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Incidence and determinants of lost to follow up among patients on antiretroviral therapy

Research Report in Statistics, Number 25, 2020

Clare Nyabonyi Mauti

June 2020

Submitted to the School of Mathematics in partial fulfilment for a degree in Master of Science in Biometry

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Master Thesis
Submitted to the School of Mathematics in partial fulfilment for a degree in Master of Science in Biometry

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Abstract

Death is ofttimes ignored in lost to follow up studies yet it is a competing event in such cases as it is informative of its probability.A couple of studies have been done on incidence and determinants of lost to follow up however solid estimates may be found if death as a competing event is taken into account rather than censoring. The goal of the study seeks to find out the incidence and determinants of lost to follow up with and without death as a competing event. Cox proportional hazards model and Fine-Gray's subdistribution hazards model were employed to model the outcome of the determinants on lost to follow up. Kaplan-Meier graph was done to describe the probability of lost to follow up in the cox proportional hazards model while cumulative incidence function was done to describe the incidence of lost to follow up while taking death as competing event into account.Each variable was tested for the assumption of proportional hazards before inclusion in the final model using Schoenfeld residuals. 1047 patients ($\geq$ 15 years) were included in the study. The overall lost to follow up rate was 14% with 2.4 per 100-person years incidence rate. Being male, having CD4 count of $<$ 200 mm^3 and a younger age (15-30 years) were significant determinants of lost to follow up, hence there is need to give extra attention to these groups of people in order to improve HIV care service delivery

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Declaration and Approval

I the undersigned declare that this dissertation is my original work and to the best of my knowledge, it has not been submitted in support of an award of a degree in any other university or institution of learning.

Signature Date

Clare Nyabonyi Mauti
Reg No. I56/7875/2017

In my capacity as a supervisor of the candidate's dissertation, I certify that this dissertation has my approval for submission.

Signature Date

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Dedication

This research work is dedicated to myself.

Contents

Acknowledgments

Special thanks to to the almighty God for this far He's seen me through, my supervisor Dr Nelson Owuor for his patient advice and guidance throughout the research process, my mother Tabitha for giving her all to see me through this long journey and to whom I'm greatly indebted.

Clare Nyabonyi Mauti

Nairobi, 2020.

1 Introduction

1.1 Background of the Study

Human Immunodeficiency Virus (HIV) is believed to have originated from Kinshasa the capital city of Democratic republic of Congo around year 1920 during which there was a cross-species transmission of the virus to human beings from chimpanzees. Acquired Immunodeficiency Syndrome (AIDS) was first beheld in 1981 and in 1983 the HIV virus was found to be the cause of AIDS.The first case of HIV in Kenya was reported in 1984.According to WHO, approximately 37.9 million people live with the virus of whom 36.2 million are adults and 1.7 million are children (<15 years old) (Organization et al., 2014). Sub-Saharan Africa (sSA) with 12% of the world's population has two-thirds of the all people infected with the virus (UNAIDS, 2011).In Kenya 1.6 million people live with the HIV virus of whom 1.4 million are adults and 0.12 million are children (<15 years old) with an estimated 4.7% adult prevalence (15-49 years old). To date HIV has no cure albeit antiretroviral therapy can help manage the virus enabling those infected live longer and healthier, though the achievement of this depends on regular patient follow up.

The United Nations Programme on HIV/AIDS in may 2014 floated the 90-90-90 targets which aims to have 90% of all PLWHIV to be diagnosed, 90% of those diagnosed with HIV to obtain treatment and 90% of those in treatment to achieve viral suppression by the year 2020 (on HIV/AIDS (UNAIDS) et al., 2017).Frequent testing to achieve the first 90, free diagnosis and treatment through the adoption of treat all approach and same day initiation to attain the second 90 and adoption of strategies that support patient adherence to treatment and reduce number lost to follow up to realize the last 90 were among the suggested measures to achieve this audacious target. Globally by 2018; 79% of PLWHIV were aware of their status, those who new their status and were obtaining antiretroviral treatment were 78% and 86% of those obtaining treatment were virally suppressed.In Kenya by 2018; 89% of PLWHIV knew they were living with the virus, 68% of those who had HIV were accessing antiretroviral care and 51% of those receiving treatment were virally suppressed.

Among HIV infected people, retention in care is critical in obtaining good health outcomes as well as preventing transmitting the virus to other people. Lost to follow up (LTFU) is linked with poor viral suppression, treatment failure and higher risk of death (Mugavero et al., 2009; Tripathi et al., 2011; Mugavero et al., 2014). In sub-Saharan Africa death rates among patients LTFU has been estimated at between 12% and 87% (Brinkhof et al., 2009). In addition, HIV positive individuals who are LTFU spread the virus at an

estimate of 6.6 transmissions per 100 person-years as contrasted to 0.0 transmissions per 100 person-years in people who had the virus suppressed. Reduced LTFU therefore plays a critical role in attaining and sustaining undetectable viral load thereby minimizing death and transmission to others.

With increased availability of ART treatment, the challenge for HIV programs and the public sector is to deliver high quality care (Thida et al., 2014). Viral suppression as one of the key markers of treatment success is used to determine the effectiveness of HIV programs service delivery (Organization et al., 2010; Giordano et al., 2007).Sub-optimal adherence to treatment leads to increased risk of transmitting the virus. Individuals with undetectable viral loads do not transmit the virus Bavinton et al. (2018); Rodger et al. (2019, 2016) which has led to the common slogan "Undetectable = Untransmittable".Cost benefit models suggest that arbitrations geared towards improved retention in care have an epidemiological and economic influence (Maulsby et al., 2017; Shah et al., 2016). Anthony et al suggested simple and standardized routine monitoring systems, reliable ascertainment of true patient outcomes, link strengthening between and within health facilities and community among others as key interventions that may help improve patient retention(Harries et al., 2010).

