Adults Receiving HIV Care Before the Start of Antiretroviral Therapy in Sub-Saharan Africa: Patient Outcomes and Associated Risk Factors

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Background: Gaining understanding of the period before antiretroviral therapy (ART) is needed to improve treatment outcomes and to reduce HIV transmission. This study describes the cascade of enrollment in HIV care, pre-ART follow-up, and predictors of mortality and lost to follow-up (LTFU) before ART initiation.

Methods: We conducted a cohort study among HIV-infected adult patients not yet started on ART in 4 HIV Sub-Saharan African programs. Patient follow-up began at enrollment and ended at the earliest of death, transfer-out, ART initiation, last visit date, or 60 months postenrollment. Risk factors for death and LTFU were investigated during the periods 0–6 and 6–60 months.

Results: A total of 55,789 patients (65.4% women) were included as follows: 44.2% in clinical stage 3 or 4, with median CD4 of 261 cells per microliter [interquartile range (IQR): 125–447]. Patient care started with a median of 3 days (IQR: 0–11) after HIV diagnosis, and 31,104 of 55,789 (55.8%) patients had CD4 counts performed within 1 month of enrollment. Of 47,283 patients with known ART eligibility status at enrollment, 36,969 (78.2%) patients required ART and 27,798 of 36,969 (75.7%) patients initiated therapy. Median follow-up was 2.5 months (IQR: 0.9–13.1). Mortality and LTFU rates were 3.9 per 100 person-years [95% confidence interval (CI): 3.7 to 4.1] and 28.3 per 100 person-years (95% CI: 27.8 to 28.8), respectively. Regardless of period, increased mortality and LTFU were associated with male, lower body mass index, advanced clinical stage, and lower CD4 cell count.

Conclusions: Short delays between HIV testing and care enrollment were observed in our HIV programs, but delays to determine ART eligibility were long. Interventions to initiate ART earlier, specifically targeted to men, are needed to improve patient retention in Africa.

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INTRODUCTION

The public health priority for the management of HIV-infected patients is to provide access to combined antiretroviral therapy (ART), for those in need of treatment. This explains why, until recently, most efforts have been invested to scale-up access to ART in resource-limited settings, and much of the research has focused on the evaluation of treatment outcomes after the start of therapy.[1,2] The success of HIV programs was primarily judged on the basis of how many patients start therapy instead of on the percentage of patients eligible for and started on ART[3] or on retention of patients before the start of treatment. More recently, delays in determination of patient eligibility have also been examined. Nevertheless, evaluations of the effectiveness of HIV programs should not be restricted to the study of retention in care of patients receiving ART but should also consider their ability to identify HIV-infected individuals, to timely determine eligibility for ART, and to monitor and retain in care patients not yet eligible.[4,5] All these factors are important at individual level to reduce HIV-related mortality and morbidity, and they may contribute to decrease transmission of HIV infection.

Recently, Rosen and Fox[6] reported that less than one-third of patients testing positive for HIV in sub-Saharan Africa receive uninterrupted HIV care before ART initiation. Reasons for not starting ART despite patient eligibility include differences in eligibility criteria for therapy start, patient death or lost to follow-up (LTFU) before treatment initiation, misinformation about the importance of pre-ART care, limited program capacity, and insufficient drugs and/or skilled health workers. The relative importance of these reasons varies across countries and HIV programs.

To improve the quality and effectiveness of HIV care, it is necessary to monitor and evaluate patient follow-up before and after the start of ART. The identification of risk factors associated with increased mortality and retention before the start of therapy will help to improve patient long-term outcomes of those subsequently starting ART. Most Medecins Sans Frontieres (MSF)–supported HIV programs have electronic monitoring data systems that include information on patients receiving pre-ART care. In these programs, 20%–30% of the

patients who are currently receiving HIV care have not yet started ART (unpublished data, annual medical activities data, Médecins Sans Frontières, December 2011). We know that before the start of therapy, the dropout rate is high, especially early after program enrollment. However, we know little about the characteristics of these patients, about the factors associated with LTFU, and about the dynamics of dropping out. As such, we conducted a longitudinal study to evaluate the cascade of engagement in HIV care, characteristics, outcomes, and associated risk factors among patients not receiving ART in 4 HIV programs.

METHODS

Study Design and Study Population

We performed a longitudinal analysis of prospectively collected electronic monitoring data from HIV-positive adult patients (≥15 years old) treated in 4 HIV programs supported by MSF-France in sub-Saharan Africa (2 in Kenya: 1 in an urban slum and the other in a rural district hospital; 1 highly decentralized in a rural district of Malawi; and 1 in a rural hospital district of Uganda). Patients were included if they entered the HIV program between January 1, 2004, and December 31, 2010, that is, at least 1 year before the administrative censoring of the database. Patient clinical and laboratory data were collected prospectively using the FUCHIA software (Follow-Up and Care of HIV Infection and AIDS, Epicentre, Paris, France).

