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Novel FujiLAM assay to detect tuberculosis in HIV-positive ambulatory patients in four African countries: a diagnostic accuracy study

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Summary

Background Development of rapid biomarker-based tests that can diagnose tuberculosis using non-sputum samples is a priority for tuberculosis control. We aimed to compare the diagnostic accuracy of the novel Fujifilm SILVAMP TB LAM (FujiLAM) assay with the WHO-recommended Alere Determine TB-LAM Ag test (AlereLAM) using urine samples from HIV-positive patients.

Methods We did a diagnostic accuracy study at five outpatient public health facilities in Uganda, Kenya, Mozambique, and South Africa. Eligible patients were ambulatory HIV-positive individuals (aged ≥15 years) with symptoms of tuberculosis irrespective of their CD4 T-cell count (group 1), and asymptomatic patients with advanced HIV disease (CD4 count <200 cells per µL, or HIV clinical stage 3 or 4; group 2). All participants underwent clinical examination, chest x-ray, and blood sampling, and were requested to provide a fresh urine sample, and two sputum samples. FujiLAM and AlereLAM urine assays, Xpert MTB/RIF Ultra assay on sputum or urine, sputum culture for *Mycobacterium tuberculosis*, and CD4 count were systematically carried out for all patients. Sensitivity and specificity of FujiLAM and AlereLAM were evaluated against microbiological and composite reference standards.

Findings Between Aug 24, 2020 and Sept 21, 2021, 1575 patients (823 [52·3%] women) were included in the study: 1031 patients in group 1 and 544 patients in group 2. Tuberculosis was microbiologically confirmed in 96 (9·4%) of 1022 patients in group 1 and 18 (3·3%) of 542 patients in group 2. Using the microbiological reference standard, FujiLAM sensitivity was 60% (95% CI 51–69) and AlereLAM sensitivity was 40% (31–49; p<0·001). Among patients with CD4 counts of less than 200 cells per µL, FujiLAM sensitivity was 69% (57–79) and AlereLAM sensitivity was 52% (40–64; p=0·0218). Among patients with CD4 counts of 200 cells per µL or higher, FujiLAM sensitivity was 47% (34–61) and AlereLAM sensitivity was 24% (14–38; p=0·0116). Using the microbiological reference standard, FujiLAM specificity was 87% (95% CI 85–89) and AlereLAM specificity was 86% (95 CI 84–88; p=0·941). FujiLAM sensitivity varied by lot number from 48% (34–62) to 76% (57–89) and specificity from 77% (72–81) to 98% (93–99).

Interpretation Next-generation, higher sensitivity urine-lipoarabinomannan assays are potentially promising tests that allow rapid tuberculosis diagnosis at the point of care for HIV-positive patients. However, the variability in accuracy between FujiLAM lot numbers needs to be addressed before clinical use.

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Introduction

Tuberculosis accounts for 1·5 million deaths worldwide annually and remains the leading cause of death in people with HIV.[1] Tuberculosis diagnosis is key in combating the disease. The large decrease in people newly diagnosed with tuberculosis linked to health service disruptions caused by the COVID-19 pandemic has increased mortality due to tuberculosis.[1]

The development of biomarker-based tests that can diagnose tuberculosis using non-sputum samples, which enables initiation of tuberculosis treatment on the same day, is a high priority for tuberculosis control.[2] The first point-of-care test endorsed by WHO was the Alere Determine TB-LAM Ag test (AlereLAM; Abbott, Waltham, MA, USA), a lateral flow assay that detects the mycobacterial lipoarabinomannan (LAM) antigen in urine. The use of urine samples is a key advantage since some patients (14–63%), particularly those who are seriously ill, cannot produce sputum samples.[3,4] The AlereLAM assay increases tuberculosis diagnosis,[3–8] reduces mortality among symptomatic patients admitted to hospital,[9,10] is well accepted by test users,[11] and is cost-effective.[12–14] In a meta-analysis, AlereLAM sensitivity was 42% in patients with symptoms of tuberculosis

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Research in context

Evidence before this study

The Fujifilm SILVAMP TB LAM (FujiLAM) is a novel point-of-care assay that detects the mycobacterial lipoarabinomannan (LAM) antigen in urine to identify tuberculosis. FujiLAM can detect lower LAM concentrations than the currently WHO-recommended urine-based point-of-care Alere Determine TB-LAM Ag test (AlereLAM; Abbott, Waltham, MA, USA). In a meta-analysis, AlereLAM sensitivity was estimated at 42% in HIV-positive patients with symptoms of tuberculosis (29% in ambulatory settings) with 92% specificity.

We searched PubMed Central from database inception to Aug 23, 2022, for studies or reports of lipoarabinomannan for the diagnosis of tuberculosis. We used the search terms "("tuberculosis" OR "tb") AND ("lipoarabinomannan" OR "lam") AND ("Fuji*") AND ("HIV")". No language restrictions were applied. Our search identified five relevant publications that reported results on the accuracy of the FujiLAM assay for diagnosis of tuberculosis in adults with HIV. One study done in South Africa, one in Ghana, and one in Nigeria used previously collected clinical and laboratory data and stored frozen urine samples from HIV-positive patients. A meta-analysis included the studies conducted in South Africa and Ghana and an additional dataset from Viet Nam. One prospective study that included a small sample of HIV-positive patients in Zambia (n=68) used fresh urine samples. Reported sensitivities ranged between 71% and 75% and specificities between 89% and 93%. No data were available from large prospective studies.

Added value of this study

This is the first large multicentre prospective study to assess the diagnostic accuracy of the novel FujiLAM urine assay for the diagnosis of tuberculosis in adults with HIV. Diagnostic accuracy was assessed using microbiological and composite reference standards and compared with AlereLAM. In post-hoc analyses, FujiLAM accuracy was assessed by test lot number. Ambulatory HIV-positive patients with signs and symptoms of tuberculosis irrespective of their CD4 count and asymptomatic patients with advanced HIV disease were included from four countries in sub-Saharan Africa (Uganda, Kenya, Mozambique, and South Africa) with a high prevalence of HIV and tuberculosis. We found that FujiLAM identified a considerable proportion of HIV-positive patients who had microbiologically confirmed tuberculosis and that it was more sensitive than the currently recommended AlereLAM across all CD4 count strata and in both groups of patients, with similar specificity. However, FujiLAM sensitivity and specificity varied by lot number.

