Original Research Article

Contribution of TB-LAM urine test to tuberculosis diagnosis in HIV-infected adultpatients in Burkina Faso

ABSTRACT

Aims: With the aim of improving the diagnosis of tuberculosis in patients living with HIV, we set out to evaluate the contribution of the TB-LAM urine test to the diagnosis of tuberculosis in PLWHA in Burkina Faso, in real life.
Methodology: The study was conducted in the Infectious Diseases Departments of the Yalgado OUEDRAOGO (CHU-YO), Souro SANOU (CHU-SS) and Bogodogo (CHU-B) University Hospitals. These 03 centers are among the most important reference centers in Burkina Faso.This was a descriptive and analytical cross-sectional study with prospective data collection over 12 months, from January 1, 2023 to December 31, 2023, and involved PLWH inpatients and outpatients. Data were collected using the KoBoCollect v1.30.1 application and analyzed using STATA 16 software. Binary uni and multivariate logistic regression with a statistical significance level of 0.05 was used to identify associated factors.
Results:A total of 113 patients were included in the study. The mean age was 43 ± 1.35 years, with a sex ratio of 0.85. The TB-LAM urine test was positive in 76 patients, for a positivity rate of 67.26%. The diagnosis of tuberculosis was confirmed by bacteriology in accordance with the national tuberculosis management protocol in 18/113 (15.93%) patients. Bacilloscopy and the Xpert test performed on all biological fluids, combined with the TB-LAM urine test, enabled the diagnosis of 81/113 (71.68%) patients in the study. Patients already on antiretroviral therapy (ORa=0.06 [0.06-0.73], p=0.02) were less likely to test positive for urinary TB-LAM, and those with unexplained asthenia (ORa=15.76 [1.19-20.66], p=0.03) were more likely to test positive.
Conclusion: The TB-LAM urine test, combined with other tuberculosis diagnostic tools, increases the diagnostic yield of tuberculosis in PLWHA.

Keywords: Tuberculosis, PLHIV, Diagnosis, TB-LAM, Real life, Burkina Faso.

1. INTRODUCTION

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) infection form a deadly combination that carries a heavy burden worldwide, particularly in developing countries [1]. It is the most frequent opportunistic infection among HIV-infected patients in Sub-Saharan Africa, and is responsible for a quarter of all HIV-related deaths [1-3].

TB is difficult to diagnose in HIV-infected patients [2]. Clinical and radiologic manifestations are less specific, and direct sputum examination is often negative because of low sensitivity. In addition to the time-consuming cultivation process, the Xpert molecular test is less accessible in developing countries [2,3]. What's more, patients co-infected with HIV and TB at an advanced stage of immunodepression

often have a low bacillary load in sputum and other fluids (ascites, urine, pleural and pericardial effusion...), which reduces the sensitivity of the traditional diagnostic test (bacilloscopy) and even newer diagnostic tests, in this case the Xpert MTB/RIF test [4].

For this category of patients, urine tests offer an alternative means of diagnosing TB, in addition to conventional diagnostic tests. The World Health Organization (WHO) recommends the use of the TB Lipoarabinomannan (TB-LAM) urine test as an aid to the diagnosis of TB in patients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 ≤ 100 cells/mm3, or HIV-positive patients who are severely ill regardless of CD4 cell count, or whose CD4 cell count is unknown[5]. In fact, TB-LAM urine test is a tool capable of detecting an antigenic particle of Mycobacterium tuberculosis excreted in urine called lipoarabinomannan. According to the WHO, in hospital settings, the overall sensitivity of the TB-LAM urine test is 56% (95% CIr, 41-70%) and the overall specificity 90% (95% CIr, 91-95%) in patients with a CD4 cell count of less than 100 cells/mm 3[6].

Given the problem of TB diagnosis and its severity in PLWHA, we conducted a study on the contribution of TB-LAM urine test, to improve TB diagnosis in this population in Burkina Faso in real life.

2. MATERIAL AND METHODS

The study was carried out in the infectious diseases departments of the Yalgado OUEDRAOGO, Souro SANOU and Bogodogo University Hospitals. These 03 centers are among the main reference centers in Burkina Faso.

