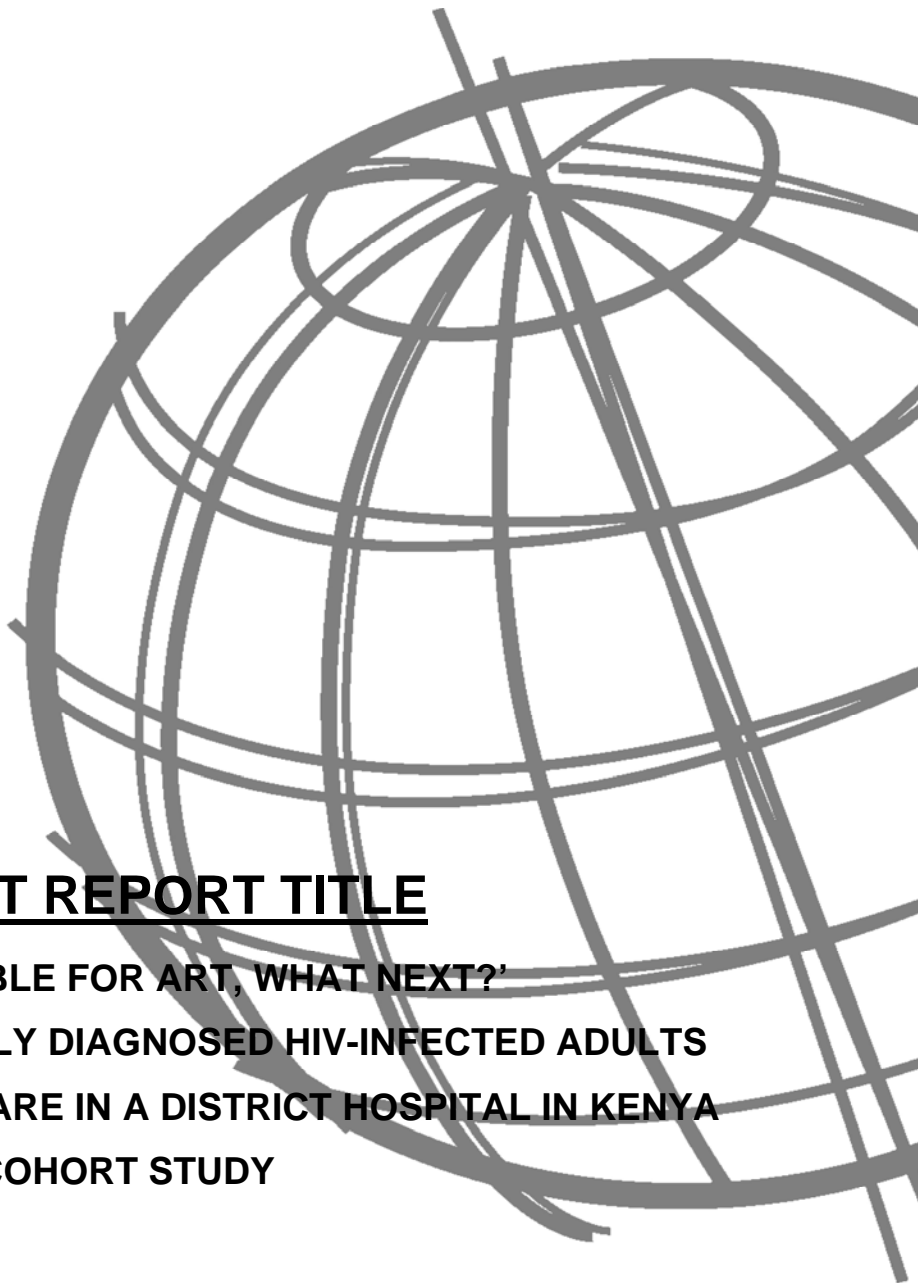




LONDON
SCHOOL *of*
HYGIENE
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MEDICINE



PROJECT REPORT TITLE

'I AM NOT ELIGIBLE FOR ART, WHAT NEXT?'

**EARLY DROP OUT OF NEWLY DIAGNOSED HIV-INFECTED ADULTS
FROM ROUTINE PRE-ART CARE IN A DISTRICT HOSPITAL IN KENYA
A COHORT STUDY**

Candidate #: 491262

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Author's role

With the guidance of my supervisor, I played the following roles in this project:

- Established the concept for the project
- Designed the analysis plan
- Sought for approval from the LSHTM ethics committee
- Reviewed and summarized the literature
- Obtained, cleaned and managed the data
- Performed the analysis
- Interpreted the results
- Wrote up the dissertation.

Abstract

Background

Patient drop out is a major barrier to the success of HIV programmes. More attention has been given to drop out in ART programmes. Understanding the dynamics of pre-ART drop out in patients ineligible for ART is critical towards designing interventions aimed at improving retention.

Objective

To determine the rate and baseline predictors of early drop out for newly diagnosed HIV infected ART ineligible adults registering for HIV care in a district hospital in Kenya.

Methods

A prospective cohort study was conducted. Eligible patients registering for HIV care between July 2008 and August 2009 were followed up for six months. Routinely collected data was used to assess predictors of pre-ART drop out. We defined drop out as patients who did not return for care in more than two months from the scheduled date of appointment. We further assessed for predictors of non-follow up and lost to follow up (LTFU).

Results

Of the 530 patients meeting the eligibility criteria, 189 (35.6%) dropped out from pre-ART care at a rate of 119.8/100 person-years. Of these, 96 (50.7%) never returned for follow up after registration. Distance (>5 km vs. <1 km: Adjusted hazard ratio 3.7 [2.6 – 5.2]), marital status (married vs. single: 0.5 [0.3 – 0.7]), time updated season (wet vs. dry: 0.6 [0.5 – 0.8]), entry point (outpatient/VCT vs. in-patient: 0.6 [0.4 – 0.9]) and education (secondary/higher vs. no schooling: 2.0 [1.2 – 3.1]) were independently associated with pre-ART drop out. Distance and marital status independently predicted non-follow up while distance, education and time updated season independently predicted LTFU. Importantly, disease severity was not associated with pre-ART drop out.

Conclusions

More than a third of newly diagnosed HIV infected, ART ineligible patients dropped out of care six months after registration. These findings warrant consideration of an enhanced pre-ART package of care aimed at improving retention.

Key words: “HIV”, “drop out”, “non follow up”, “lost to follow up”, “retention”, “pre-ART”

Abstract word count: 300 words

1.0 INTRODUCTION

1.1 Background

The past decade has experienced a substantial roll out in the provision of HIV/AIDS services, particularly in Sub Saharan Africa (SSA) where the epidemic is home to an estimated 22.4 million people – around two-thirds of the people living with HIV globally ¹. With the scale up of these programmes at different levels of HIV service provision, various challenges have emerged. A critical barrier to the scale up of these services has been widely reported as attrition of patients from care, especially so for those on anti-retroviral therapy (ART). The main cause of attrition has been identified as lost to follow up (LTFU) which accounted for up to 56% of attrition in ART programmes ².

By the end of 2008, approximately 3 million people were receiving ART in SSA compared to 2 million people at the end of 2007. Coverage of ART in this region was estimated at 44% [41 – 48%] of those in need in 2008 compared to 33% [30 – 36%] in 2007 ³. This has resulted in substantial improvement in the prognosis of HIV infected people. Prior to the availability of ART, the median interval from HIV infection to AIDS-related death was less than 10 years. Median survival was less than a year for those diagnosed with AIDS ⁴. In the ART era, the estimated median survival time has now been shown to be more than 35 years for a young person diagnosed with HIV infection ⁵. Immunological and virological outcomes on ART in low and middle income countries have also been encouraging ⁶⁻⁸. These developments suggest a major achievement by HIV/AIDS programmes.

However, the success of these programs is also largely dependent on other indicators. These include the ability to identify HIV-infected individuals, linking these individuals to HIV care, determining ART eligibility, monitoring those not yet eligible for ART to facilitate timely transition to treatment, initiating care among those eligible, and ensuring sustainable access to care (for both ART eligible and ineligible patients) over time. As access to these services grows, attention is now shifting from the immediate need to get patients into care, to the long term challenges of keeping patients in care and on treatment.

In many settings, especially in SSA, there is a growing concern that patients who have been diagnosed with HIV infection and registered for HIV care drop out, only to present themselves later with advanced HIV infection necessitating immediate ART initiation. Studies following patients from time of ART initiation show high rates of early attrition and mortality, which has mostly been attributed to the late access for ART ^{2, 9-11}.

A large proportion of HIV-infected patients initiating ART, up to 60% in some settings, drop out immediately after starting ART ¹²⁻¹⁵. A recent review of ART programs in SSA found rates of LTFU ranging from 20% at 6 months to nearly 40% at 2 years after ART initiation with weighted mean retention rates of 79.8% at 6 months, 75.1% at 12 months, and 61.6% at 24 months ². Most strategies to improve follow-up generally focus on bringing lost patients back into the health care system through outreach teams and collaboration with community organizations. An attempt to trace LTFU patients from a HIV programme in Malawi determined that 50% had died, 27% could not be found, and most of the rest had stopped ART ¹⁶. In Zambia's national treatment program, more than two thirds of patients who had dropped out of care could not be contacted, even after multiple attempts ¹⁷. In a systematic review on outcomes of patients lost from HIV care and treatment programs in resource limited settings, 20-60% of patients who could be traced had died ¹⁸.

Severe immune suppression has also been observed at the time of ART initiation as indicated by low CD4 and high viral load counts at start of ART ^{10-11, 19}. Observational studies show that most deaths among patients on ART occur in the early months after treatment initiation and that mortality declines substantially thereafter ^{11, 20-22}.

From a cost versus benefit perspective, LTFU is therefore a major challenge because tracing patients is evidently resource-intensive and often unsuccessful. Given that most of these patients may have already died, it has been suggested that preventing LTFU by directing major efforts towards earlier HIV diagnosis, effective linkage to care and timely initiation of ART may be more effective at improving outcomes.

1.2 Literature review

To enhance our understanding of attrition from HIV programmes, an electronic literature search was conducted on PUBMED database. The main aim of the search was to identify and review studies assessing drop out from HIV programmes in SSA. The search was restricted to (HIV/AIDS) studies on (Attrition/Drop out/Lost to follow up) in (SSA) after 2004; the year where most SSA countries rolled out ART programmes. Our search yielded 1081 studies which were initially reviewed by title and reduced to 74 papers. The abstracts of these papers were further reviewed and resulted to 31 relevant studies (Appendix 1).

Most (24/31) of these were observational studies from patients started on ART and followed up over durations ranging from 3-48 months. Overall, these studies were carried out to assess adherence, LTFU and mortality as their main outcomes. The main independent risk factors for

LTFU as determined by these studies were lower baseline BMI, lower CD4 count, lower haemoglobin, WHO stage III/IV, younger patients and being male. These data therefore suggest that drop out from ART programmes is mainly associated with severe disease and immunosuppression as indicated by the BMI, CD4 count and staging.

To the best of our knowledge and as at the time of the literature search, only three out of the 31 studies had exclusively assessed drop out in patients prior to ART, with outcomes being initiation on treatment for ART eligible patients¹⁹, LTFU in ART-eligible patients before they are started on treatment²³ and pre-ART lost to care²⁴. Of these, only one study conducted in Durban, South Africa, has assessed predictors of pre-ART LTFU. In this study, pre-treatment loss to care was defined as failure to have a CD4 count within 8 weeks of HIV diagnosis. They found that reported distance (≥ 10 km from the hospital), a reported history of TB treatment and referral for care by a health care provider to be independently associated with increased risk of pre-treatment lost to care²⁴. However, they did not assess for any clinical or immunological predictors for drop out, presumably because they defined pre-treatment loss to care as failure to have a CD4 count within 8 weeks of HIV diagnosis for the latter. Moreover, none of these studies exclusively assessed pre-ART drop out in patients who are not eligible for ART at enrolment into HIV care.

1.3 Rationale for study

Whereas outcomes relating to ART programmes have received most attention, a better understanding of pre-ART dynamics is also necessary. While most studies describe the rates of drop out after ART initiation, little is known about drop out of recently diagnosed HIV infected adults ineligible for ART after enrolment into care but prior to starting ART in resource limited settings. Understanding the predictors of pre-ART attrition are critical towards designing interventions aimed at retaining these patients in care and ensuring timely initiation of ART.

1.4 Aims and objectives

The main aim of this study was to determine the rate of early drop out of newly diagnosed HIV infected adults not yet eligible for ART and to identify baseline predictors associated with pre-ART drop out in a district hospital in Kenya. Since we were interested in which baseline predictors might predict pre-ART drop out, all factors were assessed and hence, no primary exposure or a study hypothesis was pre-determined.

2.0 METHODS

2.1 Study site

Kenya is one of the high HIV prevalence countries in SSA that has extensively rolled out HIV care services to its citizens. These services are generally provided in comprehensive care centres (CCC), a model prototype of care that offers HIV care and treatment services. Each CCC features a set of common core services, including: a care-based counselling and testing service to establish an HIV diagnosis; a clinical ability to diagnose, treat and manage opportunistic infections; counselling for treatment adherence and nutrition; and delivery of ART. People with HIV can also access a variety of additional services that may be provided offsite but which are linked, ensuring greater coordination in their care and saving them time. These include treatment for tuberculosis, home-based care, inpatient care, services for preventing mother-to-child HIV transmission, and management of sexually transmitted infections other than HIV. Free antiretroviral (ARV) services became available in the public health centers in 2004.

The study was conducted at the Comprehensive Care and Research Clinic (CCRC) within Kilifi District Hospital (KDH); a public health care institution located in the Coastal province of Kenya. The province has one of the highest adult seroprevalence of HIV in the country, estimated at 7.9% in 2007²⁵. Provinces are further subdivided to administrative regions called districts. Kilifi district is one of the poorest districts in the country and has low levels of literacy. The community is mainly agrarian and relies on subsistence farming for sustenance. The hospital is linked to other parts of the district and the neighboring districts to the north and the south with one main tarmac road (Figure 1). This road serves as the main route of public transport within the district. KDH provides health care services to a catchment population of approximately 250,000 people within the district, the majority of whom seek HIV services from the CCRC. In an attempt to decentralize HIV services, a few other peripheral public health centers within the district have recently been upgraded to offer HIV care.