The pre-ART medical follow-up provided in programs is performed in accordance with national guidelines, which are based on the World Health Organization (WHO) recommendations. HIV diagnosis is based on the existence of 2 HIV-positive rapid antibody tests. Patients are seen by nurses, clinical officers, or medical staff every 3 or 6 months depending on their level of immunosuppression. Clinical assessment encompasses clinical staging and monitoring of nutritional status. CD4 cell count testing is scheduled every 6 months and is used to determine ART eligibility in patients with early stage of clinical disease (WHO clinical stage 1 or 2). Viral load monitoring is not routinely performed. Eligibility criteria for ART start evolved over time following changes in WHO recommendation[7–11] and was based on CD4 cell count levels and WHO clinical staging as follows: CD4 cell count <200 cells per milliliter, clinical stage 4 irrespective of CD4 cell count; since January 2007, clinical stage 3 irrespective of CD4 cell count; and since March 2010, CD4 cell count <350 cells per microliter and/or WHO clinical stage 3 or 4. HIV care provision in these sites started between April 2001 and September 2002. All services related to HIV care, including laboratory testing, provision of combined ART, and management of opportunistic infections and hospitalization, were free of charge.

Statistical Methods

Patient study follow-up started at the date of program enrollment and ended at the earliest of death, transfer-out, ART initiation, last clinical visit date, or 60 months postenrollment. LTFU was defined as having missed an appointment for more than 6 months among patients who had not initiated ART, been transferred outside the program, or died during the study period.[12]

Patient characteristics were summarized using frequencies and percentages for categorical variables and median and interquartile range (IQR) for continuous variables. Access to HIV care was assessed through calculation of the time between HIV testing and enrollment in the program. We also described the number of pre-ART visits per patient and the time between successive clinic visits. To study the delay in initial eligibility determination, we examined temporal changes in the proportions of patients with a recorded CD4 cell count measurement within 1 and 3 months of enrollment. To evaluate the continuity of pre-ART care in the program, we reported the frequency, duration, and timing of temporal interruptions in follow-up (not attending a clinic visit for at least 60 days after the appointment date). The delay in ART start was estimated among ART eligible patients at enrollment (2010 definition: CD4 cell count <350 cells/μL and/or in WHO clinical stage 3 or 4) who initiated therapy.[11]

Kaplan–Meier estimates of mortality and LTFU were calculated within 2 time periods, 0–6 and 6–60 months after program entry. Risk factors for mortality and LTFU were evaluated using a parametric survival model with Weibull distribution for the 0-month to 6-month period, when mortality and LTFU rates were higher; and a Cox proportional hazards models for the 6-month to 60-month period. Factors considered for adjustment were as follows: sex, age (continuous variable), mode of entry in the program (in- or outpatient services, voluntary counseling and testing or prevention of mother-to-child transmission of HIV infection, medical referral, other, and missing), WHO clinical stage (1, 2, 3, 4, and missing), CD4 cell count (<50, 50–199, 200–349, 350–499, ≥500, and missing cells/μL), body mass index (BMI: <18.5, ≥18.5, and missing kg/m^2), previous history of ART use, and recorded diagnosis of tuberculosis. In addition, we fitted separate Cox proportional hazards models to obtain estimates of associations with the baseline ART eligibility status that did not include initial clinical stage and CD4 cell count to avoid colinearity. Final multivariable models were fitted using a backward stepwise approach. Statistical significance was assessed with the likelihood ratio test at 5% level. All estimates were adjusted for year of program inclusion and site. In addition, complete case analyses to assess the impact of missing data on our estimates were performed by excluding patients who had incomplete covariate data (CD4 counts, clinical stage, and BMI) from the population analyzed. We also performed a competing risk analysis to obtain risk factor estimates of mortality adjusted for LTFU.[13]

Analyses were performed using Stata 12.1 software (Stata Corporation, College Station, TX).

Ethical Considerations

All MSF-supported projects are implemented in collaboration with the Ministry of Health and within the frame of signed Memorandums of Understandings. Electronic monitoring data are collected in agreement with the Ministry of Health to monitor and evaluate the HIV programs. The study was

approved by the Comité de Protection des Personnes de Saint Germain en Laye, Paris, France.

RESULTS

A total of 55,789 adult patients were included in the analyses, 54.3% of them were treated in Malawi, 26.1% in Uganda, and 19.6% in Kenya. The number of patient inclusions remained stable over the study period.

Patients were enrolled in the programs in median 3 days (IQR: 0–11) after being tested positive for HIV. The percentages of individuals with a recorded CD4 cell count within 1 and 3 months of inclusion were 55.8% and 70.1%, respectively. These percentages increased over time from 9.3% and 27.3% in 2004 to 77.8% and 86.7% in 2010, respectively ($P < 0.001$).

At program enrollment, patient median age was 33 years (IQR: 27.5–40.0) and 65.4% of individuals were women (Table 1). The median BMI was 19.6 kg/m^2 (IQR: 17.7–21.7), 10.1% of patients had a recorded diagnosis of tuberculosis, and 44.2% were in stage 3 or 4 (n = 22,779). Sixty-three percent of patients had CD4 <350 cells per microliter (n = 24,837). Only 307 individuals had history of ART (0.6%) and/or prevention of mother-to-child transmission of HIV infection use (2.9%) before program entry.