Implications of all the available evidence

Next-generation, higher sensitivity urine-LAM assays, are promising tests that can potentially improve the diagnosis of tuberculosis in patients with HIV. However, the variability in accuracy between FujiLAM lot numbers needs to be addressed before clinical use.

(45% in patients with CD4 counts of <200 cells per µL, 16% in those with CD4 counts of ≥200 cells per µL, and 29% in ambulatory settings), with 92% specificity.[15] WHO currently recommends AlereLAM to assist in tuberculosis diagnosis in people with HIV with signs and symptoms of tuberculosis, and in severely immunosuppressed patients irrespective of symptoms (ie, among people admitted to hospital with advanced HIV disease, or ambulatory with CD4 counts of <100 cells per µL).[16] Despite these recommendations, AlereLAM uptake by national programmes has been slow.[17]

The Fujifilm SILVAMP TB LAM (FujiLAM; Fujifilm, Tokyo, Japan) is a new point-of-care urine-based test that can detect lower LAM concentrations than AlereLAM using high affinity monoclonal antibodies directed towards largely *Mycobacterium tuberculosis*-specific LAM epitopes. Two studies in South Africa and Ghana assessing the diagnostic accuracy of FujiLAM in HIV-positive patients have reported higher FujiLAM sensitivities than AlereLAM when using frozen urine samples and previously collected clinical or laboratory data (70% *vs* 42% in South Africa; 74% *vs* 53% in Ghana) and slightly lower FujiLAM specificities compared with AlereLAM (91% *vs* 95% in South Africa; 89% *vs* 96% in Ghana).[18,19] A retrospective study in Nigeria and a prospective study in Zambia with a small number of people with HIV (70 and 68 patients, respectively) have reported similar accuracy.[20,21] These results suggest that the assay has the potential to improve tuberculosis diagnosis in people with HIV. However, to date, no evidence is available from large, prospective, diagnostic accuracy studies.

We aimed to assess the accuracy of the FujiLAM assay to diagnose tuberculosis from fresh urine samples in people with HIV at high risk of tuberculosis (either with symptoms of tuberculosis or asymptomatic with advanced HIV disease) in four countries in sub-Saharan Africa (Uganda, Kenya, Mozambique, and South Africa).

Methods

Study design and participants

We did a diagnostic accuracy study comparing FujiLAM and AlereLAM assays against microbiological and composite reference standards of tuberculosis at five outpatient public health facilities (HIV and tuberculosis clinics attached to referral hospitals and primary health-care clinics) in four countries: Uganda, Kenya, Mozambique, and South Africa (appendix p 2). We consecutively approached and enrolled HIV-positive ambulatory individuals (aged ≥15 years) with signs or symptoms of tuberculosis irrespective of their CD4 T-cell count (group 1), and asymptomatic patients with

See Online for appendix

advanced HIV disease (group 2). Signs and symptoms of tuberculosis were defined as cough, fever, weight loss, night sweats (of any duration), or signs of extrapulmonary tuberculosis. Asymptomatic patients were those without any of these signs and symptoms. Advanced HIV disease was defined as a CD4 count of less than 200 cells per μL, or HIV clinical stage 3 or 4 at the time of the consultation.[22] Patients receiving tuberculosis treatment were excluded.

The study protocol was approved by the National Ethics Committees in each country and by Médecins Sans Frontières Ethics Review Board (appendix p 3). Written informed consent (or assent for minors aged 15–17 years) was obtained from all study adult participants and from parents or guardians. This study follows guidance for non-sputum tests diagnostic accuracy evaluations[23] and conformed to the Standards for Reporting of Diagnostic Accuracy Studies reporting guidelines (appendix pp 4–5).

Procedures

At the initial consultation, all participants underwent clinical examination, chest x-ray, and blood sampling, and were requested to provide a fresh urine sample, and two sputum samples at an interval of at least 30 min. Patients unable to produce a sputum sample spontaneously were offered sputum induction. Sex was self-reported by the participants (male or female). FujiLAM and AlereLAM urine assays, Xpert MTB/RIF Ultra assay (Xpert Ultra; Cepheid, Sunnyvale, CA, USA) on sputum or urine, sputum culture for *M tuberculosis*, and CD4 count were systematically carried out for all patients at this consultation. Xpert Ultra was performed on urine for patients unable to produce two sputum samples, and on other non-respiratory samples for patients with signs of extrapulmonary tuberculosis. In South Africa, *M tuberculosis* culture was occasionally performed on urine on clinician request. In Uganda, sputum smear microscopy was systematically performed. Retinoscopy and thoracic or abdominal ultrasound were occasionally done in addition to other investigations for extrapulmonary or disseminated tuberculosis. Clinicians made decisions regarding patients' management and tuberculosis treatment based on the results of the assessments, with the exception of the FujiLAM assay. Patients with symptoms of tuberculosis who had not started on tuberculosis treatment were re-assessed after 7 days. All patients were followed up for 6 months after enrolment.

Urine FujiLAM and AlereLAM tests were performed at the point of care on fresh urine immediately after clinician assessment, following each manufacturer's instructions. The LAM tests were independently done by trained clinical, laboratory, or lay workers, who were masked to clinical and microbiological results, and to the results of the other LAM test. The FujiLAM test was also read by a second reader, masked to the first reading results, to assess inter-reader agreement. A schema of the testing procedures is shown in the appendix (pp 6–7). In the case of invalid results, the test was repeated up to two times.

Xpert Ultra was performed on one of the two sputum samples collected, on urine, and on extrapulmonary specimens if indicated. Additionally, the two sputum and extra-pulmonary samples were cultured using the Mycobacterial Growth Indicator Tube liquid culture (Becton Dickinson, Franklin Lakes, NJ, USA) and on the Lowenstein-Jensen solid culture medium (sputum only). The Bioline TB Ag MPT64 test (Abbott) or Standard Q TB MPT64 Ag (SD Biosensor, Suwon, South Korea) were used to differentiate *M tuberculosis* complex from non-tuberculous mycobacteria. The personnel performing Xpert Ultra and culture were masked to FujiLAM and AlereLAM results. CD4 T-cell count was performed using the Pima Analyser (Abbott) or the FacsCalibur Flow Cytometer (Becton Dickinson).

