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Accuracy and incremental yield of urine Xpert MTB/RIF Ultra vs. Determine TB-LAM for diagnosis of pulmonary tuberculosis

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Abstract

The performance of urine Xpert MTB/RIF Ultra (Xpert Ultra) for pulmonary TB diagnosis is unknown. HIV-positive and HIV-negative adults were enrolled at two health facilities in Kampala, Uganda. We compared the accuracy of urine Xpert Ultra and Determine TB-LAM in reference to sputum-based testing (positive Xpert MTB/RIF or culture), and assessed incremental yield. Urine Xpert Ultra had low sensitivity (17.2%, 95% CI 12.3–23.2) but high specificity (98.1%, 95% CI 94.4–99.6). Sensitivity reached 50.0% (95% CI 28.2–71.8) among HIV-positive patients with CD4 <100 cells/μL. Compared to Determine TB-LAM, urine Xpert Ultra was 9.4% (95% CI 3.8–14.9, p=0.01) more sensitive, and 17.2% (95% CI 4.5–29.8, p=0.01) more sensitive among HIV-positive patients. However, the incremental sensitivity of urine Xpert Ultra relative to sputum Xpert MTB/RIF was only 1% (95% CI −0.9 to 2.8). Urine Xpert Ultra could be an alternative for patients with advanced HIV infection unable to produce sputum.

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Keywords

tuberculosis; diagnostics; urine; Xpert Ultra; lipoarabinomannan

1. Introduction

Semi-automated nucleic acid amplification testing (NAAT) with Xpert MTB/RIF (Cepheid, Sunnyvale, USA) has greatly improved the ability to diagnose pulmonary tuberculosis (TB) in low-resource settings (World Health Organization, 2013). Xpert MTB/RIF Ultra ("Xpert Ultra") is a next-generation cartridge designed to lower the limit of detection and improve sensitivity (Chakravorty et al., 2017). A multi-center study found that, compared to Xpert MTB/RIF sputum testing with Xpert Ultra was 17% (63% vs. 46%) more sensitive in smear-negative patients and 13% (90% vs. 77%) more sensitive in HIV-positive patients (Dorman et al., 2018). Consequently, the World Health Organization (WHO) has recommended that Xpert Ultra should be used in all settings where Xpert MTB/RIF was in place (World Health Organization, 2017).

In addition to potential utility for diagnosing renal TB (Atherton et al., 2018), urine testing with Xpert Ultra may provide an opportunity to further increase diagnostic yield and/or an alternative means of pulmonary TB diagnosis when patients are unable to expectorate sputum. In pulmonary TB, studies among HIV-positive adults have found that urine testing with the older generation Xpert MTB/RIF cartridge had limited additional yield when combined with sputum-based testing, but was a useful alternative when sputum was unavailable (Lawn et al., 2015, Lawn et al., 2012, Peter et al., 2012). In comparison to Determine TB-LAM, a single study from South Africa found that urine Xpert MTB/RIF had the same sensitivity (both 48%), but higher specificity (98% vs. 85%) (Peter et al., 2012). However, it remains unknown whether the increased analytical sensitivity of Xpert Ultra can improve the clinical utility of urine-based testing for pulmonary TB.

We conducted the first study of urine Xpert Ultra testing among adults with presumed pulmonary TB. Our objectives were to compare the diagnostic accuracy of urine Xpert Ultra and Determine TB-LAM, and calculate the additional yield of one or both urine tests relative to sputum Xpert MTB/RIF alone.

2. Materials and Methods

2.1 Study design and population

In this cross-sectional study, from April to December 2018, we enrolled consecutive hospitalized and outpatient adults (>18 years) HIV-positive and HIV-negative who were undergoing sputum-based pulmonary TB evaluation at Kiruddu hospital and Kisenyi Health Center IV in Kampala, Uganda. At the time of the study, routine sputum-based TB testing at both sites was performed using the Xpert MTB/RIF assay. We included all patients with positive sputum Xpert MTB/RIF results and a random sample of patients with negative Xpert MTB/RIF results (1:1 sampling) tested on the same day. We excluded patients if 1) Xpert MTB/RIF test results were indeterminate; 2) they were already on anti-TB treatment

or had taken agents with anti-TB activity such as amino quinolones in the prior 12 months; 3) they reported a prior episode of TB; or 4) they refused or were unable to provide informed consent. The Makerere University School of Medicine Research and Ethics Committee, the Uganda National Council for Science and Technology and the University of California San Francisco Committee on Human Research reviewed and approved the study. This study was performed according to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines (Cohen et al., 2016).

