Mortality and its determinants among HIV-1 infected patients on antiretroviral therapy in a referral centre in Yaounde, Cameroon: a retrospective cohort study

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Mortality and its determinants among HIV-1 infected patients on antiretroviral therapy in a referral centre in Yaounde, Cameroon: a retrospective cohort study

Short title: Determinants of death among patients with HIV infection

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ABSTRACT

Objectives: Mortality has decreased in people with human immunodeficiency virus (HIV) infection, subsequent to the improved access to antiretroviral therapy (ART). We assessed the incidence and determinants of fatal outcomes among patients with HIV-1 infection, started on ART in a referral treatment centre for HIV infection in Yaounde, Cameroon.

Design: Cohort study with baseline assessment between 2007 and 2008, and follow-up until June 2012.

Setting: The approved centre for HIV treatment of the Yaounde Jamot, in capital city of Cameroon.

Participants: Patients with HIV infection who were started ART between 2007 and 2008 at the study centre.

Outcome measures: All-cause mortality over time, with the accelerated failure time models were used to relate baseline characteristics with mortality occurrence during follow-up.

Results: Of the 1444 patients included, 827 (53.7%) were men, and median age (25^{th}-75^{th} percentiles) was 38 (31-45) years. The median duration of follow-up was 14.1 (1.1-46.4) months, during which 235 deaths were recorded (cumulative incidence rate: 16.3%), including 208 (88.5%) during the first year of follow-up. Baseline predictors of mortality were male gender [adjusted hazard ratio 2.15 (95%CI: 1.34-3.45)], active tuberculosis [2.35 (1.40-3.92)], WHO stages III-IV of the disease [3.63 (1.29-10.24)], low weight [1.03 (1.01-1.05) per kilogramme], low CD4 count [1.04 (1.01-1.07) per 10/mm^3) and low haemoglobin levels [1.12 (1.00-1.26) per g/dl].

Conclusions: Death rate among patients with HIV is very high within the first year of starting ART in this centre. Early start of the treatment, at a less advanced stage of the disease, and much favourable levels of CD4 and other predictors may improve the outcomes of patients, but would have to be tested.

Word count – 267

Key words: HIV infection, death, determinants, cohort

ARTICLE SUMMARY

Article focus

- To investigate mortality occurrence and determinants among patients with HIV-1 infection, started on antiretroviral therapy in a major reference treatment centre

Key messages

- Death rate among patients with HIV is very high within the first year of starting ART in this centre
- Male gender, active tuberculosis, advanced stage of the disease, low CD4 count, low weight and low haemoglobin levels at baseline were significant predictors of all-cause mortality during the follow-up

Strengths and limitations

- Strengths of the study include the large sample size and the use of robust methods to relate baseline predictors to the outcome occurrence during follow-up.
- The study was based on data collected from patient files and clinical registers, and as expected there were missing data, particularly on the true outcome of patients were lost-to-follow-up.

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a major global health problem. Sub-Saharan Africa (SSA), with about 68% of the global population with HIV, is the most affected region in the world. [1] HIV related mortality appears to be higher in developing than in developed countries. [2] Hopefully, mortality rates are on the decline with the improved access to antiretroviral therapy, [3] while explaining factors of the residual deaths seems to vary significantly across populations. Studies in SSA have found that mortality rate is particularly high during the first year of starting antiretroviral therapy, [4] with male sex, cachexia, advanced stage of the disease, low CD4 count, anaemia, high viral load at baseline, and poor adherence to treatments being the main determinants of death. [5-8]

In Cameroon, about 105,000 people with HIV infection were on antiretroviral therapy by the end of the year 2011, [9] A study conducted in 2006 in a rural unit for HIV treatment in the northern part of the country, found a mortality rate of 20.2/100 person-years among HIV patients receiving antiretroviral therapy. [10] This figure however, has not been updated since the introduction of free access to antiretroviral therapy in the country. Thus, the aim of this study was to determine the mortality rate and its determinants among patients with HIV-1 infection, started on antiretroviral therapy in a reference treatment centre in Cameroon.

PARTICIPANTS AND METHODS

Study setting

The study was conducted in the approved HIV treatment centre of the Yaounde Jamot Hospital (YJH) in the Capital city of Cameroon. The study setting has been described in detail previously elsewhere. [11, 12] In brief, YJH is the referral centre for tuberculosis and chest diseases for the Capital city (Yaounde) and surrounding areas. It has an approved treatment centre (ACT) that provides care to people with HIV infection. As of June 2011, the active file of HIV infected persons followed in the centre was 2250 patients.

Care of patients with HIV infection

During the study period, patients with HIV infection were started on antiretroviral therapy in the presence of a CD4 count below 200/mm^3 or superimposed condition other than tuberculosis, characteristic of WHO stage IV of the disease severity, [13] Patients fulfilling these criteria were referred to the ACT for treatment inception and follow-up. A medical file was created under the supervision of the attending physician and included socio demographic, clinical and biological data of the patient. Files of eligible patients were presented at weekly meetings during which the appropriate treatment regimen for each patient was decided. First line treatment regimens included two nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, lamivudine, tenofovir) and one non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz). Second line regimens comprised two nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, lamivudine, tenofovir) and a protease inhibitor (indinavir, lopinavir/ritonavir). These regimens were all dispensed to patients free of charge and they were all started on prophylactic treatment with cotrimoxazole. All patients had a session with trained psychosocial advisors, to improve adherence to prescribed therapies.

Patients registered at the YJH's ACT are seen on a monthly basis for prescription renewal. For those on a regimen comprising zidovudine (AZT) and/or nevirapine (NVP), haemoglobin (AZT) and/or liver transaminases (NVP) levels are monitored at two weeks from starting treatment. A biological profile is requested every six months, comprising a CD4 count, full blood count, liver transaminases and creatinin (only for patients receiving tenofovir), and results are recorded in the clinical file.

Outcome

During the study period, patients who failed to report for consultation for three consecutive months were traced by community liaison agents using the contact details on the file. All-cause mortality was considered for all deceased patients at any time after starting antiretroviral therapy. The time-to-death (in months) was the interval from the start of the antiretroviral therapy to date of death (or date of the last recorded visit when the date of death was unknown). Loss-to-follow-up (defaulter) was considered for patients who failed to return for consultation for three consecutive months and was unsuccessfully traced by liaison agents, [14] Transfer was considered for patients who at any time were definitively transferred to receive care in another centre. The follow-up for all patients was until June 2012, death, transfer and loss to follow-up, whichever came first.

Data collection

For the purpose of this study, patients with HIV started on antiretroviral therapy between January 2007 and December 2008 were identified via antiretroviral treatment registries. All patients with HIV-1 infection, aged 18 years and above, started on antiretroviral during this period were included in the study, and followed until June 2012 (5.5 years). The study was approved by the regulatory board of YJH.

The following data were then retrieved in the medical files of eligible patients: sex, baseline age (in years), residence (urban vs. rural), weight, presence of opportunistic infection, CD4 count, haemoglobin levels, total lymphocytes and platelet counts, antiretroviral regimens; the outcome, and estimated time to the outcome occurrence. The duration of follow-up for patients still actively followed-up was censored in June 2012.

Statistical analysis

Data analysis used SPSS v17.0 (SPSS Inc., Chicago, USA) and SAS/STAT® v 9.1 for Windows (SAS Institute Inc., Cary, NC, USA). Results are presented as count and percentages, mean and standard deviation or median and 25th-75th percentiles. The chi square test, Student's t-test and equivalents were used to compare baseline characteristics. The Kaplan-Meir estimator and accelerated failure time models, implemented with the use of LIFETEST and LIFEREG procedures of SAS were used to investigate the baseline characteristics associated with mortality during the first 60 months of follow-up (corresponding to the observed duration of follow-up for > 95% of participants). A p-value < 0.05 was used to characterise statistically significant results.

RESULTS

Baseline characteristics of the study population

In 2007 and 2008, a total of 1444 patients with HIV infection [including 827 women (57.3%)] were started on antiretroviral treatment at the YJH's ACT. Medical files were available for all of them. However, data were missing on some characteristics for few participants. Analyses for those characteristics are restricted to participants with valid data, and their number indicated where relevant. The baseline demographic, clinical and biological characteristics of participants are summarised in Table 1. The median age (25th-75th percentiles) was 38 (31 - 45) years overall, 40 (34 - 47) years in men and 35 (30 - 43) years in women, $p < 0.0001$. In all 85.6% of participants were urban dwellers and about the same proportion were started on antiretroviral therapy at WHO stage III-IV of disease severity, similarly among men and women (both $p \geq 0.82$, Table 1). The main opportunistic infection was tuberculosis, which was found in 428 (29.6%) patients, and was more frequent in men than in women (34.7% vs. 27.9%, $p = 0.0003$). The median CD4 count (25th - 75th percentiles) was 99 (36 - 161) per mm^3 overall, 89 (33 - 155) in men and 105 (39 - 166) in women ($p = 0.018$).

Follow-up and outcome

The median duration of follow-up (25th - 75th percentiles) was 14.4 (1.0 - 46.2) months overall, 9.1 (0 - 44.1) months in men and 20.3 (1.3 - 47.3) months in women (p = 0.0001). At the final evaluation, 235 (cumulative incidence rate 16.3%) were deceased, 590 (40.8%) were lost to follow-up, 173 (12%) had been transferred to another centre, while 446 patients (30.9%) were still under active follow-up in the centre. The median duration of follow-up (25th - 75th percentiles) for non-fatal outcomes was 4.5 (0-23.8) months for defaulters, 8.2 (2.5 -20.3) months for transfer out, and 50.5 (45.9 - 56.7) months for active follow-up cases.

Of the 235 deaths recorded, 208 (88.5 %) deaths occurred early (within the first year of ART) while 27 (11.5 %) were late-occurring deaths. Overall, 54.9 % of all deaths occurred within one month of starting antiretroviral therapy, 19.6 % between 1 and 3 months, 8.5 % between 3 and 6 months and 5.5% between 6 and 12 months. The cumulative survival probability from Kaplan-Meier estimators was 84.7% (95 % confidence interval: 82.7 - 86.7) at 6 months, 83.3% (81.3 - 85.4) at 12 months, 81.7% (79.5 - 83.9) at 24 months, and 79.3% (76.0 - 82.5) at 60 months of follow-up. The survival probability from Kaplan-Meier estimators and Weibull plot of the cumulative distribution function for all-cause mortality are depicted in Figure 1.

Determinants of all-cause mortality

The estimated cumulative distribution function for all-cause mortality by major subgroups is depicted in figure 2. In sex and age adjusted analyses, male sex, active tuberculosis, WHO stage III-IV of the disease, lower weight, lower CD4 count and lower baseline haemoglobin level were potential determinants of all-cause mortality (Table 2). In multivariable Weibull regression models with simultaneous adjustment for age, sex, and all the potential factors, all determinants remained significantly associated with all-cause mortality during follow-up (Table 2). Effect estimates (hazard ratio) and 95% confidence intervals were 2.15 (1.34-3.45) for male sex, 2.35 (1.40-3.92) for active tuberculosis, 3.63 (1.29-10.24) for WHO stage III-IV of the disease severity, 1.03 (1.01-1.05) per kilogram lower weight, 1.04 (1.01-1.07) per 10 lower CD4/mm^3 and 1.12 (1.00-1.26) for each g/dl lower baseline haemoglobin (Table 2).

DISCUSSION

This study conducted in a referral centre for tuberculosis and HIV care in Cameroon revealed a high mortality rate among patients started on antiretroviral therapy, with the large majority of death occurring during the first year of starting the treatment. Male gender, active tuberculosis, advanced stage of the disease, low CD4 count, low weight and low haemoglobin levels at baseline were significant predictors of all-cause mortality during follow-up. Accounting for these factors may help in refining the prescription of antiretroviral therapy and improve the outcome of care among patients with HIV infection.

The survival probability at one year of follow-up after starting antiretroviral therapy was found to be much lower (83.3% vs. 77%) in a previous study among 1187 patients with HIV infection in a rural setting in the Northern part of Cameroon. [10] This study however, was conducted prior to the implementation of the program of free access to antiretroviral therapy in the country, which suggests that this strategy has likely improved survival among HIV patients in the country. It can also be speculated that the difference between this previous study and our study just reflects differences in the level of care provided in a referral centre like ours, and a rural centre where care can be very basic. The similarities in the baseline profile of participants across the two studies are in support of this hypothesis. For instance, in both studies over 85% of participants were started on antiretroviral therapy while at the WHO stage III or IV of the disease severity, while pre-ARV CD4 count was lower than $50/mm^3$ in over a quarter of participants at baseline. However, the one-year survival rate in our study is within the range of those reported in previous studies. In recent meta-analysis of those studies, the pooled estimated one-year probability of death from studies conducted in Africa was 17% (95% confidence interval: 11-24%), [6, 15]

Predictors of mortality identified in our study were essentially those described in existing reports, [6, 15] The adverse profile of modifiable risk factors clearly suggest that patients with HIV in our centre are started on ART at an advanced stage of the disease. This likely reflects the fact that in this setting, with the exception of screening in particular circumstances such as during pregnancy or pre-surgical intervention, people with HIV infection mostly get screened only when they seek medical care with clinical symptoms. This is a common attitude across Africa, which may explain the higher early mortality rate on ART in Africa, compared with other parts of the world, [6] In addition to the advanced clinical stage of the disease on the WHO scale at presentation, body weight, CD4 count and haemoglobin levels were low at baseline, and all significantly associated with high risk of mortality during follow-up as previously reported. [5-8] The prevalence of active tuberculosis in our study was possibly inflated by the nature of the study setting as a referral centre for tuberculosis treatment, where most patients with both HIV and tuberculosis are likely to be referred for care. The resulting subsample of participants with both conditions has possibly increased our statistical power for uncovering baseline active tuberculosis as a risk factor for fatal outcomes among people with HIV started on antiretroviral therapy. Such an association has been inconsistently reported in previous studies. [6, 10, 16]

The main non-modifiable risk factor of mortality in our study was male sex. This was not fully explained by sex differences in the level of other risk factors. Indeed, with the exception of baseline CD4 count which was lower in men, other factors were equally distributed among men or women or rather showed more favourable levels in men. Other studies have shown that adherence to prescribed ART was better in women than in men, [17] which can explain differing rates of fatal outcomes between men and women started on ART.

Our study has some limitations, including the missing data, which are expected for a study conducted based on data collected from patients files, and when dealing with large numbers of participants. Drop-out through losses to follow-up potentially include deceased patients, and may be in high proportion based on some studies. [18] Therefore, the reported mortality rate in our study is likely underestimated. But such a bias is unlikely to affect the associations of major risk factors with the mortality outcome as shown elsewhere. [10] Our study also has major strengths including the large sample size, which increased our statistical power to reliably characterise the predictors of mortality. The death rate following ART initiation as found in our study and previous studies is not constant over time. It is very high in the early months of starting the treatment, and subsequently drops and stabilises at a much lower rate. Many previous studies have been based on statistical methods that assume constant death rates over time such as the person-year methods, and have likely generated less reliable estimates. We have attempted to address this limitation by applying the accelerated failure time models in our study.

In conclusion, mortality rate among patients with HIV-1 infection started on antiretroviral therapy in this setting remain unacceptably high. Deaths occur mostly within the first year of starting treatment and essentially among patients with clinical and biological profiles compatible with an advanced stage of the disease at the time antiretroviral treatment is started. Strategies for early detection of patient with HIV and the clinically asymptomatic stages followed by early initiation of antiretroviral therapy needs to be developed and tested in this setting. Recent Cameroonian guidelines of HIV treatment allowing the prescription of antiretroviral therapy to patients with CD4 count lower than 350/mm^3 would probably reduce the mortality rate in this setting.

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Competing interests: None.

Ethics approval: Ethics approval was provided by the Institutional Review Board of Yaounde Jamot Hospital.

