



Determinants of sputum ordering for tuberculosis diagnosis in people living with HIV in the Greater Accra Region, Ghana

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Abstract

Background: This study assessed factors associated with sputum ordering for tuberculosis (TB) diagnosis in people living with HIV (PLHIV) who were screened positive for TB in three hospitals providing HIV care and treatment services in the Greater Accra region of Ghana.

Objective: This study assessed the factors associated with sputum ordering in PLHIV with a positive TB symptom screen test.

Methods: A mixed-method cross-sectional study was undertaken at three hospitals providing HIV care and treatment services in the Greater Accra region of Ghana. The study involved a review of 400 patients' charts and in-depth interviews with health workers involved in the care and treatment of PLHIV. Bivariate analysis using a Chi-square test and Logistic regression for multivariate analysis were used to establish factors associated with sputum ordering. Factors having a $p \leq 0.05$ were considered significantly associated with sputum ordering. Inductive thematic analysis was used to explain the associated factors.

Results: Of the 400 charts reviewed, 67.7% were female patients with a median age of 39 (IQR 31 – 49). TB screening was recorded in 78% ($n = 312/400$, 95% CI: 73.6 – 82.0) of the patients, of whom ninety-two (92) patients had a positive TB screen test. Only 57.6% ($n = 53$) who had a positive screen test had sputum ordered for further TB testing. In the multivariate analysis, the patient's general appearance was described as abnormal (OR = 3.05, $p = 0.036$), having more than one TB symptom (OR = 3.42, $p = 0.028$) and presence of an alternative presumptive diagnosis (OR = 0.34, $p = 0.023$) were associated with having a sputum test ordered. High patient numbers, the inability to produce sputum, the unwillingness of moderately sick patients to provide sputum and the cost associated with chest X-rays were perceived as the challenges to further testing for TB.

Conclusion: Almost half of PLHIV with a positive TB screen test did not have a sputum test documented. This calls for instituting measures to address the barriers to TB screening among people living with HIV/AIDS for effective TB and HIV comorbidity management.

Keywords: Tuberculosis, Screening, HIV, PLHIV, sputum, Case finding, Ghana

INTRODUCTION

An estimated 10 million people develop Tuberculosis (TB) each year, a number that has remained stable [1-3]. Tuberculosis is the top-most cause of mortality from a single infectious agent, ranking above Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) [2]. In 2018, an estimated 1.2 million TB deaths occurred in HIV-uninfected people and 251,000 deaths in HIV-infected people [1]. This high mortality of TB is unacceptable and

underscores the importance of early TB detection and treatment, especially in people living with HIV (PLHIV) [4]. The CD4-T lymphocyte cells help to coordinate the immune response to fight infection [5]. When these cells are destroyed, the cellular immune function becomes impaired hence increasing the risk of the individual acquiring many infections [6]. HIV is the most recognized risk factor for the progression from TB infection to active TB disease [4]. The risk of developing active TB disease is 20 to 37 times greater in HIV-infected persons than in HIV-uninfected persons [7]. In most high-burden TB/HIV countries, including Ghana, many of the estimated new TB cases are un-notifiable [8]. Only 64% of the estimated 10 million new TB cases in HIV-uninfected persons and

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51% of the estimated 0.9 million new TB cases in HIV-infected persons were reported in 2017 [2]. The World Health Organization (WHO) notes that this may be due to underreporting or under-diagnosis of TB; either patients do not or cannot access health care, or they are missed when they finally do access healthcare [1].

The World Health Organization recommends systematic screening of TB for all PLHIV and other most at-risk populations at every clinic visit [9]. It is also recommended that further evaluation should be made with Gene-Xpert-MTB/RIF or Acid-Fast Bacillus (AFB) microscopy for PLHIV who are found to be TB positive on a screening test where the former is not available [10]. Adults and adolescents infected with HIV are considered to have a positive TB screen test if they have any of the four symptoms of current cough, fever, weight loss or night sweats [11]. Children at least one year of age living with HIV were considered to have a positive TB screen test if they have any of the four symptoms; cough, fever, poor weight gain and history of contact with a TB patient [12]. Whereas this recommendation was made for TB screening among PLHIV, only a small proportion of PLHIV with a positive TB symptom screen test are referred for sputum examination for TB detection, even in high-burden TB/HIV settings [13]. For example, only 13.2%, 8%, and 37.1% of HIV-infected patients with a positive TB screen test had a sputum order documented for gene expert examination or chest x-ray for further active TB detection in Uganda, Kenya and Tanzania, respectively [14-16]. In addition, only 54.9% of HIV-infected patients with a positive TB symptom screen test were referred for sputum smear examination in Uganda [14].