This was an analytical cross-sectional study with data collection over 12 months, from January 1 to December 31, 2023. Our source population was all HIV-infected patients hospitalized or seen in consultation in the 03 departments with suspected TB or showing signs of WHO hazards during the study period. All HIV-positive patients, naïve or on ARV treatment, presenting clinical signs suggestive of TB and WHO danger signs (Respiratory Rate (RR)>30/min, Heart Rate (HR)>120 min, temperature>39°C, inability to walk unaided) were included. All patients who met the above inclusion criteria were exhaustively enumerated. HIV-infected patients already diagnosed with active TB, and those receiving anti-TB treatment for less than 12 months were not included.
We consider as case of bacteriologically confirmed tuberculosis: this refers to a patient whose biological sample has been shown to be positive by smear microscopy, culture or rapid diagnostic tests.

Diagnostic procedures

Urines from patients meeting the inclusion criteria were collected after admission to hospital or consultation by the attending physician for TB-LAM urine testing. Abbott Determine™ TB-LAM Ag tests were used. This is a rapid immunochromatographic test on urine samples. It comes in strip form and is performed manually by applying 60 µL of urine to the area of the strip dedicated to the sample. After application, the urine migrates to the "patient" and "control" areas of the strip. The test strips are

read visually after incubation at room temperature for 25 minutes. Band intensity is quantified on a scale of 1 to 4. A reference card supplied in the kit was used to determine the grade of intensity of the reactive bands (grade 1: low intensity to grade 4: high intensity). The test result was read by the physician who performed it, and the test was considered positive when at least grade 1 was obtained. Patients with a positive AML-TB test were considered to have disseminated TB.

Acid-fast bacillus testing and Xpert MTB/RIF tests were performed on sputum, gastric aspiration fluid (if coughing was suspected) and any other biological samples required for the diagnosis of pulmonary and extra-pulmonary TB, whenever possible. If the smear microscopy (bacilloscopy) and/or Xpert MTB/RIF test came back positive, the patient was considered to have bacteriologically confirmed TB.

Data analysis

Data were analyzed using Stata 16.1 software. Quantitative variables were described in terms of means, while qualitative variables were expressed in terms of numbers and percentages. To identify factors associated with TB-LAM urine test positivity, we used univariate binary logistic regression, and a threshold of $p < 0.2$ was used for inclusion in the multivariate analysis. The significance level was then 0.05.

Patient anonymity and confidentiality were maintained throughout the study. Patients with a positive Xpert test and/or bacilloscopy were treated as TB patients in accordance with the national TB management protocol. Those with only a positive TB-LAM urine test were also put on anti-TB treatment.The TB-LAM tests were provided by the National Program for the Control of Tuberculosis.

3. RESULTS AND DISCUSSION
RESULT

3.1. Demographic, clinical and paraclinical characteristics of patients

A total of 113 PLWHA made up our sample. The mean age of the patients was 43 ± 1.35 years [17 and 80 years] (Table 1).

Table 1: Demographic characteristics and history of study patients

Features	Number (N=113)	Percentage (%)
Age		
< 19	4	3.54
[19-34]	27	23.89
[35-44]	26	23.01
≥ 45	56	49.56
Gender		
Female	61	53.98

Male	52	46.02
Type of HIV		
HIV1	107	94.69
HIV2	3	2.65
HIV1+2	3	2.65
Opportunistic infection		
No	83	73.45
Tuberculosis	16	14.16
Cerebral toxoplasmosis	3	2.65
Neuromeningeal cryptococcosis	2	1.77
Zona	9	7.96
ARV treatment		
Yes	54	47.78
No	59	52.21

Patients over 45 years of age accounted for 49.56%. The sex ratio (M/F) was 0.85 in favor of females (53.98%). A history of opportunistic infections was found in 26.55% of patients. These were dominated by TB in all clinical forms, and herpes zoster in 14.16% and 7.96% respectively. HIV-1 accounted for 94.69% of cases. Anorexia (82.3%), unexplained asthenia (77.88%), cough ≥ 2 weeks (66.37%), fever ≥ 2 weeks (58.4%) were present in our patients (Table 2).