Contributors: VPM, collected data, co-analysed the data and drafted the manuscript. EWPY conceived the study, supervised data collection, co-analysed the data and drafted the manuscript. APK contributed to study design, data analysis, drafting and critical revision of the manuscript. CK supervised data collection and critically revised the manuscript. All authors approved the final version of the manuscript.

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Table 1 Demographic, clinical and biological profile of HIV patients started on antiretroviral therapy at the Yaounde Jamot Hospital in 2007 and 2008

Characteristics	Overall	Men	Women	p-value
n	1444	617	827	
Median age, years (25th-75th percentile)	38 (31-45)	40 (34-47)	35 (30-43)	<0.0001
Residence, n (%)				0.98
Urban	1236 (85.6)	528 (85.6)	708 (85.6)	
Rural	208 (14.4)	89 (14.4)	119 (14.4)	
Tuberculosis, n (%)	428 (29.6)	214 (34.7)	214 (27.9)	0.0003
Weight, Kg				<0.0001
< 50, n (%)	308/1322 (23.3)	69/570 (12.1)	239/752 (31.8)	
50-60, n (%)	535/1322 (40.5)	204/570 (35.8)	331/752 (44.0)	
>60, n (%)	479/1322 (36.2)	297/570 (52.1)	182/752 (24.2)	
Median (25th-75th percentile)	57 (50 - 65)	61 (54-68)	54 (47.5-60)	<0.0001
WHO stage, n (%)				0.82
I and II	186/1295 (14.4)	78/553 (14.1)	108/742 (14.6)	
III and IV	1109/1295 (85.6)	475/553 (85.9)	634/742 (85.4)	
Platelets, X1000/mm^3	244 (180– 320)	229 (173-309)	259 (190-330)	0.0005
Total lymphocytes, X10/mm^3	130 (90–190)	130 (90-201)	130 (90-190)	0.88
CD4, /mm^3				0.21
< 50, n (%)	468 (32.4)	216 (30.5)	256 (30.5)	
50-99, n (%)	257 (17.8)	111 (18.0)	142 (17.6)	
100-200, n (%)	562 (38.9)	231 (37.4)	331 (40.0)	
>200, n (%)	157 (10.9)	59 (9.6)	98 (11.8)	
Median (25th-75th percentile)	99 (36.2-161)	89 (33-155)	105 (39-166)	0.018
Haemoglobin, g/dl,				<0.0001
< 8, n (%)	235/1388 (16.9)	67/594 (11.3)	168/794 (21.2)	
8-10, n (%)	506/1388 (36.5)	178/594 (30.0)	328/794 (41.3)	
>10, n (%)	647/1388 (46.6)	349 (58.7)	298 (37.5)	
Median, (25th-75th percentile)	9.9 (8.5-11.2)	10.5 (9-12)	9.5 (8.1-10.7)	<0.0001

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; WHO, World Health Organisation

Table 2 Determinants of all-cause mortality among HIV-positive patients started on antiretroviral therapy

Variable	Age and sex adjusted		Multivariable adjusted	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Age, per year	1.01 (0.98-1.03)	0.56	1.01 (0.99-1.03)	0.37
Male sex	1.44 (0.94-2.11)	0.10	2.15 (1.34-3.45)	0.002
Rural residency	1.14 (0.62-2.09)	0.68	-	
Active tuberculosis	1.59 (0.97-2.61)	0.07	2.35 (1.40-3.92)	0.002
WHO stage III-IV	4.57 (1.68-12.47)	0.004	3.63 (1.29-10.24)	0.02
Weight, per kg lower	1.04 (1.02-1.06)	0.0002	1.03 (1.01-1.05)	0.01
Platelet count, per 1000 lower	1.01 (0.99-1.03)	0.53	-	
CD4 count, per 10/mm3 lower	1.06 (1.02-1.09)	0.003	1.04 (1.01-1.07)	0.02
Haemoglobin, per g/dl lower	1.14 (1.03-1.26)	0.02	1.12 (1.00-1.26)	0.05
AZT based regimens	0.91 (0.51-1.62)	0.76	-	

AZT, zidovudine; CI, confidence interval; WHO, World Health Organisation

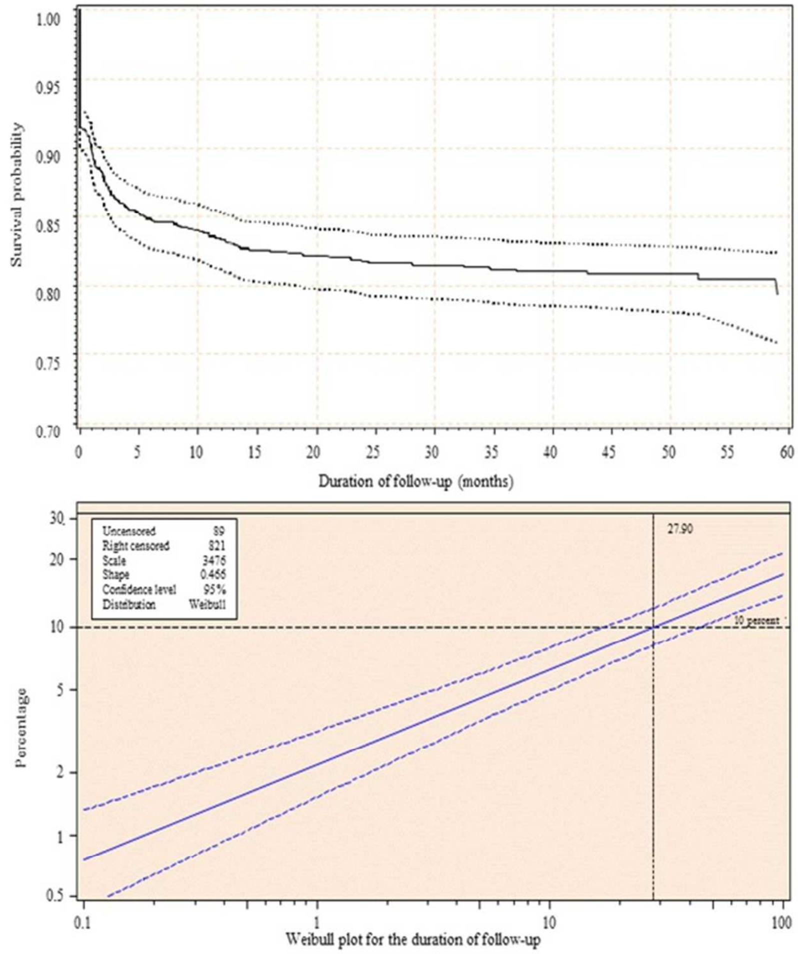

Figure 1: Survival probability from Kaplan-Meir estimator (upper panel) and Weibull plot showing the cumulative distribution function for mortality during follow-up of patients with HIV infection who started antiretroviral treatment at the Yaounde Jamot Hospital in 2007 and 2008
203x196mm (96 x 96 DPI)

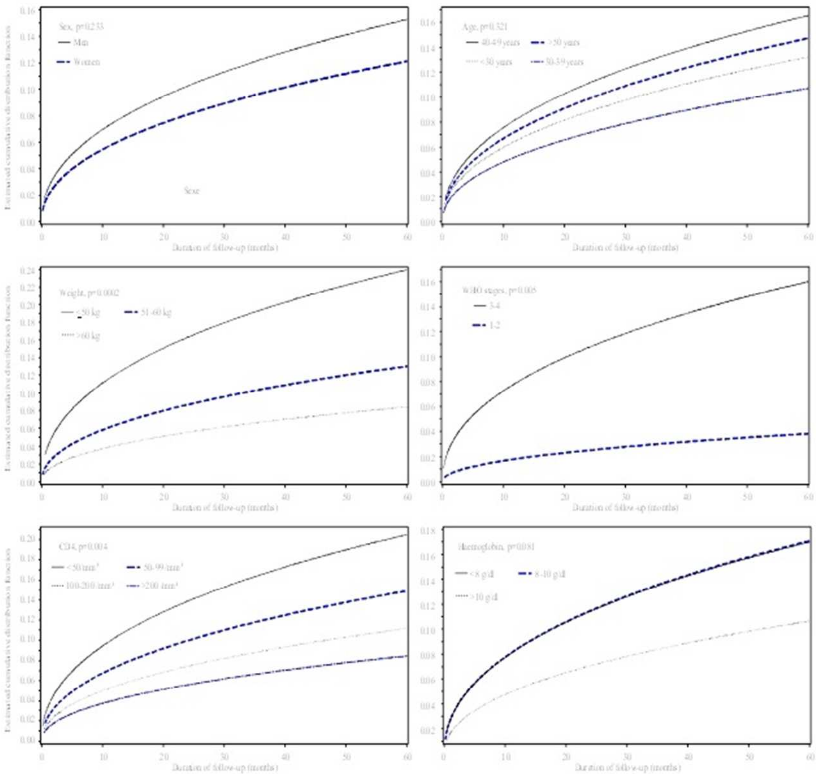

Figure 2: Estimated cumulative distribution function for all-cause mortality by major subgroups among patients with HIV infection who started antiretroviral treatment at the Yaounde Jamot Hospital in 2007 and 2008
203x160mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	/
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	/
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	/
		Case-control study—For matched studies, give matching criteria and the number of controls per case	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	/
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4,5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	/
		(*c*) Explain how missing data were addressed	/
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	/
		Case-control study—If applicable, explain how matching of cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	/
		(c) Consider use of a flow diagram	/
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	/
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	/
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	/
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	/
Discussion			
Key results	18	Summarise key results with reference to study objectives	7,8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7,8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Mortality and its determinants among patients infected with HIV-1 on antiretroviral therapy in a referral centre in Yaounde, Cameroon: a retrospective cohort study

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Research Checklist Determinants of deaths HIV.doc

Mortality and its determinants among patients infected with HIV-1 on antiretroviral therapy in a referral centre in Yaounde, Cameroon: a retrospective cohort study

Short title: Determinants of death among patients with HIV infection

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ABSTRACT

Objectives: Mortality has decreased in people with human immunodeficiency virus (HIV) infection, subsequent to the improved access to antiretroviral therapy (ART). We assessed the incidence and determinants of mortality among patients with HIV-1 infection, started on ART in a referral treatment centre for HIV infection in Yaounde, Cameroon.

Design: Cohort study with baseline assessment between 2007 and 2008, and follow-up during five years until June 2012.

Setting: The accredited HIV treatment centre of the Yaounde Jamot Hospital, in capital city of Cameroon.

Participants: People living with HIV infection who started ART between 2007 and 2008 at the study centre.

Outcome measures: All-cause mortality over time, with the accelerated failure time models were used to relate baseline characteristics with mortality occurrence during follow-up.

Results: Of the 1444 patients included, 827 (53.7 %) were men, and the median age (25^{th}-75^{th} percentiles) was 38 (31- 45) years. The median duration of follow-up was 14.1 (1.1 - 46.4) months, during which 235 deaths were recorded (cumulative incidence rate: 16.3 %), including 208 (88.5 %) during the first year of follow-up. Baseline predictors of mortality were male gender [adjusted hazard ratio 2.15 (95 % Confidence Interval : 1.34 - 3.45)], active tuberculosis [2.35 (1.40 - 3.92)], WHO stages III-IV of the disease [3.63 (1.29 - 10.24)], low weight [1.03 (1.01-1.05) per kilogramme], low CD4 count [1.04 (1.01 - 1.07) per $10/mm^3$) and low haemoglobin levels [1.12 (1.00 - 1.26) per g/dl].

Conclusions: Death rate among patients with HIV is very high within the first year of starting ART in this centre. Early start of the treatment, at a less advanced stage of the disease, and much favourable levels of CD4 and other predictors could reduce early mortality, but would have to be tested.

Word count – 288

Key words: HIV infection, death, determinants, cohort, Cameroon, antiretroviral therapy

ARTICLE SUMMARY

Article focus

- To investigate mortality occurrence and determinants among patients with HIV-1 infection, started on antiretroviral therapy in a major reference treatment centre

Key messages

- Death rate among patients with HIV is very high within the first year of starting antiretroviral therapy in this centre
- Male gender, active tuberculosis, advanced stage of the disease, low CD4 count, low weight and low haemoglobin levels at baseline were significant predictors of all-cause mortality during follow-up

Strengths and limitations

- Strengths of the study include the large sample size and the use of robust methods to relate baseline predictors to the outcome occurrence during follow-up.
- The study was based on data collected from patient files and clinical registers, and as expected there were missing data, particularly on the true outcome of patients who were lost-to-follow-up.

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a major global health problem. Sub-Saharan Africa (SSA), with about 68 % of the global population with HIV, is the most affected region in the world. [1] HIV related mortality appears to be higher in developing than in developed countries. [2] Hopefully, mortality rates are on the decline with the improved access to antiretroviral therapy (ART), [3] while explaining factors of the residual deaths seems to vary significantly across populations. Studies in SSA have found that mortality rate is particularly high during the first year of starting antiretroviral therapy, [4] with male sex, cachexia, advanced stage of the disease, low CD4 count, anaemia, high viral load at baseline, and poor adherence to treatments being the main determinants of death. [5-8]

In Cameroon, about 105,000 people living with HIV (PLHIV) infection were on ART by the end of the year 2011, [9] A study conducted in 2006 in a rural unit for HIV treatment in the northern part of the country, found a mortality rate of 20.2/100 person-years among HIV patients receiving ART. [10] This figure however, has not been updated since 2007, year of the introduction of free access to ART in the country. Thus, the aim of this study was to determine the mortality rate and its determinants among patients with HIV-1 infection, started on ART in a reference treatment centre in Cameroon.

PARTICIPANTS AND METHODS

Study setting

The study was conducted in the accredited HIV treatment centre (ATC) of the Yaounde Jamot Hospital (YJH) in the Capital city of Cameroon. The study setting has been described in detail previously elsewhere. [11, 12] In brief, YJH is the referral centre for tuberculosis and chest diseases for the Capital city (Yaounde) and surrounding areas. It has an ATC that provides care to PLHIV. As of June 2011, a total of 2250 PLHIV were followed in the centre.

Care of patients with HIV infection

During the study period, PLHIV were started on ART in the presence of a CD4 count below $200/mm^3$ or superimposed condition of the WHO stage IV of the disease severity other than tuberculosis. [13] Patients fulfilling these criteria were referred to the ATC for treatment inception and follow-up. A medical file was created under the supervision of the attending physician and included socio demographic, clinical and biological data of the patient. Files of eligible patients were presented at weekly meetings during which the appropriate treatment regimen for each patient was decided. First line treatment regimens included two nucleoside reverse transcriptase inhibitors (zidovudine, lamivudine, tenofovir) and one non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz). Second line regimens comprised two nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, lamivudine, tenofovir) and a protease inhibitor (indinavir, lopinavir/ritonavir). These regimens were all dispensed to patients free of charge and they were all started on prophylactic treatment with cotrimoxazole. All patients had a session with trained psychosocial advisors, to improve adherence to prescribed therapies.

Patients registered at the YJH's ATC are seen on a monthly basis for prescription renewal. For those on a regimen comprising zidovudine (AZT) and/or nevirapine (NVP), haemoglobin (AZT) and/or liver transaminases (NVP) levels are monitored at two weeks from starting treatment. A biological profile is requested every six months, comprising a CD4 count, full blood count, liver transaminases and creatinin (only for patients receiving tenofovir), and results are recorded in the clinical file.

Outcome

During the study period, patients who failed to report for consultation for three consecutive months were traced by community liaison agents using the contact details on the file. All-cause mortality was considered for all deceased patients at any time after starting ART. The time-to-death (in months) was the interval from the start of the ART to date of death (or date of the last recorded visit when the date of death was unknown). Loss-to-follow-up (defaulter) was defined as patients who failed to return for consultation for three consecutive months and were unsuccessfully traced by liaison agents, [14] Transfer was considered for patients who at any time were definitively transferred to receive care in another centre. The follow-up for all patients was until June 2012, death, transfer and loss to follow-up, whichever came first.

