

Diagnostic accuracy of GeneXpert MTB/RIF in musculoskeletal tuberculosis: High sensitivity in tissue samples of HIV-infected and HIV-uninfected patients

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Background. GeneXpert MTB/RIF is useful for the diagnosis of pulmonary TB in adults, but there is limited evidence on its usefulness in extrapulmonary TB.

Objectives. To investigate the diagnostic accuracy of GeneXpert MTB/RIF in HIV-infected and HIV-uninfected patients with suspected musculoskeletal TB.

Methods. A prospective study of patients with suspected musculoskeletal (bone and joint) TB was undertaken. The diagnostic accuracy of GeneXpert MTB/RIF was compared with the reference standards of culture and histopathology.

Results. A total of 206 biopsies from 201 patients (23% HIV-infected) were evaluated. The sensitivity and specificity of GeneXpert MTB/RIF was 92.3% (84/91) and 99.1% (114/115), respectively. GeneXpert MTB/RIF detected 8.8% more cases than culture (84/91 (92.3%) v. 76/91 (83.5%), respectively; $p=0.069$). GeneXpert MTB/RIF also detected all 4 multidrug-resistant TB cases and an additional 2 rifampicin-resistant cases in culture-negative samples. The sensitivity of GeneXpert MTB/RIF in HIV-infected patients was 96.9% (31/32) v. 89.6% (43/48) in HIV-uninfected patients ($p=0.225$).

Conclusion. GeneXpert MTB/RIF is an accurate test for the detection of TB in tissue samples of HIV-infected and HIV-uninfected patients with suspected musculoskeletal TB. A positive GeneXpert MTB/RIF result should be regarded as microbiological confirmation of TB.

S Afr Med J 2017;107(10):854-858. DOI:10.7196/SAMJ.2017.v107i10.11186

Musculoskeletal TB occurred in ~3% of the estimated 8.6 million people who developed tuberculosis (TB) in 2012.^[1] Among these, spinal TB was the most common orthopaedic manifestation, and may lead to neurological deficits in 23 - 76% of cases.^[2] Timely and accurate diagnosis of musculoskeletal TB and initiation of the appropriate therapy is crucial to prevent associated morbidity.

GeneXpert MTB/RIF (Cepheid, USA) was recently introduced as an automated onsite nucleic acid amplification test as a fast and accurate alternative diagnostic test to culture for pulmonary TB. In a recent meta-analysis,^[3] GeneXpert MTB/RIF was reported to have a sensitivity of 90% for *Mycobacterium tuberculosis* and a 94% sensitivity for rifampicin resistance in pulmonary TB in adults.

In a second meta-analysis^[4] of the accuracy of GeneXpert MTB/RIF on tissue samples (other than lymph nodes), using culture as a reference standard, the reported pooled sensitivity was 81.2% (95% confidence interval (CI) 67.7 - 89.0) and specificity was 98.1% (95% CI 87.0 - 99.8). However, these were samples from various tissues and currently there are no large studies reporting on the accuracy of GeneXpert MTB/RIF for musculoskeletal disease. Non-automated nucleic acid amplification assays have reported sensitivities of 61 - 83% for musculoskeletal TB.^[5-9]

Only a few studies have investigated GeneXpert MTB/RIF for musculoskeletal disease, including a case report,^[10] a small study on 71 spinal samples that we undertook,^[11] and another study on 29 spinal tissue samples.^[12] GeneXpert MTB/RIF had sensitivities of 72% and 82% in HIV-uninfected and HIV-infected patients, respectively; however, the reference standard in the study^[12] was based on clinical and radiological findings only. It was also not conducted onsite and

the results were only available after ~6 days, compared with 27 days for culture tests. Another study^[13] compared GeneXpert MTB/RIF in 60 orthopaedic fluid samples with culture and found a sensitivity of 63.6%. To our knowledge, there is no large study reporting on the accuracy of GeneXpert MTB/RIF in tissue samples, using culture as a reference standard and no study has assessed whether the accuracy of GeneXpert MTB/RIF is affected by HIV or the location of the disease, such as spinal compared with extraspinal disease.

We aimed to assess the accuracy of GeneXpert MTB/RIF in surgical biopsies of HIV-infected and HIV-uninfected adults with suspected musculoskeletal TB. We also compared the time to availability of results for GeneXpert MTB/RIF with that of culture results, and differences in the accuracy of spinal and extraspinal samples.

