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High diagnostic yield of tuberculosis from screening urine samples from HIV-infected patients with advanced immunodeficiency using the Xpert MTB/RIF assay

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Abstract

We determined the diagnostic yield of the Xpert MTB/RIF assay for tuberculosis (TB) when testing small volumes of urine from ambulatory HIV-infected patients prior to starting antiretroviral therapy (ART) in South Africa. Compared to a gold standard of sputum culture, the sensitivity of urine Xpert among those with CD4 cell counts of <50, 50-100 and >100 cells/ μ L were 44.4%, 25.0% and 2.7% ($P=0.001$), respectively. Urine Xpert testing provides a means of rapid TB diagnosis in patients with advanced immunodeficiency and poor prognosis. These data are indicative of high rates of TB dissemination and renal involvement in this clinical population.

Keywords

HIV; tuberculosis; screening; diagnosis; Africa; urine; Xpert MTB/RIF; antiretroviral

INTRODUCTION

Tuberculosis (TB) is a leading cause of morbidity and mortality in HIV-infected patients accessing antiretroviral treatment (ART) programmes or requiring medical admission to hospitals in sub-Saharan Africa.¹⁻⁵ However, diagnosis of TB in these patient groups is often missed or delayed as a result of the non-specific clinical presentation, high rates of sputum smear-negative, extrapulmonary and disseminated disease, and the limited utility of pulmonary radiology.^{6,7} There is a great need for new diagnostic tools to increase the sensitivity and speed of diagnosis in these patient groups, especially in view of their high mortality and the risk of nosocomial TB transmission.

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Conflicts of interest

The authors have no conflicts of interest to declare

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A range of new diagnostics for TB is now emerging, employing various different technologies.⁸ One area of renewed interest has focused on the potential for TB diagnosis to be made from analysis of urine samples. Urine is an attractive sample for diagnosis as it is simple to obtain, even from very ill patients who may not be able to produce sputum. Urine sampling does not generate hazardous infectious aerosols and urine is relatively clean and easy to handle in the laboratory. Urine may be cultured,⁹ tested by polymerase chain reaction (PCR) for mycobacterial transrenal DNA¹⁰ or tested for specific mycobacterial antigens such as lipoarabinomannan (LAM).¹¹⁻¹³

More recently, the Xpert MTB/RIF rapid molecular assay^{14,15} (hereafter referred to as 'Xpert') has been endorsed by the World Health Organization (WHO) as a replacement for sputum smear microscopy.¹⁶ However, there are also reports of Xpert being used to diagnose TB by testing a range of extrapulmonary samples, including urine.^{17,18} In this study, we therefore determined the diagnostic sensitivity of Xpert MTB/RIF when testing small volumes of urine obtained from HIV-infected patients being screened for TB prior to starting antiretroviral therapy (ART) in South Africa.

METHODS

The ART service in Gugulethu township, Cape Town, South Africa, and the burden of TB among these patients have previously been described.^{2,19} The patients in this study were enrolled into the parent study¹² between 12th March 2010 and 20th April 2011 to assess the diagnostic accuracy of the urine LAM point-of-care assay (Determine TB-LAM). Consecutive eligible HIV-infected patients were recruited from among patients newly referred to the clinic for ART. Study eligibility criteria included age >18 years, being ART-naïve and having no current TB diagnosis. All participants provided written informed consent and the study was approved by the research ethics committees of the University of Cape Town, South Africa, and the London School of Hygiene & Tropical Medicine, UK.

Following recruitment at their first visit to the clinic, patients' demographic details were recorded and they were clinically characterized. A standardised TB symptom-screening questionnaire (including the WHO symptom screen for HIV-associated TB²⁰) was completed and routine baseline investigations and screening tests for TB were done. Two sputum samples were requested from each patient; a spot specimen was first obtained followed by a second obtained by induction using nebulised 3% hypertonic saline. Urine samples were also collected and stored at -20°C within 3 hours. Blood CD4 cell counts and plasma viral load were measured on all patients via the routine laboratory services. Chest radiographs were obtained and reported by an experienced reader certified in the use of the chest radiograph reading and recording system.^{21,22}

Patients were followed up within the routine ART service and patients diagnosed as having TB were referred to TB clinics within the township for treatment. ART service records of those with TB were reviewed to ascertain deaths within the first 90 days after enrolment.