Table 2: Clinical characteristics of study patients

Features	**Number (N=113)**	**Percentage (%)**
Constants		
Temperature ≥ 39°C	16	14.16
Heart rate ≥ 120 beats/min	15	13.27
Respiratory rate ≥ 30 beats/min	16	14.16
Undernutrition (BMI ≤ 18.5 Kg/m $)^2$	39	34.51
QSOFA*≥2	21	18.58
General condition of OMS (n=113)		
I	12	10.62
II	28	24.78
III	39	34.51
IV	34	30.08

Functional signs		
Anorexia	93	82.30
Unexplained asthenia	88	77.87
Cough ≥ 2 weeks	75	66.37
Fever ≥ 2 weeks	66	58.41
Night sweats	39	34.51
Abdominal pain	35	30.97
Diarrhea	25	22.12
Chest pain	22	19.47
Hemoptoic sputum	5	4.42
Pleuropulmonary signs		
Lung condensation	76	67.26
Pleural fluid effusion	10	8.85
Extra-pulmonary signs		
Neurological signs	34	30.09
Peripheral adenopathy	20	17.70
Digestive signs	30	26.55

*quick sequential organ failure assessment

The proportion of patients with signs of TB impregnation (anorexia, unexplained asthenia, cough ≥ 2 weeks, fever ≥ 2 weeks and night sweats) was 23.01%. Pulmonary condensation syndrome was found in 67.26% of patients, followed by neurological (30.09%) and digestive (26.55%) signs.

The TB-LAM urine test was positive in 76 (67.26%) patients. Acid-fast bacillus testing of various biological fluids, carried out on 33 patients, was positive in 7 (21.21%). In 20.73% (17/82) of cases, the Xpert test was positive. The mean CD4 count was 132.29 ± 13.06 cells/mm^3 and 81.54% had a CD4 count of less than or equal to 200 cells/mm^3 (Table 3).

Table 3: Paraclinical characteristics of study patients

Features	Number (N=113)	Percentage (%)
CD4 count (n = 65) (cells/µl)		
< 100	28	43.07
[100-200[	25	38.46

≥ 200	12	18.46
Hemoglobin (n = 101) (g/dl)		
Normal	6	5.94
Mild anemia	16	15.84
Moderate anemia	42	41.58
Severe anemia	37	36.63
Acid-fast bacillus (n = 33)		
Positive	7	21.21
Negative	26	78.79
Xpert test (n = 82)		
Positive	17	20.73
Negative	65	79.27
TB-LAM (n = 113)		
Positive	76	67.26
Negative	37	32.74

Seven out of twelve patients (7/12) or 58.33% with a CD4 count above 200 cells/mm^3 had a positive urine TB-LAM test. Severe anemia was present in 36.63% of patients. On chest X-ray, alveolar-interstitial opacities were found (72.22% of patients) and miliaria (5.55%).

3.2. Tuberculosisdiagnostic

Bacteriologically confirmed TB was diagnosed in 18/113 (15.93%) patients according to the national TB management protocol. Bacilloscopy and/or the Xpert MTB/RIF test, whatever the biological fluid, combined with the TB-LAM urine test, enabled the diagnosis of 81/113 (71.68%) patients. The urinary TB-LAM test coupled with bacilloscopy increased the number of TB cases from 26.92% (7/26) to 88.95% (23/26), i.e. a 3.30-fold increase. The TB-LAM urine test coupled with the Xpert MTB/RIF test led to an increase in TB cases from 26.15% (17/65) to 98.46% (64/65), i.e. a 3.76-fold increase.

3.3. Factors associated with TB-LAM positivity

In multivariate analysis, two factors were significantly associated with a positive TB-LAM urine test (Table 4). Patients with unexplained asthenia (ORa=15.76 [1.19-20.66], *p=0.**03***) were 15.76 times more likely to have a positive urine test than those without this symptom. Patients on antiretroviral therapy (ORa= 0.06 [0.06-0.73], *p=0.02*) were 94% less likely to have a positive TB-LAM test than those not on antiretroviral therapy.

Table 4: Univariate and multivariate analysis of factors associated with TB-AML urine test positivity.

