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Time Stratified COX Regression: Five-year follow-up of attrition risk among HIV positive adults, Bamako

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ABSTRACT

This study evaluated the association between longer distance to hospital and attrition (loss to follow-up and death) rate in a cohort of HIV positive adults initiating Highly active antiretroviral therapy (HAART) at the Teaching University Hospital of Point G in Bamako, Mali.

We included all patients who initiated HAART between July 2004 and July 2009 at the Teaching University Hospital of Point G. Patients were considered to be in attrition if they did not show up for consultation within 90 days of their expected visit date. The Time Stratified COX model was used to estimate the risk of attrition among patients living further from the hospital. The analysis was adjusted for age at cohort entry, sex, and Marital status. All analyses were performed using SAS® V.9.4 (SAS Institute).

Of 3042 patients included, 79.5% experienced attrition with 60 months follow-up. Attrition was highest during the first six months of HAART (reference: Bamako; out of Bamako, HR 1.40[1.23;1.59]). After 24 months of compliance the HAART, the risk of attrition becomes non-significant (reference: Bamako; out of Bamako, HR 1.09[0.91;1.31]).

This study detected an increased risk of attrition within the first 24 months of HAART among patients living further from hospital. But, after 24 months this risk becomes non-significant.

To decrease the risk of attrition, the HAART program should focus on patient with less than 24 months of HAART history.

INTRODUCTION

Highly active antiretroviral therapy (HAART) was introduced in 1996 in developed countries and acknowledged as the standard of care for people with HIV/AIDS ever since. HAART became widely accessible in resource-limited countries after the Doha declaration was adopted in 2001, which enabled developing countries to circumvent patent rights to increase access to essential medicines. In addition, the large funds were provided by the US President's Emergency Plan for AIDS Relief (PEPFAR), which was established in 2002, and by the Global Fund for AIDS, Tuberculosis and Malaria, operating since 2003. Early results from antiretroviral treatment (ART) programmes in African countries have been promising (1). In many ART programmes in Africa the attrition rates following initiation of HAART are very high. The rates of attrition during the treatment period are not well understood (2). The effectiveness of ART of programmes should be evaluated regularly using key indicators including percentage of deaths, percentage of patients lost to follow-up (LTFU), and percentage of patients remaining on ART in the programme. Among these indicators, retention is the most meaningful, as poor retention in care predicts poor survival with HIV infection (3).

We conducted an observational study to determine the attrition rate and examined existing patterns for attrition using Time Stratified COX regression.

METHODOLOGY

DATA COLLECTION AND STUDY COHORT

We used data from an open cohort of 3042 HIV-infected patients followed at the Teaching University Hospital of **Point G** in Bamako, Mali. Data were collected prospectively from July 2004 to July 2009. Participants gave a verbal informed-consent at enrollment either at the first appointment related to their HIV diagnosis or during the follow up. Data collected included sociodemographic information (such as ethnic group, profession, residency, sex, etc.), a complete history of antiretroviral therapy and the results of laboratory tests, such as: CD4 cell count, HIV-RNA viral load, which were evaluated every 3 months.

We included all patients on HAART between July 2004 and July 2009 at the Teaching University Hospital of Point G. Patients were considered to be in attrition if they did not show up for consultation within 90 days of their expected visit date. The exposure variable of interest is the patient's residency. The potential confounding variables were: sex, age at cohort entry, marital status, profession, year of HAART initiation, type of HIV (HIV1, HIV2, HIV1+2) and treatment.

Table 1. Data Descriptor Table

Dataset's Name	Variable Name	Variable Type	Variable Label
DSN_LOSSOFFOLLOWUP_12MAY19	Age	2	Patient Age
	Codeprof	2	Profession
	DeathDate	2	Death Date
	Followuptime	2	Time to event
	HIVTYPE	2	HIV TYPE
	Maritalstatus	2	Marital status
	Outcome_attrition	1	Attrition (0=No, 1=Yes)
	Residence	2	Residence
	Sex	2	Sex
	ID	1	Patient ID
	Visitdate	2	Visit Date
	Year	2	Year of HAART initiation