The CCRC was set-up in 2003 and has since registered approximately 7000 HIV-positive patients for care with more than 3000 patients ever started on ART. The standards of care are provided according to the National AIDS and STI Control Programme (NAS COP) guidelines which are largely adopted from the WHO guidelines. Participants routinely undergo rapid HIV testing, voluntarily or provider initiated, at different settings within and outside the hospital setting. While some of the confirmed HIV infected people are referred to the peripheral health centers, majority are referred to the CCRC for registration into HIV care.

In the CCRC, care is provided by trained nurses and clinical officers; an equivalent to the medical assistants in the United States. These are the primary contacts of all patients seen. A medical officer in charge is usually available for more complicated cases.

Laboratory investigations including hematology and immunology are routinely requested at registration into care and every six months thereafter or when deemed necessary by the attending clinician. Newly registered patients are immediately started on cotrimoxazole and a two week appointment is given to assess for side effects and discuss laboratory results. Patients are deemed ART-eligible if they meet the WHO criteria i.e. a CD4 cell count of less than 200 cells/ul or clinical stage III/IV. Patients meeting the eligibility criteria are then initiated on ART and followed up monthly thereafter. The clinic has a consistent supply of the United State's President's Emergency Plan for AIDS Relief (PEPFAR) funded antiretrovirals offered to eligible patients at no cost. Those not eligible for ART continue to receive a package of pre-ART care, including cotrimoxazole, and are subsequently monitored at 1-2 month intervals.

In 2008, a 'Food By Prescription (FBP)' programme sponsored by the World Food Programme was introduced in the clinic for patients who met a pre-defined eligibility criteria that included a body mass index (BMI) of less than 18.5kg/m². Patients meeting these criteria benefit from monthly rations of food including cereals, flour and cooking oil. One of the main aims of the food programme was to enhance retention of patients for HIV care. Amongst other interventions, active tracing of defaulting patients was instituted for those enrolled in the FBP programme.

Due to out-migration, patients requesting to transfer their care to other health facilities were issued with a standard referral note and their status updated on the electronic database. Data on deaths was passively captured and dependant on reporting by health staff from in-patient wards, relatives, friends or acquaintances.

2.2 Study design

A prospective programmatic hospital cohort was designed to follow up all adults (≥ 15 years old) registering at the CCRC for HIV care from 01st July 2008 to 31st August 2009 and who were not yet eligible for ART. Patients were followed up for six months from first registration at the CCRC. Exclusions included patients who were diagnosed with HIV infection greater than three months before registration into care as our interest was with newly diagnosed patients and not patients who may have previously registered, dropped out and were now resuming care. Ineligibility for ART, an inclusion criterion for this present study, was determined by (i) CD4 count ≥ 200 (ii) WHO stage 1 or 2 in the absence of a CD4 count, or (iii) patients who did not have a CD4 count

or WHO staging at baseline. The latter were included in the analysis as it was argued that by principal of not having assessed for these criteria, they were yet to be proved to be ART eligible.

2.3 Study size

Formally, *a-priori* calculation of sample size is useful when planning a new study. However, our analysis was performed on routinely collected data that were already available. Thus, the main aim of this *post-hoc* sample size determination was to assess whether the analysis of the data will produce results with sufficient statistical precision to contribute substantially to the literature²⁶. Due to a paucity of data on pre-ART drop out, we estimated our sample size using drop out data from ART programmes. A systematic review on patient retention in antiretroviral treatment programs in SSA reported weighted mean retention of 79.1% at 6 months². Assuming a pre-ART drop out rate of 20% at 6 months in our setting, the risk of newly diagnosed adults registered for HIV care dropping out for a size of 384 patients will be estimated with a precision of $\pm 4\%$ at 95% confidence interval. Our data had more than 500 patients fitting our eligibility criteria for this study.

2.4 Sources of data

Data on socio-demographic, clinical and immunological characteristics of patients were collected at different levels and captured in an electronic data system. Upon registration at the CCRC, socio-demographic data were collected using a standardized questionnaire by trained counselors and entered into an electronic data system by a trained data clerk. Subsequently, at every follow-up visit, anthropometry and clinical data were captured and entered into the electronic database on real time. Anthropometries were routinely taken by trained nurses while clinical data were captured by trained clinical officers. Immunological data were captured into an electronic system upon receipt of laboratory results by a trained data clerk before filing with the patients' individual paper records.

2.5 Exposure variables

Socio-demographic data included date of birth, date of HIV diagnosis, date of registration at CCRC, religion, marital status, education level, sub-location of residence and entry point. Entry point is the site at which patients were HIV diagnosed and referred from for care. Sub-location is the smallest administrative region in which the patients reside in the district. Age at registration into care was derived from the dates of birth and registration and grouped into 10-year bands to ensure similar distribution of frequencies in the three age groups. Newly diagnosed patients were determined if their date of registration into HIV care was less than three months from the

date of HIV diagnosis. Patients from the male/female wards, maternity ward and the amenity wards were defined as having been referred from the in-patient department while those from antenatal clinics (ANC), Voluntary Counseling and Testing (VCT) Clinics and all other outpatient clinics were defined as having been referred from the out-patient department.

Population density data at the sub-location level was derived from the Kenyan 1999 national population census and linked to individual patient data using sub-location as the link identifier. A median population density within the district was determined according to the distribution at sub-location level. Sub-locations with a population density of more than the median were termed densely populated (urban) while those with a population density less than the median were termed sparsely populated (rural).

Actual distance from sub-locations in which patients resided to the hospital, and the closest distance from the sub-location to the main road leading to the hospital, were estimated using ArcInfo. In brief, a vector dataset was put together using three shape files: sub-locations, main road and the hospital. Centroids co-ordinates were generated as point features for each sub-location using a proximity analysis tool. Near distances were then estimated from centroids to the nearest feature of the road and to the hospital.

Seasons at registration and at drop out were determined from the dates at registration and last clinic appointment respectively. These were stratified to wet seasons (March – June, October – November) and dry seasons (December - February, July - September).

Clinical data included WHO staging I/II and BMI which was conventionally grouped into ≤ 18.5 kg/m² (malnourished) or > 18.5 kg/ m² (not malnourished). Immunological data comprised CD4 counts and hemoglobin levels which were both stratified conventionally to three categories (200-350, 351-500 and > 500 cells/uL) and four categories (< 8 , 8-10, 10.1-12, > 12 g/dL) respectively.

2.6 Outcome variables

Loss to follow-up is a commonly reported outcome in follow up studies in different fields. In the HIV context, various studies have used different definitions of lost to follow up depending on; when a CD4 count was done post-HIV diagnosis²⁴, days from the last clinic visit^{16, 27-32}, date from scheduled clinic appointment^{9, 33-34} and if screening in ART-eligible patients was completed²³ (Appendix 1).

Recently, data on a multisite HIV treatment cohort in Lusaka, Zambia, were used to determine an empirical “days-late” definition of LTFU among patients on ART. They looked forward in their

database to determine which patients returned for care after one year as their gold standard, after being determined LTFU at a given point in time according to a range of days-late intervals. The best-performing LTFU definition was determined to be 56 days after a missed appointment visit with a sensitivity of 84.1%, a specificity of 97.5% and misclassification of 5.1%. The 60-day threshold performed similarly well, with only a marginal difference (<0.1%) in misclassification. Hence, their analyses suggest that 60 days since the last appointment was a reasonable definition of LTFU ³⁵.

Definition of outcome

The primary outcome of this study was pre-ART drop out over a six month follow up period following first registration into HIV care. Based on the evidence above, we defined 'drop out' as patients who were more than two months (60 days) late for a scheduled appointment. We further assessed drop out from two end points of interest; (i) Patients who registered for HIV care but never returned over the given follow up period of six months (referred henceforth as 'non-follow ups'), and (ii) Patients who made at least one follow up after registration but dropped out subsequently (referred henceforth as 'lost to follow up'), where drop out used the same definition as above.

Person time at risk

Person-time at risk began on the date of registration into HIV care. All patients who were in follow up six months after registration were censored at six months of follow up. To facilitate survival analysis, we assumed non-follow up patients contributed one day of follow up each; the first day spent on registration and care. Lost to follow up (LTFU) patients were censored at their last attended visit date. Patients who had died or transferred HIV care to other health facilities were included in the analysis and were censored at their last attended visit date.

Since we were interested in determining pre-ART drop out, all patients who initiated ART during the follow up period were censored at the date they started ART. Considering patients in the FBP programme were selectively chosen and tracing implemented for defaulters, these patients were also censored at date of enrolment into the FBP programme (Figure 2). These strict criteria were chosen to ensure that the effect of these time varying risk factors is not reflected in our analyses.

2.7 Statistical methods

All analyses were carried out using Stata statistical software (Stata Intercooled version 11, StataCorp, College Station, Texas, USA). The data were presented according to the STROBE guidelines on cohort studies ²⁶.

Cohort Characteristics

Baseline characteristics of the cohort were described. Continuous data were assessed for their distribution by histograms and box plots. A new variable was created to represent missing data for immunological variables. This was tabulated against the other baseline characteristics and the outcome to determine if they differed with those with complete observations. An extra category was also created for missing data in individual risk factors and presented in the description of the basic distribution of the data after stratification into categories. Means and standard deviations were used to present normally distributed data. Median and interquartile ranges (IQR) were used to present data that were not normally distributed. Minimum and maximum values were also presented for continuous variables. Cross tabulations of categorical data with gender were done to describe their distribution by frequencies and percentages. Colinearity was assessed amongst risk factors using a scatter plot (for continuous variables) and more formally using correlation coefficient. Recoded categorical variables were subsequently used in the analysis. Although using categorical variables for continuous data may result in loss of information, this was done as it results in models that are easier to use and practical to interpret. The analysis was then carried out in three phases:

Analysis 1: Predictors of time to drop out

Cox proportional hazard regression analysis was used since the rate of drop out varied rapidly over time and the registration/drop out times were well defined. We assessed for proportionality visually using the Nelson Aalen curves and ascertained this more formally using the Likelihood Ratio Test (LRT). Lexis expansion was also adopted to assess the hazard of dropping out based on changing seasons by splitting the follow up period into wet and dry seasons. A univariable analysis was done to assess for individual predictors of drop out. Hazard ratios (HR), 95% Confidence Intervals (C.I) and Likelihood Ratio Test (LRT) p-values were presented. The Kaplan-Meier (KM) method was used to estimate the survival probability of dropping out from HIV care within 6 months of follow up time. We further assessed for differences in time to drop out by CD4 count (given its *a-priori* likelihood of importance) and by any other predictor that was determined to be associated with drop out using the KM curves and a log rank test. For

ordinal risk factors showing a general association with drop out, we further assessed for dose-response and quadratic relationships with the test for linear trend and departure from linearity respectively, using the LRT.

A multivariable Cox proportional hazard regression analysis using a forward stepwise model building approach was then adopted to estimate adjusted HR and 95% C.I for predictors of early drop out of newly diagnosed HIV infected adults from pre-ART care. In brief, variables were ordered according to their strength of association and added in turn to assess if they retained, lost or acquired an effect on drop out. LRT was used to assess the best fitting model. Since seasonal drop out was matched on time, it became unidentifiable and could not be distinguished from follow up time in proportional hazard analysis. The risk factors identified in the final Cox model were therefore fit with the time updated season using poisson regression.

Analysis 2: Predictors of non-follow up

Since these patients never returned after registration, time updated season was not assessed in this analysis. Logistic regression was used to assess baseline predictors for non-follow up. A univariable analysis was done. Crude odds ratios (ORs), 95% C.I and Likelihood Ratio Test (LRT) p-values were presented. A forward stepwise model building approach was used to set up a multivariable logistic regression model. Adjusted ORs, 95% C.I and LRT p-values were presented for predictors independently associated with non-follow up.

Analysis 3: Predictors of time to LTFU

We were also interested in finding out if LTFU patients shared the same predictors as non-follow ups. Hence, we assessed for predictors of time to LTFU from pre-ART care. A univariable followed by a multivariable Cox proportional hazard regression analysis using a forward stepwise approach was conducted to assess for independent predictors of LTFU in the third part of the analysis. Hazard ratios (HR), 95% C.I and Likelihood Ratio Test (LRT) p-values were presented. Time updated season was assessed as in 'drop out' analysis described above.

Reliability

Being a programmatic study, we were compelled to assess the reliability of the data collected. We used BMI as a proxy of the other risk factors to assess this. Since anthropometry data was collected at every individual visit, and newly registered patients were initially given a two weeks appointment as described above, we assumed it was unlikely that the BMI would substantially

change in the given period. Hence, we used these two repeated BMI measurements (stratified into less than or more than 18.5Kg/m²) to assess the agreement between them.

2.8 Ethics

This study used data from a parent project for which national scientific and ethics approval (Kenya medical research institute, Scientific Steering Committee No. 1341) was granted. Permission from the Principal Investigator to use the data for this project was also granted. The study was approved by the Ethics Committee of the London School of Hygiene and Tropical Medicine, University of London, in partial fulfilment leading to the award of a Master of Science in Epidemiology.

3.0 RESULTS

Cohort Characteristics

Out of the 1242 patients registering for care at the CCRC between 01st July 2008 and 31st August 2009, 868 were adults aged ≥ 15 years recently diagnosed with HIV. Of these, 530 (61.1%) were not eligible for ART at enrolment and were included in this analysis. During the six month follow up period, 134 patients were either started on ART (59, [12.8%]) or FBP (45 [10.2%]) or both (30 [34.1%]). One hundred and eighty nine (35.6%) of the newly diagnosed adults not yet eligible for ART satisfied the case definition for drop out during the 6 months following registration, of whom 96 (50.1 %) were non-follow ups (Figure 3).

