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 Anti-tuberculosis Treatment among Pulmonary Tuberculosis Patients: a Qualitative and Quantitative Study”. We carefully read and revised it again. Here are responses.

**Reviewer:** Earl Hershfield

**Major compulsory revisions:**

1. Data collection: "representative samples": does not fit with rest of sentence.

**Response:**

We modified the part of “data collection” as the following:

**“Data collection**

This study was designed with a mixture of both quantitative and qualitative methods in order to gain a deeper understanding of the situation. For quantitative study, a multi-stage sampling strategy was implemented. Firstly, we select 13 municipalities as the first sampling unit. In each municipality, one county (district) was randomly selected as the study site. In each site, 60 sputum smear positive TB patients registered since 2006 were continuously collected as study subjects (given that the confidence interval=95%, estimated non-adherent proportion=20%, relative precision=0.2P, design efficiency=2, and the study site=13, the total estimated sample size was 780). After informed consent, a structured questionnaire was used to collect data by trained investigators. Patient’s basic characteristics, socioeconomic status, treatment history and adherence were investigated. Non-adherent patients were presented with 16 options for reasons of non-adherence…”

2. Why only non-adherent patients and local health workers had in-depth interviews?

**Response:** One of the main aims of this study is to explore the underlying reasons for non-adherence of TB patients. Besides the quantitative study, we also conducted a qualitative study by inviting 20 TB patients (10 from Xuanwu and 10 from Taichang) and 10 local health workers (from Taichang, including 5 village doctors and 5 community hospital doctors), for in-depth interview. Among 20 TB patients, 15 were non-adherent patients. The reason for inviting more non-adherent patients for in-depth interview is that we want to explore the factors associated with patient’s non-adherence. The reason for inviting local health workers is that we want to analyze patient’s non-adherence from the side of health care provider.
3. What are liver protection drugs, name them, and quote literature for their use.

**Response:** The number of people being prescribing “liver protection drugs” worldwide is not known, but it is generally agreed that it is almost universal for TB patients in China. Such liver protection drugs include herbal preparations, manufactured herbal products, combinations of vitamins and other non-herbal substances and manufactured pharmaceutical preparations (see Table 1). Recently, Liu et al reviewed 85 research articles carried out in China (77), India (2), Russia (4), Ukraine (2) and found that there was no reliable evidence to support prescription of drugs or herbs to prevent liver damage in people under tuberculosis treatment[^1].
4. Hepatic adverse reactions of 11.9% appear high. Were they biochemical only or biochemical plus a clinical component?

**Response:** In China, there are no standard criteria for diagnosing hepatic injury induced by anti-tuberculosis drugs. Either biochemical tests or clinical symptoms were implemented. Even for laboratory, the diagnostic criteria are also different. Xia et al reviewed literatures about adverse drug reactions (ADR) to anti-tuberculosis

