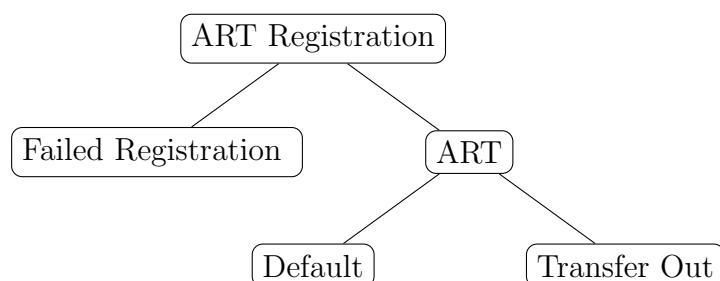


Figure 4.13: A flow diagram Showing states and transitions

- Transition 1 : from registration to failed registration
- Transition 2 : from registration to ART
- Transition 3 : from ART to Default .i.e. lost to follow-up
- Transition 4 : from ART to transfer out

Table 4.8 and 4.9 presents the fitted models that are further discussed in the following sub-sections.

Table 4.8: Multi-state Model from Registration to Failed Initiation or ART

Predictor	Failed Registration			ART		
	Obs.		Norm. based	Obs.		Norm. based
	HR	P-Value	95% CI	HR	P-Value	95% CI
Management						
CHAM	Ref					
MoH	1.37	0.093	0.95, 1.99	1.04	0.383	0.95, 1.14
Facility Level						
Health centre	Ref					
Hospital	10.75	< 0.001	8.45, 13.67	0.35	< 0.001	0.30, 0.41
Status at Reg.						
Lactating	Ref					
Pregnant	1.10	0.387	0.89, 1.37	0.98	0.638	0.90, 1.07
Age Group						
Adolescent	Ref					
Adult	1.03	0.695	0.90, 1.17	1.08	0.114	0.98, 1.19
ART Education						
No	Ref					
Yes	0.09	< 0.001	0.07, 0.12	2.82	< 0.001	2.43, 3.26
Clinical condition						
Asymptomatic	Ref					
Symptomatic	1.13	0.707	0.59, 2.19	0.81	0.005	0.70, 0.94

Note: Ref is the reference category

Table 4.9: Multi-state Model from ART to Default or Transfer Out

Predictor	Default			TO		
	Obs.		Norm. based	Obs.		Norm. based
	HR	P-Value	95% CI	HR	P-Value	95% CI
Management						
CHAM	Ref					
MoH	0.76	0.134	0.53, 1.09	2.89	0.055	0.98, 8.54
Facility Level						
Health centre	Ref					
Hospital	0.96	0.894	0.55, 1.69	1.69	0.292	0.64, 4.50
Status at Reg.						
Lactating	Ref					
Pregnant	1.40	0.096	0.94, 2.09	0.49	0.091	0.22, 1.12
Age Group						
Adolescent	Ref					
Adult	0.83	0.369	0.55, 1.24	0.79	0.591	0.33, 1.87
ART Education						
No	Ref					
Yes	0.75	0.236	0.47, 1.20	1.86	0.406	0.43, 7.99
Clinical condition						
Asymptomatic	Ref					
Symptomatic	1.39	0.323	0.72, 2.69	0.45	0.445	0.06, 3.45

Note: Ref is the reference category

Failed Registration state

The rates of transition to failed registration state were significantly different across categories of facility level and ART education at registration. The rates were non-significantly different across management, status at registration, age group and clinical condition.

The risk of transition was 37% higher among the women in MoH facilities compared to women in CHAM facilities ($HR = 1.37$; $CI = 0.95, 1.99$). Women in hospitals had significantly higher transition rate of more than 10 times higher than women in health centres. The hazard ratio of hospital relative to health centres was $HR = 10.75$ with a CI of 8.45, 13.67. Failed registrations among pregnant women were 10% higher relative to lactating women at $HR = 1.10$ with a CI of 0.89, 1.37. Adult and adolescent women had a very similar risk of a failed registration. The hazard ratio of adults relative to adolescents was $HR = 1.03$ with a CI of 0.90 to 1.17. ART education reduced the risk of a failed registration by 91% ($HR = 0.09$); $CI = 0.07, 0.12$. The risk of a failed registration among symptomatic women was 13% higher compared to asymptomatic women.

