Author's response to reviews

Title: Default from tuberculosis treatment in Tashkent, Uzbekistan; Who are these defaulters and why do they default?

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Author's response to reviews: see over
Tashkent 20 May, 2008

Dear Dr. Marlee,

On behalf of all authors I wish to thank the reviewers for their comments; we have made the necessary adjustments in response. Please find below the comments of both reviewers and our response.

Reviewer Douglas Fraser Wares:
Major Compulsory Revisions
The authors present important data and information on what appears to be a weak aspect of the TB programme in Tashkent, Uzbekistan, namely an unacceptably high default rate amongst new PTB patients. The manuscript however needs to be revised in order to give readers a better understanding of the specific setting, namely the setting of TB control in a Former Soviet Union country. There is need of some discussion on why the default rate overall in Uzbekistan is significantly lower than in Tashkent. Also the authors need to make the discussion section clearer and crisper in the presentation of possible interventions and solutions to overcome both the systems and socio-economic issues that they have identified.

- We have revised the manuscript, provided more detail about the set up of TB control in the former Soviet Union and about the current TB program in Uzbekistan. Comments on the difference in default rates between Tashkent and Uzbekistan as a whole and comments on possible interventions are provided and we discuss them in response to the specific comments below.

Specific comments
“Background” section
1. To give readers a better understanding of the specific setting, it would be useful if the authors provide more details of the actual TB systems in place in Uzbekistan and population data for the country and Tashkent. What TB services and facilities are available generally in Uzbekistan, and specifically in Tashkent? Is it correct that like in many countries of the FSU previously as well as being a vertical service with much emphasis on in-patient care, TB services in Uzbekistan also provided adherence enablers to TB patients e.g. provision of transport vouchers, nutritional support, etc? If correct and if such enablers have now been withdrawn, along with the overall weakening of the health services post break-up of the FSU, this is important background information to be provided to readers.

- In response to these comments the system has been described in more detail in the first 2 paragraphs of the ‘back ground’ section. Currently no enablers are being used, the 7th paragraph of the ‘discussion’ section mentions enablers as a possible solution for certain groups of defaulters.
2. Treatment regimens need to be provided as it is not clear what actually is the duration of the intensive phase treatment.
- We have changed this section as follows: *Treatment regimens have been standardized; the regimen for new patients consists of a 2 months intensive phase with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol, followed by a 4 month continuation phase with Rifampicin and Isoniazid*.

3. Both failure and death rates in Tashkent are high. Is there data to answer whether these high rates could be due to MDR-TB or HIV co-infection? If known are MDR-TB and HIV rates different in Tashkent to other parts of the country?
- The only drug sensitivity data available for Uzbekistan are from the Karakalpakstan region for 2001 and from Tashkent for 2006. MDR-TB was found among 13% and 14.8% respectively of new pulmonary TB patients. Both areas have higher failure and death rates than the average for Uzbekistan, most probably this is related to MDR-TB. Data from other regions are not available, making it impossible to properly assess the impact of MDR-TB on death rates.

- For 2006, WHO estimate the TB incidence rate (all forms) for Uzbekistan at 121/100,000, whereas the incidence rate for HIV positive TB cases (all forms) is estimated at 1/100,000. In our study we found a higher than expected HIV prevalence among new cases registered, 5% among defaulters and 6% among controls (table 1). Relatively high death rates in Tashkent may therefore be related to HIV. However since we sampled only defaulters and patients who have successfully completed treatment, we are unable to assess the exact impact of HIV on death rates.

"Results" section
1. If the assumption that a 6 month SCC regimen was used, the median of 200 days on treatment for the control group suggests that there was a significant amount of treatment interruptions even in this control group. The same appears to be true for those who defaulted after completing the intensive phase as median given for this group is 89 days. Or is this an artefact from using median and not mean duration?
- The reason for longer duration of treatment is the fact that treatment is often extended based on radiographic findings. We have added this information to the 2nd paragraph of the background section: ‘However treatment is still under the control of specialist doctors and duration of both phases of treatment is often extended based on radiographic findings’.

