ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence, time and determinants of tuberculosis treatment default in Yaounde, Cameroon: a retrospective hospital register-based cohort study
AUTHORS	Eric Walter Pefura Yone, André Pascal Kengne, Christopher Kuaban

VERSION 1 - REVIEW

REVIEWER	Barbara Castelnuovo Director Longitudinal Cohorts Unit Infectious Diseases Institute Kampala Uganda I declare no conflict of interest
REVIEW RETURNED	22/08/2011

THE STUDY	Review Title: Incidence, time and determinants of tuberculosis treatment default in Yaounde, Cameroon: a retrospective hospital register-based cohort study In general avoid too many abbreviations such as CDT and ATT, they make the paper less readable. Authors: Pefura Yone, Eric (contact); Kengne, Andre; Kuaban, Christopher In this study Yone et al. conducted a retrospective analysis to identify risk factors for TB treatment default in Cameroon. This is an important study, as little is known about the reasons for this high rate of default in Sub Saharan Africa. Introduction No comments Methods Definition sections The authors should clarify the following: "Patients with past exposure to ATT are usually all smear-positive". The authors should support this with more information. "Usually smear positive". In their clinic? Data from other studies (reference?)? "Other cases of tuberculosis" : can the authors provide any example of "other"? Statistical methods The authors decided to explore the risk factor for defaulting using 2 different models In the first model they use logistic regression- primary analysis In a second model, since the time of treatment discontinuation,

death or transferred is known, they use Cox regression model – secondary analysis
I suggest the authors present the Cox model only as their main analysis as it is more representative of the patients retained and lost during TB treatment
The logistic model should be briefly presented as a secondary analysis, if not completely left out

Results
Please specify clearly the study period
Re-write the results according to the changes suggested in the methods
The authors should give a brief summary for Figure 2 and 3 explaining with their words what the figures represent. For example be explicit on the difference in probability of discontinuation according to the setting of intensive phase.

Tables
The results of univariate and multivariate analysis should be displayed as a single table

Discussion

The entire discussion needs more editing and rephrasing and the first paragraph needs to be rewritten
1. The authors should put their data (proportion of defaulters) in prospective with data from other countries. Is the program doing better or worse? They should also discuss the fact that the WHO definition for defaulters was used, while studies with a more strict definition show higher proportion of defaulters.
2. "Before the re organization of the fight against tuberculosis in Cameroon and roll out of the DOT strategy, ATT discontinuation was 10% higher among new patients with smear positive tuberculosis in the study center. It is not clear what the comparison is. If the authors have data before the introduction of DOT, they should clearly compare them with the 21.2 and 21,7 found in their study

"The effects of non consent for HIV screening on ATT discontinuation has not been confirmed by other studies" the authors should rephrase this. Other studies did not fail to confirm this, but they simply did not investigate this potential risk factor

"That no systematic effort was in place to trace patients who dropped out during the year of the study has probably introduced some biases in our ranking of patients according to the outcome of care. For instance, some patients who died in-between ATT drug collection visit would have been inappropriately classified as drop-out. However, the effects of misclassification if any would need to be very important to invalidate our findings.". What supports this conclusion? In fact other studies have shown that when there is no active tracking of patients there could be a lot of misclassification (see IAS 2011 abstract TUPE472 - Evaluation of the impact of TB-HIV integrated care in reducing the proportion of patients defaulting anti TB treatment in a large urban HIV clinic in Kampala, Uganda); this is also very common in HIV care (see Dalal JAIDS 2008 and Brinkhof, Plos One 2009)
The fact that the real outcome of the patients in this program is not verified is a major limitation of this study and these results should be taken with caution. For example, patients with unknown serostatus are often patients at high risk of HIV infection; maybe those patients

	don't come back to the clinic not because they discontinued treatment but because died of tuberculosis (more sever in HIV infected patients) or other opportunistic infections
	At the end of the discussion it is not clear if DOT has improved outcomes in patients on anti TB treatment
	Which other determinants of TB treatment discontinuation the authors think should be studied by future prospective studies?
	References Although they are relevant and up to date, I suggested above another couple of references

