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Evaluation of XpertMTB/RIF performance for diagnosis of tuberculosis among HIV positive patients in northern Tanzania

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Abstract
Background: Diagnosis of tuberculosis (TB) in patients co-infected with HIV poses an important challenge because of the low sensitivity and specificity of microscopy, the standard diagnostic method**.** This study aimed to evaluate the performance of the XpertMTB/RIF tool for TB diagnosis among TB-HIV co-infected patients.
Methods: This was a cross-sectional analytical study conducted at Kibong'oto Infectious Disease Hospital in northern Tanzania and involved 69 patients. The performance of the XpertMTB/RIF and microscopy using LJ culture were determined and compared. Demographic, clinical, laboratory and radiological data were collected.
Results: XpertMTB/RIF had a higher sensitivity (100%), specificity (100%), positive predictive value (79.2%) and negative predictive value (98.9%) as compared to microscopy. There was a strong correlation between XpertMTB/RIF, microscopy and Löwenstein–Jensen (LJ) culture in terms of their sensitivity and specificity.
Conclusion: While using TB symptoms screening tool alone in HIV infected individuals may result into overtreatment, relying on microscopy alone has the potential of TB under-diagnosing, miss-diagnosing and delayed treatment. Our results show XpertMTB/RIF to be highly sensitive and specific to detect all culture positive TB cases among HIV patients. We recommend the adoption of XpertMTB/RIF as an early TB diagnosis tool among HIV patients for early detection of TB among HIV patients.

Keywords: tuberculosis, HIV/AIDS, XpertMTB/RIF, diagnosis, performance, Tanzania

Introduction

Tuberculosis (TB) remains among the leading global infectious diseases that are responsible for higher mortalities. The burden of this disease has been high globally for more than ten years. Recent estimates by the World Health Organization indicate that the incidence of TB among people living with HIV is 62,000 with mortality rate of 53 per 100,000 (WHO, 2015). There has been an increase in global incidence of TB by 40% from 1990 to 2008 (World Health Organization, 2009). This increase in TB infection rate has been attributed to HIV epidemic (World Health Organization, 2009). Global TB data show that in 2014, there were approximately 9.6 million incidence of TB. In the same year, data indicate that there were an estimated 1.2 million new HIV-positive TB cases accounting for about 12% of all TB cases, three-quarters of which were from the African Region (World Health Organization, 2015). Although the prevalence of TB among people living with HIV/AIDS in Tanzania was previously reported to be 8.5% in 2008 (Ngowi *et al.*, 2008), the prevalence is likely to be higher at present.

HIV infection is known to be associated with tuberculosis, a phenomenon that worsens the outcome of either of the co-infecting diseases, particularly so if diagnosis and treatment are delayed (Gandhi *et al.*, 2010; Kwan & Ernst, 2011). This fact calls for the need of prompt and accurate diagnosis of the infections and treatment initiated as early as possible. The use of microscopy alone in detection of TB positive individuals among HIV infected patients has frequently led to missing of substantial numbers of true TB positive cases in Tanzania (Swai *et al.*, 2011) with consequences of providing Isoniazid Prophylactic Therapy (IPT) to inappropriate individuals who would otherwise deserve a full course of TB treatment. Together with other factors, misdiagnosis and mistreatment have the obvious

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adverse consequences of development of isoniazid resistance mycobacteria (Balcells *et al.*, 2006) and hence are likely to result into multi-drug resistant tuberculosis (MDR-TB).

The XpertMTB/RIF tool, endorsed by WHO in 2011 (WHO, 2013) has the potential to diagnose TB and MDR-TB earlier and more accurately than microscopy. It has been introduced in Tanzania programmatic TB diagnostic algorithm among HIV patients in 2011. We envisage that the adoption and use of new diagnostic tools with increased accuracy for TB diagnosis such as XpertMTB/RIF can be integrated in active TB case screening and significantly increase the success of TB control programmes which are virtually using microscopy as the principal diagnostic tool. However, the XpertMTB/RIF performance in active case detection among HIV positive TB patients has not been evaluated in Tanzania. The HIV infected patients tend to have atypical and/or asymptomatic TB leading to difficult and delayed diagnosis when using microscopy, and hence increased rates of morbidity and mortality (Aderaye *et al.*, 2004). In this study, we evaluated the performance and effectiveness of XpertMTB/RIF, compared to microscopy, in TB detection among HIV positive patients using Lowenstein-Jensen culture as a gold standard.