Men were more likely to present at an advanced stage of disease than women; 52.3% of men were in clinical stage 3 or 4 compared with 39.8% of women ($P < 0.001$); and median CD4 cell count was lower in men (203 vs 0.291 cells/μL, $P < 0.001$).

TABLE 1. Patient Characteristics at Enrollment in the HIV Programs of Malawi, Kenya, and Uganda, 2004–2010 (N = 55,789)

Characteristics	
Women, n (%)	36,508 (65.4)
Median age (IQR), (yrs)	33.0 (27.5–40.0)
BMI (kg/m^2)	
Median (IQR)	19.6 (17.7–21.7)
<18.5	18,583 (35.0)
≥18.5	35,229 (65.0)
Missing	1907
Clinical stage, n (%)	
1	17,834 (34.6)
2	10,950 (21.2)
3	15,373 (29.8)
4	7406 (14.4)
Missing	4226
CD4 cell count (cells/μL)	
Median (IQR)	261 (125–447)
<50	3934 (10.1)
50–199	11,423 (29.2)
200–349	9480 (24.2)
350–499	6407 (16.4)
≥500	7843 (20.1)
Missing	16,702
History of ART use, n (%)	307 (0.6)
Diagnosis of tuberculosis, n (%)	5651 (10.1)
Mode of program entry, n (%)	
In- or outpatient services	30,358 (65.0)
VCT or PMTCT	9826 (21.1)
Medical referral	4170 (8.9)
Other	2329 (5.0)
Missing	9106

PMTCT, prevention of mother-to-child transmission of HIV infection; VCT, voluntary counseling and testing.

Study Follow-Up and Interruption of HIV Care

Overall, median duration of pre-ART follow-up per patient was 2.5 months (IQR: 0.9–13.1). Median duration of follow-up for individuals who received HIV care for more than 6 months (n = 20,686) was 19.1 months (IQR: 11.1–33.5).

During the study follow-up, a total of 5348 patients (9.6%) interrupted HIV care temporarily at least once for a median duration of 109 days (IQR: 77–214). Eighty-five percent of interruptions happened during the 6-month to 60-month period (median duration of 126 days, IQR: 84–254), and the proportion of patients with temporal care discontinuations remained stable over time.

ART Eligibility and Therapy Start

Of the 47,283 patients with known ART eligibility status at enrollment, 36,969 (78.2%) required ART. Patients who were eligible at enrollment had a median follow-up of 1.5 months (IQR: 0.9–4.6), those who were not eligible had a median follow-up of 18.4 months (IQR: 8.5–32.2), and patients with unknown eligibility status had a median follow-up of 6.2 months (IQR: 0.7–21.1). Among eligible patients, 27,998 (75.7%) started ART during the study follow-up (Fig. 1). Of those not initially eligible, 5103 became eligible during the study follow-up and were started on therapy. Before ART initiation, patients had a median number of 1 CD4 cell count measurement (IQR: 0–2), and 4 clinic visits (IQR: 2–8) with intervals between visits of 1.02 months (IQR: 0.60–2.76). The overall median delay in ART start was 2.1 months (IQR: 0.9–8.2) for the 34,719 patients who initiated treatment and was 1.5 months (IQR: 0.9–3.9) for the 27,998 patients who were eligible and started ART. This delay was positively associated with the initial CD4 count levels ($P < 0.001$), 1.2 months for patients with CD4 <50 cells per microliter, 1.3 months for 50–199 cells per microliter, 3 months for 200–349 cells per microliter, 15.9 months for 350–499 cells per microliter, and 23.5 months for >500 cells per microliter. Among patients eligible for and initiated on ART at enrollment, 9610 (34.3%) received treatment within 1 month of program entry, median delay before ART start being 1.5 months (IQR: 0.9–3.9).

Mortality

Overall, 1843 of 55,789 (3.3%) patients died before receiving ART, a median of 1.6 months (IQR: 0.7–4.4), after program entry. About 1399 (75.9%) of the deaths were among patients eligible for therapy at program inclusion.