REVIEWER	Estifanos Biru Shargie Senior Technical Officer The Global Fund to Fight AIDS, Tuberculosis and Malaria
REVIEW RETURNED	01/09/2011

THE STUDY	Some of the figures presented in these sections need revision (see comments to authors).
GENERAL COMMENTS	General Comments This article addresses one of critical issues in TB control efforts in Cameroon—treatment interruption and associated factors. The paper adds to the knowledge of interplay between various factors at individual, family and community levels that affect successful treatment completion. Specific comments Introduction 1. The authors claim that most studies on anti-TB treatment interruption in Africa are inconsistent or too heterogeneous to provide reliable conclusions. Yet, it is not clear how this particular study could address those limitations and provide a more reliable conclusion that could better inform health service delivery and policy. Furthermore, the authors include two references on studies conducted in Cameroon on the same issue, but paradoxically argue that no relevant study has been conducted in Cameroon. If those studies represent the pre-DOTS era of TB treatment (as mentioned for one of them in the discussion section), it could be mentioned as such; but that does not imply the studies were not relevant. 2. The authors should describe how and what this study adds to the existing knowledge on factors determining treatment interruption. 3. Please ensure consistent use of terms. Keep interchangeable use of terms to the minimum to the extent possible. All of the following terms are used in just two paragraphs of the introduction, to mean the same thing: treatment discontinuation, interruption, non-adherence, defaulting. Also, see additional terms in results section page 8, 1st paragraph ("lost to follow-up") and discussion section para 1 ("drop-out"). 4. Please avoid non-standard abbreviations (e.g., ATT) in the text, unless they are absolutely necessary. Methods 5. Some of the statistical tests mentioned in the methods section (Mann-Whitney U test, Fisher's exact test) do not appear in the results section. Please focus on those analyses that formed the basis for the reported results. 6. It would greatly enhance the analysis if the authors could have access to and include the outcome data for transferred out patients.

	Otherwise, TB treatment outcome analysis should follow the standard approach, and treatment success and default rates should be calculated as a percentage out of the sum of all outcome categories (including transfer out, failure and death). The approach for the comparative (univariate and multivariate) analyses is sound however, as it limits the comparison between those successfully completed treatment and those defaulted from treatment.
	Results
7. Please check and ensure consistencies in figures provided in the text, table 1 and figure 1 (particularly for outcome categories).
8. The study would have benefited better from tracing and documenting outcome for those transferred out to other health facilities. In principle, the outcome of those transferred out to other facilities should be tracked and recorded or analysed as a category. To this effect, treatment success and default percentages should be presented as per the standard guidelines, as is presented in table 1 (also see comment 6 above).
9. Determination of treatment discontinuation: Make reference to Table 3 at the end of the paragraph.
Discussion
10. The literature review in both the introduction and discussion sections is rather shallow, and should be strengthened with more in-depth review and inclusion of some missed reference on recent studies that assessed treatment interruption in Africa (Kandel et al, 2008; Elbireer, et al 2011) . Some of previous studies attempted to trace patients and understand reasons why they defaulted; others looked at physical distance from treatment centre (not just urban vs rural dichotomy). Lack of such information should be discussed as one of the limitations of the current study.
11. Treatment success and default figures presented in this section should be corrected in line with the comments in the results section. |

VERSION 1 – AUTHOR RESPONSE

Reviewer: Barbara Castelnuovo

In general avoid too many abbreviations such as CDT and ATT, they make the paper less readable.

Our answer- we have fixed this

In this study Yone et al. conducted a retrospective analysis to identify risk factors for TB treatment default in Cameroon. This is an important study, as little is known about the reasons for this high rate of default in Sub Saharan Africa.

Introduction
No comments

Methods

Definition section

The authors should clarify the following:

"Patients with past exposure to ATT are usually all smear-positive". The authors should support this with more information. "Usually smear positive". In their clinic? Data from other studies (reference?)?

Our answer – Patient with past exposure to ATT are usually smear-positive (exceptionally smear negative or have extra-pulmonary tuberculosis), both in our cohort and elsewhere. We have now backed up our claim with reference 2.