Clinicians interpreted chest x-ray results using a checklist, which consisted of the most common tuberculosis radiological findings, with a pictogram and a final interpretation of the chest x-ray as: suggestive of tuberculosis, abnormal not suggestive of tuberculosis, and normal. Two external radiologists, masked to the clinical and laboratory information, read the x-rays at a later stage. In case of discordant interpretation by clinicians and one external radiologist, a third reading by the other radiologist was performed and the interpretation with at least two concordant results was used for the classification of the patients as probable tuberculosis using a composite reference.

Data were collected on paper forms and entered into an electronic database using the REDCap software (Vanderbilt University, Nashville, TN, USA) at the study site.

Outcomes

The primary outcome of the study was the diagnostic accuracy of FujiLAM compared with the microbiological reference standard. Secondary outcomes were the diagnostic accuracy of FujiLAM compared with the composite reference standard, the diagnostic accuracy of AlereLAM against both reference standards, and the FujiLAM inter-reader agreement.

For the microbiological reference standard, confirmed tuberculosis was defined as at least one positive Xpert Ultra or *M tuberculosis* culture result from any sample; tuberculosis-negative cases were defined as at least two negative Xpert Ultra or culture results, including at least one sputum; all others were defined as unclassifiable.

For the composite reference standard, confirmed tuberculosis or probable tuberculosis defined tuberculosis. Patients with probable tuberculosis were those who did not meet the definition of confirmed tuberculosis, for whom a decision to treat for tuberculosis was made by the clinician and who had one or more of the following: positive sputum smear microscopy,

chest x-ray suggestive of tuberculosis, ultrasound or retinoscopy suggestive of tuberculosis, or clinical diagnosis of extrapulmonary tuberculosis. Tuberculosis-negative cases were those with at least one negative result on Xpert Ultra or culture on at least one sample (respiratory sample for patients with symptoms and any sample if asymptomatic) who did not meet the criteria for probable or confirmed tuberculosis, without a chest x-ray suggestive of tuberculosis and with no clinician's decision to treat tuberculosis; unclassifiable patients were those remaining.

For both reference standards, only samples obtained, investigations performed, and treatment decisions made within 30 days after enrolment were used to classify patients. Patients with positive Xpert or culture results in samples obtained after 30 days were deemed unclassifiable. For FujiLAM and AlereLAM, only tests done at initial consultation were considered. None of the index tests were included in the reference standards.

Statistical analysis

A sample size of 88 individuals with confirmed tuberculosis was required to estimate a FujiLAM sensitivity of 70% against the microbiological reference standards with a 95% CI width of 10%. For group 1, based on the assumption of a 10% tuberculosis prevalence and assuming that 10% of patients had no results, the final sample size was 990 patients. For group 2, due to the low proportion of asymptomatic patients with advanced HIV disease during interim data review, we estimated that it was feasible to enrol at least 500 patients. Based on an expected tuberculosis prevalence of 4%, this would allow a sensitivity of 70% to be estimated with 95% CI width of 20%.

Continuous variables were summarised as median and IQR and categorical variables as counts and percentages. Patients were classified as seriously ill if they had a temperature higher than 39°C, a respiratory rate higher than 30 respirations per minute, cardiac rate of less than 120 beats per min, or inability to walk unaided.[16]

The FujiLAM and AlereLAM diagnostic accuracies were assessed in patients with valid results for both tests, by calculating the sensitivity and specificity against the microbiological and composite reference standards, and stratified by CD4 count in all patients, and separately in patients from group 1 and group 2. All proportions were calculated and reported with their 95% CIs. In sensitivity analyses, all unclassifiable patients were considered tuberculosis-negative to avoid excluding any patient from analysis. After study completion, the Foundation for Innovative Diagnostics (FIND) and the FujiLAM manufacturer reported variability of FujiLAM accuracy by lot number.[24] Therefore, we performed post-hoc analyses of the accuracy of FujiLAM against the microbiological reference standard by lot number. In additional exploratory analyses, we compared the intensity of the positive FujiLAM (weak or strong as interpreted by the reader) and AlereLAM results (grades 1–4 as per the manufacturer scale) according to the microbiological reference standard and assessed the