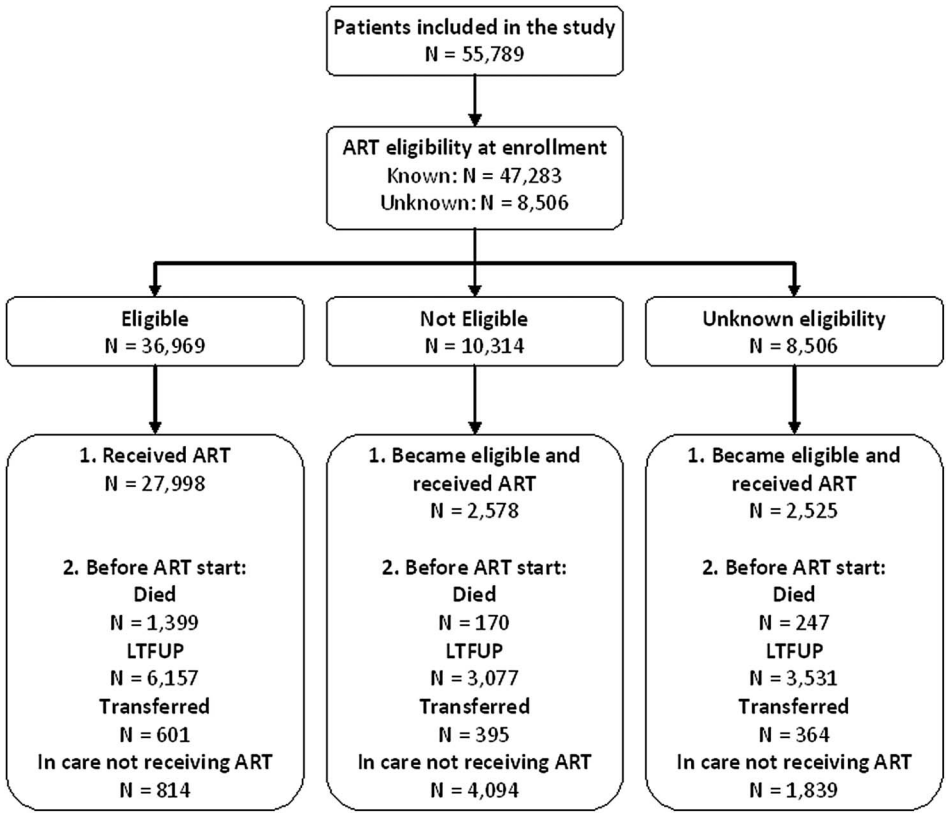

FIGURE 1. Flow chart of patients included in the study, Malawi, Kenya, and Uganda, 2004–2010.

The overall rate of mortality was 3.9 per 100 person-years. Cumulative estimates were 1.3% [95% confidence interval (CI): 1.2% to 1.5%] at 1 month (rate: 41.5 per 100 person-years), 3.8% (95% CI: 3.6% to 4.0%) at 6 months (1–6 months rate: 9.8 per 100 person-years), 4.6% (95% CI: 4.3%–4.8%) at 12 months (6–12 months rate: 1.7 per 100 person-years), and 5.6% (95% CI: 5.4%–5.9%) at 24 months (12–24 month rate: 1.2 per 100 person-years). Mortality was significantly higher in patients eligible for ART initiation than in those not eligible (log-rank test $P < 0.001$; Fig. 2A). Rates were 8 per 100 person-years and 0.9 per 100 person-years, respectively, and 2.6 per 100 person-years for patients with unknown eligibility status.

Results of the multivariate analysis are presented in Table 2. Six-month mortality was higher in patients with initial advanced clinical disease [adjusted hazard ratio (aHR) = 5.96, 95% CI: 4.90 to 7.23 for stage 4 compared with stage 1]. Mortality was lower in women than in men (aHR = 0.65, 95% CI: 0.59 to 0.72) in patients with higher CD4 cell count (aHR = 0.11, 95% CI: 0.08 to 0.15 for >500 compared with <50 cells/μL) and in those with BMI ≥18.5 kg/m^2 (aHR = 0.39, 95% CI: 0.34 to 0.44 compared with <18.5 kg/m^2). The same risk factors for mortality were identified during the 6–60 month period, with the highest hazard ratio observed for patients in clinical stage 4 (aHR = 3.0, 95% CI: 1.95 to 4.62). Long-term pre-ART mortality also increased with age (10 years unit aHR = 1.19, 95% CI: 1.08 to 1.30) and was higher in patients diagnosed with tuberculosis (aHR = 1.65, 95% CI: 1.13 to 2.40).

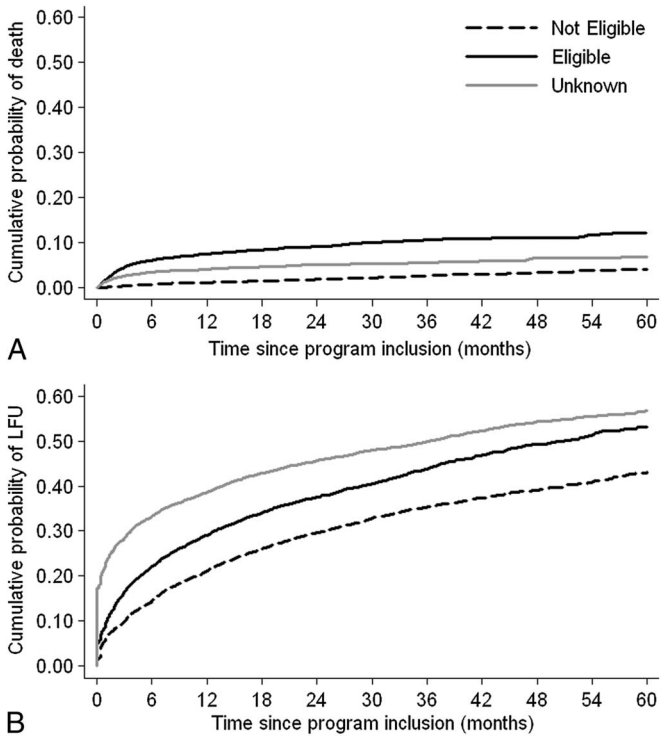

FIGURE 2. Kaplan–Meier estimates of mortality (A) and LTFU (B) of patients receiving pre-ART HIV care stratified by eligibility status at program entry in Malawi, Kenya, and Uganda, 2004–2010.

