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Loss to follow-up occurs at all stages in the diagnostic and follow-up period among HIV-infected patients in Guinea-Bissau: a 7-year retrospective cohort study

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ABSTRACT

Objectives: To describe loss to follow-up (LTFU) at all stages of the HIV programme.

Design: A retrospective cohort study.

Setting: The HIV clinic at Hospital National Simão Mendes in Bissau, Guinea-Bissau.

Participants: A total of 4080 HIV-infected patients.

Outcome measures: Baseline characteristics, percentages and incidence rates of LTFU as well as LTFU risk factors at four different stages: immediately after HIV diagnosis (stage 1), after the first CD4 cell count and before a follow-up consultation (stage 2), after a follow-up consultation for patients not eligible for antiretroviral treatment (ART; stage 3) and LTFU among patients on ART (stage 4).

Results: Almost one-third of the patients were lost to the programme before the first consultation where ART initiation is decided; during the 7-year observation period, more than half of the patients had been lost to follow-up (overall incidence rate=51.1 patients lost per 100 person-years). Age below 30 years at inclusion was a risk factor for LTFU at all stages of the HIV programme. The biggest risk factors were body mass index <18.5 kg/m^2 (stage 1), male gender (stage 2), HIV-2 infection (stage 3) and CD4 cell count <200 cells/μL (stage 4).

Conclusions: In this study, LTFU constituted a major problem, and this may apply to other similar ART facilities. More than half of the patients were lost to follow-up shortly after enrolment, possibly implying a high mortality. Thus, retention should be given a high priority.

ARTICLE SUMMARY

Strengths and limitations of this study

- First study on loss to follow-up (LTFU) among HIV-infected patients in Guinea-Bissau.
- Describes LTFU at all stages of the HIV programme.
- Large dataset with several years of follow-up.
- Active follow-up was limited to telephone calls.
- Missing data from a number of patients.

INTRODUCTION

An estimated 34 million people are infected with HIV and the number is growing. Sub-Saharan Africa is the most affected region, and in some areas antiretroviral treatment (ART) is not available. The coverage of ART is lowest in West and Central Africa where only 30% of the patients in need of ART actually receive it.[1]

ART has significantly reduced mortality and improved life expectancy of HIV-infected patients,[2] but the success critically depends on regular patient follow-up.[3] ART requires a large commitment from the patient and without good adherence viral resistance will develop.[4 5] Adherence to treatment may be considered more important than the potency of any ART regimen.[6] Loss to follow-up (LTFU) of HIV-infected patients is closely related to ART adherence and is becoming an increasing problem in sub-Saharan Africa as ART programmes expand and staff-to-patient ratios decrease.[7 8] In a systematic review of ART in sub-Saharan Africa, the authors found that up to 40% of patients were lost to follow-up, with large variation in retention rates between programmes.[9] The risk of LTFU is usually highest during the first 6 months after starting ART.[8] Furthermore, mortality among patients lost to follow-up in sub-Saharan settings has been reported to range from 20% to 87%.[3] This implies that standard survival analyses that censor

follow-up time at the last visit to an HIV clinic will underestimate the overall mortality.[10 11]

Regular monitoring is needed to determine when to start ART,[12 13] and high rates of LTFU before this initiation have been reported in several African settings.[14–16] However, little information is available about LTFU in patients not eligible for ART and the outcome of these patients in sub-Saharan Africa.

The term 'loss to programme' covers patient mortality, LTFU and patients transferring to another HIV clinic. A recent meta-analysis of loss to programme in sub-Saharan Africa has described that patients may become lost to follow-up at different stages. Going though six studies with a total inclusion of 58 746 patients diagnosed with HIV, the authors found that 72% of the patients had a CD4 cell count measured, 40% were eligible for ART and only 25% of the patients initiated ART.[17] A systematic review found large variations in LTFU between these stages.[18]

There is an urgent need to understand why patients are lost to follow-up.[19 20] A better understanding of risk factors for tracing success and mortality among these patients could help to develop targeted interventions to prevent LTFU.[21] This understanding may be achieved by describing the epidemiology and risk factors of LTFU. As the extent and causes of LTFU may differ between patients at different stages,[17 18] the description should be made by stratifying patients into these groups. The aim of this study was to describe the epidemiology of LTFU including risk factors in patients at all stages of an HIV programme.