1.2 Statement of the Problem

Classical survival analysis assumes non-informative censoring meaning individuals who remain under follow up have the same probability of event of interest occurring in the future as those individuals who are no longer being followed (because of study drop out or censoring) as if losses to follow-up were random/non-informative at any given point (Austin et al., 2016). In competing risks analysis (extension of survival analysis) events that may prevent the occurrence of event of interest (competing risks) are taken into account. Many clinical studies often ignore the presence of competing risks which often opens to inaccurate estimation of event of interest's cumulative incidence. Moreover a theoretical population where there are no competing events is not often case moreover in scientific settings. Koller and Michael et al Koller et al. (2012) found out competing risk issues in 70% of clinical studies done on individuals prone to competing risks. Death is a competing event of LTFU but is often overlooked yet it is informative of its probability. A couple of studies on LTFU and its determinants have been conducted however solid findings on the degree and determinants of LTFU can be found if death as a competing event is taken into account rather than censoring (Teshale et al., 2020). There was narrow proof on incidence and determinants of LTFU within the area of study with/without presence of competing risks, this study will compare the model where death is a competing event of LTFU with the model where death is considered as censored and tease out the differences (if any) that arise.

1.3 Study Objectives

1. To estimate the incidence rate of LTFU with and without death as a competing event
2. To determine the determinants of LTFU with and without death as a competing event
3. To compare findings of the incidence rate and determinants of LTFU with and without death as a competing event

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1.4 Significance of the Study

LTFU remains the main challenge to prosperity of HIV initiatives especially is sub-Saharan Africa. It may result to poor adherence, drug resistance and toxicity, discontinuation of treatment and treatment failure which leads to increased risk of death (Kaplan et al., 2000). With the test and treat (T & T) approach introduced since 2012, it is therefore important to have information regarding LTFU in routine health care delivery in order to sustain project quality and come up with selected strategies that minimize LTFU and thereby prevent death.

2 Literature Review

The rate of LTFU ranges between 10 to 26 per 100 person-years in African region Mberi et al. (2015) with the incidence rate increasing for each additional year on ART while in Asia-Pacific region it varies between 2.8 to 7.1 per 100 person years Alvarez-Uria et al. (2013); Nicole et al. (2017). According to Jiamsakul et al. (2019) the observed differences in the rates over these areas could be explained by strength of clinical monitoring to support treatment adherence and re-engage those who fall out. A systematic review by Fox & Rosen (2010) found out that LTFU is the frequent attrition source at 59% succeeded by death at 41%, they further described median attrition of 22.6% at 12 months, 25% at 24 months and 29.5% at 36 months.

A study done on patients on ART in Caribbean, Central and South America Network (CCASAnet), subjects were predominantly male (63%). LTFU cumulative incidence rate was 18.2% five years after ART initiation. Younger age, advanced disease stage at ART initiation were among the risk factors to being lost to follow up (Carriquiry et al., 2015).A similar study in national AIDS program in Thailand found out the cumulative incidence of lost to follow to be 12.8% with high baseline CD4 count of ($\geq$ 350) and non-advanced disease stage as predisposing factors of LTFU (Teeraananchai et al., 2018).In India, cumulative incidence rate of LTFU at 1, 2, 3, 4 and 5 years was found to be 8.2%, 10.6%, 14.1%, 16.8%, 18.5% and 18.9% respectively, $<$ 25 years of age, being single, having CD4 count of $<$ 100 and being homeless were linked with higher risk of LTFU while female gender was associated with a reduced risk. No significant difference was observed in terms of LTFU risk between patients on anti-tuberculosis drugs at baseline with those not on the same treatment (Alvarez-Uria et al., 2013).Dalal et al in their study in Johannesburg, South Africa (Dalal et al., 2008) found out LTFU rate to be 16.4% with age, gender and ethnicity not being predictive of LTFU risk while death accounted for 48% of those LTFU. A similar study in the same country by kamban et al revealed CD4 cell count of less than or equal to 500 cells/mm3 to be indicative of LTFU in a test and treat set up, they further clarified that patients starting treatment under test and treat setting may often start treatment in good health hence not able to appreciate treatment which might hinder them from expected commitment to care.

In a cohort enrolled on study in pharmacovigilance in South Africa 65.5% of the patients were female and LTFU rate was 23.4% with a median time on ART of 21.5 months with 10.3 per 100 person-years incidence rate in the earliest year of ART and 40.5 per 100 person years in year eight of taking ART. Lack of a committed partner, baseline CD4 count of $>$ 200 cells/ml, self employment, last viral load and last WHO stage three or four were

more likely to get LTFU while patients with adverse ART event were at a decreased risk of being LTFU (Mberi et al., 2015).A study by Musonda et al in Zambia described LTFU rate to be between 8.7 to 13.6 person years with patients of male, younger age, higher CD4 count,lower heamoglobin and lower BMI to be at elevated risk of LTFU with 62.6% of the patients in the study site being females and median age at baseline of 34 years (Li et al., 2013).

In Cameroon lost to follow up was recorded at 94.6 per 1000 persons years with 66.7% deaths of traced LTFU cases observed. Factors related to higher lost to follow up risk were over 5 kilometres distance from clinic, being single, more than 500 cells/microliter CD4 cell count and having partners with unknown HIV status (Bekolo et al., 2013).In Nigeria 30.6% of the patients were LTFU with males, non-pregnant female, patients on $\geq$ 3 months refill, patients whose viral loads were not suppressed and being on second line regimen were significant risk factors to LTFU (Aliyu et al., 2019).

In Ethiopia's Mizan-Aman Hospital, 53.9% of the ART patients were females. The hospital recorded a LTFU rate of 26.7% with a cumulative incidence of 8.8 per 1000 person months. Having $<$ 200 cells/mm^3 baseline CD4 count, adolescents, non-isoniazed prophylaxis and regimen substitution were found to increase rate of LTFU (Berheto et al., 2014). A similar study in North West Ethiopia looking at the oucomes of LTFU revealed death as the most reason accounting for 47.9% of all patients LTFU (Wubshet et al., 2013). In Pawi General Hospital, North West Ethiopia female patients were 56.2% with majority aged 32 years, 47.3% were married, 44.8% were illiterate and 2.5% had reached higher educational level. LTFU was described to be 22.6% with an incidence rate of 116 per 1000 person years.Further, about half of the patients were LTFU during the first half year on treatment and 73% within a year. Being 15-28 years, WHO stage four and not being on isoniazed prophylaxis were significant determinants of LTFU (Assemie et al., 2018).