Of the 530 patients included in the analysis, 118 (22.3%) were male. At registration, the patients had a mean age of 32.4 (standard deviation (s.d) 10.2, minimum-maximum (min-max) 15.1 – 78.2) years, CD4 count of 450.3 (s.d. 200.1, min-max 200.0 – 1276.0) cells/uL and BMI of 21.2 (s.d. 3.7, min-max 13.5 – 38.7) kg/m². The average distance from their home to the hospital was 11.4 (s.d. 10.2, min-max 0.8 – 44.5) km and from home to main road was 3.4 (s.d. 5.4, min-max 0.0 – 41.7) km. Most of the patients were referred for HIV care from VCT centres (53.8%) and registered for care during the dry season (57.4%). Compared to their female counter-parts, male patients were more likely to be single (17.8% vs. 10.9%), more educated (34.8% vs. 13.4%) and with a higher hemoglobin level (12.2 vs. 9.7 g/dL) (Table 1).

Population density at the sub-location level was not normally distributed with a median of 24.3 (IQR, 1.2 – 242.8) people/km². This was grouped into “urban” and “rural” using a cut-off of 25people/km². Direct distance to the hospital was found to be correlated with near distance to the main road (correlation coefficient, 0.75). We decided to exclude direct distance to the

hospital from further analysis based on the argument that patients living far from hospital but near the main road were, in fact, closer to the hospital than those living far from the main road, other assumptions held constant.

We were unable to estimate the distance and population density from some patients as sub-location data was either missing 21 (4.0%) or the patients lived outside the district 49 (9.2%). Baseline clinical and immunological data was also missing from 55 (10.4%) and 188 (35.5%) patients respectively.

Analysis 1: Predictors of time to drop out

Overall, 530 newly diagnosed HIV-infected adults contributed 157.8 person years of follow up. Of these, 189 (35.6%) dropped out from pre-ART care at a rate of 119.8/100 pyo. In the univariable analysis, marital status, distance to main road, entry point and time updated season were found to be associated with drop-out from HIV care (Table 2). KM survival probabilities for some of these risk factors are illustrated in figure 4.

Marital status, distance to the main road, time updated season and entry point were independent predictors of drop-out from HIV care in the multivariable analysis. Compared to single patients, married patients had half the rate (Hazard Ratio, HR [95% C.I.], p-value; 0.5 [0.3 – 0.7], p-value <0.01) while separated/divorced/widowed patients had 40% reduction (0.6 [0.3 – 0.9], p-value <0.01) of dropping out from HIV care. Patients were also less likely to drop out during the wet season compared to the dry season (0.6 [0.5 – 0.8], p<0.01).

There was good evidence suggesting a linear trend for pre-ART drop out with increasing distance to main road (LR $\chi^2 = 4.41$, p=0.03). Patients living more than five kilometres from the main road were almost four fold more likely to drop out compared to patients living within a kilometre from the main road (3.7 [2.6 – 5.2], p<0.01).

After adjusting for the effect of distance from the main road, the effect of education status on pre-ART drop out was strengthened away from the null. There was a general increase in the rate of drop out with increasing education status. Patients who had a secondary/higher education had a two-fold increase in the rate of pre-ART drop out compared to those with no schooling (2.0 [1.2 – 3.1], p=0.02).

Analysis 2: Predictors of non-follow up

This analysis was based on the 530 recently HIV diagnosed adults of whom 96 (18.1%) never returned for any follow up visit over the 6 month period. In the univariable analysis, distance to

main road and marital status were strongly associated with non-follow up. Entry point showed good evidence while age showed weak evidence of an association with non-follow up (Table 3).

In the multivariable analysis, only distance from the main road and marital status independently predicted non-follow up from HIV care. Compared to those living within a kilometer, patients living within 1-5km from the main road had almost three times the odds of not returning for care after registration (Odds Ratio (OR), [95% C.I], p-value; 2.7 [1.4 – 5.4], $p < 0.01$) while those living more than 5 km from the main road had the greatest odds of being in non-follow up (7.1 [3.9 – 12.6], $p < 0.01$). Married patients were associated with a 80% reduction in the odds of being non-follow up (0.2 [0.1 – 0.5], $p < 0.01$) while separated/divorced/widowed patients had a 70% reduction in odds of being in non-follow up (0.3 [0.1 – 0.6], $p < 0.01$), compared to single patients. After adjusting for the effect of distance to the road, the OR for entry point was attenuated to one (0.7 [0.4 – 1.2], $p = 0.17$). Immunological predictors for non-follow up were not assessed in this analysis as only 2 of the 96 non-follow ups had a CD4 test done.

Analysis 3: Predictors of time to LTFU

In this phase, we restricted our analysis to those patients who made at least one follow up visit after registration into HIV care ($n = 434$). Of these, 93 (21.4%) were determined LTFU at a rate of 59.0/100 pyo. Univariable analysis showed time updated season to have a good association with LTFU (0.6 [0.4 – 0.9], $p = 0.03$). Distance to the main road showed a weak association with LTFU. All the other risk factors had poor evidence of an association with LTFU (Table 4).

In the multivariable analysis, patients were less likely to be LTFU in the wet season compared to the dry season (HR [95% C.I], p-value; 0.6[0.4 – 0.9], $p = 0.02$). Adjusting the effect of distance to the main road on LTFU with education status strengthens both their effects, pushing their HR away from the null. Patients with a secondary/higher education were more likely to be LTFU (2.3 [1.2 – 4.1], $p < 0.01$) compared to those with no schooling (overall LR $\chi^2 = 8.1$, $p = 0.02$). Similarly, patients living more than 5km from the main road were more likely to be LTFU (1.8 [1.1 – 3.0], $p = 0.01$) compared to those living within a kilometer, (overall LR $\chi^2 = 6.8$, $p = 0.03$).

Reliability of the data

Of the newly diagnosed adults registered for HIV care, 259 (48.9%) had anthropometries taken at registration into care and repeated exactly two weeks later. At registration, 68 (26.4%) of these had a BMI of less than 18.5 kg/m². A repeat measurement after two weeks showed 66 (25.6%) of the same patients having a BMI of less than 18.5 kg/m². This gives a 95.8% agreement and a 63.7% expected agreement with a kappa of 0.88 ($z = 12.5$, $p < 0.01$).

4.0 DISCUSSION

Our findings from a routine HIV care clinic in a district hospital in Kenya suggest that more than a third of recently diagnosed HIV-infected patients registered for pre-ART care drop out before six months of follow up. Moreover, half of these drop outs were enrolled but never returned for follow up care. We report an overall dropout rate of 119.8/100 person years in this resource scarce setting. Distance, marital status, time updated season, entry point and education status independently predicted drop out. Distance and marital status were the only independent predictors of non-follow up while distance, education status and time updated season independently predicted LTFU.

Patients living further from the main road were less likely to be retained in pre-ART care. These findings are consistent with a recent study which has also shown that pre-ART patients were more likely to be lost to care if they lived further from the care centre ²⁴. Longer distances from the road and the hospital introduce accessibility challenges, as patients have to spend more money for travel and time away from work. Although HIV services are mostly offered free of charge, these indirect costs have been shown to be a deterrent to retention of patients in care and this may be an explanation in our study. Indeed, a few studies assessing for reasons of drop out from ART care showed the main cause of failure to follow up was financial, with transport costs being one of the biggest obstacles^{23, 36}. Considering the poverty levels in this setting, patients living further distances from the main road may also have opted for HIV care in a more accessible clinic without notifying the CCRC of their transfer. However, this is unlikely as all new registrations are informed and encouraged to seek HIV services from alternative peripheral centers close to their homes. For those opting for a transfer, a form is filled and patients formally referred to care centers of their choice.

Data from our setting also suggests that patients were more likely to drop out in the dry seasons. This may be explained by the fact that the community is mainly agrarian and thrives socio-economically during the wet seasons. In the dry seasons however, the community is forced to seek alternative socio-economic activities to sustain their livelihoods which may necessitate working long hours or even out-migration to other districts in search of jobs, hence dropping out of HIV care. To the best of our knowledge, this is the first study that has assessed the effect of time updated season on drop out from HIV care. A previous study assessed time from a different concept; the effect of calendar year on loss to follow up in patients on ART. They found an increased risk of dropout per unit increase in the years since the programme was started ³⁰.

Single patients were also more likely to drop out from HIV care immediately after registration. A plausible explanation to this may be that single patients do not have a support person; someone to confide in, which can be negatively affected by HIV-related stigma. This has been shown in a recent meta-ethnography to be an important barrier to adherence and retention in care³⁷. Most single people are also conventionally young, and young age has been found to be a risk factor for LTFU, albeit in patients on ART³⁴. In our setting, single patients were younger (mean [s.d], 25.9 [6.9]) compared to those married (32.4 [9.7]) or separated/widowed/divorced (35.8 [11.5]). However, age was not found to be a risk factor for drop out. Moreover, marital status appeared not to be confounded by age.

Interestingly, patients with a secondary/higher education were two-fold more likely to drop out of pre-ART care compared to patients with no schooling. However, this finding was not evident in non-follow up, suggesting that educated patients were likely to come back after registration for follow up visits but drop out thereafter. Distance to the road negatively confounds the effect of education status on drop out and LTFU. To the best of our knowledge, no previous study has assessed the effect of education on pre-ART drop out. Out-migration in search of employment may explain the drop out of educated patients from HIV care in our setting. However, this interpretation is in contrast to that from an urban HIV clinic in Durban, South Africa, which followed up ART eligible patients before starting treatment³⁸. They found unemployment, which was seen to represent socioeconomic status, to be independently associated with loss to care. This difference may be because their study was conducted in a pre-dominantly urban context where the more educated participants did not have to out-migrate in search of employment. Unlike in our cohort, participants in their study also had to pay for HIV services which may reflect the financial burden amongst the unemployed in their study.

Patients were more likely to drop out if they were referred from the in-patient wards. This finding is similar to that from the South African Test, Identify and Link (STIAL) cohorts which found that patients referred for HIV care by a health practitioner were more likely to be lost to care²⁴. This may be because self referred patients (who mostly volunteer for testing and undergo counseling) are better prepared and more willing to accept their status and subsequent care. Entry point was not associated with LTFU. For non-follow up, entry point was positively confounded by the effect of distance to main road. This is plausible as entry point is directly related to distance (patients are referred from distant peripheral clinics to the district hospital for admission and in-patient care) and independently associated with non-follow up (patients are more likely to drop out of HIV care if they are referred from the in-patient wards).

Importantly, severe diseases/immunosuppression as determined by laboratory markers (CD4 count, hemoglobin levels) and clinical markers (WHO staging, BMI) did not predict drop out from pre-ART care in this setting. Most previous studies on loss to HIV care in patients started on ART have identified lower CD4 counts, lower BMI, WHO staging III & IV, and lower hemoglobin levels to be independently associated with drop out. To date, we are unaware of any other study that has assessed the effect of these markers on pre-ART drop out in SSA.

In view of the fact that previous literature suggests severe immune suppression and high rates of early mortality at the time of ART initiation from ART programmes ^{10-11, 19}, it is plausible that recently HIV-infected patients register for care and drop out while they are still healthy, only to present later with advanced HIV infection. If this is the case, then we argue that focusing and redirecting resources towards provision of an enhanced standard package of pre-ART care would be more cost effective and beneficial in the long term. This is especially considering attempts to trace LTFU patients from ART programme determined that 50% had died, 27% could not be found ¹⁶. Tracing patients has also been proved to be resource intense and often unsuccessful ³⁹.

The pre-ART package of care may include a structured framework of counseling and support at registration into HIV care. This approach has been applied in ART programmes to enhance retention and ART adherence in different settings with relative success⁴⁰. Evidently, the same approach is equally important in pre-ART patients registering for HIV care. Other pre-ART care services may include provision of prophylactic anthelmintics, isoniazid preventive therapy (IPT), multivitamins and nutritional support in form of food programmes, especially during the dry seasons for the latter. These interventions, especially targeted at the population at high risk of drop out, may serve as an incentive for follow up and counter the indirect costs incurred to attend care for those coming from far. They also have the potential to be more cost effective and beneficial in the long term. An improved pre-ART package of care will not only serve to enhance retention, but also slow disease progression, enable timely initiation on ART for those eligible, reduce early mortality and prolong overall survival. Indeed, cotrimoxazole, which is one of the pre-ART services currently offered in our setting, has been shown to reduce morbidity and slow HIV disease progression substantially ⁴¹. Intervention studies on anthelmintics and IPT have also shown that these cheap and readily available interventions administered in pre-ART patients have the potential to slow HIV disease progression by reducing tuberculosis incidence, lowering viral load and increasing CD4 count ⁴²⁻⁴³.

Our findings should be interpreted in light of several limitations. Firstly, more than a third of the immunological data were missing. This may have reduced the power of our study to show an effect of CD4 count and hemoglobin levels on pre-ART drop out, which may suggest that the findings on these risk factors could have occurred by chance. Moreover, this may also suggest that those without missing immunological data may be different to those with missing data, hence selection bias. However, the HR could have been biased either way i.e. if more patients with a missing CD4 count actually had lower CD4 counts, this suggests patients should have either been excluded from the analysis (as they were ART eligible) or were more likely to drop out if they had advanced HIV disease. On the contrary, if more of these patients had higher CD4 counts, then it would suggest that patients were more likely to drop out if they were healthier. Additionally, clinical indicators have been found to be equally good as markers of immunosuppression and are in fact, the most commonly adopted method of assessing for HIV disease severity in resource limited settings. Our data had almost 90% of the clinical data available.

Secondly, different definitions have been used to assess drop out in different studies, with each having its pros and cons. Although we used an outcome definition which was empirically defined, this definition was only studied in patients on ART. Thus applying the definition on a pre-ART cohort may be deemed inappropriate as it may seem too restrictive. The narrow time interval used may have resulted to patients being misclassified as drop outs even when they resumed care immediately after. In our case, this may have resulted to an overestimation of the drop out rate. However, this was unlikely to have had any effect on the predictors of drop out from pre-ART care. This limitation implies need for a standardized approach to defining drop out in the pre-ART population based on empiric evidence.