METHODS

Setting and patients

All patients treated according to the national guidelines from an HIV clinic at Hospital National Simão Mendes (HNSM) in Bissau, the capital of Guinea-Bissau, were included in this retrospective cohort study. The outpatient ART centre of HNSM is the largest ART centre in Guinea-Bissau. The study population consisted of HIV-infected individuals diagnosed at the HIV clinic at HNSM between 1 June 2005 and 1 June 2012. Patients diagnosed with HIV in the period 1 March 2011 to 1 June 2012 who were not eligible to ART were excluded from the analyses, as they did not have 210 days of follow-up and could therefore not be considered either LTFU or on follow-up.

At the first visit to the clinic, HIV testing was performed and basic demographic information was collected. Schooling was defined as attending classes with the purpose of learning how to read; Koranic schools were not included in this definition. At the day of HIV diagnosis, patients were given a requisition for laboratory analyses (CD4 cell count, biochemistry and haematology). The blood samples were usually drawn at the clinic the following day and the patients were asked to return to the clinic within 7 days. At this consultation, the decision to initiate ART was made based on WHO guidelines. If ART initiation was decided, the patients received ART the same day as the consultation. All services, including ART, were free of charge for all HIV-infected patients.

Active follow-up

When diagnosed with HIV, the patients were provided with a unique registration number and a personal card stating the date of next appointment at the clinic. At HIV diagnosis, all patients were asked to provide their own telephone number and the number of a contact person to be used during active follow-up. Patients on ART were contacted if they had not been at the clinic for 3 months after the date of the last visit, and patients not eligible for ART were contacted if they had not been at the clinic for 180 days. Patient contact by telephone was attempted at least twice on two separate days.

Loss to follow-up

Patients on ART were considered lost to follow-up if they had not visited the clinic for 90 days (60 days after the next appointment),while patients without treatment were noted as LTFU if they had not been at the clinic for 7 months (1 month after the date of the next appointment). Information on patient mortality and clinic transfer was collected by personal information and telephone calls with contact persons and from the hospital wards. Patient confidentiality was at no point broken.

Laboratory methods

Venous blood samples were collected for biochemical analyses (alanine aminotransferase, aspartate transaminase, creatinine) and haematology (haemoglobin, CD4 cell count, platelets). Orphée, Mythic, Diamond Diagnostics, USA was used to measure haematology. For biochemical analyses, the Reflotron Plus System, Roche diagnostics or BA-88 Mindray biochemistry analyser was used. CD4 cell counts were performed by flow cytometry using Partec CyFlow SL_3 (Cyflow SL, Partec, Munster, Germany). HIV screening was carried out with a rapid test in the clinic (Determine HIV-1/2 assay (Abbott Laboratories, 72 Abbott Park, Illinois, USA) and confirmation and discrimination using SD Bioline HIV 1/2 3.0 (Standard Diagnostics Inc, Kyonggi-do, South Korea). As confirmation, an additional Bioline test was performed at the National Public Health Laboratory according to the standard recommendations from the National HIV programme of Guinea-Bissau.

Statistical methods

We compared the demographic, clinical and laboratory features of patients on or without ART using χ^2 test for categorical variables. Continuous variables were compared using the two-sample t test (normal distribution) or Wilcoxon rank-sum test (non-normal distribution). Abnormal biochemical and haematological values were defined in accordance with the reference levels used at HNSM. Logistic regression was used for the analysis of

risk factors for LTFU among patients lost to programme before a follow-up consultation after CD4 measurement. The Cox proportional hazard model was used to calculate LTFU risk factors among patients not eligible for ART and patients on ART. Patients on ART were included in the regression analysis by the date of ART initiation. Follow-up time until ART initiation was included in the analysis of patients not eligible for ART. Variables associated with LTFU in the univariate model ($p<0.10$) were included in a multivariate model. In case of missing data, a 'missing data' group was made and included in the analysis to avoid exclusion of patients. Patients who died or were transferred to another HIV clinic were censored by the estimated time of death and time of transfer, respectively. The remaining patients were censored on 1 September 2012. The incidence rates (IR) of LTFU were calculated by Poisson regression analysis. To include all patients in the calculation of the overall IR of LTFU, the patients who had only been at the clinic on the day of HIV testing were considered to have 1 day of follow-up. All statistical analyses were carried out using Stata IC 11.0 (StataCorp, College Station, Texas, USA).

