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Predictors of Loss to Follow-up in Children Receiving Antiretroviral Treatment in Johannesburg, South Africa

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Johannesburg, 2011

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science (Med) in Epidemiology & Biostatistics.

DECLARATION

I, Mazvita Molleen Sengayi (student number 473265) am submitting my research report in partial fulfilment of the requirements of the MSc (Med) in the field of Epidemiology and Biostatistics at the University Of Witwatersrand School Of Public Health. This report has not been submitted before for any degree at any other university. I hereby declare that this research report is my own work. Where I have used the thoughts or ideas of others, the required referencing conventions have been adhered to.

Signed: 

Date : 30 September 2011

DEDICATION

I dedicate this work to my loving husband Idaishe Muchengeti and my son Nzwirashe Muchengeti for all the personal and financial sacrifices they have made for me to pursue my studies. I also dedicate this report to all children living with HIV/AIDS.

Mazvita Molleen Sengayi

September 2011

ABSTRACT

Introduction

Ninety percent of the world's 2.1 million HIV-infected children live in sub-Saharan Africa and 2.5% of South African children are living with HIV. As HIV care programmes scale-up, loss to follow-up is on the rise.

The aim of the study was to determine the rate of loss to follow-up (LTFU) in children receiving antiretroviral treatment and to identify baseline characteristics associated with LTFU and temporary interruption of follow-up (TIFU) in these children. The reasons given by caregivers for clinic non-attendance were also explored.

Materials and Methods

The study is a retrospective analysis of data that was prospectively collected as part of routine clinical care of HIV-infected children at the Harriet Shezi Children's Clinic in Soweto, Johannesburg. Children aged 12 years or less that had initiated highly active antiretroviral therapy (HAART) at the clinic between 1 April 2004 and 31 December 2008 and had been on treatment for at least 3 months, were included in the study. Follow-up was censored on 30 September 2009. Kaplan-Meier methods were used to estimate time to LTFU or TIFU. Cox proportional hazards models were fitted to investigate associations between baseline characteristics and LTFU as well as TIFU. Pie charts and frequency tables were used to describe reasons for clinic non-attendance.

Results

Of the 2536 children included in the study, 174 (6.86%) were LTFU at the end the study period. The cumulative probabilities of LTFU at 6 months, 12 months and 2 years were found to be 0.9% (95% CI 0.67 – 1.47), 2.85% (95% CI 2.26 – 3.59) and 5.22% (95% CI 4.36 – 6.25) respectively. Independent predictors of LTFU were WHO clinical stage 3 or 4 [HR 2.14 (95% CI 1.22 – 3.73) p=0.026] and younger age [HR 0.91 (95% CI 0.84 – 0.99) p=0.008] the hazard of LTFU decreasing by 9% for every 1 year increase in age. A total of 338(13.32%) children interrupted follow-up for at least 6months before returning to care. Factors independently associated with TIFU were taking a protease inhibitor based regimen [HR 1.67 (95% CI 1.18 – 2.35) p=0.004] and being moderately

underweight [HR 0.66 (95% CI 0.45 – 0.99) p=0.043] was protective. Social reasons (46.43%) and financial reasons (10.05%) together accounted for the majority of reasons given for clinic non-attendance. Caregiver-related problems (53.22%) were the commonest social reasons given for missing a clinic visit.

Conclusions

These LTFU rates are much lower than those found in studies where children on HAART duration of less than 3 months were included and may reflect on true LTFU with minimal effect of unreported early mortality. WHO clinical stage 3 or 4 and younger age independently predicted LTFU. Independent predictors of TIFU were moderate underweight and being on a PI-based regimen. LTFU is not necessarily permanent with most of those who interrupt follow-up returning to care. The main reasons why children miss clinic appointments are social. Caregiver-related problems are important reasons for clinic non-attendance in children on HAART.

Recommendations

Initiating children on HAART in earlier disease stages may reduce LTFU. Strategies to improve LTFU need to target younger children and there is need for further research to investigate why young children are especially vulnerable to LTFU. Caregivers of children who temporarily interrupt follow-up can potentially provide a unique opportunity for health workers to learn the true reasons why children get LTFU. Such caregivers may also be targeted for more intensive adherence counselling. Further studies on the implications of TIFU on the development of resistance to antiretroviral drugs are needed. Primary caregivers of children need to be encouraged to identify secondary caregivers who can bring the child to the clinic in the event that the primary caregiver is unable to bring the child.

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ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Treatment
CDC	Centres for Disease Control
ECHO	Enhancing Children's HIV Outcomes
HAART	Highly Active Antiretroviral Therapy
HAZ	Height-for-age Z-score
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSCC	Harriet Shezi Children's Clinic
IQR	Interquartile Range
LTFU	Loss to Follow-up
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NSP	National Strategic Plan for HIV&AIDS and STIs 2007-2011
PI	Protease Inhibitor
SD	Standard Deviation
SSA	Sub-Saharan Africa
TIFU	Temporary Interruption of Follow-up
WAZ	Weight-for-age Z-score
WHZ	Weight-for-height Z-score

Chapter 1: Introduction

The chapter begins with a general overview of the burden of HIV in sub-Saharan Africa and in South Africa. The implications of the scale-up of antiretroviral treatment in HIV care treatment programmes on loss to follow-up are explored. The published literature on loss to follow-up is reviewed and the chapter ends with a description of the aims and objectives of the study.

1.1 Background

Sub-Saharan Africa (SSA) is home to 90% of the world's 2.1 million HIV-infected children and of all the people living with HIV in sub-Saharan Africa, 10% of them are children (1). In South Africa at the end of 2007, 280 000 children were infected with HIV and the prevalence of HIV in children aged between 2 and 14 years was 2.5% (1.9-3.5%) (2, 3).

Despite having such a high disease burden, the increasing national and political commitment to the treatment and care of HIV in South Africa is encouraging. The National Strategic Plan for HIV&AIDS and STIs 2007-2011 (NSP) aims to provide a comprehensive HIV care and treatment package to 80% of people living with HIV by 2011 (4).According to the South Africa Country Progress Report on the Declaration of Commitment on HIV/AIDS released in March 2010, there has been some progress with 81% of children and 55% of adults in need of HAART receiving treatment at the end of November 2009(4).

Enhancing Children's HIV Outcomes (ECHO) is a non-profit organisation which supports the South African department of health in the paediatric HIV roll-out programme at several sites in South Africa. The study is set at the Chris Hani Baragwanath Hospital Harriet Shezi Children's Clinic (HSCC) in Soweto which is ECHO's flagship clinic. The HSCC started providing government-sourced antiretroviral treatment in April of 2004 and the cumulative number of children ever started on treatment at the HSCC as of June 2010 was 3577.

1.2 Statement of the Problem

The initial hope, improvement of survival and quality of life associated with highly active antiretroviral therapy (HAART) in people infected with HIV faces the new challenge of retaining patients in long term care. LTFU may potentially lead to inaccurate mortality estimates (5), making assessment of the effectiveness of HIV care programmes problematic. Adult HIV care programs in sub-Saharan Africa are reportedly retaining only about 60% of their patients in the first two years (6).

While children in HIV care programs have a much higher retention than adults, a rise in LTFU has been observed as paediatric HIV care programmes scale-up (7-9). A trend of increase in LTFU over time was observed in a pooled analysis of the 16 paediatric HIV care programmes in sub-Saharan Africa which form the Kids' Antiretroviral Treatment in Lower-Incomes Countries (KIDS-ART-LINC) Collaboration. The risk of LTFU was 2.8% (95%CI: 1.9 to4.1) at 6 months, 4.6% (95%CI: 3.4 to 6.2) at 1 year, and 8.4% (95%CI: 6.5 to 10.7) at 2 years (7).

In a study of the outcomes of the South African national paediatric antiretroviral treatment programme which analysed data from 7 public sector ART programmes in Gauteng, Western Cape and Kwazulu-Natal provinces, the retention at 3 years after initiation was 81.4%(95% CI 80.1-82.6)(8). Of concern however, is the increase in LTFU over time. In the same study, LTFU at 1 year after initiation was much higher in children who started ART during or after 2006[8.2% (95% CI 7.1-9.4)] compared to those who had started ART before 2004 [2.2 %(95%CI 1.1-4.7)] (8).

1.3 Justification

The study of LTFU and other treatment outcomes in HIV care has been used to monitor and improve programme effectiveness, using patient retention as a measure of quality of care (10). Some patients who are deemed LTFU are misclassified deaths (11, 12), unreported transfers (13) and temporary treatment interrupters (11). It is therefore important to examine the risk factors and reasons for LTFU in order to make appropriate recommendations for patient retention in HIV care programmes.

Now that the scaling-up of antiretroviral treatment has gained momentum in South Africa, the question is not only how many children can be put on treatment, but also how many can be retained in care.

While several studies have been done in South Africa on the reasons, characteristics, the extent and contributing factors of LTFU in adults on HAART (14, 15), there is limited data on the reasons for LTFU and the predictors of LTFU in children on HAART in South Africa.

1.4 Literature Review

1.4.1 The Rate of Loss to Follow-up in Paediatric HIV Care Programmes

Studies of patient outcomes in African paediatric HIV care programmes have shown varying rates of LTFU. In the KIDS-ART-LINC collaboration which included paediatric cohorts from Benin, Ivory Coast, Ghana, Burundi, Zimbabwe, Rwanda, Uganda, Kenya and Zambia, overall cumulative probabilities of LTFU at 1 year and 2 years of follow-up were 5.0% (95%CI: 4.1 to 6.1) and 10.3% (95%CI: 8.9 to 11.9) respectively(7). The International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) reported a one-year LTFU rate of 7% in a pooled analysis of 10 paediatric ART programmes from South Africa, Malawi, Mozambique and Zimbabwe (5). A study of outcomes of the South African national paediatric ART which was also done by the IeDEA-SA collaboration reported a one-year LTFU rate of 2.2%(95%CI 1.1-4.7) for patients who initiated ART before 2004. In comparison, the one-year LTFU rate of patients who had started ART during or after 2006 in the same study was much higher [8.2% (95% CI 7.1-9.4)](8). Smaller studies done in South Africa have reported lower LTFU rates. A study done in Cape Town to evaluate outcomes of children on different ART regimens reported overall LTFU rates of 1.3% (95% CI 0.5-3.4) at 1 year and 3.7% (95% CI 1.9-7.2) at 2 years(16). Sinikithemba clinic in KwaZulu-Natal has a family centred model of care and reported LTFU rate of 0% within a median follow-up time of 8 months (17).

1.4.2 Loss to follow-up and Mortality

Assessing attrition or LTFU in HIV care programs has been clouded by high mortality rates with unreported mortality contributing to LTFU. In a study done in Northern Malawi

to determine the true outcomes of adult patients who were deemed LTFU, 50% of them had actually died and 27% could not be traced (18). A study on the characteristics and outcomes of adults lost to follow-up in Johannesburg, South Africa showed that 16.4% of patients were LTFU (defined as missing a scheduled visit for a minimum of 6 weeks) during the follow-up period of 15 months. Just under 70% of all those LTFU were traced, and nearly half of all those traced had died (15). Linkage of vital registration and clinic data of patients who were LTFU at Themba Lethu clinic in Johannesburg, showed that 37.2% of patients traced had actually died and mortality estimates were adjusted from 4.2% to 10.9%(19).

Most children initiating HAART in resource-poor settings start treatment at advanced stages of illness leading to high mortality rates especially in the first 3 months of HAART initiation (1, 5, 20, 21). Unreported deaths may inflate LTFU and conversely underestimate mortality. Characteristics of children who were lost to follow-up were similar to those of deceased children in a retrospective case cohort study done in Malawi to investigate predictors of mortality and LTFU among children taking HAART (20). Deceased children had similar median ART duration, mean age, mean weight and CD4 counts with those LTFU. WHO stage 4 was independently associated with both mortality and LTFU in these children (20). This suggests that many of those LTFU were actually deceased.

1.4.3 Predictors of Loss to follow-up

Several studies in paediatric HIV care programmes in resource-poor settings have shown an association between clinical markers of disease severity and LTFU (20, 22-24). Severe immune suppression and severely low weight-for-height z-score were associated with LTFU in HIV-infected children attending a comprehensive HIV clinical care programme in Western Kenya (23). Severe clinical status was also significantly associated with LTFU in the KIDS-ART-LINC collaboration study (7). A diagnosis of HIV-related malignancy predicted LTFU in Malawian children during their first year of HAART (22). In Haitian children, baseline malnutrition as measured by weight-for-age z-score (median WAZ -3, IQR -3.7 to -1.8) was more common in children who subsequently became LTFU (25). CDC clinical stage C and being treated at a

regional/university hospital predicted LTFU among children taking HAART in Thailand (24).

Socioeconomic factors also play a role in LTFU. Children depend on adults for treatment adherence and their adherence has been shown to be dependent on characteristics of the caregiver and the relationship with the caregiver (26, 27) . Caregiver characteristics which have been associated with improved adherence to ART in children include biological relationship with the child, caregivers who are on ART, caregiver permanence, higher caregiver education and comprehension of ART and caregivers who have disclosed their own or the child status to others (27). In the Paediatric AIDS Clinical Trials Group (PACTG) 219C cohort study – a multicentre clinical trial in the United States, LTFU was associated with lack of participant compensation, low caregiver education level, child's age greater than 15 years, higher viral load, children starting school and mothers beginning employment (28). Orphans, older children and children receiving food supplementation were less likely to become LTFU in HIV-infected children in Western Kenya (23).

1.4.4 Reasons for Clinic non-attendance

There are several studies conducted in adults attending HIV care treatment programmes in Africa where patients who were LTFU were traced and their actual reasons for clinic non-attendance ascertained (14, 15, 18, 29). In rural Uganda, common reasons given for clinic non-attendance were lack of transportation or money and child or work responsibilities (29). In a study at Themba Lethu clinic in Johannesburg, South Africa the most commonly cited reason for clinic non-attendance was financial (34%) and 27% of those deemed LTFU had died. Less common reasons were transfer to another clinic, using medical aid or private treatment, use of traditional medicine and social reasons such as incarceration (14). In a similar study at Johannesburg Hospital adult clinic the reasons for being LTFU among those traced, other than death were relocation, clinic transfer, hospitalization, medication toxicity and financial problems (15).

In paediatric HIV care programs in SSA, reasons for being LTFU were found to include poverty-related factors, frequent relocation, transfers and illness or death of a

caregiver(1). There were no studies found which were done in South Africa exploring the reasons for non-attendance in paediatric HIV care programmes.

1.4.5 Conclusion

Rates of LTFU in paediatric HIV care programmes in SSA range from 1.3% to 8.2% after 1 year of follow-up and from 3.7%-10.3% after 2 years of follow-up (5, 8, 16). Mortality clouds the assessment of LTFU; many of those deemed LTFU may be dead (15, 18). Patients become LTFU because they are dead, rather than that poor adherence and clinic non-attendance leads to death. Clinical predictors of LTFU (severe malnutrition as measured by weight-for-age and weight-for-height z-scores, WHO stage 4 or CDC stage C and a diagnosis of HIV-related malignancy) also predict mortality and this may reflect unreported deaths (7, 23-25). When patients are actually traced and their actual reasons for being LTFU are investigated, mainly socioeconomic reasons are given for being LTFU (14, 15, 18, 29).

1.5 Definition of Terms

There is no consensus in published literature as to the definition of loss to follow-up (30). Depending on the time interval between scheduled visits, LTFU has been defined as last patient contact with the care facility for a minimum time period ranging from 30days to one year (30). Several studies of outcomes in HIV care programmes in Southern Africa have defined LTFU as last patient contact with the clinic of more than 6 months before database closure (5, 8, 29, 31).Children at the HSCC have 3-monthly scheduled visits and allowing a time period of at least 6 months before a child could be deemed LTFU was appropriate.

Kranzer et al. (2010) defined treatment interruption as a patient-initiated episode of more than 30 days of stopping ART followed by subsequent resumption of treatment (32). Hill et al. (2010) defined temporary LTFU as a gap in care of at least one year (33).