Laboratory procedures

Sputum specimens were processed using standardised protocols and quality assurance procedures by a centralised accredited laboratory as described in detail previously.^{12,23} In brief, samples were decontaminated with N-acetyl-L-cysteine and sodium hydroxide and concentrated by centrifugation. Smears prepared from the sputum pellets underwent fluorescence microscopy. Equal volumes of the remaining pellet were tested by the Xpert assay and by liquid culture using Mycobacterial Growth Indicator Tubes (MGIT, Becton Dickinson, Sparks, Maryland, USA), which were incubated for up to 6 weeks. Cultures positive for acid-fast bacilli were identified as *Mycobacterium tuberculosis* complex using

the MTBDR_{plus} assay (Hain Lifesciences, Nehren, Germany), which also provided genotypic assessment of susceptibility to rifampicin and isoniazid. Phenotypic drug susceptibility testing was also done in liquid culture using the modified proportion method.

Frozen urine samples were defrosted and retrospectively analysed for the presence of LAM using both the Clearview MTB-ELISA (Alere, Waltham, MA, USA) the Determine TB-LAM point-of-care test strips (Alere, Lot #101102) with strict adherence to the manufacturer's instructions.¹² Defrosted urine samples (2.0 mL) were also concentrated by centrifugation, the pellet resuspended in 0.75 mL of phosphate buffer and then tested using the Xpert assay according to the manufacturer's instructions.

Definitions and analysis

Patients were defined as having TB if *Mycobacterium tuberculosis* was cultured from one or more sputum samples. Patients were then categorized as having urine Xpert-positive or urine Xpert-negative disease. Clinical, microbiological and radiological characteristics and 90-day outcomes of patients with Xpert-positive and Xpert-negative TB were compared using the Wilcoxon rank-sum test, t-test, chi-square and Fisher's exact tests as appropriate. Logistic regression analysis was used to identify factors independently associated with urine Xpert-positive test results. All statistical tests were two-sided at alpha=0.05.

RESULTS

TB diagnoses

Among 602 patients recruited, 535 produced at least 1 sputum sample and a specimen of urine. Sputum culture results were available from 516 patients and these yielded 85 diagnoses of culture-positive TB. The remainder (n=431) were sputum culture-negative. TB cases were young adults of whom more than one half were female (Table 1). The median plasma viral load was high and the median (interquartile range) CD4 cell count was 138 cells/ μ L (IQR 63-205). A positive WHO TB symptom screen was recorded in 82.1% of TB patients but only 25.0% reported a cough lasting \geq 2 weeks. Disease was sputum smear-positive in 28.6% of cases and smear-negative in 71.4% (Table 1). Xpert testing of sputum was positive in 58.3% from the first sample and 70.2% when testing both sputum samples.

Yield of TB diagnoses from testing urine with Xpert MTB/RIF

Of the patients with sputum culture-positive TB and available urine Xpert results (n=84), 16 tested positive, giving a sensitivity of 19.0% (95%CI, 11.3-29.1). The sensitivity was strongly associated with blood CD4 cell count (Figure 1a). It was higher in those with counts $<$ 50 cells/ μ L (44.4%; 95%CI, 21.5-69.2) compared to those with counts of 50-150 cells/ μ L (25.0%; 95%CI, 10.7-44.9) or $>$ 150 cells/ μ L (2.7%; 95%CI, 0.1-14.2).

Xpert testing of both sputum and urine samples produced a small incremental diagnostic yield over Xpert testing of sputum only. When Xpert testing was done on one sputum sample, an additional 4 cases of TB were diagnosed by also testing urine samples with Xpert (sensitivity: 58.3% versus 63.1%). When testing 2 sputum samples, an additional 2 cases of TB were diagnosed by also testing urine samples with Xpert (70.2% vs 72.6%).

