Author's response to reviews

Title: Analysis of undiagnosed tuberculosis-related deaths identified at post-mortem among HIV-infected patients in Russia: a descriptive study

Authors:

Yanina Balabanova (y.balabanova@qmul.ac.uk)
Vladimir Tchernyshev (orgmet-tptd@yandex.ru)
Igor Tsigankov (Glvrach-tptd@yandex.ru)
Svetlana Maximova (svetlana-maximova0@rambler.ru)
Natalya Mikheeva (natalyamikheeva@rambler.ru)
Ljudmila Fedyukovitch (fedjuk11@rambler.ru)
Sergey Kuznetsov (noobesity@rambler.ru)
Ivan Fedorin (soptdlab@gmail.com)
Francis Drobniewsky (f.drobniewski@qmul.ac.uk)

Version: 3 Date: 9 September 2011

Author's response to reviews: see over
Dear Dr Ruhwald,

Thank you for your letter regarding our manuscript “Analysis of undiagnosed tuberculosis-related deaths identified at post-mortem among HIV-infected patients in Russia: a descriptive study” submitted to the BMC Infectious Diseases.

We have addressed all the points from the reviewer below and in the text of the manuscript and hope that the manuscript now is suitable for the next review.

Sincerely,

Yanina Balabanova, Vladimir Tchernyshev, Igor Tsigankov, Svetlana Maximova, Natalya Mikheeva, Ljudmila Fedyukovitch, Sergey Kuznetsov, Ivan Fedorin, Francis Drobniewski
Reviewer's report
Title: Analysis of undiagnosed tuberculosis-related deaths identified at post-mortem among HIV-infected patients in Russia: a descriptive study
Version: 2 Date: 27 June 2011
Reviewer: Pernille Ravn

Reviewer's report:
This is well written paper revealing a lack of awareness and skills diagnosing TB in HIV patients and the problems associated with marginalized populations. To put the magnitude of the problem into perspective I suggest that you include the following information:

Total number of admissions, total number of deaths in the study period, number of patients autopsied and information on the causes of “non-TB deaths”, and on “non-HIV related TB deaths”?

Unfortunately the information on the total number of admissions is available only for the main city tuberculosis hospital where the co-authors work. In the study period there were 750 admissions of patients with TB and 119 deaths of patients co-infected with HIV and TB. Almost all of the diseased patients were subjected to the post-mortem examination; 68 of them died for reasons not related to TB and the rest of the fatalities were attributable to TB. We realize that it does not answer your question as the hospitals involved into the study were non-TB general health care hospitals. We agree that presenting the data on general indicators of hospital admissions and autopsies would be interesting, but unfortunately we did not have this information at the time of the analysis. At the moment requesting this information would mean a logistically lengthy and complicated administrative procedure that needs to be done through the Regional Ministry of Health. Obtaining these data might therefore take several weeks if not months. We would, if the editor agrees, prefer not to initiate this request due to these foreseeable local difficulties.

Would you know if any patient dying from TB was HIV tested post mortem?

According to national policy, all TB patients are tested for HIV before death unless they actively object. In cases when a death from TB occurred within 24 hours of a hospital admission and HIV-test was not done, an HIV test is conducted post-mortem, should post-mortem examination take place.

Do you have information on the duration of HIV before admission/death?

The duration from HIV diagnosis varied between 5 months and 4 years among deceased patients; we do not have data on the actual/probable time of HIV infection.

Several pt did not come for their CD4 cell count. Are CD4 test and VL for free or do you patients have to pay?

The tests are free of charge. To clarify this issue in the text, we have added the following (page 5, second paragraph from the bottom): “Although all patients were known to be HIV positive, in none of the cases during the three months prior to hospital admission was a CD4 count or viral load (VL) test performed (usually due to the patient missing their appointment; these tests are free of charge for all patients).”

Chest X-ray.
You write in p 5 that “no abnormalities consistent with TB registered”. How many X rays were described as “normal” and how many had “abnormal findings”? 
In twelve cases other abnormalities of an unidentified nature were reported at the first CXR review. To clarify this issue, the paragraph describing the CXR findings is re-phrased as following: “In twelve cases other radiological abnormalities of an unidentified nature were reported. In these cases, a second routine review of the CXR was performed by radiologists who were not blinded towards the results of the first examination. It suggested that…..”

The second reading of chest X-ray was this done routinely/blindly or after knowing the post mortem diagnosis? Please specify.