Materials and Methods

Study site and design

This was a cross-sectional analytical study conducted at Kibong'oto Infectious Diseases Hospital (KIDH) from September 2014 to March 2015. Consecutive sampling technique was used whereby all patients seen at the hospital Care and Treatment Centre (CTC) during data collection period were included in the study if they met all inclusion criteria. The inclusion criteria were: consenting to participate in the study, being HIV positive and anti-retroviral (ARV) naive and being able to produce enough sputum for investigation. All patients who had been on isoniazid prophylactic therapy (IPT) or anti-TB therapy for the past 18 months from the time of study commencement were excluded.

Data collection

The study enrolled 78 patients who were HIV positive and ARVs naïve, who were above 15 years of age and attending at the KIDH HIV clinic for care and treatment. Patients who fulfilled the eligibility criteria were included. Patients' demographic data were collected using a specially designed data capturing form. The World Health Organization tuberculosis symptoms screening tool was used to look for any cardinal TB symptoms. Subsequently patients were instructed on how to collect the sputa (> 5mls) which was portioned for microscopy (ZN), Löwenstein–Jensen (LJ) culture and XpertMTB/RIF investigations. Nine patients were excluded because they were either not able to produce enough sputum, or their sputa were of low quality leading to inability to properly do one or both of the sputum investigations (microscopy, XpertMTB/RIF, LJ culture).

Sputum smear slides for microscopy were prepared by flooding slides with Auramine stain for about 20 minutes. Then slides were rinsed with tap water and a decolorizing solution (acid-alcohol) was poured on the slides and left for about 2 minutes. Slides were rinsed again with excess water and flooded with potassium permanganate solution for a minute. After a final rinsing, slides were left to air-dry. Dry slides were examined by microscopy. Sputum for XpertMTB/RIF investigation was mixed with the XpertMTB/RIF buffer solution, and shaken vigorously 20 times. The mixture was then incubated at room temperature for about 5 minutes. It was then shaken again 20 times and left to incubate for another 10 minutes. Afterwards, diluted specimen samples were pipetted into the appropriate cartridge of the XpertMTB/RIF for TB diagnosis. The automatically computer generated results were read.

Sputum portion for LJ (Lowenstein-Jensen) culture was initially decontaminated with 4% of sodium hydroxide followed by addition of sufficient amount of distilled water to achieve a volume of

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50ml in a centrifuge tube. The mixture was then centrifuged at 1,800 X g for 30 minutes. Sediments were inoculated on the LJ media slant using a sterile Pasteur pipette. The tubes were left overnight and then put back in an up-right position with loosened caps for 72hours after when tube caps were tightened. Results were read weekly from the inoculation day for eight weeks. All laboratory procedures were performed at Kibong'oto Hospital Laboratory. Regardless of their sputum results, all study participants had chest radiography, provided blood for full blood picture and CD4 count (The later only collected if it was not done and/or documented in the patient's hospital file within the previous month). Samples and data collection from the participating patients were done at a single encounter with the patient.

Data analysis

Data were analysed by using the STATA software where associations were determined by using Chi-square test and Mann-Whitney test. Sensitivity, specificity, positive predictive values and negative predictive values were calculated by using an R package called BDPV. Cut off value for alpha (α) was 0.05.

Ethical considerations

Ethical clearance was sought from Kilimanjaro Christian Medical University College Research and Ethics Committee (Certificate # 726). Permission from KIDH Management was obtained. All participants consented to participate in the study voluntarily. Patients' confidentiality and privacy were strictly observed.

Results

A total of 78 patients were involved and 69 of them were analysed. Thirty-eight, (55%) of those analysed were females, and 55 (80%) were below 50 years of age (Table 1). The mean and median age of the study population was 41.8 and 42 years, respectively. Eighteen (26%) patients had used some medications including antibiotics two weeks prior to enrolment. Fifty-seven (83%) of these patients were on co-trimoxazole preventive therapy (CPT).

Table 1: Patients' characteristics distribution (n=69)

Variable	Category	N	Percent (%)
Age	Above 50 years	14	20
	Below 50 years	55	80
Sex	Male	31	45
	Female	38	55
Domicile	Within Siha District	44	64
	Outside Siha District	25	36
Education	Primary	64	93
	Post Primary	5	7
Occupation	Mining	4	6
	Others	65	94
Cigarette Smoking	Yes	9	13
	No	60	87
Alcohol drinking	Yes	21	30
	No	48	70
Previous antibiotic medication	Yes	18	26
	No	51	74
Cotrimoxazole	Yes	57	83
	No	12	17

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All 9 patients diagnosed to have TB had at least one of the TB symptoms. Six (67%) of those diagnosed with TB presented with cough though the difference was not statistically significant compared to those who had no cough. Six (0.09%) of all patients presented with haemoptysis but only 2 (33.3%) of them had a positive LJ culture. Night sweat, presence of consolidation and cavities in chest radiographs were associated with the increased chance of diagnosing TB with either XpertMTB/RIF or LJ culture, p-values are 0.022, <0.000 and <0.000 respectively. Being symptomatic or asymptomatic for TB using the WHO symptom screening tool, was not associated with the diagnosis of TB by XpertMTB/RIF or culture LJ (Table 2). None of the study patients was found to have pleural effusion. Five (71.4%) patients among those who had consolidation were diagnosed to have TB, and 5 (62.5%) of the 8 patients with cavities had TB (Table 2).

