Author's response to reviews

Title: Adherence to Anti-tuberculosis Treatment among Pulmonary Tuberculosis Patients: a Qualitative and Quantitative Study

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Author's response to reviews: see over
Dear editors and reviewers,

Thanks a lot for the comments on our manuscript entitled with “Adherence to Antituberculosis Treatment among Pulmonary Tuberculosis Patients: a Qualitative and Quantitative Study”. We carefully read and revised it again. Here are responses.

**Reviewer:** Salla Atkins

1. **Major compulsory revisions**

   - Please do another language check before this is published.

   **Response:**
   
   We invited another native English speaker to help check the manuscript and corrected several errors.

2. **Minor essential revisions**

   - Please move detailed information about loss to follow up from discussion to beginning of results.

   **Response:**
   
   In the revised version, we moved the information about loss to follow up from discussion to the beginning of the results.

   - Please provide the reference for the type of content analysis used.

   **Response:**
   
   We added two references for content analysis in the revised version.
- Aim to provide policy makers with recommendation for interventions to improve
TB treatment in China is not applicable. Study was only conducted in Jiangsu Province
and is not representative of entire China.

Response:
We changed it to “Our goal was to provide policy-makers with recommendation for more
organized TB control program to improve the adherence to anti-tuberculosis treatment”.

- change retreated patients to retreatment patients

Response:
We changed retreated patients to retreatment patients in the revised version.

- Mention that sampling for qualitative part was convenience sampling

Response:
In the revised version, we mentioned that sampling for qualitative study was convenience
sampling.

- Mention what the training and background of interviewers were in text.

Response:
We mentioned that interviewers for quantitative study were trained local TB dispensary
staff and interviewers for qualitative study were trained professionals from Jiangsu
Provincial Center for Disease Prevention and Control.

For quantitative study:
“After obtaining informed consent, trained local TB dispensary staff interviewed all participants with a structured questionnaire, including basic characteristics, socioeconomic status, treatment history and adherence to anti-tuberculosis treatment.”

For qualitative study:

“Interviews were conducted in local health facilities by trained professionals from Jiangsu Provincial Center for Disease Prevention and Control with Chinese Mandarin.”

- Page 11, top line, reference 4 seems incorrect. Reference 4 in fact present different groupings of factors than what the authors present (5 groupings, where social and economic are merged, for example). Reference 13 there is correct. Please re-check your referencing carefully.

Response:

In the revised version, we only kept reference 13. As we added two references in the part of method, the number of reference 13 has now been changed to 15.

3. Discretionary revisions

- Have you considered, that given there was better adherence when drugs were delivered, that there was some issue of transport? Did this not emerge from qualitative findings? It would make sense that patients too ill to walk long distances, or poor ones without means to pay for transport would adhere less well.

Response:

There emerged some issues about the inconvenience for patients to take drugs in the village clinics. However, this seemed not to be an important element in the current study.
This study was conducted in Jiangsu Province, which is ranked as a relative rich area of China. Primary Health Care (PHC) has been strengthened in Jiangsu for decades, resulting in higher coverage rate of community health center and village clinics. It usually takes several minutes to less than half an hour for the patients walking to the clinics from their homes. For those old or too ill to walk to the clinics, the local doctors are responsible for delivering drugs to their home. Thus, we didn’t further discuss the issue about transport in this manuscript. However, former studies have proved that cost of transportation is related to healthcare seeking delay and diagnosis delay, because to acquire the TB diagnosis, patients need to travel to the town or center of the county which cost much more than walk to the local clinics.

Reviewer: Susan van den Hof

Major Compulsory Revisions

1. In the results, a new category regarding observed treatment is introduced: ‘deliver drugs to patient’s home. It is not clear to me what it means exactly. How often are they delivered (every dose, every month?) and does this also mean that taking of the drugs is supervised? If yes, that would mean that 113/670=17% is not observed taking treatment. If no, 35% is not observed taking treatment. More information is needed to be able to understand why this factor is important for adherence. Please describe in the manuscript which percentage of patients take drugs supervised by someone else.