ART state

The rates of transition 2 were significantly different across categories of facility level, ART education at registration and clinical condition. The rates were non-significantly different across management, status at registration and age group.

The risk of making transition 2 among women MoH facilities was 4% higher com-

pared to women in CHAM facilities ($HR = 1.04; CI = 0.95, 1.14$). Women in hospitals had a significant lower risk of transitioning to ART relative to health centres. The risk of transitioning to ART in hospitals 65% lower ($HR = 0.35; CI = 0.30, 0.41$). The risk of transition to ART state among pregnant was 2% lower relative to lactating women. The hazard ratio was $HR = 0.98$ with a CI of 0.90, 1.09. The transition probability to ART state among adult women relative to adolescent women 8% higher. The hazard ratio of adults relative to adolescents was $HR = 1.08$ with a CI of 0.98, 1.19. ART education increased the rate of transition to ART by 182% ($HR = 2.82; CI = 2.43, 3.16$). Transition rates among symptomatic women 19% lower ($HR = 0.81; CI = 0.70, 0.94$).

Default state

The rates of transition 3 were all non-significantly different across categories of all independent variables.

The risk of transition was 24% lower among the women in MoH facilities compared to women in CHAM facilities ($HR = 0.76; CI = 0.53, 1.09$). Risk of making transition 3 was 3% lower among women in hospitals compared to health centres. Risk of default among pregnant women was 40% higher relative to lactating women at $HR = 1.40$ with a CI of 0.94, 2.09. The risk of default among adults relative to adolescents was lower. The hazard ratio of adults relative to adolescents was $HR = 0.83$ with a CI of 0.55, 1.24. The risk for transition to default state was lower among women with ART education. The hazard ratio was 25% lower ($HR = 0.75; CI = 0.47, 1.20$). Symptomatic woman were 39% more likely to default

relative to asymptomatic women ($HR = 1.39; CI = 0.72, 2.69$).

Transfer-out state

The rates of transition 4 were not significantly different across categories of all the covariates.

The risk for transition to transfer out state was 189% higher among the women in MoH facilities compared to women in CHAM facilities with a hazard ratio and confidence interval of ($HR = 2.89; CI = 0.98, 8.54$). Women in hospitals had a higher risk of transitioning to transfer out state relative to health centres. The risk of transitioning to transfer out among women in hospitals 69% higher ($HR = 0.69; CI = 0.64, 4.50$). Transfer out among pregnant women was 51% less relative to lactating women at $HR = 0.49$ with a CI of 0.22, 1.12. The risk of transfer out among adults and adolescent was lower. The hazard ratio of adults relative to adolescents was $HR = 0.79$ with a CI of 0.33, 1.87. Transition rates were 86% higher among women who ART education ($HR = 1.86; CI = 0.43, 7.99$). The rates of making transition 4 were 55% lower among symptomatic relative to asymptomatic ($HR = 0.45; CI = 0.06, 3.45$).

Results from the fitted multi-state models suggest management authority is not an important factor predicting all the 4 transitions. This is not consistent with findings from both the Cox model and Competing risks model presented in tables 4.3 and. 4.5 respectively. The results of the Cox model and Competing risks models summarises the effects of management over the whole follow period while multi-state model splits the period into 3 periods.

Facility level was significant in predicting failed registration and ART initiation. This is likely because hospitals have a larger catchment area relative to health centres. Further, the majority of the catchment population are relatively closer facility in health centres. Women are therefore likely to transfer from hospitals to health centres that are closer to their residence. Furthermore, ART patient sometimes transfers without notifying the originating facility (i.e. silent transfers). This is likely an attempt to reduce the cost of accessing health services. Therefore, some of the failed registration might include silent transfers.

Status at registration and group, were both not significant in all the 4 transitions. Similar to facility level, these results are not consistent with findings from both the Cox model and Competing risks model presented in tables 4.3 and. 4.5 respectively.