The sensitivity of urine Xpert testing was approximately two-thirds of that observed using the Determine TB-LAM point-of-care assay for LAM. The overall sensitivity of this assay for all TB patients was 28.6% (19.2-39.5) and for those with CD4 cell counts of $<$ 50 cells/ μ L, 50-150 cells/ μ L and $>$ 150 cells/ μ L, sensitivities were 66.7% (41.0-86.7), 32.1% (15.9-52.4) and 8.1% (1.7-21.9), respectively (Figure 1b).

Comparison of urine Xpert-positive and negative cases

We compared the characteristics and microbiological results of patients with urine Xpert-positive (n=16) and urine Xpert-negative (n=68) disease (Table 1). Those with urine Xpert-positive disease were younger, tended to have lower body mass indices and haemoglobin concentrations and higher neutrophil counts. They also had more advanced HIV, with higher viral loads and a much lower median CD4 cell count compared to patients with urine Xpert-negative disease.

Multivariate logistic regression analysis was done and this included CD4 cell count, viral load and those patient characteristics and blood tests results that were found to be significantly associated with Xpert status in univariate analysis in Table 1. A positive urine Xpert result was independently associated with just two patient characteristics - younger age and lower CD4 cell counts. Assigning patients with CD4 cell counts of >150 cells/ μ L as the reference group, the adjusted odds of a positive urine Xpert result among patients with CD4 cell counts of either 50-150 cells/ μ L or <50 cells/ μ L were 13.6 (95%CI, 1.33-139) and 20.1 (95%CI, 1.72-233), respectively (P=0.010).

Although there were no significant differences in the pulmonary radiographic features of disease comparing the two groups of patients (Table 1), patients with urine Xpert-positive TB had evidence of high mycobacterial burden. They had higher frequencies of positive sputum smear microscopy and positive sputum Xpert results, shorter time to culture positivity and a higher frequency of detectable LAM in urine (Table 1).

Drug resistance

Four cases of multi-drug resistant TB (MDR-TB) were confirmed by phenotypic and genotypic assessment of sputum culture isolates. Rifampicin resistance was detected in all of these cases by Xpert testing of sputum. Xpert detected *M. tuberculosis* in the urine of only one of these patients but correctly identified rifampicin resistance. In addition, results of Xpert done on urine samples also reported rifampicin resistance in two other patients whose sputum isolates were drug susceptible. These were either false-positive Xpert results or represented mixed infection with resistant and susceptible strains.

Urine samples from non-TB cases

Of patients (n=431) with negative sputum cultures, we tested urine samples from a sample of consecutive patients equal in number to the TB cases studied (n=84). The characteristics of these patients (data not shown) were very similar to those of non-TB patients in the overall cohort included in the parent study,¹² indicating that these were a representative sample. Urine specimens from these 84 patients were tested using Xpert and all were negative.

Mortality

Outcomes up to 90 days from screening were assessed. During follow-up, 4/16 (25%) of urine Xpert-positive patients died compared to 1/68 (1.5%) of urine Xpert-negative patients (P=0.004). All deaths occurred within the first 30 days.

DISCUSSION

In this study, one fifth of ambulatory HIV-infected patients with advanced immunodeficiency and sputum culture-positive pulmonary TB had *M. tuberculosis* that was detectable when testing small volumes of urine with the Xpert assay. The diagnostic yield was strongly associated with blood CD4 cell count with almost one half of those with CD4 cell counts <50 cells/ μ L testing positive whereas the yield at CD4 counts >150 cells/ μ L was

very low. There was a small incremental diagnostic yield from Xpert assays when spot urine samples were tested in addition to sputum samples. This represents an alternative rapid diagnostic modality in HIV-infected patients with advanced immunodeficiency.