Features			**Univariate**		**Multivariate**	
	Total (N= 113)	**TB-LAM + (n = 76)**	**ORa [95% CI]**	***p***	**ORa [95% CI]**	***p***
Age						
< 45	57	39(68.42%)				
≥ 45	56	37(66.07%)	0.89[0.41-1.97]	.79		
Gender						
Female	61	41(67.21%)	0.99[0.45-2.19]	.99		
Male	52	35(67.31%)				
History						
ART	54	32(59.26%)	0.49[0.22-01.10]	.08	**0.06[0.06-0.73]**	***.02***
History of tuberculosis	19	17(89.47%)	5.04[1.09-23.14]	***.03***		
Functional signs						
Fever ≥ 2 weeks	66	46(69.70%)	1.30[0.58-2.88]	.51		
Cough≥ 2 weeks	75	52(69.33%)	1.32[0.58-2.99]	.51		
Anorexia	93	68(73.12%)	4.08[1.49-11.14]	***.01***	3.25[0.32-32.84]	.31
Unexplained asthenia	88	66(75.00%)	5[1.92-13.01]	***.00***	15.76[1.19-20.66]	***.03***
Night sweats	39	31(79.49%)	2.49[1.01-6.18]	.05		
General signs						
General condition						
WHO						
I + II	38	25(65.79%)	0.90[0.39-02.06]	.81		
III + IV	75	51(68.00%)	1.92[0.48-02.52]	.81		
T° > 39	18	15(83.33%)	2.78[0.75-10.31]	.12	3.1[0.28-34.07]	.35
RR > 30 c/mn	16	11(68.75%)	1.08[0.34-03.38]	.89	-	**-**
HR > 120	15	13(86.67%)	3.66[0.77-16.92]	.10	-	**-**
Undernutrition	39	33(84.62%)	2.75[0.92-08.22]	.07	-	**-**
QSOFA* ≥ 2	21	12(57.14%)	0.58[0.22-01.54]	.27	-	**-**
Physical signs						

Lung						
Condensation	76	57(75.0%)	2.84[1.24-6.50]	***.01***	-	**-**
Extra pulmonary						
Neurological signs	34	23(67.65%)	1.04[0.44-2.46]	.91	-	**-**
Abdominal pain	35	25(71.43%)	1.32[0.55-3.15]	.52	-	**-**
WHO clinical stage 3 + 4	83	60(72.29%)	2.28[0.96-5.41]	.06	-	**-**
CD4 (n= 65) (cell/ml)						
<100	28	20(71.43%)	1.11[0.34-3.57]	.86	-	**-**
100-200	25	17(69.23%)	0.66[0.15-2.56]	.51	-	**-**
>200	12	7(58.33%)	-	**-**	-	**-**
Hemoglobin (n=101) (g/dl)						
Severe anemia	37	29(54.50%)	2.17[0.85-5.50]	.10	20.26[0.77-52.00]	.07
Hyponatremia	30	19(63.33%)	0.73[0.27-1.93]	.53	-	**-**
Thoracic X-ray(n=84)						
Abnormal	74	55(74.32%)	6.75[1.58-28.78]	***.01***	0.11 [0.00-2.51]	.16
Normal	10	3(30.00%)				

*quick sequential organ failure assessment

4. DISCUSSION

This study enabled us to achieve our objective, which was to assess the contribution of the TB-LAM urine test to the diagnosis of TB in PLWHA in the infectious diseases departments of 3 university hospitals.

We observed a TB-LAM urine test positivity rate of 67.25%. Our results are similar to those found in Ivory Coast by Ouédraogo (62%), in Democratic Republic of Congo by Pembe et al (54%) and in South Africa by Shah et al (59%)[7-9]. This high performance of the urinary TB-LAM test in our patients could be explained by the fact that the majority of our patients were at an WHO advanced stage of HIV infection (72.29%). Most hospitalized TB/HIV co-infected patients are bedridden and in a state of advanced immunosuppression, often unable to produce sputum for acid-fast bacillus testing and Xpert[10]. This rapid diagnostic test could help reduce

