Author's response to reviews

Title: Spectrum of clinical disease in a cohort of 135 hospitalised HIV-infected patients from north India

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Response to comments by Dr. Kenrad Nelson:

1. Comment: "The strength of this paper is that it reports a consecutive sample of HIV-positive patients. The weakness is that it suffers from "referral bias". It is incorrect to call this sample a "cohort" - since this term refers to a population identified prior to an outcome. However, all of these patients already had HIV/AIDS on admission to the hospital from an unknown but large population base. They are a highly selected sample."

Response: We agree with the esteemed reviewers that it is not correct to call this study group as a cohort, as has been expressed by both esteemed reviewers. Accordingly, the term, 'series' has been used in place of 'cohort', in the revised manuscript. (The term 'cohort' is replaced with 'series' in the title and in all places where it appears in the text and tables.)

To avoid any bias we studied consecutive patients with HIV/AIDS admitted to the hospital. However, we agree with the esteemed reviewer that being a hospital-based study though inevitable, there is a chance for referral bias. The likely impact of such a bias is that patients with rapidly fatal illnesses as well as those with milder symptoms who got treated at local health facilities may not have been proportionately represented in the study group. This point is being included in the discussion, in the revised manuscript (Page-11, paragraph-3 and page-12, paragraph-1).

2. Comment: "The authors do not contrast their findings with other clinical reports from elsewhere in India. Such comparisons could be useful."

Response: While we have mentioned that the findings are at large in consonance with the findings of earlier studies from other parts of India (a very few in number), there are not many differences except for the occurrence of disseminated Penicillium marneffei infection in the north-eastern states of India. This point is being highlighted in the revised manuscript (Page-14, paragraph-1).

3. Comment: "What is the policy of INH prophylaxis of HIV positive patients in India or at All India Institute of Medical Sciences?"

Response: Regarding the policy of INH prophylaxis of HIV-infected patients, we would like to mention that the practice at the All India Institute of Medical Sciences and other institutions in India is, HIV-infected patients are not given INH prophylaxis. This is probably due to apprehension that inadvertently, patients with active tuberculosis might be treated with INH monotherapy. This apprehension might be unfounded. A more important reason we feel, is the futility of chemoprophylaxis for fixed duration, which does not protect against reinfection in a setting where the prevalence of tuberculosis is high among the general population.

4. Comment: "What is the policy of HIV screening of patients with TB in India or at All India Institute of Medical Sciences? What is the policy of screening of hospital admissions at All India Institute for HIV? How many hospitalised patients who were HIV positive could have been missed in this study? What is the policy of HIV screening of adults admitted to All India Institute of Medical Sciences?"

Response: At our Institute, the policy is to screen all patients with newly diagnosed tuberculosis for HIV
co-infection. While this the general practice, we can not be sure that all patients with tuberculosis were in fact screened for HIV co-infection. In our Institute, all patients referred as being ‘HIV-positive’ undergo retesting for HIV infection. Apart from this, patients with tuberculosis, patients reporting risk factors such as high-risk sexual behaviour, if the patient happens to be the source of needle-stick injury and those with clinical presentation suggestive of underlying immunosuppression are screened for HIV infection. We do not routinely screen all hospitalised patients or all patients posted for surgical procedures for HIV infection. Despite this selective screening policy, it is unlikely that a considerable number of patients were missed since the prevalence of HIV infection in the general population in India, especially the north Indian states is less than 1%.

The policy for HIV screening in our hospital has been spelt out briefly, in the revised manuscript (Page-5, paragraph-3).

5. Comment: "What is the referral policy to send HIV/AIDS patients to New Delhi and All India Institute of Medical Sciences for treatment? Could it be that TB patients who are HIV positive with low CD4+ counts are more likely to be referred and admitted to hospital, whereas PCP patients are treated in the local community with Bactrim?"

Response: There are no guidelines in place in India, at the present moment, regarding when to refer a HIV-infected patient to tertiary level centres. Referral is at the discretion of the physicians as well as the patients. In India, HIV-infected patients are usually treated in tertiary level centres, due to lack of expertise and facilities at primary and district level hospitals. Moreover, for reasons of privacy, patients and their kin prefer treatment at places far off from their home towns. However, as expressed by the esteemed reviewer, it is well possible that milder cases of Pneumocystis jiroveci pneumonia were treated in the local hospitals and hence were not represented in the study group.

In the revised manuscript, the referral practices in India and the possible limitations due to referral bias are addressed in the discussion section (Page-11, paragraph-3 and page-12, paragraph-1). The catchment area of the hospital is delineated in the methods section (Page-5, paragraph-2).

6. Comment: "How many patients with cough or pulmonary disease who were negative for TB were screened for PCP with Bronchoscope or Induced Sputum?"