The second readings were performed routinely while the patients were still alive, but not blindly to the first readings. We have added this information to the sentence on the page 5, last paragraph: “However, after a second routine review of the CXR radiologists who were not blinded towards the results of the first examination, suggested that ten cases (35%) were presumptively TB arguing that it might have had an atypical presentation due to the advanced stage of immunosuppression.”

In all cases a sputum sample was examined for AFB. Was sputum taken from all 29 patients? Please specify. If all patients had a sputum examined than the physician must have had some suspicion for TB.

Yes, sputum was taken from all 29 patients according to the standards of hospital care for newly admitted HIV-positive patients. Therefore the physicians have ordered AFB microscopy as one of a battery of tests without any specific suspicion or targeting for TB in individual cases. To clarify this issue, we have amended the following sentence (page 6, third paragraph): “In all 29 cases a sputum sample was microscopically examined for the presence of acid-fast bacilli by the GHC laboratories according to national standards of hospital care for newly admitted HIV-positive patients”.

P 6 last paragraph. All patients were subjected to autopsy examination…. In 100% of cases TB was established as the cause of death….. Because post mortem diagnosis of TB was used as an inclusion criteria this cannot also be a result.

Agree; this sentence is moved to the Methods section. The relevant sentence in the Results section is amended to: “The autopsy results confirmed that in 16 cases (55%) M. tuberculosis was both extrapulmonary as well as pulmonary; in 5 patients (17%) in addition to pulmonary TB, TB meningitis was diagnosed”

Immunological tests:
Antibody assay:
P6: 11 were tested with an antibody assay and 1 was pos and 9 neg. What about the last patient?

This is a typo error; there were ten negative tests. The changes are made in the sentence.

Could you provide manufacturer and trade names?

The tests that were used belonged to several commercial systems manufactured in Russia and India; however we would prefer to abstain from specifying manufacturers’ exact names in the manuscript text as it adds little to the recognised overall poor quality and reliability of the tests but might point out at individual companies and therefore inadvertently provoke a local conflict. We have added the following sentence to reflect recent WHO policy statement against the use of these assays:” Recently issued policy statement by the World Health Organisation advises strongly against the use of
commercial serological assays presenting evidence for their inconsistent and imprecise findings.” and referenced the respected source.

You write that the test have poor specificity and from your study the test also seem to have a poor sensitivity as only 1/9(10) had a positive test (p6) TST please define the cut off for pos test.

The cut-off for positive tests in adults is 12 mm; there is no specific recommendations on the test interpretation in HIV-positive individuals.

Microbiology/pathology: Other co-morbidities were found. How were those diagnosis made. And how was it determined that the cause of death was due to TB and i.e. not due to PCP?

Standard pathological examination included the following procedures: “Representative samples of internal organs were fixed in 10% formalin solution, in order to preserve the tissue for histological examination. Detailed description of all changes found macroscopically and microscopically was documented. Prior to microscopy, all tissue sections were stained routinely with haematoxylin and eosin. For each major organ, a maximum of three sections were taken. To detect acid-fast bacilli a section from every lobe of the lungs, one from the left and right main bronchus and trachea, the hilar and mediastinal lymph nodes was taken. Fresh gloves and blades were used for every organ sampled. Tissue sections were treated with special stains including Ziehl-Neelsen for acid-fast bacilli, Gram’s stain for bacteria, periodic acid-Schiff for fungi and Giemsa stain for Pneumocystis jeroveci.” (Methods section). The differential diagnosis between PCP and TB was based on absence of CXR findings consistent with a diagnosis of PCP.

It would be useful to describe in more details the macroscopic findings followed by the result of the microscopy in the affected organs.

Agree, however, the article focuses on different aspects of clinical management of the deceased patients and brings attention to the tests that were applied or not while the patients were still alive. We would prefer not to shift the main message towards the pathology findings. This paper was initiated by a group of clinicians; we have used routine notes that were available at the time of the analysis and it would be extremely difficult at the moment to retrieve those from the hospital archives as well as have a further discussion with the pathologists who had performed the autopsies.

Conclusion:
It seems to me that the general physicians actually had a good suspicion of TB by ordering AFB microscopy on all patients and requesting a TB /HIV expert to review the patients in 66% of the cases. Therefore also HIV/TB specialist apparently need more training/education.

Agree, the training is needed on non-specific presentation of TB in immunocompromised individuals.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.