Table 1: Categorisation of drugs and herbs by main ingredients

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Description of Ingredients</th>
<th>Number of studies</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbal preparations</td>
<td>Yue hua wan</td>
<td>Various combinations of more than 11 Chinese herbs decocted in water</td>
<td>1</td>
<td>China [10]</td>
</tr>
<tr>
<td></td>
<td>Bu ji yang fei bao gan decoction</td>
<td>11 herbs decocted in water</td>
<td>1</td>
<td>China [12]</td>
</tr>
<tr>
<td>Phytotherapy</td>
<td>Infusions of a combination of herbs (on average 25) tailored to individual patients</td>
<td></td>
<td>1</td>
<td>Russia [13]</td>
</tr>
<tr>
<td>Finished manufactured herbal products</td>
<td>Hu gan pian</td>
<td>Tablets including a combination of six ingredients (herbs, animal extract, green bean)</td>
<td>8</td>
<td>China [14-21]</td>
</tr>
<tr>
<td></td>
<td>Silmarin</td>
<td>Extract of milk thistle</td>
<td>11</td>
<td>China [22-32]</td>
</tr>
<tr>
<td></td>
<td>Astragalus</td>
<td>Plant extract given intravenously</td>
<td>1</td>
<td>China [33]</td>
</tr>
<tr>
<td></td>
<td>Astragalus sinesis</td>
<td>Tincture containing: coumarins; ferrocoumarins; tanning substances; sugars; saponins; ascorbic acid; flavonoids; phytosterols; tocopherols</td>
<td>1</td>
<td>Russia [34]</td>
</tr>
<tr>
<td></td>
<td>Biphenylcarboxylate</td>
<td>Tablet with extract of wu wei zi plant combined with glucorolactone</td>
<td>2</td>
<td>China [35-36]</td>
</tr>
<tr>
<td></td>
<td>Biphenylcarboxylate</td>
<td>Extract of wu wei zi combined with glucorolactone</td>
<td>1</td>
<td>China [37]</td>
</tr>
<tr>
<td></td>
<td>Wu zhi capsule</td>
<td>Capsules with extract of the fruit of the wu wei plant</td>
<td>3</td>
<td>China [38-40]</td>
</tr>
<tr>
<td></td>
<td>San shen bao gan capsule</td>
<td>Capsules containing combination of 13 herbs</td>
<td>1</td>
<td>China [41]</td>
</tr>
<tr>
<td></td>
<td>Hugan ji fei granule</td>
<td>Granule containing a combination of 12 herbs</td>
<td>1</td>
<td>China [42]</td>
</tr>
<tr>
<td></td>
<td>Oleanolic acid</td>
<td>Tablet with extract of Swertia herb</td>
<td>5</td>
<td>China [43-47]</td>
</tr>
<tr>
<td></td>
<td>Hugan yao</td>
<td>Extract of Swertia herb combined with inosine and Vit C</td>
<td>1</td>
<td>China [48]</td>
</tr>
<tr>
<td></td>
<td>Dan shen</td>
<td>Injectable preparation of Chinese sage (Salvia Millocortis Bunge)</td>
<td>3</td>
<td>China [49-51]</td>
</tr>
<tr>
<td></td>
<td>Stadinu</td>
<td>Tablets containing a combination of: Andrographis Paniculata; Eclipta alba; Peumus Boldus Molina; Cynura scolymus; Furaria pervilopa</td>
<td>1</td>
<td>India [52]</td>
</tr>
<tr>
<td></td>
<td>Gastrina</td>
<td>Chelidonium majus; Taraxacum officinale; Cardus crispus (curled thistle extracted with ethanol)</td>
<td>1</td>
<td>Russia [53]</td>
</tr>
<tr>
<td></td>
<td>Optiliv</td>
<td>Capsules containing extracts of Andrographis paniculata; Prenanthes laureola; Eclipta alba; Boerhavia diffusa; Azaderachta indica; Swertia chirata; Solanum nigrum; Terminalia arjuna; Aphananthis rohukula; Terminalia chebula; Furaria indica; Exipients</td>
<td>1</td>
<td>India [11]</td>
</tr>
<tr>
<td></td>
<td>Glycyrrhizin</td>
<td>Capsules or injection containing extract of liquorice (gan cao)</td>
<td>6</td>
<td>China [54-59]</td>
</tr>
<tr>
<td></td>
<td>Amantadin</td>
<td>Tablet containing plant extract</td>
<td>1</td>
<td>China [60]</td>
</tr>
<tr>
<td></td>
<td>Spirin or Spirulina</td>
<td>Derived from blue-green algae, contains proteins, vitamins and essential amino acids</td>
<td>2</td>
<td>China [61-62]</td>
</tr>
<tr>
<td>Combinations of vitamins and other non-herbal substances</td>
<td>Tropolin (ti ao pu zao ni or xai xia)</td>
<td>Ramification of Glycine (amino acid)</td>
<td>1</td>
<td>Ukraine [63]</td>
</tr>
<tr>
<td></td>
<td>Glutathione (GSH) (tae te or a tuo mo lan)</td>
<td>Injectable antioxidant</td>
<td>5</td>
<td>China [81-85]</td>
</tr>
<tr>
<td></td>
<td>ATP</td>
<td>Adenosine Triphosphate</td>
<td>1</td>
<td>China [86]</td>
</tr>
<tr>
<td></td>
<td>Inosine</td>
<td>Inosine combined with vitamin C</td>
<td>1</td>
<td>China [87]</td>
</tr>
<tr>
<td></td>
<td>Essentielle</td>
<td>Vitamin B6, vitamin B12, derivatives of vitamin B3 (nicotinamide), vitamin E and essential phospholipids</td>
<td>1</td>
<td>China [88]</td>
</tr>
<tr>
<td></td>
<td>Gan ning pian</td>
<td>Liver hydrolysate, compounds of vitamin B, inositol, vitamin B6 and vitamin B12</td>
<td>1</td>
<td>China [89]</td>
</tr>
<tr>
<td></td>
<td>Tocopherol acetate</td>
<td>Vitamin E</td>
<td>1</td>
<td>Ukraine [90]</td>
</tr>
<tr>
<td></td>
<td>Ghusoricilactone</td>
<td>Manufactured drug</td>
<td>3</td>
<td>China [91-93]</td>
</tr>
<tr>
<td></td>
<td>Zinocry</td>
<td>Manufactured drug</td>
<td>1</td>
<td>Russia [94]</td>
</tr>
</tbody>
</table>