TABLE 2. Associations Between Individual-Level Factors and Mortality During the 0–6 and 6–60 Months Pre-ART Follow-Up Periods in Malawi, Kenya, and Uganda, 2004–2010

Characteristics at Inclusion	0–6 Months			6–60 Months		
	Crude HR (95% CI)	Adjusted HR (95% CI)	Adjusted SHR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Adjusted SHR (95% CI)
Sex						
Male	1	1	1	1	1	1
Female	0.45 (0.40 to 0.49)	0.65 (0.59 to 0.72)	0.70 (0.63 to 0.78)	0.43 (0.35 to 0.53)	0.59 (0.48 to 0.74)	0.63 (0.50 to 0.79)
Age in years (per 10 unit increase)	1.11 (1.06 to 1.17)	—	—	1.29 (1.18 to 1.41)	1.19 (1.08 to 1.30)	1.22 (1.10 to 1.35)
BMI (kg/m²)						
<18.5	1	1	1	1	1	1
≥18.5	0.21 (0.18 to 0.23)	0.39 (0.34 to 0.44)	0.42 (0.37 to 0.48)	0.43 (0.35 to 0.53)	0.61 (0.49 to 0.77)	0.62 (0.48 to 0.80)
Missing	3.48 (2.97 to 4.08)	3.10 (2.63 to 3.65)	2.04 (1.71 to 2.43)	2.60 (1.40 to 4.82)	2.28 (1.21 to 4.29)	1.30 (0.61 to 2.79)
Clinical stage						
1	1	1	1	1	1	1
2	1.68 (1.36 to 2.07)	1.31 (1.06 to 1.62)	1.34 (1.08 to 1.65)	1.61 (1.21 to 2.12)	1.48 (1.11 to 1.97)	1.41 (1.05 to 1.90)
3	4.19 (3.54 to 4.97)	2.61 (2.17 to 3.14)	2.33 (1.93 to 2.81)	2.51 (1.93 to 3.27)	1.95 (1.44 to 2.66)	1.78 (1.29 to 2.44)
4	14.07 (11.87 to 16.68)	5.96 (4.90 to 7.23)	4.73 (3.86 to 5.79)	5.39 (3.70 to 7.85)	3.00 (1.95 to 4.62)	2.15 (1.30 to 3.54)
Missing	2.01 (1.53 to 2.64)	1.73 (1.30 to 2.29)	1.66 (1.25 to 2.20)	1.13 (0.74 to 1.73)	1.16 (0.75 to 1.80)	1.12 (0.72 to 1.76)
CD4 cell count (cells/μL)						
<50	1	1	1	1	1	1
50–199	0.30 (0.25 to 0.37)	0.44 (0.36 to 0.53)	0.45 (0.37 to 0.55)	0.45 (0.19 to 1.06)	0.67 (0.28 to 1.62)	1.20 (0.41 to 3.52)
200–349	0.10 (0.08 to 0.12)	0.18 (0.14 to 0.23)	0.24 (0.18 to 0.30)	0.10 (0.05 to 0.20)	0.20 (0.09 to 0.44)	0.35 (0.13 to 0.92)
350–499	0.07 (0.05 to 0.09)	0.15 (0.12 to 0.21)	0.22 (0.16 to 0.29)	0.07 (0.03 to 0.14)	0.15 (0.07 to 0.32)	0.27 (0.11 to 0.72)
≥500	0.04 (0.03 to 0.06)	0.11 (0.08 to 0.15)	0.15 (0.11 to 0.21)	0.05 (0.03 to 0.11)	0.13 (0.06 to 0.29)	0.25 (0.09 to 0.65)
Missing	0.63 (0.54 to 0.73)	1.45 (1.23 to 1.71)	1.17 (0.99 to 1.39)	0.10 (0.05 to 0.20)	0.22 (0.10 to 0.47)	0.28 (0.11 to 0.73)
Diagnosis of tuberculosis						
No	1	—	—	1	1	1
Yes	3.38 (3.00 to 3.82)	—	—	4.36 (3.21 to 5.92)	1.65 (1.13 to 2.40)	1.46 (0.96 to 2.22)
Mode of program entry						
VCT or PMTCT	1	—	—	1	1	1
In- or outpatient services	1.26 (1.10 to 1.46)	—	—	1.26 (0.96 to 1.64)	1.43 (0.98 to 2.08)	1.51 (1.02 to 2.21)
Medical referral	1.50 (1.21 to 1.85)	—	—	0.73 (0.44 to 1.23)	0.67 (0.39 to 1.17)	0.67 (0.38 to 1.19)
Other	1.51 (1.18 to 1.94)	—	—	0.87 (0.45 to 1.69)	1.07 (0.51 to 2.24)	1.04 (0.48 to 2.23)
Missing	0.54 (0.43 to 0.68)	—	—	0.95 (0.64 to 1.40)	1.38 (0.78 to 2.44)	1.31 (0.79 to 2.16)
Eligibility to ART at enrollment*						
No	1	1	1	1	1	1
Yes	9.26 (7.18 to 11.95)	6.29 (4.85 to 8.16)	5.16 (4.00 to 6.66)	2.64 (2.09 to 3.34)	2.24 (1.73 to 2.90)	2.02 (1.56 to 2.63)
Unknown	5.26 (3.96 to 6.98)	4.42 (3.31 to 5.91)	3.53 (2.64 to 4.71)	1.28 (0.95 to 1.73)	1.16 (0.83 to 1.61)	1.09 (0.76 to 1.55)

