Author's response to reviews

Title: Predictors of Mortality among TB-HIV Co-infected Patients being treated for Tuberculosis in Northwest Ethiopia: A retrospective cohort study

Authors:

Balewgizie Sileshi (bg.sileshi@gmail.com)
Nigussie Deyessa (negdaysun@yahoo.com)
Belaineh Girma (bgirma@msh.org)
Muluken Melese (mmelese@msh.org)
Pedro Suarez (psuarez@msh.org)

Version: 3  Date: 28 April 2013

Author's response to reviews:

Explanations to Reviewer’s Report
Reviewer-1: Amare Deribew

Minor essential revisions:
Please revise for grammatical or spelling errors again.
Ok I have thoroughly revised the grammar and spelling based on my colleagues’ comment besides my own revision.

Some other minor essential revisions include:

Methods:
• Please review this sentence: Patients diagnosed as having HIV in any of HIV Counseling and testing protocols (i.e., Voluntary counseling and testing, Provider initiated HIV counseling and testing units) registered in Pre-ART and ART log books according to the status of disease progression. 
Some part of the sentence was missed.
• Please clearly define ambulatory in the text
I have included definition of functional status in the methodology. Ambulatory: able to perform activities of daily living

Results:
• Please revise the word ‘TB location site in the table’. It should be type of TB
Ok I have corrected

Discussion
• Please clarify which group are these patients in the discussion: (These groups of patients may have been diagnosed as having HIV and TB, before their clinical and immunological conditions deteriorate). Non-ART cohorts
• Please remove acronym in the text. Every abbreviation should be explained in the text for the first time.
I have revised.

- Why smear positive TB cases are at higher risk of death compared to the smear negative cases? This is not in line with literature? Please give possible justification.

Ok in the document EPTB were at higher risk of death compared to smear negative cases and possible justification was explained.

Major compulsory revisions:

Methods:

- Please clearly describe the study settings including the health centers. You have only mentioned only the hospital.

According to 2011/12 report of Bahir Dar health center, a total of 4, 420 PLWHA ever enrolled of which 1, 133 were currently on ART. In the same year the health center reported 135 TB patients (33 smear positive PTB, 53 smear negative and 49 EPTB). The 2011/12 report of Abay Health center showed 756 PLWHA enrolled of which 326 were currently on ART. The Health Center also reported 162 TB patients (29 smear positive PTB, 38 smear negative and 96 EPTB). Han Health Center reported 1, 726 PLWHA were ever enrolled (407 currently on ART) and 112 TB patients were registered in the year 2011/12.

- The design and the patient recruitment procedure are not clearly described the methods. Please describe the design in the method and elaborate the sampling procedure? You have a diagram at the end but you didn’t even cite it in the method.

We conducted a retrospective cohort study in governmental health institutions in Bahir Dar, Ethiopia, from August, 2011 to January, 2012. Bahir Dar town was chosen purposely to get adequate number of sample with proper and complete patient record profile. In the town there are seven governmental health institutions, of which three were newly opened during data collection period. Therefore we included four health institutions (Felege Hiwot Refferal Hospital, Bahir Dar Health Center, Han Health Center and Abay Health Center) for the study which delivers TB service, Pre-ART and ART service for TB/HIV co-infected patients. During April 2009 – September 2011, 849 TB-HIV co-infected patients were registered in four health institutions. A total of 422 TB-HIV co-infected patients (272 ‘On ART’ and 150 ‘Non-ART’ cohorts) were included for the study [Figure 1].

- How were patients followed? What was done in each follow up?

TB-HIV co-infected patients followed in ART clinic and TB clinic. In TB clinic patients are put on direct observation treatment (DOTS) in the first two month (intensive phase). And these patients are assessed for drug side effects. For smear positive PTB patients their sputum smear is followed up at 2nd, 5th and completed of treatment if patients are new. For previously treated patient the sputum follow up period is a different one.

For patients who start ART drug adherence and side effects are assessed. For newly enrolled patient into ART care, the patient is assessed at 2 weeks and
follow up is made at 3 month interval. During each follow up, each patient is assessed for adherence, side effect, opportunistic infections, nutritional status and immunological response

- It is clear that TB-HIV patients who start ART late or not at all are at higher risk of death. Would you please give strong evidence how you avoided selection bias in this case?

