**Author's response to reviews**

**Title:** HIV testing, HIV status and outcomes of treatment for tuberculosis in a major diagnosis and treatment centre in Yaounde, Cameroon: a retrospective cohort study

**Authors:**

Eric Walter Pefura Yone ([pefura2002@yahoo.fr](mailto:pefura2002@yahoo.fr))
Christopher Kuaban ([ckuaban@yahoo.com](mailto:ckuaban@yahoo.com))
André Pascal Kengne ([apkengne@yahoo.com](mailto:apkengne@yahoo.com))

**Version:** 3  **Date:** 18 April 2012

**Author's response to reviews:** see over
Cover letter
Submission of a revised manuscript
Manuscript ID: 1295103466641440 entitled "HIV testing, HIV status and outcomes of treatment for tuberculosis in a major diagnosis and treatment centre in Yaoundé, Cameroon: a retrospective cohort study"

By Eric Walter Pefura Yone et al
Dear Editor,
We are grateful to the reviewers for their time and comments on our manuscript (referenced above). We have addressed their comments and queries and would like to submit an updated version of our manuscript for consideration for publication in the Journal. Changes in the main document have been inserted with the use of red color. In addition we are providing below a point-by-point response to each query from the reviewers.
We look forward to the outcome of our submission.

Reviewer 1: Fidele Kanyimbu Mukinda
1. Major Compulsory Revisions
   o Methods
   # Definition and classification:
   “The following international definitions are applied: [2, 3, 5] 1) smear-positive pulmonary tuberculosis (PTB+) - acid-fast bacillary (AFB) found in at least two sputum specimens”

   R/ The current WHO recommendation is to have at least one sputum
   Would you like please to update your evidence.
   Our answer: we are well aware of the new WHO recommendations which however are being implemented in Cameroon only as from this year. However, at the time data was collected for the currently study, the diagnostic criteria we have referred to where those applied in the study setting. There is just no way to retrospectively modify this.

   # Data collection
   “This was a retrospective cohort study”
R/ The key features of a retrospective COHORT STUDY are not reported in your manuscript; for me this is rather a cross-sectional study. Please refer to the STROBE guidelines for reporting on observational study.

Our answer: The reviewer would agree with us that in the current study, participants were assessed at baseline (diagnosis of tuberculosis and treatment initiation). Thereafter, they were followed up over time to monitor the outcomes of treatment. Following such a design, we are still of the opinion that our study met the criteria of a cohort study. The label ‘retrospective’ relate to the fact that the study was based on existing registers and patients files. We know that this is debatable as some would still call it ‘prospective study’ and not ‘retrospective’.

# Statistical methods

“multinomial Logistic regression models were used to investigate the effects of HIV testing...”

R/ Your manuscript did not report the criteria to be found where Logistic regression is applied. There are guidelines for reporting Logistic regression in which the following criteria should/must be reported (see references below):

# Analytic criteria: Sufficient events per variable, Conformity with linear gradient for, Tests for interactions, Collinearity, Validation, Statistical significance, Goodness-of-fit measures.

# Documentation criteria: Selection of predictor variables, Coding of variables, Fitting procedure

See the following references: Ottenbacher KJ, Ottenbacher HR, Tooth L, Ostir GV. A review of two journals found that articles using multivariable logistic regression frequently did not report commonly recommended assumptions. J Clin Epidemiol 2004 Nov;57(11):1147-1152.


Our answer: We thank the reviewer for this comment and the suggested references. We however feel that the suggested criteria apply mostly to circumstances where multivariable models are constructed and there is an interest in the performance of the overall model in the derivation sample. In the current study, we haven’t developed a prediction model, that is attempting to identify the best set of determinants that will explain the occurrence of the outcome of interest in the study population. We have rather assessed the independent
association of pre-specified variables with an outcome of interest, which is a step prior to model development as we have extensively described elsewhere recently (Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, Grobbee DE. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012 Mar 7. [Epub ahead of print]). For such a purpose, the approach usually consist of demonstrating the association in univariable (or minimally adjusted) model, then after adjustment for possible extraneous determinants, which is what we have done. Thereafter, measures of the association (odd ratio or beta coefficients) are reported with the indication of whether they are significant or not.

