The clinical utility of the urine based lateral flow lipoarabinomannan (LF-LAM) assay in HIV infected adults in Myanmar

Josh Hanson
Tuberculosis is the commonest cause of death in HIV infected patients globally.

Limited access to laboratory services in low and middle income countries means that almost half the fatal cases of TB/HIV co-infection are unrecognised before their deaths.

The point-of-care, urine-based, lateral flow lipoarabinomannan (LF-LAM) test may expedite TB diagnosis in HIV positive patients.

However almost all of the studies that have evaluated the test have taken place in sub-Saharan Africa.
Lipoarabinomannan (LAM)

1. Glycophospholipid anchor
   - Myo-Inositol-Phosphate
   - Fatty acids

2. Mannan core

3. Arabinan domain with variable side-chains and mannose capping
Clinical utility of LF-LAM testing in HIV positive patients in Myanmar

The test
The test

- Hold the card alongside the patient window and read the result
- If the result line is hard to define refer to the package insert
- Store the card in the kit pouch away from direct light and heat
- Do not use the card beyond the expiration date
WHO recommendations for use (2015)

- LF-LAM may assist in the diagnosis of TB in HIV positive adult in-patients with signs and symptoms of TB who have a CD4 cell count ≤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)

- LF-LAM should not be used as a screening test for TB. (strong recommendation, low quality of evidence)
Mortality benefit in sub-Saharan Africa

Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial


Overall 8 week mortality in LAM group 23%, compared with 25% in the no LAM group. Risk ratio 0.83 (95%CI 0.73-0.96) p=0.01.
Clinical utility of LF-LAM testing in HIV positive patients in Myanmar

Relevance to Asia

TB
- Cambodia
- Sierra Leone
- Brazil
- Central African Republic
- Congo
- Lesotho
- Liberia
- Namibia
- UR Tanzania
- Zambia

MDR-TB
- Bangladesh
- DPR Korea
- Pakistan
- Philippines
- Russian Federation
- Viet Nam
- Mozambique
- Myanmar
- Nigeria
- Papua New Guinea
- South Africa
- Thailand
- Zimbabwe

TB/HIV
- Botswana
- Cameroon
- Chad
- Ghana
- Guinea-Bissau
- Malawi
- Swaziland
- Uganda

Azerbaijan
Belarus
Kazakhstan
Kyrgyzstan
Peru
Republic of Moldova
Somalia
Tajikistan
Ukraine
Uzbekistan

WHO Global tuberculosis report 2016
Clinical utility of a diagnostic test

<table>
<thead>
<tr>
<th></th>
<th>Disease present</th>
<th>Disease absent</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>A (True positive)</td>
<td>B (False positive)</td>
<td>POSITIVE PREDICTIVE VALUE (A/A+B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test negative</td>
<td>C (False negative)</td>
<td>D (True negative)</td>
<td>NEGATIVE PREDICTIVE VALUE (D/C+D)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SENSITIVITY (A/A+C)</td>
<td>SPECIFICITY (B/B+D)</td>
<td></td>
</tr>
</tbody>
</table>
The study

• Hypothesis: Use of LF-LAM testing can be used to facilitate TB diagnosis and reduce TB-related mortality in HIV positive patients in Asia

• 517 consecutive patients (54 inpatients and 463 outpatients) enrolled between July and December 2015 at a tertiary referral hospital in Yangon, Myanmar
• Median (IQR) CD4+ count 270 (128-443) cells/mm³
• 360 (70%) on ART
• 14 (3%) on IPT
The study

- All patients had a detailed history, full physical examination, chest x-ray and sputum testing (Xpert and culture) for TB
- LF-LAM test performed at baseline by study doctors; result correlated with clinical course over the ensuing 6 months
- The patients’ treating clinicians were unaware of LF-LAM result
- No extrapulmonary testing for TB was possible
- Endpoint: confirmed TB, empirical TB therapy, hospitalisation or death during 6 months of follow-up
Clinical utility of LF-LAM testing in HIV positive patients in Myanmar

LF-LAM results

- 201/517 (39%) had a positive result (≥ grade 1)
- 43 (8%) ≥ grade 2
- 20 (4%) ≥ grade 3