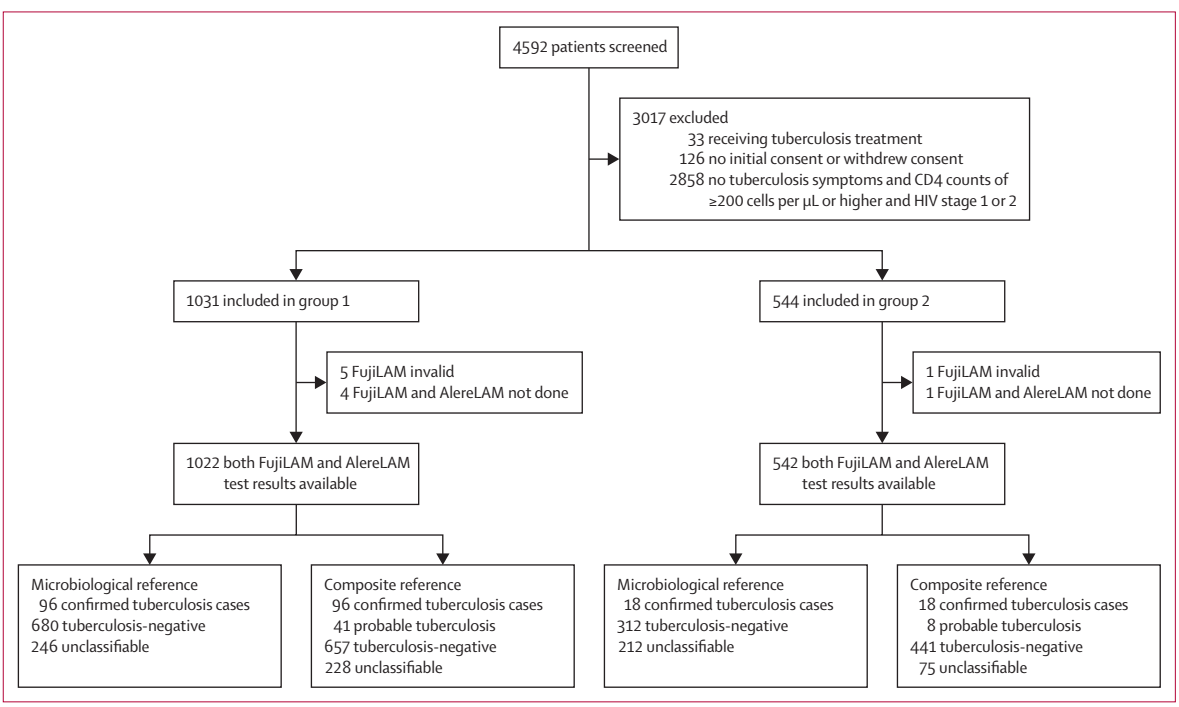


Figure 1: **Study flowchart**
Group 1 included HIV-positive ambulatory individuals (aged ≥15 years) with signs or symptoms of tuberculosis irrespective of their CD4 T-cell count. Group 2 included asymptomatic patients with advanced HIV disease. FujiLAM=Fujifilm SILVAMP TB LAM assay. AlereLAM=Alere Determine TB-LAM Ag test.

	Group 1 (n=1031)	Group 2 (n=544)
Sex		
Women	590 (57·2%)	233 (42·8%)
Men	441 (42·8%)	311 (57·2%)
Age, years	43 (35–53)	37 (30–45)
CD4 count, cells per µL	528 (272–770)	128 (66–181)
CD4 range, cells per µL		
<200	193/1026 (18·8%)	467/543 (86·0%)
200–349	137/1026 (13·4%)	22/543 (4·1%)
350–499	152/1026 (14·8%)	20/543 (3·7%)
≥500	544/1026 (53·0%)	34/543 (6·3%)
On ART	927 (89·9%)	495 (91·0%)
Seriously ill*	60 (5·8%)	8 (1·5%)
Tuberculosis suggestive symptoms		
Cough	965 (93·6%)	NA
Fever	453 (43·9%)	NA
Night sweats	404 (39·2%)	NA
Weight loss	345 (33·5%)	NA
Difficulty breathing	250 (24·2%)	NA
Haemoptysis	30 (2·9%)	NA
Chest x-ray		
Suggestive of tuberculosis	212 (20·6%)	63 (11·6%)
Abnormal with other signs	254 (24·6%)	150 (27·6%)
Normal	510 (49·5%)	276 (50·7%)
Not done	55 (5·3%)	55 (10·1%)
Extrapulmonary tuberculosis diagnosis	6 (0·6%)	4 (0·7%)
Decision to treat for tuberculosis	236 (22·9%)	72 (13·2%)
At least one urine-based test result available†	1027 (99·6%)	543 (99·8%)
At least one sputum-based test result available‡	929 (90·1%)	335 (61·6%)
Sputum spontaneously produced	753/929 (81·0%)	43/335 (12·8%)
Sputum induced	159/929 (17·1%)	278/335 (83·0%)
No information on successful sputum collection method	17/929 (1·8%)	14/355 (4·2%)
FujiLAM		
Positive	166 (16·1%)	81 (14·9%)
Negative	856 (83·0%)	461 (84·7%)
Invalid	5 (0·5%)	1 (0·2%)
Not done	4 (0·4%)	1 (0·2%)
FujiLAM positive intensity		
Light line	125/166 (75·3%)	62/81 (76·5%)
Dark line	41/166 (24·7%)	19/81 (23·5%)
AlereLAM		
Positive	179 (17·4%)	78 (14·3%)
Negative (no line)	755 (73·2%)	420 (77·2%)
Negative (line lighter than grade 1)	93 (9·0%)	45 (8·3%)
Invalid	0	0
Not done	4 (0·4%)	1 (0·2%)
AlereLAM positive grade		
1	147/178 (82·6%)	70/76 (92·1%)
2	13/178 (7·3%)	1/76 (1·3%)
3	6/178 (3·4%)	3/76 (3·9%)
4	12/178 (6·7%)	2/76 (2·6%)
Xpert Ultra (sputum samples)		
M tuberculosis detected	83 (8·0%)	12 (2·2%)
M tuberculosis not detected	825 (80·0%)	313 (57·5%)
Invalid, error, or no result	5 (0·5%)	3 (0·6%)
Not done	118 (11·5%)	216 (39·7%)
Xpert Ultra (non-respiratory samples)		
M tuberculosis detected	12 (1·2%)	6 (1·1%)
M tuberculosis not detected	187 (18·1%)	467 (85·9%)
Invalid, error, or no result	3 (0·3%)	7 (1·3%)
Not done	829 (80·4%)	64 (11·8%)
M tuberculosis culture in sputum		
Positive	71 (6·9%)	7 (1·3%)
Negative	763 (74·0%)	311 (57·2%)
Non-tuberculous mycobacteria	7 (0·7%)	4 (0·7%)
Contaminated	18 (1·8%)	3 (0·6%)
Not done	172 (16·4%)	219 (40·3%)
Microbiological reference§		
Confirmed tuberculosis	96/1022 (9·4%)	18/542 (3·3%)
Not tuberculosis	680/1022 (66·5%)	312/542 (57·6%)
Unclassifiable	246/1022 (24·1%)	212/542 (39·1%)
Composite reference§		
Confirmed tuberculosis	96/1022 (9·4%)	18/542 (3·3%)
Probable tuberculosis	41/1022 (4·0%)	8/542 (1·5%)
Not tuberculosis	657/1022 (64·3%)	441/542 (81·4%)
Unclassifiable	228/1022 (22·3%)	75/542 (13·8%)

Data are n (%), median (IQR), or n/N (%). Group 1 included HIV-positive ambulatory individuals (aged ≥15 years) with signs or symptoms of tuberculosis irrespective of their CD4 T-cell count. Group 2 included asymptomatic patients with advanced HIV disease. ART=antiretroviral therapy. NA=not applicable. FujiLAM=Fujifilm SILVAMP TB LAM assay. AlereLAM=Alere Determine TB-LAM Ag test. Xpert Ultra=Xpert MTB/RIF Ultra assay. *M tuberculosis*=*Mycobacterium tuberculosis*. *Patients were classified as seriously ill if they had a temperature of >39°C, a respiratory rate of >30 respirations per min, a cardiac rate of >120 beats per minute, or inability to walk without help. †Urine-based FujiLAM or AlereLAM results. ‡Sputum-based Xpert Ultra or *M tuberculosis* culture laboratory results. §Microbiological and composite reference classification for patients with valid FujiLAM and AlereLAM results and included in the accuracy analyses.