4. Hepatic adverse reactions of 11.9% appear high. Were they biochemical only or biochemical plus a clinical component?
drugs published among 1996-2005 in China \cite{2}. The overall incidence of hepatic injury is 11.9% (including 111 studies, range from 0.75% to 71.43%), which is the highest one among all kinds of ADR induced by anti-tuberculosis therapy. For 84 studies based on biochemical test, the incidence of hepatic injury varied from 0.75% to 71.05%, with the median at 16.51%. For 14 studies based on clinical symptoms, the incidence of hepatic injury varied from 1.56% to 60.00%, with the median at 15.35%. No significant difference was found between these two groups. Compared to reports in other countries, the incidence of hepatic seems higher. It may attribute to the different diagnostic criteria in China.

5. What were the other adverse reactions and how many patients stopped drug taking because of them?

**Response:** In the quantitative study, the main reasons for non-adherence listed by patients were adverse reactions of anti-tuberculosis drugs (37.8%), relieved symptoms (26.8%), long course regimen and large dose of drugs (15.9%), worry about dangers of drugs (15.9%), other disorders (15.9%), financial burden and medical expenditure (15.9%). We did not further explore the different kinds of adverse reactions and their effects on the treatment interruption.

6. A completion rate of at least 90% appears high for this study, other programs use only 80% of doses for completion. Explain. Quote literature.

**Response:** There are different definitions of “treatment interruption” in different literatures. For example:

(1) “treatment interrupters” were patients who stopped taking treatment for 8 or more weeks in the course of the treatment period \cite{3}.

(2) Patients are labeled as non-adherent if their treatment is interrupted for 2 consecutive months or more\cite{4}.

(3) Patients were deemed non-adherent when they had missed 2 consecutive weeks of TB treatment, or 20% of the total quantity of TB drugs \cite{5}.

(4) “Interruption of treatment” was defined as those who missed their last three doses; or had run out of medicine for more than a week\cite{6}.

(5) Patients who had missed 10% of the total prescribed doses of TB drugs were deemed as non-adherent \cite{7, 8}.

In the present study, we defined the completion rate of at least 90%, based on
“Chinese National Guidelines for Controlling and Prevention of Tuberculosis”. This definition was also used in other studies in China [7, 8].

7. How do patients know the difference between generic drugs and privately purchased ones?
Response: Free anti-tuberculosis drugs provided by local government are limited to the specified brands. Though it is only hearsay without scientific evidences that free drugs are worse than private expense drugs, such information is spread among patients in many sites. Local doctors also admitted that they sometimes recommend patients, especially those aged and weak patients to buy private expense drugs rather than to use freely delivered drugs. As mentioned by one doctor in our study, “if we only deliver free anti-tuberculosis drugs rather than selling private expense drugs to patients, how can we get the bonus?”

8. Is there continuing education for private physicians and health workers about TB.
Response: Yes, in China, private physicians and health workers are demanded to be continually educated, including knowledge on TB. However, compared with health workers in upper level hospitals, rural village doctors and private physicians are still lack of awareness of diagnosis and treatment of TB.