Ethical statement

The Bissau HIV cohort has been approved by the National Ethics Committee in Guinea-Bissau (Parecer NCP/No.15/2007). Upon inclusion, the patients provided a voluntary, signed and dated informed consent or a fingerprint if illiterate. The cohort has an open approval to use data from patients' records as long as patient confidentiality is not broken.

Stages of LTFU

Loss to programme and LTFU could occur at four different stages (figure 1): LTFU immediately after HIV diagnosis (stage 1), LTFU after the first CD4 cell count and before a follow-up consultation (stage 2), LTFU after a follow-up consultation for patients not eligible for ART (stage 3) and LTFU among patients on ART (stage 4).

RESULTS

Baseline characteristics

Between June 2005 and June 2012, 4080 patients were diagnosed with HIV at HNSM; 2724 with HIV-1, 727 with HIV-2, 486 with HIV-1/2 and 143 with an unknown HIV type (table 1). Among the included 4080 patients, a significantly higher percentage of women than men were HIV-2 positive (20.2% vs 15.2%, $p<0.01$), and HIV-1 positive patients were more likely to be male than female (73.5% vs 67%, $p<0.01$). The overall mean age was 37.6 years (95% CI 37.2 to 37.9); age was significantly lower among HIV-1 infected (mean age 35.6 years) than HIV-2 infected patients (mean age 43.9 years, $p<0.01$). The mean age of HIV-1/2 dually infected patients was 39.4 years. In total, 3470 patients had a baseline CD4 measurement and the median CD4 cell count was 210 cells/µL (IQR 97–391). The HIV-2 infected patients had a significantly higher baseline CD4 cell count (median 260 cells/µL (IQR 115–491)) than the HIV-1 (median 202 cells/µL (IQR 89–362)) and HIV-1/2 dually infected patients (median 205 cells/µL, IQR 108–368 ($p<0.01$)).

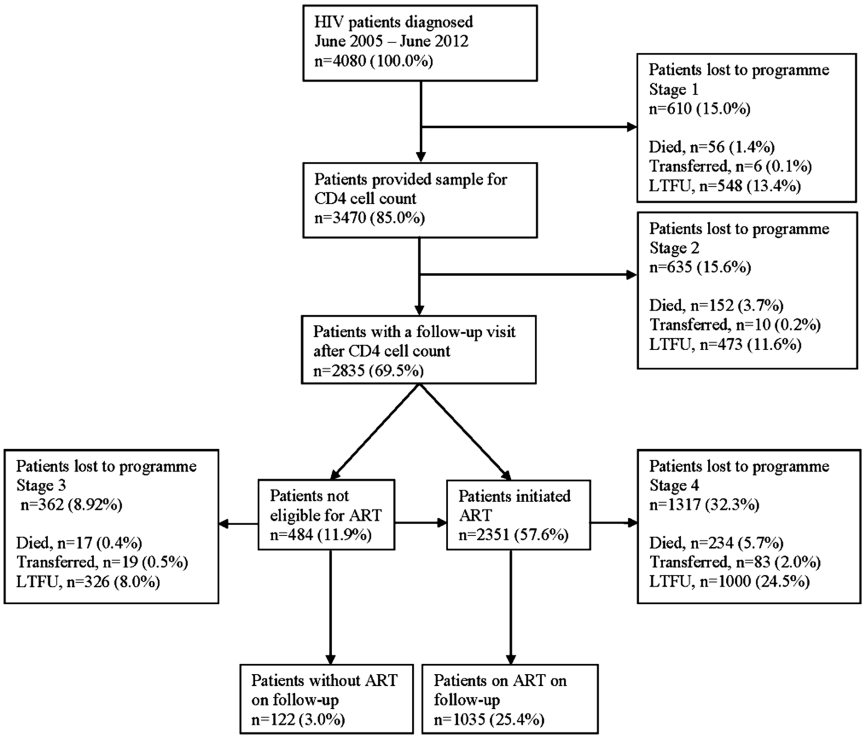

Figure 1 Flow chart and outcome by 1 September 2012 of patients included in the study.