Data collection

For the purpose of this study, patients with HIV started on ART between January 2007 and December 2008 were identified via antiretroviral treatment registries. All patients with HIV-1 infection, aged 18 years and above, started on ART during this period were included in the study, and followed until June 2012 (5.5 years). The study was approved by the regulatory board of YJH.

The following data were then retrieved in the medical files of eligible patients: sex, baseline age (in years), residence (urban vs. rural), weight in Kg, presence of opportunistic infection, CD4 count (in cells/mm^3), haemoglobin levels in g/dl, total lymphocytes and platelet counts, antiretroviral regimens; outcome (death, loss to follow up, transfer out, still alive and followed up), and estimated time to the outcome occurrence in months. The duration of follow-up for patients still actively followed-up was censored in June 2012.

Statistical analysis

Data analysis used SPSS v17.0 (SPSS Inc., Chicago, USA) and SAS/STAT® v 9.1 for Windows (SAS Institute Inc., Cary, NC, USA). Results are presented as count and percentages, mean and standard deviation or median and 25^{th}-75^{th} percentiles. The chi square test, Student's t-test and their non-parametric equivalents were used to compare baseline characteristics. The Kaplan-Meir estimator and accelerated failure time models, implemented with the use of LIFETEST and LIFEREG procedures of SAS were used to investigate the baseline characteristics associated with mortality during the first 60 months of follow-up (corresponding to the observed duration of follow-up for > 95% of participants). Candidate predictors included age (in years), gender (male vs. female), residency (rural vs. urban), active tuberculosis, WHO stages of the disease (III-IV vs. I-II), weight (in kg), platelet count (per 1000), CD4 count (per 10/mm^3), haemoglobin level (in g/dl) and ART regimen (AZT vs. no AZT). Candidate predictors were tested one at a time in a basic model that included gender and age as covariates. Then significant predictors (based on a p-value <0.10) were entered together in a multivariable model, and significant ones kept in the final model alongside age and gender. The reference category (or direction of continuous predictors) was always rearranged as appropriate to identify levels associated with increased mortality risk. A p-value < 0.05 was used to characterise statistically significant results.

RESULTS

Data available

In 2007 and 2008, a total of 1444 PLHIV [including 827 women (57.3 %)] were started on ART at the YJH's ATC. Medical files were available for all of them. However, data were missing on some characteristics for few participants. Analyses for those characteristics are restricted to participants with valid data, and their number indicated where relevant. Furthermore, a total of 470 participants had missing data for at least one of the candidate predictors, and were therefore excluded from regression analysis. Compared with excluded participants, the 974 included in regression analysis had similar age (38.3 vs. 38.8 years, p = 0.44), mean CD4 count (102 vs. 111/mm^3, p = 0.06). Furthermore, they had similar proportion of men (42.5 % vs. 43.2 %, p = 0.82), similar distribution across WHO stages of disease severity (p = 0.75), a borderline higher prevalence of active tuberculosis (31.1% vs. 26.6%, p = 0.044), a borderline lower baseline weight (57.6 vs. 59.1 kg, p=0.045) and lower platelet (262000 vs. 243000/mm^3, p = 0.035), and a significantly lower haemoglobin level (9.9 vs. 10.4 g/dl, p < 0.001).

Baseline characteristics of the study population

The baseline demographic, clinical and biological characteristics of participants are summarised in Table 1. The median age (25^{th}-75^{th} percentiles) was 38 (31 - 45) years overall, 40 (34 - 47) years in men and 35 (30 - 43) years in women, p < 0.0001. In all 85.6 % of participants were urban dwellers and about the same proportion were started on ART at WHO stage III-IV of disease severity, similarly among men and women (both p $\geq$ 0.82, Table 1). The main opportunistic infection was tuberculosis, which was found in 428 (29.6 %) patients, and was more frequent in men than in women (34.7 % vs. 27.9 %, p = 0.0003). The median CD4 count (25^{th} - 75^{th} percentiles) was 99 (36 - 161) per mm^3 overall, 89 (33 - 155) in men and 105 (39 - 166) in women (p = 0.018).

Follow-up and outcome

The median duration of follow-up (25^{th} - 75^{th} percentiles) was 14.4 (1.0 - 46.2) months overall, 9.1 (0 - 44.1) months in men and 20.3 (1.3 - 47.3) months in women (p < 0.0001). At the final evaluation, 235 (cumulative incidence rate 16.3 %) were deceased, 590 (40.8 %) were lost to follow-up, 173 (12 %) had been transferred to another centre, while 446 patients (30.9 %) were still under active follow-up in the centre. The median duration of follow-up (25^{th} - 75^{th} percentiles) for non-fatal outcomes was 4.5 (0 - 23.8) months for defaulters, 8.2 (2.5 - 20.3) months for transfer out, and 50.5 (45.9 - 56.7) months for active follow-up cases.

Of the 235 deaths recorded, 208 (88.5 %) deaths occurred early (within the first year of ART) while 27 (11.5 %) were late-occurring deaths. Overall, 54.9 % of all deaths occurred within one month of starting antiretroviral therapy, 19.6 % between 1 and 3 months, 8.5 % between 3 and 6 months and 5.5% between 6 and 12 months. The cumulative survival probability from Kaplan-Meier estimators was 84.7 % (95 % confidence interval: 82.7 - 86.7) at 6 months, 83.3 % (81.3 - 85.4) at 12 months, 81.7 % (79.5 - 83.9) at 24 months, and 79.3% (76.0 - 82.5) at 60 months of follow-up. The survival probability from Kaplan-Meier estimators and Weibull plot of the cumulative distribution function for all-cause mortality are depicted in Figure 1. The cumulative mortality rate was 16.8 % (79/470) among participants with missing data on at least one of the candidate predictor variables, and 16.6 % (162/974) among those with valid data, p = 0.93.

Determinants of all-cause mortality

The estimated cumulative distribution function for all-cause mortality by major subgroups is depicted in figure 2. In sex and age adjusted analyses, male sex, active tuberculosis, WHO stage III-IV of the disease, lower weight, lower CD4 count and lower baseline haemoglobin level were potential determinants of all-cause mortality (Table 2). In multivariable Weibull regression models with simultaneous adjustment for age, sex, and all the potential factors, all determinants remained significantly associated with all-cause mortality during follow-up (Table 2). Effect estimates (hazard ratio) and 95% confidence intervals were 2.15 (1.34 - 3.45) for male sex, 2.35 (1.40 - 3.92) for active tuberculosis, 3.63 (1.29 - 10.24) for WHO stage III-IV of the disease severity, 1.03 (1.01 - 1.05) per kilogram lower weight, 1.04 (1.01 - 1.07) per 10 lower CD4/mm^3 and 1.12 (1.00 - 1.26) for each g/dl lower baseline haemoglobin (Table 2).

DISCUSSION

This study conducted in a referral centre for tuberculosis and HIV care in Cameroon revealed a high mortality rate among patients started on ART, with the large majority of death occurring during the first year of starting the treatment. Male gender, active tuberculosis, advanced stage of the disease, low CD4 count, low weight and low haemoglobin levels at baseline were significant predictors of all-cause mortality during follow-up. Accounting for these factors may help in refining the prescription of ART and improve the outcome of care among patients with HIV infection.

The survival probability at one year of follow-up after starting ART was found to be much lower (83.3 % vs. 77 %) than in a previous study among 1187 PLHIV infection in a rural setting in the Northern part of Cameroon. [10] This study however, was conducted prior 2007, year of the implementation of the program of free access to ART in the country, which suggests that this strategy has likely improved survival among PLHIV in the country. It can also be speculated that the difference between this previous study and our study just reflects differences in the level of care provided in a referral centre like ours, and a rural centre where care can be very basic. The similarities in the baseline profile of participants across the two studies are in support of this hypothesis. For instance, in both studies over 85 % of participants were started on ART while at the WHO stage III or IV of the disease severity, while pre-ARV CD4 count was lower than 50/mm^3 in over a quarter of participants at baseline. However, the one-year survival rate in our study is within the range of those reported in previous studies. In recent meta-analysis of those studies, the pooled estimated one-year probability of death from studies conducted in Africa was 17 % (95 % confidence interval: 11-24 %), [6, 15] Predictors of mortality identified in our study were essentially those described in existing reports. [6, 15] The adverse profile of modifiable risk factors clearly suggests that patients with HIV in our centre are started on ART at an advanced stage of the disease. This likely reflects the fact that in this setting, with the exception of screening in particular circumstances such as during pregnancy or pre-surgical intervention, PLHIV mostly get screened only when they seek medical care with clinical symptoms. This is a common attitude across Africa, which may explain the higher early mortality rate on ART in Africa, compared with other parts of the world.[6] In addition to the advanced clinical stage of the disease on the WHO scale at presentation, body weight, CD4 count and haemoglobin levels were low at baseline, and all significantly associated with high risk of mortality during follow-up as previously reported. [5-8] It is of note that at the time this study was conducted, most patients were started on ART at CD4 count below 200/mm^3. Recent WHO recommendations favour ART initiation at CD4 count below 350/mm^3. Their uptake may potentially reduce early mortality rate, as a result of many patients starting treatment at favourable CD4 levels. The prevalence of active tuberculosis in our study was possibly inflated by the nature of the study setting as a referral centre for tuberculosis treatment, where most patients with both HIV and tuberculosis are likely to be referred for care. The resulting subsample of participants with both conditions has possibly increased our statistical power for uncovering baseline active tuberculosis as a risk factor for mortality among PLHIV started on antiretroviral therapy. Such an association has been inconsistently reported in previous studies. [6, 10, 16]

Free access to ART was introduced in Cameroon in May 2007 [17]. We have recently reported rate of non-adherence to ART to be as high as 34 % among patients with HIV receiving chronic care at the YJH in the era of free access to ART [12]. In the absence of any assessment of the adherence to ART in the current study, it is difficult to speculate of a contribution, if any, of non-adherence to ART to the observed high mortality in our study. However, such as effect is likely marginal in this setting where mortality mostly occurs early when patients have not been exposed to ART enough to derive therapeutic benefits. Furthermore, existing instruments for measuring adherence to ART are likely unsuitable for investigating premature mortality risk. The main non-modifiable risk factor of mortality in our study was male sex. This was not fully explained by sex differences in the level of other risk factors. Indeed, with the exception of baseline CD4 count which was lower in men, other factors were equally distributed among men or women or rather showed more favourable levels in men. Other studies have shown that adherence to prescribed ART was better in women than in men, [18] which can explain differing rates of mortality between men and women started on ART.

Our study has some limitations, including the missing data, which are expected for a study conducted based on data collected from patients files, and when dealing with large numbers of participants. Drop-out through losses to follow-up potentially include deceased patients, and may be in high proportion based on some studies. [19] Therefore, the reported mortality rate in our study is likely underestimated. But such a bias is unlikely to affect the associations of major risk factors with the mortality outcome as shown elsewhere. [10] In the absence of any evaluation of the adherence to ART, particularly among early mortality survivors, we were unable to investigate a potential effect of non-adherence to ART on mortality risk in the current study. Our study also has major strengths including the large sample size, which increased our statistical power to reliably characterise the predictors of mortality. The death rate following ART initiation as found in our study and other published studies is not constant over time. It is very high in the early months of starting the treatment, and subsequently drops and stabilises at a much lower rate. Many previous studies have been based on statistical methods that assume constant death rates over time such as the person-year methods, and have likely generated less reliable estimates of the association of predictors with mortality risk. We have attempted to address this limitation by applying the accelerated failure time models in our study. Unlike Cox models for instance, regression parameters estimates from accelerated failure time models are robust to the omitted covariates, and are unaffected by the choice of probability distribution.

In conclusion, mortality rate among patients with HIV-1 infection started on antiretroviral therapy in this setting remain unacceptably high. Deaths occur mostly within the first year of starting treatment and essentially among patients with clinical and biological profiles compatible with an advanced stage of the disease at the time when antiretroviral treatment is started. Strategies for early detection of patient with HIV and the clinically asymptomatic stages followed by early initiation of antiretroviral therapy needs to be developed and tested in this setting. Recent Cameroonian guidelines of HIV treatment allowing the prescription of antiretroviral therapy to patients with CD4 count lower than 350/mm^3 would probably reduce the mortality rate in this setting.

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Competing interests: None.

Ethics approval: Ethics approval was provided by the Institutional Review Board of Yaounde Jamot Hospital.

Contributors: VPM, collected data, co-analysed the data and drafted the manuscript. EWPY conceived the study, supervised data collection, co-analysed the data and drafted the manuscript.

APK contributed to study design, data analysis, drafting and critical revision of the manuscript. CK supervised data collection and critically revised the manuscript. All authors approved the final version of the manuscript.

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Table 1 Demographic, clinical and biological profile of HIV patients started on antiretroviral therapy at the Yaounde Jamot Hospital in 2007 and 2008

Characteristics*	Overall	Men	Women	p-value
n	1444	617	827	
Median age, years (25^{th}-75^{th} percentile)	38 (31-45)	40 (34-47)	35 (30-43)	<0.0001
Residence, n (%)				0.98
Urban	1236 (85.6)	528 (85.6)	708 (85.6)	
Rural	208 (14.4)	89 (14.4)	119 (14.4)	
Tuberculosis, n (%)	428 (29.6)	214 (34.7)	214 (27.9)	0.0003
Weight, Kg				<0.0001
< 50, n (%)	308/1322 (23.3)	69/570 (12.1)	239/752 (31.8)	
50-60, n (%)	535/1322 (40.5)	204/570 (35.8)	331/752 (44.0)	
>60, n (%)	479/1322 (36.2)	297/570 (52.1)	182/752 (24.2)	
Median (25^{th}-75^{th} percentile)	57 (50 - 65)	61 (54-68)	54 (47.5-60)	<0.0001
WHO stage, n (%)				0.82
I and II	186/1295 (14.4)	78/553 (14.1)	108/742 (14.6)	
III and IV	1109/1295 (85.6)	475/553 (85.9)	634/742 (85.4)	
Platelets, X1000/mm^3	244 (180– 320)	229 (173-309)	259 (190-330)	0,0005
Total lymphocytes, X10/mm^3	130 (90–190)	130 (90-201)	130 (90-190)	0.88
CD4, /mm^3				0.21
< 50, n (%)	468 (32.4)	216 (30.5)	256 (30.5)	
50-99, n (%)	257 (17.8)	111 (18.0)	142 (17.6)	
100-200, n (%)	562 (38.9)	231 (37.4)	331 (40.0)	
>200, n (%)	157 (10.9)	59 (9.6)	98 (11.8)	
Median (25^{th}-75^{th} percentile)	99 (36.2-161)	89 (33-155)	105 (39-166)	0.018
Haemoglobin, g/dl,				<0.0001
< 8, n (%)	235/1388 (16.9)	67/594 (11.3)	168/794 (21.2)	
8-10, n (%)	506/1388 (36.5)	178/594 (30.0)	328/794 (41.3)	
>10, n (%)	647/1388 (46.6)	349 (58.7)	298 (37.5)	
Median, (25^{th}-75^{th} percentile)	9.9 (8.5-11.2)	10.5 (9-12)	9.5 (8.1-10.7)	<0.0001

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; WHO, World Health Organisation

* For all characteristics with missing values, estimates are based of the subset of participants with valid data for each relevant characteristic, and new denominators always provided.