In this study, the following terms were defined as follows:

Loss to follow up (LTFU): A child was defined as LTFU if their last date of contact with the clinic was more than 6 months before the date of database closure (30 September 2009) and were not known to have died or transferred(5, 8, 29, 31).

Temporary interruption of follow up (TIFU): A child returns to care after at least 6 months of no contact with the clinic.

1.6 Objectives

General

To determine the rate of LTFU in children receiving ART and identify baseline characteristics associated with LTFU

Specific Objectives

1. To determine the rate of loss to follow-up in children who have been receiving HAART for at least 3 months in a large urban paediatric clinic in Johannesburg South Africa
2. To identify baseline characteristics that independently predict LTFU in this population
3. To assess baseline characteristics that predict temporary interruption of follow-up
4. To describe the reasons for clinic non-attendance in children on HAART

Chapter 2: Materials and Methods

Introduction

The study design, site, population and methodology are described in this chapter. The methods used for the selection of study participants are explained. The dataset used for identification of predictors of LTFU is described. The details of a second dataset used for describing reasons for clinic non-attendance are also presented. Definitions of all the study variables are given. The measures taken to ensure quality data are also described. The chapter ends with a review of the data processing methods and ethical considerations.

2.1 Study Design

A Retrospective Analytic Cohort Design

The study is a retrospective analysis of data that was prospectively collected as part of routine clinical care of HIV-infected children at the Harriet Shezi Children's Clinic in Soweto.

2.2 Study Site

The Harriet Shezi Children's Clinic is a paediatric HIV rollout site situated at the Chris Hani Baragwanath Hospital, an academic tertiary referral hospital in Soweto, Johannesburg. The HSCC started offering government-sourced antiretroviral treatment on the 1st of April 2004 and a total of 3577 children had been started on antiretroviral treatment as of June 2010. All children enrolled at the HSCC are HIV-infected and antiretroviral treatment is started based on the prevailing South African national guidelines (34). The HSCC was chosen as the study site because it has one of the largest HIV paediatric cohorts in South Africa. This site is likely to be representative of urban paediatric HIV care in the South African public sector and patient records are conveniently stored electronically, allowing for efficient secondary data analysis.

2.3 Study Population

The study population consists of all HIV-infected children enrolled at the HSCC with at least 3 months of follow-up after ART initiation.

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2.4 Study Sample

STATA version 11(STATA Corporation, College Station, TX) software package was used for power calculations. The Stata command stpower logrank can be used to estimate power for survival data when sample size and effect size (expressed as hazard ratio) are known. This command was used to plot power curves using the estimated sample size of 3000. (See Appendix 5 – Power Calculations for Sample Size)

Using a total of 3000 patients, a two-sided test, and an alpha of 0.05, the statistical power was estimated to be more than 90% and would be able detect any significant difference in LTFU rates for all adjusted comparisons between predictors.

2.4.1 Predictors of Loss to Follow-up Dataset

The study sample consisted of 2536 children who initiated HAART at the Harriet Shezi Clinic between 1 April 2004 and 31 December 2008 and met the inclusion criteria described below. The study start date of April 1 2004 marks the beginning of the South African national antiretroviral roll-out programme when the HSCC started receiving government-sourced antiretroviral drugs. Children who had been started on donor-sourced antiretroviral drugs prior to this date were excluded from the study. Children who were initiated on HAART after 31 December 2008 were excluded because they did not have adequate follow-up time (at least 9months) at database closure of 30 September 2009.

Inclusion Criteria:

- Aged 12 years or less at time of HAART initiation
- had been on HAART for at least 3 months at their last recorded clinic visit or at database closure (30 September 2009)

Exclusion Criteria:

- Had been on HAART for less than 3 months at their last recorded clinic visit or at database closure (30 September 2009)
- Older than 12 years at HAART initiation

Those who had been on HAART for less than 3 months were excluded because of the high mortality during the first 3 months on HAART which can be perceived as LTFU. Children older than 12 years were excluded because adolescents may have unique characteristics and predictors to LTFU compared with younger children. Children who were transferred out or left ART care at HSCC during the study time period for other confirmed reasons were censored.

2.4.2 Reasons for Clinic non-attendance Dataset

A separate dataset created for the purposes of routine tracing of children who miss their scheduled appointments at the HSCC was used. The Defaulter Tracer database is based on the Defaulter tracer form (Appendix 1) which captures demographic information and telephonic responses given by caregivers when children who miss their visits are traced. All children enrolled at the HSCC who were ever traced for missing their appointments and had complete demographic information were included in the analysis. These children were traced between 18 June 2007 and 11 December 2010. The children had missed appointments between 17 June 2007 and 18 November 2010. A total of 3460 calls were made to trace 2244 children with complete records who had missed at least one scheduled appointment in the given time period.

2.5 Data Management

2.5.1 Measurement

A multiple clerk and single entry databases created as part of routine clinical HAART care at Harriet Shezi clinic were used. These data were initially collected for the purposes of monitoring and evaluation of the Harriet Shezi paediatric HIV care programme under the ECHO paediatric clinics. Demographic, clinical and laboratory data were entered into an electronic database by data clerks after every clinic visit.

Data on reasons for clinic non-attendance was extracted from the Defaulter tracer database which was also created as part of routine care. (See Appendix 1: Defaulter tracer form Follow-up Question 1) Caregivers of children who had missed their scheduled appointments were contacted telephonically by trained counsellors and asked why the child had missed their visit. The counsellor recorded the responses on the form and this information was later entered into an electronic database by data

clerks. Most calls were made the same day the child missed their visit but if the caregiver could not be contacted, several attempts were made to contact the caregiver even 3 months after the last clinic visit.

2.5.2 Study Variables

Exposure Variables: Predictors of LTFU

Demographic Characteristics

- Age was defined as age of child at HAART initiation. It was calculated from Date of Birth and Date of HAART initiation. Age was categorized into the following categories: 0 – 11.9 months, 12 – 36.9 months, 36 – 59.9 months and 60 months to 12 years. Similar age-group categories are used in the World Health Organization (WHO) classification of HIV-associated immunodeficiency using CD4 percentage (35) in children and allow for comparison of levels of immunodeficiency in children of different ages.
- Sex was defined as sex of child which was either male or female.
- Primary caregiver relationship at HAART initiation was categorized into 4 categories: mother, grandmother, other family members and other non-family (institutions, foster care, neighbours, and guardians). The role of the extended family and especially, grandmothers, in taking over the care of HIV-infected children in the event of HIV-related parental illness or death, has been well-documented hence this classification(36-38). The number of children who had non-family members as their primary caregivers were also too few to allow any further classification.

Clinical Features

- Weight-for-age z-score (WAZ), Height-for-age z-score (HAZ) and Weight-for-height z-score (WHZ) at HAART initiation: Z scores were calculated from baseline weight and height observations using the 1978 CDC/WHO growth reference curves and Epi Info Nutrition version 3.5.1 software. The more recent WHO 2007 reference charts go up to 10 years only for WAZ computation, since

WAZ needed to be calculated for all children aged 12 or less at baseline, they could not be used. Additionally, STATA S/E is required to run the WHO 2007 Do files. The student had the Student version of STATA, Stata I/C which does not have the capacity to run the 2007 Do files. Z scores are sex-independent and allowed for comparisons of levels of malnutrition across different sexes and age groups. WAZ, HAZ and WHZ were categorized into <-3, -2 to -3 and >-2. WHO Global Database on Child Growth and Malnutrition uses a Z-score cut-off point of <-2 for moderate malnutrition (underweight, stunting or wasting) and <-3 for severe malnutrition (underweight, stunting or wasting) (39).

- CD4 cell % at HAART initiation was categorized into <15% and ≥ 15%.These percentages mean different severity of immunodeficiency depending on the age of the child.
- Immune suppression is a variable that was created from age, CD4% and CD4 cell count based on the WHO classification of HIV-associated immunodeficiency (Table 2.1). Immune suppression has two categories none/mild and advanced/severe immune suppression.

Table 2.1: WHO Classification of HIV-associated Immunodeficiency using CD4 Count

Classification of HIV-associated Immunodeficiency	Age-related CD4 Values			
	<11 months	**12 – 35 months**	**36 – 59 months**	**≥ 5 years**
Not Significant	>35%	>30%	>25%	>500 cells/mm³
Mild	30 – 35%	25 – 30%	20 – 25%	350 – 499 cells/mm³
Advanced	25 -29%	20 – 25%	15 – 19%	200 – 349 cells/mm³
Severe	<25%	<20%	<15%	<200 cells/mm³ or <15%

Source: Management of HIV infection and antiretroviral therapy in infants and children: A clinical manual. World Health Organization, 2006.(35)

- Plasma HIV viral load at HAART initiation measured in copies/mL was classified into <100 000, 100 000 to 1 million and >1 million copies/mL. Logarithm$_{10}$ of plasma HIV viral load at HAART initiation was analysed as a continuous variable.
- WHO clinical stage at baseline was analysed as a binary variable with the categories WHO stage 1/2 and WHO stage 3/4. This was necessitated by the fact that the HSCC changed from the 3-stage WHO classification to the 4-stage WHO classification in late 2004, so children who were previously classified as stage 3 were now classified as stage 4.
- Year of HAART initiation was analysed as a categorical variable with the 5 categories; 2004, 2005, 2006, 2007 and 2008.
- Tuberculosis at baseline was a binary variable with those who had ever had a diagnosis of TB (current or previous) and those who had not.
- Initial regimen at initiation of treatment was categorised as NNRTI-based or PI-based.

Outcome Variables: Predictors of LTFU

- Loss to Follow-up (LTFU): A child was defined as LTFU if their last date of contact with the clinic was more than 6 months before the date of database closure (30 September 2009) and were not known to have died or transferred.
- TIFU (Temporary interruption of follow-up): A child returns to care after at least 6 months of no contact with the clinic.

Variables: Reasons for clinic non-attendance

The reasons for missing scheduled clinic appointments were classified categorically according to the responses given when the caregivers were telephoned.

2.5.3 Data Quality Control

Range checks for outliers were done using histograms and box and whisker plots for continuous variables. Duplicates were removed from the dataset. Consistency checks to identify inconsistencies in the data were done e.g. checking whether dates of initial visit, initial viral load, CD4 count and ART initiation were all larger than date of birth.

2.5.4 Data Processing Methods and Analysis

STATA version 11(STATA Corporation, College Station, TX) software package was used for all statistical analyses. All statistical significance was calculated at the 5% significance level.

The study population variables were described and are presented in Table 1. Table 1 also shows the proportion of missing values for each variable. Analysis of missing values using Chi-squared tests was done to investigate whether missing data were associated with the outcome (LTFU) and is presented in Appendix 2.

Categorical variables were described using frequency tables and their association with LTFU was tested using the Chi-squared test of proportions. Continuous variables were tested for the assumption of normality using histograms, normal quantile plots and standardised normal probability plots (Appendix 3). Normally distributed continuous variables were summarized in terms of mean and standard deviation and were tested for their association with LTFU using the Student's t test. Non-normal continuous variables were summarized in terms of median and inter-quartile range and their association with LTFU was tested using the Wilcoxon rank-sum test. Pie charts and frequency tables were used to describe the reasons for clinic non-attendance.

Time-to-event analysis was the primary method of analysis used. The time axis was years from HAART initiation and all children were censored at their last visit or on 30 September 2009.Period incidence rates and cumulative probabilities of LTFU and TIFU at specified intervals were calculated. Kaplan-Meier estimates of LTFU and TIFU were determined. Logrank tests of equality of survival functions and trend tests were done to compare Kaplan Meier curves. Cox proportional hazards models were fitted to investigate associations between baseline characteristics and LTFU as well as TIFU. Global tests (using Schoenfeld residuals) and graphical tests for validity of the proportional hazards assumptions were done and are presented in Appendix 4. Variables with p value< 0.1 in univariate analysis were considered for the multivariate Cox models. These were added to the models starting with the one with the smallest p value. Variables which violated the proportional hazards assumption were excluded from the model. The final model had fewer variables with the smallest Wald test p value.

Accounting for Non-Proportional Hazards

There are several approaches to dealing with departures from the proportional hazards assumption. These include stratifying analysis by the variable with the time-varying effect, partitioning the time axis and reporting hazard ratios for each time interval, abandoning the Cox model all together and using other statistical models such as additive models and restricting follow-up to a shorter time window in which the proportional hazards assumption holds (40). Additional models were run restricting follow-up time to 12 months and variables that violated the proportional hazards assumption were considered in these models. These are shown in Tables 6.1 and 10.1 for LTFU and TIFU respectively.

2.6 Ethical Considerations

To protect the identities of participants, the datasets used unique patient identifiers and not patient names. Any other potential identifiers were removed from the datasets before they were provided for analysis. Data were stored in the student's personal laptop which has password restricted access. The information obtained from this study will be used to improve care at the Harriet Shezi clinic and at other paediatric ART sites in the country. Ethical approval was sought and was granted by the University of Witwatersrand ethics committee (Clearance Certificate M10940, approved 1st October 2010, See attached copy of certificate on the last page).

Chapter 3: Results

Introduction

In this chapter, the results of the study are presented with the aim of fulfilling the objectives of the study. The chapter starts with a description of the overall cohort characteristics of the study sample. The incidence rates and cumulative probabilities of LTFU and TIFU are reported. Associations between LTFU and baseline variables are then explored and the predictors of LTFU identified. Similarly, associations between TIFU and exposure variables are investigated and predictors of TIFU are identified. The chapter ends with a description of the reasons given for clinic non-attendance.

3.1 Cohort Description

A total of 2937 children were initiated on HAART at HSSC between 01 April 2004 and 31 December 2008. Of these, 190 were excluded because they were older than 12 years at HAART initiation and 211 were excluded because at their last clinic visit they had been on HAART for less than 3 months. The remaining sample had 2536 children. A flow chart of children included in the study is shown in Figure 1.

Table 1 summarizes the overall cohort characteristics of the study sample including the proportion of missing data for each variable. The variable weight-for-height z-score had the highest proportion of missing values with 27.29% of data missing. Missing data for all variables were not associated with LTFU, except for the variable sex (See Appendix 2: Analysis of missing data) which only had 2 values missing (0.08%).

The median age was 4.46 years (IQR 1.73 – 7.35) and 48.46% (1229) of the children were female. The majority of the children (59.03%) had mothers as their primary caregivers at HAART initiation. Most of the children had advanced/severe immunodeficiency (78.59%) at the start of treatment and 63.56% had WHO clinical stage 3 or 4.

