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EVALUATION OF GENEXPERT FOR THE DIAGNOSIS OF HIV ASSOCIATED TB AND RIFAMPICIN RESISTANCE IN GUYANA

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ABSTRACT: BACKGROUND: In countries like Guyana, where there is a heavy Tuberculosis (TB) burden, delays in the diagnosis of TB can have a detrimental outcome. This concern has led to invention and evaluation of different approaches to TB laboratory diagnosis. In this study, we compared the performance of light-emitting diode (LED) fluorescent microscopy (FM) and GeneXpert for the diagnosis of tuberculosis. METHODS: A retrospective study was conducted between September 2014 and July 2016. Data was extracted from the National Public Health Reference Laboratory Log books. RESULTS: A total of 568 patients were included based on their test results containing data on GeneXpert and LED FM. This study found that GeneXpert and LED FM was able to detect MTB in 162 (29%) and 76 (13%) cases respectively. The detection rate among HIV infected patient was higher with 69% for GeneXpert and 28% for LED FM. The Rifampicin resistance was found 14.2% in PTB patients. CONCLUSION: It can be concluded from this research that the detection rate of GeneXpert is much higher than that of the LED FM when testing for Tuberculosis. Thus, the implementation of GeneXpert can dramatically improve the diagnosis of tuberculosis and ultimately patient outcome.

KEY WORDS: AIDS, LED FM, Rifampicin

INTRODUCTION:

Tuberculosis (TB) has emerged as the most common infectious disease caused by *Mycobacterium tuberculosis* (MTB) and also one of the top 10 causes of death worldwide. WHO reported 10.4 million people developed TB, 1.7 million died from the disease and over 95% of TB deaths occur in low and middle income countries.[1] At the same time, global burden of multidrug-resistant TB (MDR-TB) was estimated to be 480,000 cases leading to estimated 210,000 deaths.[2] The fact that TB is emerging as a multi-drug resistant (MDR) TB is most worrisome, especially to isoniazid (INZ) and rifampicin (RIF).[3] HIV infected people are 20-30 times more likely to develop active TB causing management of TB much complicated. Accurate and rapid diagnosis is very important in earlier treatment initiation and better treatment outcomes. Culture is/was the gold standard in diagnosing TB but requires up to 2 to 8 weeks. [4] Sputum smear

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microscopy is the only and widely accessible technique in most facilities of the developing world. Microscopy technique being inexpensive and requires no complicated equipment, can diagnose the most infectious patients in high prevalence areas.[5] GeneXpert diagnosis can be made within 2 hours and it is widely recommended by WHO as the initial diagnostic test for TB. It is now becoming a big challenge in diagnosing multi-drug resistant and extensively drug-resistant TB as well as HIV-associated TB. Similar to other resource limited countries/ settings, Guyana is also facing a major challenge in treating TB- HIV patients.[6] The objectives of this study is to evaluate for the first time the introduction of GeneXpert in Guyana among HIV positive and negative patients.

METHODS AND METHODS:

This was a laboratory based, retrospective study done at the National Public Health Reference Laboratory (NPHRL). The study evaluated GeneXpert with LED FM in Guyana. Data on all TB test requests between September 2014 and July 2016 were extracted for the study from National Public Health Reference Laboratory. A total of 568 patients were included in this study from various clinics located at Georgetown Public Hospital Cooperation (GPHC) as well as other Regional Hospitals. Patients were selected based on their test results containing data on both GeneXpert MTB/RIF and LED FM. Since this study do not have a gold standard method, a Bayesian approach was used. The agreement between the two testing methods were evaluated by calculating positive and negative agreement indices according to the theory proposed by Graham and Bull (1998). Considering the readings of the two tests reported as either positive or negative, the values a, b, c and d denote the observed frequencies for each possible combination of ratings by tests 1 and 2.

a) the number of samples positive with both tests.

b) the number of samples negative with test 1 and positive with test 2.

c) the number of samples positive with test 1 and negative with test 2.

d) the number of samples negative with both tests.