***Program1**. The code for creating the Data Descriptor Table is shown below*

```
proc contents data= lofp.dsn_lossoffollowup_12may19 out=DDT(keep=MEMNAME NAME
LABEL TYPE);
run;
ods excel file="d:\01 sas folder\pharmasug\pharmasug 2019\02 output\DDT.xlsx";
proc print data=ddt label noobs; run;
ods excel close ;
```

STRATIFIED COX (SC) MODEL

The "stratified Cox model" is a modification of the Cox proportional hazards (PH) model that allows for control by "stratification" of a predictor that does not satisfy the PH assumption. Predictors that are assumed to satisfy the PH assumption are included in the model, whereas the predictor being stratified is not included.

TIME STRATIFIED COX (SC) MODEL

In this study, we were interested by tracking the pattern for attrition for the 6, 12, 18, and 24 first months of HAART. We performed a time stratified Cox regression model. We stratified follow up period by 6 months, 12 months, 18 months, 24 months and more than 24 months

The standard Cox PH model formula is usually written as:

$$hi(t) = \lambda_{0(t)} \exp(\beta_{1} x_{i1} + \ldots + \beta_{k} x_{ik})$$

This equation says that the hazard for individual i at time t is the product of two factors:

1. A function λ0(t) that is left unspecified, except that it can't be negative
2. A linear function of a set of k fixed covariates, which is then exponentiated

The function λ0(t), called the baseline hazard function ,can be regarded as the hazard function for an individual whose covariates all have values of 0 (4). The exponential expression of k fixed covariates is the exponential of the sum of the k explanatory X variables (5).

The non-informative censoring assumption and the proportional hazards assumption are very important for the use of the Cox PH model. The non-informative censoring assumption is met when the censored individuals are representative of all who remained in the risk set at time t with respect to the rate of failure. The non-informative censoring depends on the distribution of time-to-event and the distribution of time-to-censorship (5). The PH assumption is especially important for the covariate of interest that is the patient residency (6). The PH assumption for a binary variable means that the survival curves for two strata must have hazard functions that are proportional over time (i.e. parallel hazard curves). The code of testing PH assumption is shown below.

Program2*. The code for making Kaplan-Meier curve and log-log curve is shown below*

```
proc lifetest data= lofp.dsn_lossoffollowup_12may19 method=km plots=(s,lls);
        time Followuptime*Outcome_attrition n (0);
        strata adresidence ;
run;
```

proc lifetest – This procedure is used to obtain survival estimates and plots. By default, the Kaplan-Meier method is used. It will generate output for the log rank and Wilcoxon test statistics if stratifying by a covariate.

dsn_lossoffollowup_12may19– is the analysis dataset name.

method=km – km stands for Kaplan-Meier, it is also known as the product-limit. It is the default method in **proc lifetest** to compute the survival estimates and plots**.** However, there are several other methods.