Thirdly, non-differential misclassification of our exposure and outcome variables may have occurred. Being a programmatic cohort, data were routinely collected and measurement errors in the clinical and laboratory data may have arisen. This may have resulted to a dilution of our HRs towards the null. However, an assessment of the reliability of the data showed good agreement in a proxy risk factor, suggesting that the data is dependable and random errors were limited.

Fourthly, we followed patients over the first six months from registration into HIV care but estimated drop out using patients' last missed visit. Patients who may have dropped out immediately after registration but resumed care during the defined follow up period would have been determined to be in follow up by our definition. This would have resulted in an

underestimation of our drop out rate. However, the short follow up period used to determine early drop out would have made this highly unlikely.

Lastly, we assessed for a broad range of risk factors including socio-demographic, clinical and laboratory data which were routinely collected. In the process, we managed to assess variables which have been previously determined as independent risk factors. This may never rule out the possibility of unknown confounding. Measures to assess socio-economic status would have enhanced our understanding of travel costs and accessibility of HIV services in our setting. Clinic level factors, rather than individual level attributes could also contribute to pre-ART drop out. We were unable to assess these attributes as our data was only collected from one HIV clinic.

In conclusion, more attention has been given to drop out amongst patients on ART. Our study sheds more light on the burden of pre-ART drop out and identifies risk factors for potential interventions. In our setting, more than a third of recently diagnosed HIV-infected adults registered for pre-ART care dropped out before six months of follow up. Half of these drop outs never returned for follow up care after registration. Distance, marital status, education status, entry point and time updated season were independently associated with drop out. Importantly, severe HIV disease was not associated with pre-ART drop out. These findings warrant consideration of an enhanced pre-ART package of care aimed at improving retention. Improved retention has the potential to slow HIV disease progression, enable timely initiation of ART, reduce early mortality after starting ART and prolong overall survival. Hence, an improved pre-ART care package especially targeted at those recently HIV-diagnosed patients who are more at risk of dropping out from care may be both beneficial and cost effective in the long term.

Our findings may not be generalizable as the study was conducted in one clinic in a peri-urban location. Bigger studies are needed to assess the burden and risk factors for pre-ART drop out in different settings. If the findings are consistent, then more studies are warranted to assess cost effectiveness, adherence and side effects of these interventions targeted at the pre-ART populations to justify their roll out.

5.0 FIGURES AND TABLES

Figure 1: A map showing the location of the Comprehensive Care & Research Clinic (CCRC) within the Kilifi District Hospital (KDH) and the main road linking the hospital to other parts of the district and neighbouring districts to the north and the south.

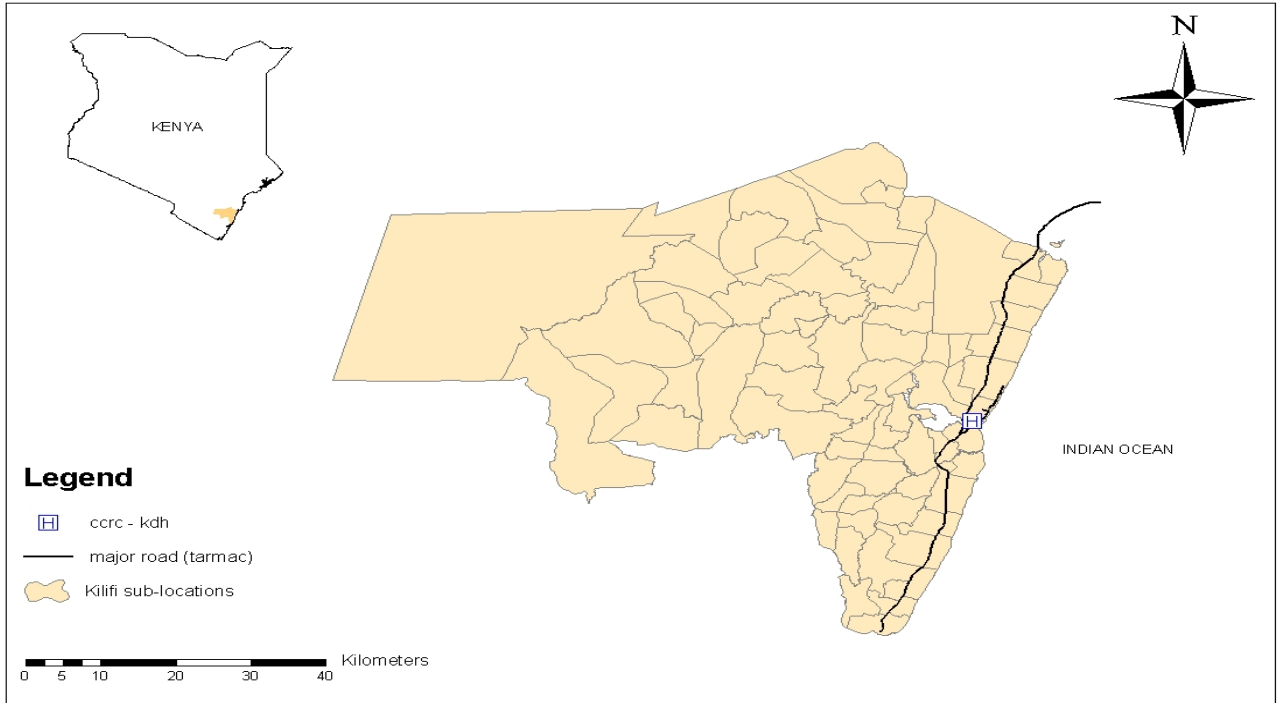


Figure 2: Diagram illustrating different end points for patients registered for HIV care over a 6-month follow up period in a district HIV clinic in Kenya.

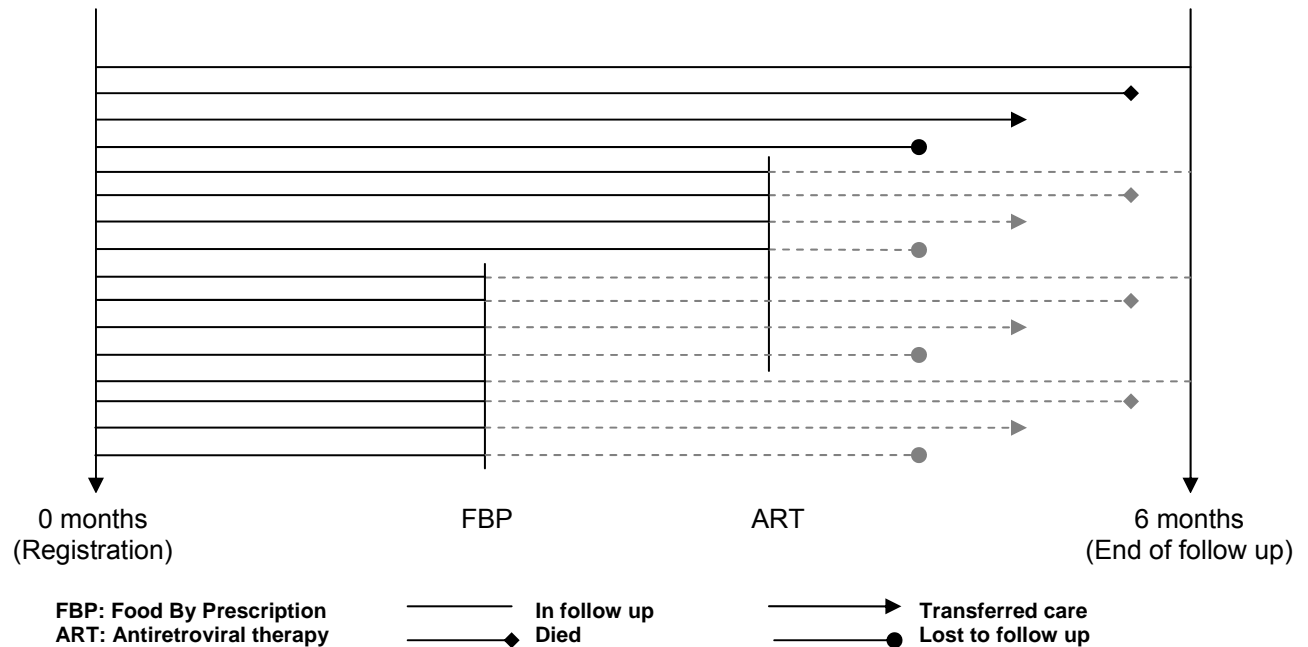
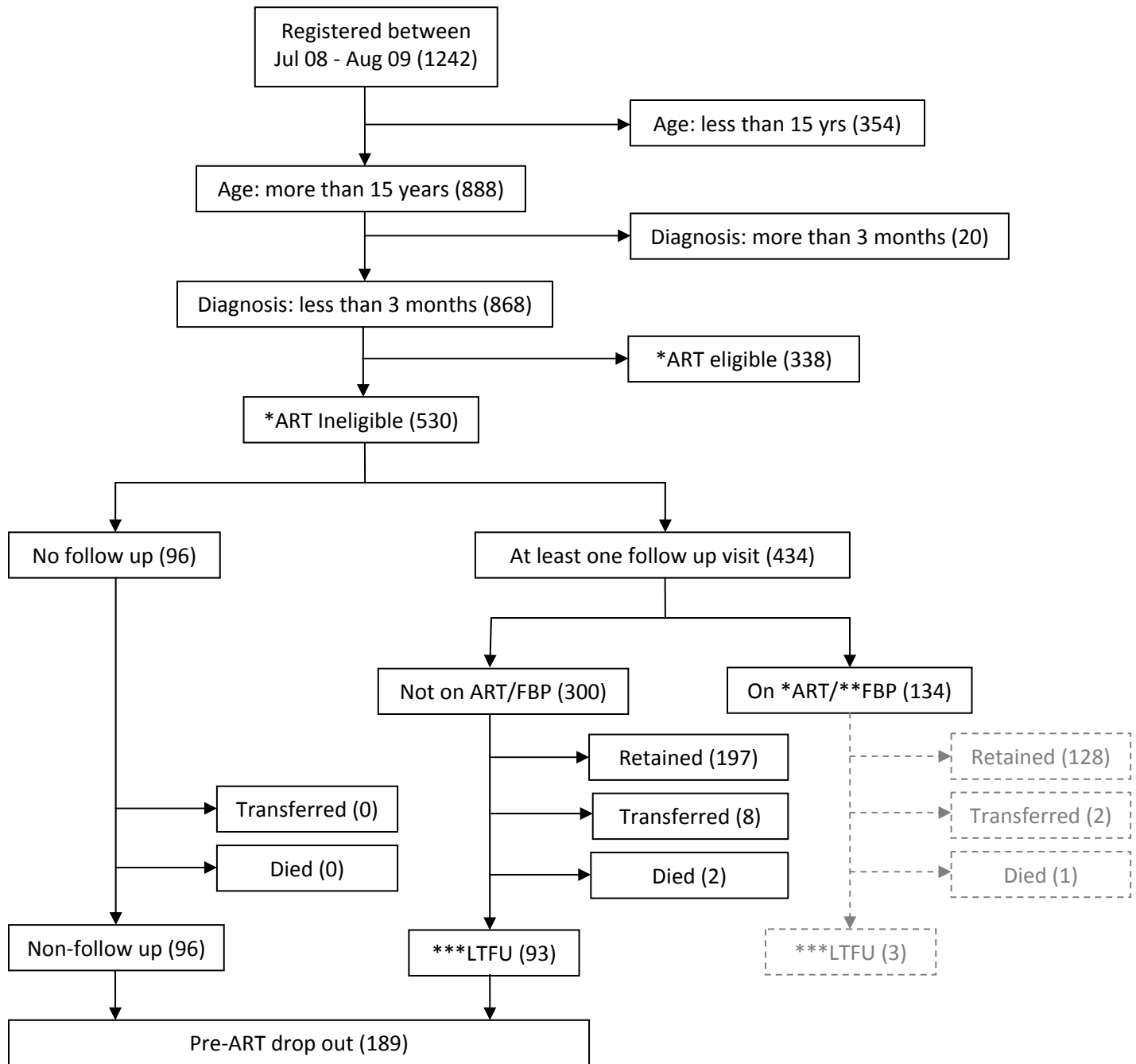


Figure 3: Figure 3: Diagram showing the flow of HIV infected adults registered and followed up for routine HIV care for 6 months in a district hospital in Kenya (N=1242).



*ART (Antiretroviral Therapy), **FBP (Food By prescription), ***LTFU (Lost to follow up),

Figure 4: Kaplan Meier (KM) curves showing drop out of newly diagnosed HIV infected adults from pre-ART care for some risk factors, followed up over 6 months in a district hospital in Kenya (N=530).