Table 2 Determinants of all-cause mortality among HIV-positive patients started on antiretroviral therapy (n = 1444)

Variable	Age and sex adjusted		Multivariable adjusted	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Age, per year	1.01 (0.98-1.03)	0.56	1.01 (0.99-1.03)	0.37
Male sex	1.44 (0.94-2.11)	0.10	2.15 (1.34-3.45)	0.002
Rural residency	1.14 (0.62-2.09)	0.68	-	
Active tuberculosis	1.59 (0.97-2.61)	0.07	2.35 (1.40-3.92)	0.002
WHO stage III-IV	4.57 (1.68-12.47)	0.004	3.63 (1.29-10.24)	0.02
Weight, per kg lower	1.04 (1.02-1.06)	0.0002	1.03 (1.01-1.05)	0.01
Platelet count, per 1000 lower	1.01 (0.99-1.03)	0.53	-	
CD4 count, per 10/mm3 lower	1.06 (1.02-1.09)	0.003	1.04 (1.01-1.07)	0.02
Haemoglobin, per g/dl lower	1.14 (1.03-1.26)	0.02	1.12 (1.00-1.26)	0.05
AZT based regimens	0.91 (0.51-1.62)	0.76	-	

AZT, zidovudine; CI, confidence interval; WHO, World Health Organisation

Mortality and its determinants among patients infected with HIV-1 on antiretroviral therapy in a referral centre in Yaounde, Cameroon: a retrospective cohort study

Short title: Determinants of death among patients with HIV infection

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ABSTRACT

Objectives: Mortality has decreased in people with human immunodeficiency virus (HIV) infection, subsequent to the improved access to antiretroviral therapy (ART). We assessed the incidence and determinants of mortality among patients with HIV-1 infection, started on ART in a referral treatment centre for HIV infection in Yaounde, Cameroon.

Design: Cohort study with baseline assessment between 2007 and 2008, and follow-up during five years until June 2012.

Setting: The accredited HIV treatment centre of the Yaounde Jamot Hospital, in capital city of Cameroon.

Participants: People living with HIV infection who started ART between 2007 and 2008 at the study centre.

Outcome measures: All-cause mortality over time, with the accelerated failure time models were used to relate baseline characteristics with mortality occurrence during follow-up.

Results: Of the 1444 patients included, 827 (53.7 %) were men, and the median age (25^{th}-75^{th} percentiles) was 38 (31- 45) years. The median duration of follow-up was 14.1 (1.1 - 46.4) months, during which 235 deaths were recorded (cumulative incidence rate: 16.3 %), including 208 (88.5 %) during the first year of follow-up. Baseline predictors of mortality were male gender [adjusted hazard ratio 2.15 (95 % Confidence Interval : 1.34 - 3.45)], active tuberculosis [2.35 (1.40 - 3.92)], WHO stages III-IV of the disease [3.63 (1.29 - 10.24)], low weight [1.03 (1.01-1.05) per kilogramme], low CD4 count [1.04 (1.01 - 1.07) per 10/mm^3) and low haemoglobin levels [1.12 (1.00 - 1.26) per g/dl].

Conclusions: Death rate among patients with HIV is very high within the first year of starting ART in this centre. Early start of the treatment, at a less advanced stage of the disease, and much favourable levels of CD4 and other predictors could reduce early mortality, but would have to be tested.

Word count – 288

Key words: HIV infection, death, determinants, cohort, Cameroon, antiretroviral therapy

ARTICLE SUMMARY

Article focus

- To investigate mortality occurrence and determinants among patients with HIV-1 infection, started on antiretroviral therapy in a major reference treatment centre

Key messages

- Death rate among patients with HIV is very high within the first year of starting antiretroviral therapy in this centre
- Male gender, active tuberculosis, advanced stage of the disease, low CD4 count, low weight and low haemoglobin levels at baseline were significant predictors of all-cause mortality during follow-up

Strengths and limitations

- Strengths of the study include the large sample size and the use of robust methods to relate baseline predictors to the outcome occurrence during follow-up.
- The study was based on data collected from patient files and clinical registers, and as expected there were missing data, particularly on the true outcome of patients who were lost-to-follow-up.

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a major global health problem. Sub-Saharan Africa (SSA), with about 68 % of the global population with HIV, is the most affected region in the world. [1] HIV related mortality appears to be higher in developing than in developed countries. [2] Hopefully, mortality rates are on the decline with the improved access to antiretroviral therapy (ART), [3] while explaining factors of the residual deaths seems to vary significantly across populations. Studies in SSA have found that mortality rate is particularly high during the first year of starting antiretroviral therapy, [4] with male sex, cachexia, advanced stage of the disease, low CD4 count, anaemia, high viral load at baseline, and poor adherence to treatments being the main determinants of death. [5-8]

In Cameroon, about 105,000 people living with HIV (PLHIV) infection were on ART by the end of the year 2011, [9] A study conducted in 2006 in a rural unit for HIV treatment in the northern part of the country, found a mortality rate of 20.2/100 person-years among HIV patients receiving ART. [10] This figure however, has not been updated since 2007, year of the introduction of free access to ART in the country. Thus, the aim of this study was to determine the mortality rate and its determinants among patients with HIV-1 infection, started on ART in a reference treatment centre in Cameroon.

PARTICIPANTS AND METHODS

Study setting

The study was conducted in the accredited HIV treatment centre (ATC) of the Yaounde Jamot Hospital (YJH) in the Capital city of Cameroon. The study setting has been described in detail previously elsewhere. [11, 12] In brief, YJH is the referral centre for tuberculosis and chest diseases for the Capital city (Yaounde) and surrounding areas. It has an ATC that provides care to PLHIV. As of June 2011, a total of 2250 PLHIV were followed in the centre.

Care of patients with HIV infection

During the study period, PLHIV were started on ART in the presence of a CD4 count below 200/mm^3 or superimposed condition of the WHO stage IV of the disease severity other than tuberculosis. [13] Patients fulfilling these criteria were referred to the ATC for treatment inception and follow-up. A medical file was created under the supervision of the attending physician and included socio demographic, clinical and biological data of the patient. Files of eligible patients were presented at weekly meetings during which the appropriate treatment regimen for each patient was decided. First line treatment regimens included two nucleoside reverse transcriptase inhibitors (zidovudine, lamivudine, tenofovir) and one non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz). Second line regimens comprised two nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, lamivudine, tenofovir) and a protease inhibitor (indinavir, lopinavir/ritonavir). These regimens were all dispensed to patients free of charge and they were all started on prophylactic treatment with cotrimoxazole. All patients had a session with trained psychosocial advisors, to improve adherence to prescribed therapies.

Patients registered at the YJH's ATC are seen on a monthly basis for prescription renewal. For those on a regimen comprising zidovudine (AZT) and/or nevirapine (NVP), haemoglobin (AZT) and/or liver transaminases (NVP) levels are monitored at two weeks from starting treatment. A biological profile is requested every six months, comprising a CD4 count, full blood count, liver transaminases and creatinin (only for patients receiving tenofovir), and results are recorded in the clinical file.

Outcome

During the study period, patients who failed to report for consultation for three consecutive months were traced by community liaison agents using the contact details on the file. All-cause mortality was considered for all deceased patients at any time after starting ART. The time-to-death (in months) was the interval from the start of the ART to date of death (or date of the last recorded visit when the date of death was unknown). Loss-to-follow-up (defaulter) was defined as patients who failed to return for consultation for three consecutive months and were unsuccessfully traced by liaison agents, [14] Transfer was considered for patients who at any time were definitively transferred to receive care in another centre. The follow-up for all patients was until June 2012, death, transfer and loss to follow-up, whichever came first.

Data collection

For the purpose of this study, patients with HIV started on ART between January 2007 and December 2008 were identified via antiretroviral treatment registries. All patients with HIV-1 infection, aged 18 years and above, started on ART during this period were included in the study, and followed until June 2012 (5.5 years). The study was approved by the regulatory board of YJH.

The following data were then retrieved in the medical files of eligible patients: sex, baseline age (in years), residence (urban vs. rural), weight in Kg, presence of opportunistic infection, CD4 count (in cells/mm^3), haemoglobin levels in g/dl, total lymphocytes and platelet counts, antiretroviral regimens; outcome (death, loss to follow up, transfer out, still alive and followed up), and estimated time to the outcome occurrence in months. The duration of follow-up for patients still actively followed-up was censored in June 2012.

Statistical analysis

Data analysis used SPSS v17.0 (SPSS Inc., Chicago, USA) and SAS/STAT® v 9.1 for Windows (SAS Institute Inc., Cary, NC, USA). Results are presented as count and percentages, mean and standard deviation or median and 25^{th}-75^{th} percentiles. The chi square test, Student's t-test and their non-parametric equivalents were used to compare baseline characteristics. The Kaplan-Meir estimator and accelerated failure time models, implemented with the use of LIFETEST and LIFEREG procedures of SAS were used to investigate the baseline characteristics associated with mortality during the first 60 months of follow-up (corresponding to the observed duration of follow-up for > 95% of participants). Candidate predictors included age (in years), gender (male vs. female), residency (rural vs. urban), active tuberculosis, WHO stages of the disease (III-IV vs. I-II), weight (in kg), platelet count (per 1000), CD4 count (per $10/mm^3$), haemoglobin level (in g/dl) and ART regimen (AZT vs. no AZT). Candidate predictors were tested one at a time in a basic model that included gender and age as covariates. Then significant predictors (based on a p-value <0.10) were entered together in a multivariable model, and significant ones kept in the final model alongside age and gender. The reference category (or direction of continuous predictors) was always rearranged as appropriate to identify levels associated with increased mortality risk. A p-value < 0.05 was used to characterise statistically significant results.

RESULTS

Data available

In 2007 and 2008, a total of 1444 PLHIV [including 827 women (57.3 %)] were started on ART at the YJH's ATC. Medical files were available for all of them. However, data were missing on some characteristics for few participants. Analyses for those characteristics are restricted to participants with valid data, and their number indicated where relevant. Furthermore, a total of 470 participants had missing data for at least one of the candidate predictors, and were therefore excluded from regression analysis. Compared with excluded participants, the 974 included in regression analysis had similar age (38.3 vs. 38.8 years, p = 0.44), mean CD4 count (102 vs. $111/mm^3$, p = 0.06). Furthermore, they had similar proportion of men (42.5 % vs. 43.2 %, p = 0.82), similar distribution across WHO stages of disease severity (p = 0.75), a borderline higher prevalence of active tuberculosis (31.1% vs. 26.6%, p = 0.044), a borderline lower baseline weight (57.6 vs. 59.1 kg, p=0.045) and lower platelet (262000 vs. 243000/mm^3, p = 0.035), and a significantly lower haemoglobin level (9.9 vs. 10.4 g/dl, p < 0.001).

Baseline characteristics of the study population

The baseline demographic, clinical and biological characteristics of participants are summarised in Table 1. The median age (25^{th}-75^{th} percentiles) was 38 (31 - 45) years overall, 40 (34 - 47) years in men and 35 (30 - 43) years in women, p < 0.0001. In all 85.6 % of participants were urban dwellers and about the same proportion were started on ART at WHO stage III-IV of disease severity, similarly among men and women (both p $\geq$ 0.82, Table 1). The main opportunistic infection was tuberculosis, which was found in 428 (29.6 %) patients, and was more frequent in men than in women (34.7 % vs. 27.9 %, p = 0.0003). The median CD4 count (25^{th} - 75^{th} percentiles) was 99 (36 - 161) per mm^3 overall, 89 (33 - 155) in men and 105 (39 - 166) in women (p = 0.018).

Follow-up and outcome

The median duration of follow-up (25^{th} - 75^{th} percentiles) was 14.4 (1.0 - 46.2) months overall, 9.1 (0 - 44.1) months in men and 20.3 (1.3 - 47.3) months in women (p < 0.0001). At the final evaluation, 235 (cumulative incidence rate 16.3 %) were deceased, 590 (40.8 %) were lost to follow-up, 173 (12 %) had been transferred to another centre, while 446 patients (30.9 %) were still under active follow-up in the centre. The median duration of follow-up (25^{th} - 75^{th} percentiles) for non-fatal outcomes was 4.5 (0 - 23.8) months for defaulters, 8.2 (2.5 - 20.3) months for transfer out, and 50.5 (45.9 - 56.7) months for active follow-up cases.

Of the 235 deaths recorded, 208 (88.5 %) deaths occurred early (within the first year of ART) while 27 (11.5 %) were late-occurring deaths. Overall, 54.9 % of all deaths occurred within one month of starting antiretroviral therapy, 19.6 % between 1 and 3 months, 8.5 % between 3 and 6 months and 5.5% between 6 and 12 months. The cumulative survival probability from Kaplan-Meier estimators was 84.7 % (95 % confidence interval: 82.7 - 86.7) at 6 months, 83.3 % (81.3 - 85.4) at 12 months, 81.7 % (79.5 - 83.9) at 24 months, and 79.3% (76.0 - 82.5) at 60 months of follow-up. The survival probability from Kaplan-Meier estimators and Weibull plot of the cumulative distribution function for all-cause mortality are depicted in Figure 1. The cumulative mortality rate was 16.8 % (79/470) among participants with missing data on at least one of the candidate predictor variables, and 16.6 % (162/974) among those with valid data, p = 0.93.

Determinants of all-cause mortality

The estimated cumulative distribution function for all-cause mortality by major subgroups is depicted in figure 2. In sex and age adjusted analyses, male sex, active tuberculosis, WHO stage III-IV of the disease, lower weight, lower CD4 count and lower baseline haemoglobin level were potential determinants of all-cause mortality (Table 2). In multivariable Weibull regression models with simultaneous adjustment for age, sex, and all the potential factors, all determinants remained significantly associated with all-cause mortality during follow-up (Table 2). Effect estimates (hazard ratio) and 95% confidence intervals were 2.15 (1.34 - 3.45) for male sex, 2.35 (1.40 - 3.92) for active tuberculosis, 3.63 (1.29 - 10.24) for WHO stage III-IV of the disease severity, 1.03 (1.01 - 1.05) per kilogram lower weight, 1.04 (1.01 - 1.07) per 10 lower CD4/mm^3 and 1.12 (1.00 - 1.26) for each g/dl lower baseline haemoglobin (Table 2).

DISCUSSION

This study conducted in a referral centre for tuberculosis and HIV care in Cameroon revealed a high mortality rate among patients started on ART, with the large majority of death occurring during the first year of starting the treatment. Male gender, active tuberculosis, advanced stage of the disease, low CD4 count, low weight and low haemoglobin levels at baseline were significant predictors of all-cause mortality during follow-up. Accounting for these factors may help in refining the prescription of ART and improve the outcome of care among patients with HIV infection.