"Other cases of tuberculosis" : can the authors provide any example of "other"?
Our answer – we have now provided an example on page 5, with reference to a patient relapsing for a second time and in whom microorganisms are sensitive to standard regimens. It reads:
"patient relapsing for a second time for tuberculosis, with involved mycobacterium being sensitive to antituberculosis, and treated for 6 months with standard regimens"

Statistical methods

The authors decided to explore the risk factor for defaulting using 2 different models
In the first model they use logistic regression- primary analysis
In a second model, since the time of treatment discontinuation, death or transferred is known, they use Cox regression model – secondary analysis
I suggest the authors present the Cox model only as their main analysis as it is more representative of the patients retained and lost during TB treatment
The logistic model should be briefly presented as a secondary analysis, if not completely left out

Our answer – we now present Cox regressions models as main analysis and have removed logistic regression models from the manuscript. As a result of doing this and to capture some information initially presented only with logistic regression analysis in the former Table 2, we have now updated the new Table 1 with those information.

Results
Please specify clearly the study period

Our answer – this has been fixed

Re-write the results according to the changes suggested in the methods

Our answer – the result section has been re-written as appropriate

The authors should give a brief summary for Figure 2 and 3 explaining with their words what the figures represent. For example be explicit on the difference in probability of discontinuation according to the setting of intensive phase.

Our answer – In addition to the figure legends, we have added the statements below to the narrative section of the results to further explain the data in figure 3. On page 10, it reads:
"At each time point during follow-up the probability of treatment discontinuation was always lower in patients hospitalized during intensive treatment phase than in those treated as outpatients during intensive phase. Similarly, discontinuation probability was always lower in patients with known status for HIV infection than in those with unknown status."

Tables
The results of univariate and multivariate analysis should be displayed as a single table

Our answer – We have fixed it (see new table 2)

Discussion

The entire discussion needs more editing and rephrasing and the first paragraph needs to be rewritten

1. The authors should put their data (proportion of defaulters) in prospective with data from other countries. Is the program doing better or worse? They should also discuss the fact that the WHO definition for defaulters was used, while studies with a more strict definition show higher proportion of defaulters.
Our answer – We have accounted for this suggestion by 1) highlighting the discontinuation rate in our summary paragraph , 2) comparing our findings with those from other African countries in a second paragraph and 3) by interpreting them in the context of the country in a 3rd paragraph. All together the 3 paragraphs read:

"In this study, we have assessed the incidence of antituberculosis treatment discontinuation and predictors of treatment discontinuation in a large cohort of patients with tuberculosis treatment in a major referral centre in Cameroon. Treatment success rate was 68.4% and the cumulative incidence of treatment discontinuation was 20% overall and 19.4% among patients with smear-positive pulmonary tuberculosis. Discontinuation was most likely to occur in patients treated as outpatients and those with unknown status for HIV infection.
Treatment discontinuation in our study was based on the World Health Organisation's definition, which refers to a defaulter as a patient who's treatment has been discontinued for at least two consecutive months.[2] Compared with other few studies from Africa that have used similar definition, discontinuation rate in our cohort was similar to that reported by Shargie and co-workers in South Ethiopia, [11] lower that the rate found by Kaona and his colleagues in Zambia,[12] and higher than the rate by Tekle et al in Arsi in Ethiopia.[13] The above studies however differs from our study in a number of respects. The largest of those studies had 20% fewer patients than our cohort,[13] while the two others less than ¼ the number of participants in our sample. [11, 12]. Furthermore, the two studies in Ethiopia involved only rural participants, with one based only on patients with either smear-positive tuberculosis,[12], while the study in Zambia was based on a cross-sectional sample of urban dwellers.[13] In general, it has been recognised that using a stricter definition for treatment discontinuation results in much higher rates than when using the World Health Organisation's definition.[7]
Before the reorganisation of the fight against tuberculosis in Cameroon and roll out of the DOT strategy, antituberculosis treatment discontinuation rate was 31.7% among adults with PTB+ in the Yaounde Jamot Hospital.[14] Our study would tend to suggest that implementation of the DOT strategy has positively impacted on antituberculosis treatment discontinuation, with an 12% drop, although much efforts are still needed to bring the rate below 10%. The currently observed discontinuation rates are twice higher than the expected <10%, a requirement if the 85% antituberculosis treatment success rates prescribed in the millennium development goals are to be achieved.[15] Treatment discontinuation is a major challenge to programmes against tuberculosis, in the sense that non-adherence to antituberculosis treatment is associated with reoccurrence of the disease, preservation of reservoirs for micro-organism dissemination, emergence of drug resistant species of mycobacterium and increased tuberculosis related deaths.[16]"