Ghana is among the top 30 countries with a high TB/HIV burden [3]. In 2018, Ghana's estimated TB incidence rate was 148 per 100,000 population, resulting in an estimated 44,000 incidence of TB [1]. The incidence rate of TB among PLHIV was 29 per 100,000 translating into 8,600 TB cases among PLHIV [17]. More men than women developed TB in the same year; 26,000 vs 18,000 new TB cases [18]. In the same period, there were 11,000 deaths due to TB among HIV-negative patients and 4,800 deaths due to TB among PLHIV [2]. Of the estimated 44,000 new TB cases in 2018, only 32.3% ($n = 14,289$) were reported [1]. This low TB case detection negates all efforts to end TB by the year 2050. The low TB detection in both HIV-infected and uninfected people has been singled out as one of the challenges affecting TB control in Ghana [20]. This low TB case detection may partly be attributed to an incomplete evaluation of patients with a positive TB screen test to determine their definitive TB status. Only 27.5% of PLHIV with a positive TB symptom screen test had a documented sputum order for Acid Fast Bacillus (AFB) smear microscopy [21]. The proportion only increased slightly to 50.7% after an audit and feedback intervention [22]. This study assessed the factors

associated with sputum ordering in PLHIV with a positive TB symptom screen test in the Greater Accra region of Ghana.

MATERIALS AND METHODS

Study design and sites

The study was conducted in three purposively selected (based on HIV-infected patients registered) public hospitals providing HIV care and treatment in the Greater Accra region. These were the Greater Accra Regional Hospital, Tema General Hospital and La General Hospital. Greater Accra is one of the sixteen administrative regions of Ghana, occupying a total land surface of 3,254 km². With a total population of 4,010,054 in 2010, it is Ghana's second most populated region [23]. The study population was PLHIV, who came to the hospital between April and June 2019, and healthcare providers were involved in screening and evaluating TB in PLHIV.

Study Design

We conducted a concurrent mixed-method study. The quantitative component involved a cross-sectional retrospective chart review in which records of HIV-infected patients who came for health care between April and June 2019 were reviewed. The quarter of April to June was purposively selected so that the study results represent current practice. The qualitative component involved in-depth interviews with the healthcare providers involved in the screening and testing for TB in PLHIV.

Sample size and patient population

The sample size for the quantitative component was calculated using the Leslie Kish 1994 formula: $n = \frac{Z^2PQ}{\delta^2}$

Where Z is the normal standard deviation at a 95% confidence level; P is the estimated prevalence of the problem under investigation; $Q = 1 - P$; δ is the precision [24]. Using $P = 0.507$ [25] and a precision of 5% gave a minimum sample of 385. At each hospital, charts of patients who came for health care between April and June 2019 were obtained. Using disproportionate random sampling, 133 patient charts were selected at each study site. Healthcare workers for the in-depth interviews were purposively selected depending on their role in screening and evaluating PLHIV for TB.

Data collection

Quantitative data were analyzed using Stata version 15.0 (Stata Corporation, College Station, TX, USA) [26]. Descriptive characteristics of the categorical variables were summarized using frequencies, proportions and median for continuous variables. For bivariate analysis, the Chi-square test was used to determine the association between the outcome variable and the various independent variables. Fisher's exact test was used when the expected frequencies were < 5 . Multivariate logistic regression was used to determine factors independently associated with

sputum ordering. The backward elimination method was used to construct the multiple logistic regression model using a threshold of 0.2 to eliminate variables from the model. The likelihood ratio test for nested models was used to test the null hypothesis that the automatically selected multiple logistic regression model was a better fit for the data than the manually constructed model. Variables with a $p \leq 0.05$ were considered significant. Inductive thematic analysis was used for qualitative data to determine emerging themes. The main themes were presented with sub-themes. The qualitative data presentation was backed with quotes that resonated well with the main themes and sub-themes.