The survival probability at one year of follow-up after starting ART was found to be much lower (83.3 % vs. 77 %) than in a previous study among 1187 PLHIV infection in a rural setting in the Northern part of Cameroon. [10] This study however, was conducted prior 2007, year of the implementation of the program of free access to ART in the country, which suggests that this strategy has likely improved survival among PLHIV in the country. It can also be speculated that the difference between this previous study and our study just reflects differences in the level of care provided in a referral centre like ours, and a rural centre where care can be very basic. The similarities in the baseline profile of participants across the two studies are in support of this hypothesis. For instance, in both studies over 85 % of participants were started on ART while at the WHO stage III or IV of the disease severity, while pre-ARV CD4 count was lower than 50/mm^3 in over a quarter of participants at baseline. However, the one-year survival rate in our study is within the range of those reported in previous studies. In recent meta-analysis of those studies, the pooled estimated one-year probability of death from studies conducted in Africa was 17 % (95 % confidence interval: 11-24 %), [6, 15] Predictors of mortality identified in our study were essentially those described in existing reports. [6, 15] The adverse profile of modifiable risk factors clearly suggests that patients with HIV in our centre are started on ART at an advanced stage of the disease. This likely reflects the fact that in this setting, with the exception of screening in particular circumstances such as during pregnancy or pre-surgical intervention, PLHIV mostly get screened only when they seek medical care with clinical symptoms. This is a common attitude across Africa, which may explain the higher early mortality rate on ART in Africa, compared with other parts of the world.[6] In addition to the advanced clinical stage of the disease on the WHO scale at presentation, body weight, CD4 count and haemoglobin levels were low at baseline, and all significantly associated with high risk of mortality during follow-up as previously reported. [5-8] It is of note that at the time this study was conducted, most patients were started on ART at CD4 count below 200/mm^3. Recent WHO recommendations favour ART initiation at CD4 count below 350/mm^3. Their uptake may potentially reduce early mortality rate, as a result of many patients starting treatment at favourable CD4 levels. The prevalence of active tuberculosis in our study was possibly inflated by the nature of the study setting as a referral centre for tuberculosis treatment, where most patients with both HIV and tuberculosis are likely to be referred for care. The resulting subsample of participants with both conditions has possibly increased our statistical power for uncovering baseline active tuberculosis as a risk factor for mortality among PLHIV started on antiretroviral therapy. Such an association has been inconsistently reported in previous studies. [6, 10, 16]

Free access to ART was introduced in Cameroon in May 2007 [17]. We have recently reported rate of non-adherence to ART to be as high as 34 % among patients with HIV receiving chronic care at the YJH in the era of free access to ART [12]. In the absence of any assessment of the adherence to ART in the current study, it is difficult to speculate of a contribution, if any, of non-adherence to ART to the observed high mortality in our study. However, such as effect is likely marginal in this setting where mortality mostly occurs early when patients have not been exposed to ART enough to derive therapeutic benefits. Furthermore, existing instruments for measuring adherence to ART are likely unsuitable for investigating premature mortality risk. The main non-modifiable risk factor of mortality in our study was male sex. This was not fully explained by sex differences in the level of other risk factors. Indeed, with the exception of baseline CD4 count which was lower in men, other factors were equally distributed among men or women or rather showed more favourable levels in men. Other studies have shown that adherence to prescribed ART was better in women than in men, [18] which can explain differing rates of mortality between men and women started on ART.

Our study has some limitations, including the missing data, which are expected for a study conducted based on data collected from patients files, and when dealing with large numbers of

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participants. Drop-out through losses to follow-up potentially include deceased patients, and may be in high proportion based on some studies. [19] Therefore, the reported mortality rate in our study is likely underestimated. But such a bias is unlikely to affect the associations of major risk factors with the mortality outcome as shown elsewhere. [10] In the absence of any evaluation of the adherence to ART, particularly among early mortality survivors, we were unable to investigate a potential effect of non-adherence to ART on mortality risk in the current study. Our study also has major strengths including the large sample size, which increased our statistical power to reliably characterise the predictors of mortality. The death rate following ART initiation as found in our study and other published studies is not constant over time. It is very high in the early months of starting the treatment, and subsequently drops and stabilises at a much lower rate. Many previous studies have been based on statistical methods that assume constant death rates over time such as the person-year methods, and have likely generated less reliable estimates of the association of predictors with mortality risk. We have attempted to address this limitation by applying the accelerated failure time models in our study. Unlike Cox models for instance, regression parameters estimates from accelerated failure time models are robust to the omitted covariates, and are unaffected by the choice of probability distribution.

In conclusion, mortality rate among patients with HIV-1 infection started on antiretroviral therapy in this setting remain unacceptably high. Deaths occur mostly within the first year of starting treatment and essentially among patients with clinical and biological profiles compatible with an advanced stage of the disease at the time when antiretroviral treatment is started. Strategies for early detection of patient with HIV and the clinically asymptomatic stages followed by early initiation of antiretroviral therapy needs to be developed and tested in this setting. Recent Cameroonian guidelines of HIV treatment allowing the prescription of antiretroviral therapy to patients with CD4 count lower than 350/mm^3 would probably reduce the mortality rate in this setting.

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Competing interests: None.

Ethics approval: Ethics approval was provided by the Institutional Review Board of Yaounde Jamot Hospital.

Contributors: VPM, collected data, co-analysed the data and drafted the manuscript. EWPY conceived the study, supervised data collection, co-analysed the data and drafted the manuscript.

APK contributed to study design, data analysis, drafting and critical revision of the manuscript. CK supervised data collection and critically revised the manuscript. All authors approved the final version of the manuscript.

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Table 1 Demographic, clinical and biological profile of HIV patients started on antiretroviral therapy at the Yaounde Jamot Hospital in 2007 and 2008

Characteristics*	Overall	Men	Women	p-value
n	1444	617	827	
Median age, years (25th-75th percentile)	38 (31-45)	40 (34-47)	35 (30-43)	<0.0001
Residence, n (%)				0.98
Urban	1236 (85.6)	528 (85.6)	708 (85.6)	
Rural	208 (14.4)	89 (14.4)	119 (14.4)	
Tuberculosis, n (%)	428 (29.6)	214 (34.7)	214 (27.9)	0.0003
Weight, Kg				<0.0001
< 50, n (%)	308/1322 (23.3)	69/570 (12.1)	239/752 (31.8)	
50-60, n (%)	535/1322 (40.5)	204/570 (35.8)	331/752 (44.0)	
>60, n (%)	479/1322 (36.2)	297/570 (52.1)	182/752 (24.2)	
Median (25th-75th percentile)	57 (50 - 65)	61 (54-68)	54 (47.5-60)	<0.0001
WHO stage, n (%)				0.82
I and II	186/1295 (14.4)	78/553 (14.1)	108/742 (14.6)	
III and IV	1109/1295 (85.6)	475/553 (85.9)	634/742 (85.4)	
Platelets, X1000/mm^3	244 (180– 320)	229 (173-309)	259 (190-330)	0,0005
Total lymphocytes, X10/mm^3	130 (90–190)	130 (90-201)	130 (90-190)	0.88
CD4, /mm^3				0.21
< 50, n (%)	468 (32.4)	216 (30.5)	256 (30.5)	
50-99, n (%)	257 (17.8)	111 (18.0)	142 (17.6)	
100-200, n (%)	562 (38.9)	231 (37.4)	331 (40.0)	
>200, n (%)	157 (10.9)	59 (9.6)	98 (11.8)	
Median (25th-75th percentile)	99 (36.2-161)	89 (33-155)	105 (39-166)	0.018
Haemoglobin, g/dl,				<0.0001
< 8, n (%)	235/1388 (16.9)	67/594 (11.3)	168/794 (21.2)	
8-10, n (%)	506/1388 (36.5)	178/594 (30.0)	328/794 (41.3)	
>10, n (%)	647/1388 (46.6)	349 (58.7)	298 (37.5)	
Median, (25th-75th percentile)	9.9 (8.5-11.2)	10.5 (9-12)	9.5 (8.1-10.7)	<0.0001

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; WHO, World Health Organisation

* For all characteristics with missing values, estimates are based of the subset of participants with valid data for each relevant characteristic, and new denominators always provided.

Table 2 Determinants of all-cause mortality among HIV-positive patients started on antiretroviral therapy (n = 1444)

Variable	Age and sex adjusted		Multivariable adjusted	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Age, per year	1.01 (0.98-1.03)	0.56	1.01 (0.99-1.03)	0.37
Male sex	1.44 (0.94-2.11)	0.10	2.15 (1.34-3.45)	0.002
Rural residency	1.14 (0.62-2.09)	0.68	-	
Active tuberculosis	1.59 (0.97-2.61)	0.07	2.35 (1.40-3.92)	0.002
WHO stage III-IV	4.57 (1.68-12.47)	0.004	3.63 (1.29-10.24)	0.02
Weight, per kg lower	1.04 (1.02-1.06)	0.0002	1.03 (1.01-1.05)	0.01
Platelet count, per 1000 lower	1.01 (0.99-1.03)	0.53	-	
CD4 count, per 10/mm3 lower	1.06 (1.02-1.09)	0.003	1.04 (1.01-1.07)	0.02
Haemoglobin, per g/dl lower	1.14 (1.03-1.26)	0.02	1.12 (1.00-1.26)	0.05
AZT based regimens	0.91 (0.51-1.62)	0.76	-	

AZT, zidovudine; CI, confidence interval; WHO, World Health Organisation

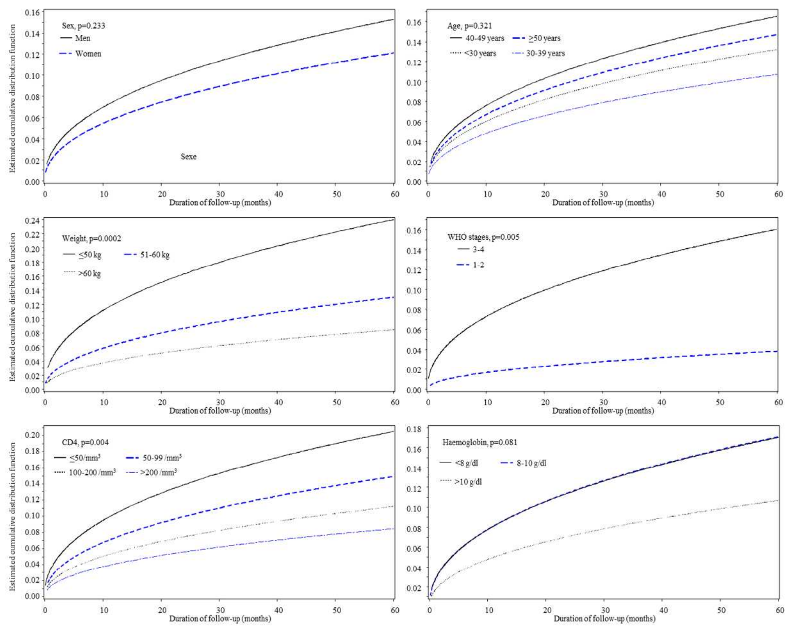

Figure 2: Estimated cumulative distribution function for all-cause mortality by major subgroups among patients with HIV infection who started antiretroviral treatment at the Yaounde Jamot Hospital in 2007 and 2008
297x209mm (300 x 300 DPI)

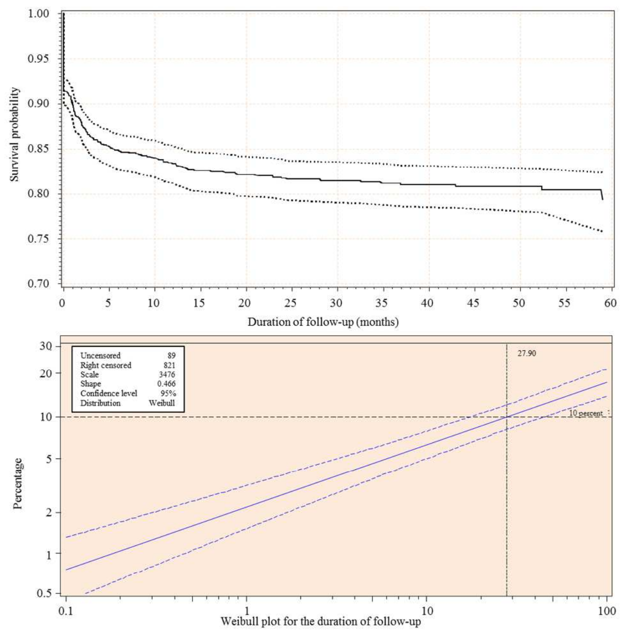

Figure 1: Survival probability from Kaplan-Meir estimator (upper panel) and Weibull plot showing the cumulative distribution function for mortality during follow-up of patients with HIV infection who started antiretroviral treatment at the Yaounde Jamot Hospital in 2007 and 2008
297x209mm (300 x 300 DPI)

Mortality and its determinants among patients infected with HIV-1 on antiretroviral therapy in a referral centre in Yaounde, Cameroon: a retrospective cohort study

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Mortality and its determinants among patients infected with HIV-1 on antiretroviral therapy in a referral centre in Yaounde, Cameroon: a retrospective cohort study

Short title: Determinants of death among patients with HIV infection

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ABSTRACT

Objectives: Mortality has declined in people with human immunodeficiency virus (HIV) infection, subsequent to the improved access to antiretroviral therapy (ART). We assessed the incidence and determinants of mortality among patients with HIV-1 infection, started on ART in a referral treatment centre for HIV infection in Yaounde, Cameroon.

Design: Cohort study with baseline assessment between 2007 and 2008, and follow-up during five years until June 2012.

Setting: The accredited HIV treatment centre of the Yaounde Jamot Hospital, in capital city of Cameroon.

Participants: People living with HIV infection who started ART between 2007 and 2008 at the study centre.

Outcome measures: All-cause mortality over time; accelerated failure time models used to relate baseline characteristics to mortality occurrence during follow-up.

Results: Of the 1444 patients included, 827 (53.7%) were men, and the median age (25^{th}-75^{th} percentiles) was 38 (31-45) years. The median duration of follow-up was 14.1 (1.1-46.4) months, during which 235 deaths were recorded (cumulative incidence rate: 16.3%), including 208 (88.5%) during the first year of follow-up. Baseline predictors of mortality were male gender [adjusted hazard ratio 2.15 (95% confidence interval : 1.34-3.45)], active tuberculosis [2.35 (1.40-3.92)], WHO stages III-IV of the disease [3.63 (1.29-10.24)], low weight [1.03 (1.01-1.05) per kilogramme], low CD4 count [1.04 (1.01-1.07) per 10/mm^3 lower CD4) and low haemoglobin levels [1.12 (1.00-1.26) per g/dl lower].

Conclusions: Mortality rate among patients with HIV is very high within the first year of starting ART in this centre. Early start of the treatment, at a less advanced stage of the disease, and favourable levels of CD4 and other predictors could reduce early mortality, but would have to be tested.

Word count – 270

Key words: HIV infection, mortality, determinants, cohort, Cameroon, antiretroviral therapy

ARTICLE SUMMARY

Article focus

- To investigate mortality occurrence and determinants among patients with HIV-1 infection, started on antiretroviral therapy in a major reference treatment centre

Key messages

- Mortality rate among patients with HIV is very high, particularly within the first year of starting antiretroviral therapy in this centre
- Male gender, active tuberculosis, advanced stage of the disease, low CD4 count, low weight and low haemoglobin levels at baseline were significant predictors of all-cause mortality during follow-up

Strengths and limitations

- Strengths of the study include the large sample size and the use of robust methods to relate baseline predictors to the mortality occurrence during follow-up.
- The study was based on data collected from patient files and clinical registers, and as expected there were missing data, particularly on the true outcome of patients who were lost-to-follow-up.

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a major global health problem. Sub-Saharan Africa (SSA), with about 68% of the global population with HIV, is the most affected region in the world.[1] HIV related mortality appears to be higher in developing than in developed countries.[2] Hopefully, mortality rates are declining with the improved access to antiretroviral therapy (ART),[3] while explaining factors for the residual deaths seem to vary significantly across populations. Studies in SSA have found that mortality rate is particularly high during the first year of starting ART,[4] with male sex, cachexia, advanced stage of the disease, low CD4 count, anaemia, high viral load at baseline, and poor adherence to treatments being the main determinants of mortality.[5-8]

In Cameroon, about 105,000 people living with HIV (PLHIV) infection were on ART by the end of the year 2011.[9] A study conducted in 2006 in a rural unit for HIV treatment in the northern part of the country, found a mortality rate of 20.2/100 person-years among HIV patients receiving ART.[10] This figure however, has not been updated since 2007, the year of introduction of free access to ART in the country. Thus, the aim of this study was to determine the mortality rate and determinants among patients with HIV-1 infection, started on ART in a reference treatment centre in Cameroon.

PARTICIPANTS AND METHODS

Study setting and participants

The study was conducted in the accredited HIV treatment centre (ATC) of the Yaounde Jamot Hospital (YJH) in the capital city of Cameroon. The study setting has been described in details previously.[11,12] In brief, YJH is the referral centre for tuberculosis and chest diseases for the Capital city (Yaounde) and surrounding areas. It has an ATC that provides care to PLHIV. As of June 2011, a total of 2,250 PLHIV were followed in the centre. Patients received at ATC between January 2007 and December 2008, aged 18 years and above, and who were started on ART, were included in the study.

