Author's response to reviews

Title: Test characteristics and potential impact of the urine LAM lateral flow assay in HIV-infected outpatients under investigation for TB and able to self-expectorate sputum for diagnostic testing

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Dear Professor Stout and colleagues,

Re: Peter et al. Test characteristics and potential impact of the urine LAM lateral flow assay in HIV-infected outpatients under investigation for TB and able to self-expectorate sputum for diagnostic testing

I would be most grateful if you would consider this manuscript for publication as an original article in your journal. The manuscript details the first large multicentre study of the point-of-care urine LAM lateral flow assay in primary care practice, allowing for accurate evaluation of diagnostic accuracy across three sub-Saharan African countries. Sputum smear microscopy, despite poor sensitivity in TB HIV co-infection, remains the frontline TB diagnostic tool in the majority of high burden resource-poor settings, while many more wealthy countries are scaling up frontline Xpert MTB/RIF testing for HIV-infected patients with suspected pulmonary TB. However, Xpert MTB/RIF sensitivity is reduced in HIV-infected compared to uninfected patients and the infrastructure, electricity and cost remain major obstacles to widespread implementation. Thus, many countries are very interested in novel low-cost point-of-care TB diagnostic tools, particularly non-sputum based tools.

In 2013, the Alere Determine™ TB LAM Ag lateral flow strip test became the first commercially available bedside urine test for TB diagnosis with results available within 25 minutes using just 60ul of urine. Data from different settings evaluating the diagnostic accuracy of the urine LAM strip test in HIV-infected persons have shown modest overall sensitivity, which improves with advanced immunosuppression and TB disease severity necessitating hospitalisation\(^1,2\).

We would like to draw the editors’ attention to the fact that our study only considered outpatients able to expectorate sputum. Notably, patients with suspected pulmonary TB able to provide sputum for diagnostic testing are the major subgroup presenting to primary care facilities for frontline TB testing (>90%). Although preliminary data suggest that this is not the subgroup most likely to benefit from LAM, existing data has major limitations and has been inadequate to allow for clear recommendations to TB programs about this use of LAM in this important and dominant subgroup. Major issues with available data that make recommendation formulation difficult include the following:

1. LAM strip test performance characteristics differ substantially amongst published outpatients studies. The early evaluations in South African ARV-clinic setting (Lawn et al *Lancet Infectious diseases* 2012\(^3\)) differ from more recent evaluations in South Africa and Uganda

ii) The study populations are heterogeneous. Studies include out- and inpatients (Nakiyingi et al. *JAIDS* 2014), and patients able to self-expectorate sputum with those unable to provide sputum samples for TB diagnostic testing. Sample acquisition methods differ between studies and include the availability of non-routine methods such as sputum induction or the use of invasive sampling. Extra-pulmonary TB and Pulmonary TB patients are considered together. Finally, studies use different LAM strip test cut-points (grade-1 or grade-2), which further limits comparability.

iii) No impact data, or estimates thereof, on the incremental use of adjunctive LAM testing on patient important outcomes such as same-day treatment initiation, morbidity, and drop-out.

Thus, despite available data, guideline developing bodies, such as the WHO diagnostic working group, have insufficient data to provide clear recommendation about the use of urine LAM testing in the majority of TB patients in TB HIV endemic settings. Indeed, program directors continue to question why the only commercially available and affordable POC TB test is unavailable for frontline testing? The data outlined in our manuscript is a major step towards guideline development.

Our evaluation of urine LAM strip test performance in a well-defined cohort of 1095 patients with suspected TB formed part of a parent randomised controlled trial comparing Xpert MTB/RIF with same-day smear microscopy in primary care clinics of three sub-Saharan African countries recently published in the *Lancet*.

Our study is able to provide the following conclusion:

**In African HIV-TB co-infected outpatients able to self-expectorate sputum LAM had limited sensitivity even at low CD4 counts, and offers no incremental value over Xpert-MTB/RIF or smear microscopy. LAM is unlikely to impact TB-related morbidity and patient dropout, and may only improve same-day treatment initiation in primary care clinic settings without chest radiography available.**

Our study is novel and has a number of important strengths including:

1. The first, and only, large multicentre study of urine LAM lateral flow assay in primary care practice allowing evaluations of diagnostic accuracy across three sub-Saharan African countries. Previously only single centre and country studies are available.
2. Study design and end-points of the parent study offered a unique opportunity to explore the effect and potential impact of LAM, used in combination with either Xpert MTB/RIF or sputum smear microscopy, on:
   i) A well-defined patient population able to expectorate sputum (the majority of out-patient TB disease in HIV-infected or uninfected patients), and
   ii) Patient-important outcomes including morbidity, time-to-treatment initiation and drop-out. This impact data is essential for guiding policy.

We have requested fast-track review of this manuscript as we feel this is warranted. The WHO diagnostic working group plans to review urine LAM data in the last quarter of 2014 and make endorsement decisions and recommendations for optimal test use. They have already requested our data for this process making the need for publication pressing. Furthermore, National TB programs are anxious to incorporate this inexpensive POC TB diagnostic into diagnostic algorithms and it is essential that incorporation is appropriately targeted.
All the authors have contributed to this work and agreed to its content. The study has received all the relevant ethics, provincial and governmental approvals.

Thank you for considering our manuscript for publication in your journal.

Best wishes,

Keertan Dheda     Jonathan Peter

Relevant recent references