Minor Revisions:
1. Explain what "withdrawal beforehand" means.
Response: Here, “withdraw beforehand” means stop treatment before the prescribed course. To assist readers understand, we modified the sentence as the following: “Such a long course easily leads to treatment interruption or default beforehand, which contributes to prolonged infectiousness, drug resistance, relapse and death”

2. What is "Laobing"?
Response: “Laobing” is a traditional term of tuberculosis in ancient China, which can be translated as “phtisis”. Considering the term laobing is not known to most foreign readers, we revised the sentence as the following: “TB was named as “Phtisis” and regarded as a deadly disease several years ago in China.”
Discretionary Revisions

1. Remove all anecdotal references.

*Response:* We removed all anecdotal reference in the revised version.
**Reviewer:** Salla Atkins

**Reviewer's report:**
I found the report interesting, but lacking in some ways. It is always difficult to incorporate qualitative and quantitative research. I find the results interesting, but feel that further thinking and analysis could be conducted in order to make them more interesting. I would also appreciate further emphasis on how the Chinese context influences these issues differently and how these results differ from existing research. It is also important to have an idea of the questionnaires used when seeing results and discussions.

**Response:** In the revised version, we modified the part of “discussion”, trying to make quantitative study results cooperating with the findings from qualitative study. We also further emphasized on how Chinese context influenced these issues differently and how these results differ from existing research.

In the revised version, we also briefly introduced the outline used from qualitative study as the following:

“For qualitative study, 20 TB patients (from Xuanwu and Taichang, men 15, women 5, newly treated 18, previously treated 2) were invited for in-depth interview. A semi-schematized guide covering general as well as specific questions was utilized. The theme of in-depth interview focused on patient’s health-care seeking history, knowledge and attitude to TB and their adherence to TB treatment. Ten local health workers from Taichang, including 5 village doctors and 5 community hospital doctors, were also invited for in-depth interview. Themes for in-depth interview included the current TB control program in the village/community, the main difficulties in implementing DOTS, advices for the current TB program, treatment adherence of patients in corresponding village/community and main reasons for non-adherence.”

Minor essential revisions I recommend a full edit by a translator or first language English speaker. The manuscript contains a number of grammatical and spelling errors, and terms not commonly used in the English language e.g. Table 1 – “primer” school. Table 1: “crude odds ratio”. Background: “withdrawal beforehand” – this term especially is used throughout the manuscript and it is not clear what this means. Results: “intermittent interruption” – how was this defined? Data collection (p.5) – distract instead of district. p.7 – regime instead of regimen. p.7 use of etc. directly above findings from qualitative study – not common practice.
Response: We corrected several errors in the revised version.

Major compulsory revisions
p.4. The authors should state more clearly for what they aim to develop recommendations. It is also unusual to conduct a study in order to inform further research – what kind of research?
Response: We agree to the reviewer’s suggestions and have modified the sentence as the following:
“It is hoped that the paper will provide policy-makers with recommendation for interventions on patient’s adherence to the treatment of tuberculosis”.

P.5. While the authors make a commendable attempt at describing the setting, for an international audience it is not sufficient. Especially given the paper’s findings, it would be useful to know more about the culture, but especially about the socioeconomic characteristics of these districts.
Response: In the revised version, we gave more information about Jiangsu Province including the economy and culture as the following:
“This study was carried out in Jiangsu province, which locates along the eastern coast of China. It covers an area of 102.6 thousand square kilometer, about 1% of the total area of the country. Jiangsu province governs 13 municipalities and 106 counties (districts), with the population of 74 million. The population density is 736 per square kilometer, which is ranked as the densest one in China. The annual net capita income of farmers was 6561 Yuan ($964), and the annual employee’s salary was 27234 Yuan ($4005). The average life expectancy of the local population was 75.3 years old, with men at 72.9 and women at 77.9 years old respectively. DOTS (direct observed therapy, short course) has been introduced since 1990s and now covered 100% at county level. Internet based surveillance system has been set up since 2004. All newly diagnosed TB should be registered in the local TB dispensary and reported through internet.”