ART education was significant in predict failed registration and ART initiation. The women with ART education were better informed and subsequently prepared for ART. The challenges that might force women out of treatment are discussed during the education sessions. For example, how to disclose their HIV status to spouse and the whole family. Women with ART education were therefore likely to have support from spouse and family members.

Clinical condition was significantly associated with ART initiation. Symptomatic women had a lower rate of ART initiation. Similar to discussion in the Cox model, this is likely because a bigger proportion are mildly symptomatic. These women are clinically symptomatic but they do not feel ill themselves. Therefore, the default patterns among symptomatic women are not reflective of the clinical condition.

Finally, all the predictors were non significant in predicting the default and TO states. This is likely due to the pattern of attrition that is high from 3 until 6 months. Subsequently, the majority of defaulters are already out of treatment by the time a cohort reaches ART state.

4.6 Summary

The findings of this study show that attrition is highest from 3 months until 6 months. Further, the study revealed important factors at both facility level and individual level affecting PMTCT programming. In addition, this study has also revealed changes of hazards in the context of competing events and also changes in the first 21 months after ART registration.

CHAPTER 5

Conclusions and Recommendations

The study sought to explore facility level and individual level predictors of attrition among Option B+ women in Malawi. It further describe the changes in predictors of attrition from ART treatment in the context of competing events. The study also measured the default rates in the first 21 months of ART among option B+ women. This was to inform effective and efficient implementation of Option B+ intervention.

5.1 Conclusion

The findings suggest that management authority, facility level, status at initiation, age group, ART education and clinical condition are significantly associated with attrition from ART. The association of the predictors and attrition, however, varies from ART registration to ART treatment follow-up and follow-up outcomes. On the other hand, location of residence did not have an effect on attrition from ART.

Facilities managed by MoH, older age and ART education have been found to be significantly associated with lower default rate among Option B+ women. Hospitals, pregnancy and symptomatic women were found to be significantly associated

with a higher default rate.

These results are similar to results found in other studies. Boyles et al found that pregnancy and younger age were associated with an increased risk of attrition (Boyles et al., 2011). Boyles and colleagues studied attrition in a general ART cohort. The results found in this study therefore are similar to studies of attrition in a general ART cohort. The levels of attrition however are higher in Option B+ women. Tenthani et al found that women who started under Option B+ compared to women who started for their own health and facilities with a high patient burden had high attrition rates (Tenthani et al., 2014). Tenthani and colleagues however limited their study to facilities that had electronic medical records. This limitation is inherently biased as only high burden facilities have electronic medical records. Furthermore, follow-up period was limited to the first 6 months after ART registration. This study has gone further to study attrition from randomly selected facilities from across the country. The follow-up period was also longer. The results are however still similar. Similarity of results is probably because most of attrition from ART among Option B+, occurs in the first 3 months after registration.

Others, studied a different aspect of attrition. Tweya et al followed up on patients that had been considered defaulted and studied the real reasons they had defaulted (Tweya et al., 2013). Transfers to other facilities and financial constraints were found to be primary causes of ART discontinuation. Du Toit et al studies attrition among pre-ART patients (Du Toit et al., 2014). None of the factors studied by Du Toit and colleagues were significantly associated with retention in

pre-ART. Overall, these factors might have contributed to the attrition among Option B+ women however this study focused on the facility level factors.

Various models were used in the reviewed studies. Boyles et al used multiple Cox proportional hazard regression analysis, adjusted for competing risks. Tenthani et al used multiple logistic regressions with a random effect for the cohorts and competing risk regression to examine variables associated with attrition. Similarly, this study used competing risks survival model. Across the studies, modelling sub-hazards was probably an appreciation that the other possible events are competing in a ART cohort. Du Toit et al used logistic regression to explore factors associated with retention in HIV care in the pre-ART group. In logistic regression, odds ratio of an outcome given the predictors is modelled. The studies that used logistic model were primarily interested in the association between attrition and other factors. This study however aimed at modelling rates of change of association between attrition and other factors in the first 21 months of ART. Tweya et al used log-binomial regression to compare categories of tracing outcomes with baseline characteristics of patients considered defaulted. In log-binomial, relative risk of an event is modelled. Finally, both logistic and log-binomial models were used to model the probability of an outcome but not the changes of probability of an outcome over time.