Table 2: Association of TB features in HIV co-infection with XpertMTB/RIF results

TB Feature	Symptoms	Microscopy +ve	LJ culture +ve	XpertMTB/RIF +ve	X^2 p value
Cough	Y (36)	4	6	6	0.351
	N (33)	2	3	3	
Haemoptysis	Y (6)	2	2	2	0.122
	N (63)	4	7	7	
Fever	Y (21)	2	4	4	0.327
	N (48)	4	5	5	
Weight loss	Y (17)	1	2	2	0.857
	N (52)	5	7	7	
Night Sweat	Y (12)	3	4	4	0.022*
	N (57)	3	5	5	
Chest Pain	Y (22)	3	4	4	0.386
	N (47)	3	5	5	
Shortness of breath	Y (7)	1	2	2	0.198
	N (62)	5	7	7	
Fatigability	Y (25)	3	3	3	0.846
	N (44)	3	6	6	
Symptomatic	Y (60)	6	9	9	0.474
	N (9)	0	0	0	
Consolidation	Y (7)	4	5	5	< 0.000**
	N (62)	2	4	4	
Cavities	Y (8)	4	5	5	<0.000**
	N (61)	2	4	4	
Lymphadenopathy	Y (5)	0	0	0	0.369
	N (64)	6	9	9	
Pleural effusion	Y (0)	0	0	0	-
	N (69)	6	9	9	

*Significant at 0.05; **Significant at 0.01; Associations were only between TB features of HIV positive patients and positive results by the ExpertMTB/RIF test

In this study the XpertMTB/RIF correctly detected 9 patients as TB positives and 60 as non-TB cases. On the other hand, microscopy detected 5 patients who were true positives, 1 false positive, 59 true negative and 4 false negative (Table 3). Among the 9 patients with TB diagnosis none had rifampicin resistance or multi-drug resistant TB.

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Table 3: General performance results for XpertMTB/RIF and microscopy versus Lowenstein-Jensen culture

Test		LJ positive	LJ negative	Total
Microscopy negative		5	1	6
Microscopy positive		4	59	63
	Total	9	60	69
Xpert positive		9	0	9
Xpert negative		0	60	60
	Total	9	60	69

Key: LJ- Lowenstein-Jensen; Microscopy sensitivity=5/9 (55.6%); XpertMTB/RIF sensitivity=9/9 (100.0%)

In this study, the XpertMTB/RIF had a very high sensitivity and specificity of 100 % than microscopy. In addition, the test had high positive Predictive Value (PPV) of 79.2% and a Negative Predictive Value (NPV) of 98.9%. Among those who were symptomatic for TB, XpertMTB/RIF had a similar sensitivity and specificity as the total study participants (Table 4). Sensitivity and PPV of the XpertMTB/RIF could not be calculated for the asymptomatic patients because none was found to be LJ culture positive.

Table 4: Comparison of XpertMTB/RIF and microscopy as compared to LJ as a gold standard

Performance parameter	Test	Performance value (CI)	TB clinical features Symptomatic (n=60)	Asymptomatic (n=9)
Sensitivity	XpertMTB/RIF	100 (66.4-100.0)	100 (66.3-100.0)	-
	Microscopy	55.6 (21.4-86.3)	55.6 (21.2-86.3)	-
Specificity	XpertMTB/RIF	100 (94.0-100.0)	100 (93.0-100.0)	100 (66.2-100.0)
	Microscopy	98.3 (91.0-100.0)	98.3 (89.6-100.0)	100 (66.2-100.0)
PPV	XpertMTB/RIF	79.2 (39.0-91.5)	76.5 (35.6-90.2)	-
	Microscopy	75.6 (28.9-95.9)	72.4 (25.8-95.2)	-
NPV	XpertMTB/RIF	98.9 (95.0-99.6)	98.9 (95.0-99.6)	100 (66.2-100.0)
	Microscopy	96.0 (92.0-98.0)	95.6 (92.0-98.0)	100 (66.2-100.0)
LR (+)	XpertMTB/RIF	-	-	-
	Microscopy	33.3 (4.4-253.7)	28.3 (3.7-215.0)	-
LR (-)	XpertMTB/RIF	0	0	1
	Microscopy	0.45 (0.22-0.94)	0.45 (0.22-0.94)	1