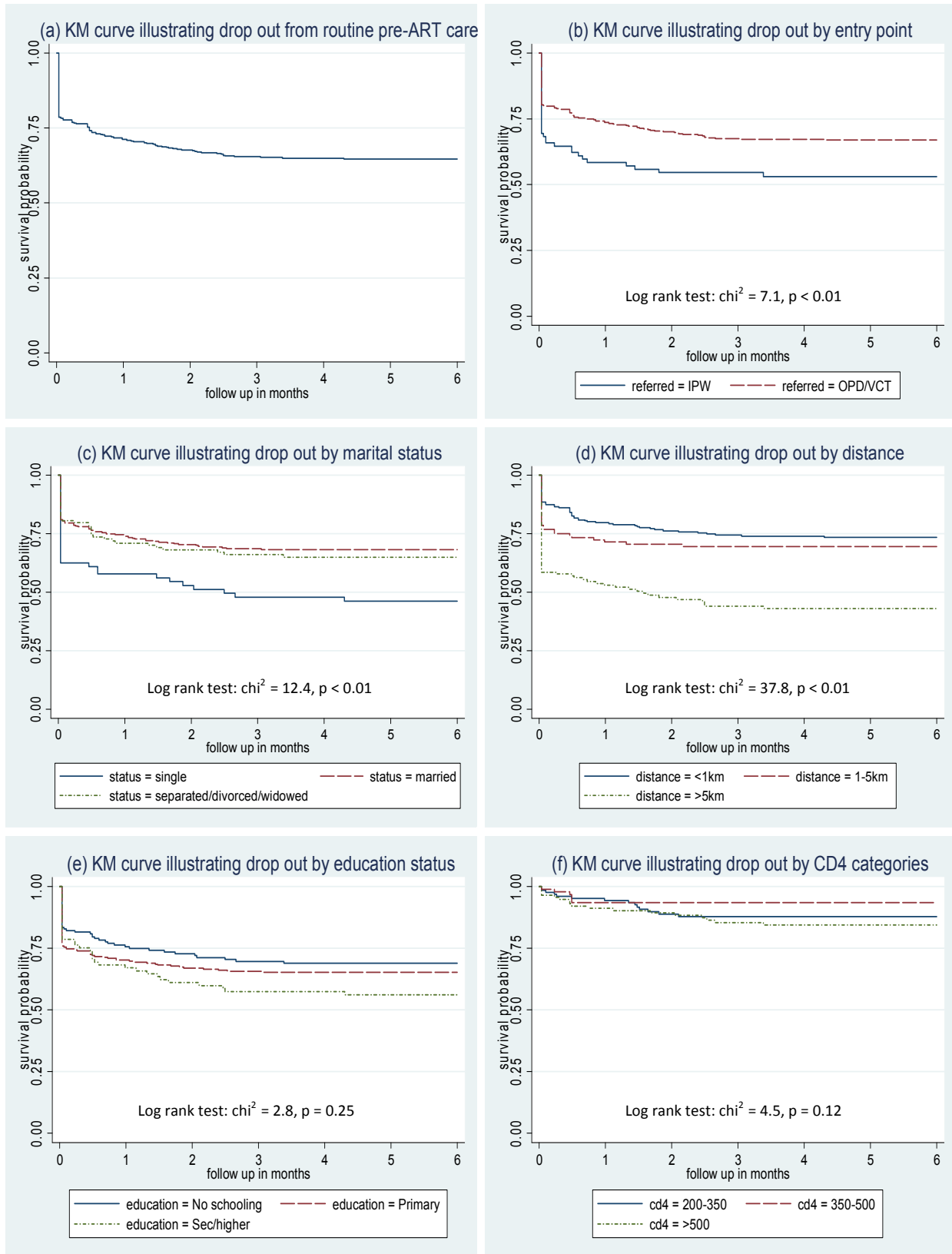


Table 1: Distribution of baseline characteristics of newly diagnosed HIV-infected ART ineligible adults registered for routine HIV care in a district hospital in Kenya (N=530).

Risk Factor	Categories	Frequency [%]		
		Males (n=118)	Females (n=412)	Total (n=530)
*Age (years)	Mean [s.d]	36.7 [10.3]	31.2 [9.9]	32.4 [10.2]
	[Min – Max]	[17.8 – 70.3]	[15.1 – 78.2]	[15.1 – 78.2]
Age group (years)	15.0 – 25.0	12 [10.2]	117 [28.4]	129 [24.3]
	25.1 – 35.0	47 [39.8]	179 [43.5]	226 [42.6]
	> 35.0	59 [50.0]	116 [28.2]	175 [33.0]
Marital status	Single	21 [17.8]	45 [10.9]	66 [12.5]
	Married (mono/poly)	85 [72.0]	259 [62.9]	344 [64.9]
	Separated/Divorced/Widowed	12 [10.2]	108 [26.2]	120 [22.6]
∞Entry point	In-patient wards	18 [75.3]	67 [16.3]	85 [16.0]
	Out-patient clinics	20 [16.9]	140 [33.9]	160 [30.2]
	VCT centers	80 [67.8]	205 [49.8]	285 [53.8]
Religion	Christian	67 [56.8]	269 [65.3]	336 [63.4]
	Muslim	27 [22.9]	71 [17.2]	98 [18.5]
	Others	24 [20.3]	72 [17.5]	96 [18.1]
Education status	No schooling	15 [12.7]	143 [34.7]	158 [29.8]
	Primary schooling	62 [52.5]	214 [51.9]	276 [52.1]
	Secondary/Higher	41 [34.8]	55 [13.4]	96 [18.1]
Population density (sub-location level)	Rural (<25 people/km ²)	50 [42.4]	181 [43.9]	231 [43.6]
	Urban (>25people/km ²)	48 [40.7]	181 [43.9]	229 [43.2]
	Missing	20 [16.9]	50 [12.1]	70 [13.2]
*Distance from home to the hospital (km)	Mean [s.d]	10.9 [9.5]	11.6 [10.5]	11.4 [10.2]
	[Min – Max]	[0.8 – 36.3]	[0.8 – 44.5]	[0.8 – 44.5]
Group distance from home to the hospital (km)	<5.0	43 [36.4]	144 [35.0]	187 [35.3]
	5.0 – 20.0	39 [33.1]	147 [35.7]	186 [35.1]
	>20.0	31 [26.3]	105 [25.5]	136 [25.7]
	Missing	5 [4.2]	16 [3.9]	21 [4.0]
*Distance from home to the main road (km)	Mean [s.d]	2.9 [4.1]	3.5 [5.8]	3.4 [5.4]
	[Min – Max]	[0.0 – 19.5]	[0.0 – 41.7]	[0.0 – 41.7]
Group distance from home to the road (km)	<1.0	57 [48.3]	203 [49.3]	260 [49.1]
	1.0 – 5.0	30 [25.4]	88 [21.4]	118 [22.3]
	>5.0	26 [22.0]	105 [25.5]	131 [24.7]
	Missing	5 [4.2]	16 [3.9]	21 [4.0]
Season at registration	Dry	71 [60.2]	233 [56.6]	304 [57.4]
	Wet	47 [39.8]	179 [43.5]	226 [42.6]
WHO staging	Stage I	49 [41.5]	209 [50.7]	258 [48.7]
	Stage II	51 [43.2]	166 [40.3]	217 [40.9]
	Missing	18 [15.3]	37 [7.0]	55 [10.4]
*BMI (Kg/m ²)	Mean [s.d]	20.5 [2.8]	21.4 [3.9]	21.2 [3.7]
	(Min – Max)	[14.8 – 32.9]	[13.5 – 38.7]	[13.5 – 38.7]
BMI groups (Kg/m ²)	< 18.5	16 [13.6]	83 [20.2]	99 [18.7]
	≥ 18.5	83 [70.3]	284 [68.9]	367 [69.3]
	Missing	19 [16.1]	45 [10.9]	64 [12.1]
*CD4 count (cells/uL)	Mean [s.d]	428.9 [177.3]	455.9 [205.6]	450.3 [200.1]
	(Min – Max)	[201.0 – 960.0]	[200.0 – 1276.0]	[200.0 – 1276.0]
CD4 groups (cells/uL)	200 – 350.0	31 [26.3]	99 [24.0]	130 [24.5]
	350.1 – 500.0	20 [17.0]	77 [18.7]	97 [18.3]
	> 500.0	20 [17.0]	95 [23.1]	115 [1.7]
	Missing	47 [39.8]	141 [34.2]	188 [35.5]
*Hemoglobin (g/dL)	Mean [s.d]	12.2 [1.9]	9.7 [2.0]	10.2 [2.2]
	(Min – Max)	[8.2 – 16.0]	[4.8 – 18.0]	[4.8 – 18.0]
Hemoglobin groups (g/dL)	<8.0	0 [0.0]	47 [11.4]	47 [8.9]
	8.0 – 10.0	6 [5.1]	67 [16.3]	73 [13.8]
	10.1 – 12.0	22 [18.6]	65 [15.8]	87 [16.4]
	> 12.0	20 [17.0]	24 [5.8]	44 [8.3]
	Missing	70 [59.3]	209 [50.7]	279 [52.6]

*Mean ([s.d] standard deviation) and ([Min – Max] Minimum/Maximum) included for continuous variables, ∞Site where patients have been referred from, BMI (Body Mass Index), VCT (Voluntary Counseling and Testing), WHO (World Health Organization).

Table 2: Univariable and multivariable analysis to determine predictors for pre-ART 'drop out' in newly diagnosed HIV infected adult patients registered for routine HIV care in a district hospital in Kenya (N=530).

Risk factors	Categories	Drop out [n/pyo] n=189	^β KM Survival probability	Cox univariable analysis			Cox multivariable analysis		
				Crude HR	95% C.I	^α P-value	[‡] Adjusted HR	95% C.I	^α P-value
Gender	Male	48/36.6	0.61	1.0	-				
	Female	141/121.2	0.66	1.0	0.7 – 1.3	0.78	-	-	-
Age group (years)	15.0 – 25.0	54/36.3	0.59	1.0	-				
	25.1 – 35.0	78/67.8	0.66	0.8	0.5 – 1.1				
	>35.0	57/53.7	0.68	0.7	0.5 – 1.0	0.11	-	-	-
Marital status	Single	36/16.5	0.46	1.0	-		1.0	-	
	Married (mono/poly)	111/106.8	0.68	0.5	0.3 – 0.7		0.5	0.3 – 0.7	
	Separated/Divorced/Widowed	42/34.5	0.65	0.6	0.4 – 0.9	<0.01	0.6	0.3 – 0.9	<0.01
Entry point	In-patient wards	41/22.2	0.53	1.0	-		1.0	-	
	Out-patient /VCT centers	148/135.7	0.67	0.5	0.4 – 0.7	<0.01	0.6	0.4 – 0.9	0.01
Religion	Christian	120/100.4	0.65	1.0	-				
	Muslim	30/31.7	0.70	0.8	0.5 – 1.2				
	Others	39/25.6	0.58	1.2	0.8 – 1.8	0.18	-	-	-
Education status	No schooling	48/47.4	0.69	1.0	-		1.0	-	
	Primary schooling	99/83.4	0.65	1.3	0.9 – 1.8		1.4	0.9 – 2.1	
	Secondary/Higher	42/27.0	0.56	1.5	1.0 – 2.3	0.14	2.0	1.2 – 3.1	0.02
Population density (sub-location level)	Rural (<25 people/km ²)	70/74.1	0.70	1.0	-				
	Urban (>25people/km ²)	68/74.7	0.71	1.0	0.7 – 1.4	0.86	-	-	-
Group distance from home to the road (km)	<1.0	72/89.0	0.73	1.0	-		1.0	-	
	1.0 – 5.0	36/34.9	0.69	1.2	0.8 – 1.8	0.03 [†]	1.4	0.9 – 2.1	
	>5.0	74/27.7	0.43	3.2	2.3 – 4.4	<0.01	3.7	2.6 – 5.2	<0.01
Season at registration	Dry	115/92.3	0.63	1.0	-				
	Wet	74/65.5	0.68	1.0	0.7 – 1.4	0.86	-	-	-
**WHO staging	I	69/88.7	0.73	1.0	-				
	II	66/68.3	0.71	1.2	0.9 – 1.7	0.30	-	-	-
**BMI groups (Kg/m ²)	< 18.5	26/28.9	0.72	1.0	-				
	≥ 18.5	103/126.3	0.73	0.9	0.6 – 1.4	0.57	-	-	-
**CD4 groups (cells/uL)	200 – 350.0	16/45.5	0.88	1.0	-				
	350.1 – 500.0	9/41.7	0.93	0.5	0.2 – 1.2				
	> 500.0	17/45.3	0.84	1.0	0.5 – 2.0	0.23	-	-	-
**Hemoglobin groups (g/dL)	<8.0	7/17.2	0.86	1.0	-				
	8.0 – 10.0	6/28.1	0.91	0.5	0.2 – 1.5				
	10.1 – 12.0	12/35.5	0.86	0.7	0.3 – 1.8				
	> 12.0	7/18.0	0.87	0.8	0.3 – 2.4	0.65	-	-	-
*Time updated season	Dry	103/71.8		1.0	-		1.0		
	Wet	86/86.0		0.7 ^{*1}	0.5 – 0.9	0.01	0.6 ^{*2}	0.5 – 0.8	<0.01

*Time varying covariate expanded to assess for the hazard of drop out over changing seasons using poisson regression; (¹ univariable, ² adjusted for marital status, entry point, education status, distance to the road), ^β Kaplan Meier Survival probabilities at six months of follow up, ^α Likelihood Ratio Test p-value, [†] P-value for trend, [‡] Adjusted for other variables, BMI (Body Mass Index), VCT (Voluntary Counseling and Testing), WHO (World Health Organization). **Missing data: WHO staging (n=55 [10.4%]), BMI (n=64 [12.1%]), CD4 count (n=188 [35.5%]), Hemoglobin (n=279 [52.6%])

Table 3: Univariable and multivariable analysis to determine predictors for 'non-follow up' in newly diagnosed HIV infected adult patients registered for routine HIV care in a district hospital in Kenya (N=530).

Risk factors	Categories	Non-follow up [%] n=96	Univariable analysis			Multivariable analysis		
			Crude OR	95% C.I	^α P-value	[‡] Adjusted OR	95% C. I	^α P-value
Gender	Male	25/118 [21.4]	1.0	-				
	Female	71/412 [17.2]	0.8	0.5 – 1.3	0.33	-	-	-
Age group (years)	15.0 – 25.0	32/129 [24.6]	1.0	-				
	25.1 – 35.0	33/226 [14.6]	0.5	0.3 – 0.9				
	>35.0	31/175 [17.8]	0.7	0.4 – 1.1	0.07	-	-	-
Marital status	Single	23/66 [34.9]	1.0	-		1.0	-	
	Married (mono/poly)	51/344 [14.8]	0.3	0.2 – 0.6		0.2	0.1 – 0.5	
	Separated/Divorced/Widowed	22/120 [18.3]	0.4	0.2 – 0.8	<0.01	0.3	0.1 – 0.6	<0.01
Entry point	In-patient wards	23/85 [26.7]	1.0	-				
	Out-patient/VCT centers	73/445 [16.4]	0.5	0.3 – 0.9	0.02	-	-	-
Religion	Christian	61/336 [18.2]	1.0	-				
	Muslim	14/98 [14.3]	0.8	0.4 – 1.4				
	Others	21/96 [21.9]	1.3	0.7 – 2.2	0.39	-	-	-
Education status	No schooling	24/158 [15.2]	1.0	-				
	Primary schooling	54/276 [19.5]	1.4	0.8 – 2.3				
	Secondary/Higher	18/96 [19.0]	1.3	0.7 – 2.5	0.51	-	-	-
Season at registration	Dry	53/304 [17.5]	1.0	-				
	Wet	43/226 [19.0]	1.1	0.7 – 1.7	0.67	-	-	-
Population density (sub-location level)	Rural (<25 people/km ²)	30/229 [8.6]	1.0	-				
	Urban (>25people/km ²)	22/231 [20.0]	1.4	0.8 – 2.6	0.23	-	-	-
Group distance from home to the road (km)	<1.0	23/260 [8.9]	1.0	-		1.0	-	
	1.0 – 5.0	21/118 [17.7]	2.2	1.2 – 4.2		2.7	1.4 – 5.4	
	>5.0	49/131 [37.4]	6.1	3.5 – 10.7	<0.01	7.1	3.9 – 12.6	<0.01
**WHO staging	Stage I	20/258 [7.7]	1.0	-				
	Stage II	25/217 [11.5]	1.6	0.8 – 2.9	0.16	-	-	-
**BMI groups (Kg/m²)	< 18.5	8/99 [8.1]	1.0	-				
	≥ 18.5	36/367 [9.8]	1.2	0.6 – 2.7	0.60	-	-	-

^α Likelihood Ratio Test p-value, [‡] Adjusted for other variables, BMI (Body Mass Index), VCT (Voluntary Counseling and Testing), WHO (World Health Organization).

