Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV

Policy update (2019)

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GTB
Background

• In 2018, an estimated 860,000 (8.6%) of the 10.0 million people who developed TB worldwide were HIV-positive.

• Tests based on the detection of LAM antigen in urine have emerged as potential point-of-care tests for TB.

• The currently available urinary LAM assays have suboptimal sensitivity, and are therefore not suitable as diagnostic tests for TB in all populations.

• However, unlike traditional diagnostic methods, urinary LAM assays demonstrate improved sensitivity for the diagnosis of TB among PLHIV. The estimated sensitivity is even greater in patients with lower CD4 cell counts.
WHO recommendations: LF-LAM

• WHO has initially recommended LF-LAM in 2015:
  • HIV-positive adults and children with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count ≤ 100 cells/µL, or
  • HIV-positive patients who are seriously ill regardless of CD4 cell count or with unknown CD4 cell count

• In May 2019, WHO GTB and HIV Department convened a Guideline Development Group to review evidence from an updated systematic review:
  • Assess the available data on the accuracy (sensitivity and specificity) of LF-LAM for diagnosis of active TB in HIV-positive adults, adolescents and children with signs and symptoms of TB; in individuals irrespective of signs and symptoms of TB; and in individuals with advanced HIV disease;
  • Assess the available data related to the impact of LF-LAM’s implementation on mortality and other outcomes that are important to patients;
  • Collect and review economic data on affordability, cost and cost–effectiveness of the use of LF-LAM, to assist in the diagnosis of TB;
  • Collect and review end-user data on feasibility, acceptability and equity of the use of LF-LAM, to assist in the diagnosis of TB; and
  • Outline issues to be addressed by WHO in subsequent policy recommendations
The 15 included studies involved 6814 participants, 1761 (26%) with TB.

Eight of the studies evaluated the accuracy of AlereLAM for TB diagnosis in participants with signs and symptoms suggestive of TB involving 3449 participants, 1277 (37%) with TB.

Seven studies evaluated the accuracy of AlereLAM for diagnosis of unselected participants that may or may not have had TB signs and symptoms at enrolment involving 3365 participants, 439 (13%) with TB.
## Overview of diagnostic accuracy of Alere LAM

### Type of analysis

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic participants</th>
<th>Unselected participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies (total participants)</td>
<td>Participants with TB (%)</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>8 studies (3449)</td>
<td>1277 (37%)</td>
</tr>
<tr>
<td></td>
<td>7 studies (3365)</td>
<td>432 (13%)</td>
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<tr>
<td>By setting</td>
<td></td>
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<tr>
<td>Inpatient</td>
<td>6 studies (2253)</td>
<td>868 (39%)</td>
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<tr>
<td></td>
<td>3 studies (537)</td>
<td>159 (30%)</td>
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<tr>
<td>Outpatient</td>
<td>4 studies (1136)</td>
<td>409 (34%)</td>
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<tr>
<td></td>
<td>6 studies (2828)</td>
<td>213 (10%)</td>
</tr>
<tr>
<td>By CD4 cell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 &gt; 200</td>
<td>3 studies (738)</td>
<td>163 (22%)</td>
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<tr>
<td></td>
<td>1 study (156)</td>
<td>11 (7%)</td>
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<tr>
<td>CD4 &gt; 100</td>
<td>4 studies (1825)</td>
<td>722 (40%)</td>
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<tr>
<td></td>
<td>2 studies (706)</td>
<td>82 (12%)</td>
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<tr>
<td>CD4 &gt; 100</td>
<td>4 studies (1519)</td>
<td>425 (28%)</td>
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<tr>
<td></td>
<td>4 studies (952)</td>
<td>115 (12%)</td>
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<tr>
<td>CD4 ≤ 200</td>
<td>4 studies (1239)</td>
<td>512 (41%)</td>
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<tr>
<td></td>
<td>3 studies (417)</td>
<td>130 (31%)</td>
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<tr>
<td>CD4 101-200</td>
<td>4 studies (586)</td>
<td>210 (36%)</td>
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<tr>
<td></td>
<td>1 study (103)</td>
<td>13 (13%)</td>
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<tr>
<td>By CD4 and setting</td>
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<td></td>
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<tr>
<td>CD4 ≤ 200</td>
<td>2 studies (1009)</td>
<td>348 (34%)</td>
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<tr>
<td></td>
<td>1 study (54)</td>
<td>14 (26%)</td>
</tr>
<tr>
<td>CD4 ≤ 100</td>
<td>2 studies (734)</td>
<td>270 (37%)</td>
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<tr>
<td></td>
<td>2 studies (600)</td>
<td>84 (13%)</td>
</tr>
<tr>
<td>CD4 101-200</td>
<td>2 studies (275)</td>
<td>78 (28%)</td>
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<tr>
<td></td>
<td>1 study (9)</td>
<td>4 (44%)</td>
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<tr>
<td>CD4 ≤ 200</td>
<td>1 study (249)</td>
<td>97 (39%)</td>
</tr>
<tr>
<td></td>
<td>2 studies (652)</td>
<td>68 (10%)</td>
</tr>
<tr>
<td>CD4 ≤ 100</td>
<td>1 study (121)</td>
<td>48 (40%)</td>
</tr>
<tr>
<td></td>
<td>2 studies (217)</td>
<td>46 (21%)</td>
</tr>
<tr>
<td>CD4 101-200</td>
<td>1 study (128)</td>
<td>51 (40%)</td>
</tr>
</tbody>
</table>