In a close study in Masaku, Uganda LTFU incidence rate was 7.5 per 100 person years of observation. The rate went higher with duration of follow up from 8.9%, 12%, 15.8%, 18% and 20.2% at half-year, first, second, third and fourth years respectively. Patients initiated on treatment within 7 days following diagnosis, 200-350 cells/ml CD4 cell count, lack of a telephone phone and WHO clinical stage 3 or stage 4 were at an elevated likelihood of LTFU while baseline age $\geq$ 25 years, at least primary education and $\geq$ 30 BMI was connected with a lower risk of LTFU (Kiwanuka et al., 2020). In a similar study done in Wakiso district, Uganda 60.5% of the patients were female and half were married with 43.6% of them being below 30 years. The LTFU incidence was 21 per 1000 person months. having normal weight, receiving care from a hospital rather than a lower facility, lack of telephone contact were among the factors significantly associated with LTFU besides stigmatization and long waiting times from key informant interview (Opio et al., 2019).

A similar study done in central kenya revealed 67.7% of the patients were female and LTFU at 36 months was 27.2%. having a younger age (20-35 years), being male, being single or divorced, having a baseline BMI of $<$ 18.5 kg/m2 were factors associated with LTFU (Wekesa et al., 2020). An alike study in western Kenya looking at the outcomes of patients LTFU revealed that 21% of them were actually dead (Rachlis et al., 2015). Ojwang et al did a similar study among the youth in Kisumu Kenya where over half of the participants were females, with a median age of 20 years. LTFU for this group was documented at 26% with an overall incidence rate of 529 per 1000 person years. Being pregnant , CD4 cell count $>$ 350, not being on antiretroviral therapy, and non-disclosure of virus infection status predicted LTFU while enrolment clinic, WHO stage,employment status,age, marital status and education level were not linked with LTFU (Ojwang' et al., 2016).Young women are twice as likely to be infected with HIV than their men counter parts according to UNAIDS 2017, because of vulnerabilities created by unequal cultural, economic and social status.

According to another study done in western Kenya by Ochieng' Ooko et al men with HIV had more chances of LTFU than women. The study further suggests that failure of returning to care in men could be due to advanced ailment or death since they present to care later than women therefore at an increased risk of clinical outcomes, in the contrary, women delayed to return to care because of personal/family commitments. Not having disclosed HIV infection to anyone multiplied LTFU chances because non-disclosure is related with poor adherence to treatment and failure to achieve viral suppression. Individuals with more CD4 cell count had higher chances of failing to return to care and treatment after enrolment contrary to another study that revealed patients with advanced disease were more susceptible to be LTFU and might have been at an increased of death (Ochieng-Ooko et al., 2010).

3 Methodology

3.1 Study design

A retrospective analysis done on HIV infected individuals initiated on treatment from 2005 to 2019 at Gesusu Sub-District Hospital located at Getacho sub-location, Gesusu location in Nyaribari Masaba Constituency, Kisii Couty. The hospital offers in-patient,family planning,home based care, community based integrated management of childhood diseases as well as anti-retroviral therapy. The beginning of follow up time (time zero) was marked by the time a patient was initiated on ART and follow up period was between Aug 2005 to June 2020. Follow up period ended if a patient died, transferred out to another facility, was lost to follow up or censored at the end of June 2020. Patients who transferred out contributed to follow up time up to the date of transfer out.

The study population was HIV infected adults (15 years and above) enrolled in care at Gesusu Sub-District Hospital between 2005 and 2019 and were to be followed up at the hospital. Patients who transferred in to the facility were eliminated from the study.

The main variable of intrest was LTFU described as failure of the patient to come to the clinic for atleast 90 days from the date of their last to come again date. Lost to follow up was determined by comparing the patient's most recent scheduled to come again date as noted in the database with the baseline date as (30th June 2020) and not yet classified as dead or transferred out.The risk factors of LTFU considered were; age at enrolment, gender, marital status, last CD4 count, ownership of a telephone set and presence of a treatment supporter. Data was extracted from the electronic medical records database, cleaned and analyzed in R.

Descriptive statistics of patient socio-demographic and clinical characteristics were done. Continuous variables were characterised be means (standard deviation) and medians (IQR) while categorical variables ere characterised by frequencies and percentages. Multivariable cox regression as well as subdistribution hazards regression ware employed to evaluate adjusted determinants LTFU time. The proportional hazards assumption was determined for each predictor variable added in the final model using Schoenfeld residuals that were scaled and log of time for each variable.Kaplan-Meier curves were used to describe the probability of LTFU in the cox regression. cumulative incidence function (CIF) was done graphically to describes the incidence of LTFU while taking death as competing event into account.

3.2 Competing risks regression model

Censoring is the distinguishing aspect of survival data where by the event time is unobserved for censored subjects. Such data present special problems in analyzing them hence it is necessary to consider the design employed to get survival data in order to adequately deal with censoring. Censoring can be categorized into two broad categories:

1. Right censoring: event is seen above a certain value but its unknown by how much. This is further classified into type 1 censoring (event is seen if it happens before some specified time), type 2 censoring whereby study carries on until k individuals fail and competing risks censoring which is a unique category of random censoring that arises when some individuals in the study encounter some competing event that makes them to be withdrawn from the study, hence event of interest is not observed for such cases.
2. Left/Interval censoring: an individual has experienced event of interest before being seen in the study.

Traditional survival analysis makes the assumption of non-informative/independent sampling, that is, subjects who remain under study at any given point in time have similar future risk of event occurrence as those no longer being followed as if losses to follow up were random and thus non-informative. Thus there is possibility of just a single event and either the event time is assumed to occur at some future time t or observed. In some instances however, more than one event type is possible and the happening of one event prevents the happening of the other event(s). Traditional survival analysis methods in such situations are therefore inappropriate as the event of interest is neither censored nor observed and as such may lead to overestimation of the cumulative incidence of an event in the presence of competing risks because;

1. Assumption of non-informative censoring maybe violated
2. The estimation of event probability is interpreted as occurring in a setting where competing event(s) do not occur.

Letting T be event time, the survivor and hazard functions are of interest in traditional survival analyses, while in the event of competing risks the cumulative incidence function(CIF) is of particular concern.