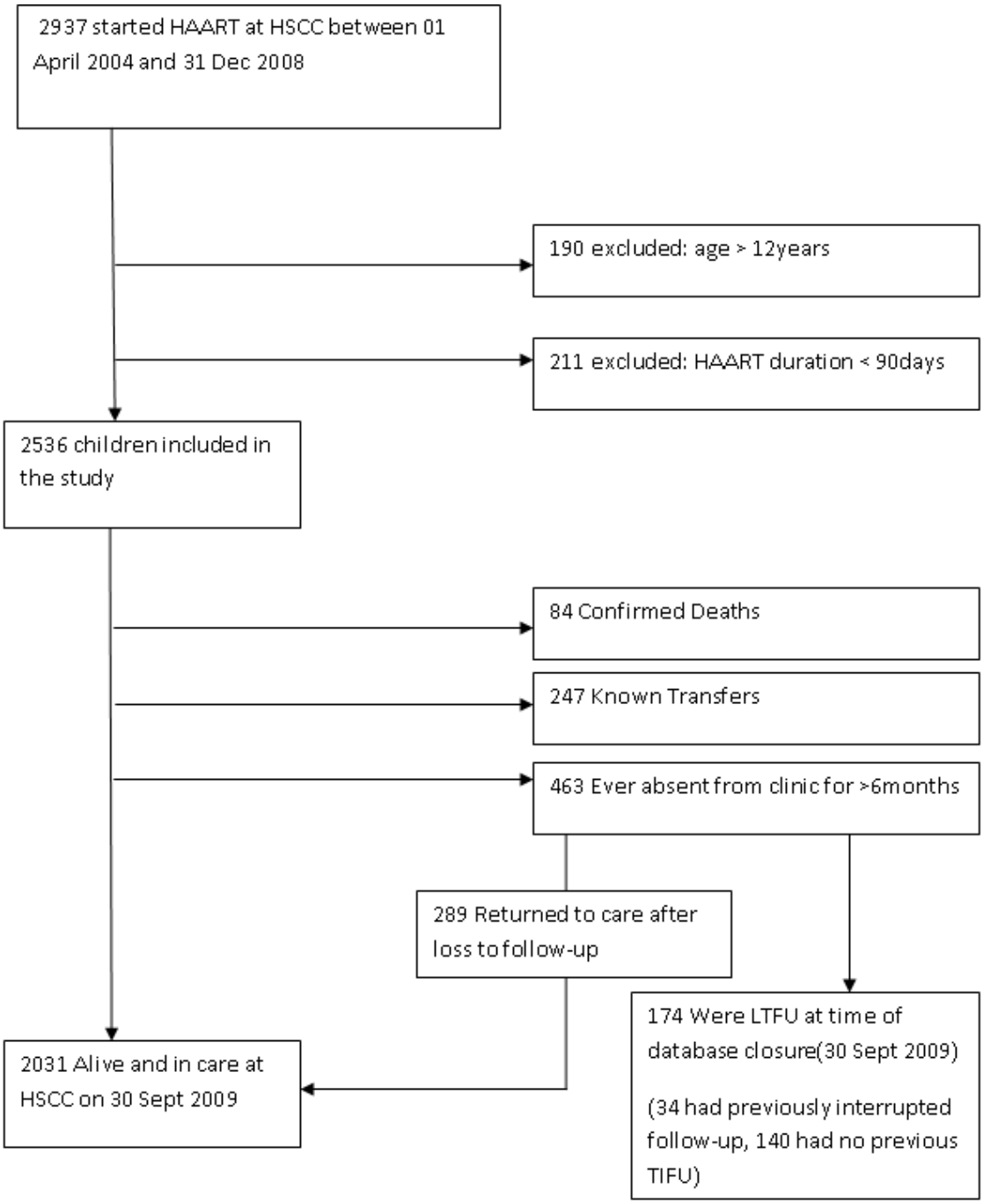

Figure 1: Flow chart of HIV-infected children initiating HAART at HSCC between 01 April 2004 and 31 December 2008

Table 1 : Overall Cohort Characteristics

Characteristic	N	%
Sex n ,%		
Male	1305	51.46
Female	1229	48.46
Data missing	2	0.08
Age at HAART initiation n ,%:		
0-11.9months	410	16.17
12months-35.9months	550	21.69
36months -59.9months	430	16.96
60months-12years	1146	45.19
Median (IQR)	4.46 (1.73 – 7.35)	
Year of Starting HAART n ,%		
2004	279	11.00
2005	647	25.51
2006	575	22.67
2007	484	19.09
2008	551	21.73
Primary Caregiver n ,%		
Mother	1497	59.03
Grandmother	411	16.21
Other Family	419	16.52
Foster Care/Institution/Neighbour/Guardian	171	6.74
Data Missing	38	1.50
Weight-for-age Z score n ,%:		
>-2 (Not underweight)	1022	40.30
-2 to -3 (Moderately underweight)	512	20.19
<-3 (Severely underweight)	398	15.69
Data missing	604	23.82
Mean (Standard Deviation)	-1.97 (1.28)	
Height-for-age Z score n ,%:		
>-2 (No stunting)	716	28.23
-2 to -3 (Moderate stunting)	604	23.82
<-3 (Severe stunting)	597	23.54
Data missing	619	24.41
Mean (Standard Deviation)	-2.41 (1.35)	
Weight-for-height Z score n ,%:		
>-2 (No wasting)	1596	62.93
-2 to -3 (Moderate wasting)	173	6.82
<-3 (Severe wasting)	75	2.96
Data missing	692	27.29
Mean (Standard Deviation)	-0.61 (1.29)	

Immune suppression[1] n ,%:		
Not significant/Mild	105	4.14
Advanced/Severe	1993	78.59
Data missing	438	17.27
WHO Clinical Stage n ,%:		
1/2	644	25.39
3/4	1612	63.56
Data missing	280	11.04
TB prior to HAART n ,%		
No	1457	57.45
Yes	1063	41.92
Data missing	16	0.63
CD4 cell % n ,%:		
< 15%	682	26.89
≥ 15%	1431	56.43
Data missing	423	16.68
Mean (Standard Deviation)	12.63 (7.93)	
Plasma Viral Load (copies/mL) n ,%		
<100 000	875	34.50
100 000 to 1 million	814	32.10
> 1 million	208	8.20
Data missing	639	25.20
Log_{10} Viral Load		
Mean (Standard Deviation)	11.67 (2.23)	
Initial Regimen		
NNRTI-based	1620	63.88
PI-based	900	35.49
Data missing	16	0.63

[1] WHO classification of HIV-related immunodeficiency in children according to age (See Table 2.1 for details)

Table 2 shows baseline characteristics of children who were LTFU and those who were not. Log_{10} viral load, CD4 percentage, weight-for-age z-score, height-for-age z-score and weight-for-height z-score were normally distributed and Student's t tests were done to test for differences between those LTFU and those who were not. Normality assumption tests are presented in Appendix 3. Age was not normally distributed and the Wilcoxon rank-sum test was done. Chi-squared tests were performed for all categorical variables.

Table 2 : Associations between Baseline Characteristics and LTFU (N=2536)

Characteristic	No Loss to Follow-up		Loss to Follow-up		P value[1]
Sex (N=2534) n ,%					
Male	1212	92.87	93	7.13	
Female	1149	93.49	80	6.51	0.538
Age at HAART initiation (N=2536) n ,%:					
0-11.9months	375	91.46	35	8.54	
12months-35.9months	497	90.36	53	9.64	
36months -59.9months	404	93.95	26	6.05	**0.003**
60months-12years	1086	94.76	60	5.24	
Median (IQR)	4.60 (1.79 – 7.43)		2.83 (1.21 – 5.53)		**<0.001**
Primary Caregiver (N=2498) n ,%					
Mother	1374	91.78	123	8.22	
Grandmother	392	95.38	19	4.62	
Other Family	401	95.70	18	4.30	**0.008**
Foster Care/Institution/Neighbour/Guardian	160	93.57	11	6.43	
Weight-for-age Z score (N=1932) n ,%:					
>-2 (Not underweight)	964	94.32	58	5.68	
-2 to -3 (Moderately underweight)	477	93.16	35	6.84	0.072
<-3 (Severely underweight)	362	90.95	36	9.05	
Mean (Standard Deviation)	-1.96 (1.27)		-2.17 (1.40)		0.073
Height-for-age Z score (N=1917) n ,%:					
>-2 (No stunting)	682	95.25	34	4.75	
-2 to -3 (Moderate stunting)	564	93.38	40	6.62	**0.016**
<-3 (Severe stunting)	545	91.29	52	8.71	
Mean (Standard Deviation)	-2.40 (1.34)		-2.66 (1.55)		**0.037**
Weight-for-height Z score (N=1844) n ,%:					
>-2 (No wasting)	1490	93.36	106	6.64	
-2 to -3 (Moderate wasting)	159	91.91	14	8.09	0.491
<-3 (Severe wasting)	72	96.00	3	4.00	
Mean (Standard Deviation)	-0.61 (1.30)		-0.65 (1.18)		0.724
Immune suppression[2] (N=2098) n ,%:					
Not significant/Mild	97	92.38	8	7.62	
Advanced/Severe	1860	93.33	133	6.67	0.706
WHO Clinical Stage (N=2256) n ,%:					
1/2	612	95.03	32	4.97	
3/4	1491	92.49	121	7.51	**0.030**
TB prior to HAART(N=2520) n ,%					
No	1351	92.72	106	7.28	
Yes	996	93.70	67	6.30	0.340
CD4 cell % (N=2113) n ,%:					
< 15%	633	92.82	49	7.18	

≥ 15%	1338	93.50	93	6.50	0.556
Mean (Standard Deviation)	12.60 (7.91)		12.91 (8.24)		0.656
Plasma Viral Load (N=1897)(copies/mL) n ,%					
<100 000	831	94.97	44	5.03	
100 000 to 1 million	750	92.14	64	7.86	**0.030**
> 1 million	190	91.35	18	8.65	
Log_{10} Viral Load (N=1897)					
Mean (Standard Deviation)	11.64 (2.22)		12.04 (2.35)		**0.046**
Initial Regimen (N=2520) n, %					
NNRTI-based	1530	94.44	90	5.56	
PI-based	818	90.89	82	9.11	**0.001**

[1] P value for chi squared test for categorical variables, Student's t test for normally distributed continuous variables and Wilcoxon Rank-sum test for non-normal continuous variables

[2] WHO classification of HIV-related immunodeficiency in children according to age (See Table 2.1 for details)

The baseline median age among those who did not subsequently become LTFU was 4.60 years (IQR 1.79 – 7.43) and was significantly higher than that of children who became LTFU (median 2.83 IQR 1.21 – 5.53, p<0.001). Children who became LTFU had lower baseline HAZ (mean-2.66 SD 1.55) compared to those who did not (mean-2.40 SD 1.34, p=0.037). Those who became LTFU had higher log_{10} viral load (mean 12.04 SD 2.22) compared to those who did not (mean 11.64 SD 2.35, p=0.046).

The variables initial regimen, age group, plasma HIV viral load group, WHO clinical stage and primary caregiver relationship had significant associations with LTFU.

3.2 Loss to Follow-up

3.2.1 Overall Loss to Follow-up

During the study period (01 April 2004 to 30 September 2008) a total of 174 children became lost to follow-up out of the 2536 enrolled between 01 April 2004 and 31 December 2008. These children contributed a total of 6713.52 child-years and the overall incidence of LTFU during the entire study period was 2.59 per 100 child-years (95% CI 2.23 – 3.01).The median follow up time since ART initiation was 2.61 years (range 0.25 – 5.49 years).

Figure 2 and Table 3 show the Kaplan Meier cumulative probabilities of LTFU over the entire study period. The one-year and 2-year risk of LTFU were 2.85% (95% CI 2.26 – 3.59) and 5.22% (95% CI 4.36 – 6.25) respectively. The five year cumulative probability of LTFU was 11.64% (95% CI 9.65 – 14.01).

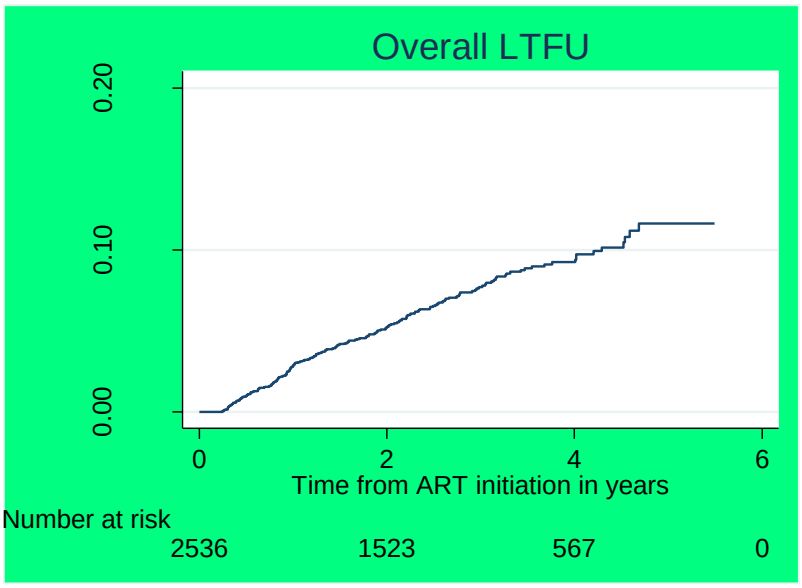

Figure 2 : Kaplan-Meier Estimates of Loss to Follow-up

Table 3 : Cumulative Probability of LTFU

Time	Cumulative Probability of LTFU (%) (95%CI)	
6 months	0.99	(0.67 – 1.47)
12 months	2.85	(2.26 – 3.59)
18 months	4.19	(3.44 – 5.09)
2 years	5.22	(4.36 – 6.25)
2.5 years	6.55	(5.54 – 7.73)
3 years	7.71	(6.57 – 9.04)
3.5 years	8.87	(7.59 – 10.36)
4 years	9.25	(7.91 -10.79)
4.5 years	10.15	(8.64 – 11.91)
5 years	11.64	(9.65 – 14.01)
5.5 years	11.64	(9.65 -14.01)

Table 4 shows period incidence rates of LTFU at specified 6-month follow-up periods. The period incidence rate was initially high, being 3.73 per 100 child-years (95% CI 2.78

– 5.01) in the period 6 months – 1 year. From one year of follow-up to 3.5 years the period incidence rate varied little, ranging from 2.14 to 2.77 per 100 child-years. Thereafter it was erratic and there were fewer children who had been followed up for more than 3.5 years as reflected by decreasing person-time contributed and the wider confidence intervals of the LTFU rates.

Table 4 : Period Incidence Rate of LTFU at specified times after HAART initiation

Period	Person-time in Child-years	Failures (Number of children LTFU)	LTFU Rate Per 100 child- years (95%CI)
6 months – 1 year	1178.08	44	3.73 (2.78 – 5.01)
1 year – 18 months	1009.26	28	2.77 (1.92 – 4.02)
18 months – 2 years	839.52	18	2.14 (1.35 – 3.40)
2 years – 2.5 years	703.85	20	2.84 (1.83 – 4.40)
2.5 years – 3 years	597.42	15	2.51 (1.51 – 4.16)
3 years – 3.5 years	464.99	12	2.58 (1.47 – 4.54)
3.5 years – 4 years	346.15	3	0.87 (0.27– 2.69)
4 years – 4.5 years	215.47	5	2.32 (0.97 – 5.57)
4.5 years – 5 years	85.05	4	4.70 (1.77 – 12.53)
Total	6713.52	174	2.59 (2.23 – 3.01)

3.2.2 Predictors of Loss to Follow-up

Kaplan Meier estimates of the probability of LTFU by variables with significant log rank tests ($p<0.05$) are presented below Figures 3 to 6. Significant trend tests are also reported.

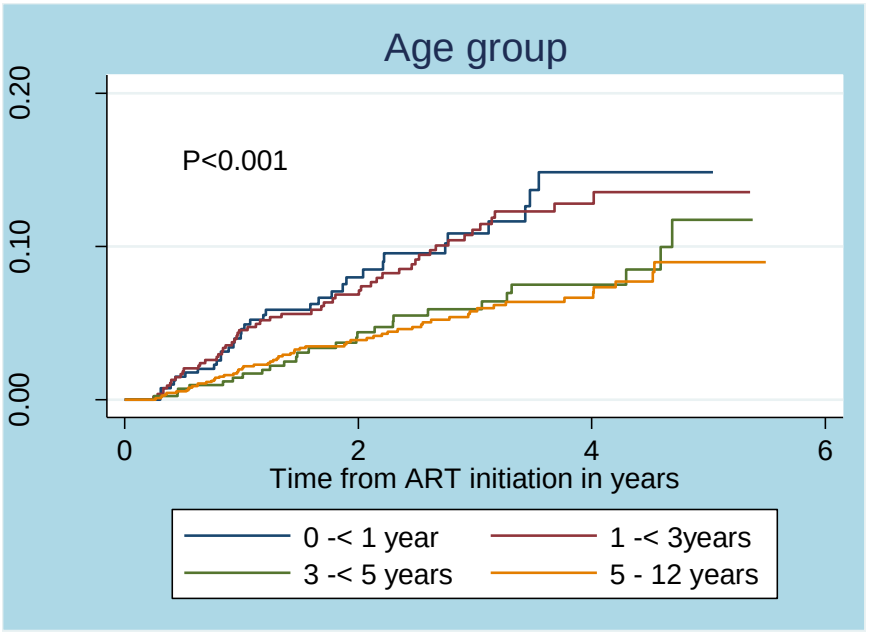

Figure 3 : Kaplan Meier estimates of LTFU by age group

Younger children were more likely to become LTFU compared to older children. The logrank test of equality of survival functions was significant (p<0.001).The trend test was also significant p<0.001.