p.5. Why was one county randomly selected?
Response: The common administrative system in China is Province→Municipality→County (district) →Town→Village. This study was conducted in Jiangsu Province, where it governs 13 municipalities and each municipality governs 5-13 counties (districts). For quantitative study, multi-stage sampling strategy was implemented.
Firstly, we select 13 municipalities as the first sampling unit. In each municipality, one county (district) was randomly selected as the study site. In each site, 60 sputum smear positive TB patients registered since 2006 were continuously collected as study subjects with the total estimated sample size at 780.

p.5. How was the sample of 780 arrived at? How was it calculated? What was the estimated power?

**Response:** The sample size was calculated based on Openepi software ([www.openepi.com](http://www.openepi.com)). Given that confidence interval=95%, estimated non-adherent proportion=20%, relative precision=0.2P, design efficiency (deff)=2, the estimated sample size=768. For each study site, the estimated sample size is 768/13=59.1. Thus in each county, we set the sample size as 60. Totally, the estimated sample size is 780.

p.5. There is insufficient information about the participants in the qualitative study. How many participants were there? Where did they come from? Who was a doctor, who a patient? What about gender, age and treatment history was considered before selection?

**Response:** In the revised version, we described the participants in the qualitative study in detail.

“For qualitative study, 20 TB patients (from Xuanwu and Taichang, men 15, women 5, newly treated 18, previously treated 2) were invited for in-depth interview. A semi-schematized guide covering general as well as specific questions was utilized. The theme of in-depth interview focused on patient’s health-care seeking history, knowledge and attitude to TB and their adherence to TB treatment. Ten local health workers from Taichang, including 5 village doctors and 5 community hospital doctors, were also invited for in-depth interview. Themes for in-depth interview included the current TB control program in the village/community, the main difficulties in implementing DOTS, advices for the current TB program, treatment adherence of patients in corresponding village/community and main reasons for non-adherence.”

p.5. Who conducted the interviews? What was their training and background? Did all the participants speak Mandarin as their first language? Where were they interviewed? What themes were focused on in the interview, and in the questionnaire?

**Response:** The interview was conducted by staffs of Jiangsu Provincial Center for
Disease Control and Prevention. They had several years’ working experience in TB control and prevention and had been trained for the field study. All participants spoke Mandarin as their first language. The interview was conducted in the local health facilities.

The themes focused in the interview were as the following:

“For TB patients:
1. Could you briefly describe your family and socioeconomic status?
2. Could you describe what you have experienced when you sought for health-care service?
3. Does TB significantly influence your individual life or family life and how much?
4. Did you keep the state of TB as a secret to others?
5. Could you take drugs regularly? What are the difficulties you faced during the treatment episode?
6. Do you know the effect of treatment interruption? What is the reasons for treatment interruption?
7. Do you think which kind of tools or methods can help you take drugs regularly?

For doctors:
1. Can you describe the current TB program in your village/community? What is the most important issue in TB control program and what is the main problem in implementing these programs.
2. How about the treatment adherence among TB patients in your village/community?
3. What is the main reasons for non-adherence of TB patients?
4. Can you strictly implement DOT strategy? What is the real situation and how about its effects on patient’s adherence?
5. If you can implement DOT strategy, what is the reason?
6. If you can’t implement DOT strategy, what is the reason?
7. How to improve patient’s adherence? Could you give some recommendations?”

p.6. Were translations and transcriptions checked by anyone or backtranslated?
Response: Two trained staffs in Jiangsu Pro vincial CDC translated the tape-recorded interview and it is further checked by the team leader.

p.6. Which method of content analysis was used? There are several. What steps were taken in analysis? How many people and who did analysis? Experience and training?
Response: In the revised version, we described the data analysis method in detail:
“For qualitative study, content analysis was applied. Tape-recorded in-depth interview was firstly transcribed in Chinese characters and then translated into English by two trained staffs in Jiangsu Provincial Center for Disease Prevention and Control (CDC). Codes were then developed based on the original terms used by participants. The transcripts and notes were then analyzed thematically by categorizing the interview data under the main topic headings. The codes were then presented, discussed and checked within research team. Tentative categories and sub-categories were created from the clustered codes, and subsequently main themes emerged based on the patterns and relationship between the categories.”