* CD4 cell count and clinical stage were not included in this model for estimations of HR and SHR.
PMTCT, prevention of mother-to-child transmission of HIV infection; HR, hazard ratio; SHR, subhazard rate ratio; VCT, voluntary counseling and testing.

Compared with patients not eligible for ART at program entry, those eligible had aHR = 6.29 (95% CI: 4.85 to 8.16) during the first 6 months of follow-up and 2.24 (95% CI: 1.73 to 2.90) during the 6–60 month period. Patients with unknown eligibility status had aHR = 4.42 (95% CI: 3.31 to 5.91) and 1.16 (0.83–1.61), respectively (Table 2).

Analyses restricted to patients with complete data showed consistent results. Results obtained from the competing-risk regression were similar to those obtained with the Cox model (where LTFU were considered as censored), although the size of the estimates was generally smaller (Table 2).

Lost to Follow-Up

A total of 12,765of 55,789 (22.9%) patients were LTFU before receiving ART in median 1.5 months (IQR: 0.03–7.72)

after program entry, 6157 (48.2%) of them were eligible for ART at inclusion. The overall LTFU rate was 28.3 per 100 person-years. Kaplan–Meier cumulative estimates were 11.1% (95% CI: 10.9% to 11.4%) at 1 month (rate: 161.5/100 person-years), 21.7% (95% CI: 21.3% to 22.2%) at 6 months (1–6 month rate 64.9/100 person-years), 28.2% (95% CI: 27.7% to 28.7%) at 12 months (6–12 month rate: 17.5 per 100 person-years), and 36.2% (95% CI: 35.6% to 36.8%) at 24 months (12–24 month rate: 15.9 per 100 person-years). Higher estimates were found in patients eligible for ART at program entry (Fig. 2B), with rates of 38.3 per 100 person-years, compared with rates 16.5 per 100 person-years in patients not eligible and 34.2 per 100 person-years in individuals with unknown eligibility status.

As observed for mortality, being LTFU during the first 6 months of HIV care was associated with severe HIV disease at program inclusion (Table 3). Higher ratios were seen in patients in clinical stage 3 (aHR = 1.27, 95% CI: 1.20 to 1.36) or 4 (aHR = 1.69, 95% CI: 1.56 to 1.83). Lower ratios were found in patients with BMI $\geq$18 kg/m^2 (aHR = 0.85, 95% CI: 0.80 to 0.89), CD4 cell count $>$50 cell s per microliter, in women (aHR = 0.71, 95% CI: 0.68 to 0.74), and in individuals of older age (aHR = 0.84, 95% CI: 0.82 to 0.86, per 10 unit increase). The same associations were identified during the 6-month to 60-month period.

The aHR for ART eligible patients were 1.40 (95% CI: 1.31 to 1.49) in the 0–6 months and 1.12 (95% CI: 1.03 to 1.22) in the 6–60 months period, and 2.86 (2.67 to 3.07) and 1.16 (1.05 to 1.27), respectively, for patients with unknown eligibility status at program entry (Table 3). Analyses restricted to patients with complete data showed consistent results.

DISCUSSION

We report the outcomes of HIV-positive patients registered in 4 HIV African programs before the start of ART. Despite short delays in enrollment in HIV care after HIV testing, most patients presented with advanced stage of HIV disease, and 75.7% of those eligible for treatment were started on ART. Before the start of therapy, 23% of patients dropped out and 3% died. Increased mortality and LTFU were observed in patients presenting with advanced HIV disease and in men. Compared with patients not eligible for ART, those eligible had a 6-fold increased risk of death during the first 6 months of care and a 2-fold increase in the following four-and-half years.