### Difference in diagnostic accuracy between inpatients and outpatients

Best diagnostic accuracy seen inpatients with CD4 <100 cells

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Difference in diagnostic accuracy between inpatients and outpatients

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Overall accuracy

8 studies

Participants with TB (%)

1277 (37%)

Pooled sensitivity (95% CrI)

42% (31 to 55)

Pooled specificity (95% CrI)

91% (85 to 95)
Economic evaluation

• A systematic review of economic evaluations on the urine-based LF-LAM for the diagnosis of active TB in HIV-positive individuals was carried out identified six studies from settings in sub-Saharan Africa;
• Economic evidence for the implementation and scale-up of LF-LAM is still limited.
• Studies showed a consistent trend, suggesting that LF-LAM could be cost-effective in a population of African adults living with HIV (particularly amongst hospitalized patients).
• Three studies assessed cost-effectiveness amongst hospitalized HIV-positive adults, all suggesting LF-LAM containing algorithms could be cost-effective across the countries and models evaluated including South Africa, Uganda, and Malawi.
• Additional local evidence and economic evaluation may be necessary as countries decide whether to roll-out LF-LAM for different population groups.
User perspective evaluation

15 semi-structured interviews were conducted during February and March 2019 with clinicians, nurses, programme officers, laboratory staff, and patient advocates in Uganda, Kenya and South Africa.

- Generally perceived as an easy to use, low maintenance/equipment requiring, quick test that crucially does not rely on sputum but on a more easily available and safer specimen;
- LF-LAM clearly addresses a need in a population in which TB is hard to diagnose.
- Concern regarding the suboptimal sensitivity of the test, cross-reactions and the difficulty of reading faint results
- Confidence in the test result is dependant on
  - Ensuring that the test is not used as a stand alone test but embedded in a clinical decision algorithm; and
  - Using test results in combination with clinical suspicion of TB or other evidence in case of asymptomatic patients.
2015 recommendation
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/ mm$^3$, or HIV positive patients who are seriously ill$^a$ regardless of CD4 cell count or with unknown CD4 cell count (conditional recommendation; low quality of evidence).

2019 recommendation
In inpatient settings, WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
- with signs and symptoms of TB (pulmonary and/or extrapulmonary) (strong recommendation; moderate certainty in the evidence about the intervention effects). or
- with advanced HIV disease or who are seriously ill (strong recommendation; moderate certainty in the evidence about the intervention effects). or
- irrespective of signs and symptoms of TB and with a CD4 count ≤ 200 cells/mm$^3$ (strong recommendation; moderate certainty in the evidence about the intervention effects).

Changes
- Increased strength of the recommendation.
- Improved quality of evidence.
- Increased scope of the recommendation:
  - all symptomatic or seriously ill inpatients, irrespective of CD4 cell count;
  - all inpatients with advanced HIV disease; and
  - inpatients with or without signs and symptoms of TB who have a CD4 cell count <200.
Updated Recommendations (2)

2015 recommendations
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 cell count or with unknown CD4 cell count, based on the generalization of data from in-patients.

2019 recommendations
In outpatient settings WHO suggests using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
• with signs and symptoms of TB (pulmonary and/or extrapulmonary) or “seriously ill” (conditional recommendation; low certainty in the evidence about test accuracy).
• irrespective of signs and symptoms of TB and CD4 count < 100 cells/ mm³ (conditional recommendation; very low certainty in the evidence about test accuracy).