2.2 Participant recruitment

To identify eligible patients, we screened the Xpert MTB/RIF testing log at each study site daily to identify all patients who submitted sputum for TB testing. Using the log, study staff first approached all patients with positive test results and then a random 1:1 sample of patients with negative test results. Patients were approached on the wards (if hospitalized) or when they returned to collect test results (if outpatient) to confirm eligibility and obtain informed consent.

2.3 Study procedures

Upon enrollment, we obtained a detailed demographic and medical history using a standardized form and collected blood for HIV testing and CD4 count (if HIV-positive), spot sputum samples and spontaneously voided urine from all patients. Sputum samples were used to perform Xpert MTB/RIF testing × 1 in all patients, and mycobacterial culture on solid and liquid media × 2 in patients with negative Xpert MTB/RIF results (i.e., culture was not performed to confirm positive Xpert MTB/RIF results). Trained laboratory technologists in the Kiruddu Hospital Microbiology Laboratory and the Makerere University College of Health Sciences Mycobacteriology Laboratory conducted all TB testing following standard protocols for Xpert Ultra (Chakravorty et al., 2017), Determine TB-LAM (Lawn, 2012), and mycobacterial culture (Stop TB Partnership Global Laboratory Initiative, 2014). Standard dipstick urinalysis was performed on all urine samples, and then tested using Xpert Ultra and Determine TB-LAM. Urine for Xpert Ultra testing was centrifuged (Thermo Scientific Heraeus Megafuge 8R Compact, Waltham, Massachusetts, USA) using swing-out rotor at 3000 rpm (2173 × g) ambient temperature for 15 minutes prior to adding sample reagent to deposit at a ratio of 1:1. For culture, sputum samples were digested and decontaminated using the sodium hydroxide/N-acetyl-L-cysteine method with a final concentration of 1.5%, neutralized with sterile phosphate-buffered solution, centrifuged, and re-suspended in phosphate-buffered solution. One Mycobacterial Growth Indicator Tube (MGIT) and one Lowenstein-Jensen (LJ) slant were inoculated with the decontaminated samples. Prior to inoculation a cocktail of antibiotics containing PANTA (polymyxin, amphotericin B, nalidixic acid, trimethoprim, azlocillin) mixed with OADC (oleic acid, bovine serum albumin, dextrose, and catalase) were added to MGIT tubes. MGIT tubes were incubated in a BACTEC MGIT 960 instrument (BD; Franklin Lakes, USA) for up to 42 days and LJ slants were incubated at 37° C for up to 8 weeks. Blood agar plates were prepared for to check for contamination of positive MGIT tubes or LJ slants, and a stained Ziehl Neelsen (ZN) smear was examined to check for the presence of AFB. Speciation was then performed to confirm the presence of *M. tuberculosis* complex using SD Bioline strips (SD MPT64TB Ag kit, South Korea).

2.4 Definitions of reference standard and index tests

We used results of sputum Xpert MTB/RIF and mycobacterial culture as the reference standard. We considered patients to have TB if they had either positive Xpert MTB/RIF based on routine testing, or positive culture if sputum Xpert MTB/RIF testing was negative. We considered patients not to have TB if both Xpert MTB/RIF and culture results were negative, excluding those with <2 negative culture results due to contamination. The index tests included urine Xpert Ultra and urine Determine TB-LAM. We followed WHO recommendations for categorizing urine Xpert Ultra (trace results considered positive only among HIV-infected patients) and Determine TB-LAM (positive if Grade 2 or higher) results (World Health Organization, 2015, 2017). Staff performing the index testing were blinded to the reference testing and vice versa. We considered an index test to be false-positive when the test result was positive but sputum Xpert MTB/RIF and culture results were negative.

2.5 Statistical Approach

We summarized demographic and clinical data using appropriate descriptive statistics and calculated the sensitivity and specificity of each index test (urine Xpert Ultra and urine Determine TB-LAM) along with the 95% confidence interval (CI) using our reference standard definition of TB. In our primary analysis, we compared differences in sensitivity and specificity between index tests using McNemar's test for paired proportions, and by HIV status and CD4 cell count category using chi-squared or Fisher's Exact tests. We also calculated the incremental sensitivity of urine Xpert Ultra and Determine TB-LAM testing alone and in combination relative to Xpert MTB/RIF overall and among HIV-positive participants. Individuals with missing results were excluded. We used STATA 15 (StataCorp, College Station, TX, USA) for all analyses.