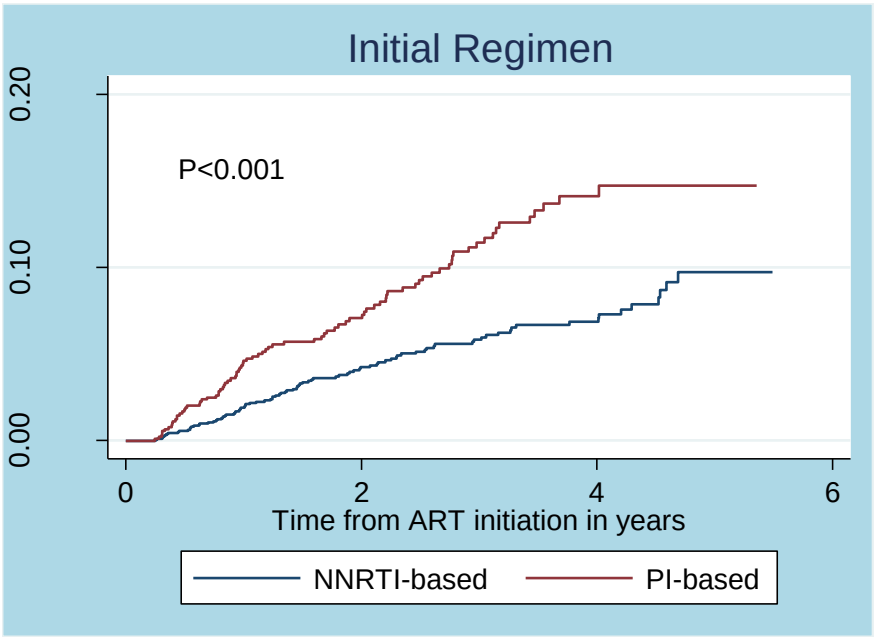

Figure 4 : Kaplan Meier estimates of LTFU by initial regimen

Children who were initiated on a PI-based regimen (protease inhibitor) were more likely to become LTFU compared to those initiated on a NNRTI-based (non-nucleoside reverse transcriptase inhibitor) regimen.

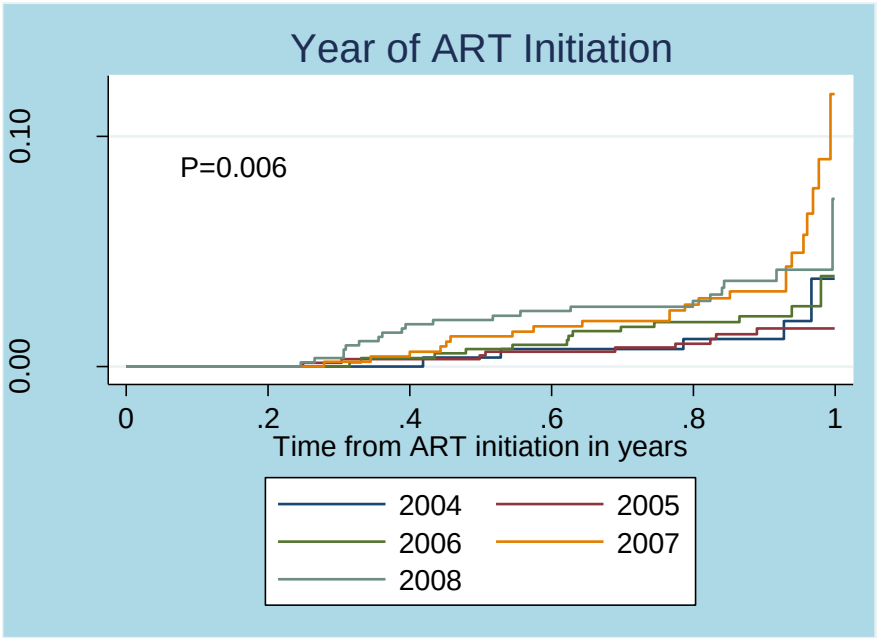

Figure 5 : Kaplan Meier estimates of LTFU by year of HAART initiation in the first year of follow-up

Children who initiated HAART in 2007 and 2008 had a higher probability of LTFU than those who initiated HAART during or before 2006. The trend test was significant p=0.001.

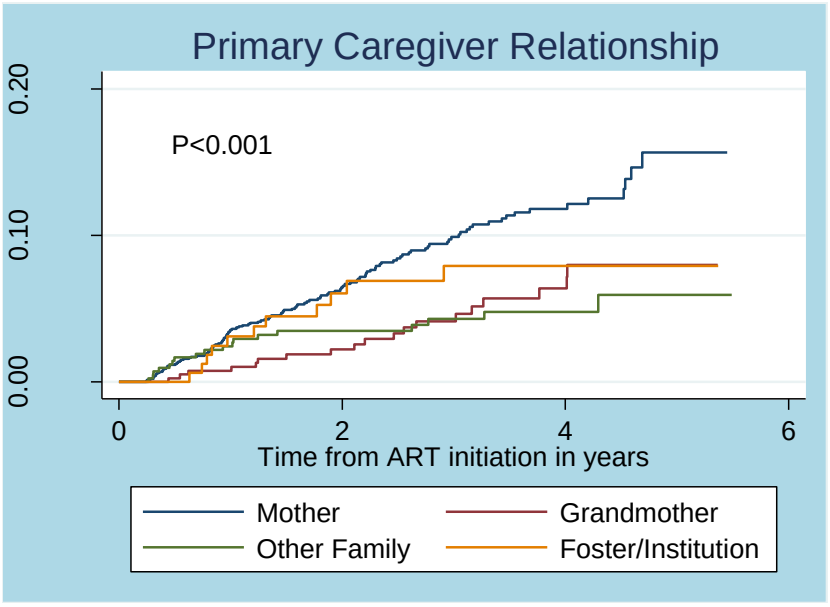

Figure 6 : Kaplan Meier estimates of LTFU by primary caregiver relationship

Children who had their mothers as primary caregivers at HAART initiation had the highest LTFU. Those in foster care or institutions had higher LTFU than those being taken care of by their grandmothers or other relatives. The trend test was significant p=0.001.

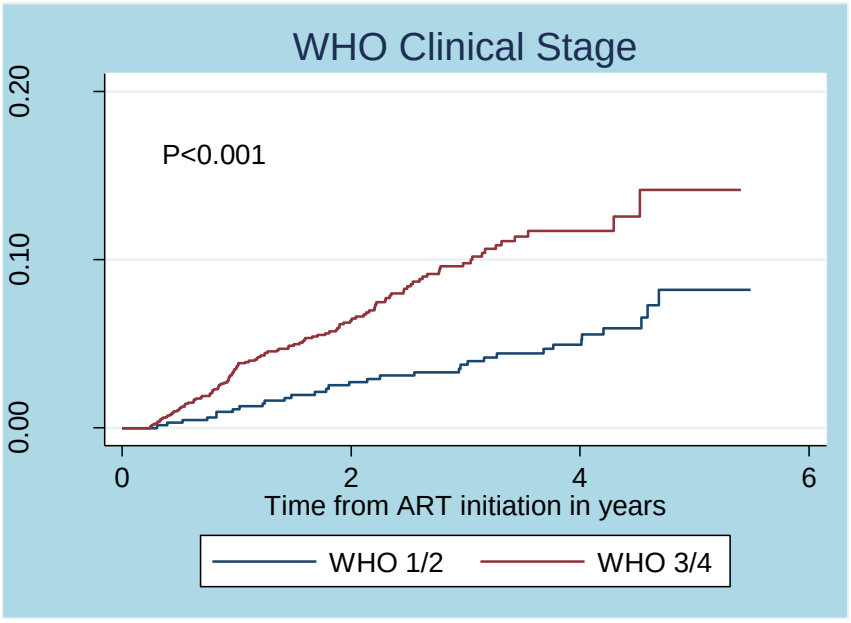

Figure 7 : Kaplan Meier estimates of LTFU by WHO clinical stage

Children with more advanced clinical disease (WHO clinical stages 3 or 4) were more likely to be LTFU than those with WHO clinical stages 1 or 2.

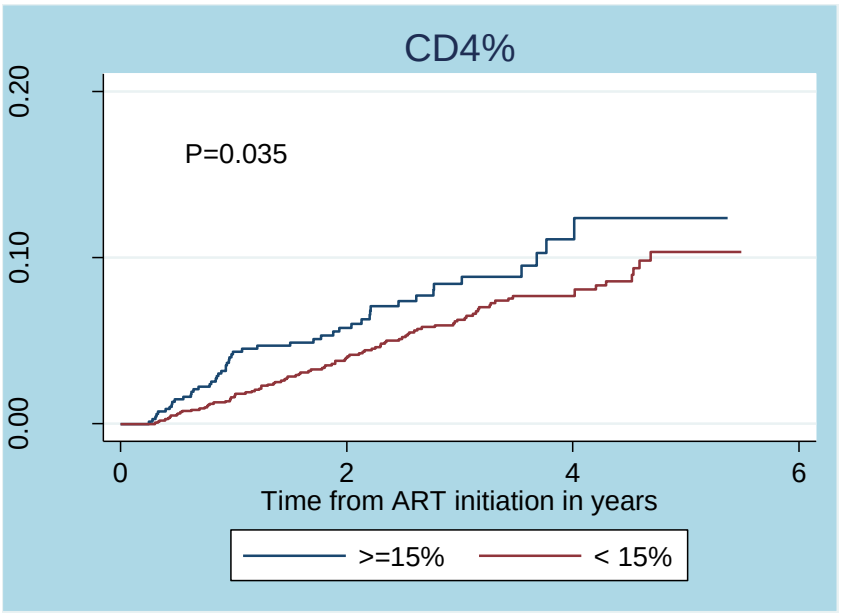

Figure 8 : Kaplan Meier estimates of LTFU by CD4 cell percentage

Children with a CD4 cell percentage of less than 15 were less likely to become LTFU than those with CD4 percentage equal or greater to 15.

Table 5 : Univariate Cox Proportional Hazards Model: LTFU

Characteristic	Hazard Ratio	95% Confidence Interval	P Value
Sex (N=2534)			
Male	1		
Female	0.93	0.69 – 1.25	0.628
Age Group at HAART initiation (N=2536)			
0-11.9months	1		
12months-35.9months	0.92	0.60 – 1.41	0.688
36months -59.9months	0.54	0.32 – 0.90	**0.018**
60months-12years	0.49	0.32 – 0.74	**0.001**
Age at HAART initiation (continuous)	0.90	0.86 – 0.95	**<0.001**
Year of Starting HAART[1] (N=2536)			
2004	1		
2005	0.77	0.26 – 2.29	0.633
2006	1.28	0.45 – 3.58	0.644
2007	2.60	0.98 – 6.85	0.054
2008	2.16	0.81 – 5.76	0.124

Primary Caregiver (N=2498)			
Mother	1		
Grandmother	0.48	0.30 – 0.78	**0.003**
Other Family	0.44	0.27 – 0.72	**0.001**
Foster Care/Institution/Neighbour/Guardian	0.67	0.36 – 1.23	0.196
Weight-for-age Z score (N=1932)			
>-2 (Not underweight)	1		
-2 to -3 (Moderately underweight)	1.16	0.76 – 1.76	0.492
<-3 (Severely underweight)	1.58	1.04 – 2.40	**0.031**
Height-for-age Z score (N=1917)			
>-2 (No stunting)	1		
-2 to -3 (Moderate stunting)	1.31	0.83 – 2.08	0.242
<-3 (Severe stunting)	1.68	1.09 – 2.59	**0.019**
Weight-for-height Z score (N=1844)			
>-2 (No wasting)	1		
-2 to -3 (Moderate wasting)	1.26	0.72 – 2.20	0.418
<-3 (Severe wasting)	0.61	0.19 – 1.92	0.397
Immune suppression[2] (N=2098)			
Not significant/Mild	1		
Advanced/Severe	0.70	0.34 – 1.43	0.325
WHO Clinical Stage (N=2256)			
1/2	1		
3/4	2.34	1.57 – 3.48	**<0.001**
TB prior to HAART(N=2520)			
No	1		
Yes	0.93	0.69 – 1.27	0.652
CD4 cell % (N=2113)			
≥ 15%	1		
< 15%	0.69	0.49 – 0.98	**0.036**
CD4 cell % (continuous)	0.99	0.97 – 1.03	0.896
Plasma Viral Load (N=1897)(copies/mL)			
<100 000	1		
100 000 to 1 million	1.42	0.97 – 2.08	0.075
> 1 million	1.74	1.01 – 3.01	**0.047**
Log_{10} Viral Load (N=1897)	1.07	0.98 – 1.16	0.116
Initial Regimen (N=2520)			
NNRTI-based	1		
PI-based	1.93	1.43 – 2.60	**<0.001**

[1] Analysis of the variable "Year of HAART initiation" was restricted to 1 year of follow-up to minimize the effect of time on this variable

[2] WHO classification of HIV-related immunodeficiency in children according to age (See Table 2.1 for details)

Cox proportional hazards models were fitted to identify predictors of LTFU. The variable primary caregiver relationship violated the proportional hazards assumption. All other

variables fulfilled the assumption of proportional hazards (See Appendix 4: Tests for proportional hazards assumption). The variable year of HAART initiation interacted with time and the analysis of this variable was restricted to the first year of follow-up. Table 5 shows hazard ratios for each variable in univariate analysis.

In univariate analysis, severe underweight (WAZ<-3), severe stunting (HAZ <-3) and WHO stage 3 or 4 were significantly associated with a greater risk of LTFU. Children who were severely underweight had a 58% greater chance of LTFU compared to those who were not underweight. Severely stunted children had a 68% greater risk of LTFU than children who were not stunted. Children who were WHO stage 3 or 4 were 2.34 times more likely to become LTFU compared to those who were WHO stage 1 or 2 at baseline.

Having a grandmother or other relatives as primary caregivers at baseline was significantly associated with a lower risk of LTFU than being cared for by one's own mother. Older children were less likely to become LTFU, the hazard of LTFU decreasing by 10% for every 1 year increase in age. CD4 cell percentage of less than 15 was associated with a 31% less chance of LTFU. This association was lost when CD4 cell percentage was analysed as a continuous variable. Children with a plasma HIV viral load of greater than one million copies per ml were 1.74 times more likely to become LTFU than those with a viral load of less than 100 000 copies/ml. Children taking PI-based regimens were nearly twice as likely to become LTFU as those taking NNRTI-based regimens.

Year of HAART initiation was not associated with LTFU in the first year of follow-up.

Sex of child, having TB prior to HAART initiation, weight-for-height z-score, immune suppression and $\log_{10}$ viral load had no significant association with LTFU in univariate analyses.

Table 6 : Multivariate Cox Proportional Hazards Model: LTFU

Characteristic	Hazard Ratio	95% Confidence Interval	P Value
Age at HAART Initiation	0.91	0.84 – 0.99	**0.026**
WHO Stage			
1/2	1		
3/4	2.14	1.22 – 3.73	**0.008**
Height-for-age Z score			
>-2 (Not stunted)	1		
-2 to -3 (Moderately stunted)	1.10	0.65 – 1.85	0.725
<-3 (Severely stunted)	1.07	0.62 – 1.83	0.816
CD4 cell % (N=2113)			
≥ 15%	1		
< 15%	0.67	0.43 – 1.04	0.075
Plasma Viral Load (N=1897)(copies/mL)			
<100 000	1		
100 000 to 1 million	1.40	0.87 – 2.24	0.167
> 1 million	1.31	0.66 – 2.60	0.440

Table 6 shows hazard ratios for variables included in the multivariate Cox proportional hazards model. The variable primary caregiver relationship was excluded from the model because it violated the proportional hazards assumption. Age and initial regimen were collinear since children were initiated on either a PI-based regimen or NNRTI-based regimen according to their age. The variable regimen was thus excluded from the model.