Methods

We conducted a prospective observational study of consecutive patients who were >13 years of age with clinico-radiological features of musculoskeletal TB. The study was performed at a large tertiary-level hospital in South Africa (SA), in an area with one of the highest TB and HIV rates worldwide. All patients underwent a musculoskeletal tissue biopsy for suspected TB from June 2013 to March 2015 as part of the routine clinical workup. As per the current standard of care at our centre, specimens were sent for GeneXpert MTB/RIF, culture and histology, as these tests are all used to inform treatment decisions. Patients who presented at our institution with symptoms suspicious of TB and who had been tested with the GeneXpert, were included in the study. Faulty, insufficient or contaminated GeneXpert MTB/RIF and TB cultures were excluded. Patients who were <13 years of age

were also excluded from the study. Furthermore, patients who were not fit for surgery were excluded. TB treatment was not recorded.

TB was suspected if patients presented with a history of back pain for >3 months and any of the following symptoms: constitutional symptoms, chronic cough, elevated erythrocyte sedimentation rate, history of TB contact, spinal gibbus, and immune compromise or HIV. Radiological features for suspected TB of a joint were local osteopenia and erosions involving adjacent joint surfaces. Radiological red flags in spinal disease were loss of anterior vertebral height, paravertebral shadow on radiographs, shadow of a psoas abscess, adjacent vertebral endplate changes with preserved disc height, changes on chest radiographs suspicious of TB and paravertebral abscess formation on magnetic resonance imaging. Biopsies were performed by a specialised orthopaedic service at our hospital.

Musculoskeletal tissue samples were collected surgically from radiographically predetermined areas of disease in an operating room under sterile conditions. Tissue samples were taken from synovium in articular biopsies, and from bone in extra-articular biopsies. Spinal tissue biopsies were performed by a subspecialist surgical spinal team. Extraspinal lesions were biopsied by a specialised orthopaedic team. Extraspinal biopsies were collected by open approach and dissection from the area of suspected disease. Collected tissue was equally divided and sent for culture, histology and GeneXpert MTB/RIF in separate containers. The exact volume of tissue was not recorded. Indications for open spinal biopsies included instability, neurological deterioration, a large abscess or airway compromise.

Microbiology

Specimens were submitted in duplicate and in sterile saline to the microbiology laboratory for simultaneous processing. The first specimen was processed for GeneXpert MTB/RIF testing. For this, the tissue was crushed after adding 1 mL of sterile saline. GeneXpert MTB/RIF SR lysis buffer was added in a 1:3 ratio (0.5 mL of sample to 1.5 mL of buffer) and the specimen was vortexed initially and again after ten minutes. Two millilitres of the mixture were processed automatically and the result was recorded after ~90 minutes. The GeneXpert MTB/RIF tests were performed by a trained laboratory technician who was blinded to the results of the reference test.

The reference standard was liquid culture or histology. Culture tests were done on the second specimens using the automated liquid culture BACTEC MGIT 960 system (Becton Dickinson Diagnostic Systems, USA). After the addition of 1 mL saline, the entire volume of sample tissue was crushed with a pestle and mortar. The sample was subsequently incubated overnight at 37°C on 2% blood agar and checked for sterility. Sterile samples were processed via the Bactec MGIT system according to the manufacturer's instructions; any growth was decontaminated by the addition of 1 mL sodium hydroxide/citrate and *N*-Acetyl-*L*-cysteine to a final concentration of 1.5%. After 20 minutes, phosphate buffer was added to a final volume of 50 mL and centrifuged for 15 minutes at 3 000 g. The supernatant was decanted and an equal volume of phosphate buffer was added to a 0.5 mL aliquot of the supernatant before processing via the BACTEC MGIT 960 system.

A culture was regarded as negative after 42 days without growth. A Ziehl-Neelsen (ZN) stain and a haematoxylin and eosin stain were conducted in the microbiology and histopathology laboratories, respectively. Quantification of acid-fast bacilli (AFB) was conducted according to the specifications from the Centers for Disease Control and Prevention.^[14] The isolate was assessed for multidrug-resistant TB (MDR-TB) using the GenoType MTBDRplus or GenoType *Mycobacterium* CM lineprobe assays (Hain Lifescience, Germany). MDR-TB was defined as resistance to isoniazid (INH) and rifampicin.

A trained pathologist, who was experienced in diagnosing TB, reviewed the histopathology slides. Clinical data, imaging and the GeneXpert MTB/RIF test results were available to the pathologist. Histological criteria for TB were caseous necrosis, epithelioid cell granulomas or Langerhans giant cells.