Previous studies have reported that concentration of urine from HIV-infected patients by centrifugation and subsequent culture has an appreciable diagnostic yield.^{9,24,25} However, this entails collection and processing of comparatively large volumes of urine, for example pooling morning samples over three days.²⁵ Urine culture is infrequently useful as a diagnostic modality in this clinical population because of the prolonged time to culture positivity. In this study, however, we tested very small (2.0 ml) samples of urine and still found an important diagnostic yield that was similar to that obtained by culture of concentrated large volumes of urine in a study of HIV-infected patients in Thailand.⁹ The sensitivity of Xpert in our study might have been even greater had a whole urine sample been collected and concentrated.

A major advantage of Xpert is rapidity, with results being generated within 2 hours compared with culture for which the time to positivity often exceeds 3 weeks for paucibacillary clinical samples.^{11,23} Rapid diagnosis is particularly important for patients with high mortality risk. Our analyses demonstrated that similar to sputum testing,²⁶ urine Xpert testing is most likely to be positive in patients with the most advanced immunodeficiency and poor prognostic characteristics (low body mass indices and low haemoglobin concentrations). One quarter of those who retrospectively tested urine Xpert-positive TB died. Thus, this represents a particularly useful diagnostic modality in patients with low CD4 cell counts and high risk of death. We assessed ambulatory patients and yet the assay may have even greater utility among sick patients requiring hospital admission who may be unable to obtain good quality sputum samples and in whom risk of disseminated TB is high.⁵

In contrast to detection in urine of non-organism-associated transrenal DNA fragments, the Xpert assay detects intact *Mycobacterium tuberculosis* bacilli. This is because the cartridge-based processing entails sputum lysis, washing and deposition of whole mycobacteria on a filter membrane prior to ultrasonic disruption and real-time PCR amplification and detection.¹⁵ Thus, detection of *M. tuberculosis* in urine using Xpert indicates renal tract involvement with TB as the bacilli would otherwise be unable to enter the urine. The sensitivity of urine Xpert was approximately two-thirds that of Determine TB-LAM which, in contrast to Xpert, detects mycobacterial cell wall LAM antigen rather than the whole organism. This is consistent with findings from another study from Cape Town investigating the mechanisms of LAM antigenuria.²⁷ We do not know whether the sensitivity of urine Xpert might have been similar to that of the LAM assay had much larger volumes of urine been concentrated by centrifugation prior to testing.

Xpert has been found to have very high sensitivity but sub-optimal specificity for rifampicin resistance.¹⁵ In this study, two patients had rifampicin resistant *M. tuberculosis* when testing urine with Xpert, but the strains isolated from sputum were susceptible. It is not possible to ascertain whether these are false-positives (which are usually stochastic events, related to poor binding of detection probe B to the amplicon during the assay¹⁵) or whether the patients could have had disease due to two different strains. It was not possible to investigate this with molecular typing without paired isolates.

It was notable that urine Xpert results were only positive in patients with positive sputum cultures and were negative in all those who tested sputum culture-negative. Detection of *M. tuberculosis* in both urine and sputum samples indicates the presence of disseminated disease with both pulmonary and renal tract involvement and this also reflects the lack of

disease anatomic compartmentalization in patients with advanced immunodeficiency. Assessment of both sputum and urine samples using Xpert provides a means of rapid assessment for disseminated TB.

Strengths of this study include the recruitment of carefully characterised consecutive patients in a well documented clinical cohort. We do not know whether the diagnostic yield might have been greater had larger volumes of urine been tested and the relative sensitivity of urine Xpert and urine culture was not assessed. Urine testing was done retrospectively and it is not known whether prospective testing would have accelerated diagnosis or improved patient outcomes. Further prospective evaluation is needed to determine whether this provides a useful diagnostic modality during clinical care in both high and low TB burden settings.

In conclusion, analysis of urine samples using the Xpert assay provides useful diagnostic yield for TB among patients with advanced HIV-associated immunodeficiency. High rates of detection among those with low CD4 cell counts provide evidence of frequent disease dissemination.