We have acknowledged the bias. But we were interested to see factors that affect death including ART initiation. And other factors were not considered for grouping patients. Even if patients who start ART late or not at all are at higher risk of death, they were included to the study to see the exact magnitude in the local context.

- The ART group has two sub groups (those who were taking ART and developed TB later Vs. those who were taking Anti-TB and started ART later). Why did you include these groups as one? It may introduce bias since those who were taking ART for long are advantageous (more likely to have high CD4 and less likely to die). How many patients were in these sub-groups? Was there a difference in death rate among these sub-groups?

The ART group has incorporated patients who started at different periods with reference to TB occurrence. The decision for ART might have been based on different criteria’s (stage of HIV disease or CD4 count). Patients who started earlier might represent greater risk of dying than those who started ART later as result of different past disease condition. On the other hand those who are taking ART for long might have better CD4 count and better survival. We wanted to have adequate sample population to make comparison between the two groups merging both groups us adequate number of samples. But it introduced bias. We have acknowledged the potential bias that might be introduced in this case. Among 272 ART cohorts, 155 (56.99%) were taking ART before TB treatment and 117 (43.01%) were started ART during TB treatment. In contrary to our expectation slightly higher deaths observed among ART cohorts who were started ART before anti-TB medication.

- The national guideline stated that TB/HIV co-infected patients should start ART. Why the other group in the same facilities was denied ART? This issue is not clear in this paper?

According to the current national guideline, all TB patients with HIV are not illegible for ART although WHO recommends ART for all HIV/TB co infected patients. Still CD4 count and other HIV clinical staging are criteria’s in use for decision. This finding will assist to improve the decision. Different literatures showed health care providers remain reluctant to prescribe ART to HIV-infected TB patients, because of concerns about overlapping toxicity, drug-drug interactions, pill burden, and immune reconstitution inflammatory syndrome (IRIS). Findings of the 2012 sentinel TB/HIV system in Ethiopia showed 50.5% of TB/HIV co-infected patients received ART in the surveillance period.

Reviewer-2: Margaret Larrey

Minor Essential Revisions
1. Title: This states predictors of mortality among TB/HIV co-infected patients......However in the conclusion in the abstract and the body of the document only the absence of ART is emphasized. The authors should modify the conclusion.

Ok I have revised accordingly. In addition CPT remained important factor in reduction of mortality during TB treatment. The study also noted importance of early ART even at higher CD4T cell counts.

2. Abstract: Well written. Conclusions to be modified as previously suggested.

Accepted

3. The research question is well defined. In the background however, the authors provide a rationale for the study to be conducted in Ethiopia without providing adequate information on previous work done by others on predictors of TB mortality particularly in sub Saharan Africa. This will provide a foundation on which their work contributes more evidence.

In Ethiopia, there was no previous work done on predictors of mortality among TB-HIV co-infected patients.

4. The methods are appropriate but some aspects not well described. There is no explanation on why Bahir Dar was chosen and its representativeness of North West Ethiopia. There is also no explanation on how the four health institutions were selected.

Bahir Dar was chosen because of the following reasons.

1. There was high prevalence of TB-HIV co-infected patients in the town according to previous surveys.

2. Health facilities in the town started implementation of health management information system (HMIS) early (2009) and we could get patient profile cards easily and both TB-HIV services including ART were started in the area early.

3. Health institutions in the town have good patient profile recording system with optimal time.

Therefore according to the aforementioned reasons, Bahir Dar was chosen purposely to get adequate number of sample with proper and complete patient record profile. In Bahir Dar town there are seven governmental health institutions, of which three were newly opened during data collection period. Therefore we included four health institutions (one hospital, three health centers) for the study which delivers TB service, Pre-ART and ART service for TB/HIV co-infected patients.

During generalization caution must be taken because these health institutions were in urban area and where the regional state, governmental and non-governmental organizations were available. And this is included in the limitation.

5. The data is sound and the results clear.

6. Limitations: The list could be more comprehensive as half of all eligible participants had to be excluded for one reason or another. There could also have
been bias as information on adherence to medications was not available in the records.

Of course adherence for ART was available in the record, but for anti-TB medication and cotrimoxazol prophylactic therapy adherence was not available. This is considered in the limitation.

7. The discussions are balanced and supported by data, authors have acknowledged cited work and the writing is acceptable.