Study finds LF-LAM-guided TB treatment initiation reduces mortality in HIV-positive hospital inpatients

INFORMATION NOTE

8 April 2016: Diagnosis of TB in people with HIV using sputum-based tests is challenging, given the frequency of extrapulmonary TB and paucibacillary samples, and the frequent inability of such patients to expectorate sputum. In November 2015, WHO issued policy guidance on the urine-based lateral flow lipoarabinomannan (LF-LAM) assay. The WHO recommendations, based on the evaluation of the commercially available Alere Determine™ TB LAM Ag test (Alere Inc, Waltham, USA), indicate that LF-LAM may be used to assist in the diagnosis of TB in persons with HIV infection with low CD4 counts or who are seriously ill (see complete recommendations below).

A recent study based in ten hospitals in four African countries and published last month in the Lancet has found that the use of an adjunctive urine LF-LAM test significantly reduced all cause 8-week mortality in HIV-positive adults with at least one TB symptom and illness severity necessitating admission to hospital (Relative risk reduction of 17% [95% CI 4–28] for all-cause mortality at 8 weeks). Trained research nurses performed the LF-LAM test at the patients’ bedside on enrolment and made a recommendation for initiating anti-TB treatment on the basis of a positive test result; the attending physician made an independent, final decision regarding treatment initiation.

The reduction in mortality in the LF-LAM-guided treatment initiation arm of the study was attributed to more patients in this arm receiving anti-TB treatment and such treatment starting earlier than patients not receiving LF-LAM testing: “the dominant driver seems to be a large overall proportion of patients being initiated on treatment. This finding is consistent with our previous findings that LAM identifies patients with possible tuberculosis not detected by clinicians who make routine empirical treatment decisions. Thus, despite only having 50% to 70% sensitivity, depending on CD4 cell count, bedside LAM testing improves the sensitivity of clinical and chest radiograph diagnosis, and leads to rapid, life-saving, treatment initiation in the most susceptible patient subgroups, and at low cost.” Urine LAM testing has no infrastructural requirements and a cost of only US$3.50 per test (as of June 2017).


1. Except as specifically described below for persons with HIV infection with low CD4 counts or who are seriously ill*, LF-LAM should not be used for the diagnosis of TB (strong recommendation, low quality of evidence).

2. LF-LAM may be used to assist in the diagnosis of TB in HIV positive adult in-patients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/µL, or HIV positive patients who are seriously ill* regardless of CD4 count or with unknown CD4 count (conditional recommendation; low quality of evidence).

Remarks

a. This recommendation also applies to HIV positive adult out-patients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/µL, or HIV positive patients who are seriously ill* regardless of CD4 count or with unknown CD4 count, based on the generalisation of data from in-patients.

b. This recommendation also applies to HIV positive children with signs and symptoms of TB (pulmonary and/or extrapulmonary) based on the generalisation of data from adults while acknowledging very limited data and concern regarding low specificity of the LF-LAM assay in children.

3. LF-LAM should not be used as a screening test for TB. (strong recommendation, low quality of evidence).

* “seriously ill” is defined based on 4 danger signs: respiratory rate > 30/min, temperature > 39°C, heart rate > 120/min and unable to walk unaided.
Dr Jonny Peter, a specialist physician at the Groote Schuur Hospital, University of Cape Town Lung Institute, and a lead investigator of the aforementioned study, provides the following illustrative cases in which LF-LAM has positively assisted in TB treatment initiation decisions, especially in atypical clinical presentations of TB in HIV-positive patients with advanced immunosuppression:

1. **32 year old woman, HIV-positive, CD4 count of 8 cells/µL**
   Presenting with chronic diarrhoea, some loss of weight. No cough or night sweats. Examination found no fever, adenopathy or hepatosplenomegaly. Chest X-ray normal.

2. **43 year old man, HIV-positive, CD4 count of 85 cells/µL**
   Started on tenofovir, emtricitabine and efavirenz anti-retrovirals 2 weeks prior to presentation with fever and acute renal failure. Patient had been feeling well before anti-retrovirals were started. Examination showed no lymphadenopathy or hepatosplenomegaly. Chest X-ray normal.
   Urine LAM positive, no TB cultures possible unless renal biopsy performed. Good response to TB treatment.

3. **28 year old woman, HIV-positive, CD4 count of 22 cells/µL, anti-retroviral naïve**
   Presenting with paraparesis and incontinence. No fever or constitutional symptoms. Examination showed no abnormalities besides her neurology. No neck stiffness. CSF showed elevated protein and lymphocytes. Spine and chest x-ray normal.
   Urine LAM positive. CSF culture later TB positive after 26 days. Good response to TB treatment.

4. **32 year old woman, HIV status unknown but suspected clinically**
   Presenting with fever, constitutional symptoms and fatigue. Chest X-ray shows hilar lymphadenopathy. Unable to produce sputum despite attempted sputum induction.
   Urine LAM positive. Good response to TB treatment.

5. **51 year old man, HIV-positive, CD4 count unknown**
   Presenting with two week history of fever and abdominal pain. Examination showed hepatomegaly. Chest X-ray normal. No samples attained for TB testing.
   After initial investigations (>1 week of hospitalisation) at a secondary level hospital referred to tertiary investigations as a pyrexia of unknown aetiology.
   Urine LAM positive, no TB cultures possible. Discharged after temperature settled following 4 days of in-patient TB treatment. Good response on 2 month follow-up.

6. **48 year old woman, HIV-positive, CD4 count of 110 cells/µL, started on antiretroviral therapy 3 weeks ago**
   Presented with cough, shortness of breath and fever. Required oxygen therapy and admission to hospital. Chest x-ray showed right upper lobe pneumonia. Also noted to have hepatosplenomegaly.
   Treated for community acquired pneumonia but urine LAM positive. Antibiotics stopped and TB treatment commenced.
   Expectorated sputum Xpert MTB/RIF negative (likely poor quality sputum sample). Good response to TB treatment.

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