Table 1 Baseline characteristics of all patients diagnosed with HIV

Baseline characteristics	Number n/N	Percentage
Sex		
Male	1345/3937	34.2
Female	2592/3937	65.8
Age stratification (years)		
≤30	1271/4003	31.8
30–39	1330/4003	33.2
≥40	1402/4003	35.0
HIV type		
HIV-1	2724/3937	69.2
HIV-2	727/3937	18.4
HIV-1/2	486/3937	12.3
CD4 cell count (cells/μL)		
≤200	1656/3470	47.7
201–350	785/3470	22.6
>350	1029/3470	29.7
Anaemia*		
Yes	2107/2486	84.8
No	379/2486	15.2
Nutritional status (kg/m^2)		
BMI ≤18.5	972/2902	33.5
BMI >18.5	1930/2902	66.5
Marital status		
Single	990/3992	24.8
Married	2189/3992	54.8
Divorced	239/3992	6.0
Widowed	574/3992	14.4
Religion		
Muslim	1614/3769	42.8
Catholic	1039/3769	27.6
Protestant	252/3769	6.7
Animist	864/3769	22.9
Schooling		
Yes	2560/3904	65.6
No	1344/3904	34.4
Geographic site of residence		
Bissau	2654/2969	89.4
Outside Bissau	315/2969	10.6

*Haemoglobin below normal range: men >13 and women >12 mg/dL.
BMI, body mass index.

Patient outcome

By September 2012, 2924 (71.7%) of the included patients had been lost to the programme: 459 (11.3%) had died, 118 (2.9%) had been transferred to another HIV clinic and 2347 (57.5%) had been lost to follow-up. The overall follow-up time was 4591.1 person-years, and the overall IR of LTFU was 51.1 (95% CI 49.1 to 53.2) per 100 person-years. The overall median follow-up time was 147 days (IQR 7–653). As presented in figure 1, 610 (15%) patients did not have a CD4 cell count performed by the end of this study, 2351 (57.6%) patients had initiated ART and 484 (11.9%) patients were not eligible for ART.

Patients not eligible for ART had 927.1 person-years of follow-up and the IR of LTFU was 35.2 (95% CI 31.5 to 39.2) per 100 person-years. Among patients on ART, the follow-up time was 4012.6 person-years and median time to ART initiation was 16 days (IQR 8–47). The IR of LTFU was 24.9 (95% CI 23.4 to 26.5) per 100 person-years. We stratified these findings by time period from the date of HIV diagnosis.

Six months after HIV diagnosis, 3329 (81.6%) of all patients diagnosed with HIV were on follow-up and 751 (18.4%) had been lost to the programme. Owing to the definition of LTFU among patients without ART (clinic absence for more than 210 days), all patients lost to follow-up within the first 6-month period were patients on ART. In this period, 325 (8%) patients had died, 66 (1.6%) patients had been transferred and 360 (8.8%) patients had been lost to follow-up.

In total, 3635 patients were diagnosed with HIV before September 2011; hence, a 1-year outcome could be evaluated. In all, 318 (8.7%) patients had died, 58 (1.6%) patients had been transferred and 1527 (42%) patients were lost to follow-up, leaving 1732 (47.6%) patients on follow-up.

Data on 2-year follow-up (HIV diagnosis before September 2010) were available for 2768 patients. In this patient group, 1715 (62%) patients had been lost to the programme and the remaining 1053 (38%) patients were still on follow-up. After 2 years, 258 (9.3%) patients had died, 55 (2%) patients had been transferred and 1402 (50.1%) patients were lost to follow-up.