Table 2. Other Methods of computing the survival estimates in **proc lifetest**

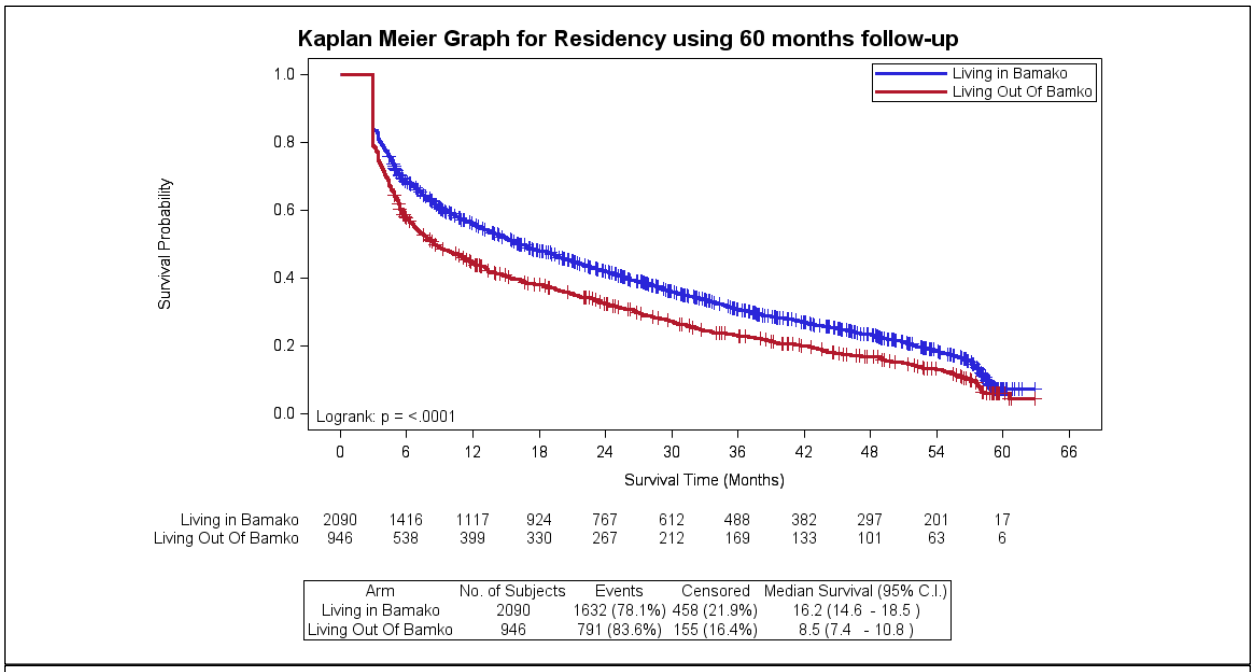
Method	DESCRIPTION
BRESLOW	If method=Breslow, the Breslow estimates will be computed.
FH	If method=fh, the Fleming-Harrington estimates will be computed.
LT	If method=lt, the life-table estimates (also known as actuarial estimates) will be computed.

plot=(s,lls) – this option produces the log-log survival curves and survival curves as well. If the PH assumption is met the log-log survival curves will be parallel.

time Followuptime*Outcome_attrition(0)– The TIME statement defines the time-to-event variable (Followuptime) and the value for censorship (outcome_attrition =0).

strata Residence– the residence was the binary variable (1= living in Bamako, 2=Living out of Bamako). The strata statement compares survival estimates for patient living out of Bamako versus patient living in Bamako. In addition, the strata statement provides the log rank test and Wilcoxon test statistics.

