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AMPATHCHAT

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The utility of the urinary lipoarabinomannan antigen in HIV-infected patients with suspected tuberculosis

The urine lipoarabinomannan test (U-lam) has been marketed as an adjunct diagnostic modality in HIV-infected patients with severe immunosuppression. The test detects a cell wall component of the *Mycobacterium tuberculosis* bacterium that is excreted in urine. The lateral flow test format of the test (Determine™ TB-LAM Ag test) is rapid and can be performed directly on urine.

In a recent meta-analysis, the overall sensitivity and specificity of the various U-lam-based assays varied between 13 and 93% and 87 and 99% respectively. Reasons for the wide variation in sensitivities and specificities may be related to various factors, such as study design, test formats (enzyme-linked immunosorbent assay versus lateral flow assay), the use of frozen versus fresh urine, batch variations between kits, different manufacturers, etc. Table 1 indicates the pooled sensitivity and specificity in smear-positive and smear-negative cases, as well as in HIV-positive and HIV-negative cases from a recently published meta-analysis.

Table 1: Sensitivity and specificity in smear-positive and smear-negative cases, as well as in HIV-positive and HIV-negative cases

	Pooled sensitivity (95% confidence interval)	Pooled specificity (95% confidence interval)
Smear-positive cases	54% (95% CI 18–86%)	90% (95% CI 83–95%)
Smear-negative cases	51% (95% CI 18–83%)	90% (95% CI 79–96%)
HIV-positive cases	47% (95% CI 26–68%)	96% (95% CI 81–100%)
HIV-negative cases	14% (95% CI 4–38%)	97% (95% CI 86– 100%)

A multicentre study on the utility of the Determine™ TB-LAM Ag test (Alere, Waltham, Massachusetts, USA) on specimens from 1 013 HIV-infected participants with suspected PTB in Cape Town, South Africa, and Kampala, Uganda, revealed that the assay performed better in Ugandan participants than in those from Cape Town ($p = 0.0008$), with a sensitivity of 45.6% vs. 28.7% respectively (see Table 2). The overall specificity was determined at 97.6% (559/573; 95% CI 95.9 - 98.7%). CD4 T-cell count ≤ 50 cells/mm^3 (adjusted odds ratio (AOR) 6.2, $p < 0.001$) or CD4 = 51 to 100 cells/mm^3 (AOR 7.1, $p < 0.001$), mycobacteraemia (AOR 6.1, $p < 0.01$) and hospitalisation (AOR 2.6, $p = 0.03$) were independently associated with a positive Determine™ TB-LAM Ag test result. Overall across both study sites, over half of the culture-confirmed cases were detected by the Determine™ TB-LAM Ag test in HIV-infected adults with CD4 ≤ 100 cells/mm^3.

Table 2: Results of the sensitivity and specificity, as well as subgroup analyses of the Determine™ TB-LAM Ag test diagnostic research trial in Cape Town and Kampala

Sensitivity	Determine™ TB-LAM Ag test	CD4 ≤ 100 cells/mm^3	Combined Determine™ TB-LAM Ag plus smear microscopy	Combined Determine™ TB-LAM Ag plus CD4 ≤ 100 cells/mm^3 plus smear microscopy
Overall	136/367 (37.1%) [95% CI 21.1–42.2%]	116/196 (59.2%) [95% CI 52.0–66.1%]	197/367 (53.7%) [95% CI 48.4–58.9%]	133/196 (67.9%) [95% CI 60.8–74.3%]
Cape Town	53/185 (28.7%) [95% CI 22.3–35.7%]	45/187 (51.7%) [95% CI 40.8–62.6%]		
Uganda	83/182 (45.6%) [95% CI 38.2–53.1%]	71/109 (65.1%) [95% CI 55.4–74.0%]		

Key: 95% CI: 95% confidence intervals

The pros of using the U-lam test

- Rapid, non-invasive and an inexpensive test.
- Alternative diagnostic test in sputum-scarce HIV-infected patients.
- Improved sensitivity is seen when the test is combined with microscopy and/or CXR and/or Xpert®MTB/RIF assay in HIV-infected patients.
- Higher sensitivity is seen in HIV-infected patients with severe immunosuppression (CD4 T-cell count <100 cells/mm^3).
- There is a survival benefit in initiating anti-TB drugs in HIV-positive inpatients with suspected TB based on the U-lam result. Bedside U-lam-guided initiation of anti-TB drugs in a recent study of 2 659 patients indicated a reduced eight-week mortality (risk ratio of 0.83 (95% CI 0.73–0.96%), p = 0.012) and relative risk reduction of 17% (95% CI 4–28%).

The cons of using the U-lam test

- The Determine™ TB-LAM Ag test may **only be used for urine specimens**; its use in other specimen types remains to be determined.
- A negative U-lam test does not rule out the need for culture and molecular TB testing.
- No TB drug sensitivity results are generated with this test.
- False positive test results from bacterial contamination are possible (commensal flora, including actinobacteria, as well as *Candida* spp.).

WHO's policy recommendations (2015)

1. Except as specifically described for persons with HIV infection with CD4 counts ≤ 100 cells/mm^3 or who are seriously ill*, U-lam **should not be used for the diagnosis of TB** (strong recommendation, low quality of evidence).
2. U-lam may be used to assist in the diagnosis of TB in HIV-positive adult **inpatients** with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a **CD4 cell count ≤ 100 cells/mm^3**, or HIV-positive patients who are seriously ill*, regardless of CD4 count or with unknown CD4 count (conditional recommendation, low quality of evidence).

Remarks

1. This recommendation also applies to HIV-positive adult **outpatients** with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count ≤ 100 cells/mm^3, or HIV-positive patients who are seriously ill*, regardless of CD4 count or with unknown CD4 count, based on the generalisation of data from inpatients.
2. 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 TB-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 as: respiratory rate > 30/min, temperature > 39 °C, heart rate > 120/min **and** unable to walk unaided.

Specimen requirements

Collect a midstream urine specimen using a sterile technique. The perineum should be wiped with sterile saline or sterile water. If the patient is catheterised, a clean catheter should be inserted prior to collection of the specimen. Fresh urine specimens, if kept at room temperature, should be processed within eight hours. Urine specimens stored at 2 °C to 8 °C should be processed within three days of collection.

Conclusion

Testing for U-lam by the Determine™ TB-LAM Ag test (Alere, Waltham, Massachusetts, USA) should be **restricted to hospitalised HIV-infected adults with severe immunosuppression (CD4 ≤ 100 cells/mm^3)**. A negative U-lam test result does not rule out the possibility of TB. It is still recommended that specimens for microscopy (by fluorescent staining methodology), culture and molecular testing (PCRs) are submitted to the laboratory. All results should be interpreted in conjunction with the clinical and radiological picture of the patient.

References available on request.

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