The issue of outcome per variable while extensively described in the literature for simple multivariable logistic regressions, it hasn’t been the case in multinomial Logistic regression where the outcome of interest is multilevel. If we use a conservative approach of investigating the power of the study based on the lowest (number) stratum of our outcome variable, which is mortality in this case, we had 86 such outcomes. Having tested up to 6 predictors would give us about 14 outcomes per variables which is largely above the 8-10 suggested in the literature. All our variables tested were categorical variables and therefore there is no issue about linearity assumption. We didn’t pre-specified interactions to be tested since there was no plausible assumption and accordingly we did not test for interaction. For the statistical significance, we have each time reported odd ratios with their 95% confidence intervals which give a direct interpretation of the significance. Validation, goodness of fit, model fitting, variable selection all relate to prediction model development, which is not the case in our study.

# References

Your referencing style is not consistent; which referencing style did you use, Vancouver, Harvard or any other. Please check accordingly especially where there are more than six authors.

Our answer: We have applied the referencing style recommended by the Journal, which with regard to the number of authors states the following for instance: « Citations in the référence list should include all named authors, up to the first 30 before adding ’et al.’. »

# Finally and most important: I just found your recent publication in BMJ Open (see reference below) which is like a copy & past compared to this manuscript (Methods, Table 1). Apart from use of abbreviations instead of full word, it seems to me that this is a duplication of the same information/paper with “manipulation of data” i.e.
the same method, same design, same study setting, same study period, same authors “could” have led to somewhat the same sample size. In addition you are even not able to acknowledge your own published paper anywhere in your current manuscript.

e.g.:
Methods: same sub-headings, same sentences and wording
Table 1: differ only by the total number (sample size) and the categorisation of age.
Unless a sound explanation in your manuscript, I think this is scientifically not acceptable.


Our answer: We have used the same dataset (patient population) to examine two completely different scientific questions. It is therefore just appropriate that method sections relating to study setting, patient-population, data collection and processing are consistent across the two papers. We cannot change standard definitions or procedure. It is however of note that the statistical analysis section is completely different across the two papers, since completely different procedures were used. It is also just appropriate that table 1 on the baseline profile is similar across the two manuscripts, and this by no way constitutes a violation of the ethics of scientific publication. There is no restriction regarding the number of papers that can be published from the same population/dataset as far as these address different research questions. We would like to reiterate that the question examined in the current paper is well different from that examined in our BMJ paper. The current paper is on the impact of HIV testing and HIV status of the outcome of care for tuberculosis, while the BMJ paper is on anti-tuberculosis treatment discontinuation and determinants. Treatment discontinuation is just one of the possible outcomes of tuberculosis care. There is therefore no duplication, nor data slicing. We have an extensive experience working on large collaborative studies including the ADVANCE trial, the Asia Pacific Cohort Studies Collaboration, the Health surveys of England where overlapping methods sections are repeated across different manuscripts without constituting a plagiarism. When appropriate previously detailed description of the methods section can be referred to in subsequent manuscripts to shorten the method section. We could for instance do it for this paper, but at the same time, we have the feeling that it would be appropriate for the reader of this paper to have a detailed description as well. However, if the reviewer/Journal feels that we should summarise the method and refer to our previous paper for more details, then we are happy to do so. Finally, we really wish that the
reviewer could compare the two manuscripts again to revise his opinion on our work. The suggestion that the current paper is nothing else than ‘data manipulation’ can be very hurting with consideration the amount of efforts dedicated to the two project and the clear absence of overlapping both of the topics covered and main results of each project.

2. Minor Essential Revisions

- **o Title page:**
  - # South African Medical research Council: change capital letter on Research
  - # Word count: Main test: change test with text
  - # Throughout the text: please be consistent with abbreviations, the paper is not easy to read. E.g.: ATT, DTC, CDT
  
  **Our answer:** fixed

- **o List of abbreviations:**
  - # AFB: acid-fast bacillary
  - R/ Please change bacillary with bacilli
  
  **Our answer:** fixed

- **o Table 1: ETB, extra-pulmonary tuberculosis**
  - R/ Please replace ETB with EPTB for consistency (ref: your list of abbreviations)
  
  **Our answer:** fixed

- **o Table 3: Bottom (legend)**
  - R/ Delete the second “LR, likelihood ratio”
  
  **Our answer:** fixed

- **o Figure 1:** the title and legend of a figure should be at the bottom of the figure; please change for consistency.
  
  **Our answer:** Please, we have just followed the recommendations of the Journal as outlined in the instructions to authors.

3. Discretionary Revisions

- **o Figure:** Will this figure be printed in color? otherwise please change colors for black/grey printing.
  
