Application of WHO Symptom Screening Approach by Non Clinicians in the Diagnosis of Pulmonary Tuberculosis among HIV Positive Individuals in the University of Uyo Teaching Hospital, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author AME designed the study. Authors AME and UEE performed the Statistical analysis. Author AME wrote the protocol and the first draft of the manuscript while authors IPO and AEO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Pulmonary Tuberculosis (PTB) is a major opportunistic infection and principal cause of mortality among HIV positive individuals. Its screening among this population ensures early detection, prompt treatment and reduction of mortality. This study aimed to assess the burden of hospital PTB initially identified by cough monitors , the type of confirmed PTB and the sensitivity and specificity of the four-symptom TB screening approach.

Study Design: A descriptive cross- sectional design was used.

Place And Duration of Study: The study was conducted at the Anti-Retroviral Therapy (ART) out-patient clinic of a tertiary hospital in southern Nigeria over a 9 months period between January to September, 2020.

Methodology: The medical records of adults diagnosed with HIV who were identified by non-clinicians to have at least one of the four symptoms (cough, weight loss, night sweats and fever) prescribed by WHO for PTB screening on attendance at the ART clinic of the University of Uyo Teaching Hospital, Uyo, Nigeria were reviewed. Data were analyzed using Stata version 13.0 Level of significance was set at $p < .05$

Results: Sixty-nine (69) out of 529 (13.0%) patients who attended the ART clinic were identified to have at least one of the four symptoms. The common PTB symptoms were cough (62, 89.9%), fever (49, 71.0%), weight loss (40, 58%) and night sweats (29, 42%). Nine (13.0%) respondents were confirmed to have rifampicin resistant PTB from Gene Xpert test. The four–symptom TB screening test had a sensitivity of 11.1%, specificity of 98.3% and a positive predictive value of 50%.

Conclusion: The use of the WHO four-symptom tuberculosis screening tool by non-clinicians, though with low sensitivity in this study, was useful in identifying drug-resistant tuberculosis in HIV positive patients when combined with Gene Xpert MTB/RIF assay.

Keywords: Tuberculosis screening; WHO four symptom approach; non-clinicians; HIV positive; Uyo.

1. INTRODUCTION

Tuberculosis is a leading cause of mortality among persons living with Human Immunodeficiency Virus (HIV), especially in the African and Asian regions, which together account for 75% of tuberculosis (TB) cases associated with HIV infection globally [1]. In many African countries, HIV infection, has been associated with above two-thirds of identified active tuberculosis cases [2]. Nigeria has been ranked sixth among the 30 high-burden TB countries of the world. She is also one of the high burden countries with TB/HIV co-infection and multidrug-resistant TB (MDR-TB) [3]. Nigeria also has an adult HIV prevalence of 1.4%, and Akwa Ibom state in southern Nigeria has the highest prevalence in the country of 5.5% [4]. While HIV is known to increase the burden of PTB, PTB is a leading cause of death among HIV positive individuals [5]. This buttresses the need for routine screening for tuberculosis in all HIV positive individuals including newly diagnosed clients.

In order to rule out the presence of a current cough, weight loss, fever, or night sweat before starting tuberculosis preventive therapy (TPT), the World Health Organization in 2011 advised

that adolescents and adults with HIV be screened for PTB using a four-symptom-based approach [6]. The 2011 WHO tools for screening of TB and TPT in HIV positive people were approved and employed in Cambodia and South Africa. A systematic review and meta-analysis in over 8000 antiretroviral therapy (ART)-naïve persons with HIV revealed a sensitivity and specificity of 78.9% and 49.6% respectively which informed the WHO recommendation [7]. The presence of any of the symptoms require further review and investigations to exclude active tuberculosis which if untreated in newly enrolled HIV positive individuals on ART, could trigger immune reconstitution inflammatory syndrome (IRIS) [8]. Contrariwise, a patient with active tuberculosis that is not screened out and commenced on tuberculosis preventive therapy is at risk of developing drug-resistant tuberculosis.

Further investigation in patients with any of the four symptoms is done using Gene Xpert MTB/RIF assay. The Gene Xpert MTB/RIF assay is rapid and has a better sensitivity than smear microscopy [9]. Unlike smear microscopy, Gene Xpert MTB/RIF assay enables the detection of rifampicin-resistant tuberculosis. Over nine-tenth of cases of rifampicin resistance have been

associated with an accompanying isoniazid resistance; hence, rifampicin resistance is used as a surrogate marker for multi-drug resistance tuberculosis (MDR-TB) [10].