3. Results

3.1 Sample characteristics

During the nine-month study period, 2,347 individuals were referred for TB testing at the two sites (Figure 1). Of these, 397 were Xpert MTB/RIF positive and 188 were enrolled. We selected a random 1:1 sample of 188 Xpert MTB/RIF negative individuals and 169 were enrolled, of which 15 participants were subsequently culture-positive. Thus, 357 participants (203 with and 154 without TB) were included in the final analysis.

Most participants (N=297, 83%) were outpatients, the median age was 32 years (IQR 25–39), and 249 (70%) were male (Table 1). The median Karnofsky score was 80 (IQR 70–90), but over a third were undernourished with a BMI <18.5 (N=144, 40%). Proteinuria of grade 2+ (100 mg/dL) or more was present in 54 (15%) participants. Among the 116 (32%) participants who were HIV positive, 34 (29%) had a CD4 cell count <100 cells/μL.

3.2 Diagnostic accuracy

As shown in Table 2, the sensitivity of urine testing was poor with both Xpert Ultra (17.2%, 95% CI 12.3–23.2) and Determine TB-LAM (7.9%, 95% CI 4.6–12.5). Urine Xpert Ultra

was 9.4% (95% CI 3.8–14.9, p<0.001) more sensitive than Determine TB-LAM. Both tests had high (>98%) specificity.

As expected, the sensitivity of urine testing varied by HIV status and degree of HIV-related immune suppression (Table 2). Sensitivity was considerably higher in HIV-positive vs. HIV-negative participants for both urine Xpert Ultra (32.8% vs. 10.1%, p<0.001) and Determine TB-LAM (15.6% vs. 4.3%, p=0.01). Urine Xpert Ultra continued to have higher sensitivity than Determine TB-LAM among HIV-positive patients (difference 17.2%, 95% CI 4.5 to 29.8, p = 0.01), without a difference in specificity.

When stratified by CD4 category, the sensitivity of urine Xpert Ultra was significantly higher among HIV-positive participants with CD4 count <100 cells/μL (50.0%, 95% CI 28.2–71.8) than CD4 count ≥100 cells/μL (23.8%, 95% CI 12.1–39.5), a difference of 26.2% (95% CI 1.6–50.7, p=0.03). The same pattern was observed for Determine TB-LAM (31.8% in CD4 count <100 cells/μL vs. 7.1% if CD4 count ≥100 cells/μL, difference 24.7%, 95% CI 3.7–45.6, p = 0.01). While urine Xpert Ultra was 18.2% more sensitive than Determine TB-LAM among individuals with CD4 count <100 cells/μL, the difference was not statistically significant (95% CI −2.5 to 38.8, p = 0.12).

3.3 Incremental yield of urine testing

Performing urine Xpert Ultra yielded two additional cases over sputum Xpert MTB/RIF (both HIV-positive, CD4 cell count 93 and 108 cells/μL, incremental sensitivity 1.0%, 95% CI −0.9 to 2.8), while performing Determine TB-LAM also yielded two additional TB cases (both HIV-positive with CD4 cell count 93 and 104 cells/μL, incremental sensitivity 1.0%, 95% CI −0.9 to 2.8) (Table 3). Adding both urine tests to sputum Xpert MTB/RIF testing yielded three additional cases (all HIV-positive as above, incremental sensitivity 1.5%, 95% CI −0.7 to 3.6). Results were similar when the analysis was limited to HIV-positive participants.

3.4 Characteristics of potential false positive cases

False positive cases were defined as a result positive by urine Xpert Ultra or Determine TB-LAM but negative by Xpert MTB/RIF and culture. There were five patients with potential false positive urine Xpert Ultra or Determine TB-LAM results, with characteristics presented in Table 4. None had both urine tests positive; three of the five were urine Xpert Ultra positive but Determine TB-LAM negative, while two were Determine TB-LAM positive but urine Xpert Ultra negative. All participants had low-grade positive results (Very Low for Xpert Ultra and Grade 2 for Determine TB-LAM), and two were HIV-positive (one urine Ultra positive and the other Determine TB-LAM positive). If all false positive cases were considered to be true TB cases (Supplemental Table 1), performing both urine tests was associated with a small increase in incremental sensitivity relative to sputum Xpert MTB/RIF (5 more cases detected, incremental sensitivity 3.8%, 95% CI 0.8 to 6.9, p = 0.01).

