Author's response to reviews

Title: Clinical characteristics and initial management of patients with tuberculous pericarditis in the HIV era: the Investigation of the Management of Pericarditis in Africa (IMPI Africa) registry

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Author's response to reviews: see over
Review 1 (Alison Elliott)

Major compulsory revisions

1. “Establishing such a registry is an interesting idea and a lot of work, and presumably the authors have some future plans for collaborative studies? In order to justify the publication of baseline, descriptive findings, it might it be helpful if this were explained at the outset”

We agree with the reviewer that a motivation for descriptive study such as ours is required. We have inserted a statement in the Background section (paragraph 3, sentence 2) indicating that the registry was designed to provide contemporary information on the clinical characteristics of patients with tuberculous pericarditis in preparation for a collaborative clinical trial of the effectiveness of adjunctive steroids in tuberculous pericarditis. For example, the observational study has provided an estimate of the distribution of pericardial syndromes (i.e., effusive vs. constrictive) and the proportions of patients with clinically apparent HIV infection across wide geographic areas of Africa. This information would be used to target the trial to the effusive forms of pericardial tuberculosis (which is the dominant mode of presentation).

2. “The authors state (methods, first paragraph) that the study was designed to examine the impact of HIV infection on clinical presentation, etc. It therefore seems unfortunate that about half the participants did not have an HIV test. Rapid HIV tests are not difficult to perform, and for the numbers of participants involved would not cost much. Despite the arguments presented for working within the constraints of the health systems involved, might it be possible to make these available to the study centres in future?”

We discuss this problem of lack of complete information on the participants, such as serological HIV testing in about half of participants, and microbiological confirmation of tuberculosis in an even lower proportion of cases, in the Discussion section (under ‘What are the limitations of the registry?’) as a major weakness of the study. However, we believe that the observational data provided by this large multi-centre study reflects contemporary practice in Africa, and lays a good basis for the improvement of healthcare
and planning future studies. However, we agree with the suggestion of the reviewer to make HIV test kits available to collaborating centres in the future.

3. “Classification of HIV status by clinician’s impression strikes me as problematic. It seems probable that clinicians would be more likely to consider sicker patients, and patients with disseminated tuberculosis, as having “clinical HIV disease”. Indeed, the association between disseminated tuberculosis and HIV is well documented, so one could argue that it would be correct for a well-informed clinician to conclude so. This would mean that the association between worse disease and HIV was “caused”, to some extent, by the clinicians’ perceptions of HIV disease, rather than by HIV. Did the clinicians specify the “clinical grounds” (page 4) on which they based their assessment; or simply give their overall impression? I think it would be appropriate to present the analysis by serological status for the subgroup for which sero-status is known, at least in addition, if not instead of, the current analysis, to show whether the same conclusion would be reached. It seems likely that one would find that the factors of interest, particularly the evidence of myocardial involvement, would appear largely among those with most advanced HIV disease.”

The attempt by clinicians to classify their patients into whether they are likely to be HIV infected or not based on clinical signs of immunosuppression is common in African medical practice. Indeed, there are a number of clinical case definitions for HIV/AIDS that have been developed in order to predict the HIV status of the patient based on clinical criteria (e.g., Colebunders R et al Lancet 1987;1:492-4; Lepage P et al AIDS 1989;3:221-5; Chibatamoto PP et al Cent Afr J Med 1996;42:141-4; Weniger BG et al J Acquir Immun Def Syndr 1992;5:1212-23). In our simple, pragmatic observational study, we did not specify the criteria to be used in this classification, but required clinicians to indicate whether HIV disease was suspected on clinical grounds.

In response to the reviewer’s recommendation, we have presented the analysis of the subgroup with serological tests for HIV as the last paragraph in the Results section (see ‘Findings in patients with known HIV serological status’), and have supplied the Tables as Additional_file 1. This analysis confirms that HIV sero-positivity is associated with ECG changes of acute pericarditis. There were some discrepancies in the outcomes that were associated with clinical HIV disease and being HIV positive. For example, radiological evidence of pulmonary disease was associated with clinical HIV disease, but not with being HIV positive. We think this may have been related to the smaller numbers of patients who were tested for HIV in the study. We have, therefore, not based our conclusions on the sub-group analysis because of the major regional differences in the frequency of testing for HIV.