the delay or difficulty in diagnosing TB, which is associated with high mortality in these coinfected patients, given that urine is easy to collect. Adding TB-LAM urine test to sputum microscopy and Xpert test increased diagnostic yield by 3.30 and 3.76 times respectively. For Stephen et al., the diagnostic yield was increased by a factor of 3.2 and 2.6 respectively when TB-LAM urine test was combined with sputum microscopy and Xpert[11]. The same applies to Ouédraogo [7] whose diagnostic yields were multiplied by 7.4 and 2.6 respectively. In 16 and 47 patients respectively for whom bacilloscopy and Xpert test were negative, TB-LAM came back positive. Pembe et al. [8]also noted in their study that, used simultaneously, TB-LAM and microscopy increased the diagnostic yield of TB cases. Although TB-LAM urine test has a lower sensitivity than Xpert test, its advantages include its ease of use, the fact that it requires no equipment or reagents, its speed of completion with results available within 30 minutes, its low cost (initially marketed at $3.50 per test) and the fact that it has the potential to be implemented at the first level of care according to the health pyramid. These various advantages make this diagnostic tool a useful test in TB diagnostic algorithm for HIV-infected patients in our healthcare facilities. Given that an optimal delay in the initiation of anti-TB treatment for patients with HIV-associated TB can reduce the risk of mortality, rapid point-of-care diagnostic tools are needed. It is therefore imperative to note the importance of using this tool in conjunction with the other existing tools in the algorithm for diagnosing TB in PLWHA (Bacilloscopy and Xpert test). This complementarity has already been reported in several other studies [7,10,12-14].

In addition, we have observed positive TB-LAM tests in patients with a CD4 ≥ 200 cells/mm^3. It could be extended to patients with a CD4 ≥ 100 cells/mm^3 subject to larger-scale studies. Achieving the objectives of the global plan to end TB requires the development of rapid, simple, accurate and less expensive tests [15]. It is in this context that TB-LAM test has been developed and evaluated in several countries [6,10,16,17]. The WHO considers that TB-LAM urine test can be used in combination with the other tests recommended for the diagnosis of TB in HIV-infected patients with symptoms of TB or advanced HIV infection [5].

The fact that the patient was on ART and had unexplained asthenia were significantly associated with TB-LAM urine test positivity in multivariate analysis.

Other authors have also made this observation [7]. This symptom is one of the danger signs described by the WHO, as well as a sign of TB impregnation. In all PLWHA, this symptom should be investigated and a TB-LAM urine test performed, especially if there are other symptoms suggestive of TB and profound immunodepression. This finding calls for rigorous monitoring of PLWHA and TB screening at every consultation. Patients who were on ART were less likely to test positive to TB-LAM urine test. Patients on ART were less likely to test positive for urinary TB-LAM. Therapeutic education for good compliance and preventive treatment of TB should be effective according to WHO recommendations. Factors such as CD4 count below 200, hospitalization, malnutrition and severe anemia have been found in the literature to be associated with a positive urinary TB-LAM test [7,10,18]. These factors should be considered when diagnosing TB in PLWHA.

The diagnosis of TB and the reading of TB-LAM urine test results were left to the direction of treating clinicians, which may be a source of selection bias. In addition, it was not possible to perform conventional TB diagnostic tests and other paraclinical examinations on all patients.

The strength of our study lies in the fact that it represents a landmark study, providing yet another tool for diagnosing TB in real-life practice. This tool could be used as an adjunct test in our care centers for PLWHA, or even at the first level of patient contact. However, the small sample size of our study would require a large-scale study to increase the statistical power of the study.

CONCLUSION

At the end of the study, the TB-LAM urine test was found to be a significant contributor to the diagnosis of tuberculosis. This means that patients can be started on treatment as soon as they come into contact with a health center. It can also be used to catch up with TB cases that escape conventional microbiological diagnostic tools. Hence the need to integrate the TB-LAM urine test into national tuberculosis diagnostic algorithms. This will undoubtedly help to reduce the heavy burden of morbidity and mortality associated with this disease. Further studies in a larger sample of patients may allow us to compare the performance of the TB-LAM urine test with the available tests in our context.

Consent

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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