The symptom screening approach could be used by lay persons (cough monitors) in active case finding of TB in both community and clinical settings and has been reported to produce rewarding results [11-14]. A study in Kenya reported that 33% of annual hospital TB burden were initially identified by cough monitors from selected outpatient areas, [15] and 4-24% contribution in a similar Nigerian study [16].

This study aimed to assess the burden of hospital TB initially identified by cough monitors in an ART out-patient clinic , the type of confirmed TB among them and the sensitivity and specificity of the four-symptom TB screening approach.

2. MATERIALS AND METHODS

2.1 Study Site

The study was conducted at the Anti-retroviral therapy (ART) clinic of the University of Uyo Teaching Hospital (UUTH), Uyo, Akwa Ibom state, southern Nigeria. The UUTH is the only federally owned tertiary health facility in Akwa Ibom state, with an estimated 6 million people. It is one of the many HIV comprehensive treatment centres in Akwa Ibom state and a referral centre for primary and secondary health facilities in and out of the state. The UUTH ART clinic is supported by FHI360 with funding from the United States Agency for International Development (USAID). At the ART clinic, there is screening for opportunistic infections (OIs) including PTB for HIV infected persons already on ARTs and newly enrolled HIV infected persons. For identification of PTB, clinical screening using the WHO 4 symptom screening approach is carried out. This is mainly done by non-clinicians at the clinic with further investigation by physicians of clients having any positive symptom for PTB using the Gene Xpert MTB/RIF assay technique, chest x-ray and other techniques. Anti-TB medications are commenced by clinicians for HIV positive individuals diagnosed with PTB and Tuberculosis Preventive Therapy (TPT) are administered to those without any of the four TB screening symptoms. Other services offered include provision of ART and follow-up care for HIV infected individuals.

2.2 Study Design

The study used a retrospective descriptive cross-sectional design to review data of HIV infected individuals who were identified to have at least one of the four symptoms (cough, weight loss, night sweats and fever) prescribed by WHO for TB screening on attendance at the adult ART clinic of the University of Uyo teaching hospital over a nine-month period between January to September, 2020.

2.3 Data Collection and Analysis

Socio-demographic features such as age, gender, level of education, WHO clinical staging, history of TB, presence of any of the symptoms using the four-symptom approach were obtained from the folders of patients. Results of Gene Xpert tests for MTB/RIF assay to confirm tuberculosis infection and the presence or absence of rifampicin resistance from sputum samples of HIV infected individuals having any of the symptoms (presumed TB patients) were also obtained from the patients' records. Anti-tuberculosis treatment was commenced for all patients confirmed to have PTB. For the newly enrolled HIV positive individuals, anti-retroviral therapy was commenced after patients had been on anti-tuberculosis drugs for 2 weeks. Rifampicin resistance was classified as high-level resistance (Isoniazid resistance with inhA and KAT G mutation), moderate level resistance (isoniazid resistance with KatGmutation) and low-level resistance (isoniazid resistance with inhA mutation [17].

Data was analysed using Stata version 13.0. Categorical variables were summarized using frequencies and percentages. Chi square test was used to determine any association between categorical variables at a p-value <0.05.

3. RESULTS AND DISCUSSION

Sixty-nine (69) out of the 529 (13.0%) HIV infected individuals who attended the clinic over the review period and were identified to have at least one of the symptoms were recruited. The mean (standard deviation) age of the respondents was 40.8 (12.3) years. Majority of the respondents were females (47, 68.1%). About half of the respondents (35, 50.7%) attained secondary education. More than half of the respondents were artisans (56, 81.2%), and in WHO clinical stage 1(50, 72.5%).Only one respondent (1.4%) had a past history of TB. (Table 1).

Table 1. Socio-demographic and Clinical Characteristics of Respondents (n=69)

Variables	Frequency	Percentage
Age		
Less than 41	41	59.4
41 and above	28	40.6
Mean +/-Standard Deviation	40.8+/-12.3	
Sex		
Male	22	31.9
Female	47	68.1
Education Level		
Primary	20	29.0
Secondary	35	50.7
Tertiary	14	20.3
Occupation		
Civil servants	4	5.8
Artisans	56	81.2
Students	9	13.0
Unemployed	1	1.4
WHO Clinical Staging		
1	50	72.5
2	7	10.1
3	11	15.9
4	1	1.5
Ever Had TB		
Yes	1	1.4
No	68	98.6

The two most common symptoms of TB manifested by respondents were cough (62, 89.9%) and fever (49, 71.0%) (Table 2).