Risk factors of LTFU

Risk factors of LTFU among patients at stages 1–4 are presented in tables 2–5. Age below 30 years at inclusion was a risk factor among patients at all stages. No schooling was a significant risk factor among patients at stages 2 and 3, and among patients at stage 4 a positive trend was found (HR 1.22 (95% CI 0.98 to 1.52), p=0.08). The biggest risk factor at each stage was body mass index <18.5 kg/m^2 (stage 1: OR 2.92 (95% CI 1.32 to 6.43)), male gender (stage 2: OR 2.10 (95% CI 1.60 to 2.76)), HIV-2 infection (stage 3: HR 2.56 (95% CI 1.91 to 3.42)) and CD4 cell count <200 cells/μL (stage 4: HR 2.71 (95% CI 2.04 to 3.61)). Geographic site of residence was not associated with LTFU at any stage. Catholic patients had a lower risk of LTFU at stage 1 (OR 0.54 (95% CI 0.34 to 0.88)) and stage 4 (HR 0.75 (95% CI 0.59 to 0.96)), and patients with anaemia had a lower risk of LTFU at stage 3 (HR 0.32 (95% CI 0.23 to 0.45)).

DISCUSSION

This retrospective cohort study investigated the outcome of 4080 HIV-positive patients, including a large proportion of HIV-2 infected patients, diagnosed at the largest HIV clinic in Bissau, Guinea-Bissau. Almost one-third of the patients had been lost to the programme before the first consultation where ART initiation was decided, and during the 7-year observation period more than half of the patients had been lost to follow-up. Age below

Table 2 LTFU risk factors in patients without a CD4 cell count (stage 1)

Stage 1 LTFU risk factors	Logistic regression, LTFU OR Univariate analysis OR (95% CI)	p Value	Multivariate analysis OR (95% CI)	p Value
Sex				
Male	1.42 (1.14 to 1.76)	<0.01	1.16 (0.75 to 1.82)	0.50
Female	1.00	–	1.00	–
Age stratification (years)				
≤30	1.00	–	1.00	–
30–39	0.50 (0.39 to 0.65)	<0.01	0.46 (0.18 to 0.77)	<0.01
≥40	0.62 (0.48 to 0.79)	<0.01	0.48 (0.27 to 0.85)	0.01
HIV type				
HIV-1	1.00	–	1.00	–
HIV-2	1.05 (0.78 to 1.41)	0.73	1.08 (0.64 to 1.83)	0.77
HIV-1/2	1.38 (0.99 to 1.91)	0.06	2.49 (1.28 to 4.85)	<0.01
Nutritional status (kg/m^2)				
BMI≤18.5	2.97 (1.36 to 6.48)	<0.01	2.92 (1.32 to 6.43)	<0.01
BMI>18.5	1.00	–	1.00	–
Marital status				
Single	0.99 (0.78 to 1.27)	0.96	0.66 (0.41 to 1.06)	0.08
Married	1.00	–	1.00	–
Divorced	0.74 (0.46 to 1.17)	0.20	0.65 (0.28 to 1.52)	0.32
Widowed	0.57 (0.41 to 0.80)	<0.01	0.72 (0.38 to 1.37)	0.32
Religion				
Muslim	1.00	–	1.00	–
Catholic	0.73 (0.57 to 0.95)	0.02	0.54 (0.34 to 0.88)	0.01
Protestant	0.40 (0.23 to 0.67)	<0.01	0.54 (0.21 to 1.38)	0.20
Animist	0.88 (0.67 to 1.16)	0.37	1.09 (0.63 to 1.88)	0.76
Schooling				
Yes	1.00	–	–	–
No	1.11 (0.89 to 1.38)	0.37	–	–
Geographic site of residence				
Bissau	1.00	–	–	–
Outside Bissau	0.34 (0.05 to 2.56)	0.30	–	–

BMI, body mass index; LTFU, loss to follow-up.

30 years at inclusion was a risk factor for LTFU at all stages. Among patients on ART, CD4 cell count <200 cells/μL was the strongest predictor of LTFU.

The main strength of this study is the large dataset with several years of follow-up. In contrast to this study, few sub-Saharan studies have addressed LTFU at all stages of the ART programme and provided risk factors of LTFU at all programme stages.[17] Furthermore, active follow-up was limited to calling patients and/or their contact person by telephone as resource-limited settings often do not have the possibility to conduct home visits. This study resembles a frequent sub-Saharan setting and the rate of LTFU and its associations may resemble that of other clinics.