Confirmed TB was defined as a positive *M. tuberculosis* culture or positive histology. A case was considered 'Not TB' if culture and histology results were negative and if there was improvement on follow-up without TB treatment. The diagnostic accuracy of GeneXpert MTB/RIF was compared with liquid culture tests and histology. Standards for the Reporting of Diagnostic Accuracy Studies (STARD) guidelines were used to design our study and report the findings.^[15]

The study was approved by the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (ref. no. 264/2013).

Statistical analysis

The sensitivity, specificity and predictive values of GeneXpert MTB/RIF, with 95% CI, were calculated using TB culture or histology as the reference standard. Data were analysed per sample using STATA 13 statistical software (STATA Corp., USA). Descriptive statistics were used to characterise the study population; normally distributed continuous data were summarised by means and 95% CIs and non-normally distributed continuous data by medians and interquartile range (IQR). Categorical data were summarised as proportions with 95% CIs. Statistical tests included two-sample tests of proportions, χ^2 , Kruskal-Wallis tests and Wilcoxon rank-sum tests. All statistical tests were two-sided at $\alpha=0.05$.

Results

A total of 207 samples were collected from 202 patients with suspected musculoskeletal TB; five patients had repeat biopsies. One sample was excluded as the culture sample was sent in formalin and had to be discarded; 206 samples were therefore included. The biopsy sites are shown in Table 1; 122 of 206 biopsies (59.2%) were performed for spinal TB. The remaining biopsies were for suspected extraspinal TB of joints or bones. Tissue samples constituted 95.1% ($n=196$) and 4.8% ($n=10$) were pus samples obtained via aspiration. The median (IQR) age of the patients was 40 (27 - 54) years; 48.3% ($n=97$) were male. In the per sample analysis, 38.5% ($n=76$) were culture-positive compared with 41.3% ($n=85$) GeneXpert MTB/RIF-positive results (Table 2).

The sensitivity of GeneXpert MTB/RIF in musculoskeletal samples was 92.3% (95% CI 84.8 - 96.9) and the specificity was 99.1% (95% CI 95.2 - 99.8) (Table 2). For culture-confirmed TB only, the sensitivity of GeneXpert MTB/RIF was 90.8% (95% CI 81.9 - 96.2; $p=0.724$), with a specificity of 87.7% (95% CI 80.8 - 92.8; $p<0.001$). All except one of the culture-negative, but GeneXpert MTB/RIF-positive, samples showed features of TB on histology.

In 98.5% ($n=203$) of samples a ZN stain was available for quantification of AFB, 15.8% ($n=32$) were positive and 84.2% ($n=171$) were negative. The sensitivity, when compared with our gold standard was 33.7% (95% CI 24.2 - 44.3), with a specificity of 99.1% (95% CI 95.1 - 99.9) (Table 2). GeneXpert MTB/RIF was positive at a median (IQR) of 1 day (1 - 1) compared with 18 days (12 - 26) for culture results ($p<0.001$). GeneXpert MTB/RIF detected 8.8% more cases than culture tests (84/91 (92.3%) v. 76/91 (83.5%), respectively; $p=0.069$).

Drug-resistant TB

All 4 MDR-TB cases detected with the lineprobe assay were also identified with GeneXpert MTB/RIF. GeneXpert MTB/RIF detected an additional 2 patients with rifampicin resistance in which the

Table 1. Characteristics of patient cohort (N=201) and biopsy sites (N=206)

	Overall	TB CP only	TB CN, histology positive	Confirmed TB	Not TB	p-value
Patients, n (%)	201	75 (37.3)	15 (7.5)	90 (44.8)	111 (55.2)	
HIV status, n (%)						0.001
Infected	46 (22.9)	24 (32.0)	8 (53.3)	32 (15.9)	14 (12.6)	
Uninfected	102 (50.7)	41 (54.7)	6 (40.0)	47 (23.4)	55 (49.6)	
Unknown	53 (26.4)	10 (13.3)	1 (6.7)	11 (5.5)	42 (37.8)	
Sex (male), n (%)	97 (48.3)	33 (44.0)	9 (60.0)	42 (20.9)	55 (49.6)	0.485
Age (years), median (IQR)	40 (27 - 54)	35 (25 - 51)	35 (24 - 52)	42 (28 - 53)	47 (28 - 57)	0.099
Biopsy sites, n (%)						
Spine	122 (59.2)					
Hip	10 (4.8)					
Knee	30 (14.6)					
Ankle and foot	9 (4.4)					
Shoulder	6 (2.9)					
Elbow	5 (2.4)					
Wrist/hand	3 (1.5)					
Bone	20 (9.7)					
Sacroiliac joint	1 (0.5)					

TB = tuberculosis; CP = culture positive; CN = culture negative; IQR = interquartile range.