During the study period, PLHIV were started on ART in the presence of a CD4 count below 200/mm^3 or superimposed conditions other than tuberculosis, compatible with the WHO stage IV of the disease severity.[13] Patients fulfilling these criteria were referred to the ATC for treatment inception and follow-up. A medical file was created under the supervision of the attending physician and included socio-demographic, clinical and biological data of the patient. Files of eligible patients were presented at weekly meetings during which the appropriate treatment regimen was decided. First line treatment regimens included two nucleoside reverse transcriptase inhibitors (zidovudine, lamivudine, tenofovir) and one non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz). Second line regimens comprised two nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, lamivudine, tenofovir) and a protease inhibitor (indinavir, lopinavir/ritonavir). These regimens were all dispensed to patients free of charge and they were all started on prophylactic treatment with cotrimoxazole. All patients had an interaction session with trained psychosocial advisors, to improve adherence to prescribed therapies.

Patients registered at the YJH's ATC are seen on a monthly basis for prescription renewal. For those on a regimen comprising zidovudine (AZT) and/or nevirapine (NVP), haemoglobin (AZT) and/or liver transaminases (NVP) levels are monitored at two weeks from starting treatment. A biological profile is requested every six months, comprising a CD4 count, full blood count, liver transaminases and creatinin (only for patients receiving tenofovir), and results are recorded in the clinical files.

Outcome

During the study period, patients who failed to report for consultation for three consecutive months were traced by community liaison agents using the contact details on the file. All-cause mortality was considered for all deceased patients at any time after starting ART. The time-to-death (in months) was the interval from the start of the ART to date of death (or date of the last recorded visit when the date of death was unknown). Loss-to-follow-up (defaulter) was defined as a patient who failed to return for consultation for three consecutive months and was unsuccessfully traced by liaison agents.[14] Transfer was considered for patients who at any time were definitively transferred to receive care in another centre. The follow-up for all patients was until June 2012, death, transfer and loss to follow-up, whichever came first.

Data collection

For the purpose of this study, patients with HIV started on ART during the study period were identified via antiretroviral treatment registries. All patients with HIV-1 infection, aged 18 years and above, started on ART during this period were included in the study, and followed until June 2012. The study was approved by the regulatory board of YJH.

The following data were retrieved in the medical files of eligible patients: sex, baseline age (in years), residence (urban vs. rural), weight in Kg, presence of opportunistic infection, CD4 count (in cells/mm^3), haemoglobin levels in g/dl, total lymphocytes and platelet counts, antiretroviral regimens; outcome (death, loss-to-follow-up, transfer out, still alive and followed-up), and estimated time to the outcome occurrence in months. The duration of follow-up for patients still actively followed-up was censored in June 2012.

Statistical analysis

Data analysis used SPSS v17.0 (SPSS Inc., Chicago, USA) and SAS/STAT® v 9.1 for Windows (SAS Institute Inc., Cary, NC, USA). Results are presented as count and percentages, mean and standard deviation or median and 25th-75th percentiles. The chi square test, Student's t-test and their non-parametric equivalents were used to compare baseline characteristics. The Kaplan-Meir estimator and accelerated failure time models, implemented with the use of LIFETEST and LIFEREG procedures of SAS were used to investigate the baseline characteristics associated with mortality during the first 60 months of follow-up (corresponding to the observed duration of follow-up for >95% of participants). Candidate predictors included age (in years), gender (male vs. female), residency (rural vs. urban), active tuberculosis, WHO stages of the disease (III-IV vs. I-II), weight (in kg), platelet count (per 1000), CD4 count (per 10/mm^3), haemoglobin level (in g/dl) and ART regimen (AZT vs. no AZT). Candidate predictors were tested one at a time in a basic model that included gender and age as covariates. Then significant predictors (based on a p-value <0.10) were entered together in a multivariable model, and significant ones kept in the final model alongside age and gender. The reference category (or direction of continuous predictors) was always rearranged as appropriate to identify levels associated with increased mortality risk. A p-value < 0.05 was used to characterise statistically significant results.

RESULTS

Data available

In 2007 and 2008, a total of 1444 PLHIV [including 827 women (57.3%)] were started on ART at the YJH's ATC. Medical files were available for all of them. However, data were missing on some characteristics for few participants. Analyses for those characteristics are restricted to participants with valid data, and their number indicated where relevant. Furthermore, a total of 470 participants had missing data for at least one of the candidate predictors, and were therefore excluded from regression analysis. Compared with excluded participants, the 974 included in regression analysis had similar age (38.3 vs. 38.8 years, p=0.44), mean CD4 count (102 vs. 111/mm^3, p=0.06). Furthermore, they had similar proportion of men (42.5% vs. 43.2%, p=0.82), similar distribution across WHO stages of disease severity (p=0.75), a borderline higher prevalence of active tuberculosis (31.1% vs. 26.6%, p=0.04), a borderline lower baseline weight (57.6 vs. 59.1

kg, p=0.04) and lower platelet (262000 vs. 243000/mm^3, p=0.03), and a significantly lower haemoglobin level (9.9 vs. 10.4 g/dl, p<0.0001).

Baseline characteristics of the study population

The baseline demographic, clinical and biological characteristics of participants are summarised in Table 1. The median age (25^{th}-75^{th} percentiles) was 38 (31 - 45) years overall, 40 (34 - 47) years in men and 35 (30 - 43) years in women, p<0.0001. In all 85.6% of participants were urban dwellers and about the same proportion were started on ART at WHO stage III-IV of disease severity, similarly among men and women (both p≥0.82, Table 1). The main opportunistic infection was tuberculosis, which was found in 428 (29.6%) patients, and was more frequent in men than in women (34.7% vs. 27.9%, p=0.0003). The median CD4 count (25^{th} - 75^{th} percentiles) was 99 (36 - 161) per mm^3 overall, 89 (33 - 155) in men and 105 (39 - 166) in women (p=0.02).

Follow-up and outcome

The median duration of follow-up (25^{th} - 75^{th} percentiles) was 14.4 (1.0 - 46.2) months overall, 9.1 (0 - 44.1) months in men and 20.3 (1.3 - 47.3) months in women (p<0.0001). At the final evaluation, 235 (cumulative incidence rate 16.3 %) were deceased, 590 (40.8%) were lost to follow-up, 173 (12 %) had been transferred to another centre, while 446 patients (30.9%) were still under active follow-up in the centre. The median duration of follow-up (25^{th} - 75^{th} percentiles) for non-fatal outcomes was 4.5 (0 - 23.8) months for defaulters, 8.2 (2.5 - 20.3) months for transfer out, and 50.5 (45.9 - 56.7) months for active follow-up cases.

Of the 235 deaths recorded, 208 (88.5 %) deaths occurred early (within the first year of ART) while 27 (11.5%) were late-occuring deaths. Overall, 54.9% of all deaths occurred within one month of starting antiretroviral therapy, 19.6% between 1 and 3 months, 8.5% between 3 and 6 months and 5.5% between 6 and 12 months. The cumulative survival probability from Kaplan-Meier estimators was 84.7% (95% confidence interval: 82.7-86.7) at 6 months, 83.3% (81.3-85.4) at 12 months, 81.7% (79.5-83.9) at 24 months, and 79.3% (76.0-82.5) at 60 months of follow-up. The survival probability from Kaplan-Meier estimators and Weibull plot of the cumulative distribution function for all-cause mortality are depicted in Figure 1. The cumulative mortality rate was 16.8% (79/470) among participants with missing data on at least one of the candidate predictor variables, and 16.6% (162/974) among those with valid data, p=0.93.

Determinants of all-cause mortality

The estimated cumulative distribution function for all-cause mortality by major subgroups is depicted in figure 2. In sex and age adjusted analyses, male sex, active tuberculosis, WHO stage III-IV of the disease, lower weight, lower CD4 count and lower baseline haemoglobin level were potential determinants of all-cause mortality (Table 2). In multivariable Weibull regression models with simultaneous adjustment for age, sex, and all the potential factors, all determinants remained significantly associated with all-cause mortality during follow-up (Table 2). Effect estimates (hazard ratio) and 95% confidence intervals were 2.15 (1.34-3.45) for male sex, 2.35 (1.40-3.92) for active tuberculosis, 3.63 (1.29-10.24) for WHO stage III-IV of the disease severity, 1.03 (1.01-1.05) per kilogram lower weight, 1.04 (1.01-1.07) per 10 lower CD4/mm^3 and 1.12 (1.00-1.26) for each g/dl lower baseline haemoglobin (Table 2).

DISCUSSION

This study conducted in a referral centre for tuberculosis and HIV care in Cameroon revealed a high mortality rate among patients started on ART, with the large majority of deaths occurring during the first year of starting the treatment. Male gender, active tuberculosis, advanced stage of the disease, low CD4 count, low weight and low haemoglobin levels at baseline were significant predictors of all-cause mortality during follow-up. Accounting for these factors may help in refining the prescription of ART and improving the outcome of care among patients with HIV infection.

The survival probability at one year of follow-up after starting ART was found to be much lower (83.3% vs. 77%) in a previous study among 1187 PLHIV infection in a rural setting in the Northern part of Cameroon.[10] This study however, was conducted prior 2007, the year of the implementation of the program of free access to ART in the country, which suggests that this strategy has likely improved survival among PLHIV in the country. It can also be speculated that the difference between this previous study and our finding just reflects differences in the level of care provided in a referral centre like ours, and a rural centre where care can be very basic. The similarities in the baseline profile of participants across the two studies are in support of this hypothesis. For instance, in both studies over 85% of participants were started on ART while at the WHO stage III or IV of the disease severity, while pre-ARV CD4 count was lower than 50/mm^3 in over a quarter of participants at baseline. However, the one-year survival rate in our study is within the range of those reported in previous studies. In recent meta-analysis of those studies, the pooled estimated one-year probability of death from studies conducted in Africa was 17% (95% confidence interval: 11-24 %).[6,15]

Predictors of mortality identified in our study were essentially those described in existing reports.[6,15] The adverse profile of modifiable risk factors clearly suggests that patients with HIV in our centre are started on ART at an advanced stage of the disease. This likely reflects the fact that in this setting, with the exception of screening in particular circumstances such as during pregnancy or pre-surgical interventions, PLHIV mostly get screened only when they seek medical care with clinical symptoms. This is a common attitude across Africa, and may explain the higher early mortality rate on ART in Africa, compared with other parts of the world.[6] In addition to the advanced clinical stage of the disease on the WHO scale at presentation, body weight, CD4 count and haemoglobin levels were low at baseline, and all significantly associated with high risk of mortality during follow-up as previously reported.[5,8] It is of note that at the time this study was conducted, most patients were started on ART at CD4 count below 200/mm^3. Recent WHO recommendations favour ART initiation at CD4 count below 350/mm^3. Their uptake may potentially reduce early mortality rate, as a result of many patients starting treatment at favourable CD4 levels. The prevalence of active tuberculosis in our study was possibly inflated by the nature of the study setting as a referral centre for tuberculosis treatment, where most patients with both HIV and tuberculosis are more likely to be referred for care. The resulting subsample of participants with both conditions has possibly increased our statistical power for uncovering baseline active tuberculosis as a risk factor for mortality among PLHIV started on antiretroviral therapy. Such an association has been inconsistently reported in previous studies.[6,10,16]

Free access to ART was introduced in Cameroon in May 2007.[17] We have recently reported rates of non-adherence to ART to be as high as 34% among patients with HIV receiving chronic care at the YJH in the era of free access to ART.[12] In the absence of any assessment of the adherence to ART in the current study, it is difficult to speculate on a contribution, if any, of non-adherence to ART to the observed high mortality in our study. However, such an effect is likely marginal in this setting where mortality mostly occurs early when patients have not been exposed to ART enough to derive therapeutic benefits. Furthermore, existing instruments for measuring adherence to ART are likely unsuitable for investigating premature mortality risk. The main non-modifiable risk factor of mortality in our study was male sex. This was not fully explained by sex differences in the level of other risk factors. Indeed, with the exception of baseline CD4 count which was lower in men, other factors were equally distributed among men or women or rather showed more favourable levels in men. Other studies have shown that adherence to prescribed ART was better in women than in men, [18] which can explain differing rates of mortality between men and women started on ART.

Our study has some limitations, including the missing data, which are expected for a study conducted on data collected from patients files, and when dealing with large numbers of participants. Drop-out through losses to follow-up potentially included deceased patients, and may be in high proportion based on some studies.[19] Therefore, the reported mortality rate in our study is likely underestimated. But such a bias is unlikely to affect the associations of major risk factors with the mortality outcome as shown elsewhere.[10] In the absence of any evaluation of the adherence to ART, particularly among early mortality survivors, we were unable to investigate a potential effect of non-adherence to ART on mortality risk in the current study. Our study also has major strengths including the large sample size, which increased our statistical power to reliably characterise the predictors of mortality. The mortality rate following ART initiation as found in our study and other published studies is not constant over time. It is very high in the early months of starting the treatment, and subsequently drops and stabilises at a much lower rate. Many previous studies have been based on statistical methods that assume constant mortality rates over time such as the person-year methods, and have likely generated less reliable estimates of the association of predictors with mortality risk. We have attempted to address this limitation by applying the accelerated failure time models in our study. Unlike Cox models for instance, regression parameters estimates from accelerated failure time models are robust to the omitted covariates, and are unaffected by the choice of probability distribution.

In conclusion, mortality rate among patients with HIV-1 infection started on antiretroviral therapy in this setting remains unacceptably high. Deaths occur mostly within the first year of starting treatment and essentially among patients with clinical and biological profiles compatible with an advanced stage of the disease at the time when antiretroviral treatment is started. Strategies for early detection of patient with HIV at the clinically asymptomatic stages followed by early initiation of antiretroviral therapy, need to be developed and tested in this setting. Recent updates of the country's guidelines for HIV treatment, recommending prescription of antiretroviral therapy at CD4 count lower than 350/mm^3 have a potential for significantly reducing premature mortality among people with HIV in this setting.

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Competing interests: None for all authors.

Ethics approval: Ethics approval was obtained from the Institutional Review Board of the Yaounde Jamot Hospital.

Contributors: VPM, collected data, co-analysed the data and drafted the manuscript. EWPY conceived the study, supervised data collection, co-analysed the data and drafted the manuscript. APK contributed to study design, data analysis, drafting and critical revision of the manuscript. CK supervised data collection and critically revised the manuscript. All authors approved the final version of the manuscript.

Data sharing: No additional data available.

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Table 1 Demographic, clinical and biological profile of HIV patients started on antiretroviral therapy at the Yaounde Jamot Hospital in 2007 and 2008

Characteristics*	Overall	Men	Women	p-value
n	1444	617	827	
Median age, years (25th-75th percentile)	38 (31-45)	40 (34-47)	35 (30-43)	<0.0001
Residence, n (%)				0.98
Urban	1236 (85.6)	528 (85.6)	708 (85.6)	
Rural	208 (14.4)	89 (14.4)	119 (14.4)	
Tuberculosis, n (%)	428 (29.6)	214 (34.7)	214 (27.9)	0.0003
Weight, Kg				<0.0001
< 50, n (%)	308/1322 (23.3)	69/570 (12.1)	239/752 (31.8)	
50-60, n (%)	535/1322 (40.5)	204/570 (35.8)	331/752 (44.0)	
>60, n (%)	479/1322 (36.2)	297/570 (52.1)	182/752 (24.2)	
Median (25th-75th percentile)	57 (50 - 65)	61 (54-68)	54 (47.5-60)	<0.0001
WHO stage, n (%)				0.82
I and II	186/1295 (14.4)	78/553 (14.1)	108/742 (14.6)	
III and IV	1109/1295 (85.6)	475/553 (85.9)	634/742 (85.4)	
Platelets, X1000/mm^3	244 (180– 320)	229 (173-309)	259 (190-330)	0.0005
Total lymphocytes, X10/mm^3	130 (90–190)	130 (90-201)	130 (90-190)	0.88
CD4, /mm^3				0.21
< 50, n (%)	468 (32.4)	216 (30.5)	256 (30.5)	
50-99, n (%)	257 (17.8)	111 (18.0)	142 (17.6)	
100-200, n (%)	562 (38.9)	231 (37.4)	331 (40.0)	
>200, n (%)	157 (10.9)	59 (9.6)	98 (11.8)	
Median (25th-75th percentile)	99 (36.2-161)	89 (33-155)	105 (39-166)	0.02
Haemoglobin, g/dl,				<0.0001
< 8, n (%)	235/1388 (16.9)	67/594 (11.3)	168/794 (21.2)	
8-10, n (%)	506/1388 (36.5)	178/594 (30.0)	328/794 (41.3)	
>10, n (%)	647/1388 (46.6)	349 (58.7)	298 (37.5)	
Median, (25th-75th percentile)	9.9 (8.5-11.2)	10.5 (9-12)	9.5 (8.1-10.7)	<0.0001

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; WHO, World Health Organisation
* For all characteristics with missing values, estimates are based of the subset of participants with valid data for each relevant characteristic, and new denominators always provided.

