Reviewer’s report

Title: The limitations of sputum microscopy for the diagnosis of HIV-associated pulmonary tuberculosis in Tanzania

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Reviewer: Dick Menzies

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Strengths of the paper

1. Diagnosis of tuberculosis in HIV infected individuals is difficult and therefore the topic is of considerable interest.
2. The laboratory facilities were typical of those in many low income countries. In particular the use of LJ media which is the least expensive and least complex method of cultures makes the results more generalizable to other low income settings.
3. The laboratory had participated in a program of external quality control and had performed well.
4. The study was prospective and the patients were consecutive.
5. The study was well executed and with large number of patients.
6. The comparison of semi-quantitative smear and culture results is interesting - a real plus.

Major required revisions

1. Interpretation my most serious objection to the paper is in their interpretation of the findings. This paper describes a screening or active case finding program among HIV infected individuals. Therefore persons detected with disease are inevitably to have fewer symptoms and less extensive disease. In most studies of the results of screening for active TB the majority of cases detected are smear negative. Hence their findings are not a reflection of the limitations of the test but rather a reflection of the patient population studied, and the inherent bias that any screening program will detect less advanced forms of disease. Hence their conclusion should NOT be that cultures are needed for diagnosis of pulmonary TB when patients are presenting with symptoms (ie passive case-finding as recommended by the WHO). They COULD conclude that cultures are needed if one is screening for active TB. This is a very different conclusion but would be founded on the data they present. The authors should review the literature on active screening for TB disease in other settings and compare their results with these other screening studies, where most patients are smear negative.

2. Clinical information on those who were detected with active TB along the
lines of point 1 above it would be of great interest to know more about the patients who were identified. Were they symptomatic, did they have other manifestations of HIV, were chest x-rays done and if so what were the findings? I could understand that chest x-rays would not be done routinely but perhaps they were done in the subgroup found to have active TB? Some description of the type and extent of radiographic abnormalities, and/or other clinical indicators of disease severity would help interpret the findings better.

3. **False positive smears**

The authors have assumed that positive smears with negative cultures are false positive smears. However, LJ media is well known to have lower sensitivity for the diagnosis of active TB (80-85% in most studies). This should be acknowledged, and it would be of great interest to know more about the group of patients with positive smears and negative cultures. Were these individuals treated, were chest x-rays done, or other investigations performed in order to decide whether these were true or false positive smears?

4. Similarly, I would like to know more about those who are smear negative yet culture positive. For example, if three cultures were done, were they concordant positive or were the positive cultures also discordant (ie 1/3 or 2/3 positive)? Earlier studies have shown that patients who are smear negative but culture positive often have discordant cultures.

5. The results of sequential sputum examinations are somewhat surprising and I am not sure they inform the current debate on the number of sputum smears that are required. The added yield of the third specimen is in contrast to the findings of a recently published systematic review. In fact the third added yield simply because the second specimen contributed so little. (and so, in fact two specimens were enough in this study too just the order of the specimens is unusual). It was the morning specimen collected by patients at home and brought with them to the clinic, that had poor yield. This is quite surprising because many believe this should be a better specimen because it is the early morning specimen obtained when people first get up. Instead it had actually worse yield than the two on the spot specimens.

The authors should provide further information about this. For example, a table among patients with any positive culture or smear showing how many were positive on the first, and negative on the second test, or vice versa. Similarly comparing the first and third as well as second and third. If there was a tendency that the second smear and culture was generally worse than the first and the third, this would suggest problems in sputum collection at home. This may reflect poor instructions, or very good instructions for the spot specimens. It is even possible that patients submitted less good specimens intentionally, because they were highly motivated to participate in the study and believed that being diagnosed with active TB might lead them to be excluded. (This last is pure conjecture on my part of course).

Minor but compulsory changes
1. The abbreviations SC and SM should be eliminated. It is really not that helpful for the average reader and spelling out sputum microscopy and sputum culture is not that onerous either on the writer nor the reader. The gain in clarity is worth it.

What next?

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Based on your assessment of the validity of the manuscript, what do you advise should be the next step?

- Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest

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- An article whose findings are important to those with closely related research interests

Quality of written English

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- Acceptable

Statistical review

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Is it essential that this manuscript be seen by an expert statistician?

- No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests

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I declare I have no competing interests