Let T be time till the happening of event of interest, such that $T \geq 0$ and $S(t)$ such tha t : $S(t) = Pr(T > t)$, where $(t) \leq 1$ and $S(t)$ is monotone and non-increasing equaling 0 as t approaches infinity. The cumulative distribution function is complement to the survival

function and is shown by: $F(t) = Pr(T \leq t = 1 - S(t))$. The Kaplan-Meier (KM) estimator/product limit estimator is used to estimate the survival function in non-informative right censoring and is estimated by;

$$\widehat{S}_{KM}(t) = \prod_{k:t_{(k)} \leq t} (1 - \frac{d_k}{n_k}) \tag{1}$$

where n_k is the number of subjects at risk at time $t_{(k)}$ and d_k is the number of failures at time $t_{(k)}$.

The cumulative incidence estimate the complement of KM survival estimate describes the crude incidence of event of interest prior to or at a given time and can be shown as:

$$\widehat{F}_{KM}(t) = 1 - \widehat{S}_{KM}(t) = \sum_{k:t_{(k)} \leq t} (\frac{d_k}{n_k}) \widehat{S}_{KM}(t_{k-1}) \tag{2}$$

Hazards of a single event

The cox proportional hazards model is employed in modelling survival on a set of predictors. It being a non-parametric model, no distributional assumptions on survival for the data are required. It utilizes the hazard and exponential functions to evaluate the effects of predictors. Hazard function describes the instantaneous risk of failure illustrated as:

$$h(t) = \lim_{t \to 0} \frac{Prob(t \leq T < t + \triangle t | T \geq t)}{\triangle t} \tag{3}$$

Equation 3 gives the probability of experiencing failure immediately after time T, given that the individual is still at risk at that point in time. With interest in a single event the cox proportional hazards regression model can be illustrated as;

$$h(t|\mathbf{Z}) = h_0(t) e^{(\beta^{\mathbf{T}} \mathbf{Z})} \tag{4}$$

where $\mathbf{Z}$ is p-dimensional vector of explanatory variables with regression estimates β and $h_o(t)$ is the hazard when $\mathbf{Z}$=0. When using the hazard ratio to compare subjects with distinct values of $\mathbf{Z}$ the hazard ratio can be equated to:

$$\frac{h(t|Z_1)}{h(t|Z_2)} = \frac{h_0(t) e^{(\beta^{\mathbf{T}} \mathbf{Z_1})}}{h_0(t) e^{(\beta^{\mathbf{T}} Z_2)}} = e^{\beta^{\mathbf{T}} (Z_1 - Z_2)} \tag{5}$$

If the hazard ratio is > 1, there is a higher risk for the occurrence of that event in subjects where Z_1 is present, and a ratio less than one means there is a reduction in the hazard of that event in subjects where Z_1 is present. A hazard ratio of 1 means there is little to no

difference in the effect of the predictor variables on the risk of the event. The model can be written in a log-linear format as:

$$\log(h(t|Z)) = \log(h_0(t)) + \beta^{\mathbf{T}}\mathbf{Z} \tag{6}$$

coefficients of the regression can be interpreted as log-hazard ratios.

Hazard function is associated to the survival function by;

$$S(t|\mathbf{Z}) = [S_o(t)]e^{(\beta^{\mathbf{T}}\mathbf{Z})} \tag{7}$$

where $S_0(t)$ is survival function when the predictors are equal to zero. Hence under cox proportional hazards, inferences about the hazard and survival of individuals can be made as well as between individuals based on their covariate values. The model assumes the hazard ratio for two individuals with specific predictor variable values are a constant independent of time.

Estimating the Probability of an Event with Competing Risks

The Cumulative Incidence Function (CIF) is an extension of the KM cumulative incidence. The concept of the CIF is similar to the KM estimate where it focuses on the probability of a specific event occurring. The CIF estimate, however, estimates the occurrence of an event in an environment where all competing risks are accounted for. This adaptation can be clearly seen in the formulation of the CIF, which is shown below:

$$CIF_d(t) = Pr(T \leq t, D = k) \tag{8}$$

where $CIF_d(t)$ is the probability of encountering the d^{th} event before time t and before a different type of event occurs and D is the event that occurs. One shortcoming of this approach is that you can only observe a single failure time for each subject because the joint survival is not identifiable hence when calculating the CIF, the primary focus is in the event that occurs first.

Modeling Hazards with Competing Risks

Using cox proportional hazards(CPH) model to estimate effects of predictors on the hazard of events can be used but it overestimates the effects in competing risks presence. Hence when considering multiple events, two hazard functions are introduced:

1. Cause-specific hazard function
2. Subdistribution hazard function

The first method employs CPH regression but distinguishes models between each failure type. Defining the instantaneous rate of the d^{th} event type as:

$$h_d^{cs}(t) = \lim_{x \to 0} \frac{Prob(t \leq T < t + \triangle t, D = d | T \geq t)}{\triangle t} \tag{9}$$

and the second is given by:

$$h_d^{sd}(t) = \lim_{x \to 0} \frac{Prob(t \leq T < t + \triangle t, D = k | T \geq t \cup T < t \cap D \neq d)}{\triangle t} \tag{10}$$

denoting the immediate risk of experiencing the d^{th} event in individuals yet to fail from this event type. Although the exact interpretation changes between the two hazard functions, their major difference is their corresponding risk set.The cause-specific hazard function looks at patients that are currently risk free (subjects who have not experienced any failure type) therefore decreasing at the occurrence of any other event. Whereas, the subdistribution hazard function analyzes a risk set that contains event free subjects, which includes those who have experienced a competing event at a previous time. Individuals who have not failed from the cause of interest remain in the risk set until they are either censored or experience failure (Austin et al., 2016; Putter et al., 2007).

The effects of predictors on the cause-specific hazards can be modelled for cause d as:

$$h_d^{cs}(t|\mathbf{Z}) = h_{d,0}(t) e^{\beta_d{}^{\mathbf{T}} \mathbf{Z}} \tag{11}$$

where β_d is the estimated predictor effects of cause d and $h_{d,0}(t)$ is the baseline cause-specific hazard of cause d.

In the presence of competing risks, the cause-specific hazard model analysis is completely standard, but does not have a simple interpretation due to its dependence on the predictors and baseline values for the models of all other failure causes. In response to this, Putter et al. (2007); Fine & Gray (1999) modified the cause-specific hazard regression model by redefining the hazard using the subdistribution hazard technique. Regression on the cumulative incidence function takes on the same format as that in cox proportional hazards model but baseline hazard is now defined using subdistribution hazard function as below:

$$h_d^{sd}(t|\mathbf{Z}) = h_{d,0}(t)e^{\beta_d{}^{\mathbf{T}}\mathbf{Z}} \quad \textbf{(12)}$$

For this reason, the subdistribution hazard model can subsequently evaluate the cumulative incidence function for each specific event in response to predictors, something the cause specific hazard model fails to do.