"Discussion" section
1. The authors present data which suggest that default rates amongst new smear positive PTB patients are significantly different in Tashkent compared with the other parts of Uzbekistan as for the former it is given as 18% and for Uzbekistan overall as 7%. However the authors do not discuss or suggest any reasons why the default rate is significantly higher in Tashkent and/or why lower in other parts of the country. It would strengthen the paper if this difference was discussed by the authors. Are there differences in the available health care facilities? Is ambulatory care more common outside of Tashkent? Are there other possible reasons such as less unemployment etc?
- Social problems associated with default are indeed likely to be more common in urban areas than in rural areas, we have added this information to the first paragraph of the ‘discussion’ section.

2. Unlike other studies, males appear not to be significantly at higher risk of defaulting. Also default similar across all age groups. Can the authors suggest why this was the case in Tashkent?
- We did find differences in default rates of the different sexes and of the different age groups although the differences were not significant. We revised the 5th paragraph of the ‘results’ section
to explain that (in accordance with table 1) men were more likely to default than women and
dividuals aged 65+ were more likely to default than young people. However these differences
were not statistically significant, the study may just have lacked power to show significant
differences.

3. It appears from the study that smear positive cases had a lower risk of default.
The authors postulate that this could be due to over-diagnosis of smear negative cases.
Do the authors have data or information to back this statement up?
Alternatively could it be that there more emphasis was given by the system/staff to the
smear positive cases compared to those who were smear negative? Or if HIV co-infection
is common amongst TB patients in Tashkent, with a resultant greater proportion of smear
negative cases amongst those co-infected, could it be that this is the reason that smear
negative cases have a greater default rate as they are not improving on TB treatment?
- We have added the following information to the 2nd paragraph of the ‘discussion’ section: ‘Smear
negative pulmonary TB may have been over diagnosed, only 394 out of 1087 pulmonary TB
patients (36%) were smear positives’. To us 36% smear positives is low. We do not have other
data to support the statement that smear negative pulmonary TB might be over diagnosed. We
found no association between HIV and default (OR 0.78, 95% CI 0.26 - 2.30).

4. Both failure and death rates in Tashkent are high. Could MDR-TB or HIV co-infection
be playing a role here? Also could MDR-TB or HIV co-infection be playing a role in
default? Such patients may not do well on SCC and may choose to leave treatment if not
getting better.
- We found no apparent association between HIV infection and default (OR 0.78, 95% CI 0.26 -
2.30); in response to the comments from the reviewer this information has been added to the
‘results’ section (4th paragraph). DST data are not available for the 2005 cohort, therefore it was
not possible to assess the link between MDR-TB and default.

5. The authors state that in a recent systematic review of default in developing countries,
default occurs more in the CP. Although not having seen the paper referenced by the
authors, this somewhat contradicts findings of many studies that suggests default is
common in IP and around the time of the switch to CP.
- The article referred to is inconclusive but it does state that: ‘Data suggest, but do not conclude,
that the majority of defaulters across the studies completed the 2-month intensive phase of
treatment’.

Also routine admission of TB patients is widespread in the FSU countries unlike in the
majority of developing countries where treatment is fully ambulatory. The authors highlight
that routine admission in a TB hospital is a major obstacle to patient’s adherence to
treatment. It is not exactly clear how long the routine hospitalization of TB patients is for
TB patients in Uzbekistan. The authors suggest that it “…should be limited to a maximum
of 60 days…” suggesting that at present hospitalization is meant to be for longer than 60
days. If this is correct, then is it correct that hospitalization is expected to be for a longer
time period than the duration of IP, assuming the IP used is 2 months?
- In response to the request for more information on the current system of TB control in Uzbekistan
we have added the following lines to the ‘background’ section: ‘Patients are still hospitalized
during the intensive phase but continuation phase treatment is provided on an out-patient basis,
usually at a general primary health care (PHC) facility. Treatment regimens have been
standardized; the regimen for new patients consists of a 2 months intensive phase with Isoniazid,
Rifampicin, Pyrazinamide and Ethambutol, followed by a 4 month continuation phase with
Rifampicin and Isoniazid [4]. However treatment is still under the control of specialist doctors
and duration of both phases of treatment is often extended based on radiographic findings'. We believe this answers the question.