Young age and WHO clinical stage 3/4 independently predicted LTFU. Those with WHO clinical stage 3 or 4 were 2.14 times more likely to be LFTU compared to those who had WHO stage 1 or 2. Older children were less likely to become LTFU, the hazard of LTFU decreasing by 9% for every 1 year increase in age. Severe stunting, CD4 cell percentage ≥ 15 and plasma HIV viral load >1million copies/ml were longer associated with LTFU in the multivariate model. The global test for the overall model showed that the proportional hazards assumption had not been violated, p=0.898.

Table 6.1: Multivariate Cox Proportional Hazards Model Restricting Time to 1 year: LTFU

Characteristic	Hazard Ratio	95% Confidence Interval	P Value
Age at HAART Initiation	0.94	0.85 – 1.04	0.222
WHO Stage			
1/2	1		
3/4	2.54	1.06 – 6.09	**0.037**
CD4 cell %			
≥ 15%	1		
< 15%	0.48	0.26 – 0.86	**0.014**
Primary Caregiver			
Mother	1		
Grandmother	0.27	0.06 – 1.15	0.076
Other Family	1.01	0.46 – 2.24	0.974
Foster Care/Institution/Neighbour/Guardian	0.89	0.27 – 2.92	0.852

Table 6.1 shows a multivariate model in which follow-up time was restricted to the first 12 months to account for non-proportional hazards. After restricting follow-up time to 12 months, all variables met the proportional hazards assumption (See Appendix 4). WHO stage 3/4 and CD4% were significantly associated with LTFU. Age at HAART initiation no longer predicted LTFU after restricting follow-up time to 12 months.

3.3 Temporary Interruption of Follow-up

3.3.1 Overall Temporary Interruption of Follow-up

During the study period (01 April 2004 to 30 September 2009) a total of 338 children ever temporarily interrupted follow-up (i.e. returned to care after absence from the clinic for at least 6 months). Only the first episode of TIFU per child was counted (single-failure per subject analysis).

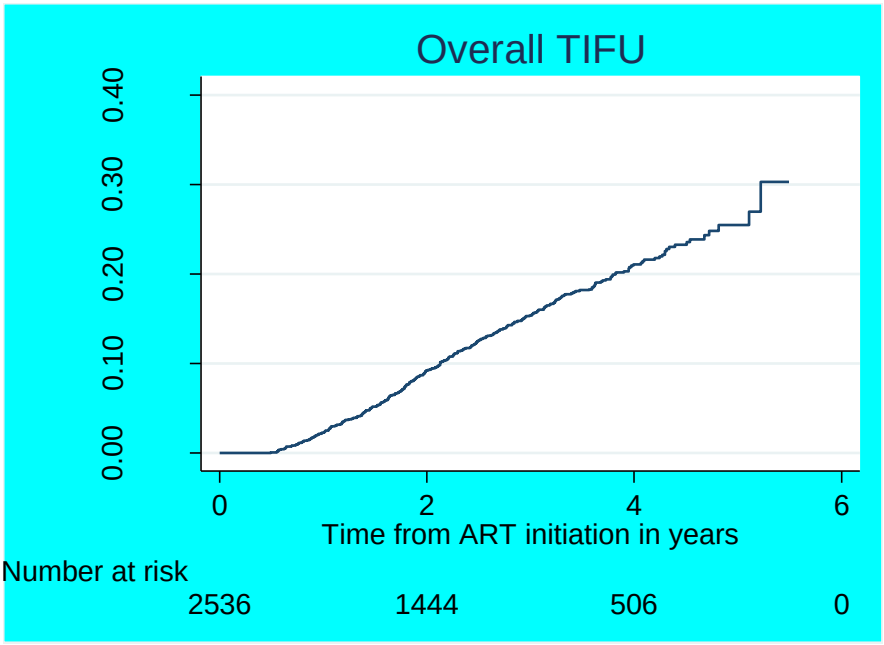

Figure 9 : Kaplan-Meier Estimates of Temporary Interruption of Follow-up

Figure 9 and Table 7 show the Kaplan Meier cumulative probabilities of TIFU up to a maximum follow-up time of 5 years. The one-year and 2-year risk of TIFU were 2.29% (95% CI 1.76 – 2.98) and 9.21% (95% CI 8.0 – 10.58) respectively. The five year cumulative probability of TIFU was 25.47% (95% CI 22.47 – 28.79). The cumulative probability of TIFU rose steadily over time.

Table 7 : Cumulative Probability of TIFU

Time	Cumulative Probability of TIFU (%) (95%CI)
12months	2.29 (1.76 – 2.98)
2years	9.21 (8.0 – 10.58)
3years	15.37 (13.72 – 17.21)
4years	21.08 (18.94 -23.42)
5years	25.47 (22.47 – 28.79)

Table 8 shows period incidence rates of TIFU at 1 year follow-up periods up to a maximum follow-up time of 5 years. The period from 1 – 2 years had the highest incidence of TIFU [7.18 per 100 child-years (95% CI 6.04 – 8.53)] and the period from 0 – 1 year had the lowest incidence of TIFU [2.22 per 100 child-years (95% CI 1.70 –

2.90)]. The overall incidence of TIFU was 5.23 per 100 child-years (95% CI 4.70 – 5.82).

Table 8 : Period Incidence Rate of TIFU at Specified Times after HAART Initiation

Period	Person-time in Child-years	Failures (Number of children TIFU)	TIFU Rate Per 100 child-years (95%CI)	
0 months – 1 year	2430.18	54	2.22	(1.70 – 2.90)
1 year – 2 years	1796.62	129	7.18	(6.04 – 8.53)
2 years – 3 years	1216.55	86	7.07	(5.72 – 8.73)
3 years – 4 years	734.12	51	6.95	(5.27 – 9.14)
4 years – 5 years	267.74	16	5.97	(3.66 – 9.75)
Total	6458.06	338	5.23	(4.70 – 5.82)

3.3.2 Predictors of Temporary Interruption of Follow-up

Kaplan Meier estimates of the probability of TIFU by variables with significant log rank tests ($p<0.05$) are presented below in Figures 10 to 12.

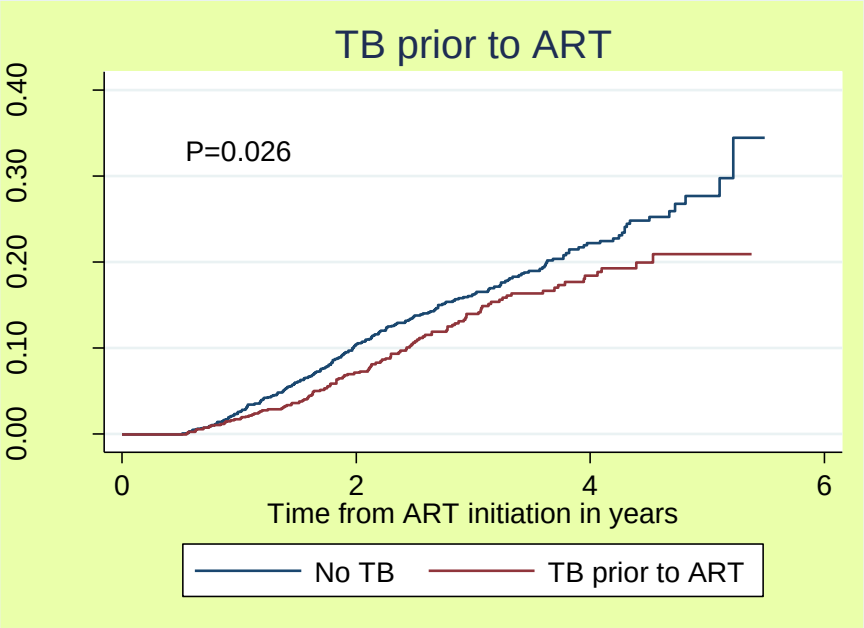

Figure 10 : Kaplan-Meier Estimates of TIFU by TB prior to HAART initiation

Children who had ever had TB prior to HAART initiation were less likely to temporarily interrupt follow-up than those who had not.

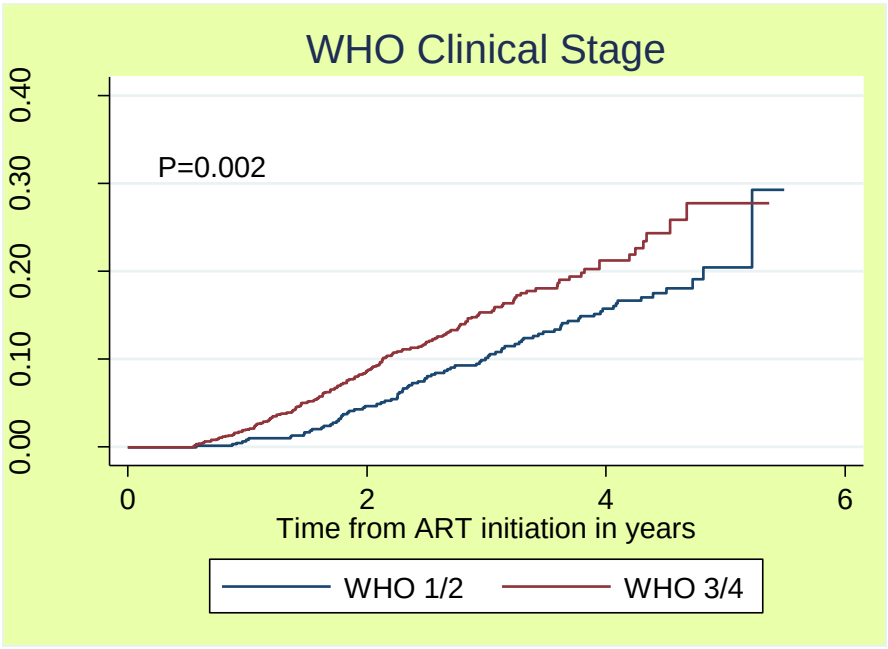

Figure 11 : Kaplan-Meier Estimates of TIFU by WHO clinical stage

Children with WHO clinical stages 3 or 4 had a greater risk of LTFU than those with WHO clinical stages 1 or 2.

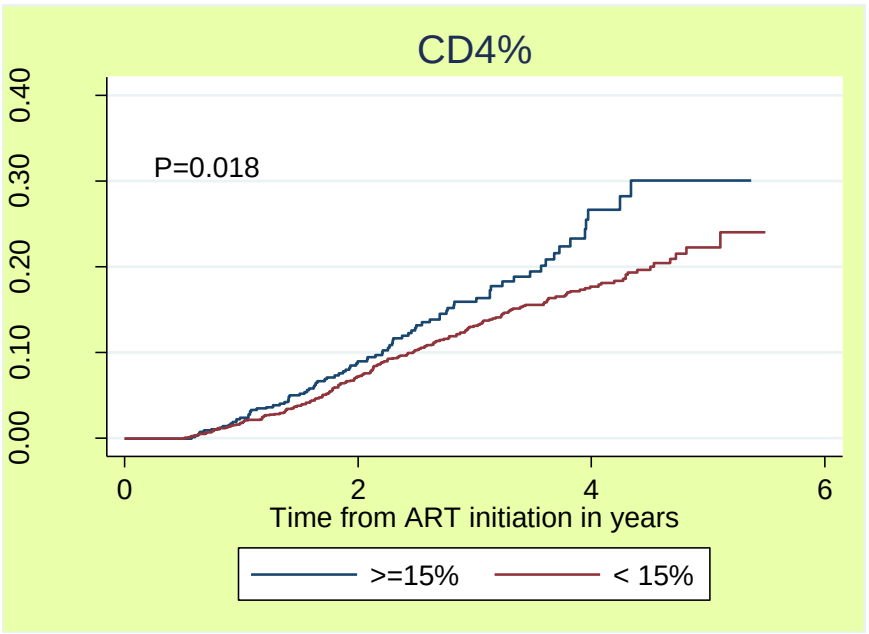

Figure 12 : Kaplan-Meier Estimates of TIFU by CD4 cell percentage

Children with CD4 cell percentage of ≥ 15% had higher risk of temporarily interrupting follow-up than those with CD4 cell percentage <15.

Table 9 : Univariate Cox Proportional Hazards Model: TIFU

Characteristic	Hazard Ratio	95% Confidence Interval	P Value
Sex (N=2534)			
Male	1		
Female	0.92	0.74 – 1.14	0.455
Age Group at HAART initiation (N=2536)			
0-11.9months	1		
12months-35.9months	0.64	0.46 – 0.88	**0.006**
36months -59.9months	0.48	0.33 – 0.69	
60months-12years	0.54	0.40 – 0.72	**<0.001**
			<0.001
Age at HAART initiation (continuous)	0.95	0.92 – 0.97	**0.007**
Year of Starting HAART[1] (N=2536)			
2004	1		
2005	0.79	0.29 – 2.13	0.640
2006	1.25	0.49 – 3.24	0.638
2007	1.02	0.37 – 2.81	0.968
2008	1.16	0.43 – 3.10	0.765
Primary Caregiver (N=2498)			
Mother	1		
Grandmother	0.52	0.37 – 0.73	**<0.001**
Other Family	0.51	0.36 – 0.71	**<0.001**
Foster Care/Institution/Neighbour/Guardian	0.78	0.51 – 1.19	0.249
Weight-for-age Z score (N=1932)			
>-2 (Not underweight)	1		
-2 to -3 (Moderately underweight)	0.73	0.51 – 1.04	0.080
<-3 (Severely underweight)	1.30	0.94 – 1.79	0.110
Height-for-age Z score (N=1917)			
>-2 (No stunting)	1		
-2 to -3 (Moderate stunting)	1.11	0.79 – 1.56	0.560
<-3 (Severe stunting)	1.14	0.82 – 1.60	0.432
Weight-for-height Z score (N=1844)			
>-2 (No wasting)	1		
-2 to -3 (Moderate wasting)	1.24	0.79 – 1.93	0.346
<-3 (Severe wasting)	1.47	0.82– 2.63	0.202
Immune suppression[2] (N=2098)			
Not significant/Mild	1		
Advanced/Severe	1.03	0.55 – 1.93	0.931
WHO Clinical Stage (N=2256)			
1/2	1		

3/4	1.50	1.15 – 1.96	**0.003**
TB prior to HAART(N=2520)			
No	1		
Yes	0.77	0.62 – 0.97	**0.026**
CD4 cell % (N=2113)			
≥ 15%	1		
< 15%	0.74	0.57 – 0.95	**0.018**
CD4 cell % (continuous)	0.99	0.97 – 1.03	0.896
Plasma Viral Load (N=1897)(copies/mL)			
<100 000	1		
100 000 to 1 million	1.15	0.87 – 1.51	0.317
> 1 million	1.78	1.22 – 2.61	**0.003**
Log_{10} Viral Load (N=1897)	1.08	1.01 – 1.14	**0.016**
Initial Regimen (N=2520)			
NNRTI-based	1		
PI-based	1.49	1.20 – 1.85	**<0.001**

[1] Analysis of the variable "Year of HAART initiation" was restricted to 1 year of follow-up to minimize the effect of time on this variable

[2] WHO classification of HIV-related immunodeficiency in children according to age (See Table 2.1 for details)

Cox proportional hazards models were fitted to identify predictors of TIFU. The variables age, plasma HIV viral load group and primary caregiver relationship violated the proportional hazards assumption. All other variables fulfilled the assumption of proportional hazards (See Appendix 4). Table 9 shows hazard ratios for each variable in univariate analyses.

WHO clinical stage, history of TB prior to HAART, CD4 cell percentage and log_{10} plasma HIV viral load had significant associations with TIFU in univariate analysis. Children with WHO clinical stage 3/4 were 1.5 times more likely to interrupt follow-up than those with stages 1/2. Children with a positive history of TB prior to HAART initiation had a 23% less risk of TIFU than those without. Children on PI-based regimens had greater risk of TIFU than those on NNRTI-based regimens (HR 1.49 95% CI 1.20 – 1.85, p<0.001).