Studies suggest the subdistribution model is more appropriate when the objective is risk analysis and clinical prediction models, while the cause-specific hazard models is pertinent when epidemiological processes are questioned.

Goodness of Fit

Diagnostics must be run to examine the proportional hazards assumption that is made in both modeling techniques. The assumption relies on the idea that the cox proportional hazards and subdistribution proportional hazards do not depend on time. There are many methods to testing the relationship of the hazard ratios to time and whether they should be included in the model such as the Schoenfeld residuals, Martingale and Cox-Snell residuals. We will analyze the Schoenfeld residuals, visually and statistically, to address the proportional hazards assumption when looking at both hazard functions because this technique is practical for time dependent predictors.

Statistical Software

R programming language (version 4.0.2) was used ato do all the analyses. The survfit function in survival package was used to estimate the KM survival curves while the cuminc function in package cmprsk was used to estimate the CIF. The coxph function in survival package modelled the cox proportional hazards model while the FGR function in riskRegression package modelled the subdistribution proportional hazards model. The function cox.zph was used to analyze and present the proportional hazards assumption of every covariate prior to being fitted in the model.

4 Results

1047 patients were enrolled into the study during the period November 2003 to June 2020. 74% of the patients were female while 25% were males. 34 years was the median age at ART initiation with majority of the patients being between 31-49 years. 75% of the patients were in a marital union, 64% owned a mobile phone, 54% had a treatment supporter and 51% had CD4 count of 500 and above as at the last clinic visit. The details are shown below. Overall LTFU rate was 14%.

Variable	Statistics	Frequencies	Percentages
Survival Status	**Alive**	**790**	**76%**
	Dead	**38**	**4%**
	LTFU	**141**	**14%**
	Transferred out	**78**	**7%**
Gender	**Male**	**275**	**26%**
	Female	**772**	**74%**
Age	**Mean(sd):35(11)**		
	Min<Med<Max:15<34<70		
	IQR(CV):15(0)		
Age Category	**15-30**	**395**	**38%**
	31-49	**546**	**52%**
	50+	**106**	**10%**
Marital Status	**In a union**	**786**	**75%**
	Not a union	**261**	**25%**
Cellphone Ownership	**No**	**372**	**36%**
	Yes	**675**	**64%**
Treatment Supporter	**No**	**482**	**46%**
	Yes	**565**	**54%**
Last CD4 count	**$< 200\ mm^3$**	**178**	**17%**
	200 - 499 mm^3	**339**	**32%**
	500+ mm^3	**530**	**51%**

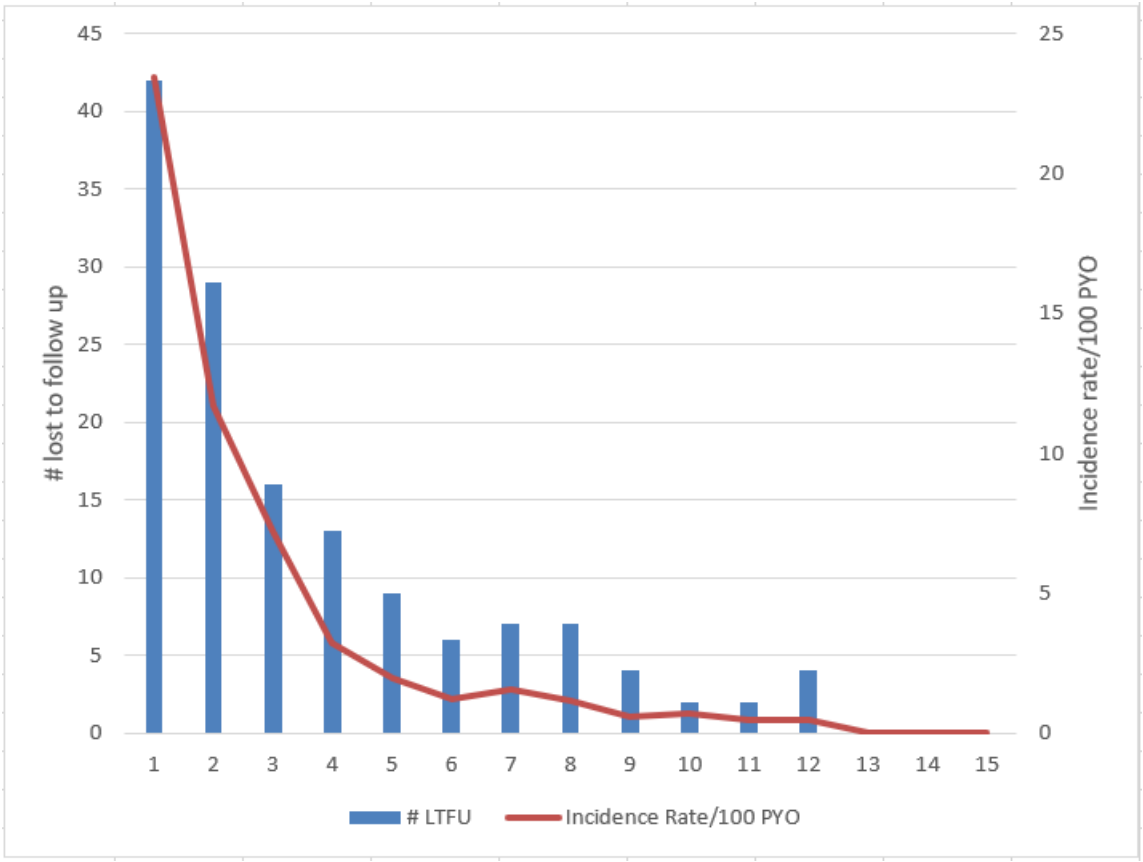

Figure 1. Absolute number of patients on ART LTFU (barchart) compared to LTFU per 100 person years of observation

141 patients were LTFU over 5,866 person years of observation. Overall incidence rate was 2.4 per 100-person years. 23% of the patients were lost immediately after enrolment with no LTFU incidences recorded in the year 13,14 and 15.