Response: Regarding evaluation of patients with respiratory symptoms for Pneumocystis jiroveci pneumonia: Of the patients who had cough (57 patients) or dyspnoea (34 patients), 14 patients in each group were negative for tuberculosis. Among which, 14 patients in total, underwent sputum induction (the rest had active expectoration). Of the 14 patients who underwent sputum induction, four cases of Pneumocystis jiroveci pneumonia were diagnosed. None of these patients underwent bronchoscopy.

7. Comment: "I disagree that the study of Ablashi et al (ref #28) has clearly shown that the reason for the rarity of KS in Asia is due to uncommon infections with HHV-8. This survey has not included a sufficient number or spectrum of patients from Asia to draw definite conclusions. Others have found a high seroprevalence of HHV-8 in Thailand, for example."

Response: We agree with the esteemed reviewer that the study by Ablashi et al., has not included sufficient number of healthy individuals/HIV-1 infected patients, so as to draw definite conclusions. However, this is the only data available on the seroprevalence of HHV-8 infection in the Indian subcontinent and it is well documented that in India, Kaposi’s sarcoma is a rarity. Only a handful of cases have been reported so far, from India.

Response to comments by Dr. Roger Detels:

1. Comment: "Discussion needs to reflect the nature of the populations."

Response: As suggested by the esteemed reviewer, we have delineated the catchment area of the hospital in the revised manuscript (Page-5, paragraph-2). We have also discussed the referral practices in India and the possible influence of this on the applicability of the findings of the present study to other parts of India, in the revised manuscript (Page-11, paragraph-3 and page-12, paragraph-1).

2. Comment: "Was 135 the total number of patients admitted or included in the study?"
Response: The total number of HIV-infected patients admitted during the study period was 135 and all patients were included in the study.

The statement regarding the number of patients admitted and those included in the study has been clarified in the results section, in the revised manuscript (Page-8, paragraph-3).

3. Comment: "Were there any refusals to provide risk or other data?"

Response: We would like to clarify that all patients were questioned regarding premaritital and/or extramarital sexual exposure, homosexual practices, injectable drug use and blood transfusion. Patients reported as Yes or No, to these questions. None of the patients refused to give a specific answer to these questions.

The footnote of Table-1 has been corrected in the revised manuscript: the word 'denied' is used in place of 'refused', so as to avoid confusion (Page-17, line-1).

4. Comment: "The authors attempt to establish that this distribution of patients seen in a tertiary hospital reflects the distribution for all HIV infected individuals in India. This is unlikely. Conditions causing rapid death would be unlikely to be transported to Delhi. The actual referral to the tertiary hospital depended on the referring physicians. Patients living closer to Delhi were more likely to be referred than patients from the Northeast States, the south and large cities with their own referral hospitals."

Response: We agree with the esteemed reviewer that being conducted at a tertiary level hospital, rapidly fatal as well as milder illnesses may not have been proportionately represented in the study group. Moreover, we agree with the esteemed reviewer that the findings of the present study may not apply well to south as well as north-east Indian states. However, we did not find any gross differences from the findings of the studies from other parts of India, except for the occurrence of Penicillium marneffei infection in Manipur state.

In the revised manuscript, referral practices in India and the possible limitations due to referral bias are addressed in the discussion section (Page-11, paragraph-3 and page-12, paragraph-1).

5. Comment: "The order of illnesses in Table 2 should go from highest to lowest to assist the comprehension of the reader. The Figures should be numbered in the sequence in which they appear in the narrative."

Response: We are thankful to the esteemed reviewer for his suggestions to improve the way data and figures have been presented. We have incorporated these changes in the revised manuscript, as suggested.

In the revised manuscript, contents of Table-1, 2 and 4 (Pages-16, 18, 19, 22 and 23) have been rearranged in the descending order of frequency and Figure-1 and 2 have been numbered as per the sequence they appear in the narrative. The citations of the figures in the text have also been modified accordingly.

6. Comment: "The authors have not commented on the high proportion of transfusion-related cases."

Response: Though a considerable number of patients in this study reported blood transfusions in the past, it is difficult to ascribe causal association. In India, over the last decade, blood transfusion practices have become legally regulated and controlled with stringent monitoring by Honourable courts, thereby ensuring universal screening of all blood products for HIV infection. For this reason, a history of blood transfusion in these patients is merely incidental and might not have a causal relation with HIV infection.

The significance of high proportion of transfusion-related HIV infection is discussed in the revised manuscript (Page-12, paragraph-2).

7. Comment: "The authors refer to their patients as a cohort. It would be more appropriate to refer to them as a series as they were not followed up beyond their hospital stay."

Response: We are happy to comply with the suggestion by the reviewer and accordingly the term 'series' is used in place of 'cohort', all through out the revised manuscript, including the title and tables.