2. "Before the re organization of the fight against tuberculosis in Cameroon and roll out of the DOT strategy, ATT discontinuation was 10% higher among new patients with smear positive tuberculosis in the study center. It is not clear what the comparison is. If the authors have data before the introduction of DOT, they should clearly compare them with the 21.2 and 21,7 found in their study
Our answer – we now provide those figures as described in the paragraph above
"The effects of non consent for HIV screening on ATT discontinuation has not been confirmed by other studies" the authors should rephrase this. Other studies did not fail to confirm this, but they

simply did not investigate this potential risk factor

Our answer – The relevant sentence now reads:
"The effects of non-consent for HIV screening on antituberculosis treatment discontinuation have not been investigated by other studies."

"That no systematic effort was in place to trace patients who dropped out during the year of the study has probably introduced some biases in our ranking of patients according to the outcome of care. For instance, some patients who died in-between ATT drug collection visit would have been inappropriately classified as drop-out. However, the effects of misclassification if any would need to be very important to invalidate our findings.". What supports this conclusion? In fact other studies have shown that when there is no active tracking of patients there could be a lot of misclassification (see IAS 2011 abstract TUPE472 - Evaluation of the impact of TB-HIV integrated care in reducing the proportion of patients defaulting anti TB treatment in a large urban HIV clinic in Kampala, Uganda); this is also very common in HIV care (see Dalal JAIDS 2008 and Brinkhof, Plos One 2009)

Our answer – We take the point of the reviewer and have now referred to studies he has suggested (our reference 24-26). Our statement however was specific to the findings from our study. In that regard, under the assumption that all defaulters were true defaulters and that all those transferred were also defaulters, we would end up with a worst case scenario of 26% rate for treatment discontinuation, which is still lower than the rates reported in the same setting previously (indicating improvement) and still within the range of rates reported from other African countries in recent years. Similarly, meeting the treatment success rate of 85% (currently 68.2%) means that at least 83% of those classified as defaulters, or 63% of those classified as defaulters or transferred did achieve a treatment success. Both figures are unrealistic. Although we recognized that there would have been some misclassifications, we are still confortable that these will not seriously impact on the conclusions of the study.

The fact that the real outcome of the patients in this program is not verified is a major limitation of this study and these results should be taken with caution. For example, patients with unknown serostatus are often patients at high risk of HIV infection; maybe those patients don't come back to the clinic not because they discontinued treatment but because died of tuberculosis (more sever in HIV infected patients) or other opportunistic infections

Our answer – We agree with the reviewer's analysis, but would also like to bring forward the fact that we haven't claimed any causal association between testing for HIV and outcomes of care for tuberculosis. That patients with unknown status for HIV who didn't report back could be mostly patients actually with HIV infection and who may have died of TB, HIV infection or other opportunistic infection is plausible. We feel however that this would still be the direct consequence of the missed opportunity of testing these patients as a by-product of diagnosing them and treating them for tuberculosis. Therefore, actions to limit such possible deaths (if true) would still involve new strategies to increase the uptake of HIV test among those diagnosed with tuberculosis. Therefore, our conclusions would still be valid. Finally, we really feel that this finding is more a hypothesis generating one and that all possible explanations should be explored.

At the end of the discussion it is not clear if DOT has improved outcomes in patients on anti TB treatment

Our answer – we have updated the conclusion paragraph to indicate that DOT has improved the outcomes of care for tuberculosis in our setting. The new paragraph reads:

"In conclusion, antituberculosis treatment discontinuation in this setting is relatively high, and tends to

occur more during the continuation phase of the treatment. Patients who receive treatment on the outpatient basis during the intensive phase and those who do not consent for HIV screening are more likely to be those who will interrupt their antituberculosis treatment. Specific actions targeting these subgroups would likely improve the outcomes of care for tuberculosis in this centre. That patients treated entirely on ambulatory basis were less like to achieve good outcomes of care as compared to those hospitalised during intensive treatment phase, together with much higher discontinuation rates in the same setting in the pre-DOT era, all suggest that DOT strategy is associated with improved outcomes of care for tuberculosis in this setting. Prospective studies are needed to investigate other determinants of antituberculosis treatment discontinuation and refine the incidence data based on a more objective ascertainment of the outcomes of care."