Minor revisions

1. “Methods, page 4: As well as defining criteria for haemodynamic instability it would be helpful if the New York Heart Association functional classification were defined. They have a website that could be referred to, also”

We have inserted an explanation of the New York Heart association functional classification, and added the website reference in the second last paragraph on page 4, under ‘Methods’.
2. “Discussion, page 6: The first statement may be a little sweeping; such a result would require a registry with less selection bias as to regions included.”

We agree with the reviewer’s comment that the statement may be generalizing more widely than is justified by the data. We have revised the statement to indicate that it refers to ‘parts of Cameroon, Nigeria and South Africa’.

3. “Discussion, page 6. Is there some text missing after “with the exception of Cameroon”? Or perhaps that statement just needs a little more explanation?”

We have added the explanatory statement to clarify the point being made.

4. “Discussion, page 6, end of third paragraph. Is 17 the correct reference? I have only been able to access the abstract, but it appears to be about ECG findings rather than HIV prevalence. Prevalence much higher than 55% has been reported for tuberculous pericarditis in parts of Africa where HIV is more prevalent, including Tanzania as mentioned in the previous sentence, so I wonder about this statement in any case.”

We agree with the reviewer, and have deleted the statement ‘which is similar to estimates obtained in other studies’ as suggested by the reviewer.

Reviewer 2 (Lesley LJ Burgess)

Reviewer 2 suggests that our conclusions are not supported by the data. Our conclusions are two fold. First, a statement of the key findings of the study (i.e., the association of ECG changes of myopericarditis, poor effort tolerance, and disseminated tuberculosis in patients with pericardial tuberculosis and clinical signs of HIV infection) which is based on the findings in the study. Second, we speculate that pericardial tuberculosis and clinical evidence of HIV infection may select a high risk group for intensive treatment.

We believe that these are a reasonable conclusion to draw from these data.

Major compulsory revisions

1. “The authors describe the methodology for indirect tests (eg ADA) but these results are not presented. Given that the laboratory diagnosis is difficult in this group of patients, it would be beneficial to be able to view the clinical culture results.”

The results of pericardial fluid analyses are presented in Table 6 (i.e., ADA, microscopy and culture).

2. “The details of treatment that these patients received is not specified in terms of drug or route. As this is a fairly contentious issue, this information would be of interest.”

We have indicated in the text that all the drugs (anti-tuberculosis, adjunctive steroids, and anti-retrovirals) were administered orally.

3. “In the methodology, the authors mention that patients were followed up for a period of 6-12 months. This data is not presented in the results section.”
This report is concerned with the baseline characteristics of the patients enrolled in the registry. We do mention in the ‘Methods’ section that the information on the follow-up is currently being analyzed and will be the subject of a subsequent report.

**Minor revisions**

1. “*Methodology, page 4, paragraph 2: adenosine deaminase is spelt incorrectly.*”
   The spelling error has been corrected. Thank you.

2. “*The format of the references: the titles should not be bolded.*”
   The format of the references has been set to the style of BMC Infectious Disease, which requires the titles of the reference to be in bold lettering.

3. “*Table 4 is missing a legend to explain the symbols used*”
   The Table 4 legend to explain the symbols has been inserted.

We have also made the following changes to the manuscript:

1. **Title:** We have changed the title of the manuscript from 'Clinical characteristics and management of patients with tuberculous pericarditis in Africa in the HIV era' to ‘Clinical characteristics and initial management of patients with tuberculous pericarditis in the HIV era: the *Investigation of the Management of Pericarditis in Africa (IMPI Africa)* registry’
2. **Background:** First paragraph, first sentence – we have replaced ‘…primary-care and secondary care…’ with ‘clinical’.
3. **Results:** we have deleted the statement ‘…of patients with suspected tuberculous pericarditis in Africa’ from the first three subheadings because of redundancy.

Yours sincerely

Bongani M. Mayosi