FIG1. Kaplan-Meier curves for Patient Residency and Sex



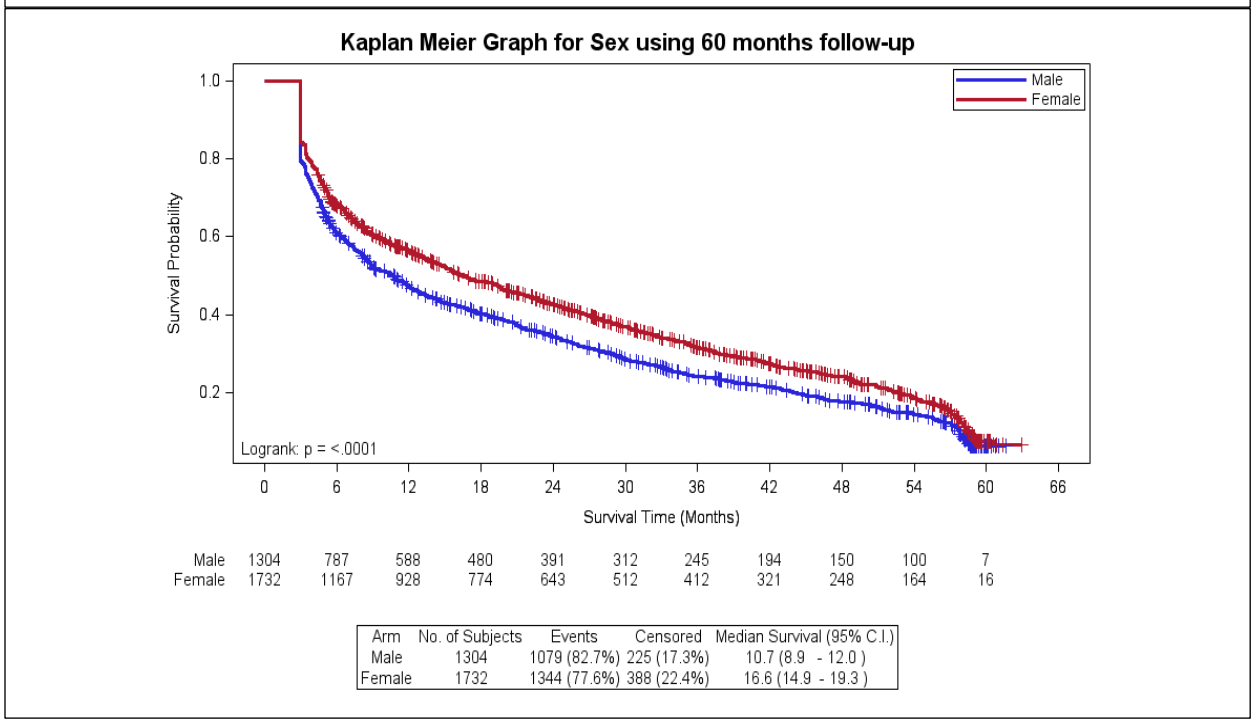
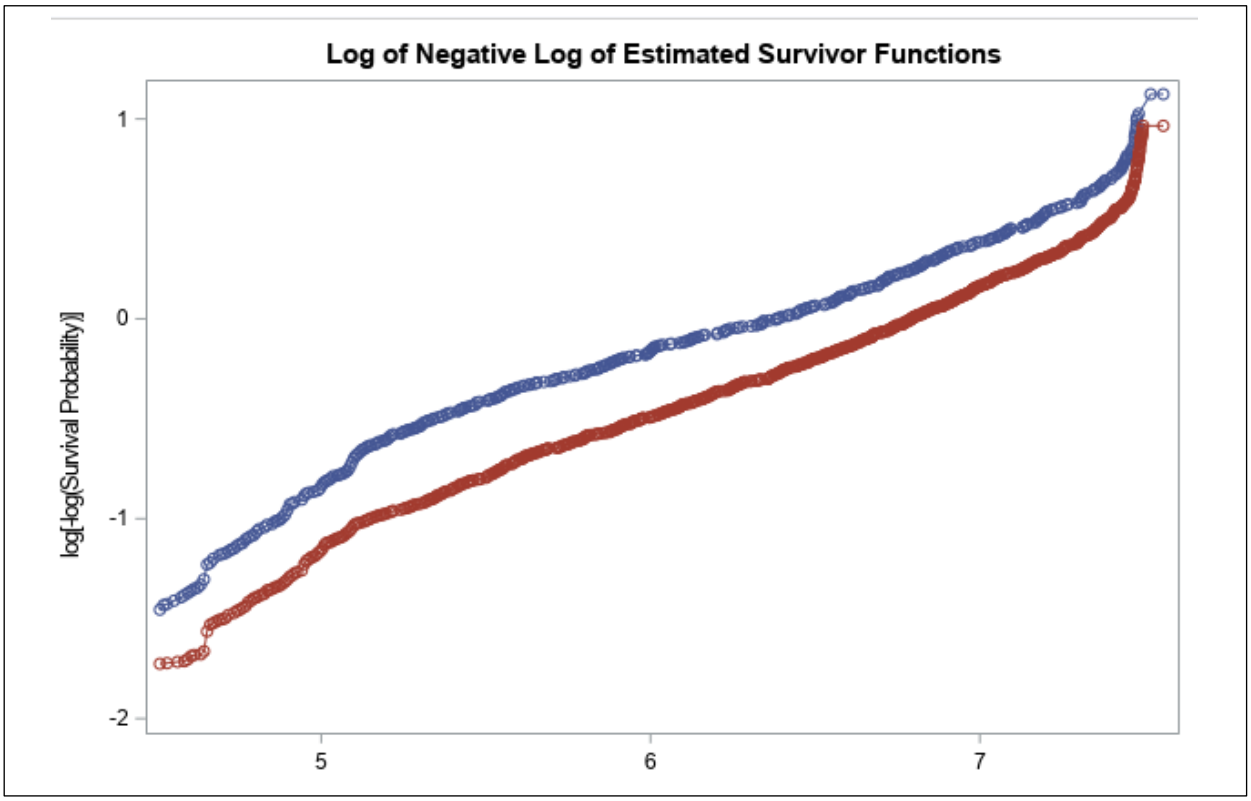


FIG2. Log-Log curve for PH assumption verification



SAS plots log(survival time) rather than survival time on the horizontal axis by default for loglog curves. The log-log survival curves are parallel. The PH assumption is assumed to follow for patient's residency.