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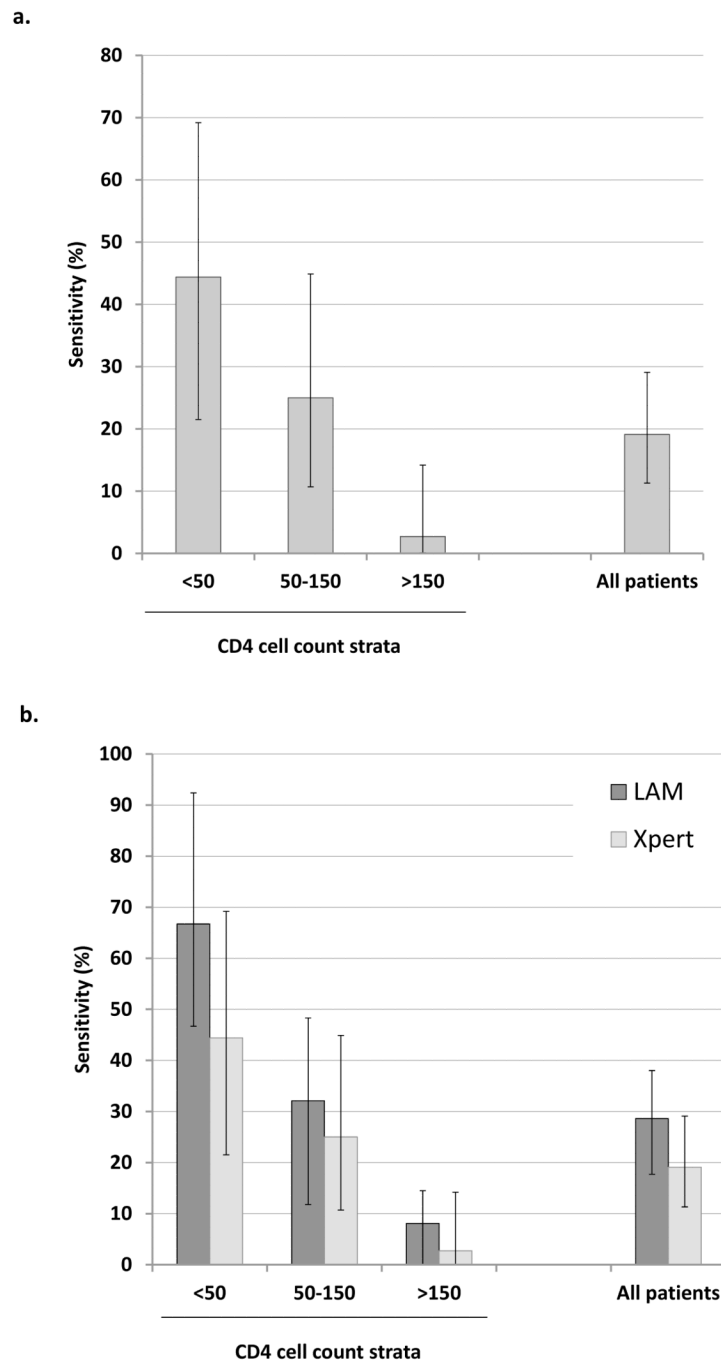


Figure 1.

(a) The sensitivity (%; 95%CI) of the Xpert MTB/RIF assay for tuberculosis (TB) when testing urine samples obtained from HIV-infected patients (n=84) with sputum culture-confirmed pulmonary TB. Sensitivity is also shown stratified by CD4 cell count for the 83 patients for whom CD4 cell counts were available. (b) Comparison of the sensitivity of urine Xpert with that of Determine TB-LAM Ab point-of-care diagnostic assay that diagnoses TB by detecting mycobacterial lipoarabinomannan (LAM) in urine.

Table 1

Characteristics and results of radiological and microbiological investigations in patients with sputum culture-positive tuberculosis (TB), comparing those whose urine samples tested Xpert-positive with those whose samples tested Xpert-negative.