Considering default and transfer out as competing events, the overall conclusion was slightly different. Management, status at registration, age group, ART education and clinical condition were associated with attrition from ART. Considering default as the event of interest, facilities managed by MoH, pregnant women,

adult women, women with ART education and clinical condition were still significantly associated with a lower default rate. Hospital was still found to be non-significantly associated with a higher default rate. Considering transfer out as the event of interest, pregnancy, adult women and symptomatic women were still associated with a lower transfer out rate. Finally, facilities managed by MoH, hospital and ART education had an increasing non-significant effect transfer out rate. Competing risks models were also used in other studies on attrition (Tenthani et al., 2014) (Boyles et al., 2011) as noted above. Similar results were found in these studies.

There were changes in hazards ratios across the 4 states covering the first 21 months after ART registration. Facilities managed by MoH were found to be non-significantly associated with a higher risk of failure to register, transfer out and a non-significant association with ART initiation and default. Hospitals hospitals were significantly associated with a lower risk of failed registration and ART initiation. After ART initiation, hospitals were found to be non-significantly associated with a higher risk of default and transfer out. Referral hospitals were found to be significantly associated with a higher risk of failed registration, ART initiation and default. Status at initiation hazard ratios varied across the 4 states. Pregnancy was associated with a higher risk of failed registration, ART initiation and default. Lower risk of transfer out. The association between pregnancy with failed initiation and default was significant. Association of pregnancy with ART state and transfer out state was non-significant. Adults were associated with lower risk of all outcomes across the whole continuum of ART treatment in the first 21 months. The association however was non-significant across all outcomes. ART

education was associated with a significant lower risk of a failed registration and default. A higher risk of ART initiation and transfer out. The association with ART was significant. There were variations in effect of clinical condition across both the 4 states.

Cause-specific proportional hazards and proportional sub-hazards modelling approaches produced similar results in modelling default rate from ART. However, proportional sub-hazards modelling accounts for the possibility that other events can occur. Accounting for competing events presents a more realistic reflection of reality. Therefore, a thorough understanding of the characteristics affecting outcomes can be gained through fitting sub-hazards with transfer out as competing events. Boyles and colleagues considered transfer outs as still in follow-up on ART. Transfer outs were therefore neither censored nor competing events (Boyles et al., 2011).

5.2 Study Limitations

Several limitations affected the study. First, the study used secondary data from the PROBE study. PROBE study was not powered sufficiently enough to satisfy the objective of this study. Specifically, the variable clinical condition had insufficient sample of Option B+ women that were symptomatic. This resulted in failure to estimate parameters a competing risks model stratified by clinical condition.

Second, the study used routine hospital data. Routine hospital data is inherently poor particularly in resource limited context like Malawi. For example, routine

hospital data is usually incomplete and sometimes inconsistent. It is therefore important to interpret studies that use routine hospital data within the context of the limitations.

Finally, the study would have been stronger if other characteristics were included in the modelling. It was however not possible to include all characteristics that have been found to be significantly associated with attrition from ART in similar studies. Distance from the health facility to patients' place of residence has been found to be an important predictor of attrition. Routine hospital data does not include distance in Malawi. PROBE study dataset subsequently did not include this variable.

5.3 Recommendations

This study focused on the facility level factors influencing attrition from ART. Several factors/predictors were found to be associated with attrition in this study. It is therefore important that the factors that significantly associated with attrition should be integrated in PMTCT programming.

The factors studied in this study were management, status at initiation, facility level, age group, ART education, clinical condition and location. We however do not fully understand the other factors related attrition, for example distance and viral suppression among the women retained. Future studies on attrition of women on Option B+ should include these factors in modelling.

Competing risks modelling of censored ART data showed small differences as com-

pared to Cox modelling. Sub-hazards modelling of attrition is a more thorough because it takes into account the possibility that competing events can occur. Further research on modelling approaches is therefore recommended.