Which other determinants of TB treatment discontinuation the authors think should be studied by future prospective studies?

Our answer – Please, in the limitation section of our discussion (second last paragraph), we had already listed predictors that we were unable to investigate because of the nature of our data source. These include "patient's knowledge about tuberculosis, distance from treatment centre to patient's residence, side effects of antituberculosis treatment and chronic alcohol abuse".

References
Although they are relevant and up to date, I suggested above another couple of references

Our answer – Those references have been added.

Reviewer: Estifanos Biru Shargie

This article addresses one of critical issues in TB control efforts in Cameroon—treatment interruption and associated factors. The paper adds to the knowledge of interplay between various factors at individual, family and community levels that affect
successful treatment completion.

Specific comments

Introduction

1. The authors claim that most studies on anti-TB treatment interruption in Africa are inconsistent or too heterogeneous to provide reliable conclusions. Yet, it is not clear how this particular study could address those limitations and provide a more reliable conclusion that could better inform health service delivery and policy. Furthermore, the authors include two references on studies conducted in Cameroon on the same issue, but paradoxically argue that no relevant study has been conducted in Cameroon. If those studies represent the pre-DOTS era of TB treatment (as mentioned for one of them in the discussion section), it could be mentioned as such; but that does not imply the studies were not relevant.

Our answer – The inconsistencies/heterogeneity in studies on anti-TB interruption is the result of a recent systematic review conducted on those issues in Africa by Castelnuovo (our reference 7). While the systematic in itself may have its own limitations (single author), the findings clearly suggested that previous studies have been inconsistent in their definition of treatment discontinuation for instance; and the two largest studies included had been based on data collected about 15 years ago, and therefore reflecting more the pre-highly active antiretroviral therapy era. Of the recent studies (3 in

total in ref 7) one has recruited only smear positive patients; another has enrolled only patients with co-infection (tuberculosis-HIV) and a 3rd one used a cross sectional design. Because of those heterogeneities and the small sample of recent studies, we therefore believe that our study based on more recent data and a large sample would better reflect the true situation and would better inform policies at least at the Country level.

The reviewer is right by suggesting that we have referred to two previous studies from Cameroon. We would like to bring out the fact that we had indicated in the introduction already that no study on treatment discontinuation had been conducted in Cameroon after the complete roll out of DOT strategy to the whole country. Our reference 14 (from Cameroon) report on a study conducted in the pre-DOT era in the country, while our reference 6 (still from Cameroon) did not specifically examine the question of treatment discontinuation and provided no other information beyond the cumulative rate. The study indeed had a completely different focus. It is of note that the first author of both papers is also a co-author on the current manuscript, and we will not downgrade our own work just for the purpose of getting a new paper out. We have expanded the rational paragraph (second paragraph on page 4) to further reflect the above. The new sentences (at the end of the paragraph) read:
"In this context therefore, updated information are needed on antituberculosis treatment discontinuation and determinants that reflects both the DOT era and recent improvements in the access to HIV testing and treatment, in order to guide further improvement in the outcomes of care for tuberculosis."
2. The authors should describe how and what this study adds to the existing knowledge on factors determining treatment interruption.