p.6. last two sentences under results: Do these refer to the qualitative or quantitative research?
Response: The main reasons for non-adherence listed by patients come from the quantitative study.
“The main reasons for non-adherence listed by patients were shown in table 2, which were adverse reactions of anti-tuberculosis drugs (37.8%), relieved symptoms (26.8%), long course regimen and large dose of drugs (15.9%), worry about dangers of drugs (15.9%), other disorders (15.9%), financial burden and medical expenditure (15.9%).”

p.6. quantitative study – why did the others (not the 85.7%) not participate in the study? Did all participants for the qualitative study agree to participate, how many were initially approached?
Response: 14.1% of selected subjects were not traced and involved in the analysis, with the risk of selection bias. The main reasons for loss to follow up were migration, out for employment, changed address or telephone number, death, and refuse to join the study, etc. We further compared some key characteristics of 670 TB patients involved in the analysis and 110 patients lost to follow up. No significant difference was found in the distribution gender between these two groups (The proportion of men was 71.2% vs. 73.0%). However, the study subjects were a little bitter older than the patients lost to follow up (51.4±19.5 vs. 49.4±19.0 years old). It might attribute to the higher migrant rate among young patients, which resulted in the higher proportion of loss to follow up among them.
For qualitative study, 20 TB patients (from Xuanwu and Taichang, men 15, women 5, newly treated 18, previously treated 2), 10 local health workers from Taichang (including 5 village doctors and 5 community hospital doctors) were invited for in-depth interview. Finally 19 patients (95%) and 9 doctors (90%) were successfully interviewed.

p.6. Health insurance – does not mean much if we do not know the socioeconomic status of the participants.

Response: We agree to this opinion. Thus, in the revised version, we further analyzed the economic status of TB patients. We used the family monthly income per capita as the index of economic status. The association between family income and the risk for treatment interruption was explored.

p.7. How does hundreds or thousands of Yuan relate to the average salary? This finding is difficult to interpret without this information

Response: In the part of “Study sites” of the revised version, we described the average annual income of population in Jiangsu Province, which could help readers understand the article. This sentence was modified as the following:
“The extra cost varies from hundreds to thousands Yuan per month (The annual net capita income of farmers was 6561 Yuan and the annual employee’s salary was 27234 Yuan in 2007)”.

p.7. Who “demanded” patients to be hospitalized?

Response: To make readers easy to understand, we revised the sentence as the following:
“For patients treated in urban specialized TB dispensary, they are usually recommended by the clinical doctors to be hospitalized, which cost much more than those treated at rural dispensaries.”

p.9. “prefer to take drugs back home and… conceal their disease…” What are the implications of this to adherence? Do patients who take treatment home not adhere, or those at the clinic? I struggled to find how DOT was related to adherence.

Response: In China, DOT is implemented within the framework of national DOTS strategy: TB drugs should be “swallowed” under the direct observation of village
health workers during the whole episode of treatment for sputum smear positive patients and at least the intensive period for sputum smear negative patients. However, several studies have proved that strict DOT is not respected in China whilst China can still maintain its high cure rate without strict DOT [5]. The underline reasons are not clear. Though some randomized and controlled trials of DOT with or without the other components have shown no benefits from it [3, 9, 10], it is still believed that with no new drugs or adjuvant therapy available to shorten the length of treatment, DOT is the best mean we have at our disposal for TB control [11]. As mentioned in this study, compared with self-supervision, DOT by health workers can significantly decrease the risk for non-adherence. Nevertheless, good health services are necessary but not sufficient in treatment completion. Patients still need to choose to take drugs. Only when the supportive patient-doctors relations are built, rather than the authoritarian supervision implicit, may it improve treatment adherence and help to control TB.

p.10. How does incorrect addresses result in risk of default? Does it result in risk of default, or risk of not being able to trace potential defaulters?