**Missing data: WHO staging (n=55 [10.4%]), BMI (n=64 [12.0%])

Table 4: Univariable and multivariable analysis of predictors for Pre-ART 'loss to follow up' in newly diagnosed HIV infected adult patients registered for routine HIV care in a district hospital in Kenya (N=434).

Risk factors	Categories	LTFU [n/pyo] n=93	Cox univariable analysis			Cox multivariable analysis		
			Crude HR	95% C.I	^α P-value	[‡] Adjusted HR	95% C.I	^α P-value
Gender	Male	23/36.5	1.0	-				
	Female	70/121.1	0.9	0.6 – 1.5	0.72	-	-	-
Age group (years)	15.0 – 25.0	22/36.2	1.0	-				
	25.1 – 35.0	45/67.7	1.0	0.6 – 1.7				
	>35.0	26/53.6	0.8	0.4 – 1.4	0.42	-	-	-
Marital status	Single	13/16.5	1.0	-				
	Married (mono/poly)	60/106.7	0.7	0.4 – 1.2				
	Separated/Divorced/Widowed	20/34.4	0.7	0.3 – 1.4	0.44	-	-	-
Entry point	In-patient wards	18/22.1	1.0	-				
	Out-patient /VCT centers	75/135.5	0.7	0.4 – 1.2	0.26	-	-	-
Religion	Christian	59/100.3	1.0	-				
	Muslim	16/31.7	0.9	0.5 – 1.5				
	Others	18/25.6	1.2	0.7 – 2.1	0.58	-	-	-
Education status	No schooling	24/47.3	1.0	-		1.0	-	
	Primary schooling	45/83.3	1.1	0.7 – 1.8		1.1	0.7 – 1.9	
	Secondary/Higher	24/27.0	1.8	1.0 – 3.2	0.10	2.3	1.2 – 4.1	0.02
Population density (sub-location level)	Rural (<25 people/km ²)	48/74.1	1.0	-				
	Urban (>25people/km ²)	38/74.7	0.6	0.3 – 1.1	0.11	-	-	-
Group distance from home to the road (km)	<1.0	49/89.0	1.0	-		1.0	-	
	1.0 – 5.0	15/34.9	0.8	0.4 – 1.4		0.8	0.5 – 1.5	
	>5.0	25/27.6	1.6	1.0 – 2.6	0.07	1.8	1.1 – 3.0	0.03
Season at registration	Dry	62/92.2	1.0	-				
	Wet	31/65.4	0.7	0.5 – 1.1	0.11	-	-	-
**WHO staging	I	49/88.7	1.0	-				
	II	41/68.3	1.0	0.7 – 1.6	0.88	-	-	-
**BMI groups (Kg/m ²)	< 18.5	18/28.9	1.0	-				
	≥ 18.5	67/126.2	0.8	0.5 – 1.3	0.41	-	-	-
**CD4 groups (cells/uL)	200 – 350.0	15/45.5	1.0	-				
	350.1 – 500.0	9/41.7	0.6	0.3 – 1.3				
	> 500.0	16/45.3	1.0	0.5 – 2.1	0.31	-	-	-
**Hb groups (g/dL)	<8.0	7/17.2	1.0	-				
	8.0 – 10.0	5/28.1	0.4	0.1 – 1.3				
	10.1 – 12.0	11/35.5	0.6	0.2 – 1.7				
	> 12.0	7/18.0	0.8	0.3 – 2.4	0.48	-	-	-
* Time updated season	Dry	53/71.7	1.0	-		1.0	-	
	Wet	40/85.8	0.6 ^{*1}	0.4 – 0.9	0.03	0.6 ^{*2}	0.4 – 0.9	0.02

*Time varying covariate expanded to assess for the hazard of drop out over changing seasons using poisson regression (^{*1} univariable, ^{*2} adjusted for education status and distance to the road), ^α Likelihood Ratio Test p-value, [‡]Adjusted for other variables, LTFU (Lost to follow up), BMI (Body Mass Index), VCT (Voluntary Counseling and Testing), WHO (World Health Organization), **Missing data: WHO staging (n=4 [0.9%]), BMI (n=12 [2.8%]), CD4 count (n=94 [21.7%]), Hemoglobin (n=185 [42.6%])

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7.0 APPENDICES

Appendix 1: Table summarizing findings from a literature review on drop out from HIV programmes in Sub-Saharan Africa.

No.	Author, (year)	Location (country)	Study design	LTFU definition	ART status	Sample size	Follow up period	% LTFU	Outcome	Risk factors
1	Tassie J.M et al (2010)	SSA, (22 countries)	Cohort (Aggregated data)	(post-appmt) 90 days	On ART	144038	12 mo 24 mo 36 mo 48 mo	24.8 33.2 34.4 32.8	Retention trends	-
2	Fox M.P et al (2010)	Johannesburg, (S. Africa)	Cohort	(post-appmt) 3 months	On ART	6205	4 yrs	21	Mortality in patients LTFU	History of Tuberculosis CD4 count (<100) BMI (<17.5Kg/m ²) Haemoglobin (<10.0) On treatment (<6 months)
3	Bassett I. V et al (2010)	Kwa Zulu Natal (S. Africa)	Cohort	(post-appt) 3 phone calls	Pre-ART	1474	12 mo	27	ART initiation	Gender (men) Family/friends without HIV
4	Geng E. H. et al, (2010)	Mbarara (Uganda)	Cohort	(last visit) 6 mo	On ART	3628	1 yr 2 yrs 3 yrs	16 30 39	Reasons & outcomes of patients LTFU	Financial reasons Religious reasons Sickness Other responsibilities
5	O'Brien D.P et al (2010)	20 conflict areas (SSA)	-	(undefined)	On ART	4145	12 mo	11	(MSF experience in conflict areas)	-
6.	Losina E. et al (2010)	Durban (S. Africa)	Cohort	(Post HIV dx) CD4<2 mo	Pre-ART	454	6 mo	45	Pre-treatment Loss to Care	Distance (>10km) History of TB treatment Referral (PITC)
7	Chi H. B et al (2010)	Lusaka (Zambia)	Cohort	Range of days late intervals	On ART	33704	-	-	Empiric definition of LTFU	-
8	Massaquoi M. et al(2009)	Thyolo, (Malawi)	Cohort	(Last visit) 3 months	On ART	4074	12 mo	9.9, 1.5	Retention and attrition	Site: District, Health centre
9	Palombi L. et al (2009)	(Mozambique) (Malawi) (Guinea)	Cohort	(Last visit) 3 months	On ART	3749	36 mo	8	Death Loss to follow up 2 nd line switch	Lower baseline BMI Missed visits Later calendar year
10	Yiannoutsos C. et al, (2009)	Eldoret, (Kenya)	Cohort	(Last visit) 6, 3 mo	Pre-ART On ART	8977	24 mo	36 64	Impact of LTFU on estimating Mortality	Gender (male) Age (younger) WHO stage (stage III & IV) CD4 count (lower)
11	Micek M. A et al (2009)	Beira, Chimoio (Mozambique)	Cohort	(Post-regstn) CD4<1 mo	Pre-ART On ART	3956	12 mo	23	LTFU	-
12	Losina E. et al, (2009)	Abidjan (Cote d' Ivoire)	-	(Last visit) 3 mo	On ART	6704	12 mo	18	Cost effectiveness for LTFU preventive strategies	-
13	Amuron B. et al (2009)	Jinja (Uganda)	Observational	(Screening) incomplete	Pre-ART	2483	2 mo	26	LTFU [in ART eligible patients]	Gender (male) CD4 count (Low)
14	Rougemont M. et al (2009)	Yaounde (Cameroon)	cohort	(last visit) 2 mo	On ART	312	6 mo	17	Virological treatment failure	Pharmacy refill (irregular) CDC staging (B & C)

15	Mugusi F. et al (2009)	Muhimbili (Tanzania)	Clinical trial	-	On ART	621	12 mo	16	Adherence to ART	-
16	Bassett I. V et al (2009)	Durban (S. Africa)	Cohort	(ART training) Before 3 mo	Pre-ART	501	6 mo	16	Mortality LTFU	CD4 count (Lower) Unemployment
17	Zachariah R. et al (2009)	Malawi	Cohort	(last visit) 3 mo	On ART	2316	3 mo	5	Mortality	Gender (male) Staging (IV) Weight loss
18	Brinkhof M. W. et al (2009)	10 countries (SSA & India)	Systematic review	various	On ART	6420	-	-	Outcomes of patients LTFU	Transfer care Financial problems Health (improve/worse)
19	Bajunirwe et al (2009)	Bushenyi (Uganda)	Cohort	(last visit) 3 mo	On ART	399	2 yrs	(76)	Adherence Retention	Advanced HIV (viral load) Missed visits Lack of disclosure
20	MacPherson P. et al (2009)	Bushbuckridge (S. Africa)	Cohort	Unsuccessful tracing after missed appt	On ART	1353	24 mo	2.6	Predictors of mortality	Tuberculosis Diarrhoeal disease
21	Bassett I. V. et al (2009)	Durban (S.Africa)	Cohort	(ART training visit) ≤ 3 mo	Pre-ART	501	-	16.4	Mortality Loss to care	Lower CD4 count unemployment
22	Bisson G. P. et al, (2009)	-	Perspective	-	-	-	-	-	-	-
23	Geng E.H et al, (2008)	Mbarara (Uganda)	Sampling approach	(last visit) 6 mo	On ART	3628	3.75 yrs	22.8	Outcomes of patients LTFU	-
24	Brinkhof M. W. et al (2008)	ART-LINC (Africa, Asia)	Cohort	(last visit) 6 mo	On ART	5491	6 mo	16	Risk factors for no follow up, LTFU, death	CD4 count (low) Fee for service
25	Toure S. et al (2008)	Abidjan (Cote d'Ivoire)	Cohort	(Last visit) 3 mo	On ART	10211	18 mo	21	Mortality LTFU Immune failure	low CD4 cell count low BMI low hemoglobin advanced clinical stage old age poor adherence
26	Zachariah R. et al (2008)	Nairobi (Kenya)	Cohort	(last visit) 2 mo	On ART	435	-	12	LTFU	Payment for services
27	Dalal R. P. et al (2008)	Johannesburg (S. Africa)	Cohort	(Post-appmt) 6 wks	On ART	1631	-	16.4	Causes for LTFU	Relocation/transfers Financial challenges Medication toxicity
28	Rosen S. et al (2007)	13 countries (SSA)	Systematic review	various	On ART	74192	6 12 24	(79) (75) (62)	Patient retention	-
29	Yu et al (2007)	'Nothern part' (Malawi)	-	(Last visit) 3 mo	On ART	5009	24 mo	5	True Status of patients LTFU	-
30	Karcher H. et al, (2007)	Nyanza (Kenya)	Cohort	(Post-appmt) 4 mo	On ART	159	18 mo	22	Risk factors for LTFU	Pregnancy Education (lower level) Adherence (Incomplete)
31	Lawn S. D. et al (2006)	Cape town (S. Africa)	Cohort	(Post-appmt) 4 wks	Pre-ART On ART	927	3 yrs	2.3	Determinants of mortality, LTFU	Non associated with immune status

Appendix 2: Local approval



KENYA MEDICAL RESEARCH INSTITUTE

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ESAC/PAC/SSC/2434

20th February, 2008

James Bertley
 Director, CCR
 NAIROBI

Forwarded
25/2/2008


REF: SSC No.1341 (Revised) - Antiretroviral Drug Resistance in Kihifi, Kenya

I am pleased to inform you that the above mentioned proposal in which you are the PI, was approved for implementation by the KEMRI Scientific Steering Committee (SSC), during its 14th SSC meeting held on 5th February, 2008 and has since been forwarded to the Ethical Review Committee (ERC) for consideration.

The SSC however, advises that work on this project can only start when ERC approval is received.

[Signature]
 J.C. Mwanawiro, PhD
 SECRETARY, SSC



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KEMRI/NES/7/3/1

MARCH 28, 2008

FROM: SECRETARY, KEMRI/National Ethical Review Committee
 THRO': Dr. N Peshu,
 CENTRE DIRECTOR, CGMR-C,
 NAIROBI
 TO: Dr. James Bertley (Principal Investigator)
 RE: SSC No. 1341 (Rev): Antiretroviral drug resistance in Kihifi, Kenya.

[Signature]


Dear Sir,

This is to inform you that during the 15th meeting of KEMRI/National Ethical Review Committee held on 29th MARCH 2008, the above referenced study was reviewed.

We acknowledge receipt of the following documents:

1. The study protocol
2. The Informed Consent Document in English and the Kiswahili translation

The Committee notes that in the above study you intend to determine the prevalence and impact of genotypic resistance to antiretroviral drugs among HIV-infected clients registering at Kihifi District Hospital. The Committee notes that issue of shipment and of samples and storage have been adequately addressed.