Our answer – to reflect the above, we have completed the rationale section of the introduction (second paragraph) with the last sentences of the paragraph below:
"The directly observed treatment (DOT) strategy has been recommended by the World Health Organisation (WHO),[5] for improving the outcome of care for tuberculosis. Implementation of the DOT strategy started in Cameroon in the mid 90's and was expanded to the entire country in the years 2000. Despite this, available evidence suggests that antituberculosis treatment discontinuation has remained relatively high.[6] Many factors have been linked with antituberculosis treatment discontinuation in SSA including infrequent bacilloscopic monitoring, transfer of patients across health services units, lack of family support, side effects of medications, health care systems factors and patient misinformation.[7-9] In general, studies on the determinants of antituberculosis treatment discontinuation in Africa and in cameroon are mostly out-dated and less reflective of the DOT and highly active anti-retroviral therapy (HAART) eras, and the few relevant studies are heterogeneous. [7, 8] In addition, none of the relevant study has been conducted in Cameroon after DOT implementation in this country. In this context therefore, updated information are needed on antituberculosis treatment discontinuation and determinants that reflects both the DOT era and recent improvements in the access to HIV testing and treatment, in order to guide further improvement in the outcomes of care for tuberculosis."

We have also added sentences on the strength of the study (second last paragraph of the discussion. It reads:
"This study used administrative data routinely collected for the monitoring of the national programme against tuberculosis. Because such data collection is not comprehensive, we were unable to investigate the effects of some potential determinants of antituberculosis treatment discontinuation such as patient's knowledge about tuberculosis, distance from Centre for Diagnosis and Treatment of tuberculosis to patient's residence, side effects of antituberculosis treatment and chronic alcohol abuse.[8, 9, 21-23] That no systematic effort was in place to trace patients who dropped out during the year of the study has probably introduced some biases in our ranking of patients according to the outcome of care. For instance, some patients who died in-between drugs collection visit would have been inappropriately classified as defaulters, particularly among HIV infected patients [24-26]. Our study also has major strengths including the large population and inclusion of common forms of

tuberculosis in this setting. Unlike recent studies on this topic in Africa, assessment of predictors of treatment discontinuation used robust methods to account both for the observed time to treatment discontinuation as well as differences in the duration of treatment for various forms of tuberculosis.[7] Those studies have either been based in patients with HIV and tuberculosis, or lacked information on status for HIV. Accordingly, none has investigated the effect testing on the outcome of care for tuberculosis; what our study has successfully done."

3. Please ensure consistent use of terms. Keep interchangeable use of terms to the minimum to the extent possible. All of the following terms are used in just two paragraphs of the introduction, to mean the same thing: treatment discontinuation, interruption, non-adherence, defaulting. Also, see additional terms in results section page 8, 1st paragraph ("lost to follow-up") and discussion section para 1 ("drop-out").

Our answer – this has been fixed

4. Please avoid non-standard abbreviations (e.g., ATT) in the text, unless they are absolutely necessary.

Our answer – this has been fixed

Methods

5. Some of the statistical tests mentioned in the methods section (Mann-Whitney U test, Fisher's exact test) do not appear in the results section. Please focus on those analyses that formed the basis for the reported results.

Our answer – to reflect the analysis shown in new Table 1, we now refer in the stat section to Chi square test and ANOVA and equivalents.

6. It would greatly enhance the analysis if the authors could have access to and include the outcome data for transferred out patients. Otherwise, TB treatment outcome analysis should follow the standard approach, and treatment success and default rates should be calculated as a percentage out of the sum of all outcome categories (including transfer out, failure and death). The approach for the comparative (univariate and multivariate) analyses is sound however, as it limits the comparison between those successfully completed treatment and those defaulted from treatment.

Our answer – Unfortunately, we are unable to contact those patients who were transferred. We now present estimates based on the whole population. With regard to regression analysis, and in line with suggestion from Reviewer 1, we now present only results from Cox model. This approach in our opinion is less biased in the sense that it takes into consideration only the true observed follow-up duration for each patients, allowing for instance for the censoring of those who were transferred prior to treatment completion.

Results

7. Please check and ensure consistencies in figures provided in the text, table 1 and figure 1 (particularly for outcome categories).

Our answer – The former Figure 1 has been removed as we are now dealing with the entire cohort. Table 1 has been updated to integrate information that were apparent only in the former Figure 1 and tables on logistic regressions.

8. The study would have benefited better from tracing and documenting outcome for those transferred out to other health facilities. In principle, the outcome of those transferred out to other facilities should be tracked and recorded or analysed as a category. To this effect, treatment success and default percentages should be presented as per the standard guidelines, as is presented in table 1 (also see comment 6 above).