Response:

In fact, it is not a new category regarding observed treatment. In the first version, we named it as ‘Village doctors take drugs to patient’s home’. In the second version, to make
readers easy to understand, we changed it to ‘deliver drugs to patient’s home’. According to China’s national policy, sputum smear positive TB patients should be directly observed by health workers based on the believing that DOT could improve the cure rate by assisting, supporting and monitoring patients [1]. In Jiangsu Province, patients usually visit the TB dispensary monthly and get the anti-tuberculosis drugs for the whole month. They swallow the drugs under the direct observation by doctors or family members or supervise by themselves. Due to different reasons, some patients might not attend the regular visits to TB dispensary, resulting in the interruption of treatment. In such a case, local health workers are responsible for delivering drugs to patients’ home and perform patient retrieval. Strictly, it is not a real direct observation because health workers don’t observe patients swallowing each dose of drugs. But it is still believed to be an alternative way to help increase the adherence, given that DOT is not accepted by the patient. To make it clear to readers, we described it in the section of method in the revised version as the following:

“In this study, observed treatment was divided into four categories: self-administered (patient took drugs without external observation); observed by family members or others (patient took drugs under the observation by family members or other volunteers); home-based drug delivery (local health workers sent anti-tuberculosis drugs to patients’ home regularly, but did not observe them taking each dose of drugs); and directly observed by village doctors (patients took drugs under the direct observation by village doctors each time).”
2. What does it mean exactly that health workers visited the patient at home? Is that recommended in China, and if yes, how often, by whom, and with what purpose? How is it defined in the questionnaire (should they be visited only once or a certain number of times)? This information is needed to be able to understand why this factor is important for adherence.

**Response:**

According to China national TB policy, local health worker should visit TB patients at least four times during the treatment episode, with the aim to strengthen the communications and to improve patients’ adherence to anti-tuberculosis treatment. The role of home-visiting has been proved in several studies. A study in Nepal found that over half of home visits were to enable treatment to be initiated and thus prevent primary default [2]. In another study, patients were randomized to an intervention group or a control group. Home visits were highly effective in improving the return to treatment of patients who were late for treatment (231/240, 96.3%). The intervention group showed a higher treatment success rate (94.2% versus 76.7%), lower default rate (0.8% versus 10.0%) and higher smear conversion rate after the end of treatment (92.9% versus 75.0%) than controls [3].

3. The authors have adjusted the multivariate model for adherence for all variables considered univariately. However, it seems that many of the added variables do not add to the fit of the model as only being illiterate, observed treatment and home-visiting give statistically significant results and the univariate and multivariate results are similar. A statistician should be consulted on development of the multivariate model. Also, in the
methods section it should be described how the final multivariate model was built and selected.

**Response:**

After consulting a statistician and referring to other articles [4], we modified the method used to construct the multivariate logistic regression model. In the revised version, the associations between selected factors and adherence to anti-tuberculosis treatment were presented with two tables (Table 1 for univariate analysis and table 2 for multivariate analysis). We described how the final multivariate model was built and selected in the section of method as the following:

“Predictive variables that were independently significantly associated with treatment completion in univariate analysis were included in a multiple logistic regression model to determine their relative contributions in predicting treatment adherence while simultaneously adjusting for each of their effects. The criterion for significance was set at P<0.05 based on a two-sided test.”

**Discretionary Revisions**

4. Was the occurrence of adverse events not assessed in the quantitative study, so you could say how often adverse effects, and especially liver problems, occurred in the whole patient group included in the quantitative study, except only in non-adherent patients included in the qualitative study.

**Response:**

Frequency of adverse events and its relative risk for treatment interruption were not assessed in the current quantitative study. However, more than 37% of patients regarded
it as an important reason for non-adherence. In the qualitative study, it was also mentioned as an important issue influencing patient’s adherence. This gives us clues for further studies focusing on the adverse drug reaction and its relation to treatment adherence.

5. Is treatment outcome available for the patients included in this study (and for the non-respondents) to 1. assess the effect of non-adherence on treatment outcome and 2. to assess differences between non-respondents and respondents in treatment outcome

Response:
The aim of this study was to explore factors associated with patient’s adherence and to give clues for interventions. Treatment outcome was not available in the current study which can be used to further analyze its relation to adherence. However, adherence has been demonstrated to be significantly associated with treatment outcomes previously.

6. Household registration and floating population are not terms used in the international literature. Please specify.

Response:
We changed these terms to “residence status; permanent residents and migrants”

Reviewer: Earl Hershfield
I agree with one of the other reviewers that the authors need to better define the goals[if any] of this research to who is it directed? From the response of the authors it is clear that
there needs to be a more organized control TB Program especially ensuring that TB meds
are free to the patient. Otherwise I believe the authors have answered concerns.

Response:

Thanks for the reviews. Our goal is to provide policy-makers with recommendation for
more organized TB control program to improve the adherence to anti-tuberculosis
treatment.

References

observation and adherence to tuberculosis treatment in Chongqing, China: a
conducted in remote districts of Nepal in an NGO-run tuberculosis control
3. Mohan A, Nassir H, Niazi A: Does routine home visiting improve the return
rate and outcome of DOTS patients who delay treatment? Eastern
Mediterranean health journal = La revue de sante de la Mediterranee orientale =
complete isoniazid treatment for latent tuberculosis infection in Rhode