4. Discussion

Urine testing has the potential to increase diagnostic yield and to provide an alternative means of confirming pulmonary TB in sputum-scarce patients. We conducted the first assessment of urine Xpert Ultra testing for the diagnosis of pulmonary TB. We found that urine Xpert Ultra was more sensitive than Determine TB-LAM, but like Determine TB-LAM, testing was most beneficial among HIV-positive patients with low CD4 counts. Overall, urine testing (Xpert Ultra and/or Determine TB-LAM) provided little additional yield relative to sputum Xpert MTB/RIF testing, including among HIV-positive patients.

While urine Xpert MTB/RIF has shown utility in extrapulmonary TB (Atherton et al., 2019, Atherton et al., 2018, Penz et al., 2015), polymerase chain reaction (PCR) testing of urine for pulmonary TB has shown modest results. A meta-analysis of eight studies on the use of urine NAATs for pulmonary TB found an overall sensitivity of 55% and specificity of 94% (Marangu et al., 2015). Our data on urine Xpert Ultra testing is largely consistent with prior studies evaluating urine Xpert MTB/RIF testing for pulmonary TB, including for HIV-positive patients. In two studies of HIV-positive adults in South Africa, sensitivity of urine Xpert MTB/RIF testing was 19% and 48% overall and increased to 44% and 61%, respectively, among patients in the lowest CD4 cell count stratum (Lawn et al., 2012, Peter et al., 2015). Similarly, we found that sensitivity of urine Xpert Ultra testing was 32.8% overall among HIV-positive participants, increasing to 50% among those with CD4 count <100 cells/μL. Given individuals with advanced HIV infection are at high risk of TB-related mortality (Tornheim and Dooley, 2017), urine Xpert Ultra provides an alternative means of testing when sputum is unavailable.

Urine testing with Determine TB-LAM for pulmonary TB is currently recommended as an adjunct to sputum testing in HIV-positive individuals with advanced disease or serious illness (World Health Organization, 2015). A meta-analysis found Determine TB-LAM combined with sputum Xpert MTB/RIF increased sensitivity by 13% among HIV-positive adults to 75% (Shah et al., 2014). A prospective cohort in Kenya found that Determine TB-LAM increased sensitivity of sputum or urine Xpert MTB/RIF by 11.6% to 85.3% (Huerga et al., 2017). Urine Xpert MTB/RIF as an adjunct to sputum Xpert MTB/RIF is less studied but has shown a smaller incremental yield (Lawn et al., 2012). In contrast, we did not find that urine testing with either Determine TB-LAM or urine Xpert Ultra significantly increased diagnostic yield relative to Xpert MTB/RIF testing alone. Even when including both urine tests and considering false-positive results to be true-positive, only five additional cases were identified. Further studies are needed among HIV-positive individuals with significant immunosuppression and/or serious illness to better characterize any potential benefit of urine Xpert Ultra testing as an adjunct to sputum Xpert MTB/RIF in this population.

When sputum testing is not possible, we found that urine Xpert Ultra had higher accuracy than Determine TB-LAM for pulmonary TB diagnosis. Urine Xpert Ultra was 9.4% more sensitive than Determine TB-LAM overall, without significant difference in specificity, and continued to have higher sensitivity than Determine TB-LAM among HIV-positive patients (difference 17.2%). At CD4 count <100 cells/μL, urine Xpert Ultra was 18.2% more

sensitive than Determine TB-LAM, but the sample size was small and the difference was not statistically significant. In contrast to our findings, past studies have found that urine Xpert MTB/RIF had lower or similar sensitivity to Determine TB-LAM in HIV-positive adults (Huerga et al., 2017, Lawn et al., 2012, Peter et al., 2012). While the sensitivity of Determine TB-LAM among HIV-infected participants in our study is lower than that reported in a meta-analysis (Shah et al., 2016), they noted moderate to high heterogeneity and our estimate was consistent with a previous study from Uganda of 26% sensitivity (Yoon et al., 2019). While we found urine Xpert Ultra to have higher sensitivity than Determine TB-LAM, factors such as cost, time, and availability may make Determine TB-LAM easier to implement and requires further evaluation (Lawn, 2012, Shah et al., 2013).