The proportion of specific agreement for the overall agreement (Po), the positive ratings (Ppos) (the positive agreement index), and for the negative ratings (Pneg) (the negative agreement index) were calculated as follows:

$Po = (a + d) / total$

$Ppos = 2a / 2a + b + c$

$Pneg = 2d / 2d + b + c$

Ethical approval for this study was obtained from the Institutional Review Board (IRB) of the Ministry of Public Health, Guyana.

RESULTS:

Table 1: Overall status of the total patients

Gender (565)	**n (%)**	**95% CI**	**p-value**
Male	182 (32.2)	28.6-36.6	
Female	383 (68.5)	64.5-72.3	
OVERALL			
HIV Status	**n (%)**	**95% CI**	
HIV Positive	42 (38.2)	29.1-47.9	
HIV Negative	68 (61.8)	52.1-70.9	
GeneXpert (571)	**n (%)**	**95% CI**	
D	162 (68.4)	24.7-32.3	
ND	409 (71.6)	67.7-75.3	p≤**0.05**
LED FM (564)			
Neg	488 (85.5)	83.4-89.2	
Pos	76 (13.3)	10.7-16.6	p≤**0.05**

This study included 568 patients recorded at the National Reference Laboratory during the period of September 2014 to July 2016. The mean age of patients was 41.9±14.5 (mean±SD) with minimum-maximum of 1-86 age. A total of 68% (95% CI 52.1-70.9) male and 32% (95% CI 28.6-36.6) females were in the study. 38.2% (95% CI 29.1-47.9) were HIV positive and 61.8% (95% CI 52.1-70.9) HIV negative Table 1.

Table 2: Positive and negative AI between GeneXpert and LED FM

GeneXpert		LED FM		Positive AI (95% CI)	Negative AI (95% CI)	Overall agreement	p-value
		P	N				
O	**P**	76	84	64.4 (57.9-70.5)	90.5 (88.4-92.4)	85.1 (81.9-87.9)	p=0.000
	N	0	404				
HIV (N)	**P**	25	29	63.3 (51.7-73.9)	49.1 (35.6-62.7)	57.4 (44.8-69.3)	p=0.001
	N	0	14				
HIV (P)	**P**	11	16	57.9 (40.8-73.7)	63.6 (47.8-77.6)	60.9 (44.5-75.8)	p=0.015
	N	0	14				

N=Negative, **P**=Positive, **O**=Overall

GeneXpert significantly identified 68.4% (95% CI 24.7-32.3) as determinant and 71.6% (95% CI 67.7-75.3) as non-determinant. On the other hand, LED FM identified a significant 13.3% (95% CI 10.7-16.6) as positive and 85.5 % (95% CI 83.4-89.2) as negative ($p \leq 0.05$). The agreement between the results obtained by LED FM and GeneXpert was estimated by calculating positive and negative agreement indices (Table 1). The indices showed that Overall agreement (OA) and negative agreement indices (NAI) were significantly high than positive agreement indices (PAI) (p=0.000). On the other hand, PAI among HIV negative patients were high than OA and NAI (p=0.001) and among HIV positive patients, NAI was significantly high (p=0.015).

Among HIV negative patients as well as HIV positive patients GeneXpert significantly identified high determinants than LED FM ($p<0.005$) (Table 2 &3).