Sex of child, weight-for-height z-score, height-for-age z-score, weight-for-age z-score, year of HAART initiation and immune suppression had no significant association with TIFU in univariate analyses.

Table 10 : Multivariate Cox Proportional Hazards Model: TIFU

Characteristic	Hazard Ratio	95% Confidence Interval	P Value
Log_{10} Viral Load (N=1897)	1.04	0.97 – 1.13	0.262
WHO Stage			
1/2	1		
3/4	1.16	0.81 – 1.66	0.416
TB prior to HAART(N=2520)			
No	1		
Yes	0.96	0.70 – 1.30	0.779
CD4 cell % (N=2113)			
≥ 15%	1		
< 15%	0.76	0.54 – 1.07	0.115
Weight-for-age Z score (N=1932)			
>-2 (Not underweight)	1		
-2 to -3 (Moderately underweight)	0.66	0.45 – 0.99	**0.043**
<-3 (Severely underweight)	0.89	0.59 – 1.36	0.608
Initial Regimen (N=2520)			
NNRTI-based	1		
PI-based	1.67	1.18 – 2.35	**0.004**

Table 10 shows hazard ratios of variables which were included in the multivariate model. The variables age, plasma HIV viral load group and primary caregiver relationship were excluded from the model because they violated the proportional hazards assumption.

Initiating HAART on a PI-based regimen and being moderately underweight independently predicted TIFU. WHO clinical stage, CD4 cell percentage and history of TB prior to HAART initiation no longer predicted TIFU in the multivariate model. The global test for the overall model was not significant (p=0.831).

Table 10.1: Multivariate Cox Proportional Hazards Model Restricting Time to 1year: TIFU

Characteristic	Hazard Ratio	95% Confidence Interval	P Value
WHO Stage			
1/2	1		
3/4	1.74	0.56 – 5.4	0.339
CD4 cell % (N=2113)			
≥ 15%	1		
< 15%	0.81	0.34 – 1.92	0.632
Weight-for-age Z score (N=1932)			
>-2 (Not underweight)	1		
-2 to -3 (Moderately underweight)	0.82	0.29 – 2.31	0.711
<-3 (Severely underweight)	0.53	0.17 – 1.71	0.291
Initial Regimen (N=2520)			
NNRTI-based	1		
PI-based	4.39	1.72 – 11.22	**0.002**

Table 10.1 shows a multivariate model in which follow-up time was restricted to the first 12 months to account for non-proportional hazards. After restricting follow-up time to 12 months, all variables met the proportional hazards assumption (See Appendix 4). Children on a PI-based initial regimen were 4.39 times more likely to be temporarily interrupt follow-up compared to those on an NNRTI based regimen. WAZ no longer predicted TIFU after restricting follow-up time to 12 months.

3.4 Reasons for Clinic Non-attendance

A total of 2244 children who had missed at least one clinic appointment were traced between 18 June 2007 and 11 December 2010. The children had missed appointments between 17 June 2007 and 18 November 2010. There were 3460 recorded attempts to trace these children. Twelve percent (417) of the times, the caregivers could not be contacted. Reasons for failure to contact the caregivers recorded by the counsellors included: lack of documented contact details, wrong contact number, caregiver was not at home and a message was left and the phone not being answered.

Figure 13 and Table 11 show the reasons given for missing a clinic appointment among those who were contacted.

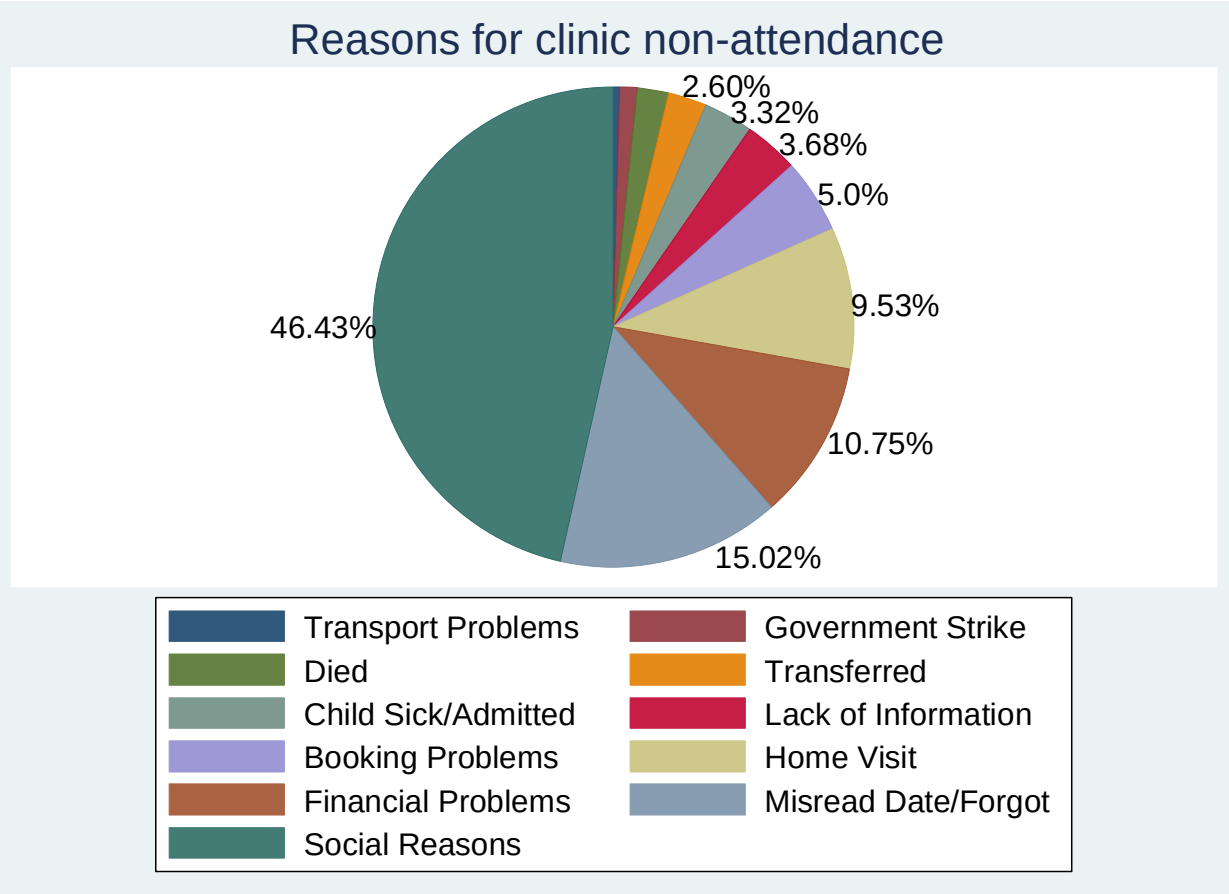

Figure 13 : Reasons for Clinic non-attendance

Table 11 : Reasons for Clinic non-attendance

Reason for Clinic non-attendance	Frequency	Percentage
Died	64	2.10
Transferred	79	2.60
Home Visit	290	9.53
Booking Problems	152	5.00
Misread/Forgot	457	15.02
Child sick/admitted	101	3.32
Financial Problems	327	10.75
Social Problems	1413	46.43
Lack of Information	112	3.68
Transport Problems	14	0.46
Government Strike	34	1.12
Total	**3043**	**100**

The most common reasons for clinic non-attendance were social reasons (46.43%) and a further analysis of social reasons is given in Figure 14 and Table 12. After social reasons misreading or forgetting the clinic appointment accounted for 15.02%, followed by financial reasons (10.75%), home visits(i.e. clinic staff had visited child's home and rebooked child or brought treatment) (9.53%) and booking problems (5.00%). Just over two percent had died and 2.60% were transfers. Other reasons given included lack of information, the child being sick or admitted, the public service strike in 2010 and transport problems.

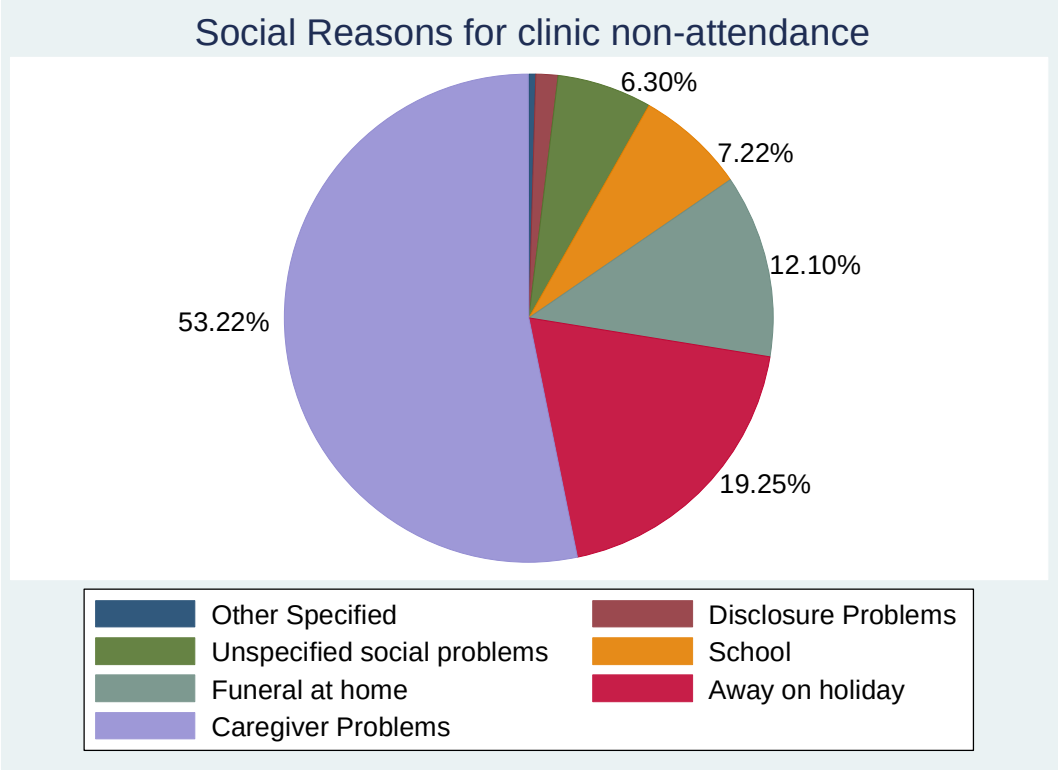

Figure 14 : Social Reasons for clinic non-attendance

Table 12 : Social Reasons for clinic non-attendance

Social Reason Given	Frequency	Percentage
Caregiver Problems	752	53.22
School	102	7.22
Funeral at home	171	12.10
Away on holiday	272	19.25
Unspecified social reasons	89	6.30
Other specified social reasons	7	0.50
Disclosure problems	20	1.42
Total	1413	100

Figure 14 and Table 12 show social reasons given for missing scheduled clinic visits. Caregiver-related problems (53.22%) were the commonest social reasons given for missing a clinic visit. Caregiver-related problems included the following: the caregiver being committed elsewhere, sick, at work, not available, taking another child to the clinic and being arrested. Other caregiver-related problems included the child being orphaned and the lack of a committed caregiver and the child being forcefully taken from their place of residence by either of the parents.

Children being away on holiday accounted for 19.25% of social reasons. Other social reasons given included having a funeral at home (12.10%), schooling activities (7.22%) such as school trips or exams and disclosure problems (1.42%). More than six percent of the times the actual social reason given was not specified or documented and only the words “social reason” were recorded. Other specified social reasons which were less common included refusal of parent or child to come to the clinic, denial that the child actually had HIV infection and having a cleansing ritual ceremony at home.

Chapter 4: Discussion

The study aimed to determine the rate of LTFU in children receiving ART and to identify baseline characteristics associated with LTFU and TIFU in these children. The findings of the study are discussed below with respect to each objective and the chapter ends with a discussion of possible limitations of the study.

4.1 Baseline Characteristics

As in other paediatric HIV care programmes (5, 8), the majority of children initiated HAART at advanced stages of the disease having WHO stage 3 or 4 and advanced or severe immune suppression. The children who were LTFU were younger, had lower HAZ, higher $\log_{10}$ viral load, and were more likely to be WHO stage 3 or 4 and to have their mother as their primary caregiver. There are some similarities and differences in baseline characteristics of those LTFU with those found in other studies. Haitian children who were LTFU had lower baseline median WAZ (-3, IQR -3.7 to -1.8) than those who were not LTFU but had no other significant differences at baseline with those retained in care (25). The mean age at baseline of children who were lost to follow-up was lower (4.30 years) than that of children who were retained in care (6.14 years) in a study done in Lilongwe, Malawi (20). Findings in this study are consistent with the Malawian study with median age at baseline being lower in children who were LTFU.

4.2 Loss to Follow-up

4.2.1 Overall Loss to Follow-up

The cumulative probabilities of LTFU at 6 months, 12 months and 2 years were found to be 0.9% (95% CI 0.67 – 1.47), 2.85% (95% CI 2.26 – 3.59) and 5.22% (95% CI 4.36 – 6.25) respectively. These are much lower than those found in the KIDS ART LINC collaboration study which were 2.6% (95% CI 2.0 – 3.4), 5.0% (95% CI 4.1 – 6.1) and 10.3% (95% CI 8.9 – 11.9) at 6 months, 12 months and 2 years respectively (7). This was probably because children who had been on HAART for less than 3 months at their last clinic visit were excluded in this study, reducing the effect of unreported deaths on LTFU.

4.2.2 Predictors of Loss to Follow-up

In univariate analysis, younger age, severe stunting (HAZ <-3), severe underweight (WAZ <-3), WHO clinical stage 3 or 4, CD4 cell percentage greater than 15%, plasma HIV viral load of greater than one million copies/ml, being on a PI-based regimen and having one's own mother as a primary caregiver predicted LTFU. After adjusting for WHO clinical stage, HAZ, age, CD4 percentage and viral load, independent predictors of LTFU were WHO clinical stage 3 or 4 and younger age. Advanced or severe immune suppression and weight-for-height z-score were not associated with LTFU.

In the KIDS ART LINC collaboration, contrary to our findings, only severe clinical status (as per WHO age-specific categories) was significantly associated with LTFU (7). A study in Western Kenya by Braitstein et al found severe immune suppression (as per WHO age-specific categories), and severe weight-for-height z-score predictive of LTFU in unadjusted analysis (23). In the same study; older children (per year) and children enrolled in later time periods were less likely to be LTFU in univariate analysis. Severe immune suppression is the only predictor that remained significant in adjusted analysis in the same study (23). The finding that advanced or severe immune suppression does not predict LTFU sharply contrasts other findings. Severe immune suppression may be responsible for the high mortality in the first 3 months of HAART, since children with HAART duration of less than 3 months were excluded, the effect of unreported deaths on LTFU was less and severe immune suppression no longer predicted LTFU. The finding that younger children are more likely to become LTFU was similar to what Brainstien et al found.

In a study of patient outcomes in the Thailand paediatric ART programme, WHO clinical stage C independently predicted LTFU (24). This is consistent with WHO stage 3 or 4 independently predicting LTFU in our study. The study on outcomes of the South African paediatric national ART programme by the IeDEA-SA collaboration found that LTFU at one year increased from 2.2%(95% CI 1.1 – 4.7) in those who commenced HAART before 2004 to 8.2%(95% CI 7.1 – 9.4) in those who commenced treatment during or after 2006 (8). Similarly, the Kaplan Meier plot of LTFU in the first year on

HAART showed that children started on HAART in 2007 and 2008 were more likely to become LTFU compared to those started before or during 2006.

The finding that children staying with their own mothers at baseline were more likely to be LTFU can be explained by the possibility that a significant number of these mothers could have died during the follow-up period resulting in the children becoming LTFU.

4.3 Temporary Interruption of Follow-up

4.3.1 Overall Temporary Interruption of Follow-up

A total of 338 (13.33% of study sample) children interrupted follow-up for at least 6 months before returning to care during the study period. This showed that LTFU is not necessarily permanent.