Table: **Patient characteristics and diagnostic tests results**

association between the intensity of the positive FujiLAM results and semi-quantitative Xpert Ultra results (in any sample) as a proxy for tuberculosis burden.

We used the McNemar's test for paired samples to compare the sensitivity and specificity of FujiLAM and AlereLAM, and the χ^2 test to compare independent proportions. FujiLAM test inter-reader agreement was assessed by calculating the κ statistic. p values of 0·05 or less were considered to indicate statistical significance.

	n	TP	FP	FN	TN	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Overall							
FujiLAM	1106	68	133	46	859	60% (51–69)	87% (85–89)
AlereLAM	1106	46	135	68	857	40% (31–49)	86% (84–88)
FujiLAM (CD4 count <200 cells per µL)	449	45	63	20	321	69% (57–79)	84% (80–87)
AlereLAM (CD4 count <200 cells per µL)	449	34	59	31	325	52% (40–64)	85% (81–88)
FujiLAM (CD4 count ≥200 cells per µL)	656	23	70	26	537	47% (34–61)	88% (85–90)
AlereLAM (CD4 count ≥200 cells per µL)	656	12	76	37	531	24% (14–38)	87% (84–89)
Group 1							
FujiLAM	776	57	85	39	595	59% (49–68)	88% (85–90)
AlereLAM	776	42	92	54	588	44% (34–54)	86% (83–88)
FujiLAM (CD4 count <200 cells per µL)	147	34	18	14	81	71% (57–82)	82% (73–88)
AlereLAM (CD4 count <200 cells per µL)	147	30	17	18	82	62% (48–74)	83% (74–89)
FujiLAM (CD4 count ≥200 cells per µL)	629	23	67	25	514	48% (35–62)	88% (85–90)
AlereLAM (CD4 count ≥200 cells per µL)	629	12	75	36	506	25% (15–39)	87% (84–89)
Group 2							
FujiLAM	330	11	48	7	264	61% (39–80)	85% (81–89)
AlereLAM	330	4	43	14	269	22% (09–45)	86% (82–89)
FujiLAM (CD4 count <200 cells per µL)	302	11	45	6	240	65% (42–83)	84% (79–88)
AlereLAM (CD4 count <200 cells per µL)	302	4	42	13	243	24% (10–48)	85% (80–89)
FujiLAM (CD4 count ≥200 cells per µL)	27	0	3	1	23	0% (0–79)	88% (70–96)
AlereLAM (CD4 count ≥200 cells per µL)	27	0	1	1	25	0% (0–79)	96% (81–99)
Overall by lot							
FujiLAM lot number 19003	382	19	82	6	275	76% (57–89)	77% (72–81)
FujiLAM lot number 20002	63	6	5	2	50	75% (41–93)	91% (81–96)
FujiLAM lot number 20003	261	10	2	7	107	59% (36–79)	98% (93–99)
FujiLAM lot number 20004	275	22	7	24	222	48% (34–62)	97% (94–99)

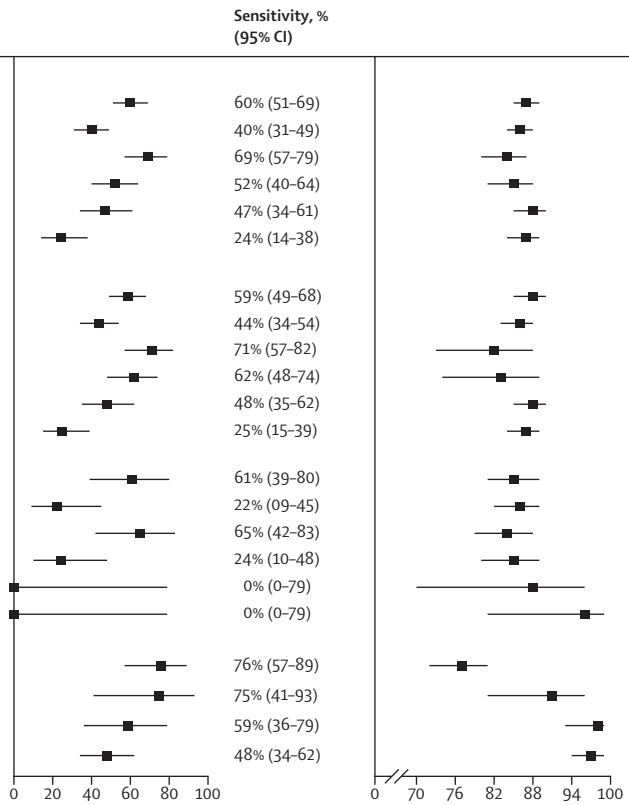


Figure 2: **Sensitivity and specificity of FujiLAM and AlereLAM diagnostic accuracy against the microbiological reference standard in patients with HIV**
Sensitivity and specificity of FujiLAM and AlereLAM by CD4 count for both groups combined, group 1, group 2, and sensitivity and specificity of FujiLAM for both groups combined by assay lot number. Group 1 included HIV-positive ambulatory individuals (aged ≥15 years) with signs or symptoms of tuberculosis irrespective of their CD4 T-cell count. Group 2 included asymptomatic patients with advanced HIV disease. FujiLAM=Fujifilm SILVAMP TB LAM assay. AlereLAM=Alere Determine TB-LAM Ag test. TP=true positive. FP=false positive. FN=false negative. TN=true negative.

Double data entry and data cleaning were performed regularly during the whole study duration. Data were analysed using R (version 4.1.3.) and Stata (version 17.0).

