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

Authors:

Bongani M Mayosi (bmayosi@uctgsh1.uct.ac.za)
Charles Shey Wiysonge (wiysonge@uctgsh1.uct.ac.za)
Mpiko Ntsekhe (mntsekhe@uctgsh1.uct.ac.za)
Jimmy A Volmink (jvolmink@cormack.uct.ac.za)
Freedom Gumede (gumede@stats.uct.ac.za)
Gary Maartens (gmaartens@curie.uct.ac.za)
Akinyemi Aje (ajeyemi@yahoo.co.uk)
Baby M Thomas (bmookens@worldonline.co.za)
Kandathil M Thomas (kthomas@wildcoast.co.za)
Abolade A Awotedu (awotedu@getafix.utr.ac.za)
Bongani Thembela (thembelab@xsinet.co.za)
Phindile Mntla (tiisetso@ul.ac.za)
Frans Maritz [Late] (maritz@ttctrials.co.za)
Kathleen Ngu Blackett (kathleen@peaslake.abel.co.uk)
Duquesne C Nkouonlack (dukes262001@yahoo.fr)
Vanessa C Burch (vanheusden-burch@kingsley.co.za)
Kevin Rebe (krebe@icon.co.za)
Andy Parish (andyp@mweb.co.za)
Karen Sliwa (sliwak@medicine.wits.ac.za)
Brian Z Vezi (brianvez@ialch.co.za)
Nowshad Alam (nowshadalam@hotmail.com)
Basil G Brown (bobrown@mweb.co.za)
Trevor Gould (tgould@pgwc.gov.za)
Tim Visser (tavisser@pgwc.gov.za)
Muki S Shey (shymuk001@mail.uct.ac.za)
Nombulelo P Magula (NMagula@tufts-nemc.org)
Patrick J Commerford (pjcomfrd@uctgsh1.uct.ac.za)

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Author's response to reviews: see over
04 December 2005
The Editor
BMC Infectious Diseases
Dear Sir/Madam

RE: MS: 1562579947779057 - 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

Thank you for the opportunity to submit a second revision of the manuscript for consideration for publication in *BMC Infectious Diseases*. We are delighted with the second reviewer’s recommendation that our paper should be published in *BMC Infectious Diseases*.

The first reviewer has raised a number of important concerns, which we have addressed below. We have presented the reviewer’s comments in quotation marks and our responses are indicated below each statement:

**Reviewer 1 (Alison Elliott)**

*Major compulsory revisions*

1. “Abstract: It does not seem to be quite correct to say that the findings were identical when stratified by serological HIV status. First, is “stratified” the correct term? That would suggest that the authors looked at the associations with clinical HIV disease in the serologically HIV positive stratum and the serologically HIV negative stratum, and the associations found for clinical HIV disease were the same in each stratum as the associations observed overall. I think what is meant is that the associations with serological HIV status were identical to the associations with clinical HIV status. Might “similar” be a better word than “identical”? The weak association with PR segment changes which, according to the discussion, is the justification for suggesting myocardial involvement in patients with clinical HIV disease, was completely absent when analysed by serostatus. The association with pulmonary tuberculosis was not so marked and no longer statistically significant; this would be in keeping with a tendency for physicians to assume that patients with evidence of tuberculosis at more than one site have HIV infection. Thus, although one may conclude that clinical HIV disease is associated with myopericarditis and disseminated tuberculosis, it may not be helpful to do so, since the evidence from this study is that real HIV infection is not associated with myocardial disease and only weakly associated pulmonary disease. On the other hand the association with ST elevation and was stronger for serological HIV status and, interestingly, associations with haemodynamic instability and with radiological cardiomegaly emerged. Perhaps HIV positive people have a more rapid accumulation of a larger amount of fluid, causing greater compromise? Indeed suggesting, as the authors propose, that more intensive early management is warranted in HIV positive cases (and, perhaps, that the relatively lower rate of use of steroids in this group may be inappropriate).”
We agree wholeheartedly with the reviewer’s comments and accept all the suggestions made above. We have revised the manuscript to emphasize the cardiac abnormalities that are associated with clinical HIV disease and HIV seropositivity. We have removed the emphasis on the association with disseminated TB as this is a given in this context, as pointed out by the reviewer.

We have incorporated the suggestions as follows:

[a] In the ‘Abstract’, we have replaced “The results were identical when statistical analysis was stratified by serological HIV status” with “Similar results were obtained for serological HIV status”.

[b] The justification for the myocardial changes is in fact the ST segment changes that were observed, which are an accepted marker of ventricular myocardial injury. PR segment deviation is thought to be indicative of atrial inflammation. To emphasize this point, we have amplified this statement, in the ‘Results’ section, under ‘Diagnostic evaluation’, first paragraph, last sentence:

“However, clinically HIV infected patients were more likely to have S-T segment elevation (P=0.03), which is indicative of myocardial injury.”

The strong relationship of HIV serostatus with ST segment elevation supports our contention that HIV infection is associated with myopericarditis in tuberculous pericarditis. There is internal consistency in this observation in that HIV positive patients have greater cardiomegaly and haemodynamic instability, which would be in keeping with a more severe cardiac disease than in HIV negative patients. We agree with the reviewer that these data support our important observation that tuberculous pericarditis should be regarded as a more severe disease in HIV-infected individuals.