Bibliography

- Beyersmann, J., Allignol, A., & Schumacher, M. (2012). *Competing Risks and Multistate Models with R*. Use R! New York, USA: Springer Science+Business Media, LLC,.
- Boyles, T. H., Wilkinson, L. S., Leisegang, R., & Maartens, G. (2011). Factors influencing retention in care after starting antiretroviral therapy in a rural south african programme. *PLoS ONE*, 6(5), e19201.
- Collett, D. (2003). *Modelling survival data in medical research*. Texts in statistical science. London, New York: Chapman and Hall.
- Cornell, M., Lessells, R., Fox, M. P., Garone, D. B., Giddy, J., Fenner, L.,, & Boule, A. (2014). Mortality among adults transferred and lost to follow-up from antiretroviral therapy programmes in south africa: A multicenter cohort study. *Journal of Acquired Immune Deficiency Syndromes*, 67(2), 67–75.
- Coutsoudis, A., Goga, A., Desmond, C., Barron, P., Black, V., & Coovadia, H. (2013). Is option b+ the best choice? *The Lancet*, 381(9863), 269–271.
- Du Toit, E., Van Schalkwyk, C., Dunbar, R., Jennings, K., Yang, B., Coetzee,

- D., & Beyers, N. (2014). Missed opportunities for retention in pre-ART care in cape town, south africa. *PLoS ONE*, *9*(5), e96867.
- Harrell, F. E. J. (2001). *Regression modeling strategies : with applications to linear models, logistic regression, and survival analysis* (illustrated, reprint ed.). . New York, USA: New York: Springer-Verlag.
- Hess, K. R. (1995). Graphical methods for assessing violations of the proportional hazards assumption in cox regression. *Statistics in Medicine*, *14*(15), 1707–1723.
- Hosmer, D. W. & Lemeshow, S. (1999). *Applied Survival Analysis: Regression Modeling of Time to Event Data* (1st ed.). New York, USA: John Wiley and Sons, Inc.
- Klein, J. P. & Moeschberger, M. L. (2003). *Survival analysis : techniques for censored and truncated data* (2nd ed.). Statistics for Biology and Health. New York, USA: Springer-Verlag New York, Inc.
- Kleinbaum, D. & Klein, M. (2012). *Survival Analysis : A Self Learning Text* (3rd ed.). Statistics for Biology and Health. LLC, 233 Spring Street, New York, NY 10013, USA: Springer Science and Business Media.
- Krentz, H. B., MacDonald, J., & Gill, J. M. (2015). The impact of transfer patients on the local cascade of HIV care continuum. *Journal of Acquired Immune Deficiency Syndromes*, *68*(2), 236240.
- Krentz, H. B., Worthington, H., & Gill, M. J. (2011). Adverse health effects for individuals who move between HIV care centers. *Journal of Acquired Immune Deficiency Syndromes*, *57*(1), 51–54.

- Kwong-Leung Yu, J., Tok, T.-S., Tsai, J.-J., Chang, W.-S., Dzimidzi, R. K., Yen, P.-H.,, & Harries, A. D. (2008). What happens to patients on antiretroviral therapy who transfer out to another facility? *PLoS ONE*, 3(4), 47–51.
- Lamb, M. R., El-Sadr, W. M., Geng, E., & Nash, D. (2012). Association of adherence support and outreach services with total attrition, loss to follow-up, and death among art patients in sub-saharan africa. *PLoS ONE*, 7(6), e38443.
- Lawal, B. (2003). *Categorical data analysis with SAS and SPSS applications*. New Jersey, USA: Lawrence Erlbaum Associates, Inc.
- Liu, X. (2012). *Survival analysis: models and applications*. Hoboken, NJ: John Wiley and Sons.
- Machin, D., Cheung, Y. B., & Parmar, M. (2006). *Survival analysis: a practical approach* (2nd ed.). London, UK: John Wiley and Sons Ltd.
- Ministry of Health (2011). *Clinical Management of HIV in Children and Adults* (2011 ed.). Lilongwe, Malawi: Ministry of Health, Malawi.
- Ministry of Health (2014). Integrated HIV program report. Technical report, Government of Malawi, Ministry of Health, Lilongwe, Malawi.
- Ministry of Health and ICF International (2015). Malawi service provision assessment(MSPA) 2013-14. Technical report, Ministry of Health and ICF International, Lilongwe, Malawi and Maryland, USA.
- Ng'andu, N. H. (1997). An empirical comparison of statistical tests for assessing the proportional hazards assumption of cox's model. *Statistics in Medicine*, 16(6), 611–626.