Table 2. Per sample comparison of the accuracy of TB culture and GeneXpert MTB/RIF tests, and agreement between GeneXpert MTB/RIF and culture drug-susceptibility testing for rifampicin resistance (N=206)

	All samples (n/N),				
	n (%)	Sens (%), 95% CI	Spec (%), 95% CI	PPV (%), 95% CI	NPV (%), 95% CI
Xpert	85/206 (41.3%)	92.3 (84.8 - 96.9)	99.1 (95.2 - 99.8)	98.8 (93.6 - 99.8)	94.2 (88.4 - 97.6)
Agreement with rifampicin resistance testing	CR	CS	CIC	CN	Total
XR	4	0	0	2	6
XS	0	64	1	13	78
XIC	0	1	0	0	1
XN	0	7	0	114	121
Total	4	72	1	129	206

Sens = sensitivity; CI = confidence interval; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; Xpert = GeneXpert MTB/RIF; CR = culture resistant; CS = culture sensitive; CIC = culture inconclusive, CN = culture negative; XR = Xpert resistant; XS = Xpert sensitive; XIC = Xpert inconclusive; XN = Xpert negative.

culture results were negative (Table 2). Therefore 6.7% (6/90) of patients with TB had rifampicin resistance. In one case INH mono-resistance was detected with the lineprobe assay.

Accuracy in samples of HIV-infected and HIV-uninfected patients

Forty-six patients (22.9%) were HIV-infected, 50.7% (n=102) of the patients were HIV-uninfected and 26.4% (n=53) were of unknown HIV status. Among the HIV-infected patients, 69.5% (32/46) had TB compared with 46.1% (47/102) of the HIV-uninfected patients and 20.7% (11/55) of the patients with unknown HIV status (p<0.001) (Table 1). The sensitivity of the GeneXpert MTB/RIF test was 96.9% (95% CI 83.8 - 99.9) in HIV-infected patients and 89.6% (95% CI 77.3 - 96.5; p=0.225) in HIV-uninfected patients. The specificity was 100% (95% CI 78.5 - 100.0) for HIV-infected patients and 98.3% (95% CI 90.8 - 99.9; p=0.621) in HIV-uninfected individuals (Table 3).

Accuracy in spinal and extraspinal samples

The sensitivity of GeneXpert MTB/RIF for spinal biopsies was 93.8% (95% CI 86.0 - 97.9) with a specificity of 97.6% (95% CI 87.4 - 99.9), compared with extraspinal biopsies, which had a sensitivity of 81.8%

(95% CI 48.2 - 99.7; p=0.164) and specificity of 100% (95% CI 95.1 - 100; p=0.186) (Table 3).

Discussion

This was the first large study to show the accuracy of GeneXpert MTB/RIF for the diagnosis of TB in extrapulmonary tissue biopsies of HIV-infected and HIV-uninfected patients with suspected musculoskeletal TB. We found that GeneXpert MTB/RIF had high sensitivities and specificities for spinal and extraspinal disease and provided additional diagnostic yield over culture tests. We noted a higher accuracy than reported in a meta-analysis evaluating GeneXpert MTB/RIF in extrapulmonary TB not involving bone or joints.^[4] In addition, GeneXpert MTB/RIF was more sensitive than non-automated nucleic acid amplification assays for musculoskeletal TB reported in other studies with sensitivities of 61 - 83%.^[5-9] Reliance on culture tests may lead to delays in diagnosis and treatment, with resultant serious morbidity, such as joint destruction, or paralysis in spinal TB.^[2] The results for GeneXpert MTB/RIF tests, including drug resistance, were available much faster than liquid culture test results, which enabled timely diagnosis and initiation of therapy.