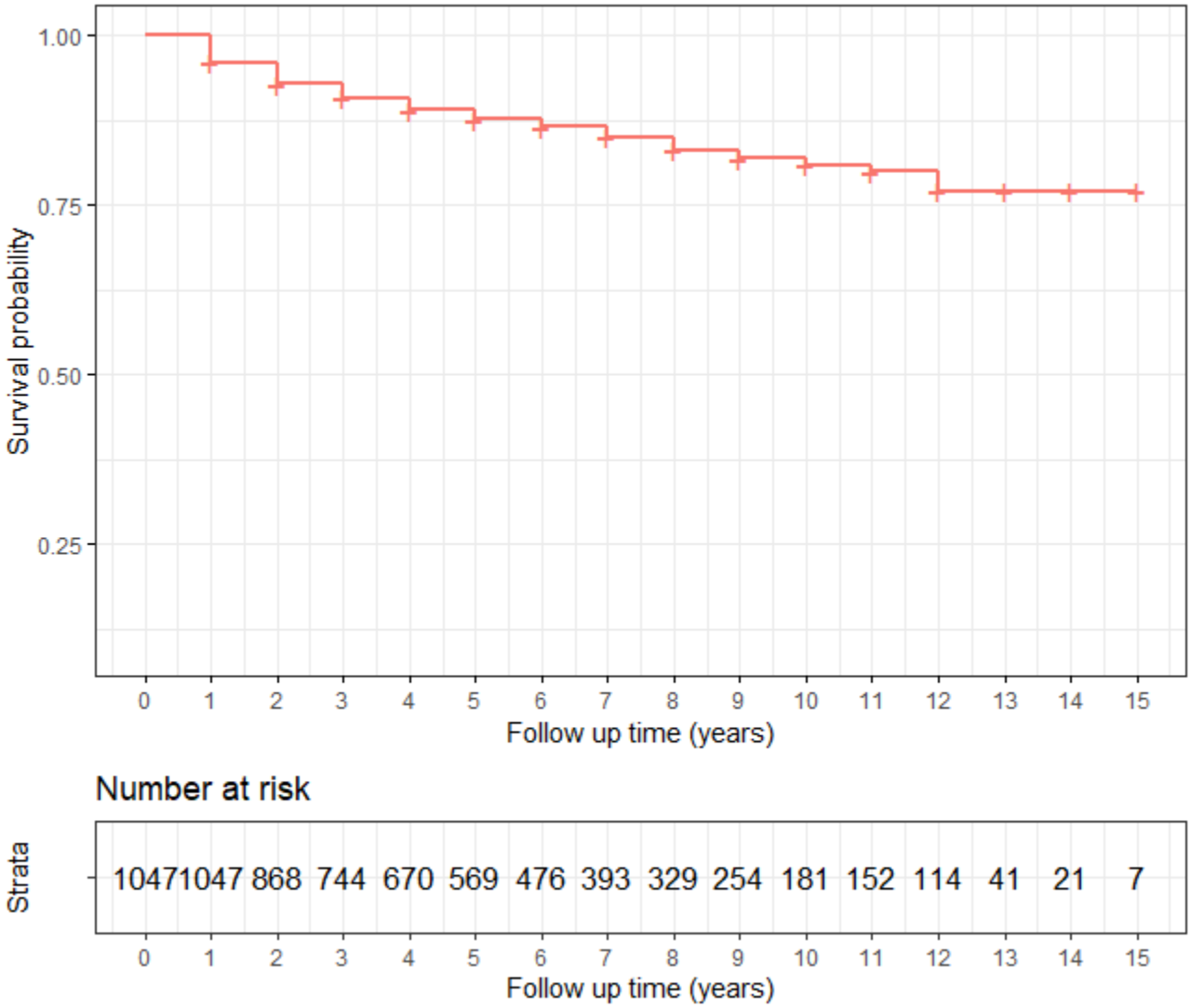

Figure 2. Kaplan-Meier curves for being LTFU among patients ($\geq$ 15 years) initiated on ART in Gesusu sub-district hospital, Kisii County
The cumulative incidence,$F(t)$ (complement of $S(t)$) of lost to follow-up at t = 5 is 0.124 and t = 10 is 0.191