Some studies in resource-limited countries have described pretreatment mortality and LTFU rates in HIV-infected adults,[5,14,15] but very few of them were conducted in rural settings. In Uganda and Gambia, mortality rates among patients eligible for ART (WHO stage 3 or 4 or CD4 cell count $<$200/μL) were 27 per 100 person-years[16] and 21.9 per 100 person-years among eligible patients infected with HIV-1 and/or HIV-2,[17] respectively. Those rates were higher than the 8 per 100 person-years reported in our programs. Differences are likely to be partly explained by differences in tracing of LTFU patients to ascertain the vital status of patients. In our programs, mortality is underestimated, given the large proportion of LTFU and the fact that patients who do not receive ART and fail to attend their clinic appointments are not routinely traced. This is also suggested by the similarity in patient baseline clinical characteristics between LTFU patients and those who died; and it is supported by findings of a previous evaluation conducted in Malawi showing that 49% of patients LTFU before receiving ART between July 2004 and September 2007 had died.[18] Ingle et al found even worse outcomes with overall pre-ART mortality rates of 53.2 per 100 person-years among eligible patients (CD4 $<$200 cells/μL) enrolled in a large HIV program in South Africa. Disparities in population characteristics originated from various settings, utilization of restrictive eligibility criteria (CD4 $<$ 200 cells/μL) coupled to a good ascertainment of vital status through efficient linkage to death registries probably explain their worse findings. The pre-ART mortality rate found in a rural Ethiopian cohort was 13.1 per 100 person-years,[19] which is higher than the 3.9 per 100 person-years rate observed in our programs. Again death status was ascertained among LTFU patients, and patients were enrolled in care at a more advanced stage of disease (62% were stage 3 or 4 compared with 44% in our report). In rural Kenya, the pre-ART LTFU rate in patients not eligible at 6 months of follow-up was 11.1 per 100 person years,[20] which is lower than the rate of 21.5 per 100 person-years observed in our cohorts during the same observation period. Applying to our data, the method developed by Brinkhof et al[21] to correct mortality estimates at 1 year of ART taking into account the rate of follow-up, the mortality estimate at 1 year increased from 4.6% (95% CI: 4.3% to 4.8%) to 12.3% (95% CI: 7.4% to 17.6%).

Two of 3 patients were eligible for ART at program inclusion and, as expected, treatment eligibility was associated with increased early and late mortality during pre-ART follow-up. Patients started ART in median 1-and-a-half month after program enrollment. Although delays in treatment initiation were shorter for severely immunosuppressed patients, waiting times were too long and could be further reduced by decreasing the length of precounseling sessions and concomitantly reinforcing counseling during the first months of ART. For instance, in Cape Town, South Africa, delays of 34 days have been achieved,[4] and good outcomes have been reported among patients treated with ART.[22,23] The scaling up of point of care CD4 testing tools planned in our programs in the coming months should also contribute to reduce the number of patient visits necessary for initial clinical evaluation and determination of ART eligibility.[24,25] This is expected to lead to decrease delays in ART initiation, especially among paucisymptomatic patients. Further reducing pre-ART mortality will require strengthening of the whole cascade of HIV care, starting from testing at an earlier stage of the disease, through implementation of new strategies to promote HIV testing at community level and delivery of CD4 count results on the same day of the initial clinical evaluation; to achieving effective enrollment and retention in pre-ART HIV care to start therapy as soon as the patients become eligible. Barriers to care access need to be adequately understood and addressed (eg, knowledge of the asymptomatic phase of disease, stigma, or direct and indirect costs related to health care)[20,26,27] and adapted strategies adopted. For instance, logistical challenges are frequently faced by patients (eg, travel distance and transportation fees) and efforts to minimize these need to be undertaken.

TABLE 3. Associations Between Individual-Level Factors and LTFU During the 0–6 and 6–60 Months Pre-ART Follow-Up Periods in Malawi, Kenya, and Uganda, 2004–2010

	0–6 Months		6–60 Months	
Characteristics at Inclusion	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
Sex				
Male	1	1	1	1
Female	0.70 (0.67 to 0.73)	0.71 (0.68 to 0.74)	0.62 (0.58 to 0.67)	0.62 (0.58 to 0.67)
Age in years (per 10 unit increase)	0.86 (0.84 to 0.88)	0.84 (0.82 to 0.86)	0.81 (0.78 to 0.84)	0.79 (0.76 to 0.82)
BMI (kg/m^2)				
<18.5	1	1	1	1
≥18.5	0.69 (0.66 to 0.72)	0.85 (0.80 to 0.89)	0.79 (0.73 to 0.85)	0.93 (0.92 to 1.21)
Missing	3.60 (3.33 to 3.90)	2.99 (2.76 to 3.25)	3.12 (2.49 to 3.91)	2.89 (2.30 to 3.63)
Clinical stage				
1	1	1	1	1
2	0.84 (0.79 to 0.89)	0.85 (0.79 to 0.90)	1.03 (0.94 to 1.12)	1.04 (0.95 to 1.13)
3	1.25 (1.19 to 1.32)	1.27 (1.20 to 1.36)	1.19 (1.09 to 1.29)	1.09 (0.99 to 1.21)
4	2.23 (2.09 to 2.37)	1.69 (1.56 to 1.83)	1.73 (1.47 to 2.03)	1.56 (1.30 to 1.87)
Missing	0.95 (0.87 to 1.04)	1.10 (1.00 to 1.21)	0.73 (0.64 to 0.83)	1.05 (0.92 to 1.21)
CD4 cell count (cells/μL)				
<50	1	1	1	1
50–199	0.60 (0.52 to 0.68)	0.66 (0.58 to 0.76)	0.54 (0.30 to 0.97)	0.80 (0.44 to 1.44)
200–349	0.54 (0.47 to 0.61)	0.60 (0.53 to 0.69)	0.30 (0.18 to 0.50)	0.59 (0.35 to 0.98)
350–499	0.67 (0.59 to 0.76)	0.71 (0.63 to 0.81)	0.28 (0.17 to 0.46)	0.52 (0.32 to 0.87)
≥500	0.79 (0.70 to 0.89)	0.82 (0.72 to 0.93)	0.31 (0.19 to 0.51)	0.56 (0.34 to 0.93)
Missing	2.77 (2.48 to 3.09)	3.93 (3.51 to 4.40)	0.39 (0.24 to 0.65)	0.73 (0.44 to 1.21)
Diagnosis of tuberculosis				
No	1	1	1	1
Yes	1.22 (1.14 to 1.30)	0.75 (0.70 to 0.81)	1.91 (1.66 to 2.20)	1.25 (1.07 to 1.47)
History of ART use				
No	1	—	1	1
Yes	0.79 (0.53 to 1.18)		1.51 (0.84 to 2.73)	1.74 (0.96 to 3.16)
Mode of program entry				
VCT or PMTCT	1	1	1	1
In or outpatient services	0.81 (0.77 to 0.86)	1.07 (1.00 to 1.15)	0.91 (0.84 to 0.99)	1.10 (0.99 to 1.22)
Medical referral	0.71 (0.64 to 0.78)	1.06 (0.96 to 1.18)	0.74 (0.64 to 0.86)	1.00 (0.85 to 1.17)
Other	1.14 (1.03 to 1.25)	1.21 (1.08 to 1.35)	1.57 (1.35 to 1.82)	1.30 (1.10 to 1.54)
Missing	0.83 (0.77 to 0.89)	1.66 (1.49 to 1.85)	0.78 (0.69 to 0.88)	1.31 (1.11 to 1.55)
Eligibility to ART at enrollment*				
No	1	1	1	1
Yes	1.50 (1.41 to 1.59)	1.40 (1.31 to 1.49)	1.19 (1.10 to 1.28)	1.12 (1.03 to 1.22)
Unknown	2.78 (2.61 to 2.96)	2.86 (2.67 to 3.07)	10.5 (0.97 to 1.14)	1.16 (1.05 to 1.27)