- Odafe, S., Torpey, K., Khamofu, H., Ogbanufe, O., Oladele, E. A., Kuti, O.,, & Chabikuli, O. (2012). The pattern of attrition from an antiretroviral treatment program in nigeria. *PLoS ONE*, 7(12), e51254.
- Quantin, C., Moreau, T., Asselain, B., Maccario, J., & Lellouch, J. (1996). A regression survival model for testing the proportional hazards hypothesis. *Biometrics*, 52(3), 874–885.
- Rollins, N. C., Becquet, R., Orne-Gliemann, J., Phiri, S., Hayashi, C., Baller, A., & Shaffer, N. (2014). Defining and analyzing retention-in-care among pregnant and breastfeeding HIV-infected women: Unpacking the data to interpret and improve PMTCT outcomes. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 67, 46–51.
- Schouten, E. J., Jahn, A., Chimbwandira, F., Harries, A. D., & Van Damme, W. (2013). Is option b+ the best choice? *Lancet*, 381(9874), 1272–3.
- Schouten, E. J., Jahn, A., Midiani, D., Makombe, S. D., Mnthambala, A., Chirwa, Z.,, & Chimbwandira, F. (2011). Prevention of mother-to-child transmission of HIV and the health-related millennium development goals: time for a public health approach. *Lancet*, 378(9787), 282–4.
- Tenthani, L., Haas, A. D., Tweya, H., Jahn, A., van Oosterhout, J. J., Chimbwandira, F., , & Southern, I. (2014). Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ('option b+') in malawi. *AIDS*, 28(4), 589–98.
- Tweya, H., Feldacker, C., Estill, J., Jahn, A., Ng'ambi, W., Ben-Smith, A.,, & Phiri, S. (2013). Are they really lost? "true" status and reasons for treatment

discontinuation among HIV infected patients on antiretroviral therapy considered lost to follow up in urban malawi. *PLoS One*, 8(9), e75761.

Vittinghoff, E., Shiboski, S. C., Glidden, D. V., & McCulloch, C. E. (2005). *Regression methods in biostatistics : linear, logistic, survival, and repeated measures models*. Statistics for Biology and Health. New York, USA: Springer Science+Business Media, Inc.

World Health Organization (2010). *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: recommendations for a public health approach* (2010 ed.). Geneva, Switzerland: World Health Organization.

World Health Organization (2013). *The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for public health approach* (2013 ed.). Geneva, Switzerland: World Health Organization.

Yehia, B. R., Stephens-Shields, A. J., Fleishman, J. A., Berry, S. A., Agwu, A. L., Metlay, J. P.,, & Network, H. R. (2015). The HIV care continuum: Changes over time in retention in care and viral suppression. *PLoS ONE*, 10(6), e0129376.

Appendices

Appendix A: PROBE Study

Sampling

Sampling of health facilities for the PROBE study.

The study looked at HIV infected pregnant and breastfeeding women who started ART in 2012. The Option B+ intervention program started in 2011. The program was not fully established in the first 6 months. Finally; women starting ART in 2013 could not be followed long enough.

The country was divided into 4 geographical areas of rural health facilities from north and central, rural districts of the southern region, Blantyre urban and Lilongwe urban. The epidemiological characteristics of the areas are different. Rural areas of northern and central regions have similar HIV prevalence; the districts in the southern region have a higher (approximately double) HIV prevalence and the 2 urban districts: Lilongwe and Blantyre. The table provides basic information that was used for the selection of the 30 sites included in the study.