2. “Results: third paragraph. There was a bias in HIV testing, with tests done in 53/74 (72%) cases with “clinical HIV disease” and 43/111 (39%) of cases without clinical HIV disease (p<0.001). This would be worth mentioning as it may have affected the findings for sensitivity and specificity of clinical diagnosis and may have influenced the reliability of observations regarding associations with serostatus.”

We accept this suggestion, and have incorporated the following statement in the ‘Results’ section, under the sub-heading ‘Clinical profile’, last paragraph:

‘There was a bias in HIV testing, with tests done in 53/74 (72%) of cases with clinical HIV disease and 43/111 (39%) of cases without clinical HIV disease (p<0.001). This bias may have affected the findings for sensitivity and specificity of clinical diagnosis and may have influenced the reliability of observations regarding associations with serostatus.’

3. “Thus, in the first paragraph of the discussion, it seems to me that rather strong assertions are made based on clinical diagnosis of HIV. It would be possible, in theory, that the associations observed were nothing to do with HIV and entirely the result of physicians’ preconceptions about HIV. To report this incautiously might lead to reinforcement of such preconceptions, so it is important to determine whether the associations are real. Now that some results by serostatus are available, the idea that HIV is associated with a more advanced functional disability is supported by the associations shown for serostatus and by the additional result
regarding haemodynamic instability. Thus it is of interest to suggest that this might be the case, pending further studies with a less biased assessment of HIV status. On the other hand, it may not be helpful to suggest that this study confirms that HIV-associated tuberculous pericarditis occurs in the context of disseminated tuberculosis: other studies suggest that, but this study could be interpreted as showing that concurrent pulmonary involvement is more common in HIV negative cases than physicians think it is.”

We have modified the first paragraph of the ‘Discussion’ section largely along the lines suggested by the reviewer. We have deleted reference to the association with disseminated pulmonary disease as this is well established. We have not discussed the issue of concomitant pulmonary tuberculosis in HIV negative patients because it was known to be present in at least 30% of patients in the pre-HIV era (Mayosi BM, Volmink JA, Commerford PJ. **Pericardial disease: an evidence based approach to diagnosis and treatment.** In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, eds. *Evidence Based Cardiology*. 2nd edition. BMJ Books 2002, BMA House, London.)

4. “The last two paragraphs of the discussion might also be reconsidered in this light. Does not the evidence from serostatus cast doubt on the evidence of myocardial involvement? Might it not be better to say that the conflicting results regarding the PR segment changes suggest the need for a more rigorous study? And the results for serostatus did suggest more radiological cardiomegaly in HIV positive cases (in contrast to the last sentence of the paragraph); thus a larger accumulation of fluid could explain the greater functional and haemodynamic instability. Incidentally, this paragraph is the first mention of greater dyspnoea or miliary disease in HIV-positive patients; if these were objectively measured they could be mentioned in the results; if these comments are speculative, they might be better omitted?”

As mentioned previously, the ST segment elevation on ECG is indicative of myocardial involvement, not PR segment deviation. Therefore, the strong association of HIV serostatus with ST segment change supports the contention that HIV-associated pericardial tuberculosis is a myopericarditis. However, we do accept that the greater accumulation of fluid may explain the greater functional and haemodynamic instability in the patients.

We have omitted the speculative comments referring to miliary tuberculosis in the last paragraph of the discussion, as suggested by the reviewer.

5. “Paragraph on limitations of the study: Suggest addition of a sentence stating that associations with clinical HIV disease should be interpreted with caution, and that, given the low percentage tested, even associations with HIV seropositivity may have been subject to bias.”

We accept this suggestion, and have inserted the following statement in the ‘Discussion’ section, under ‘What are the limitations of the registry?’:
‘The associations with clinical HIV disease should be interpreted with caution, and that, given the low percentage tested, even associations with HIV seropositivity may have been subject to bias.’

**Minor revisions**

6. “Results, second paragraph, last sentence: “association” might be a better word than “interaction” which has a specific statistical meaning which would not be correct here.”

The suggestion is accepted.

7. “Supplementary table S1: It seems that row percentages are used except in the case of “women”? Would it be better to add men to this table (as in the corresponding main table) and change the percentage to a row percentage, for consistency?”

The suggestion is accepted.

8. “Supplementary table S3: should the column headings be HIV-positive and HIV negative, as in the other supplementary tables?”

The suggestion is accepted.

We have also made the following changes to the manuscript:

1. The Abstract has been revised to emphasize the cardiac abnormalities found in HIV-associated pericardial disease, in line with the suggestions of reviewer 1.

2. Under Results, we have replaced the term ‘NYHA functional class’ with ‘dyspnoea’

3. In the ‘Discussion’ section, under ‘What are the limitations of the registry?’, we have deleted the following sentences as they are redundant:

   ‘These effects were not linked to this study and are unlikely to introduce bias into the results. Nonetheless, we have refrained from drawing conclusions on data which are substantially incomplete.’

We wish to thank reviewer 1 for the insightful comments on our manuscript, and we hope that, by accepting most of the suggestions, we have addressed the reviewer’s concerns satisfactorily.

Yours sincerely

[Signature]

Bongani M. Mayosi