Table 2 Determinants of all-cause mortality among HIV-positive patients started on antiretroviral therapy (n = 1444)

Variable	Age and sex adjusted		Multivariable adjusted	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Age, per year	1.01 (0.98-1.03)	0.56	1.01 (0.99-1.03)	0.37
Male sex	1.44 (0.94-2.11)	0.10	2.15 (1.34-3.45)	0.002
Rural residency	1.14 (0.62-2.09)	0.68	-	
Active tuberculosis	1.59 (0.97-2.61)	0.07	2.35 (1.40-3.92)	0.002
WHO stage III-IV	4.57 (1.68-12.47)	0.004	3.63 (1.29-10.24)	0.02
Weight, per kg lower	1.04 (1.02-1.06)	0.0002	1.03 (1.01-1.05)	0.01
Platelet count, per 1000 lower	1.01 (0.99-1.03)	0.53	-	
CD4 count, per 10/mm3 lower	1.06 (1.02-1.09)	0.003	1.04 (1.01-1.07)	0.02
Haemoglobin, per g/dl lower	1.14 (1.03-1.26)	0.02	1.12 (1.00-1.26)	0.05
AZT based regimens	0.91 (0.51-1.62)	0.76	-	

AZT, zidovudine; CI, confidence interval; WHO, World Health Organisation

Mortality and its determinants among ~~HIV-1~~patients infected ~~patients~~with HIV-1 on antiretroviral therapy in a referral centre in Yaounde, Cameroon: a retrospective cohort study

Short title: Determinants of death among patients with HIV infection

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ABSTRACT

Objectives: Mortality has ~~decreased~~declined in people with human immunodeficiency virus (HIV) infection, subsequent to the improved access to antiretroviral therapy (ART). We assessed the incidence and determinants of ~~fatal outcomes~~mortality among patients with HIV-1 infection, started on ART in a referral treatment centre for HIV infection in Yaounde, Cameroon.

Design: Cohort study with baseline assessment between 2007 and 2008, and follow-up during five years until June 2012.

Setting: The ~~approved centre for~~accredited HIV treatment centre of the Yaounde Jamot Hospital, in capital city of Cameroon.

Participants: ~~Patients~~People living with HIV infection who ~~were~~ started ART between 2007 and 2008 at the study centre.

Outcome measures: All-cause mortality over time~~, with the~~; accelerated failure time models ~~were~~ used to relate baseline characteristics ~~with~~to mortality occurrence during follow-up.

Results: Of the 1444 patients included, 827 (53.7%) were men, and the median age (25^{th}-75^{th} percentiles) was 38 (31-45) years. The median duration of follow-up was 14.1 (1.1-46.4) months, during which 235 deaths were recorded (cumulative incidence rate: 16.3%), including 208 (88.5%) during the first year of follow-up. Baseline predictors of mortality were male gender [adjusted hazard ratio 2.15 (95%~~CI~~ confidence interval : 1.34-3.45)], active tuberculosis [2.35 (1.40-3.92)], WHO stages III-IV of the disease [3.63 (1.29-10.24)], low weight [1.03 (1.01-1.05) per kilogramme], low CD4 count [1.04 (1.01-1.07) per $10/mm^3$ lower CD4) and low haemoglobin levels [1.12 (1.00-1.26) per g/dl lower].

Conclusions: ~~Death~~Mortality, rate among patients with HIV is very high within the first year of starting ART in this centre. Early start of the treatment, at a less advanced stage of the disease, and ~~much~~ favourable levels of CD4 and other predictors ~~may improve the outcomes of patients~~could reduce early mortality, but would have to be tested.

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Key words: HIV infection, ~~death~~mortality, determinants, cohort, Cameroon, antiretroviral therapy

ARTICLE SUMMARY

Article focus

- To investigate mortality occurrence and determinants among patients with HIV-1 infection, started on antiretroviral therapy in a major reference treatment centre

Key messages

- ~~Death~~Mortality rate among patients with HIV is very high, particularly within the first year of starting ~~ART~~antiretroviral therapy in this centre
- Male gender, active tuberculosis, advanced stage of the disease, low CD4 count, low weight and low haemoglobin levels at baseline were significant predictors of all-cause mortality during ~~the~~ follow-up

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Strengths and limitations

- Strengths of the study include the large sample size and the use of robust methods to relate baseline predictors to the ~~outcome~~mortality occurrence during follow-up.
- The study was based on data collected from patient files and clinical registers, and as expected there were missing data, particularly on the true outcome of patients who were lost-to-follow-up.

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a major global health problem. Sub-Saharan Africa (SSA), with about 68% of the global population with HIV, is the most affected region in the world~~. [1] ~~.[1] HIV related mortality appears to be higher in developing than in developed countries~~. [2]~~.[2] Hopefully, mortality rates are ~~on the decline~~declining with the improved access to antiretroviral therapy~~, [3]~~ (ART),[3] while explaining factors ~~of~~for the residual deaths ~~seems~~seem to vary significantly across populations. Studies in SSA have found that mortality rate is particularly high during the first year of starting ~~antiretroviral therapy, [4]~~ART,[4] with male sex, cachexia, advanced stage of the disease, low CD4 count, anaemia, high viral load at baseline, and poor adherence to treatments being the main determinants of ~~death. [5-8]~~mortality.[5-8]

~~In Cameroon, about 105,000 people with HIV infection were on antiretroviral therapy by the end of the year 2011, [9] A study conducted in 2006 in a rural unit for HIV treatment in the northern part of the country, found a mortality rate of 20.2/100 person-years among HIV patients receiving antiretroviral therapy. [10] This figure however, has not been updated since the introduction of free access to antiretroviral therapy in the country. Thus, the aim of this study was to determine the mortality rate and its determinants among patients with HIV-1 infection, started on antiretroviral therapy in a reference treatment centre in Cameroon.~~

In Cameroon, about 105,000 people living with HIV (PLHIV) infection were on ART by the end of the year 2011.[9] A study conducted in 2006 in a rural unit for HIV treatment in the northern part of the country, found a mortality rate of 20.2/100 person-years among HIV patients receiving ART.[10] This figure however, has not been updated since 2007, the year of introduction of free access to ART in the country. Thus, the aim of this study was to determine the mortality rate and determinants among patients with HIV-1 infection, started on ART in a reference treatment centre in Cameroon.

PARTICIPANTS AND METHODS

Study setting and participants

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The study was conducted in the ~~approved~~accredited HIV treatment centre (ATC) of the Yaounde Jamot Hospital (YJH) in the ~~Capital~~capital city of Cameroon. The study setting has been described in ~~detail~~details previously~~ elsewhere. [11, 12]~~.[11,12] In brief, YJH is the referral centre for tuberculosis and chest diseases for the Capital city (Yaounde) and surrounding areas. It has an ~~approved treatment centre (ACT)~~ATC that provides care to ~~people with HIV infection.~~PLHIV. As of June 2011, the active filea total of HIV infected persons2,250 PLHIV were followed in the centre was 2250 patients. Patients received at ATC between January 2007 and December 2008, aged 18 years and above, and who were started on ART, were included in the study.

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Care of patients with HIV infection

During the study period, patients with HIV infection were started on antiretroviral therapy in the presence of a CD4 count below 200/mm^3 or superimposed condition other than tuberculosis, characteristic of WHO stage IV of the disease severity, [13] Patients fulfilling these criteria were referred to the ACTDuring the study period, PLHIV were started on ART in the presence of a CD4 count below 200/mm^3 or superimposed conditions other than tuberculosis, compatible with the WHO stage IV of the disease severity.[13] Patients fulfilling these criteria were referred to the ATC for treatment inception and follow-up. A medical file was created under the supervision of the attending physician and included socio--demographic, clinical and biological data of the patient. Files of eligible patients were presented at weekly meetings during which the appropriate treatment regimen for each patient was decided. First line treatment regimens included two nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, lamivudine, tenofovir) and one non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz). Second line regimens comprised two nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, lamivudine, tenofovir) and a protease inhibitor (indinavir, lopinavir/ritonavir). These regimens were all dispensed to patients free of charge and they were all started on prophylactic treatment with cotrimoxazole. All patients had aan interaction session with trained psychosocial advisors, to improve adherence to prescribed therapies.

Patients registered at the YJH's ACTATC are seen on a monthly basis for prescription renewal. For those on a regimen comprising zidovudine (AZT) and/or nevirapine (NVP), haemoglobin (AZT) and/or liver transaminases (NVP) levels are monitored at two weeks from starting treatment. A biological profile is requested every six months, comprising a CD4 count, full blood count, liver transaminases and creatinin (only for patients receiving tenofovir), and results are recorded in the clinical filefiles.

Outcome

During the study period, patients who failed to report for consultation for three consecutive months were traced by community liaison agents using the contact details on the file. All-cause mortality was considered for all deceased patients at any time after starting antiretroviral therapy.ART. The time-to-death (in months) was the interval from the start of the antiretroviral therapyART to date of death (or date of the last recorded visit when the date of death was unknown). Loss-to-follow-up (defaulter) was considered for patientsdefined as a patient who failed to return for consultation for three consecutive months and was unsuccessfully traced by liaison agents, [14].[14] Transfer was considered for patients who at any time were definitively transferred to receive care in another centre. The follow-up for all patients was until June 2012, death, transfer and loss to follow-up, whichever came first.

Data collection

For the purpose of this study, patients with HIV started on antiretroviral therapy between January 2007 and December 2008ART during the study period were identified via antiretroviral treatment registries. All patients with HIV-1 infection, aged 18 years and above, started on antiretroviralART during this period were included in the study, and followed until June 2012 (5.5 years)., The study was approved by the regulatory board of YJH.

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The following data were then retrieved in the medical files of eligible patients: sex, baseline age (in years), residence (urban vs. rural), weight in Kg, presence of opportunistic infection, CD4 count, (in cells/mm^3), haemoglobin levels in g/dl, total lymphocytes and platelet counts, antiretroviral regimens; the outcome, (death, loss-to-follow-up, transfer out, still alive and followed-up), and estimated time to the outcome occurrence in months. The duration of follow-up for patients still actively followed-up was censored in June 2012.

Statistical analysis

Data analysis used SPSS v17.0 (SPSS Inc., Chicago, USA) and SAS/STAT® v 9.1 for Windows (SAS Institute Inc., Cary, NC, USA). Results are presented as count and percentages, mean and standard deviation or median and 25th-75th percentiles. The chi square test, Student's t-test and their non-parametric equivalents were used to compare baseline characteristics. The Kaplan-Meir estimator and accelerated failure time models, implemented with the use of LIFETEST and LIFEREG procedures of SAS were used to investigate the baseline characteristics associated with mortality during the first 60 months of follow-up (corresponding to the observed duration of follow-up for > 95% of participants).95% of participants). Candidate predictors included age (in years), gender (male vs. female), residency (rural vs. urban), active tuberculosis, WHO stages of the disease (III-IV vs. I-II), weight (in kg), platelet count (per 1000), CD4 count (per 10/mm^3), haemoglobin level (in g/dl) and ART regimen (AZT vs. no AZT). Candidate predictors were tested one at a time in a basic model that included gender and age as covariates. Then significant predictors (based on a p-value <0.10) were entered together in a multivariable model, and significant ones kept in the final model alongside age and gender. The reference category (or direction of continuous predictors) was always rearranged as appropriate to identify levels associated with increased mortality risk. A p-value < 0.05 was used to characterise statistically significant results.

RESULTS

Baseline characteristics of the study population

Data available

In 2007 and 2008, a total of 1444 patients with HIV infectionPLHIV [including 827 women (57.3%)] were started on antiretroviral treatmentART at the YJH's ACTATC. Medical files were available for all of them. However, data were missing on some characteristics for few participants. Analyses for those characteristics are restricted to participants with valid data, and their number indicated where relevant. Furthermore, a total of 470 participants had missing data for at least one of the candidate predictors, and were therefore excluded from regression analysis. Compared with excluded participants, the 974 included in regression analysis had similar age (38.3 vs. 38.8 years, p=0.44), mean CD4 count (102 vs. 111/mm^3, p=0.06). Furthermore, they had similar proportion of men (42.5% vs. 43.2%, p=0.82), similar distribution across WHO stages of disease severity (p=0.75), a borderline higher prevalence of active tuberculosis (31.1% vs. 26.6%, p=0.04), a borderline lower baseline weight (57.6 vs. 59.1 kg, p=0.04) and lower platelet (262000 vs. 243000/mm^3, p=0.03), and a significantly lower haemoglobin level (9.9 vs. 10.4 g/dl, p<0.0001).

Baseline characteristics of the study population

The baseline demographic, clinical and biological characteristics of participants are summarised in Table 1. The median age (25th-75th percentiles) was 38 (31 - 45) years overall, 40 (34 - 47) years in men and 35 (30 - 43) years in women, p < <0.0001. In all 85.6% of participants were urban dwellers and about the same proportion were started on antiretroviral therapyART at WHO stage III-IV of disease severity, similarly among men and women (both p > >0.82, Table 1). The main opportunistic infection was tuberculosis, which was found in 428 (29.6%) patients, and was more frequent in men than in women (34.7% vs. 27.9%, p = =0.0003). The median CD4 count (25th - 75th percentiles) was 99 (36 - 161) per mm^3 overall, 89 (33 - 155) in men and 105 (39 - 166) in women (p = =0.01802).

Follow-up and outcome

The median duration of follow-up (25th - 75th percentiles) was 14.4 (1.0 - 46.2) months overall, 9.1 (0 - 44.1) months in men and 20.3 (1.3 - 47.3) months in women (p = ≤0.0001). At the final evaluation, 235 (cumulative incidence rate 16.3 %) were deceased, 590 (40.8%) were lost to follow-up, 173 (12 %) had been transferred to another centre, while 446 patients (30.9%) were still under active follow-up in the centre. The median duration of follow-up (25th - 75th percentiles) for non-fatal outcomes was 4.5 (0- - 23.8) months for defaulters, 8.2 (2.5 - 20.3) months for transfer out, and 50.5 (45.9 - 56.7) months for active follow-up cases.

Of the 235 deaths recorded, 208 (88.5 %) deaths occurred early (within the first year of ART) while 27 (11.5 %) were late-occurring deaths. Overall, 54.9 % of all deaths occurred within one month of starting antiretroviral therapy, 19.6 % between 1 and 3 months, 8.5 % between 3 and 6 months and 5.5% between 6 and 12 months. The cumulative survival probability from Kaplan-Meier estimators was 84.7% (95 % confidence interval: 82.7—-86.7) at 6 months, 83.3% (81.3—-85.4) at 12 months, 81.7% (79.5—-83.9) at 24 months, and 79.3% (76.0—-82.5) at 60 months of follow-up. The survival probability from Kaplan-Meier estimators and Weibull plot of the cumulative distribution function for all-cause mortality are depicted in Figure 1. The cumulative mortality rate was 16.8% (79/470) among participants with missing data on at least one of the candidate predictor variables, and 16.6% (162/974) among those with valid data, p=0.93.