Role of the funding source

The study funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 24, 2020 and Sept 21, 2021, 1575 patients (823 [52·3%] women) were included in the study: 1031 patients in group 1 and 544 patients in group 2 (figure 1). The median CD4 count was 528 cells per µL (IQR 272–770) in group 1 and 128 cells per µL (66–181) in group 2, 927 (89·9%) of 1031 patients in group 1 and 495 (91·0%) of 544 patients in group 2 were on antiretroviral therapy (ART), and 60 (5·8%) patients in group 1 and eight (1·5%) patients in group 2 were seriously ill (table).

FujiLAM was positive in 166 (16·1%) of 1031 patients in group 1 and 81 (14·9%) of 544 patients in group 2. FujiLAM was invalid in 18 (1·1%) of 1571 tested patients on the first attempt and in six (0·4%) of 1571 patients after repeating the test. FujiLAM results inter-reader agreement was 98·0% (κ=0·94 [95% CI 0·91–0·96]; appendix p 8). AlereLAM was positive in 179 (17·4%) of 1031 patients in group 1 and 78 (14·3%) of 544 patients in group 2.

1022 patients in group 1 and 542 patients in group 2 had both FujiLAM and AlereLAM results, of whom 96 patients (9·4%) in group 1 and 18 patients (3·3%) in group 2 had confirmed tuberculosis, and 41 patients (4·0%) in group 1 and eight patients (1·5%) in group 2 had probable tuberculosis. In total, 458 (29·3%) of 1564 patients were unclassifiable as per the microbiological reference standard and 303 (19·4%) of 1564 patients were unclassifiable as per the composite reference standard. Among unclassifiable patients, five had positive Xpert or culture results in samples obtained after 30 days, of whom three were FujiLAM positive and none was AlereLAM positive.

Using the microbiological reference standard, FujiLAM sensitivity was 60% (95% CI 51–69) compared with 40% (31–49) for AlereLAM (p<0·0007). Among patients with CD4 counts of less than 200 cells per µL, FujiLAM

	n	TP	FP	FN	TN	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Overall							
FujiLAM	1261	78	108	85	990	48% (40–56)	90% (88–92)
AlereLAM	1261	62	57	101	1041	38% (31–46)	95% (94–96)
FujiLAM (CD4 count <200 cells per µL)	540	51	53	37	399	58% (48–68)	88% (85–91)
AlereLAM (CD4 count <200 cells per µL)	540	41	30	47	422	47% (37–57)	93% (90–95)
FujiLAM (CD4 count ≥200 cells per µL)	718	27	55	48	588	36% (26–47)	91% (89–93)
AlereLAM (CD4 count ≥200 cells per µL)	718	21	27	54	616	28% (19–39)	96% (94–97)
Group 1							
FujiLAM	794	65	58	72	599	47% (39–55)	91% (89–93)
AlereLAM	794	55	28	82	629	40% (32–48)	96% (94–97)
FujiLAM (CD4 count <200 cells per µL)	141	38	9	26	68	59% (47–70)	88% (79–94)
AlereLAM (CD4 count <200 cells per µL)	141	34	4	30	73	53% (41–65)	95% (88–98)
FujiLAM (CD4 count ≥200 cells per µL)	650	27	49	46	528	37% (27–48)	92% (89–94)
AlereLAM (CD4 count ≥200 cells per µL)	650	21	24	52	553	29% (20–40)	96% (94–97)
Group 2							
FujiLAM	467	13	50	13	391	50% (32–68)	89% (86–92)
AlereLAM	467	7	29	19	412	27% (14–46)	93% (90–95)
FujiLAM (CD4 count <200 cells per µL)	399	13	44	11	331	54% (35–72)	88% (84–91)
AlereLAM (CD4 count <200 cells per µL)	399	7	26	17	349	29% (15–49)	93% (90–95)
FujiLAM (CD4 count ≥200 cells per µL)	68	0	6	2	60	0% (0–66)	91% (82–96)
AlereLAM (CD4 count ≥200 cells per µL)	68	0	3	2	63	0% (0–66)	95% (87–98)

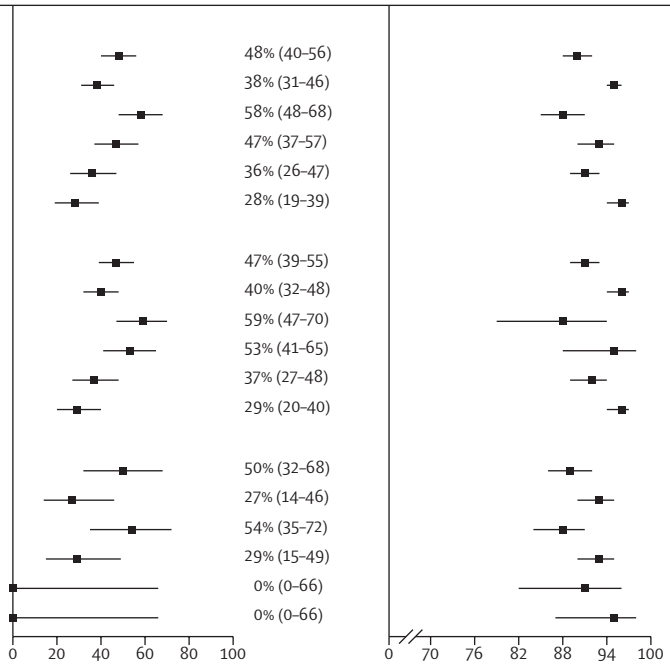


Figure 3: **Sensitivity and specificity of FujiLAM and AlereLAM against the composite reference standard in patients with HIV**
Sensitivity and specificity of FujiLAM and AlereLAM by CD4 count for both groups combined, group 1, and group 2. Group 1 included HIV-positive ambulatory individuals (aged ≥15 years) with signs or symptoms of tuberculosis irrespective of their CD4 T-cell count. Group 2 included asymptomatic patients with advanced HIV disease. FujiLAM=Fujifilm SILVAMP TB LAM assay. AlereLAM=Alere Determine TB-LAM Ag test. TP=true positive. FP=false positive. FN=false negative. TN=true negative.

was 69% (95% CI 57–79) and AlereLAM sensitivity was 52% (40–64; p=0·0218), and among patients with CD4 counts of 200 cells per µL or higher, FujiLAM sensitivity was 47% (34–61) and AlereLAM sensitivity was 24% (14–38; p=0·0116; figure 2).

