Reviewer's report

Title: LAM-ELISA shows a low sensitivity for the diagnosis of pulmonary tuberculosis in urine

Version: 1 Date: 13 May 2009

Reviewer: Gerd Michel

Reviewer's report:

Minor Essential Revisions

This paper addresses the important issues of diagnosis of active tuberculosis by detection of LAM antigen in urine. The authors used the only commercially available test for this purpose, originally produced by Chemogen Inc., which has recently been acquired by Inverness Medical Inc. This latter fact should be stated in the manuscript and the product should be referred to as the “Inverness LAM assay” for clarification.

LAM ELISA: it is unclear what type of antibodies were used for antigen capture. It is also unclear in what way the LAM reference antigen was biochemically defined and at what concentration level the assay cutoff was set. What is the LAM concentration in the “low positive control”? The CV at the cutoff level is not given and it is thus not possible to get an impression about the assay imprecision that may greatly influence the results in a qualitative ELISA format. The variable results obtained between the two urine samples tested per patient may simply be a consequence of inappropriate CV rather than true biological variation.

Absolute OD values obtained are not reported but would add valuable information about the assay characteristics.

The authors indicate that one of the potential factors influencing comparability with their earlier results using the same product could be differences in the assay configuration between an earlier version and the current one. If so, it should be stated if the answers to the technical issues raised above differ between assay versions.

The term “unprocessed” urine is misleading and should be replaced since the urine samples were boiled and centrifuged prior to use in the LAM ELISA.

Major Compulsory Revisions

The better test performance in TB-pos. / HIV-pos. vs. HIV-neg. patients is the most important finding of the study and corroborates earlier data of the same group using a different version of the LAM ELISA. While attractive in principle, the current data do, however, not confirm the relatively high sensitivity obtained with the first test version (Boehme et al.). Thus, the authors’ suggestion of considering the current commercial assay as “a valuable supplemental tool in the diagnosis of HIV-associated TB” appears much too early, if not dangerous. It
should be clearly stated that the manufacturer’s information on the reagents and test configuration is still a “black box” and that a respective product should not be used in clinical practice before it is known what is actually measured (various LAM molecular species or a single one?), what is the lot to lot variability, what are the CVs, and how product consistency is guaranteed – just to mention a few items.

In this regard is may also be noteworthy that there is no sufficient confirmation in humans that LAM passes the renal barrier without major changes (see second to last line in Introduction).

The authors should consider these issues in their discussion.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

FIND has previously evaluated the LAM assay used in this study and is currently pursing LAM detection in collaboration with other groups. FIND is a non-profit organization and I do not have any personal financial interests in this context.