Table 3. Accuracy of GeneXpert MTB/RIF in samples comparing HIV-infected with HIV-uninfected patients, and spinal with extraspinal samples (N=206)*

	N/n (%)	TP, n	FP, n	FN, n	TN, n	Sens (%), 95% CI	Spec (%), 95% CI	PPV (%), 95% CI	NPV (%), 95% CI
Total samples	206	84	1	7	114	92.3 (84.8 - 96.9)	99.1 (95.3 - 100)	98.8 (93.6 - 100)	94.2 (88.4 - 97.6)
Spinal v. extraspinal samples									
Spinal	122 (59.2)	75	1	5	41	93.8 (86.0 - 97.9)	97.6 (87.4 - 99.9)	98.7 (92.9 - 99.9)	89.1 (76.4 - 96.4)
Extraspinal	84 (40.8)	9	0	2	73	81.8 (48.2 - 97.7)	100 (95.1 - 100)	100 (70.1 - 100)	97.3 (90.7 - 99.7)
p-value						0.164	0.186	0.729	0.061
Samples from HIV-infected v. HIV-uninfected patients									
Uninfected	106 (51.5)	43	1	5	57	89.6 (77.3 - 96.5)	98.3 (90.8 - 99.9)	97.7 (88.0 - 99.9)	91.9 (82.2 - 97.3)
Infected	46 (22.3)	31	0	1	14	96.9 (83.8 - 99.9)	100 (78.5 - 100)	100 (90.0 - 100)	93.3 (68.1 - 99.8)
p-value						0.225	0.621	0.398	0.856
Unknown	54 (26.2)	10	0	1	43	90.9 (58.7 - 99.8)	100 (91.8 - 100)	100 (72.2 - 100)	97.7 (88.0 - 99.9)

TP = true positive; FP = false positive; FN = false negative; TN = true negative; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; Spec = specificity; Sens = sensitivity.

*Reference standard: TB culture or histology positive.

A further advantage of GeneXpert MTB/RIF is the ability to rapidly detect resistant cases. This feature is especially important in our setting, as SA has a large number of patients with drug-resistant TB.^[1] A meta-analysis of GeneXpert MTB/RIF for resistance testing in 566 tissue samples from 13 studies reported the prevalence of rifampicin resistance to be 5.4%. GeneXpert MTB/RIF did not detect rifampicin resistance in 2 of the 41 samples.^[4] We found 4 (4.4%) patients with MDR-TB and GeneXpert MTB/RIF detected an additional 2 cases of rifampicin-resistant TB who were culture-negative. Therefore, 6 patients (6.7%) had rifampicin-resistant TB and GeneXpert MTB/RIF detected all of these cases. The use of GeneXpert MTB/RIF in these cases enabled rapid initiation of appropriate therapy and detected 2 additional cases, which would have been otherwise undetected. A limitation of the GeneXpert MTB/RIF test is its inability to detect INH monoresistance, which was the case in one sample, although the treatment is identical to that for drug-sensitive TB in SA.^[16]

GeneXpert MTB/RIF had a similar sensitivity in samples from HIV-infected and HIV-uninfected patients. This trend was also reported in another small study.^[12] HIV-infected patients may be at a particular risk for rapid progression of disease and morbidity.^[17] The GeneXpert MTB/RIF assay may be especially useful in such populations.

Study limitations

A limitation of the study was that it was conducted among adult patients with advanced disease who required surgery at a referral hospital. The generalisability of these results to patients with less severe disease is therefore unclear; further studies of patients with milder forms of musculoskeletal disease should be conducted in peripheral hospitals. A further limitation was that the histological diagnosis was made by a single pathologist, who was not blinded to the GeneXpert MTB/RIF results. However, clear criteria for histopathological diagnosis were used, and the biopsies were consistently reviewed in a standardised way by an experienced pathologist. Different methods of sample collection were used, guided by the anatomic area as well as severity of the disease, which could have resulted in suboptimal sample collection. More aggressive (open) approaches might have resulted in a standardised way of surgical sample collection, although this may have resulted in unacceptable morbidity. A further limitation was that HIV status was unknown for several patients, thus reducing the sample size for comparison of HIV-infected and HIV-uninfected adults. However,

these numbers were similar to reports published by the WHO on our region, in which 76% of TB patients knew their HIV status in 2013.^[1]

Conclusion

GeneXpert MTB/RIF is an accurate, rapid and effective test for the detection of TB in tissue biopsies of HIV-infected and HIV-uninfected individuals with musculoskeletal TB. It should be recommended as a first-line investigation for these patients and a positive result should be regarded as microbiological confirmation of TB.

Acknowledgements. We thank Colleen Bamford from the National Health Laboratory Service for her support. We thank Linda Bewerunge for her assistance with data collection.

Author contributions. MH collected the data and wrote the manuscript; LW supervised the analysis of the data; RD was involved in the study design, recruited and operated on the patients; ML and HZ were involved in the study design and review of the manuscript.

Funding. None.

Conflicts of interest. None.

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Accepted 17 May 2017.