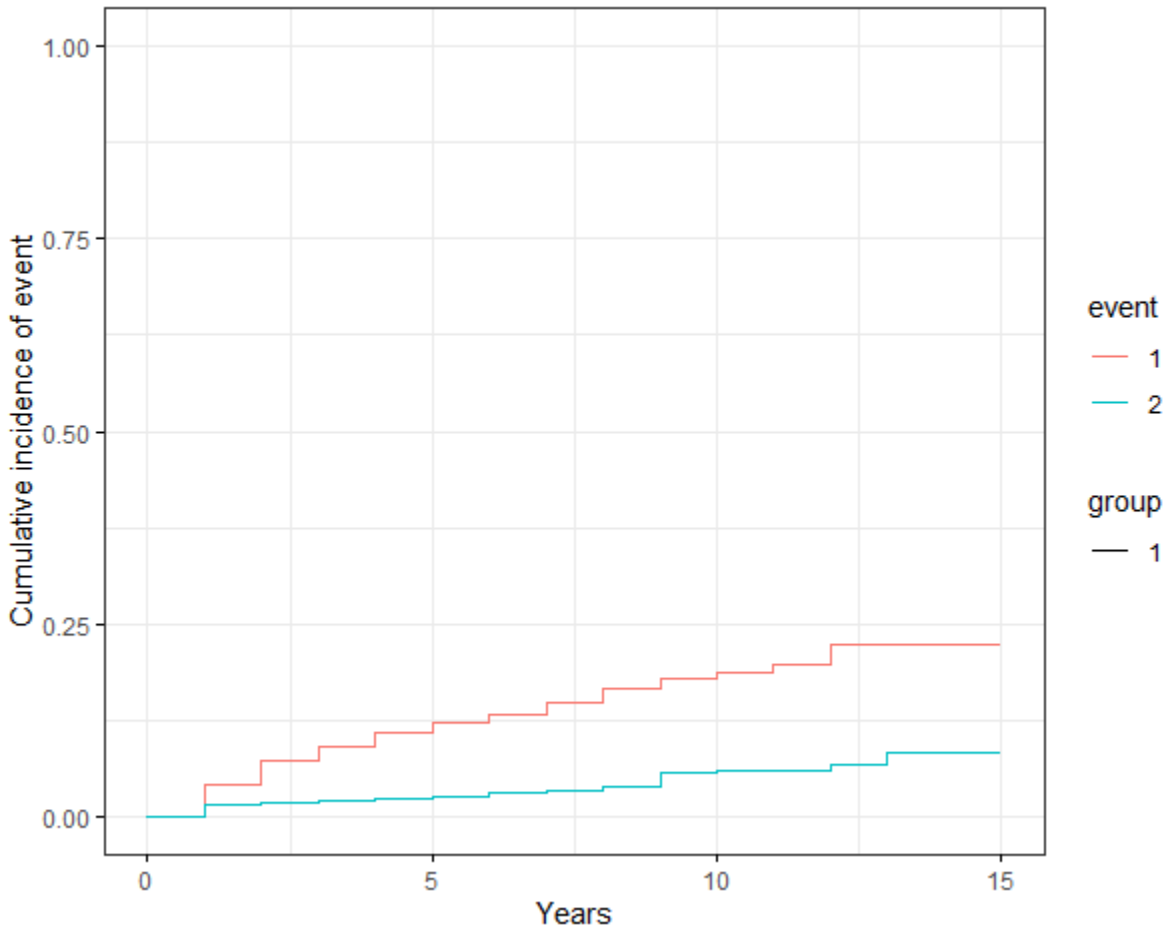

Figure 3. Cumulative Incidence Function (CIF) for being LTFU up among patients (≥ 15 years) initiated on ART in Gesusu sub-district hospital, Kisii County
Cumulative incidence of LTFU at at t = 5 is 0.122 and t = 10 is 0.186 while Cumulative incidence of death up at at t = 5 is 0.024 and t = 10 is 0.059

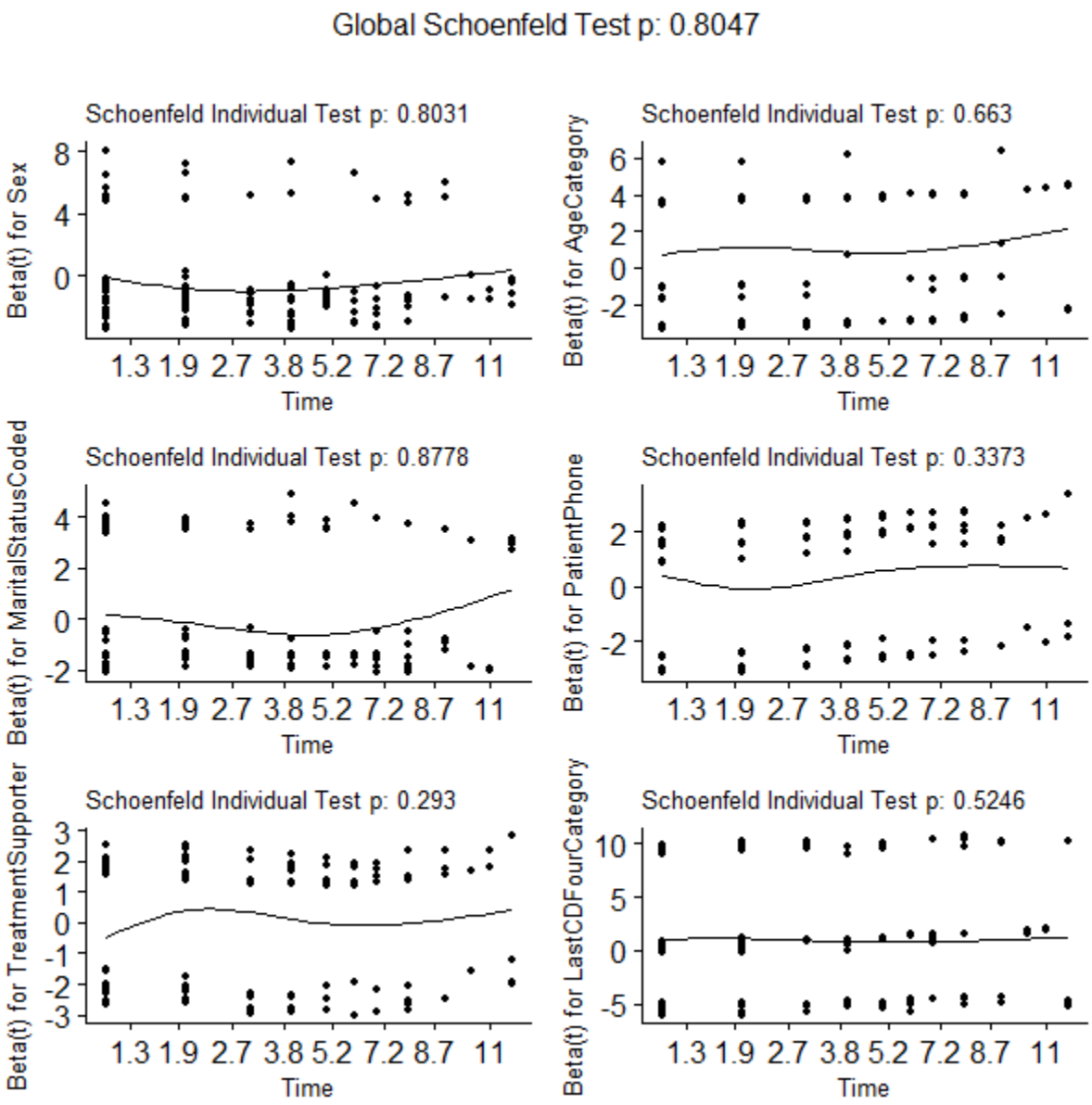

Figure 4. Schoenfeld residuals for evaluating the assumption of proportional hazards The test is not statistically significant for each of the predictor variables, the global test is also not statistically significant.The proportional hazards assumption is therefore assumed.($p-values$ > 0.05).