* CD4 cell count and clinical stage were not included in this model for estimations of HR.
HR, hazard ratio; PMTCT, prevention of mother-to child-transmission of HIV infection; VCT, voluntary counseling and testing.

Outcomes and characteristics of patients who are not eligible for ART have been poorly described in the literature.[5,28,29] In the programs studied, the high rate of LTFU observed among this group of patients highlights the difficulties faced by health workers to retain patients not eligible and frequently asymptomatic patients in care. Differences in rates of LTFU according to eligibility status were smaller than for mortality, especially after the first 6 months of care. It is likely that many of the patients who do not require therapy and who discontinue HIV care will return to the clinics when symptoms of late disease develop at a later stage. Because of the high workload in our programs, priority was given to the management of more severe cases and fewer efforts were invested to encourage retention of asymptomatic patients. Improvement of outcomes can only be achieved if sufficient resources are available and an enhanced standard package of pre-ART care is provided (eg, adapted counseling or social support).

In this study, women were less likely to die or be LTFU regardless of the severity of HIV disease at clinic presentation. Similar sex-related disparities in both access to care and clinical outcomes have been described in the literature and are unlikely to be explained by the physiological lower CD4 count levels in men.[30] Men are frequently diagnosed at a later stage of HIV disease (ie, more advanced clinical stage and lower CD4 cell counts) and consequently present late and more severely immunosuppressed.[31] Smaller proportions of men are

followed up in HIV programs[5,32] and start ART, partly because they interrupt care more frequently than women.[16] Once on ART, poorer treatment outcomes[16,31,33–39] have also been reported. Men might suffer from specific forms of stigma or feel that they were less vulnerable to HIV infection than women. Better understanding of both, the barriers in accessing and the factors facilitating long-term retention in HIV care among men, is important to design appropriate innovative interventions specifically designed for this high-risk group. Strategies of decentralization of HIV testing and care services to the work place might be effective in some contexts.

Because the study was based on the analysis of electronic monitoring data, estimates were not adjusted for some potential confounding factors such as socioeconomic and marital status or household distance to HIV clinic.[14] Although missing data on CD4 cell count or clinical stage may bias study estimates, results of the complete case analysis were consistent with those obtained when variables including separate categories for missing data were used. Second, deaths were not ascertained and the reasons for being LTFU were unknown. Therefore, we cannot exclude outcome misclassification for a certain proportion of LTFU patients who might have died. However, the competing-risk regression, where LTFU were considered as a competing event for death, showed consistent results and provided evidence of robustness of our findings.

In conclusion, this analysis identified several areas of improvement including the need to increase access to HIV program at an earlier stage of disease and to improve pre-ART care to maximize program retention and timely start of ART. Comprehensive evaluations of HIV programs should include the study of patients not started on therapy, a description of delays in treatment start as patients become eligible for treatment, and quantification of care discontinuation for both patients eligible and not eligible for ART. In the context of scaling up of HIV testing, the study of temporal trends in these indicators is important to inform program managers about the successes or insufficiencies of the operational strategies adopted. Particular attention should be paid to the effective linkage to care and long-term retention of patients not yet eligible for treatment, especially among men.

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