As the authors quite correctly highlight there appears to be “system failure” in ensuring that patients seamlessly transition from in-patient care to ambulatory care. How would the authors ensure that the referral system is improved?
- We believe that we make a suggestion for improvement of the system in the 6th paragraph of the discussion: ‘appoint for each TB patient a case manager who will be responsible for following up the patient from the moment of diagnosis until he is finally discharged from treatment’.

Also if in-patient facilities have also been weakened in recent years, does routine admission of patients also not run the risk of higher rates of nosocomial transmission?
- We agree and have added the following line to the ‘discussion’ section: ‘Since hospitalization appears to be a problem, a further shift towards ambulatory treatment may reduce default. As an added benefit this would reduce the potential for nosocomial transmission, Gelmanova et al. [12] showed prolonged admission in TB hospitals to be an important risk factor in acquiring MDR-TB’.

Risk factors for default appear to be being homeless, unemployed, a pensioner and alcohol abuse i.e. as a generalization, facets of the poor and marginalized sections of the population. Along with wider use of ambulatory care, what do the authors suggest in respect to addressing the socio-economic factors that they have identified as risk factors for default? If previously enablers and incentives were available to TB patients, should they not be re-introduced? In paragraph 3 on page 7, the authors mention certain groups which may require special attention. This is a crucial part of the discussion and would benefit from further discussion of specific interventions to address the needs of these groups who belong to the poorer and marginalized sections of the community. I here would refer the authors to a recent publication from Keshavjee et al titled “Treating MDR-TB in Tomsk, Russia.” in the Ann NY Acad Sci 1-11(2008) doi: 10.1196/annals.1425.009 in which similar issues are discussed along with the interventions made to address them.
- We have included the article mentioned as a reference based on which we advocate a flexible approach to ambulatory treatment for homeless and alcoholics (paragraph 7 of the ‘discussion’ section). In the same paragraph we also make the recommendation to design a system of social support including the use of incentives and enablers for pensioners and unemployed.

Minor Essential Revisions
“Background” section
1. The flow of the second paragraph needs to be reworked as it jumps back and forth from Uzbekistan to Tashkent, and becomes a little hard to follow.
- In response to this comment we have split the paragraph into one paragraph on Uzbekistan and one paragraph on Tashkent.

Discretionary Revisions
“Results” section
1. A flowchart could be provided to show the drop-outs at each stage in the sampling process eg start with 153 defaulters – 144 had records available – 126 had consistent data in TB Register / same for controls.
- We have considered this suggestion but eventually decided not to include this flow chart as it might distract attention from the main findings presented in this paper.
2. It would be of interest to know how many of the so-called “non-DOTS” group were “refusals of further treatment” during the in-patient period and/or “expulsions” from the in-patient ward.

- Out of 42 ‘Non-DOTS’ cases, 19 (45%) had either ‘refused further treatment’ or ‘violated hospital rules’. Since there was no difference between ‘Non-DOTS defaulter’ and other defaulter, we just restricted ourselves to the statement that: ‘There were no statistically significant associations between ‘Non-DOTS treatment’ and any of the other factors assessed’.

Reviewer: Bernt Lindtjorn

This paper identifies some of the variables that other researches have found, but also discusses reasons for defaulting that can be addressed through changes in policy. This is related to the way the health institutions deal with “difficult patients”.

How do the authors plan using the findings of this study? Can they propose specific interventions suitable for this region? A pilot study that could change policy?

- We believe that this study can be used as an advocacy tool by policy makers; we recommend making TB treatment more patient friendly by promoting ambulatory treatment. For pensioners and jobless, we recommend social support measures such as incentives and enablers; for homeless and alcoholics we recommend a flexible approach to ambulatory treatment. (7th paragraph of the ‘discussion’ section).

I hope this answers your questions; please do not hesitate to contact me in case any further clarifications are required.

With kind regards,

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