We performed a time SC model to estimate the risk of attrition among patients living further from the hospital. The association between attrition and patient residency was analyzed first in a non-adjusted regression model. Then we analyzed this association using adjusted regression models. Only the potential confounding variables that changes the initial estimate Hazard ratio by 5% or more were included in the final regression model. Our final regression model was adjusted for age, sex, profession, and coinfection. All analyses were performed using SAS® V.9.4 (SAS Institute).

***Program3**. The code for running a COX Proportional Hazard model with* **proc phreg**

```
ods output ParameterEstimates=hr_lossoffollowup;
proc phreg data=lofp.dsn_lossoffollowup_12may19;
        class residence(ref="1") sex(ref="F") maritalstatus(ref="Maried")/ param=ref;
        model  Followuptime*Outcome_attrition(0)=residence  age sex maritalstatus/rl;
run;
```

proc phreg – the **proc phreg** is used to request a COX proportional hazards model.

class residence(ref="1") sex(ref="F") maritalstatus(ref="Maried")/ param=ref;
model Followuptime*Outcome_attrition(0)=residence age sex maritalstatus/rl;
Followuptime is the time-to-event variable. Outcome_attrition is the value for censorship. Residence is the main explanatory variable. Age, Sex, Maritalstatus are the three confounding variables we controlled for. The option RL in the model statement of **proc phreg** provides 95% confidence intervals for the hazard ratio estimates.

Program4*. Formatting and reporting the output of the COX Proportional Hazard model*

```
/*Formatting the Output*/
data lofp.hr_lossoffollowup;
        length PARAMETER $ 15. HR_CI $ 35.;
        set hr_lossoffollowup ( keep = PARAMETER HAZARDRATIO HRLOWERCL HRUPPERCL
            PROBCHISQ );
        R_HAZARDRATIO =put(HAZARDRATIO, 4.2);
        R_HRLOWERCL =put(HRLOWERCL, 4.2);
        R_HRUPPERCL =put(HRUPPERCL, 4.2);
        if 0.01<=PROBCHISQ<0.05 then
                HR_CI =strip(R_HAZARDRATIO) || " (" || strip(R_HRLOWERCL) || ", " ||
                        strip(R_HRUPPERCL) || ")" || "*";
        else if 0.001<=PROBCHISQ<0.01 then
                HR_CI =strip(R_HAZARDRATIO) || " (" || strip(R_HRLOWERCL) || ", " ||
                        strip(R_HRUPPERCL) || ")" || "**";
        else if PROBCHISQ<0.001 then
                HR_CI =strip(R_HAZARDRATIO) || " (" || strip(R_HRLOWERCL) || ", " ||
                        strip(R_HRUPPERCL) || ")" || "***";
        else HR_CI =strip(R_HAZARDRATIO) || " (" || strip(R_HRLOWERCL) || ", " ||
                        strip(R_HRUPPERCL) || ")";
        drop HAZARDRATIO HRLOWERCL HRUPPERCL R_HAZARDRATIO R_HRLOWERCL
              R_HRUPPERCL;
run;
```

```
/*Generate the Excel file for output using Proc report and ODSS destination*/
ods excel file="d:\01 sas folder\pharmasug\pharmasug 2019\02
output\hr_lossoffollowup.xlsx";
proc report data= lofp.hr_lossoffollowup;
        column order Label1 ("0 to 60 Months followup" HR_CI_all)
                ("0 to 6 Months followup" HR_CI_6m )
                ("6 to 12 Months followup" HR_CI_12m)
                ("12 to 18 Months followup" HR_CI_18m )
                ("18 to 24 Months followup" HR_CI_24m )
                ("24 to 60 Months followup" HR_CI_gt_24m);
        define order /  noprint order=data ;
        define Label1 /  display ""  order=data group;
        define HR_CI_all  / display "Adjusted HR (95% CI)";
        define HR_CI_6m  / display "Adjusted HR (95% CI)";
        define HR_CI_12m  / display "Adjusted HR (95% CI)";
        define HR_CI_18m  / display "Adjusted HR (95% CI)";
        define HR_CI_24m  / display "Adjusted HR (95% CI)";
        define HR_CI_gt_24m  / display "Adjusted HR (95% CI)";
run;
ods excel close;
```