PPV=Positive Predictive Value; NPV=Negative Predictive Value; LR (+) =Positive Likelihood Ratio; LR (-) = Negative Likelihood Ratio

Microscopy, on the other hand, had a sensitivity of 55.6%, specificity of 98.3%, Positive Predictive Value (PPV) of 75.6% and a Negative Predictive Value (NPV) of 96.0%. Among the symptomatic patients, XpertMTB/RIF had a sensitivity of 55.6%, specificity of 98.0%, PPV of 72.4% and NPV of 95.6%. For the asymptomatic patients, microscopy had a specificity of 100 % and NPV of 100 %. Sensitivity and PPV for LJ culture could not be estimated as there was no asymptomatic patient who had TB by LJ culture.
We show in our results presented in Table 5 that the three diagnostic tests had strong correlations between them. XpertMTB/RIF had the strongest correlation with LJ and microscopy by 1.00 and 0.94 respectively ($p<0.01$). We also analysed data to determine how well XpertMTB/Rif is correlated to haematological parameters. The XpertMTB/RIF results correlated with CD4 count results but not with other haematological parameters. In this case, positivity for XpertMTB/RIF significantly correlated with lower CD4 counts ($p=0.013$). The median CD4 count among those with the XpertMTB/RIF positive and those with XpertMTB/RIF negative were 156 cells/µl and 341 cells/µl, respectively (Figure. 1).

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Table 5: Correlation between diagnostic tests and TB symptoms among HIV positive patients

Diagnostic test		Symptoms	LJ	XpertMTB	Microscopy
Symptoms	Correlation coefficient (CC)	1	0.409*	0.25	0.25
	P-value		0.038	0.218	0.218
	Total	26	26	26	26
LJ	CC		1	0.940**	0.940**
	P-value			0	0
	Total		26	26	26
XpertMTB	CC			1	1.000**
	P-value				
	Total			26	26
Microscopy	CC				1
	P-value				
	Total				26

*Significant at 0.05; **Significant at 0.01. XpertMTB/RIF had strong correlations with both microscopy (CC=1.000) and LJ culture (CC=0.940) *

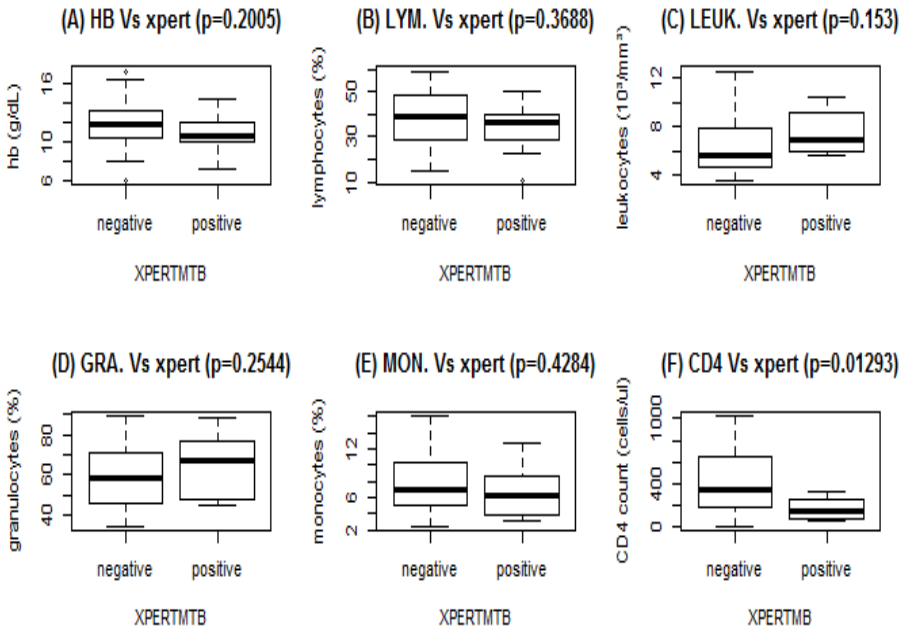

Figure 1: Correlation of XpertMTB/RIF with haematological parameters in HIV positive TB infected
Key: hb= haemoglobin; LYM=lymphocytes; LEUK=leukocytes; GRA=granulocytes; MON=monocytes; CD4= cluster of differentiation 4

Discussion

The current and the previous TB diagnostic algorithms use the WHO TB symptoms screening tool as a part of the screening process. We have found that the majority of the HIV patients presented with at