We present a well-characterized cohort of both HIV-positive and HIV-negative adults referred by clinicians for sputum-based TB testing. However, there are several limitations. We did not confirm positive sputum Xpert MTB/RIF results with culture. However, Xpert MTB/RIF is known to have high specificity (98%) (Horne et al., 2019), and we minimized the likelihood of false-positive Xpert MTB/RIF results by excluding patients treated previously for TB. We also did not directly compare urine Xpert MTB/RIF with urine Xpert Ultra, primarily because Xpert Ultra is expected to replace Xpert MTB/RIF. Because 1:1 sampling was performed to recruit Xpert-negative patients, we could not calculate positive or negative predictive value. Selection bias is also a concern as the inability to find patients was a common reason for exclusion. However, any such bias is unlikely to have a differential effect on urine Xpert Ultra vs. Determine TB-LAM and thus impact our primary finding.

Given the ease in obtaining urine, greater efforts are needed to lower the level of detection for current assays and identify novel urine-based diagnostics for pulmonary TB. A study in Peru utilized hydrogel nanocages to concentrate urine LAM and increase the sensitivity to >95% in HIV-negative adults (Paris et al., 2017). There has been growing interest in detection of trans-renal or cell-free DNA in urine for non-genitourinary TB (Fernandez-Carballo et al., 2018, Green et al., 2009). Biomarker discovery in urine also has the potential to identify novel assays for TB diagnosis (Wang et al., 2018). Meanwhile, we should take advantage of current diagnostics. Our findings support urine Xpert Ultra testing in HIV-positive individuals, in particular those with advanced disease and when sputum is unavailable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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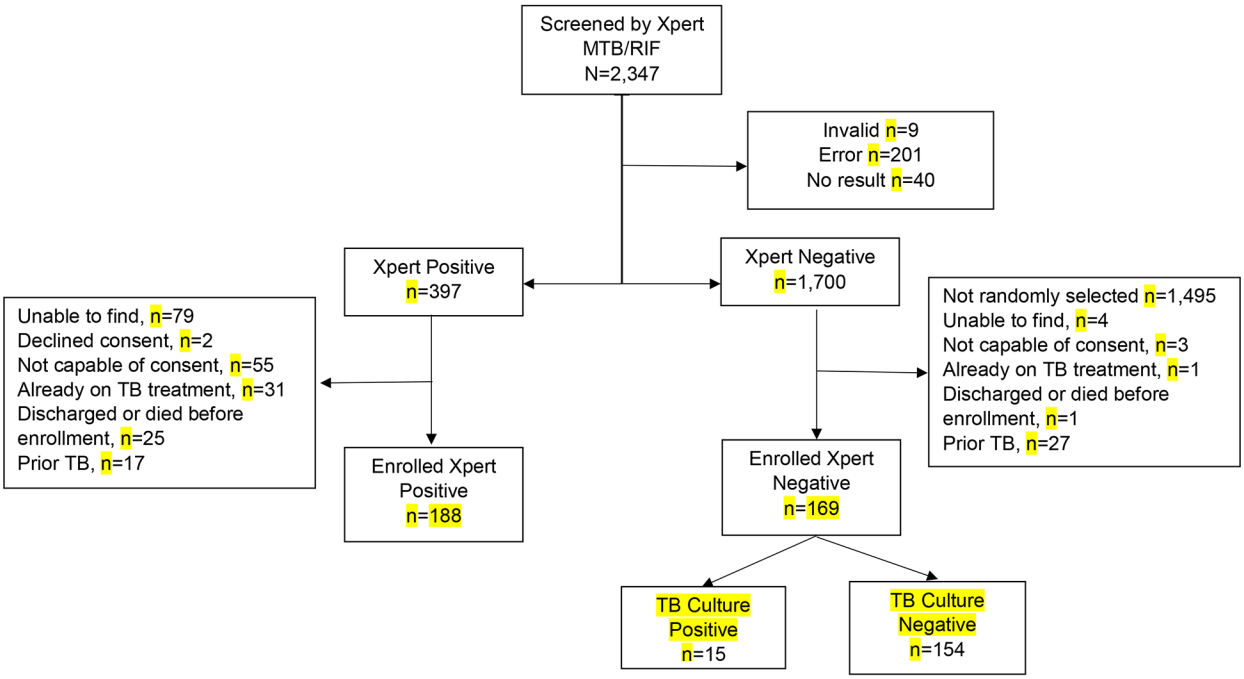

Figure 1.
Flowchart of Participants

Table 1.