Table 3: Comparison between GeneXpert and LED FM among HIV positive and HIV negative patients

GeneXpert (68)	HIV Negative						
	n (%)	95% CI	p-value	LED FM (68)	n (%)	95% CI	p-value
D	54 (79.4)	67.9-88.3	0.00	Positive	25 (36.8)	25.4-49.8	0.00
ND	14 (20.6)	11.7-32.1		Negative	43 (63.2)	50.7-74.6	
Intensity (54)							
High	12 (22.2)	12.0-35.6	0.04	+	6 (24.0)	9.4-45.1	0.14
Medium	16 (29.6)	17.9-43.6		++	13 (52.0)	31.3-72.2	
Low	20 (37.0)	24.3-51.3		+++	6 (24.0)	9.4-45.1	
Very Low	6 (11.1)	4.2-22.6					
Rifampicin							
Determinant	6 (11.1)	4.2-22.6	0.00				
Non determin	47 (87.	75.1-					

ant	0)	94.9					
Indeterminant	1 (1.9)	0.04-9.8					
GeneXpert (42)	**HIV Positive**						
D	28 (66.7)	50.5-80.4	0.00	Positive	11 (26.8)	14.2-42.9	0.00
ND	14 (33.3)	19.6-49.5		Negative	30 (73.2)	57.1-85.8	
Intensity (28)							
High	5 (17.9)	6.1-36.7	0.50	+	1 (9.0)	0.2-41.3	0.02
Medium	7 (25.0)	107-449		++	8 (72.7)	39.0-93.9	
Low	8 (28.6)	13.2-48.7		+++	2 (18.2)	2.3-51.7	
Very Low	8 (28.6)	13.2-48.7					
Rifampicin							
Determinant	3 (10.7)	2.3-28.2	0.00				
Non determinant	25 (89.3)	71.8-97.7					

DISCUSSION:

Tuberculosis always remains a major health problem in the world. TB along with HIV has increased the burden on TB infected population and health care sectors. In addition to TB, TB-HIV, the incidence of drug-resistant TB has presented new threats to the existing health sector problem of TB/HIV co-infection. Multidrug-resistant tuberculosis (MDR-TB) is defined as TB caused by strains of *M. tuberculosis* that are resistant to at least isoniazid and RIF.[7] Although RIF resistance is rare but 90% of RIF resistant isolates also exhibit resistance to isoniazid. Therefore it is suggested that the detection of RIF resistance may act as an important tool for MDR *M. tuberculosis*.[8] GeneXpert provides an accurate and rapid detection of MDR-TB and as such rapid initiation of treatment.[9]

This study confirms that GeneXpert is a rapid and suitable method for the diagnosis of TB in resource limited countries like Guyana. GeneXpert detected 68.4% of TB than LED FM which detected 13.3%. This result correlates to study conducted in Tanzia which favored GeneXpert having a detection rate of 10%.[10] A similar study detected a 9.7% detection rate in a multi-center randomized trial in countries like Zimbabwe, South Africa, Zambia and Tanzia.[11] From this study a total 16.6% co-infected HIV-TB patients was detected using GeneXpert MTB/RIF Assay as compared to 6.8% by LED FM. These percentages are much higher in another study [10] which had a detection rate of 23.6% as compared to 14.2 % for LED FM. Also a study carried out in South Africa and Ethopia among HIV infected individuals showed that GeneXpert had a detection rate of 45% more than LED FM. [12]A major factor is the difference in population of study in the latter study as compared to the present study.

This study also shows the association of the development of active TB with HIV. As it pertains to non-HIV patients, GeneXpert detected 69% cases as compared to 31% cases by LED FM. This is evidence that GeneXpert is useful in detecting PTB regardless of HIV serotype.

The limitation as mentioned earlier was that culture was not included to rule out the possibility of false positive results. The usefulness of

GeneXpert to detect RIF resistance as significant marker in MDR TB was recommended by WHO. In this present study a total of 14.2% of rifampicin resistance was detected. This percentage maybe high due to the fact that data was collected over a period of approximately 2 years. Steingart *et al*. emphasized that GeneXpert can be used as an initial diagnostic test for TB detection and RIF resistance in patients suspected of having TB, MDR-TB or HIV-associated TB.[13]

CONCLUSIONS:

It can be concluded that GeneXpert improved the detection of TB cases and also outperformed LED FM. The results of this study indicate that the implementation of the GeneXpert assay could dramatically improve the diagnosis of tuberculosis especially among HIV patients.

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