Using the microbiological reference standard, in group 1, FujiLAM sensitivity was 59% (95% CI 49–68) and AlereLAM sensitivity was 44% (34–54; p=0·0112), and in group 2, FujiLAM sensitivity was 61% (39–80) and AlereLAM sensitivity was 22% (0·09–0·45; p=0·0082). Among patients in group 1, FujiLAM sensitivity was similar in patients with CD4 counts of less than 200 cells per µL (71% [56–83]) and 200–349 cells per µL (68% [43–87]), and lower among patients with CD4 counts of 350 cells per µL or higher (35% [18–54]). AlereLAM sensitivity was 63% (47–76) in patients with CD4 counts of less than 200 cells per µL, and lower in patients with CD4 counts of 200–349 cells per µL (37% [16–62]) and CD4 counts of 350 cells per µL or higher (17% [6–36]). Using the microbiological reference standard, FujiLAM specificity was 87% (95% CI 85–89) and AlereLAM specificity was 86% (84–88; p=0·8828).

Using the composite reference standard, FujiLAM sensitivity was 48% (95% CI 40–56) and AlereLAM sensitivity was 38% (31–46; p=0·0237) and FujiLAM specificity was 90% (95% CI 88–92) and AlereLAM specificity was 95% (94–96; p<0·0001; figure 3). In sensitivity analyses in which unclassifiable tuberculosis cases were considered as tuberculosis-negative, FujiLAM specificity against the microbiological reference standard and composite reference standard was similar. However, AlereLAM specificity against the composite reference standard was lower than in primary analyses (appendix pp 9–10).

In post-hoc analyses of four different FujiLAM lot numbers used in the study, the FujiLAM accuracy point estimates against the microbiological reference standards varied by lot number. Sensitivity varied from 48% (95% CI 34–62) to 76% (57–89) and specificity from 77% (95% CI 72–81) to 98% (93–99; figure 2; appendix p 11).

A third of patients with confirmed tuberculosis (36 [31·6%] of 114 patients) were identified by the two LAM tests (figure 4). Additionally, among the 114 patients with confirmed tuberculosis, FujiLAM alone identified tuberculosis in 32 (28·1%) patients and AlereLAM alone identified tuberculosis in ten (8·8%) patients. Among 992 patients without tuberculosis, 42 (4·2%) had positive FujiLAM and AlereLAM results, 91 (9·2%) had only FujiLAM positive results, and 93 (9·4%) had only AlereLAM positive results (appendix p 12). Of the 11 patients with non-tuberculous mycobacteria isolated in sputum without *M tuberculosis*, three were both FujiLAM and AlereLAM positive.

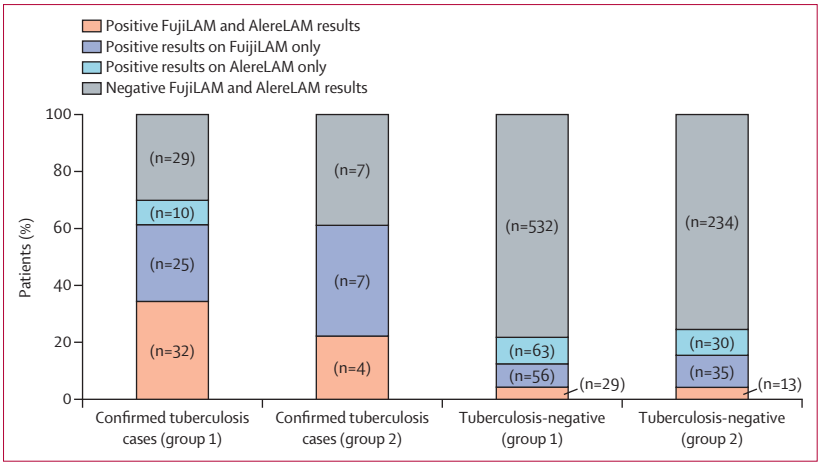


Figure 4: **FujiLAM and AlereLAM results among patients with confirmed tuberculosis and patients without tuberculosis as per the microbiological reference standard**
Group 1 included HIV-positive ambulatory individuals (aged ≥15 years) with signs or symptoms of tuberculosis irrespective of their CD4 T-cell count. Group 2 included asymptomatic patients with advanced HIV disease. FujiLAM=Fujifilm SILVAMP TB LAM assay. AlereLAM=Alere Determine TB-LAM Ag test.

As per the microbiological reference standard, weakly positive FujiLAM results and grade 1 AlereLAM results were more frequent among patients who did not have tuberculosis than patients with confirmed tuberculosis. Among patients with positive FujiLAM results, 120 (90·2%) of 133 patients without tuberculosis had weakly positive results compared with 34 (50·0%) of 68 patients with confirmed tuberculosis (p<0·0001). Among patients with positive AlereLAM, 121 (91·0%) of 133 patients without tuberculosis had grade 1 results compared with 29 (64·4%) of 45 patients with confirmed tuberculosis (p<0·0001; appendix pp 12–13).

The intensity of positive FujiLAM results was associated with semi-quantitative Xpert Ultra results (appendix p 14). Among patients with high or medium Xpert Ultra results, a higher proportion had strongly positive FujiLAM results than did those with low, very low, or trace Xpert Ultra results (p=0·0012).

Discussion

In this diagnostic accuracy study, the FujiLAM assay identified a considerable proportion of symptomatic ambulatory HIV-positive patients and asymptomatic patients with advanced HIV disease who had microbiologically confirmed tuberculosis. FujiLAM was more sensitive than AlereLAM across all CD4 count strata and both study groups. Specificity was similar for both tests. As notified after study completion by FIND and the FujiLAM manufacturer, we found variability in FujiLAM accuracy among lot numbers, which affected both sensitivity and specificity. Further investigations are required before clinical use of FujiLAM. Exploratory analyses suggest that the intensity of the FujiLAM positive results might be associated with tuberculosis bacterial load based on semi-quantitative Xpert Ultra results, and that false positive FujiLAM results might be more frequent among patients with weakly positive results.