HF $\geq$ 1 B+ provides the number of health facilities that started at least one woman on ART under Option B+. In 2012, 618 Health facilities started at least

Area	HF $\geq$ 1 B+	HF $\geq$ 30 B+	# start B+	% in area	# Selected (spare)
North & Centre	270	89	9,376	23.6%	7(1)
Lilongwe	67	24	4,403	11.1%	3(1)
Blantyre	48	22	4,074	10.3%	3(1)
South	233	177	21,648	54.9%	17(2)
Total	618	312	39,401	100%	30(5)

one pregnant or breastfeeding women on ART. HF $\geq$ 30 B+ provides the number of health facilities in which at least 30 women on ART under Option B+ were started in 2012. 35,601 (90.4%) of all women starting ART under Option B+ were started in these sites. # start B+ gives the number of women starting on Option B+. In 2012, the number of women who started ART while pregnant or breastfeeding under Option B+ was 39,401. % in area indicates the contribution of each area to the total number of women started on ART. # Selected (spare) indicates the number of sites selected in each area.

The selection of the number of sites in each area was established on the basis of the number of women starting ART in the area. The 30 study sites in each area were randomly selected using systematic random sampling. The table provides the list in all 4 areas of the selected sites and the 5 additional sites (underlined and in italics).

Area	Health Zone	District	Clinic	# initiated in 2012
------	-------------	----------	--------	------------------------

1	North	Rumphi	Rumphi district hospital	124
1	Central East	Ntchisi	Ntchisi district hospital	80
1	Central West	Ntcheu	Kasinje Health Center	60
1	North	Karonga	Nyungwe Health Centre	52
1	Central West	Ntcheu	Gowa Heath Centre	124
<u>1</u>	<u>North</u>	<u>Mzimba North</u>	<u>Thunduwike Health Centre</u>	<u>40</u>
1	Central West	Ncheu	Nzama Health Centre	37
1	Central East	Kasungu	Nkhamenya Community Hospital	30
2	Central West	Lilongwe	Area 18 Health Centre	325
2	Central West	Lilongwe	Kamuzu Central Hospital Opd1	89
2	Central West	Lilongwe	Mbabvi Health Centre	38
<u>2</u>	<u>Central West</u>	<u>Lilongwe</u>	<u>Male Mission Hospital</u>	<u>32</u>
3	South West	Mangochi	Mangochi District Hospital	587
3	South West	Mangochi	Koche Health Centre	293
3	South West	Phalombe	Sukasanje Health Centre	219
3	South West	Phalombe	Mpasa Health Centre	174
3	South West	Machinga	Nyambi Health Centre	155
<u>3</u>	<u>South West</u>	<u>Chiradzulu</u>	<u>St Joseph Mission Hospital</u>	<u>139</u>

3	South West	Thyolo	Mikolongwe Health Centre	124
3	South West	Balaka	Phalula Health Centre	110
3	South East	Mangochi	Jalasi Health Centre	91
3	South East	Mulanje	Mbiza Health Centre	79
3	South East	Thyolo	Chimvu Health Centre	72
3	South East	Mangochi	St Martins Mission Hospital	67
<u>3</u>	<u>South West</u>	<u>Thyolo</u>	<u>St Martins Molere H/C</u>	<u>66</u>
3	South West	Nsanje	Phokera Health Centre	59
4	South East	Zomba	Machinjiri Health Centre	52
4	South East	Balaka	Utale 2 Health Centre	46
4	South East	Mangochi	Katema Health Centre	42
4	South East	Thyolo	Gombe Health Centre	36
4	South East	Zomba	Police College Hospital	32
			Zomba	
4	South West	Blantyre	Bangwe Health Centre	329
4	South West	Blantyre	Mpemba Health Centre	90
4	South West	Blantyre	Madziabango Health Centre	55
4	South West	Blantyre	Chileka Sda Health Centre	39

In these sites 3,890 women started ART in 2012. The 3,890 women includes women

from the 5 spare sites. PROBE aimed at collecting data on all women who were started on ART in 30 out of 35 sites above.