The study is limited by incomplete data among a substantial number of patients (table 1); this may have affected the analyses in either direction. Furthermore, HIV type discrimination was performed by SD Bioline HIV 1/2 3.0. A study from the neighbouring country Guinea-Conakry found that SD Bioline HIV 1/2 3.0 may have overestimated the number of HIV-1/2 dually infected patients;[22] this was later confirmed in Guinea-Bissau.[23]

The prevalence of patients lost to follow-up was high in this study compared with several other African studies,[9] but the heterogenicity in the definition of LTFU makes comparisons between studies difficult. Different LTFU definitions for patients on ART have been proposed ranging from 60 days after a missed appointment to 180 days after the date of the last visit.[24 25] HIV-infected patients at HNSM are usually supplied with ART for 30 days at a time. LTFU among patients on ART was defined as 90 days of absence from the date of the last visit. To our knowledge, there are no studies from sub-Saharan Africa regarding the 'best performing' definition of LTFU among HIV-infected patients before ART initiation.

In this study, mortality was rather low while LTFU was high. Other studies performed in Africa have found that mortality was inversely related to the rate of LTFU.[3] Several of the LTFU risk factors among patients on ART were similar to the mortality risk factors among African HIV-infected patients as described elsewhere.[26 27] If a more thorough follow-up had been performed in the study period, the mortality rate would presumably be higher.

Table 3 LTFU risk factors in patients without a follow-up consultation after CD4 cell count (stage 2)

Stage 2 LTFU risk factors	Logistic regression, LTFU OR			
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Sex				
Male	1.47 (1.17 to 1.84)	<0.01	2.10 (1.60 to 2.76)	<0.01
Female	1.00	–	1.00	–
Age stratification (years)				
≤30	1.00	–	1.00	–
30–39	0.74 (0.57 to 0.96)	0.03	0.58 (0.43 to 0.79)	<0.01
≥40	0.71 (0.55 to 0.93)	0.01	0.46 (0.33 to 0.65)	<0.01
HIV type				
HIV-1	1.00	–	1.00	–
HIV-2	1.44 (1.09 to 1.90)	0.01	1.58 (1.14 to 2.19)	<0.01
HIV-1/2	1.38 (0.98 to 1.93)	0.06	1.58 (1.09 to 2.30)	0.02
CD4 cell count (cells/μL)				
≤200	0.59 (0.46 to 0.75)	<0.01	0.56 (0.42 to 0.74)	<0.01
201–350	0.41 (0.31 to 0.56)	<0.01	0.45 (0.32 to 0.62)	<0.01
>350	1.00	–	1.00	–
Anaemia*				
Yes	1.00 (0.68 to 1.48)	1.00	–	–
No	1.00	–	–	–
Nutritional status (kg/m^2)				
BMI≤18.5	1.29 (0.97 to 1.72)	0.08	1.32 (0.97 to 1.79)	0.08
BMI>18.5	1.00	–	1.00	–
Marital status				
Single	0.97 (0.75 to 1.26)	0.83	–	–
Married	1.00	–	–	–
Divorced	1.07 (0.69 to 1.66)	0.78	–	–
Widowed	0.76 (0.55 to 1.06)	0.11	–	–
Religion				
Muslim	1.00	–	1.00	–
Catholic	0.86 (0.66 to 1.13)	0.28	0.93 (0.68 to 1.27)	0.64
Protestant	0.57 (0.35 to 0.94)	0.03	0.63 (0.36 to 1.09)	0.10
Animist	0.89 (0.66 to 1.19)	0.42	0.85 (0.61 to 1.17)	0.32
Schooling				
Yes	1.00	–	1.00	–
No	1.27 (1.01 to 1.60)	0.04	1.80 (1.35 to 2.40)	<0.01
Geographic site of residence				
Bissau	1.00	–	–	–
Outside Bissau	1.22 (0.81 to 1.81)	0.34	–	–

*Haemoglobin below normal range: men >13 mg/dl, women >12 mg/dl.
BMI, body mass index; LTFU, loss to follow-up.