**Response:** Floating population are susceptible to non-adherence. Usually some nonlocal floating population would not like to provide correct address for fear of stigma. Incorrect address makes it difficult to follow up these patients and it could be a risk of default. Though there is no evidence to prove that incorrect address is associated with non-adherence, it makes local TB dispensary difficult to follow and manage the patients.

p.10. “lasting” cure – one can get TB more than once in a lifetime, there is no such thing as a lasting cure.

**Response:** We modified the sentence according to the reviewer’s suggestions as the following:

“The main interventions to prevent the spread of TB are the early detection of patients and providing them with effective treatment. However, the current long-term anti-tuberculosis therapy could easily lead to non-adherence of patients, which is an important barrier for TB control programs.”
Reviewer: Susan van den Hof

Major compulsory revisions

1. Non-response. 15% of the eligible patients were not included. Is there selective non-response that could have influenced your results? In other words, what are the reasons for non-response and in what respect are non-responders different from responders? This can be assessed instead of just mentioning that there may be selection bias.

Response: In the revised version, we further discussed the selection bias as the following:

“Secondly, 14.1% of selected subjects were not traced and involved in the analysis, with the risk of selection bias. The main reasons for loss to follow up were migration, out for employment, changed address or telephone number, death, and refuse to join the study, etc. We further compared some key characteristics of 670 TB patients involved in the analysis and 110 patients lost to follow up. No significant difference was found in the distribution of gender between these two groups (The proportion of men was 71.2% and 73.0%, respectively). However, the study subjects were a little bitter older than those lost to follow up (51.4±19.5 vs. 49.4±19.0 years old). It might attribute to the higher migrant rate among young patients, which resulted in the higher proportion of loss to follow up among them.”

2. Half of the 82 non-adherent patients were initial defaulters, and the other half took less than 90% of the prescribed medicines. For this latter group, it should be described how many doses were missed and how many stopped treatment altogether.

Response: In the present study, non-adherence was defined as “patients who had missed 10% of the total prescribed doses of TB drugs were deemed as non-adherent”, based on “China Guidelines for TB Control and Prevention”. Among 82 non-adherent patients, half of them interrupted intermittently (totally missed more than 10% doses) and 41 terminated before the prescribed course (at least missed last 10% doses).

3. It is well possible that factors associated with initial default are at least partly different from factors associated with incomplete adherence. This should be explored and results should be included. 4. Some of the factors mentioned as associated with treatment interruption (Table 2 and text) in fact are not applicable for initial defaulters. Therefore, these results should be stratified also by initial defaulters and those with
incomplete adherence.

Response: As mentioned above, in this study, we defined patients who had missed 10% of the total prescribed doses of TB drugs as non-adherent, which included intermittent interruption (totally missed more than 10% doses) and patients stopped treatment before the prescribed course (at least missed last 10% doses). Totally, there were 82 non-adherent patients and only half of them stopped treatment before the prescribed course. Within 41 patients who stopped treatment before the prescribed course, some were initial defaulters and some defaulted during the treatment episode. Due to the limited sample size of initial defaulters, we did not specifically explore the risk factors associated with it.

5. The adjusted OR's on risk factors for non-adherence are adjusted only for age and sex, while the other factors may confound each other as well. The authors should preferably build a multivariate model with complete adjustment, or at the minimum give information on the existence of confounding and effect-modification between the other factors and explain why they did not explore complete adjustment.

Response: In the revised version, we build a multivariate model with complete adjustment, as the reviewer suggested (see Table 1 in the manuscript).

4. Discussion: the paragraphs on financial burden, treatment of adverse reactions, and social context are not derived in any way from the results of this study but just a review of published literature. The discussion should relate its own findings to those found by others.

Response: We revised discussion and compared our results with findings from other studies.

Minor essential revisions
1. Background: I suspect more studies on patient adherence from China are published than the one referred to. It is recommended to give the results from other Chinese studies as the factors found there are expected to be more similar to the ones found in other countries.

Response: In the revised version, we introduced more studies on patient adherence in China.