Nine out of 69 (13.0% 95%CI: 6.8-23.6%) respondents were confirmed to have PTB from Gene Xpert MTB/RIF test, and all nine had rifampicin resistance with an equal proportion having high and moderate level of resistance to rifampicin (44.4% each) (Table 3).

The respondents confirmed of PTB using Gene xpert test had cough (88.9%) fever and weight loss (77.8% each) as their major symptoms. Five (55.6%) were in WHO clinical HIV staging 1 and none were in stage 4 (Table 4).

The sensitivity of the four-symptom TB screening test was 11.1%, with a specificity of 98.3% and a positive predictive value of 50%.(Table 5).

Table 2. Common PTB Symptoms among Respondents

Variables	Frequency	Percentage
Cough		
Yes	62	89.9
No	7	10.1
Fever		
Yes	49	71.0
No	20	29.0
Weight Loss		
Yes	40	58.0
No	29	42.0
Night Sweats		
Yes	29	42.0
No	40	58.0

Table 3. TB Results of Respondents using Gene Xpert MTB/RIF Test

Variable	Frequency	Percentage	95% Confidence Interval
Gene Xpert Results			
Positive	9	13.0	6.8-23.6
Negative	60	87.0	76.5-93.2
Rif Resistance Test (n=9)			
Mild	1	11.1	
Medium	4	44.4	
High	4	44.4	

Rif=Rifampicin

Table 4. Clinical Characteristics of Respondents with Positive Gene Xpert Test Results

Variable	Frequency	Percentage
Cough		
Yes	8	88.9
No	1	11.1
Fever		
Yes	7	77.8
No	2	22.2
Weight Loss		
Yes	7	77.8
No	2	22.2
Night Sweats		
Yes	5	55.6
No	4	44.4
WHO Clinical staging		
1	5	55.6
2	1	11.1
3	3	33.3
4	0	0.0

Table 5. Accuracy and Clinical Relevance of Screening Tool in diagnosing Tuberculosis

Characteristics	Percentage (%)	95% Confidence Interval
Prevalence	13.0	5.1-21.0
Sensitivity	11.1	3.7-18.5
Specificity	98.3	95.3-101.4
Positive Predictive Value	50.0	38.2-61.8
Negative Predictive Value	88.1	80.4-95.7

3.1 Discussion

The WHO recommended 4-symptom screening tool for TB used by lay persons helped in identifying 13% of the clinic TB burden over a nine-month period. This finding agrees with the 2-24% reported in a previous Nigerian study on the usefulness of lay persons in active case finding of TB in a health facility [16] but lower than reports from a similar study in Kenya with 33% [15]. The small proportion of TB cases identified in this study could be due to our relatively small sample size and the fact that most of our respondents were already on highly active anti-retroviral therapy (HAART). The use of this four-symptom screening approach by lay persons (cough monitors or ward cough officers) in active case finding of TB in both community and clinical settings has been reported to produce rewarding results [11-14]. This study identified nine confirmed TB cases, with all being rifampicin resistant. With rifampicin resistance detection from Gene Xpert MTB/RIF assay being a surrogate marker for multi-drug resistant tuberculosis [10], it is possible that some of the HIV positive individuals being treated for latent tuberculosis with isoniazid may already have had isoniazid resistance given the low sensitivity of

the screening tool. The use of urinary lipoarabinomanam for HIV positive individuals with advanced HIV disease (WHO Stage 3,4) has served to increase tuberculosis case detection in that cohort of patients [18]. Tuberculosis can occur at any stage of HIV disease though decline in CD4+ cell count has been associated with increasing incidence of tuberculosis [19]. Interestingly, most of our study subjects in both the suspected tuberculosis and subsequently confirmed tuberculosis cohorts were in WHO clinical stages 1 and 2 where urinary lipoarabinomannan is currently not used. Urinary lipoarabinomannan is a more sensitive test hence its use in HIV stages 3 and 4 because of their very low immunity which stops them from mounting an immune response thus making it more difficult for more conventional test to detect TB in these sub groups. It is therefore possible that as a more sensitive/specific test, it can increase the case detection of TB even in HIV stages 1&2. This emphasizes the need for intense case finding of TB among both HAART-naïve and HAART-experienced patients to prevent the development of rifampicin-resistant TB.