Sample Characteristics (N=357)

Characteristic[a]	N (%)
Age in years, median (IQR)	32 (25–39)
Male Sex	249 (70)
Cough ≥ 30 days	252 (71)
Heart rate > 120 bpm	55 (15)
Fever ≥ 39°C	17 (5)
BMI < 18.5	144 (40)
Karnofksy Score median (IQR) (n=283)	80 (70–90)
Hospitalized	60 (17)
Smoking in last 30 days	55 (15)
Proteinuria 2+ or greater[b]	54 (15)
HIV-positive	116 (32)
CD4 cell count <100 cells/μL (n=116)	34 (29)

BMI: Body Mass Index; bpm: beats per minute; IQR: Interquartile Range; TB: Tuberculosis

[a] N=357 unless indicated

[b] Defined as semi-quantitative protein level > 100 mg/dL

Table 2.

Sensitivity and Specificity of Urine Xpert Ultra and Determine TB LAM with 95% CI

	Sensitivity		Specificity	
	Urine Xpert Ultra	**Determine TB-LAM**	**Urine Xpert Ultra**	**Determine TB-LAM**
Total Cohort (N=203 with TB, N=154 No TB)	17.2[a] (12.3, 23.2)	7.9 (4.6, 12.5)	98.1 (94.4, 99.6)	98.7 (95.4, 99.8)
HIV-negative (N=139 with TB, N=102 No TB)	10.1 (5.6, 16.3)	4.3 (1.6, 9.2)	98.0 (93.1, 99.8)	99.0 (94.7, 100)
HIV-positive (N=64 with TB, N=52 No TB)	32.8[a,b] (21.6, 45.7)	15.6[b] (7.6, 26.9)	98.1 (89.7, 100)	98.1 (89.7, 100)
CD4 < 100 (N=22 with TB, N=12 No TB)	50.0[c] (28.2, 71.8)	31.8[c] (13.9, 54.9)	100 (73.5, 100)	91.7 (61.5, 99.8)
CD4 ≥ 100 (N=42 with TB, N=40 No TB)	23.8 (12.1, 39.5)	7.1 (1.5, 19.5)	97.5 (86.8, 99.9)	100 (91.2, 100)

[a] $p<0.05$ compared with Determine TB-LAM

[b] $p<0.05$ compared with HIV-negative

[c] $p<0.05$ compared with CD4 ≥ 100

Table 3.

Incremental sensitivity of urine testing relative to sputum Xpert MTB/RIF

		Incremental Yield	
Strategy	**# Additional Cases Detected**	**% Increase in Sensitivity (95% CI)**	**p-value for difference**
All Participants with TB (N=203)			
Sputum Xpert MTB/RIF	REF	REF	-
Sputum Xpert MTB/RIF +			
Urine Xpert Ultra	2	1.0% (−0. 9 to 2.8)	0. 5
Determine TB-LAM	2	1.0% (−0.9 to 2.8)	0.5
Urine Xpert Ultra + Determine TB-LAM	3	1.5% (−0.7 to 3.6)	0.25
HIV-positive with TB (N= 64)			
Sputum Xpert MTB/RIF	REF	REF	-
Sputum Xpert MTB/RIF +			
Urine Xpert Ultra	2	3.1% (−2. 8 to 9.0)	0. 5
Determine TB-LAM	2	3.1% (−2.8 to 9.0)	0.5
Urine Xpert Ultra + Determine TB-LAM	3	4.7% (−2.1 to 11.4)	0.25

Table 4.

Characteristics of patients with urine Xpert Ultra and Determine TB-LAM false-positive results[a]

	Description				
Age (Yrs)	33	21	32	42	30
Sex	Male	Male	Female	Male	Male
Patient type	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient
HIV status	Negative	Positive	Negative	Negative	Positive
CD4 count (cells/μL)	-	430	-	-	33
Prior ART use	-	Y	-	-	N
Karnofsky score	90	-	90	90	80
TB Contact	N	N	N	N	N
Symptoms last 30d					
Hemoptysis	Y	Y	N	Y	N
Fever	Y	Y	Y	N	Y
Night sweats	Y	Y	Y	Y	N
Weight loss >5kg	Y	Y	N	Y	Y
Cough	Y	Y	Y	Y	Y
Urine Xpert Ultra	Positive (VL)	Positive (VL)	Negative	Positive (VL)	Negative
Determine TB-LAM	Negative (Grade 0)	Negative (Grade 0)	Positive (Grade 2)	Negative (Grade 0)	Positive (Grade 2)

ART: antiretroviral therapy;; HIV: human immunodeficiency virus; LAM: lipoaribomannan; TB: tuberculosis; Y: Yes; N: No; VL: Very Low

[a]False positive defined as positive index test but negative sputum Xpert MTB/RIF and liquid/solid culture results