The one-year and 2-year risk of TIFU were 2.29% (95% CI 1.76 – 2.98) and 9.21% (95% CI 8.0 – 10.58) respectively. The five year cumulative probability of TIFU was 25.47% (95% CI 22.47 – 28.79). While there are no studies to compare with, risk of TIFU was high and rose steadily over time and this might have implications on development of resistance to antiretroviral drugs in patients who temporarily interrupt follow-up.

Notably, there were very few episodes of TIFU in the first year of follow-up. The frequency of visits in the first year is much higher than in subsequent years and a shorter definition of TIFU in the first year might be appropriate.

4.3.2 Predictors of Temporary Interruption of Follow-up

In univariate analysis, viral load >1million copies/ml, younger age, not having TB prior to HAART initiation, WHO clinical stage, CD4% ≥ 15%, taking a PI-based regimen and having a mother as primary caregiver were associated with TIFU. In adjusted analysis, being moderately underweight and taking a PI-based independently predicted TIFU.

4.4 Reasons for Clinic Non-attendance

Reasons for failure to contact the caregivers included having no documented contact details, wrong contact number, caregiver was not at home and a message was left and

the phone not being answered. This just highlighted the need to have correctly recorded, detailed contact details and alternative contact numbers in patient files.

Most reasons for loss to follow-up given in previous studies are socio-economic (14, 15, 18, 29) and indeed social reasons (46.43%) and financial (10.05%) together accounted for the majority of reasons given. However, the reasons given were unique because the population was paediatric and the children were traced early and not after they had already been LTFU. Only 2.10% had died, but in some studies where adult patients are traced after LTFU mortality rates of 50% have been reported (18). Misreading or forgetting the clinic appointment accounted for 15.02% of reasons given. This may reflect on lack of commitment by caregivers or a need for innovative ways of reminding caregivers of clinic appointments e.g. bulk short message services sent to all caregivers a day before the clinic appointment.

Caregiver-related problems (53.22%) were the commonest social reasons given for missing a clinic visit. The adherence of children has been shown to be dependent on characteristics of the caregiver and the relationship with the caregiver in previous studies (26). Details of the caregiver-related problems such as the caregiver being committed elsewhere, caregiver being sick, at work, not available and taking another child to the clinic; highlight the problems that caregivers of HIV-infected children face. HIV is a family disease and it is possible that other siblings of the child or parents might be infected and also needing care. There is need for caregivers to identify secondary caregivers who can take the child to the clinic in the event that the primary caregiver is unable to. Sometimes a child was forcefully taken from their place of residence by either of the parents. Where both parents of a child are alive, the parent who brings the child to the clinic should be encouraged to involve the other parent in the care of the child so that they are aware of the treatment needs of the child.

Children being away on holiday accounted for 19.25% of social reasons and schooling activities such as school trips or exams accounted for 7.22%.This showed that HAART needs to be incorporated into the normal activities of lives of children living with HIV. There is need for proper planning between the clinic and the caregivers so that children

do not miss their visits for such reasons. Having a funeral at home accounted for 12.10% of social reasons and this might reflect HIV deaths in the family.

4.5 Limitations of the study

This was an observational retrospective study using secondary data from routine ART services and only allows analysis of that which was collected. Some variables which can be potential confounders might not have been collected. Additionally, data were collected through a multiple clerk single entry database, and had some missing information. Sometimes the actual reason given for missing appointments was not specified or documented and only “social reason” was recorded. More detail could have shed more light.

The WHO classification of malnutrition by z-score cut-off points of <-2 for moderate malnutrition (underweight, stunting or wasting) and <-3 for severe malnutrition (underweight, stunting or wasting), by definition, misclassifies 2.28% of children of normal nutrition in the reference population as moderately malnourished and 0.13% as severely malnourished (39) .This should be kept in mind when results of z-scores are interpreted.

In this study, baseline characteristics were modelled to identify predictors of LTFU. After 5 years of follow-up, baseline characteristics would not be as predictive as they would be with shorter follow-up durations. Models with time-varying co-variates would have better predicted LTFU especially at longer follow-up durations.

There might be some residual effect of mortality on LTFU even after excluding those with less than 3 months follow-up on ART. The period incidence of LTFU remains high for the period 6 months to 1 year compared to subsequent periods and WHO stages 3 or 4 (which is a marker of disease severity) predicted LTFU. These findings may reflect residual mortality.

4.6 Generalisability

The HSCC is one of the largest HIV paediatric cohorts in South Africa and is likely to be representative of urban paediatric HIV care in the South African public sector. However, the quality of care at a tertiary academic hospital is likely to be higher compared to that

at lower levels of care or that in the rural areas. Therefore caution should be taken when generalizing these results to HIV care programmes in rural settings.

Chapter 5: Conclusions and Recommendations

5.1 Conclusions

The cumulative probabilities of LTFU at 6 months, 12 months and 2 years were found to be 0.9% (95% CI 0.67 – 1.47), 2.85% (95% CI 2.26 – 3.59) and 5.22% (95% CI 4.36 – 6.25) respectively .These are much lower than those found in studies where children on HAART duration less than 3 months were included and may reflect on true LTFU with minimal effect of unreported early mortality.

WHO clinical stage 3 or 4 and younger age independently predicted LTFU. Independent predictors of TIFU were moderate underweight and being on a PI-based regimen. LTFU is not necessarily permanent with 13.33% children interrupting follow-up for at least 6 months before returning to care during the study period. The main reasons why children miss clinic appointments are social. Caregiver-related problems are important reasons for clinic non-attendance in children on HAART.

5.2 Recommendations

Children with WHO stage 3 or 4 stages are more likely to become LTFU and this suggests that starting children on HAART in earlier disease stages may reduce LTFU. Strategies to improve LTFU need to target younger children and there is need for further research to investigate why young children are especially vulnerable to LTFU.

While mortality and LTFU are important indicators of effectiveness of HIV care programmes, there is need to learn more about patients who temporarily interrupt follow-up. Caregivers of children who temporarily interrupt follow-up can potentially provide a unique opportunity for health workers to learn the true reasons why children get LTFU. Such caregivers may also be targeted for more intensive adherence counselling. Further studies on the implications of TIFU on the development of resistance to antiretroviral drugs are needed and children who temporarily interrupt follow-up can be targeted for resistance testing in such studies.

Children rely on their caregivers for treatment adherence and caregivers of HIV-infected children need support in the care of these children. Caregivers should be encouraged to

form support groups within their various communities to so that they can assist each other with care of children. Primary caregivers of children need to be encouraged to identify secondary caregivers who can bring the child to the clinic in the event that they cannot. Siblings of HIV-infected children need to be tested and if found to be HIV-positive, enrolled at the same clinic and given same appointments dates. There is need for innovative ways of reminding caregivers of clinic appointments e.g. bulk short message services sent to all caregivers a day before the clinic appointment. Contact details of caregivers need to be documented correctly and alternative contact details should also be documented for efficient patient tracing. There is need for proper planning between the clinic and the caregivers so that children do not interrupt their treatment for reasons such as school trips, exams or holidays.

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Appendices

APPENDIX 1: Defaulter Tracer Form

Defaulters Follow up Form, Harriet Shezi Paediatric HIV Clinic

Name of Counsellor Nokuphumelela Zwane Current Date / /

FAMILY DEMOGRAPHIC DATA ***(copy this data from the patient file prior to the follow up visit)***

Name of Caregiver: _____ Contact Number: _____

Street Address: _____

_____

PATIENT INFORMATION ***(copy this data from the patient file prior to the follow up visit)***

Name of child: Birth date of child: / / /

Dd mm yy

Sex: Male Female Is child on ART? Yes: No

Date of missed appointment: / / / Patient's Number _____

Dd mm yy

Date started on ART: / / / Adolescent: | *yes* | *no* |

dd mm yy

FOLLOW UP INFORMATION

1. Do you know that the child missed clinic appointment? Yes: No:

CONTACTED	OUTCOMES	REASONS FOR DEFAULTING
Yes	Multiple bookings/forgotten/Funeral @ home/away on holiday/other booking problems/lack of information/disclosure problems/Caregiver had other commitments/ Caregiver was sick/orphaned and no committed caregiver / home visit/left message/ no contact/financial problem/ /misread the date/misplaced appointment card forgotten the date/came late and was rebooked/rescheduled appointment/caregiver was @ work/ Admission/writing exams/transferred /died/took another child to the clinic. Social problems Other, specify	.....
No		.....
		.....
		.....

2. Please explain to me things that made it difficult for you to bring the child to the clinic?

_____

_____

_____

_____

3. Does the caregiver know about the child's HIV status? Yes: No:
4. What are the things that encourage and motivate you to bring the child to the clinic easy?

Adherence promoting factors: please tick appropriate code.
a) Improved Child Health b) Improved School Performance c)

5. What are the things that remind you of the date to bring the child to clinic?
Adherence reminders: Please tick, you can tick more than one.
a) Appointment Card b) Wall Calendar c) Cell phone Reminder d) Telling date to the child e) Telling date to family f) Memorise the date g) Personal dairies h) Similar TCB Interval I) Week day similar.

1

HOUSEHOLD INFORMATION

6. Who is the primary caregiver of the child?
7. What is the relationship of the caregiver to the child?
8. If mother is not the main caregiver is the mother still alive? Yes: No:
9. Is the child's father involved in the care of the child? Yes: No:
10. What in the number of other adults in the Household?
11. Who of these other family members know about the child's HIV status? (May have more than one tick)

Parents	Grandparents	Aunts	Uncle	Sisters	Brothers	Cousins

12. Method of transport to clinic: a) Public Transport b) Own car c) Walk to clinic
13. What do you think about transport fee to the clinic?
    a) It is not a problem b) Causes minimal financial constraints c) Causes severe financial constraints
14. Do you have electricity in your household? Yes: No:
15. Family access to clean running water: a) In the yard b) less than 200m away d) more than 200m away

UPDATE HOUSEHOLD/CAREGIVER CONTACT DETAILS (please **check if there are changes in caregiver details)**

Name of caregiver: Telephone: _____

Street Address: _____

Name of relative living with you:
Telephone: Relationship: _____

Name of relative/friend not living with you:
Telephone Relationship: _____

Alternative Street Address: _____

_____

Contact number: _____

OUTCOME OF THIS FOLLOW UP (tick correct response)

		Comments	How to complete comment section
Back in care			*Date back in care*
Deceased			*Comment of perceived courses of death and date*
Self Transfer Out			*Where continuing treatment at and reason for self transfer*
Formal Transfer Out			*To which institution and reason of transfer*
Lost to Follow Up			*Please explain why is classified as LTFU*

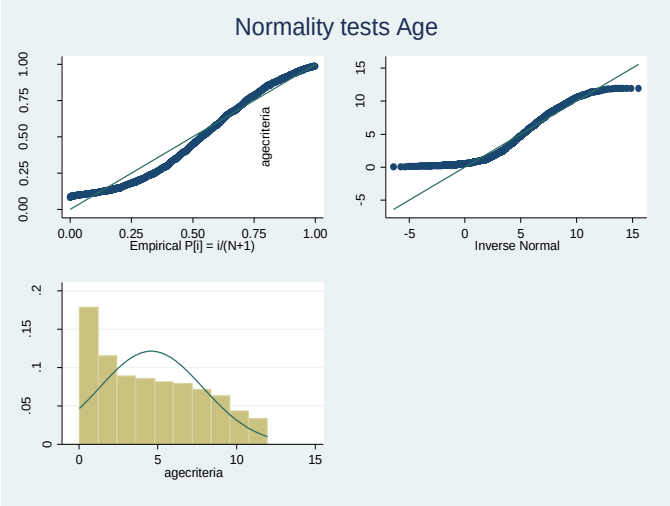
APPENDIX 2: Analysis of Missing Data

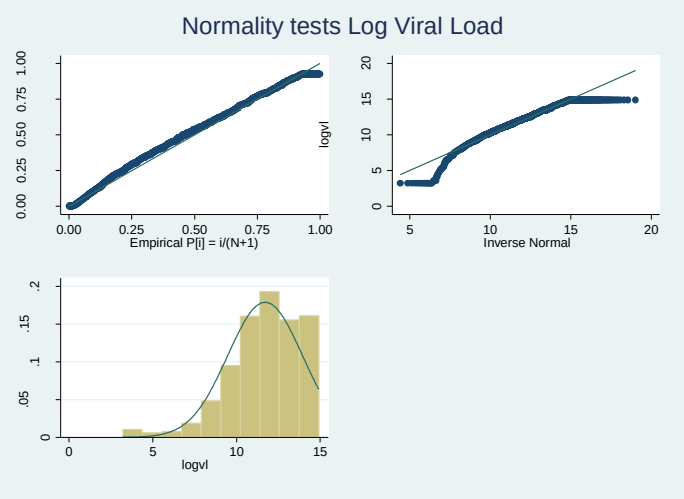
Characteristic	No Loss to Follow-up N	%	Loss to Follow-up N	%	P value
Sex					
Non-missing	2361	93.17	173	6.83	
Missing	1	50.00	1	50.00	**0.016**
Primary Caregiver Relationship					
Non-missing	2327	93.15	171	6.85	
Missing	35	92.11	3	7.89	0.800
Weight-for-age Z-score					
Non-missing	1803	93.32	129	6.68	
Missing	559	92.55	45	7.45	0.512
Height-for-age Z-score					
Non-missing	1791	93.43	126	6.57	
Missing	571	92.25	48	7.75	0.312
Weight-for-height Z-score					
Non-missing	1721	93.33	123	6.67	
Missing	641	92.63	51	7.37	0.535
WHO Clinical Stage					
Non-missing	2103	93.22	153	6.78	
Missing	259	92.50	21	7.50	0.654
Immunosuppression[1]					
Non-missing	1957	93.28	141	6.72	
Missing	405	92.47	33	7.53	0.540
CD4 cell %					
Non-missing	1971	93.28	142	6.72	
Missing	391	92.43	32	7.57	0.530
Log_{10} Viral Load					
Non-missing	1771	93.17	126	6.64	
Missing	591	92.49	48	7.51	0.452
TB prior to HAART					
Non-missing	2347	93.13	173	6.87	
Missing	15	93.14	1	6.25	0.923
Initial Regimen					
Non-missing	2348	93.17	172	6.83	
Missing	14	87.50	2	12.50	0.371

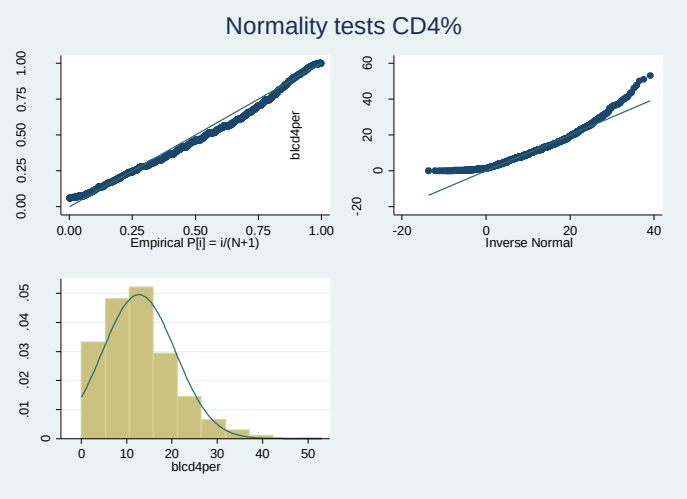
[1] WHO classification of HIV-related immunodeficiency in children according to age (See Table 2.1 for details)

Missing data were not associated with LTFU except with respect to the variable “Sex”.