The screening tool had a low sensitivity of 11%, a high specificity (98.3%) and an average positive predictive value. The sensitivity of the symptom screening tool varies in the literature. A study among pregnant women living with HIV in South Africa found a symptom screening sensitivity of 28% from 226 suspected tuberculosis patients [20]. This was attributed to physiological changes in pregnancy that may have masked tuberculosis symptoms. Other studies in South Africa not involving pregnant women had also noted low sensitivity. These studies include a community survey (sensitivity of 33%), [21] and symptom screening of gold miners (sensitivity of 29%) [22]. Some other studies reported significantly higher sensitivities including several of the studies in the WHO meta-analyses [23-26]. The heterogeneity in the sensitivities of the four-part symptom screen has been noted and the reason is still not clear [20]. Studying a mixed cohort of both HAART-naïve and HAART-experienced patients may be responsible for the low sensitivity in our study. In addition, these four symptoms are also common to other diseases such as HIV even without TB. The low sensitivity of the tool may also be attributed to the fact that the review was carried out during the COVID-19 period where cough was also a major presenting symptom.

The sensitivity of the symptom screening tool could be improved by addition of a chest radiograph [27]. Where possible, this could be helpful, especially for HV positive people who have a 5–15% annual risk of developing tuberculosis [28]. The cost and logistical difficulties of using a chest radiograph as an extra screening tool for all patients will be its limitation [29].

The inclusion of extra symptoms to the screening tool is another strategy that has been proposed to boost the sensitivity of the tool. Data from the 2010 Zambia South Africa Tuberculosis and HIV/AIDS Reduction (ZAMSTAR) survey were used in the analysis to assess this strategy [27]. The sensitivity of the screening tool increased from less than 25% from the use of only cough of at least 2 weeks duration to 38% with the addition of any three of six symptoms of tuberculosis (cough of less than 2 weeks, night sweats, weight loss, fever, chest pain and shortness of breath) or 2 or more of cough less than 2 weeks, night sweats and weight loss. In western Kenya, a survey reported a sensitivity of 41% for cough of at least 2 weeks and 82% for any symptom of tuberculosis (cough, haemoptysis, fever, night sweats and weight loss, of any duration or severity) among HIV negative individuals and 69% and 96% respectively among HIV positive individuals [30]. There is need to compare the sensitivities from the additional symptoms screening tools with the WHO four-symptom screening tool in order to determine if there will be a significant change in sensitivity. However, from our study, cough of any duration was the most significant symptom, being present in about nine-tenths of the persons that were both suspected and eventually confirmed to have tuberculosis.

The cost effectiveness and ease of deployment of the four-symptom tool, justifies its use by non-clinicians for the screening of TB until a more sensitive screening tool is discovered. Cost-effectiveness and ease of deployment by laypersons in individuals irrespective of their HIV status, must be taken into consideration in the development of new highly sensitive TB screening tools to ensure improved TB case detections in both the community and hospital settings. High school graduates trained in the symptomatic recognition of tuberculosis suspects and assisted sputum production in a Kenyan referral hospital contributed to the detection of 33% of the referral hospital's annual tuberculosis case burden [15]. The use of laypersons in

community settings through household surveys also showed rewarding results in improving active tuberculosis case detection [11-14].

The major strength of our study is the demonstration of the effectiveness of the use of symptom-based screening tool in increasing drug-resistant tuberculosis detection when combined with Gene Xpert MTB/RIF assay. A limitation of our study was the small sample size of the tuberculosis suspects recruited over a 9-month period from a single site. In addition, the review period covered the COVID-19 pandemic era where attendances at health facilities were reduced. There is therefore a need for a multi-centre study in Nigeria with accompanying larger number of participants to make the findings more generalizable. Furthermore, the screening tool relied on the symptom-complex of cough, fever, night sweat and weight loss, thus increasing the possibility of missed opportunities for patients with extrapulmonary tuberculosis or pulmonary tuberculosis patients who had difficulty producing sputum.

4. CONCLUSION

In conclusion, the WHO four-symptom screening though having a low sensitivity in tuberculosis case detection, can serve as a means of identifying drug-resistant tuberculosis patients in combination with Gene Xpert MTB/RIF assay. There is need for the development of more sensitive and cost effective screening techniques that can be deployed by individuals without specialized trainings in-order to address the problem of diagnosis of tuberculosis in HIV infected individuals in resource-constrained settings.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval was obtained from the institutional health research ethical committee of the University of Uyo Teaching Hospital.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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