“Studies of socio-economic and behavioral factors affecting patient’s adherence have
been conducted in several areas [6, 12-14]. In Hong Kong, China, by matching 102 defaulters and 306 controls, it was found that tobacco smoking, past TB with default, poor adherence, treatment side effects, and subsequent hospitalization were associated with patient’s treatment default [15]. A study combined with quantitative and qualitative method in Fujian, China, reported adherence of treatment was associated with patient’s intentioned factors and the health services provider’s behaviors, but not with gender, age, career, education level and social stigma [16]. Another study in Chongqing of China, by interviewing with patients and health staff, indicated that additional tests and drugs, especially liver protection drugs, may be considerable financial barriers to starting and continuing treatment [6]……

2. Information should be included on whether a power calculation was performed before the study.

Response: The sample size was calculated based on Openepi software (www.openepi.com). Given that confidence interval=95%, estimated non-adherent proportion=20%, relative precision=0.2P, design efficiency(deff)=2, the estimated sample size=768. For each study site, the estimated sample size is 768/13=59.1. Thus in each county, we set the sample size as 60. Totally, the estimated sample size is 780.

3. Information should be included on how many patients and health workers were interviewed for the qualitative part of the study.

Response: In the revised version, we described how many patients and health workers were interviewed for the qualitative part of the study.

“For qualitative study, 20 TB patients (from Xuanwu and Taichang, men 15, women 5, newly treated 18, previously treated 2) were invited for in-depth interview. A semi-schematized guide covering general as well as specific questions was utilized. The theme of in-depth interview focused on patient’s health-care seeking history, knowledge and attitude to TB and their adherence to the treatment. Ten local health workers from Taichang, including 5 village doctors and 5 community hospital doctors, were also invited for in-depth interview. Themes for in-depth interview included the current TB control program in the village/community, the main difficulties in implementing DOTS, advices for the current TB program, treatment adherence of patients in corresponding village/community and main reasons for non-adherence.
In-depth interviews were conducted in local health facilities with Chinese Mandarin, lasted 20-40 minutes and were tape-recorded with permission.”

4. Results (and abstract): 83.1% were treated under direct observation. Then it is not correct to say it is more than 83%, it is 83%.

Response: We have revised it in the new version.

5. the term 'treatment interruption' is not correct for most cases who were classified as non-adherent in this study and this term should not be used this way.

Response: We have revised it in the new version.

6. Abstract. in the results, instead of mentioning which characteristics are associated with non-adherence, also give the direction of the result. E.g. low education instead of educational background.

Response: We have revised it in the new version.

Discretionary revisions
1. In Table 2, the distribution of different characteristics of adherent versus non-adherent patients is given (i.e. % of males in both adherent and non-adherent patients). This reviewer would rather see the total number of males, and the number and percentage of non-adherent male patients.

Response: We revised table 1 and presented the results as the reviewer suggested.

2. Data collection. I am sure that selection of health workers was not based on age gender and treatment history. It is not clear whether patients with their own health workers were selected for the qualitative study, or some patients and some health workers without a relation between them.

Response: In the revised version, we described the basic characteristics of patients and health workers being interviewed for the qualitative part of the study.

“For qualitative study, 20 TB patients (from Xuanwu and Taichang, men 15, women 5, newly treated 18, previously treated 2) were invited for in-depth interview. A semi-schematized guide covering general as well as specific questions was utilized. The theme of in-depth interview focused on patient’s health-care seeking history, knowledge and attitude to TB and their adherence to the treatment. Ten local health
workers from Taichang, including 5 village doctors and 5 community hospital doctors, were also invited for in-depth interview. Themes for in-depth interview included the current TB control program in the village/community, the main difficulties in implementing DOTS, advices for the current TB program, treatment adherence of patients in corresponding village/community and main reasons for non-adherence. In-depth interviews were conducted in local health facilities with Chinese Mandarin, lasted 20-40 minutes and were tape-recorded with permission.”

3. The term laobing is not known to most foreign readers and it would be helpful to give the translation of the word into English.

Response: “Laobing” is a traditional term of tuberculosis in ancient China, which can be translated as “phtisis”. Considering the term laobing is not known to most foreign readers, we revised the sentence as the following:

“TB was named as “Phtisis” and regarded as a deadly disease several years ago in China.”

References