  **Our answer:** This is probably not a big issue since the Journal publishes only online.
Reviewer 2: Dr Michele D. Zeier

General comments
The research question is strong and valid. The case definition and management protocols are well-described and clear. The tables are easy to understand and well-laid-out. Reporting and interpretation of data is acceptable. The discussion in general presents a good interpretation of the results. There is adequate mention of limiting factors and the strengths of the study believable. The references seem sound and adequate. Writing is understandable with some minor errors, which are mentioned under minor revisions.
Regarding the data, an explanation and/or correction is referred to under major compulsory revisions.
Two discretionary revisions are suggested referring to the results section in the abstract.

Our answer: we thank you for the appreciation

Discretionary revisions (which are recommendations for improvement but which the author can choose to ignore)

- The result section of the abstract lists the logistic regression models in percentages. Why was this done? Suggest using odds ratio and 95% confidence intervals, as in the manuscript result section/tables.
Our answer: We have changed the presentation in the abstract to align the tables as suggested. The section on odds ration now reads:

\[Using\ \text{cure/completion\ as\ reference,\ not\ testing\ for\ HIV\ was\ associated\ with\ odds\ ratio\ of}\ 2.30\ (95\%\ \text{confidence\ interval:}\ 1.65-3.21),\ 2.26\ (1.29-3.97)\ \text{and}\ 2.69\ (1.62-4.46)\ \text{for\ the\ risk\ of\ failure/default,\ death\ and\ transfer\ respectively.\ The\ equivalents\ for\ a\ positive\ test\ among\ those\ tested\ (1419\ participants)\ were\ 1.19\ (0.88-1.59),\ 6.35\ (3.53-11.45)\ \text{and}\ 1.14\ (0.69-1.86).}\]

- Discussion: Do the authors have any suggestion as to measures that may be implemented to improve HIV testing in patients with tuberculosis or suspected tuberculosis
**Our answer:** While very important, we feel that we cannot make such recommendation with no prior understanding of those factors that determine ‘voluntary testing for HIV’ in this setting, which are among research questions our team will be investigating in the future.

**Minor essential revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)**

- The table contain alternative ` `, and `,` for decimals.
  
  **Our answer:** This has been fixed

- Consider defining confidence intervals as CI and then using the abbreviation.
  
  **Our answer:** This has been fixed

- **Title page:** Author Yone¹,²,& should it be Yone¹,²
  
  **Our answer:** It is correct as written. The symbol ‘&’ as explained further down is to indicate the corresponding author.

- **Word count:** Main test should be Main text
  
  **Our answer:** Yes, it should be ‘Main Text’, we have been fixed

- **Background:** please correct language “prevalence of HIV infection in African adult’s patients”
  
  **Our answer:** we have revised the statement. Its now reads:
  
  “prevalence of HIV infection among African adults with tuberculosis”

- **Methods:** Study setting: Please improve “since five years”
  
  **Our answer:** The whole sentence has been revised and now reads:
  
  “From year 2006 to 2011, about 1600 to 1800 patients with tuberculosis were diagnosed and treated by the CDT on an annual basis”

- **Detection and management of HIV infection:** improve “CD4 lymphocytes count”
  
  **Our answer:** It now reads ‘CD4 count’
• Monitoring and management of HIV infection: improve “patients with at least two positive smears at the 5th”

Our answer: It now reads “patient with positive smear at the 5th month or later during treatment”

• HIV testing and status: please correct “included more women (…), a more patients”

Our answer: This has been fixed

• Discussion improve “we’ve”

Our answer: This has been fixed

• Discussion: Consider starting new paragraph at “Our study also has”

Our answer: This has been fixed

• Conclusion: “coffered”. Was the use of this word intentional? Please revise the sentence.

Our answer: It should have been ‘confer’, we have fixed it

• Figure legends: “transfer” should be “transferred”; consider “defaulted” instead of “default”

Our answer: These have been fixed

Major compulsory revisions (which the author must respond to before a decision on publication can be reached)

In table 1, under Urban Residence:
When adding 968+5+7+278+67, I do not get 1390. Please explain or correct

Our answer: The reviewer is right. Death should have been 72 and not 7. We have now fixed it.

Conclusions
The significance of this study is high as it demonstrate the similar poor outcome of tuberculosis in patients that are HIV infected and those of unknown HIV status. I therefore recommend publication.