In Guinea-Bissau, many people are involved in seasonal work, especially picking cashew in the country regions, which makes them leave the capital city Bissau during the cashew season. Furthermore, Guinea-Bissau has been considered politically unstable for many years. During the civil war in 1998–1999, a substantial part of the inhabitants of Bissau fled from the capital city,[28] and several coup attempts since the clinic opened in 2005 may have influenced the degree of LTFU. However, we do not have precise data on why patients did not show up for appointments at the clinic.

Age below 30 years at inclusion was a risk factor for LTFU in all patients groups in our study. Furthermore, no schooling and male gender were risk factors at two stages. These variables have also been associated with LTFU in other studies.[19 29–32] Owing to the consistency in these risk factors, special attention should be made to avoid LTFU among these patients.

HIV-2 infection was associated with LTFU among patients at stages 2–4. The progression of HIV-2 infection is generally much slower than that of HIV-1 and a large proportion of HIV-2 infected individuals do not progress to AIDS.[33] A study from Gambia investigated pretreatment LTFU, but found no association between HIV-2 infection and LTFU,[34] which is similar to LTFU at stage 1 in our study. At the baseline characteristics, HIV-2 was associated with a higher CD4 cell count. Patients with a high CD4 cell count may be prone to LTFU due to fewer HIV-related symptoms.[35]

Table 4 LTFU risk factors in patients not eligible for antiretroviral treatment (stage 3)

Stage 3 LTFU risk factors	Cox regression, LTFU hazard rates (HR)			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Sex				
Male	0.93 (0.72 to 1.20)	0.59	–	–
Female	1.00	–	–	–
Age stratification (years)				
≤30	1.00	–	1.00	–
30–39	0.74 (0.56 to 0.97)	0.03	0.54 (0.40 to 0.73)	<0.01
≥40	0.85 (0.65 to 1.10)	0.21	0.52 (0.38 to 0.71)	<0.01
HIV type				
HIV-1	1.00	–	1.00	–
HIV-2	1.33 (1.04 to 1.69)	0.02	2.56 (1.91 to 3.42)	<0.01
HIV-1/2	0.83 (0.56 to 1.23)	0.37	0.93 (0.61 to 1.42)	0.75
Anaemia*				
Yes	0.54 (0.40 to 0.72)	<0.01	0.32 (0.23 to 0.45)	<0.01
No	1.00	–	1.00	–
Nutritional status (kg/m^2)				
BMI≤18.5	1.19 (0.91 to 1.55)	0.20	–	–
BMI>18.5	1.00	–	–	–
Marital status				
Single	0.92 (0.69 to 1.21)	0.54	–	–
Married	1.00	–	–	–
Divorced	1.03 (0.65 to 1.62)	0.91	–	–
Widowed	1.06 (0.78 to 1.44)	0.70	–	–
Religion				
Muslim	1.00	–	–	–
Catholic	0.91 (0.69 to 1.19)	0.48	–	–
Protestant	1.16 (0.76 to 1.78)	0.50	–	–
Animist	1.02 (0.76 to 1.36)	0.92	–	–
Schooling				
Yes	1.00	–	1.00	–
No	1.48 (1.18 to 1.86)	<0.01	1.37 (1.07 to 1.77)	0.01
Geographic site of residence				
Bissau	1.00	–	–	–
Outside Bissau	1.26 (0.91 to 1.75)	0.17	–	–

*Haemoglobin below normal range: men >13 and women >12 mg/dL.
BMI, body mass index; LTFU, loss to follow-up.

Anaemia seemed to have a protective effect among patients with LTFU at stage 3. Patients at this stage had a CD4 cell count >350 cells/μL and were not eligible for ART according to national guidelines. Low haemoglobin may have caused these patients to feel ill despite a higher CD4 cell count, and thus motivated patients to adhere to the HIV clinic. Differences in risk factors of LTFU in patient at stages 1–4 may be due to the differences in causes of LTFU.