Due consideration has been given to ethical issues and the study is granted approval from today the 28th MARCH 2008 to MARCH 27th 2009.

Please note that any changes to the research study must be reported to the Scientific Steering Committee and to the Ethical Review Committee prior to implementation. This includes changes to research design, equipment, personnel, funding or procedures that could introduce new or more than minimum risk to research participants.

Respectfully,
[Signature]
 R. C. Kithinji,
 For: Secretary,
 KEMRI/NATIONAL ETHICAL REVIEW COMMITTEE

Appendix 3: Combined Academic, Risk assessment and Ethics approval form

London School of Hygiene & Tropical Medicine

(University of London)



Combined Academic, Risk assessment and Ethics (CARE) approval form for MSc Project Reports

**This form must be completed electronically. For detailed guidance, please refer to the Project Handbook for your course.*

SECTION 1 – STUDENT AND COURSE INFORMATION

MSc DETAILS AND DEADLINES (deadlines to be communicated by Course Director)

Academic Year	2009-10
MSc course (and stream, where applicable)	Epidemiology
Deadline for Supervisor approval	12-02-2009
Deadline for Course Director approval	19-02-2009
Deadline for submission to Ethics Committee	Friday 26 March 2010
Target for approved form to be passed to TSO	Friday 30 April 2010

STUDENT, SUPERVISOR AND TUTOR DETAILS (to be completed by student)

Full name of student	
Student email address	
Year of study (part-time students only)	<input type="checkbox"/> First Year <input type="checkbox"/> Second Year
Supervisor name	
Supervisor email address	
Supervisor status (at time of this version of the form being completed)	<input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Provisional <input type="checkbox"/> Still to be identified
Name of personal tutor (where Supervisor is still to be identified)	

SECTION 2 – APPROVAL AND SUBMISSION STATUS

**Students please note: It is a requirement of your LSHTM degree that you obtain all required approvals before beginning your project work. To comply with legal requirements, your Supervisor and Course Director must specifically give Risk Assessment approval. Ethical approval must also be obtained if required (answers in Section 5 will help determine if so).*

STUDENT DECLARATION (to be completed for all projects)

I agree to conduct my project on the basis set out in this form, and to consult staff (initially, my Supervisor) if making any subsequent changes – especially



any that would affect the information given with respect to ethics approval.		
I agree to comply with the relevant safety requirements, and will submit a separate request for LSHTM travel insurance where relevant.		<input checked="" type="checkbox"/>
<i>*Where seeking ethical approval for a study involving human subjects, please also attach copies of any information sheets, consent forms, and other relevant documents.</i>		
Date of declaration	17/02/2010	
<i>*Further note: when submitting your final project report at the end of the summer, you should also include a copy of your approved CARE form (which will be seen by the project markers); but to preserve anonymity, the page above – with your name – should be omitted.</i>		
STAFF APPROVAL		
<i>*Staff please note: Sections 3 and 4 of the form should be completed by the student before you are asked to sign. If you tick 'no' to any of the 'Yes/No' questions below, or disagree with any of the statements given, or have any other concerns, then you should not give approval – instead, please contact the student immediately to inform them of your concerns and discuss changes which they may need to make before you may be willing to give approval.</i>		
<i>*Supervisors and Course Directors should also be aware that in the exceptional case of a request to undertake a project in a country or region to which the Foreign & Commonwealth Office advise against travel, the student would need to fill out a separate form which will then need further School-level approval by the Safety Manager and Secretary & Registrar.</i>		
SUPERVISOR'S APPROVAL (required for all projects – this approval should be given first)		
I agree that Section 3 of this form is a reasonable summary of the proposed project.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
I agree that responses in Section 4 of this form address the main risks connected with a project of this nature.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
Name of Supervisor (if not yet identified, personal tutor or Course Director should approve)		
Date of approval	19/02/2010	
COURSE DIRECTOR'S APPROVAL (required for all projects – should follow Supervisor approval)		
I agree that the academic content of the proposed project, set out at Section 3 of this form, is suitable for this MSc.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
I agree that responses in Section 4 of this form address the main risks connected with a project of this nature.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
Name of Course Director (or nominee)	Punam Mangtani and Sara Thomas	
Date of approval	17/03/2010	
DEPARTMENTAL SAFETY SUPERVISOR'S APPROVAL (only required if project involves working with pathogenic organisms, human blood or radiochemicals – should follow Supervisor approval)		
I agree that the proposed project, as set out in this form and	<input type="checkbox"/> Yes <input type="checkbox"/> No	

particularly Section 4, may proceed.		
Name of Departmental Safety Supervisor (or nominee)		
Date of approval		
ETHICAL APPROVAL (required for all projects involving human subjects or human data, except for public domain data that cannot enable the identification of living people – NB that Supervisor approval must have been received before the application is submitted to the Ethics Committee)		
Date application received	01/04/2010	
Ethics Committee application number assigned	009/302	
On behalf of the Ethics Committee, I approve the project proposal set out on this form.		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Name of Ethics Committee scrutineer	Paula Elliot	
Date of approval	23/04/2010	
SECTION 3 – APPLICATION FOR ACADEMIC APPROVAL		
<i>*All students should complete all sub-sections (3.1, 3.2 and 3.3); if particular questions are not applicable to you then please write 'N/A'.</i>		
3.1 PROJECT OUTLINE (should not normally exceed 750 words total)		
Proposed project title: (should not normally exceed 20 words)		
Predictors for early loss of newly diagnosed HIV infected patients from routine HIV care in a developing country.		
Proposed project type: <i>*See course-specific section of Project Handbook for details of project types permitted for each MSc. Be aware that restrictions may apply for individual courses.</i>		
Data analysis		
Proposed project length: <i>*For almost all students, this will be 'Standard'. Long and extended projects are only available for certain ITD courses; they have a different schedule and allow a slightly greater word count.</i>		
<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Long <input type="checkbox"/> Extended		
Background: (about 200 words) <i>*Indicate why this topic is of interest or relevance. *If the project involves work with a specific organisation please give details. *Please give any other details specifically relevant for consideration by the Ethics Committee, e.g. related to purpose.</i>		
In the past decade, there has been a scale up of provision of HIV services in developing countries. However, a major barrier to the success of HIV programmes is the attrition of patients from care [1].		

Much attention on loss to follow up has been focused in patients on antiretroviral therapy (ART) from developed settings or from controlled research settings. A systematic review on patient retention in ART programs in sub-Saharan Africa reported 21%, 25% and 38% attrition at 6, 12 and 24 months respectively with a weighted average follow-up period of 9.9 months for all the 32 publications reviewed [2]. This has major public health and economical ramifications [3]. Lost patients already on treatment risk developing and transmitting resistance strains. Active tracing of these patients is resource intense and often unsuccessful [4]. Developing strategies that prevent patients from missing appointments may be more cost-effective than tracking those who do not return [5]. There is little existing literature on predictors for loss to follow up in newly diagnosed HIV infected patients in routine care from a developing setting. To better understand loss to follow up and formulate strategies to overcome this barrier, predictors for loss to follow up have to be defined.

Hypothesis: (about 30 words, where applicable)

Stable patients with less compromised immunity are at an increased risk for being lost to follow up.

Overall aim of project: (about 30 words)

To describe predictors for early loss of newly diagnosed HIV infected adult patients from routine HIV care in a rural area in Kenya.

Specific objectives of project: (about 70 words)

- To estimate the incidence rate of loss to follow up during the first 6 months of newly diagnosed HIV infected patients registered for care.
- To determine predictors related to loss to follow up during the first 6 months in newly diagnosed HIV infected patients registered for care.

Proposed methods: (about 200 words)

Please summarise methods, and include **any relevant details for consideration by the Ethics Committee such as numbers of participants and procedures to be performed.*

- Study design: Prospective cohort study
- Outcome: Loss to follow up (defined as non-attendance of up to three months after the date of a clinic appointment)
- Sample size: Assuming an attrition of 20% within the first 6 months in this setting, the risk of newly diagnosed patients enrolling for care being lost to follow up for a size of 683 patients will be estimated with a precision of $\pm 3\%$ with a 95% confidence interval. Almost 800 patients are available for this project.
- Available data:
 - Demographic data (collected by a fieldworker at registration): date of enrolment, date of birth, date of HIV diagnosis, age, gender, marital status, education status, referral

point (PITC/VCT), location (residence).

- Clinical data (Collected prospectively by clinician at every clinic visit and entered into an electronic database by a data entry clerk): Weight, height, WHO staging, incident infection, date started on ARV, date of next appointment.
- Laboratory data (done at enrolment and after every six months): haemoglobin, lymphocyte count, CD4 count, creatinine, alanine.

- Data collection is a continuous process done on real time.

- Staggered entry: enrolment period from September 2008 to October 2009.

- Follow up period will be 6 months; data will be censored on 30th April, 2010. This will enable us determine if patients enrolled in October 2009 have met the outcome (lost to follow up).

References: (max 150 words)

**List any key references which will shape the project, including for methods to be used. It should not normally be necessary to quote more than 5 references.*

1. Brinkhof, M.W., et al., *Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries*. Bull World Health Organ, 2008. **86**(7): p. 559-67.
2. Rosen, S., M.P. Fox, and C.J. Gill, *Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review*. PLoS Med, 2007. **4**(10): p. e298.
3. Losina, E., et al., *Cost-effectiveness of preventing loss to follow-up in HIV treatment programs: a Cote d'Ivoire appraisal*. PLoS Med, 2009. **6**(10): p. e1000173.
4. Bisson, G.P. and J.S. Stringer, *Lost but not forgotten--the economics of improving patient retention in AIDS treatment programs*. PLoS Med, 2009. **6**(10): p. e1000174.
5. Myer, L. and W. el-Sadr, *Expanding access to antiretroviral therapy through the public sector--the challenge of retaining patients in long-term primary care*. S Afr Med J, 2004. **94**(4): p. 273-4.

Prior work: (only where relevant; max 100 words)

**Indicate any previous work you have done related to this project topic, including student work, professional work, or publications.*

This project is based in Kilifi district Hospital in Kenya. The data systems were originally established for an on-going longitudinal study to determine the prevalence and impact of genotypic resistance to antiretroviral drugs among HIV-infected patients. Data from this project have also been used to write up a manuscript on the dynamics and constraints of early infant diagnosis of HIV infection which is in press. I have contributed to establishing of the systems of data collection and to the early infant diagnosis project.

3.2 FEASIBILITY (about 100 words total – but can write more or write less if appropriate)

What could cause this project to fail, i.e. prevent you from achieving your objectives?

<p><i>*Please indicate any aspects of your proposed approach which could potentially experience difficulties, e.g. delays with permissions, data collection or storage problems, lack of sufficient comparable information, etc. You may also wish to mention any wider matters which could affect your project, e.g. civil unrest, natural disasters, transport availability.</i></p>
<p>A potential challenge to this project is having a clean and complete dataset for analysis. Being routine data, I anticipate missing and erroneously entered data. However, this may be a strength of the project in the long run. Not many studies have been carried out looking at attrition from HIV care prior to ART initiation in a routine developing country. Moreover, I plan to spend my April holidays working on cleaning and ensuring as complete a dataset as possible.</p>
<p>What alternative plans do you have in case you encounter any of the potential problems you have identified?</p>
<p>Observations with missing data will be compared with those without missing data for the predisposing factors. If a risk factor is found to have an association with the observations of the missing group, adjustments will have to be made. Alternatively, the missing observations can also be exempted from the final analysis. This may power down the overall effect of the study.</p>
<p>3.3 INTELLECTUAL PROPERTY, COPYRIGHT AND OTHER PERMISSIONS</p>
<p><i>*Please also see Section 5.2 regarding any specific data rights limitations arising from local ethical or research governance requirements</i></p>
<p>If you expect to use existing data, how will you obtain it and what permissions will be required?</p>
<p>I have requested permission from the person responsible, who also happens to be my supervisor from the organisation, to use the existing data. A letter of approval will follow in due time. The data will be extracted by people in the field and sent to me via mail.</p>
<p>Having considered whether intellectual property rights (IPR) or copyright issues may affect your project, will any specific agreements be required?</p> <p><i>*Please tick all boxes that apply, and attach copies of any forms/agreements (even if in draft).</i></p>
<p><input type="checkbox"/> No specific IPR, Copyright or permissions issues should apply to this project (student retains Copyright and related IPR by default, in line with LSHTM registration declaration)</p> <p><input type="checkbox"/> IPR to be retained by LSHTM (specific LSHTM form to be completed)</p> <p><input type="checkbox"/> Copyright to be transferred to LSHTM (specific LSHTM form to be completed)</p> <p><input checked="" type="checkbox"/> IPR, Copyright or other agreements/permissions required with external parties/organisations</p>
<p>Please give any further relevant details about IPR, copyright or other permissions.</p>
<p>IPR, copyright and other agreements/permission may be required from the KEMRI/Wellcome Trust Centre for Geographic Medicine and research, Coast, Kenya.</p>

SECTION 4 – APPLICATION FOR RISK ASSESSMENT APPROVAL

**All students should answer all questions in sub-section 4.1; this will make clear which of the following sub-sections you need to complete.*

Ensuring safety during project work is the responsibility of each individual student, and not of LSHTM or LSHTM staff. **Please see the Project Handbook for further guidance.*

4.1 TYPE OF RISK (to be completed by all students)

Where will the project be carried out? (please tick all that apply)

**Note that work away from LSHTM or outside the UK means any form of work for your project, not just primary data collection. Some courses may have specific restrictions on this.*

- All work will take place either at LSHTM, in libraries in the UK, or at my personal residence in the UK.** [If so, you do not need to complete either section 4.2 or section 4.3]
- Some work will take place in the UK that is away from LSHTM sites in London, is non-Library-based, and is not at my personal residence.** [If so, section 4.2 on 'Work away from LSHTM' must be completed]
- Some work will take place at my personal residence outside the UK** [If so, section 4.3 on 'Work outside the UK' must be completed]
- Some work will take place outside the UK that is not at my personal residence** [If so, both sections 4.2 and 4.3 on 'Work away from LSHTM' and 'Work outside the UK' must be completed]

Will the project involve working with or handling any of the following materials?