![Reference Scale Card Image]
## Associations with LF-LAM test positivity

<table>
<thead>
<tr>
<th></th>
<th>Total n=517</th>
<th>Positive LAM n=201</th>
<th>Negative LAM n=316</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatients</td>
<td>54 (10%)</td>
<td>35 (17%)</td>
<td>19 (6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TB symptoms</td>
<td>169 (33%)</td>
<td>90 (39%)</td>
<td>79 (29%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Advanced immunodeficiency</td>
<td>102 (20%)</td>
<td>55 (28%)</td>
<td>47 (15%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hazardous alcohol intake</td>
<td>71 (14%)</td>
<td>40 (20%)</td>
<td>31 (10%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index &lt;18</td>
<td>83 (16%)</td>
<td>41 (21%)</td>
<td>42 (13%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Haemoglobin &lt;10 g/dL *</td>
<td>162 (39%)</td>
<td>78 (46%)</td>
<td>84 (34%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

TB symptoms: cough, weight loss, night sweats, fever in last 1 month

* Only 414 patients had a haemoglobin recorded on admission
Patient course in the ensuing 6 months

- 54 (10%) had TB confirmed on sputum testing (Xpert or culture); 8 (15%) had rifampicin resistance
- 123 (27%) had empirical anti-TB therapy commenced
- 77 (15%) required hospitalisation
- 16 (3%) died
- 205 (40%) satisfied the endpoint of confirmed TB, empirical TB therapy, hospitalisation or death during follow-up
- No patients were lost to follow-up
After 6 months 97/201 (48%) with a positive LF-LAM test on enrolment, had neither died, required hospitalisation, received a TB diagnosis, or received empirical anti-TB therapy.

89/97 of these false positives were grade 1 results.
Ability of the LAM test to predict outcomes

- Even if cut-off of 2 used, 8/43 (19%) neither died, required hospitalisation, received a TB diagnosis, or received empirical anti-TB therapy in the ensuing 6 months.
Inpatients with TB symptoms

41 patients

27 positive LF-LAM
- 6 with confirmed TB
  - PPV 22% (9-42)
  - NPV 100% (77-100)
- 16 had anti-TB therapy initiated
  - PPV 59% (39-78)
  - NPV 50% (23-77)
- 4 died
  - PPV 15% (4-34)
  - NPV 86% (57-98)
- 17 died, had confirmed TB or had anti-TB therapy initiated
  - PPV 63% (42-81)
  - NPV 36% (13-65)

14 negative LF-LAM
- 0 with confirmed TB
- 7 had anti-TB therapy initiated
- 2 died
- 9 died, had confirmed TB or had anti-TB therapy initiated
Clinical utility of LF-LAM testing in HIV positive patients in Myanmar

**Negative predictive value**

Microbiologically confirmed TB diagnosis

<table>
<thead>
<tr>
<th></th>
<th>NPV</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM test</td>
<td>94.3%</td>
<td>91.1 - 96.6</td>
</tr>
<tr>
<td>TB symptoms *</td>
<td>93.7%</td>
<td>90.6 - 96</td>
</tr>
</tbody>
</table>

Primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>NPV</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM test</td>
<td>68%</td>
<td>62.6 - 73.1</td>
</tr>
<tr>
<td>TB symptoms *</td>
<td>71%</td>
<td>65.9 - 75.7</td>
</tr>
</tbody>
</table>

* TB symptoms: cough, weight loss, night sweats, fever in last 1 month

Primary endpoint: confirmed TB, empirical TB therapy, hospitalisation or death in ensuing 6 months
• 16 (3%) deaths during 6 months of follow-up
• Only 6 of these patients had a positive LAM test at baseline
• 5 of these 6 received anti-TB therapy before death (2 based on positive sputum Xpert result, 3 had empirical therapy)
• The other died without receiving anti-TB therapy, but had a laboratory confirmed diagnosis of Cryptococcal meningitis (India Ink) 87 days after enrolment.
Summary

• In this cohort the LF-LAM test had a poor positive predictive value, even in the target population
• The negative predictive value was excellent but not superior to a simple clinical history
• Knowledge of the test result would have been unlikely to avert any of the deaths in the study
• The test is unable to diagnose the presence of drug resistant TB
Meanwhile...

- Almost 1/3 of the patients were not receiving ART
- 97% of the patients were not receiving IPT
Conclusion

• Future studies may demonstrate that the LF-LAM test has utility in more nuanced, geographically-specific, diagnostic algorithms in Asia.

• However, the test added little to existing diagnostic and management strategies as a stand-alone test in this study.

• In the Southeast Asian setting, overcoming barriers to the rollout of ART and uptake of IPT are likely to have a far greater impact on reducing TB related morbidity and mortality.
Acknowledgements

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