Our answer – as said above, in the absence of contact information for those transferred prior to treatment completion, we are unable to know their final outcome. Treatment success and default rates have been updated as suggested.

9. Determination of treatment discontinuation: Make reference to Table 3 at the end of the paragraph.

Our answer – this has been fixed.

Discussion

10. The literature review in both the introduction and discussion sections is rather shallow, and should be strengthened with more in-depth review and inclusion of some missed reference on recent studies that assessed treatment interruption in Africa (Kandel et al, 2008; Elbireer, et al 2011).

Our answer – both the introduction and discussion have been expanded and new references have been added

Some of previous studies attempted to trace patients and understand reasons why they defaulted; others looked at physical distance from treatment centre (not just urban vs rural dichotomy). Lack of such information should be discussed as one of the limitations of the current study.

Our answer – we would like to draw your attention to our second last paragraph of the discussion section where we had already mentioned the lack of information on those predictors as a limitation of our study. The relevant statement reads:
"Because such data collection is not comprehensive, we were unable to investigate the effects of some potential determinants of antituberculosis treatment discontinuation such as patient's knowledge about tuberculosis, distance from Centre for Diagnosis and Treatment of tuberculosis to patient's residence, side effects of antituberculosis treatment and chronic alcohol abuse.[8, 9, 21-23]".

11. Treatment success and default figures presented in this section should be corrected in line with the comments in the results section.

Our answer - This has been fixed.

VERSION 2 - REVIEW

REVIEWER	Barbara Castelnuovo Head of longitudinal cohorts unit Research Department Infectious Diseases Institute Kampala Uganda
REVIEW RETURNED	11/10/2011

GENERAL COMMENTS	Method section "all significan predictors identified". please state clearly the level of

	significance (e.g P=0.2)

REVIEWER	Estifanos Biru Shargie, MD, MPH, PhD Senior Technical Officer Strategy Performance and Evaluation Cluster The Global Fund to Fight AIDS, Tuberculosis and Malaria 8 Chemin de Blandonnet 1214 Vernier-Geneva, Switzerland I declare that I have no conflict of interest.
REVIEW RETURNED	17/10/2011

GENERAL COMMENTS	No further major comment; the reviewers have thoroughly addressed my earlier review comments. I trust the authors will revise the text in line with the following minor comments. A. Time to TB treatment discontinuation, page 10: "..treatment discontinuation was more likely to occur…. In those hospitalized during intensive phase than in those treated as outpatient". This sentence contradicts with the results presented in table 1 and Figure 2 as well as those under "determinants of treatment discontinuation", page 10. Revise it in line with the findings and reconcile the sections. B. Page 12, paragraph 1: some of the references seem to have been misplaced (a sentence about a study in Ethiopia makes a reference to a Zambian study and vice versa). Align the text with proper reference.

Reviewer: Barbara Castelnuovo

Method section

"all significant predictors identified". please state clearly the level of significance (e.g P=0.2)

Our answer- we have fixed this (p<0.05)

Reviewer: Estifanos Biru Shargie, MD, MPH, PhD

No further major comment; the reviewers have thoroughly addressed my earlier review comments. I trust the authors will revise the text in line with the following minor comments.

A. Time to TB treatment discontinuation, page 10: "..treatment discontinuation was more likely to occur…. In those hospitalized during intensive phase than in those treated as outpatient". This sentence contradicts with the results presented in table 1 and Figure 2 as well as those under "determinants of treatment discontinuation", page 10. Revise it in line with the findings and reconcile the sections.

Our answer- Please, there are no contradictions. Indeed, the interruption of the antituberculosis treatment during the continuation phase was more frequently found among patients who were hospitalized during intensive phase. In other words, those who were treated on an outpatient basis

during the intensive phase of treatment stopped their treatment earlier (i.e. generally in intensive phase). But as a whole, the interruption of the treatment occurred especially during the continuation phase (without reference to the setting of intensive phase of treatment).

B. Page 12, paragraph 1: some of the references seem to have been misplaced (a sentence about a study in Ethiopia makes a reference to a Zambian study and vice versa). Align the text with proper reference.

Our answer- we have fixed this

Dr Eric Walter Pefura Yone