- Pathogenic organisms** Yes No
- Human blood** Yes No
- Radiochemicals** Yes No

[If 'Yes' to any of the above, Sections 4.4 and 4.5 must be completed]

Are any other potentially hazardous activities likely to be carried out during the project?

- Yes No

[If 'Yes', Section 4.5 must be completed]

Do any special requirements (e.g. disability-related issues) or other concerns need to be taken into account for either you as a student, study participants or colleagues?

- Yes No

[If 'Yes', Section 4.6 must be completed]

4.2 WORK AWAY FROM LSHTM (to be completed if any work will be done away from LSHTM, other than at your home or at libraries elsewhere in the UK)

Will the project be based in an established hospital, college,

Yes No

<p>research institute, NGO headquarters, field station or other institutional site? If 'Yes', please give the name and location of the site(s); describe approximately what proportions of your project will be spent there; and state name and role of person who has confirmed willingness to support you at each site (indicating extent of correspondence, especially what they have confirmed in writing).</p>	
<p>N/A</p>	
<p>Will you have an 'external supervisor', co-supervisor or other main advisor, or be working with any specific organisation(s), during your work away from LSHTM? If 'Yes', please indicate the name, role, contact details, and level of support that any such external advisors are expected to provide, and give details about any organisations you will be working with.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>N/A</p>	
<p>Will the project involve personal visits, interviews or interactions with people in their homes, workplaces, community settings or similar? If 'Yes', please give details, including approximately what proportion of your project this will involve.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>N/A</p>	
<p>Will the project involve lone/isolated work or significant travel? If 'Yes', please give details, including approximately what proportion of your project this will involve, and state how you can be contacted while working or travelling.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>N/A</p>	
<p>What arrangements are proposed for contact with your main supervisor while you are away from LSHTM? Indicate expected ease and frequency of contact, and communication methods to be used.</p>	
<p>N/A</p>	
<p>Please tick to confirm:</p>	<p><input type="checkbox"/> I have read the LSHTM Code of Practice on off-site work.</p>
<p>4.3 WORK OUTSIDE THE UK (to be completed if any work will be done outside the UK)</p>	
<p>What form of project work will be undertaken outside the UK? (please tick all that apply)</p>	
<p><input type="checkbox"/> Work at my family home or personal residence only</p> <p><input type="checkbox"/> Work at an established hospital, college, research institute, NGO headquarters, field station or other institutional site</p> <p><input type="checkbox"/> Work away from my personal residence or an established site</p> <p><i>*Note that for either the second or third options, you should also have completed Section 4.2.</i></p>	

Name the country/countries and region(s) in which work will be undertaken:	
Country or countries: N/A Region(s) : N/A	
Do the Foreign & Commonwealth Office's (FCO) Travel Advice Notices (www.fco.gov.uk/en/travelling-and-living-overseas/travel-advice-by-country/) advise against travel to the regions(s), country or countries involved? <i>*Note that if 'Yes', the School will not normally permit such travel for project work. In exceptional circumstances only, requests may be considered by the Safety Committee and require approval by the Safety Manager and Secretary & Registrar.</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
Please tick to confirm:	<input type="checkbox"/> I understand that LSHTM travel insurance is required for any international travel as part of my project. <i>*Travel insurance can be applied for using a separate form.</i>
4.4 WORK WITH HAZARDOUS SUBSTANCES (to be completed if the project involves any work with pathogenic organisms, human blood or radiochemicals – NB that this will require approval by the Departmental Safety Supervisor)	
Name the organism or organisms to be used:	
N/A	
Identify all potential routes of infection:	
N/A	
Name the radiochemical or radiochemicals to be used:	
N/A	
List laboratories where work with pathogens or radioisotopes will be carried out:	
N/A	
List disinfectants to be used, and describe arrangements for disposal of used material:	
N/A	
Will or might Health Surveillance be required for you or any staff working with you? If 'Yes', please give details.	<input type="checkbox"/> Yes <input type="checkbox"/> No
N/A	
4.5 PRECAUTIONS AGAINST HAZARDS (to be completed if any potentially hazardous activities are likely to be carried out during the project. Refer to Project Handbook and School safety documentation for further information. Departmental Safety Supervisor's approval should be obtained where felt appropriate by project Supervisor.)	
Indicate any procedures, activities or aspects of the proposed project which may entail hazards (including work with hazardous substances as per Section 4.4, or anything else relevant). Please set distinct hazards out separately, in a numbered list.	

N/A	
<p>Indicate the precautions you will take to prevent or mitigate such potential hazards. Please number these to refer to the specific hazards identified in the preceding question.</p>	
N/A	
<p>4.6 SPECIAL REQUIREMENTS (to be completed if the project involves any special requirements, e.g. disability-related issues, or other concerns that need to be taken into account for either you as a student, study participants or colleagues)</p>	
<p>What special requirements or concerns need to be taken into account?</p>	
N/A	
<p>Do these need to be considered in planning arrangements? If 'Yes', please give details.</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
N/A	
<p>Do these impact on supervision arrangements? If 'Yes', please give details.</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
N/A	
<p>Does the project location need to be considered in relation to these? If 'Yes', please give details.</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
N/A	
<p>Do arrangements for access to specialist medical treatment need to be considered? If 'Yes', please give details.</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
N/A	
<p>SECTION 5 – APPLICATION FOR ETHICS APPROVAL</p> <p><i>*All students should answer all questions in sub-sections 5.1 and 5.2. Answers to 5.1 will make clear whether approval by the LSHTM Ethics Committee is necessary, and which later sub-sections you may need to complete. Section 5.2 covers any external approvals required.</i></p>	
<p>5.1 SCOPE OF STUDY (to be completed by all students)</p>	
<p><i>*Before completing this part of the form, please read the Ethics Approval Policy & Procedure plus guidance notes at http://intra.lshtm.ac.uk/reference/ethicsstuds.html . This describes what to do next if formal LSHTM ethics approval is required. NB that supervisor approval must be obtained before an application is submitted to the Ethics Committee.</i></p>	
<p>Which of the following applies to your project? (please tick one option only)</p> <p><i>*Note – the term 'human data' includes any documentary data, datasets or biological samples.</i></p>	

- Project does not involve any human subjects or any human data.** [If so, formal LSHTM ethics approval is not required and you do not need to complete Sections 5.3 or 5.4]
- Project involves human data, but all this human data is fully in the public domain.** [If so, formal LSHTM ethics approval is not required and you do not need to complete Sections 5.3 or 5.4]
**Public domain human data must be: available to any member of the public without special permission; to which access is not restricted in any way; and which does not enable the identification of living people, either directly or by linking to other data.*
- Project involves some non-public-domain human data, all of which was previously collected in another study or studies.** [If so, formal LSHTM ethics approval is required and Section 5.3 must be completed]
- Project involves some additional collection of data, further to an ongoing or previously completed study or studies.** [If so, formal LSHTM ethics approval is required and Section 5.4 must be completed]
- Project is a completely new study which will involve human subjects or human data.** [If so, formal LSHTM ethics approval is required and Section 5.4 must be completed]

5.2 LOCAL ETHICAL APPROVAL OR RESEARCH GOVERNANCE APPROVAL (to be completed by all students)

** As well as approval from the LSHTM Ethics Committee, projects may require specific approval from other involved or responsible bodies. For example, in the UK you may need specific authorisation to work in an NHS facility, or to work with vulnerable groups such as patients or children. Outside the UK a wide range of requirements may apply e.g. from local or national Ethics Committees, government departments etc. **Students must investigate all potential local approval required for your project work. Failure to check or gain any necessary external approval may invalidate LSHTM approval.***

Is local approval required for the work being done (whether this approval is still to be obtained, or has already been granted)?

Yes No

**This should include any forms of ethical approval, research governance approval or other specific permissions that may apply.*

If 'Yes', give details of local approval to be obtained (this must be in place before commencing fieldwork) or which has already been granted.

**Please name all bodies whose approval is required, or indicate where work is expected to take place using permissions already granted for a 'parent' project. Where approval has already been granted, quote approval reference numbers and if possible give web links to documents.*

If 'No', explain why formal local approval is not required, and describe any less formal permissions, invitations or support you are being given for this work.

**If you will be working away from LSHTM with human subjects or human data, but cannot identify a local Ethics Committee or believe that no formal approval is required, then please give details and explain what you have done to check this. In such cases, if you do not have formal approval you should always demonstrate appropriate local support, such as*

<i>correspondence with local government officials or an involved Non-Governmental Organisation.</i>	
This project is using data from a parent project for which national scientific and ethics approval (Kenya medical research institute, Scientific Steering Committee No. 1341) was granted. Permission from the Principal Investigator to use the data for this project has been granted.	
For data to be used or collected in the project, will any specific data rights permissions be required or usage limitations apply?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
N/A	
5.3 PROJECTS USING ONLY PREVIOUSLY-COLLECTED HUMAN DATA (to be completed if project involves non-public-domain human data, datasets or biological samples previously collected in another study or studies; if collecting any new data, complete Section 5.4 instead) <i>*Further guidance is given at http://intra.lshtm.ac.uk/reference/ethicsstuds.html</i>	
Summary of purpose and methods of the <u>original study or studies</u>: (max 100 words)	
<p>The main aim of the parent study is to determine the prevalence and impact of genotypic resistance to antiretroviral drugs among HIV-infected patients registering for care and examine changes in the prevalence and types of genotypic resistance among patients receiving ART and at first-line treatment failure over a five year follow up period. All patients enrolling for care are consented and socio-demographic data captured. Clinical and immunological data is also captured at routine clinic visits. Plasma is obtained from remnant blood sample routinely drawn for viral load and resistance testing.</p> <p>Previous studies report loss to follow up as a major contributor to development of antiretroviral resistance and subsequent treatment failure. This way, the current project aims to complement the work already in progress by trying to describe predictors of loss to follow up.</p>	
Give details of all approvals under which the <u>original study or studies</u> took place: <i>*Please quote names of Ethics Committees and approval reference numbers (required if previous approval was from LSHTM); if possible give web link to original study application.</i>	
National scientific and ethics approval (Kenya medical research institute, Scientific Steering Committee No. 1341) was granted for this project.	
<u>Proposed study:</u> Ensure that the project outline given in Section 3.1 states the purpose, methods and procedures of the <u>new</u> work to be done in your project, and describes how this builds on the <u>previous</u> study or studies (for which participants will already have been recruited, data or samples collected, and procedures performed). Do not reproduce here.	
Will your analyses be for purposes <u>not covered</u> by the original application detailed above? If 'Yes', indicate how you will obtain (i) permission to use the data from the principal investigator responsible for each original study; and (ii) retrospective consent, where appropriate, from the participants in each original study.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
The analysis of data in this project will be independent of the aims of the parent project. Permission to use data from the parent project has been sought and given. The data	

collected has been delinked and use of a unique identifier is operational. Moreover, the parent protocol also explained that data collected can be used for future research by trainees and other investigators. However, a new protocol will be submitted for approval if blood samples will be used for purposes other than those stated in the parent protocol.	
Does the project involve analysis of documentary information and/or data already collected from or about human subjects? If 'Yes', specify analyses briefly.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Baseline (at registration) predictors; missing baseline risk factors will be replaced using the earliest known value (so long as its < 6 months from date of enrolment) • Cox regression will be used to identify factors associated with time to first lost to follow up. Kaplan Meier survival curves will be used to describe time to loss to follow up. • Time varying co-variates i.e. starting ART will also be considered in the analysis • Multivariable regression will be used to assess predictors associated to loss to follow up. 	
Does the project involve laboratory analysis of human biological samples already collected, or new or additional analysis of stored samples? If 'Yes', specify the laboratory analyses or tests to be performed.	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
N/A	
Specify how confidentiality will be maintained. When small numbers are involved, indicate how possible identification of individuals will be avoided.	
Data collection is done routinely. However, a password protected secure database is in use for electronic data collection. Access to this system is restricted to the study personnel. Moreover, use of a delinked data system with a unique patient identifier is also in place.	
5.4 PROJECTS COLLECTING ANY NEW HUMAN DATA (to be completed if project involves collection of human data, datasets or human biological samples – either as a completely new study, or collecting additional data further to an ongoing or previously completed study) <i>*Further guidance is given at http://intra.lshtm.ac.uk/reference/ethicsstuds.html</i>	
Proposed study: Ensure that the project outline given in Section 3.1 contains sufficient detail (inc. purpose, methods, procedures for both new data collection and any work building on previous studies), so as to allow the Ethics Committee to make an informed decision without reference to other documents. Do not reproduce here.	
Is your project a randomised trial?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Will any human biological samples be collected? If 'Yes', specify details.	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
N/A	
Will any human biological material be stored at LSHTM for more than 24 hours? If 'Yes', specify which samples and how they will be	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

stored. <i>*Further guidance is given at</i> http://intra.lshtm.ac.uk/safety/Safety%20manual-3-HTA.pdf	
N/A	
Specify the number - with scientific justification for sample size – age, gender, source and method of recruiting subjects for the study.	
N/A	
State the location and likely duration of new or additional human data collection, and the extent to which this will be carried out by you alone, or in collaboration with others, or by others.	
N/A	
State the potential distress, discomfort or hazards, and their likelihood, to which research subjects may be exposed (these may include physical, biological and/or psychological hazards). What precautions are being taken to control and modify these hazards?	
N/A	
Specify how confidentiality will be maintained. When small numbers are involved, indicate how possible identification of individuals will be avoided.	
N/A	
State the manner in which consent will be obtained from subjects and <u>supply copies of the information sheet and consent form.</u>	
<ul style="list-style-type: none"> – Written consent is normally required. Where not possible, explain why and confirm that a record of those giving verbal consent will be kept. – Where appropriate, please state if and how the information and consent form will be translated into local language(s). 	
N/A	
As well as collecting new data, will your project also make use of any human data or biological samples collected in a previous study or studies? If 'Yes', summarise the purpose and methods of the original study or studies – for which participants will already have been recruited, data or samples collected, and procedures performed. (max 100 words)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
N/A	