The sensitivity of FujiLAM was high in patients with CD4 counts of less than 200 cells per µL and in patients with CD4 counts of 200–350 cells per µL, while the sensitivity of AlereLAM was lower in patients with CD4 counts of 200–350 cells per µL than in patients with CD4 cells counts of less than 200 cells per µL. FujiLAM sensitivity at higher CD4 counts would be a substantial advantage compared with the AlereLAM test. A meta-analysis of studies using previously collected data and stored urine samples found higher FujiLAM sensitivity at lower CD4 counts (87% in patients with CD4 counts <100 cells per µL) than higher CD4 counts (44% in patients with CD4 counts ≥200 cells per µL).[25] However, neither this nor other studies have reported FujiLAM sensitivity in patients with CD4 counts between 200 and 350 cells per µL or higher than 500 cells per µL. In our study, among symptomatic patients with CD4 counts of 350 cells per µL or higher, FujiLAM sensitivity was lower (35%) than reported in HIV-negative symptomatic patients (53%) in a multicentre study,[26] and in two smaller studies (66% and 75%).[20,21] This difference might be explained by the higher proportion of HIV-negative patients with advanced or disseminated tuberculosis disease in these studies.

We report the first prospective diagnostic accuracy results of FujiLAM in asymptomatic patients with advanced HIV disease. The prevalence of tuberculosis was high in this group (3% with microbiologically confirmed and 5% with probable or confirmed tuberculosis) and FujiLAM detected around 65% of cases. A study in Ghana[19] including patients referred for ART initiation identified the majority of confirmed tuberculosis cases among symptomatic patients after the WHO symptom screen.

As previously reported, we found FujiLAM specificity tended to be lower in immunosuppressed patients[18,19,25] and slightly higher with the composite reference standards. These findings question the suitability of using only sputum microbiology results to define tuberculosis-negative cases among patients with low CD4 cell counts. FujiLAM is expected to produce fewer cross-reactions with non-tuberculous mycobacteria than AlereLAM due to highly specific antibodies.[18,20,27] We found most false positive FujiLAM results were weakly positive and occurred in specific lot numbers. One hypothesis is that some false positive results could also be due to cross-reactions with other pathogens producing weakly positive results. However, we also found an association between FujiLAM result intensity and bacterial load by Xpert Ultra. Some FujiLAM positive tests might also have been misclassified as false positive in patients with low tuberculosis bacterial load not detected by Xpert Ultra or culture.

We found differences in the FujiLAM diagnostic accuracy by lot number. One lot number (representing

30% of the tests) showed high sensitivity and suboptimal specificity whereas two lot numbers had lower sensitivity and high specificity. The cause of this variability is currently under investigation by the manufacturer, and clinical use will not be possible until this variability in performance has been addressed.

Urine samples were easily produced by almost all patients, while only three-quarters of symptomatic and less than 10% of asymptomatic patients could spontaneously produce sputum. Therefore, urine-based tuberculosis tests have a clear added value for tuberculosis diagnosis. Furthermore, as we have reported elsewhere, urine sampling for tuberculosis investigations is mostly preferred to sputum sampling by patients.[28] The FujiLAM test is considered easy to perform, including by lay health-care workers.[29]

The main limitation of our study is the possible misclassification of patients with non-microbiologically confirmed tuberculosis as tuberculosis-negative cases, which might have led to underestimation of LAM specificity against the microbiological reference standards.[23] To maximise tuberculosis detection, we systematically performed Xpert Ultra and culture in two sputum samples for all patients, Xpert Ultra in urine for patients with less than two sputum samples, and Xpert Ultra in extra-pulmonary samples if indicated. Additionally, our definition of tuberculosis-negative cases included two sputum Xpert Ultra or culture-negative results. Although this strict definition resulted in a high proportion of unclassifiable patients, LAM specificity against the microbiological reference standards in primary and sensitivity analyses (unclassified patients considered as tuberculosis-negative) was similar. Since the microbiological reference standards might yield overestimates for LAM sensitivity, we used a composite reference standard that combined clinical and pathological tests to identify patients with tuberculosis. We defined a short timeframe (30 days) between the index tests and the reference to decrease the possibility of bias. Another limitation was the precision of the FujiLAM sensitivity by CD4 count as the sample size was calculated for overall accuracy by patient group. Finally, the variability of the accuracy between FujiLAM lot numbers limits the interpretation of the overall diagnostic accuracy of FujiLAM.

Strengths of the study include the study setting of four countries with a high HIV burden with similar conditions to those of its intended use. Symptomatic patients were eligible irrespective of their CD4 count, and consequently, large numbers of patients with high CD4 counts were included, which represents the current ambulatory HIV population in many African clinics.

Clinicians in low-resource settings often rely on clinical judgement to diagnose tuberculosis due to poor availability of x-rays, difficulties in obtaining sputum samples, and delays in obtaining rapid molecular test results. Next-generation, higher sensitivity urine-LAM assays are promising tests that allow rapid tuberculosis diagnosis at the point of care for people with HIV with symptoms of tuberculosis and for asymptomatic patients with advanced HIV disease. However, the variability in accuracy between FujiLAM lot numbers needs to be addressed before clinical use.

Contributors

HH and MBa designed the study with input from WM, NTA, LO, IMT, ZN, and CH. HH oversaw and coordinated the multicentre study. NTA, LO, and WM oversaw the study in the study sites. AVL, MA, NTA, RS, and NN supervised the study implementation in the study sites. IMT, CB, TS, GO, JOO, JN, MMb, CA, SW, MMu, DA, and AA provided support to the study implementation in the study sites. IMT and EA provided support to the laboratory procedures. ZN, CH, GF, LN, MC, AG-W, and MBo provided scientific support. MBa did the statistical analysis. HH wrote the manuscript draft. AG-W and MBo provided substantial input in the manuscript. All authors had full access to all data in the study and contributed to the interpretation of data, the revision of the Article, approved the final version of the manuscript, and had final responsibility for the decision to submit for publication. HH and MBa had access to and verified all the data.

Declaration of interests

We declare no competing interests.

Data sharing

Data collected for the study will be made available on request after manuscript publication. Data will include individual deidentified participant data and the data dictionary. Requests can be addressed to the corresponding author (helena.huerga@epicentre.msf.org). Requests will be examined by a committee of relevant people involved in the study. The scientific aspects of the proposal as well as the ethical and legal implications of the data sharing will be considered. Data will be shared after approval of the proposal and after signing a data sharing agreement by all parties involved.

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