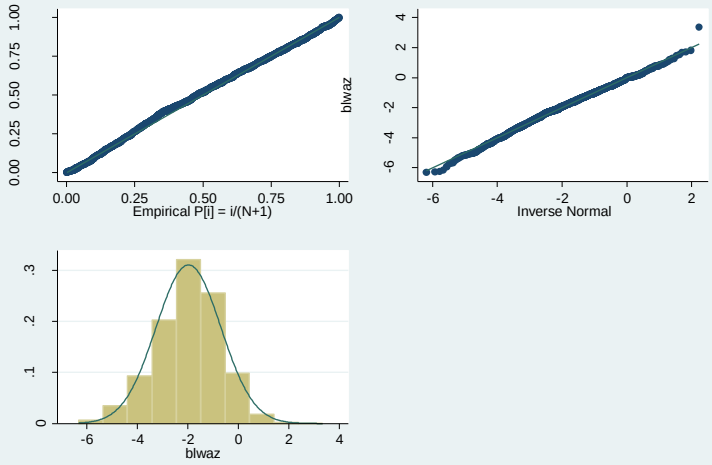
APPENDIX 3: Tests for Normality



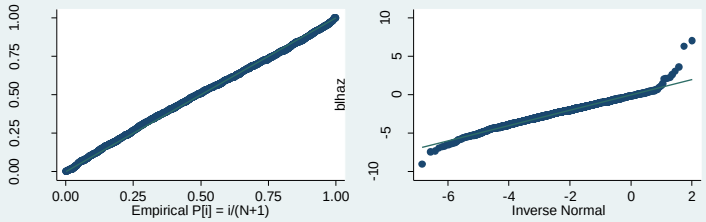


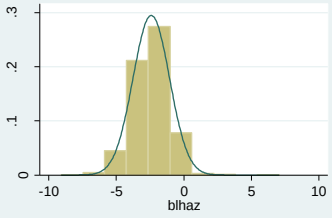


Normality tests Weight-for-age Z-score

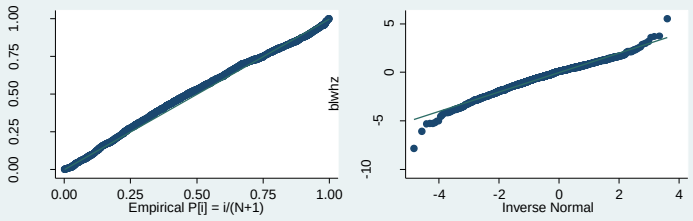


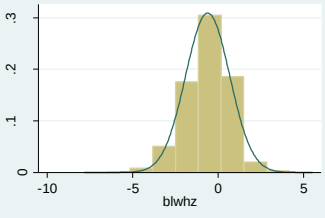
Normality tests Height-for-age Z-score





Normality tests Weight-for-height Z-score





APPENDIX 4: Tests for Proportional Hazards Assumptions

Tests for Proportional Hazard Assumption LTFU

Global Tests for Proportional Hazards Assumption: (estat phtest)

Global tests for proportional hazards assumptions based on Schoenfeld residuals were done after fitting univariate Cox models on all co-variates. With the exception of primary caregiver relationship, all co-variates had p>0.05 indicating that the proportional hazards assumption was not violated.

Characteristic	P Value Global Test for PH Assumption
Sex	0.493
Age Group at HAART Initiation	0.588
Age	0.916
Year of HAART Initiation	0.206
Primary Caregiver Relationship	0.037
Weight-for-age z-score group	0.393
Height-for-age z-score group	0.943
Weight-for-height z-score group	0.518
TB prior to HAART Initiation	0.855
WHO Stage	0.147
Immunosuppression	0.433
CD4 % group	0.709
Log_{10} Viral Load	0.639
Regimen	0.659

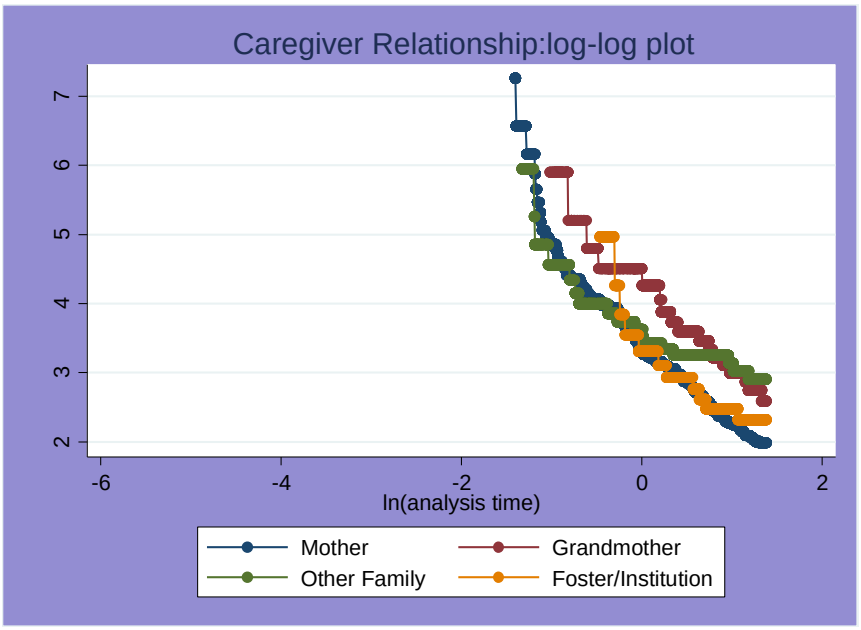
Global test for overall multivariate model p=0.898

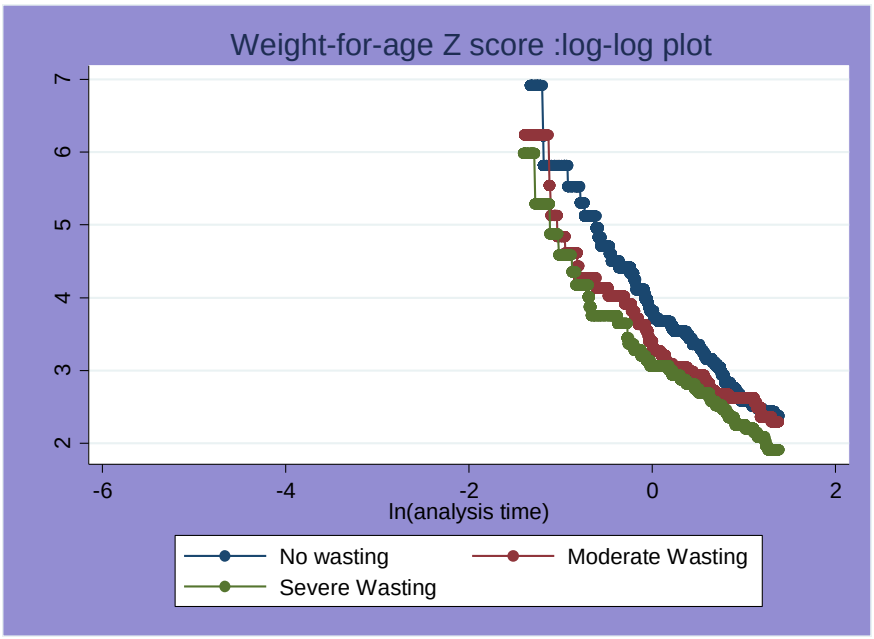
Tests for Proportional Hazards Assumption after Restricting Follow-up Time to 1 year: LTFU

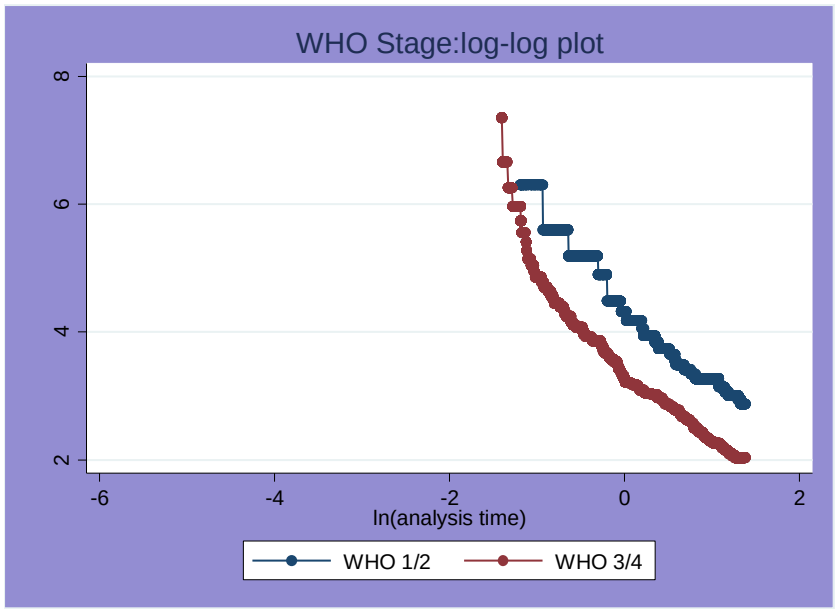
Characteristic	P Value Global Test for PH Assumption
Age Group at HAART Initiation	0.787
WHO Stage	0.767
CD4 % group	0.547
Primary Caregiver Relationship	
Grandmother	0.395
Other Family	0.185
Foster Care/Institution/Neighbour/Guardian	0.256
Global Test	0.570

Graphical Assessment of Proportional Hazards Assumption: (stphplot)

The proportional hazards assumption was also assessed graphically by plotting –ln{-ln(survival)} curves for each categorical variable by ln(analysis) time.

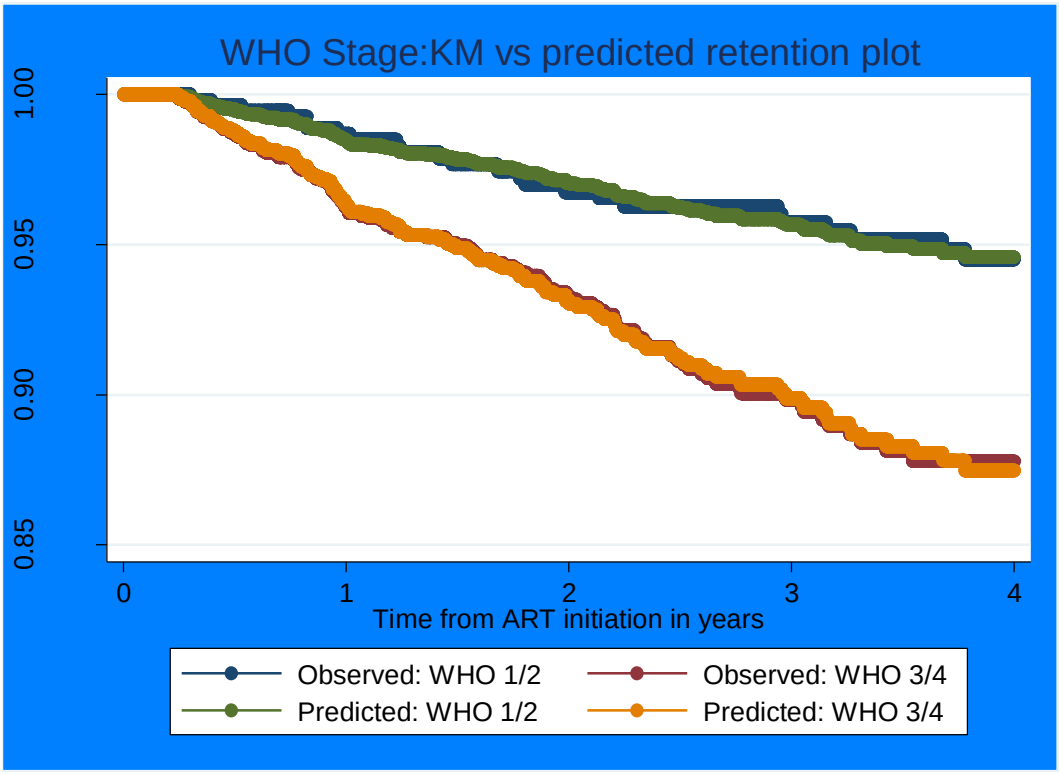


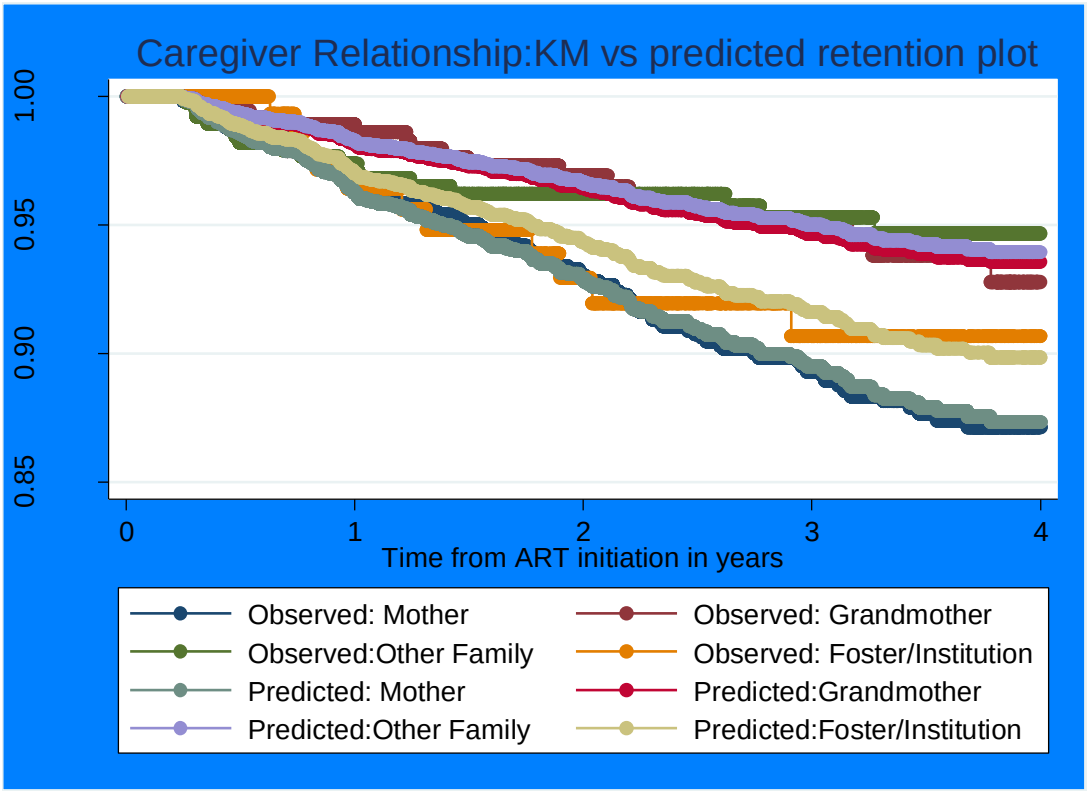




Assessment of Proportional Hazards Assumption through comparison of Kaplan-Meier observed retention curves with Cox predicted curves: (stcoxkm)

The proportional hazards assumption was assessed by comparing Kaplan-Meier observed survival (retention) curves with Cox predicted curves for categorical variables.





Tests for Proportional Hazards Assumption: TIFU

Characteristic	P Value Global Test for PH Assumption
Sex	0.916
Age Group at HAART Initiation	**0.038***
Age	**0.014***
Year of HAART Initiation	0.372
Primary Caregiver Relationship	**0.002***
Weight-for-age z-score group	0.399
Height-for-age z-score group	0.374
Weight-for-height z-score	0.700
TB prior to HAART Initiation	0.840
WHO Stage	0.075
Immunosuppression	0.194
CD4 % group	0.397
Log_{10} Viral Load	0.493
Viral Load Group	**0.009***
Regimen	0.717

***** Significant p value, proportional hazards assumption violated.

Age, age group, primary care giver relationship and viral load group violated proportional hazards assumption.

Global test for multivariate model p=0.831

Tests for Proportional Hazards Assumption after Restricting Follow-up Time to 1 year: TIFU

Characteristic	P Value Global Test for PH Assumption
Weight-for-age z-score group	
-2 to -3 (Moderately underweight)	0.384
<-3 (Severely underweight)	0.582
WHO Stage	0.356
CD4 % group	0.244
Initial Regimen	0.546
Global Test	0.502

APPENDIX 5: Power Calculations for Sample Size