RESULTS

Of 3042 patients included, 79.5% experienced attrition with 60 months follow-up. Attrition was highest during the first six months of HAART (reference: Bamako; out of Bamako, HR 1.40[1.23;1.59]). After 24 months of compliance to HAART, the risk of attrition becomes non-significant (reference: Bamako; out of Bamako, HR 1.09[0.91;1.31]).

Table 3. Baseline characteristics of the 3042 patients who were included in this study

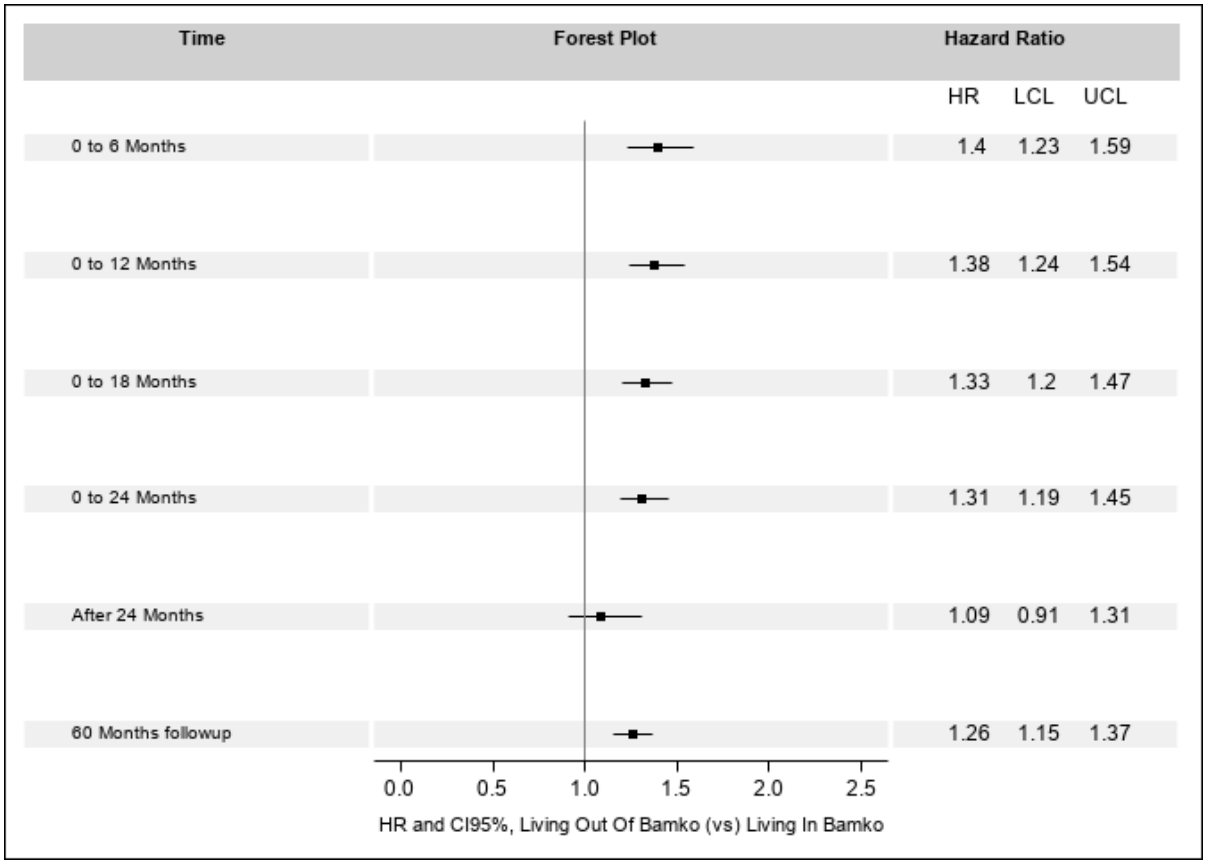
	Median (P25, P75) or N(%)			P value
	Bamako (n=2095)	Out of Bamako (n=947)	All (n=3042)	
Age (in year)				
Female	32.0(28.0,40.0)	33.0(27.0,40.0)	32.0(27.0,40.0)	
Male	40.0(34.0,46.0) 46.0)	41.0(35.0,47.0)	40.0(35.0,46.0)	
Sex				
Female	1237 (40.66)	500 (16.44)	1737 (57.10)	0.0013
Male	858 (28.21)	447 (14.69)	1305 (42.9)	
Marital Status				
Single	409 (13.45)	92 (3.02)	501 (16.47)	<0.0001
Married	1352 (44.44)	721 (23.70)	2073 (68.15)	
Divorced	11 (0.36)	6 (0.20)	17 (0.56)	
Widower	300 (9.86)	109 (3.58)	409 (13.45)	
Missing	23 (0.76)	19 (0.62)	42 (1.38)	
Cumulative, person-years 5029.7.				