Estimates of cox proportional hazards regression

Parameter	Estimate	Hazard Ratio	*error*	Wald Z	$p-value$	95% Confidence Interval	
						Lower Bound	Upper Bound
Male[Reference(Female)]	-0.4930	0.6108	0.2447	-2.015	0.0440	0.3781	0.9867
Age 31-49 years[Reference(15-30 years)]	-0.6632	0.5152	0.1824	-3.636	<0.001	0.3603	0.7366
Age 50+ years[Reference(15-30 years)]	-0.5039	0.6041	0.3481	-1.448	0.1477	0.3050	1.1952
Not in a Union [Reference(In a Union)]	-0.1015	0.9035	0.1954	-0.519	0.6035	0.6160	1.3252
Phone Ownership [Reference(No Phone Ownership)]	-0.3998	1.4047	0.1819	1.8680	0.0612	0.9834	2.006
Treatment Supporter [Reference(No Treatment Supporter)]	-0.0019	0.9981	0.1733	0.011	0.9911	0.7105	1.4020
CD4 Count $\geq$ 500 mm^3 [Reference(CD4 Count $\leq$ 200 mm^3)]	-0.3188	0.7270	0.2211	-1.442	0.1494	0.4712	1.1215
CD4 Count 200-499 mm^3 [Reference(CD4 Count $\leq$ 200 mm^3)]	-0.5301	0.5885	0.2377	-2.230	0.0257	0.3694	0.9378

The risk of lost to follow up is 38.9% lower in males than females, The hazards of lost to follow up in patients aged between 31-49 years is 48.48% lower than in those aged between 15-30 years, having CD4 count of between 200-499 mm^3 lowers the hazards of being LTFU by 41.15% as contrasted to having CD4 count $<$ 200 mm^3. Marital status, owning/not-owning a phone, having/not having a treatment supporter, being aged 50+ as compared to being aged 15-30 years and CD4 count $\geq$ 500+ as compared to CD4 count $\leq$ 200 , were not linked to LTFU.

Estimates of subdistribution hazards regression (Fine and Gray))

Parameter	Estimate	Hazard Ratio	*error*	Wald Z	$p-value$	95% Confidence Interval	
						Lower Bound	Upper Bound
Male[Reference(Female)]	-0.5020	0.6050	0.2480	-2.028	0.0430	0.3781	0.9867
Age 31-39 years[Reference(15-30 years)]	-0.6512	0.5210	0.1800	-3.613	<0.001	0.3660	0.7420
Age 50+ years[Reference(15-30 years)]	-0.4988	0.6070	0.3570	-1.395	0.1600	0.3010	1.2240
Not in a Union [Reference(In a Union)]	-0.1024	0.9030	0.1900	-0.539	0.5900	0.6220	1.3100
Phone Ownership [Reference(No Phone Ownership)]	-0.3398	1.4050	0.1810	1.8810	0.0600	0.9860	2.002
Treatment Supporter [Reference(No Treatment Supporter)]	-0.0032	1.0030	0.1700	0.019	0.9800	0.7190	1.400
CD4 Count $\geq$ 500 mm^3 [Reference(CD4 Count $\leq$ 200 mm^3)]	-0.3036	0.7380	0.2150	-1.411	0.1600	0.484	1.125
CD4 Count 200-499 mm^3 [Reference(CD4 Count $\leq$ 200 mm^3)]	-0.4895	0.613	0.229	-2.133	0.0330	0.3910	0.9610

The relative incidence of lost to follow up in males is 39.5% lower than that of females,The subdistribution hazard of lost to follow up in patients aged between 31-49 years is 47.9% lower than in those aged between 15-30 years, having CD4 count of between 200-499 mm^3 lowers the subdistributional hazards of being lost to follow up by 38.7% as compared to having CD4 count of $<$ 200 mm^3.Marital status, owning/not-owning a phone, having/not having a treatment supporter, being aged 50+ as compared to being aged 15-30 years and CD4 count $\geq$ 500+ as compared to CD4 count $\leq$ 200 , were not associated with lost to follow up.

5 Discussions

When using cumulative incidence function(CIF), the estimated incidence of lost to follow up within 10 years of ART initiation (as an example) was 0.186. This estimate was lower by 0.5% than the estimates obtained using the complement of Kaplan-Meier function (0.191). This illustrates the upward bias that can be observed when naively using the Kaplan-Meier estimate in the presence of competing risks.

With cox proportional model, the risk of LLTFU in males was 38.9% lower than that of females while in the subdistribution proportional hazards model the relative incidence of lost to follow up in males was 39.5% lower than females. In the cox proportional regression model, The hazards of LTFU in patients aged between 31-49 years is 48.48% lower than in those aged between 15-30 years while in the subdistribution proportional hazards model The subdistribution hazard of LTFU in patients aged between 31-49 years is 47.9% lower than in those aged between 15-30 years.In the cox proportional regression model, having CD4 count of between 200-499 mm^3 lowers the hazards of being LTFU by 41.15% as compared to having CD4 count < 200 mm^3 while in the subdistribution proportional hazards model having CD4 count of between 200-499 mm^3 lowers the subdistributional hazards of being LTFU up by 38.7% as compared to having CD4 count of < 200 mm^3 . While both models reveal sex,age and CD4 count to be significant indicators of LTFU, the cox regression yields an upward biased inference on LTFU since death is informative of the probability of LTFU.

Females comprised majority of patients in this study as also observed by Li et al. (2013); Berheto et al. (2014); Mberi et al. (2015) and there was a significant association between sex and lost to follow up. While some have found males to be at an increased risk of LTFUp Li et al. (2013) than females, a higher retention rate was observed in males than females (Mugisha et al., 2014).According to our study, having CD4 count of between 200-499 mm^3 lowers the LTFU risk as compared to having CD4 count of < 200 mm^3 as also observed by Ochieng' et al (Rachlis et al., 2015). Patients aged between 31-49 years had a lower risk of LTFU compared to those aged between 15-30 years

6 Conclusions and Recommendations

Competing risks happen when an individual is at risk of one mutually exclusive event. In studies involving more than one event especially clinical research, there is need for competing risks approach. The subdistribution hazards hazards allows for testing of the effect of predictors in the cumulative incidence function. I this study, younger age (15-39 years), females and those with CD4 of $< 200\ mm^3$ were at an elevated LTFU risk. This group of patients should be accorded extra attention to minimise LTFU in this study and hence improve HIV care in study region.

Further investigation is required to comprehend the reasons of LTFU as well as the true end results of such patients as their could be chances of undocumented transfers hence there is a possibility of regarding patients LTFU while in true sense they could be in HIV care at other health facilities. There is also need to take into account other factors that may be influencing LTFU that were not considered in this study like viral load, WHO stage, distance to health facility among others.

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