Various approaches have been tried to reduce the rate of LTFU including adherence support workers[36] and mobile telephone messaging,[37] but resource-limited settings may not have the economy to support this without increasing external donor support. Treating the maximal number of new patients possible has been the top priority for many public sector programmes, with the possible consequence that documenting and tracing patients with LTFU have become increasingly inadequate.[38] Interventions that prevent LTFU in resource-limited settings can substantially improve survival and may be cost-effective by international criteria. HIV treatment in these settings should include interventions to prevent LTFU.[39]

During the last decade, the CD4 cell count threshold for ART initiation has risen steadily. A recent study found ART initiation among patients with a CD4 cell count >500/μL to be beneficial based on the level of HIV RNA suppression[40] and early ART initiation among these patients has also been shown to have an enhanced recovery of CD4 cell counts.[41] Although the patient groups are not directly comparable, the IR of LTFU among patients not eligible for ART was higher than that of patients on ART. However, we are not aware of any studies evaluating the effect of early ART on LTFU in sub-Saharan Africa.

This study does not provide the causes of LTFU among HIV-infected patients in Guinea-Bissau. Social workers visiting the homes of patients may be used to

Table 5 LTFU risk factors in patients on antiretroviral treatment (stage 4)

Stage 4 LTFU risk factors	Cox regression, LTFU hazard rates (HR) Univariate analysis HR (95% CI)	p Value	Multivariate analysis HR (95% CI)	p Value
Sex				
Male	1.21 (1.06 to 1.38)	<0.01	1.41 (1.15 to 1.74)	<0.01
Female	1.00	–	1.00	–
Age stratification (years)				
≤30	1.00	–	1.00	–
30–39	0.83 (0.71 to 0.97)	0.02	0.68 (0.54 to 0.86)	<0.01
≥ 40	0.83 (0.71 to 0.97)	0.02	0.62 (0.48 to 0.79)	<0.01
HIVtype				
HIV-1	1.00	–	1.00	–
HIV-2	1.12 (0.95 to 1.33)	0.17	1.39 (1.08 to 1.80)	0.01
HIV-1/2	1.22 (1.02 to 1.46)	0.03	1.65 (1.24 to 2.18)	<0.01
CD4 cell count (cells/μL)				
≤200	2.05 (1.63 to 2.56)	<0.01	2.71 (2.04 to 3.61)	<0.01
201–350	1.83 (1.44 to 2.31)	<0.01	2.31 (1.71 to 3.13)	<0.01
>350	1.00	–	1.00	–
Anaemia*				
Yes	1.19 (0.95 to 1.48)	0.13	–	–
No	1.00	–	–	–
Nutritional status (kg/m^2)				
BMI≤18.5	1.58 (1.38 to 1.81)	<0.01	1.51 (1.23 to 1.87)	<0.01
BMI>18.5	1.00	–	1.00	–
Marital status				
Single	0.96 (0.82 to 1.11)	0.57	–	–
Married	1.00	–	–	–
Divorced	0.80 (0.60 to 1.08)	0.15	–	–
Widowed	0.91 (0.76 to 1.09)	0.31	–	–
Religion				
Muslim	1.00	–	1.00	–
Catholic	0.74 (0.63 to 0.87)	<0.01	0.75 (0.59 to 0.96)	0.02
Protestant	0.79 (0.61 to 1.03)	0.08	0.79 (0.54 to 1.15)	0.21
Animist	0.98 (0.84 to 1.15)	0.83	1.09 (0.86 to 1.39)	0.47
Schooling				
Yes	1.00	–	1.00	–
No	1.21 (1.06 to 1.38)	<0.01	1.22 (0.98 to 1.52)	0.08
Geographic site of residence				
Bissau	1.00	–	–	–
Outside Bissau	1.06 (0.85 to 1.31)	0.61	–	–

*Haemoglobin below normal range: men >13 and women >12 mg/dL.
BMI, body mass index; LTFU, loss to follow-up.

clarify the causes of absence,[20] but due to a lack of social security numbers, street names and house numbers in many countries with limited resources, follow-up is difficult. Therefore, demographic surveillance sites (DSS) are well suited to long-term follow-up of HIV-infected individuals.[42] We are currently undertaking a nested follow-up study of the cohort patients living in a DSS area in Guinea-Bissau.

CONCLUSION

In our study, we found a high rate of LTFU and some variation in the risk factors of LTFU, which may be due to different causes of LTFU at the different stages of the HIV programme. As the mortality among patients lost to follow-up regardless of ART status is substantial, an increased focus on patient retention is recommended.

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