Determinants of all-cause mortality

The estimated cumulative distribution function for all-cause mortality by major subgroups is depicted in figure 2. In sex and age adjusted analyses, male sex, active tuberculosis, WHO stage III-IV of the disease, lower weight, lower CD4 count and lower baseline haemoglobin level were potential determinants of all-cause mortality (Table 2). In multivariable Weibull regression models with simultaneous adjustment for age, sex, and all the potential factors, all determinants remained significantly associated with all-cause mortality during follow-up (Table 2). Effect estimates (hazard ratio) and 95% confidence intervals were 2.15 (1.34-3.45) for male sex, 2.35 (1.40-3.92) for active tuberculosis, 3.63 (1.29-10.24) for WHO stage III-IV of the disease severity, 1.03 (1.01-1.05) per kilogram lower weight, 1.04 (1.01-1.07) per 10 lower CD4/mm^3 and 1.12 (1.00-1.26) for each g/dl lower baseline haemoglobin (Table 2).

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DISCUSSION

This study conducted in a referral centre for tuberculosis and HIV care in Cameroon revealed a high mortality rate among patients started on ~~antiretroviral therapy~~ART, with the large majority of ~~death~~deaths occurring during the first year of starting the treatment. Male gender, active tuberculosis, advanced stage of the disease, low CD4 count, low weight and low haemoglobin levels at baseline were significant predictors of all-cause mortality during follow-up. Accounting for these factors may help in refining the prescription of ~~antiretroviral therapy~~ART and ~~improve~~improving the outcome of care among patients with HIV infection.

The survival probability at one year of follow-up after starting ~~antiretroviral therapy~~ART was found to be much lower (83.3% vs. 77%) in a previous study among 1187 ~~patients with HIV~~PLHIV infection in a rural setting in the Northern part of Cameroon~~. [10]~~.[10] This study however, was conducted prior ~~to~~2007, the year of the implementation of the program of free access to ~~antiretroviral therapy~~ART in the country, which suggests that this strategy has likely improved survival among ~~HIV patients~~PLHIV in the country. It can also be speculated that the difference between this previous study and our ~~study~~finding just reflects differences in the level of care provided in a referral centre like ours, and a rural centre where care can be very basic. The similarities in the baseline profile of participants across the two studies are in support of this hypothesis. For instance, in both studies over 85% of participants were started on ~~antiretroviral therapy~~ART while at the WHO stage III or IV of the disease severity, while pre-ARV CD4 count was lower than 50/mm^3 in over a quarter of participants at baseline. However, the one-year survival rate in our study is within the range of those reported in previous studies. In recent meta-analysis of those studies, the pooled estimated one-year probability of death from studies conducted in Africa was 17% (95% confidence interval: 11-24~~%), [6, 15]~~ %).[6,15]

Predictors of mortality identified in our study were essentially those described in existing reports~~, .[6, 15]~~[6,15] The adverse profile of modifiable risk factors clearly ~~suggest~~suggests that patients with HIV in our centre are started on ART at an advanced stage of the disease. This likely reflects the fact that in this setting, with the exception of screening in particular circumstances such as during pregnancy or pre-surgical ~~intervention, people with HIV infection~~interventions, PLHIV mostly get screened only when they seek medical care with clinical symptoms. This is a common attitude across Africa, ~~which~~and may explain the higher early mortality rate on ART in Africa, compared with other parts of the world~~, [6]~~.[6] In addition to the advanced clinical stage of the disease on the WHO scale at presentation, body weight, CD4 count and haemoglobin levels were low at baseline, and all significantly associated with high risk of mortality during follow-up as previously reported. [5-8].[5,8] It is of note that at the time this study was conducted, most patients were started on ART at CD4 count below 200/mm^3. Recent WHO recommendations favour ART initiation at CD4 count below 350/mm^3. Their uptake may potentially reduce early mortality rate, as a result of many patients starting treatment at favourable CD4 levels. The prevalence of active tuberculosis in our study was possibly inflated by the nature of the study setting as a referral centre for tuberculosis treatment, where most patients with both HIV and tuberculosis are more likely to be referred for care. The resulting subsample of participants with both conditions has possibly increased our statistical power for uncovering baseline active tuberculosis as a risk factor for fatal outcomesmortality among people with HIVPLHIV started on antiretroviral therapy. Such an association has been inconsistently reported in previous studies. [6, 10, 16].[6,10,16]

Free access to ART was introduced in Cameroon in May 2007.[17] We have recently reported rates of non-adherence to ART to be as high as 34% among patients with HIV receiving chronic care at the YJH in the era of free access to ART.[12] In the absence of any assessment of the adherence to ART in the current study, it is difficult to speculate on a contribution, if any, of non-adherence to ART to the observed high mortality in our study. However, such an effect is likely marginal in this setting where mortality mostly occurs early when patients have not been exposed to ART enough to derive therapeutic benefits. Furthermore, existing instruments for measuring adherence to ART are likely unsuitable for investigating premature mortality risk. The main non-modifiable risk factor of mortality in our study was male sex. This was not fully explained by sex differences in the level of other risk factors. Indeed, with the exception of baseline CD4 count which was lower in men, other factors were equally distributed among men or women or rather showed more favourable levels in men. Other studies have shown that adherence to prescribed ART was better in women than in men, [17][18] which can explain differing rates of fatal outcomesmortality between men and women started on ART.

Our study has some limitations, including the missing data, which are expected for a study conducted based on data collected from patients files, and when dealing with large numbers of participants. Drop-out through losses to follow-up potentially includeincluded deceased patients, and may be in high proportion based on some studies. [18].[19] Therefore, the reported mortality rate in our study is likely underestimated. But such a bias is unlikely to affect the associations of major risk factors with the mortality outcome as shown elsewhere. [10].[10] In the absence of any evaluation of the adherence to ART, particularly among early mortality survivors, we were unable to investigate a potential effect of non-adherence to ART on mortality risk in the current study. Our study also has major strengths including the large sample size, which increased our statistical power to reliably characterise the predictors of mortality. The deathmortality rate following ART initiation as found in our study and previousother published studies is not constant over time. It is very high

Formatted: No underline, Font color: Dark in the early months of starting the treatment, and subsequently drops and stabilises at a much lower rate. Many previous studies have been based on statistical methods that assume constant ~~death~~mortality rates over time such as the person-year methods, and have likely generated less reliable estimates of the association of predictors with mortality risk. We have attempted to address this limitation by applying the accelerated failure time models in our study. Unlike Cox models for instance, regression parameters estimates from accelerated failure time models are robust to the omitted covariates, and are unaffected by the choice of probability distribution.

In conclusion, mortality rate among patients with HIV-1 infection started on antiretroviral therapy in this setting ~~remain~~remains unacceptably high. Deaths occur mostly within the first year of starting treatment and essentially among patients with clinical and biological profiles compatible with an advanced stage of the disease at the time when antiretroviral treatment is started. Strategies for early detection of patient with HIV ~~and~~at the clinically asymptomatic stages followed by early initiation of antiretroviral therapy ~~needs~~, need to be developed and tested in this setting. Recent ~~Cameroonian~~updates of the country's guidelines ~~of~~for HIV treatment ~~allowing the~~ , recommending prescription of antiretroviral therapy ~~to patients with~~ at CD4 count lower than 350/mm^3 ~~would probably reduce the~~have a potential for significantly reducing premature mortality ~~rate~~among people with HIV in this setting.

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Competing interests: None for all authors.

Ethics approval: Ethics approval was ~~provided by~~obtained from the Institutional Review Board of the Yaounde Jamot Hospital.

Contributors: VPM, collected data, co-analysed the data and drafted the manuscript. EWPY conceived the study, supervised data collection, co-analysed the data and drafted the manuscript. APK contributed to study design, data analysis, drafting and critical revision of the manuscript. CK supervised data collection and critically revised the manuscript. All authors approved the final version of the manuscript.

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Table 1 Demographic, clinical and biological profile of HIV patients started on antiretroviral therapy at the Yaounde Jamot Hospital in 2007 and 2008

Characteristics*	Overall	Men	Women	p-value
n	1444	617	827	
Median age, years (25th-75th percentile)	38 (31-45)	40 (34-47)	35 (30-43)	<0.0001
Residence, n (%)				0.98
Urban	1236 (85.6)	528 (85.6)	708 (85.6)	
Rural	208 (14.4)	89 (14.4)	119 (14.4)	
Tuberculosis, n (%)	428 (29.6)	214 (34.7)	214 (27.9)	0.0003
Weight, Kg				<0.0001
< 50, n (%)	308/1322 (23.3)	69/570 (12.1)	239/752 (31.8)	
50-60, n (%)	535/1322 (40.5)	204/570 (35.8)	331/752 (44.0)	
>60, n (%)	479/1322 (36.2)	297/570 (52.1)	182/752 (24.2)	
Median (25th-75th percentile)	57 (50 - 65)	61 (54-68)	54 (47.5-60)	<0.0001
WHO stage, n (%)				0.82
I and II	186/1295 (14.4)	78/553 (14.1)	108/742 (14.6)	
III and IV	1109/1295 (85.6)	475/553 (85.9)	634/742 (85.4)	
Platelets, X1000/mm³	244 (180– 320)	229 (173-309)	259 (190-330)	0.0005
Total lymphocytes, X10/mm³	130 (90–190)	130 (90-201)	130 (90-190)	0.88
CD4, /mm³				0.21
< 50, n (%)	468 (32.4)	216 (30.5)	256 (30.5)	
50-99, n (%)	257 (17.8)	111 (18.0)	142 (17.6)	
100-200, n (%)	562 (38.9)	231 (37.4)	331 (40.0)	
>200, n (%)	157 (10.9)	59 (9.6)	98 (11.8)	
Median (25th-75th percentile)	99 (36.2-161)	89 (33-155)	105 (39-166)	0.~~01~~802
Haemoglobin, g/dl,				<0.0001
< 8, n (%)	235/1388 (16.9)	67/594 (11.3)	168/794 (21.2)	
8-10, n (%)	506/1388 (36.5)	178/594 (30.0)	328/794 (41.3)	
>10, n (%)	647/1388 (46.6)	349 (58.7)	298 (37.5)	
Median, (25th-75th percentile)	9.9 (8.5-11.2)	10.5 (9-12)	9.5 (8.1-10.7)	<0.0001

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; WHO, World Health Organisation

* For all characteristics with missing values, estimates are based of the subset of participants with valid data for each relevant characteristic, and new denominators always provided.

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Table 2 Determinants of all-cause mortality among HIV-positive patients started on antiretroviral therapy (n = 1444)

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Variable	Age and sex adjusted		Multivariable adjusted	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Age, per year	1.01 (0.98-1.03)	0.56	1.01 (0.99-1.03)	0.37
Male sex	1.44 (0.94-2.11)	0.10	2.15 (1.34-3.45)	0.002
Rural residency	1.14 (0.62-2.09)	0.68	-	
Active tuberculosis	1.59 (0.97-2.61)	0.07	2.35 (1.40-3.92)	0.002
WHO stage III-IV	4.57 (1.68-12.47)	0.004	3.63 (1.29-10.24)	0.02
Weight, per kg lower	1.04 (1.02-1.06)	0.0002	1.03 (1.01-1.05)	0.01
Platelet count, per 1000 lower	1.01 (0.99-1.03)	0.53	-	
CD4 count, per 10/mm3 lower	1.06 (1.02-1.09)	0.003	1.04 (1.01-1.07)	0.02
Haemoglobin, per g/dl lower	1.14 (1.03-1.26)	0.02	1.12 (1.00-1.26)	0.05
AZT based regimens	0.91 (0.51-1.62)	0.76	-	

AZT, zidovudine; CI, confidence interval; WHO, World Health Organisation

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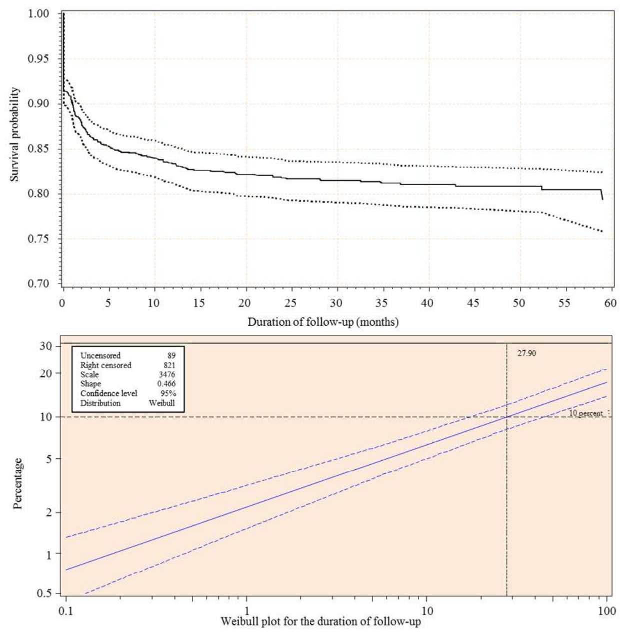

Figure 1: Survival probability from Kaplan-Meir estimator (upper panel) and Weibull plot showing the cumulative distribution function for mortality during follow-up of patients with HIV infection who started antiretroviral treatment at the Yaounde Jamot Hospital in 2007 and 2008
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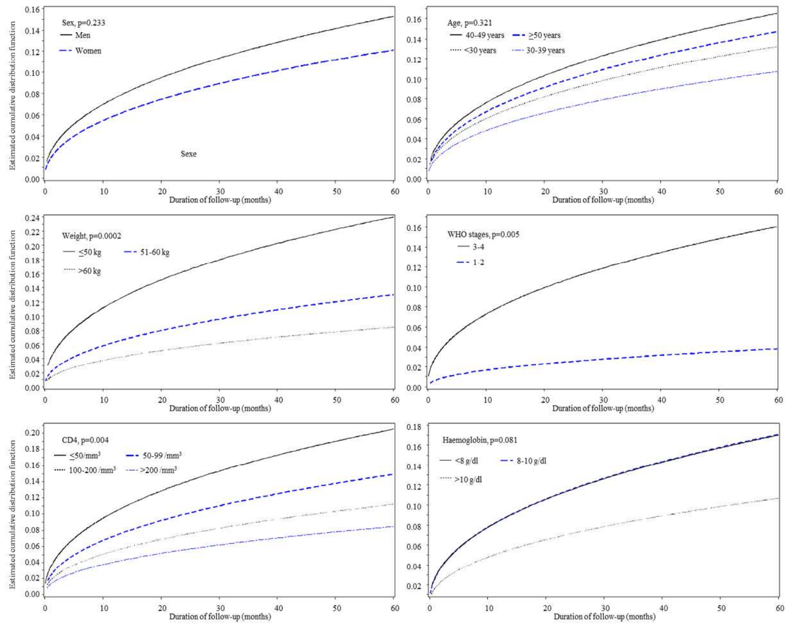

Figure 2: Estimated cumulative distribution function for all-cause mortality by major subgroups among patients with HIV infection who started antiretroviral treatment at the Yaounde Jamot Hospital in 2007 and 2008
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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	/
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	/
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	/
		Case-control study—For matched studies, give matching criteria and the number of controls per case	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5,6*
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	4,5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6,7
		(b) Give reasons for non-participation at each stage	/
		(c) Consider use of a flow diagram	/
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7
		(b) Indicate number of participants with missing data for each variable of interest	13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	/
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	/
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	/
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	/
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9,10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.