PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Mortality and its determinants among patients infected with HIV-1 on antiretroviral therapy in a referral centre in Yaounde, Cameroon: a retrospective cohort study
AUTHORS	Poka-Mayap, Virginie; Pefura-Yone, Eric Walter; Kengne, Andre; Kuaban, Christopher

VERSION 1 - REVIEW

REVIEWER	Dr SA Olowookere Department of Community Health, Obafemi Awolowo University, Ile-Ife, Nigeria
REVIEW RETURNED	15-May-2013

GENERAL COMMENTS	Good article but need some clarifications: Do the records include height of the patients as body mass index could have been reported. How many participants had missing data? It is a clinical review of deaths in the first year? Any postmortem for any death? More information needed on the catchment area of the study site

REVIEWER	Lawrence Mbuagbaw Centre for Development of Best Practices in Health, Yaounde Camerooon. McMaster University, Ontario, Canada. I declare no competing interests.
REVIEW RETURNED	15-May-2013

THE STUDY	Some terms are not used appropriately. For example fatal outcomes should be replaced with mortality. The name of the study site should also be used consistently. English editing is required. The robust methods described under strengths can be highlighted more. The STROBE checklist is used appropriately, but more detail with regards to the variables and statistical methods is required.
RESULTS & CONCLUSIONS	The discussion can be enriched by providing more detail on the context of HIV treatment in Cameroon, notably the date when treatment became free, current levels of attrition and adherence. Implementation of recent WHO guidelines to start treatment at higher CD4 counts can also be discussed.
GENERAL COMMENTS	Additional comments: 1. Extensive English grammar editing is required. 2. Refer to Jamot hospital consistently 3. Report p to 3 decimal places or ($p<0.001$) 4. Some analyses in results not mentioned in methods

	5. Discuss adherence to medication as and important yet unmeasured confounder. 6. Where there any stock-outs? 7. Include the sample sizes for the models in table 2. 8. Quantify the missing data in table 1 and in the result section 9. Figure 2 is not legible 10. Discuss attrition bias and information bias in the context of this study. Who was more likely to have missing data and how would this have affected your results. How did you deal with inaccuracies, inconsistencies and illegible patient records. 11. A sensitivity analysis with regards to missing data would be helpful 12. Use current UNAIDS standards to refer to people with HIV (person before disease) 13. Also note, if the data were not collected for the purpose of follow-up and subsequent analysis, this is not really a retrospective cohort study, but rather a cross-sectional analysis of previously collected data. 14. See attachment for additional comments.

VERSION 1 – AUTHOR RESPONSE

From the Reviewer: Dr SA Olowookere
Department of Community Health,
Obafemi Awolowo University,
Ile-Ife, Nigeria

Do the records include height of the patients as body mass index could have been reported?
Our answer: Thank you for raising this point. It would have been important indeed to include data on body mass index; however data on height were missing for about 95% of our participants, therefore precluding reliable estimation of BMI in inclusion in the manuscript.

How many participants had missing data?
Our answer: Thank you for raising this point, which we have addressed by inserting a new subheading in the results section entitled ‘data available’. It reads:
“In 2007 and 2008, a total of 1444 PLHIV [including 827 women (57.3%)] were started on ART 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. 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/mm3, 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/mm3, p=0.035), and a significantly lower haemoglobin level (9.9 vs. 10.4 g/dl, p<0.001).”

It is a clinical review of deaths in the first year? Any postmortem for any death?
Our answer: No post-mortem or audit was conducted, hence our inability to provide details on the causes of death.
More information needed on the catchment area of the study site
Our answer: Please, given that we have extensively published from this centre with detailed description of the setting over the last few years, we felt that, to avoid repetition across many paper, it

was reasonable to direct the reader to previous publications where the details requested by the reviewer are provided in details.

From the Reviewer: Lawrence Mbuagbaw
Centre for Development of Best Practices in Health, Yaounde Camerooon.
McMaster University, Ontario, Canada.

Some terms are not used appropriately. For example fatal outcomes should be replaced with mortality.
Our answer: This has been fixed.

The name of the study site should also be used consistently
Our answer: This has been fixed.

English editing is required.
Our answer: We have fixed those grammatical and spelling errors we have identified.

The robust methods described under strengths can be highlighted more
Our answer: Thank for the remark. We have expanded the section which now reads:
“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.”

The STROBE checklist is used appropriately, but more detail with regards to the variables and statistical methods is required
Our answer: We have addressed this by expanding the statistical analysis section to include the following:
“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/mm3), 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 models, 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.”

The discussion can be enriched by providing more detail on the context of HIV treatment in Cameroon, notably the date when treatment became free, current levels of attrition and adherence.
Our answer: We have addressed this by adding the sentences below to the second last paragraph on page 9.
“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 speculation 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."

Implementation of recent WHO guidelines to start treatment at higher CD4 counts can also be discussed.
Our answer: Thank you for raising this important point which we now address by adding the sentences below to the discussion; last paragraph on page 8, continuing on page 9.
"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/mm3. Recent WHO recommendations favour ART initiation at CD4 count below 350/mm3. Their uptake may potentially reduce early mortality rate, as a result of many patients starting treatment at favourable CD4 levels."