Changes
Increased scope of the recommendation:
• all outpatients with signs and symptoms of TB or seriously ill; and
• outpatients with a CD4 cell count <100, irrespective of signs and symptoms of TB.
2019 recommendation
In outpatient settings, WHO recommends against using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
- without assessing TB symptoms (strong; very low certainty in the evidence about test accuracy).
- without TB symptoms and unknown CD4 count or without TB symptoms and CD4 count $\geq 200$ cells/mm$^3$ (strong; very low certainty in the evidence about test accuracy).
- without TB symptoms and CD4 counts between 100 and 200 cells/mm$^3$ (conditional; very low certainty in the evidence about test accuracy).

Changes
- Better definition of patient populations for negative recommendation against use of LF-LAM.

2015 recommendation
Except as specifically described below for persons with HIV infection with low CD4 cell counts or who are seriously ill, LF-LAM should not be used for the diagnosis of TB (strong recommendation, low quality of evidence).
Diagnostic algorithm (1)

**INPATIENT SETTING**

- Assess for TB signs or symptoms *
- Assess if seriously ill *
- Assess for AHD *
- Perform CD4 testing (advisable)

**Population:** All hospitalized patients, including adults, adolescents and children living with HIV

- Positive for TB signs or symptoms:
  - Perform Xpert MTB/RIF (Ultra) and Urine LAM if available
  - Xpert Positive, LAM Positive: TB Treatment
  - Xpert Positive, LAM Negative: TB Treatment
  - Xpert Negative or N/A, LAM Positive: Treat for TB, perform workup to exclude DR-TB
  - Xpert Negative or N/A, LAM Negative: Clinical Management

- No TB signs and symptoms with any of following:
  - Positive for AHD and/or seriously ill *
  - CD4 < 200
  - No TB signs and symptoms AND
  - CD4 above 200 or unknown CD4

**Clinical Management**

- Perform Urine LAM

- Negative
  - Perform Xpert if available
    - Xpert Positive: TB Treatment
    - Xpert Negative or N/A: Treat for TB, perform workup to exclude DR-TB

- Positive
  - Apply AHD+ package of care
  - TB Treatment

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* AHD – Advanced HIV Disease - For adults and adolescents, and children older than five years, advanced HIV disease is defined as CD4 cell count < 200 cells/mm3 or WHO stage 3 or 4 event. All children younger than five years old are considered as having advanced HIV disease.

* WHO TB symptom screen includes presence of fever, weight loss, or any cough. "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. PLHIV with TB may also present with signs or symptoms of extrapulmonary TB including lymphadenopathy, meningo, or other atypical presentations warranting evaluation.
Diagnostic algorithm (2)

**CLINIC / OUTPATIENT SETTING**

- **Positive for TB Signs and Symptoms and/or seriously ill**
  - Perform urine AirexLAM AND Xpert if available (and culture/DST if available)

- **without TB symptoms AND not seriously ill**
  - CD4 assessment if available
    - CD4 < 100 or Stage 3/4
    - CD4 100-200
    - Unknown CD4
      - CD4 > 200
        - Apply AHD* package of care
          - Perform Xpert if available
            - Positive
              - Xpert Positive
                - LAM Positive
                  - TB Treatment
                - LAM Negative
                  - TB Treatment
              - Xpert Negative or N/A
                - LAM Positive
                  - Treat for TB, perform workup to exclude DR-TB
                - LAM Negative
                  - Clinical Management
          - Xpert Negative or N/A
            - LAM Positive
              - TB Treatment
            - LAM Negative
              - Clinical Management
      - Do not perform urine AirexLAM
        - Clinical Management

*AHD – Advanced HIV Disease - For adults and adolescents, and children older than five years, advanced HIV disease is defined as CD4 cell count <200 cells/mm3 or WHO stage 3 or 4 event. All children younger than five years old are considered as having advanced HIV disease.

*A WHO TB symptom screen includes presence of fever, weight loss, night sweats, or any cough. PWTH with TB may also present with signs or symptoms of extrapulmonary TB including lymphadenopathy, meningitis, or other atypical presentations warranting evaluation. “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.
Conclusions

• Updated policy substantially expands indications for the use of LF-LAM for TB diagnosis;

• The Alere LAM assay remains the only commercially available urine test that has been shown to reduce mortality in HIV patients with advanced disease;

• Currently uptake of the test has been limited even among hospitalized patients were the accuracy of the test is greatest;

• Identifying HIV positive individuals with signs and symptoms is critical for determining which patients should be tested with a urine LAM assays especially in outpatient settings;

• Xpert MTB/RIF Ultra is the preferred test for the diagnosis of TB among symptomatic persons with HIV who are able to produce a sputum specimen;

• More accurate (sensitive and specific) LAM based assay are needed.

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