	Total TB cases (n=84)	Urine Xpert- positive cases (n=16)	Urine Xpert- negative, cases (n=68)	P-value ^a
Patient characteristics				
Age, median (IQR)	33.1 (28.4-40.2)	27.6 (25.0-31.1)	34.1 (28.9-41.4)	0.006
Female (%)	51 (60.7)	8 (50)	43 (63.2)	0.329
BMI, median (IQR)	21.2 (19.2-26.0)	19.0 (17.8-24.4)	21.3 (19.8-26.4)	0.072
History of previous TB?	18 (21.4)	4 (25.0)	14 (20.6)	0.739
Blood Tests^b				
Hemoglobin (g/dL)	10.9 (8.8-12.4)	9.0 (7.7-10.9)	11.2 (9.2-12.7)	0.003
White blood cell count ($\times 10^9$ cells/L)	5.6 (4.6-7.7)	5.7 (5-11.2)	5.6 (4.5-7.1)	0.330
Absolute neutrophil count ($\times 10^9$ cells/L)	3.3 (2.4-5.0)	4.8 (2.4-9.1)	3.2 (2.4-4.2)	0.047
Absolute lymphocyte count ($\times 10^9$ cells/L)	1.0 (1.0-2.1)	1.2 (0.6-2.1)	1.6 (1.2-2.1)	0.128
ALT (iu/L)	21.5 (14-33.5)	26 (17-58)	20 (13.5-32)	0.060
Platelets ($\times 10^9$ cells/L)	289 (219-383)	309 (163-418.5)	282 (228.5-377.5)	0.791
CD4 cell count (cells/μL)^c				
Median	138 (63-205)	60 (25-113)	161 (72-213)	0.001
CD4 <50	18 (21.7)	8 (50)	10 (14.9)	0.001
CD4 50-150	28 (33.7)	7 (43.8)	21 (31.3)	
CD4 >150	37 (44.6)	1 (6.3)	36 (53.7)	
Log viral load (copies/ml), Median (IQR) ^b	4.8 (4.4-5.3)	5.2 (4.8-5.6)	4.7 (4.3-5.2)	0.015
WHO stage at enrolment				
1 or 2	47 (56.0)	7 (43.8)	40 (58.8)	0.275
3 or 4	37 (44.1)	9 (56.3)	28 (41.2)	
Symptoms				
Any cough, fever, night sweats or weight loss (1 symptom)	69 (82.1)	13 (81.3)	56 (82.4)	1.00
Current cough 2 weeks	21 (25.0)	6 (37.5)	15 (22.1)	0.199
Chest radiographs				
Any radiological abnormality ^a	62/81 (76.5)	14/16 (87.5)	48/65 (73.9)	0.335
Hilar and mediastinal lymphadenopathy	23/81 (28.4)	7 (43.8)	16 (24.6)	0.128
Cavitation	2 (2.5)	0	2 (3.1)	1
Parenchymal abnormality	3 (1-5)	2.5 (1-6)	3 (2-4.5)	0.919

	Total TB cases (n=84)	Urine Xpert- positive cases (n=16)	Urine Xpert- negative, cases (n=68)	P-value ^a
(median number of zones)				
Microbiological investigations				
Smear positive	24 (28.6)	9 (56.3)	15 (22.1)	0.006
Time to culture positivity median IQR (days)	16 (11-21)	11 (8.5-19.5)	16 (12-21)	0.066
Sputum Xpert positive (first result only)	49 (58.3)	12 (75.0)	37 (54.4)	0.133
Sputum Xpert positive (either result positive)	59 (70.2)	14 (87.5)	45 (66.2)	0.131
Urine LAM ELISA positive	23 (27.4)	12 (75.0)	11 (16.2)	<0.001
Determine-TB LAM positive	24 (28.6)	12 (75.0)	12 (17.7)	<0.001

ALT = alanine aminotransferase

^aComparison of Xpert-positive and Xpert-negative cases.

^bBlood tests show median values (interquartile range [IQR]). All other results show numbers (%) unless otherwise stated.

^cCD4 cell counts missing from 1 urine Xpert-negative patient.