Some analyses in results not mentioned in methods
Our answer: This has been fixed. Now in the statistical analysis we can read:
"The chi square test, Student's t-test and their non-parametric equivalents were used to compare baseline characteristics"

Discuss adherence to medication as an important yet unmeasured confounder.
Our answer: Thank you for raising this important point which we now address by adding the sentences below to the limitation section of the discussion.
"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."

Where there any stock-outs?
Our answer: Thank you for raising this important point. No major and long-lasting stock-outs occur during the study period.

Include the sample sizes for the models in table 2.
Our answer: This has been fixed

Quantify the missing data in table 1 and in the result section
Our answer: Thank you for raising this point which has now been addressed by providing a new section in the results "data available" to describe the status of our database for missing value. The new section reads:
"In 2007 and 2008, a total of 1444 PLHIV [including 827 women (57.3%)] were started on ART 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. 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/mm3, 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/mm3, p=0.035), and a significantly lower haemoglobin level (9.9 vs. 10.4 g/dl, p<0.001)."

Figure 2 is not legible
Our answer: This has been modified.

Discuss attrition bias and information bias in the context of this study. Who was more likely to have missing data and how would this have affected your results. How did you deal with inaccuracies, inconsistencies and illegible patient records.
Our answer: Please see our answer above to your first query on missing data where we provide comparison between participants with missing data and those with valid data. It is of note that we had already mentioned missing data as a limitation of our study on page 10, second paragraph. Illegible patient records if any, would have been treated as missing data at the data entry stage. In the absence of comparative data source, we are unable to reliably speculate of the issues of accuracy on consistency of the data. However, both HIV and tuberculosis records in the study centre are completed under the supervision of specialist physicians, and we do feel that data from those records would at minimum reflect the real life figures in this setting.
A sensitivity analysis with regards to missing data would be helpful
Our answer: Please, again, refer to our point above on data available. By restricting regression analysis to only participants with valid data on the predictors of interest, we think this will override the need for any further sensitivity analysis.

Use current UNAIDS standards to refer to people with HIV (person before disease)
Our answer: This has been fixed

Also note, if the data were not collected for the purpose of follow-up and subsequent analysis, this is not really a retrospective cohort study, but rather a cross-sectional analysis of previously collected data.
Our answer: Thank you for raising this point. Although, there is too much confusion in the literature about what is a retrospective cohort study, we are however still of the opinion that we have conducted a cohort study based on patients files (baseline evaluation). Indeed all patients were seen at a time-point for baseline evaluation (start of ART), when data were collected on predictors with no prior knowledge of their status for the outcome (mortality). Their status for mortality was only acquired during follow-up (passage of time), allowing for a clear establishment of the sequence of happening between levels of predictors and outcome risk, which is the essence of prospective cohort study. We do however admit that, since the study was based on data collected for other purpose, the quality and completeness of data collection could be affected.

VERSION 2 – REVIEW

REVIEWER	Lawrence Mbuagbaw Centre for Development of Best Practices in Health, Yaounde, Cameroon. Department of Clinical Epidemiology and Biostatistics, McMaster University, Canada.
REVIEW RETURNED	31-May-2013

THE STUDY	The English in this manuscript can be edited to enhance clarity and flow.
GENERAL COMMENTS	The authors have done a good job in responding to the previous comments; however, the manuscript requires some some more English language editing and consistency in the use of terms: e.g death rate vs mortality. I also believe it is the norm that p values be reported to 3 decimal places. In some places it is 2 in others 4. The heading "Care of people living with HIV" is misleading.

	You describe eligibility for care without describing eligibility for the current study. The second paragraph under data collection mentions "eligible patients" from whom data was collected without saying who they are.

VERSION 2 – AUTHOR RESPONSE

The manuscript requires some some more English language editing and consistency in the use of terms: e.g death rate vs mortality.
Our answer: We have now consistently used ‘mortality rate’ everywhere and fixed those typos and grammatical errors we could identify

I also believe it is the norm that p values be reported to 3 decimal places. In some places it is 2 in others 4.
Our answer: We thank the reviewer for making this point. We are however rather of the opinion that precision in the reporting of p-values varies across journals, type of studies and at times may rely on the authors’ preference. It is common in genetic studies to report p-values with very high level of precision (10 decimal places and far more) while for other type of studies, this level of precision may not be required. We checked guidelines from both the BMJ Open and the International Committee of Medical Journals’ editors (http://www.icmje.org/urm_full.pdf) and did not find specific recommendations on the number of decimal places in the reporting of p-values. We however found that other papers recently published in the journal reported p-values with a level of precision similar to that applied in our study. Our approach is very consistent in the sense that for all non-significant p-values we report 2 decimal points, and for significant p-values, we report decimal places up to the first non-null number, or a maximum of four decimal places.

The heading "Care of people living with HIV" is misleading.
Our answer: This sub-heading has now been removed and the preceding subheading expanded to read: “Study setting and participants”

You describe eligibility for care without describing eligibility for the current study. The second paragraph under data collection mentions "eligible patients" from whom data was collected without saying who they are.
Our answer: Thank you for raising this point which in major ways was already reflected in the manuscript. We have highlighted this further by adding the sentence below to the method section, sub-heading ‘Study setting and participants”. It reads:
“Patients received at ATC between January 2007 and December 2008, aged 18 years and above, and started on ART were included in the study.”