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least a single TB symptom but had no TB diagnosis. This implies that using clinical TB symptoms alone as screening tool in HIV infected individuals may result into overtreatment of TB (Khan & Starke, 1995; Siddiqi *et al.*, 2003). The consequences for that may include misuse of anti-TB drugs and exposing the patients to unnecessary drug adverse events due to TB treatment. On the other hand, relying on microscopy alone for TB screening in HIV patients has the potential of TB under-diagnosis and miss-diagnosis due to poor microscopy performance (Hawken *et al.*, 2001) as also indicated in this study. This is because microscopy detection threshold is higher; requiring at least 150 bacilli/ mL of sputum which is uncommon among TB infected HIV patients. Our study has found that microscopy combined with the WHO symptoms screening tool has an inferior performance, compared to XpertMTB/RIF combined with the WHO symptoms screening tool.

None of the asymptomatic patients had TB. This finding is contrary to the report by Mtei *et al.* (2005) who reported about one-third of patients diagnosed with TB were asymptomatic. The reason for this difference could be explained by the observation that, most of the participants in our study had used some antibiotics at least within two weeks prior to enrolment into the study, with majority of them on CPT. Moreover, no sputum induction was attempted in our study.

Night sweat was the only symptom predictive of TB diagnosis in our current study. In a study in Vietnam, symptom screening tool had low TB predictive capacity and led to missing of about half of the smear negative HIV PTB cases (Nguyen *et al.*, 2012). This is also an indicator that modern tests like XpertMTB/RIF with much higher accuracy in diagnosing TB are highly needed in this population. Wide variations have been observed on chest radiography among HIV patients. A study in Senegal has reported that such patients present with atypical chest radiographs, and could also present with normal or minimal chest lesions (Aderaye *et al.*, 2004). The variability could be due to differing CD4 levels among these HIV TB co-infected patients. However, another study in Iran has reported contrary observations; that these patients' radiographic presentations are not associated with CD4 count (Bakhshayesh-Karam *et al.*, 2004). These radiographic differences are likely to be due to variability in radiographic reading and interpretations (Balabanova *et al.*, 2005).

Low CD4 count was positively associated with the TB diagnosis. Other studies have found a positive association between positive TB diagnosis among HIV patients and a low CD4 count of less than 200/mm^3 (Nguyen *et al.*, 2012). This could explain the fact that most of these HIV patients have an increased risk of developing TB 20-30 times compared to the general population when their CD4 count is much less (Kwan & Ernst, 2011). This study has found that a subset of HIV patients who have lower CD4 count were likely to turn positive with XpertMTB/RIF.

In this study, the XpertMTB/RIF test showed high specificity and sensitivity. A systematic review, which had included about 27 studies about XpertMTB/RIF performance, found that XpertMTB/RIF had a pooled sensitivity of 79% and a pooled specificity of 92% - 100% among HIV patients (Steingart *et al.*, 2014). In this study, microscopy had sensitivity and a specificity of 55.6% and 98.3%, respectively which implies lower performance compared to XpertMTB/RIF. The high sensitivity of XpertMTB/RIF implies that an additional 44.4% of HIV positive TB infected individuals who would otherwise be missed by microscopy are diagnosed by XpertMTB/RIF test. Similar microscopy performances when compared to XpertMTB/RIF have been reported in previous studies (Boehme *et al.*, 2010; Theron *et al.*, 2011; Ntinginya *et al.*, 2012; Opota *et al.*, 2016).

The probability of having the disease when one tests positive and the probability of not having the disease when one tests negative seems to be slightly higher for XpertMTB/RIF as compared to microscopy. Similar findings have been observed among the symptomatic patients (Ioannidis *et al.*, 2011; Lawn *et al.*, 2011, Opota *et al.*, 2016). For the asymptomatic patients a negative test, from any of the two tests (XpertMTB/RIF or microscopy), seems to exclude the disease, as NPV was 100% (95% CI 66.2% - 100%). This could be attributed to the relatively limited small sample size in our study because some of TB patients might have been asymptomatic as previously reported (Mtei *et al.*, 2005). In this

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aspect, the performance of XpertMTB/RIF was not significantly different from that of microscopy. This was due to the broad confidence intervals resulting from the small sample size in our study. Despite this limitation, our results indicate that XpertMTB/RIF is highly sensitive and specific to detect all culture positive TB cases among HIV patients. We recommend the adoption of XpertMTB/RIF as an early TB diagnosis tool among HIV patients for early detection of TB among HIV patients.

Conflicts of interests

Authors declare no conflict of interests.

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