Table 4. Cox Regression Analyses of Characteristics Associated with attrition

	60 Months follow-up	0 to 6 Months	0 to 12 Months	0 to 18 Months	0 to 24 Months	After 24 Months
	Adjusted HR(95% CI)*	Adjusted HR(95% CI)	Adjusted HR(95% CI)	Adjusted HR(95% CI)	Adjusted HR(95% CI)	Adjusted HR(95% CI)
Living Out Of Bamko (vs)Living in Bamako	1.26 (1.15,1.37)***	1.40 (1.23,1.59)***	1.38 (1.24,1.54)***	1.33 (1.20,1.47)***	1.31 (1.19,1.45)***	1.09 (0.91, 1.31)
Patient Age (year) at cohort entry	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	0.99 (0.98, 1.00)
Male (vs) Female	1.17 (1.07,1.28)***	1.23 (1.07,1.41)**	1.24 (1.10,1.39)***	1.21 (1.08,1.35)***	1.19 (1.07,1.32)***	1.11 (0.93, 1.33)
Single (vs) Married	1.02 (0.91, 1.14)	1.06 (0.89, 1.26)	1.06 (0.92, 1.23)	1.04 (0.90, 1.19)	1.04 (0.91, 1.19)	0.96 (0.76, 1.21)
Divorced (vs) Married	1.01 (0.59, 1.70)	0.69 (0.26, 1.85)	0.99 (0.49, 1.98)	0.84 (0.42, 1.69)	0.84 (0.44, 1.62)	1.60 (0.66, 3.88)
Widower (vs) Married	0.81 (0.72,0.92)**	0.85 (0.69, 1.04)	0.77 (0.65,0.92)**	0.79 (0.67, 0.93)**	0.77 (0.66,0.90)***	0.91 (0.73, 1.13)
Missing (vs) Married	2.25 (1.49,3.40)***	2.46 (1.54,3.93)***	1.95 (1.23,3.12)**	2.22 (1.45,3.39)***	2.16 (1.41,3.29)***	7.80 (1.08, 56.2)*

Note. *The regression model was adjusted for Patient Age (in year) at cohort entry, Patient Sex, Patient Marital Status.
Abbreviations: HR, Hazard Ratio; CI, Confidence Interval.

FIG3. Time stratified Hazard Ratio for Patient living far from Point G hospital versus Patient living close to Point G hospital



CONCLUSION

This study detected an increased risk of attrition within the first 24 months of HAART among patients living further from hospital. But, after 24 months this risk becomes non-significant.

To decrease the risk of attrition, the ART programmes should focus on patient with less than 24 months of HAART history.

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The views expressed in this research are those of the authors and do not necessarily reflect the official policy or position of Malian Minister of Health.