RESULTS

Baseline and Clinical Characteristics of Patients

In total, 400 patients' charts were reviewed. Of these, 67.8% (n = 271) were females, 29.7% (n = 129) were aged 35 - 44 years and 79.8% (n = 319) were continuing clients (Table 1).

Prevalence of TB symptoms, TB Screening and Sputum Ordering

Of the 400 patients, 78.0% (n = 312, 95% CI 73.6, 82.0) were screened for TB. Of these 312 patients who were screened for TB, 29.5% (n = 92) had a positive TB screen test, and 57.6% (n = 53) had a documented sputum test. (Figure 1). Of the 92 patients with a positive TB screen test, 27.2% (n = 25) were within 45–54 years, 52.2% (n = 48) were female, and 45.6% (n = 42) were new patients (Table 2). The most common TB symptom was cough. (Figure 2).

Factors Associated with Sputum Ordering in Patients with a positive TB Screen Test

In the bivariate analysis, only patients' general appearance on the last visit was documented as abnormal ($X^2 = 9.45, p = 0.002$) with more than one TB symptom ($X^2 = 8.17, p = 0.004$) and the presence of a presumptive alternative diagnosis ($X^2 = 8.99, p = 0.003$), were significantly associated with sputum ordering for patients with a

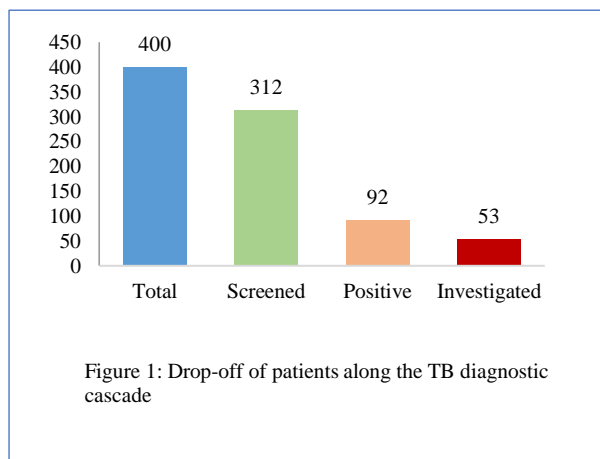


Figure 1: Drop-off of patients along the TB diagnostic cascade

positive TB screen test (Table 2).

Univariable logistic regression analysis results

Before adjustment, patients with an abnormal appearance (ORu, 4.40; 95% CI, 1.65 – 11.72) and those with more than one symptom (ORu, 4.22; 95% CI, 1.51 – 11.76), were significantly associated with higher odds of sputum order. Patients with an abnormal appearance or having more than one symptom were over four times more likely to have a sputum order than those whose general appearance was normal and those having only one TB symptom. However, the sputum order was reduced by 73% (OR, 0.27; 95% CI, 0.11–0.65) for patients with a documented alternative diagnosis compared to those with no alternative diagnosis (Table 2).

Multivariable logistic regression analysis results

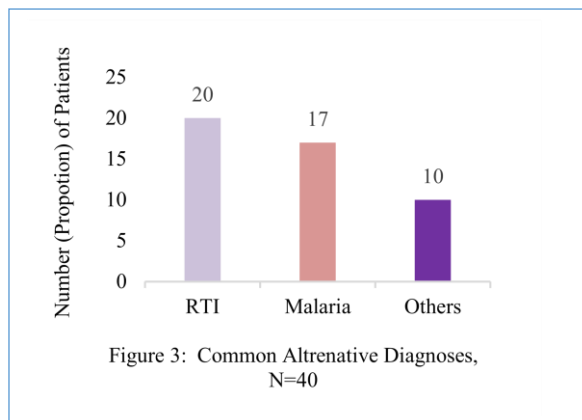
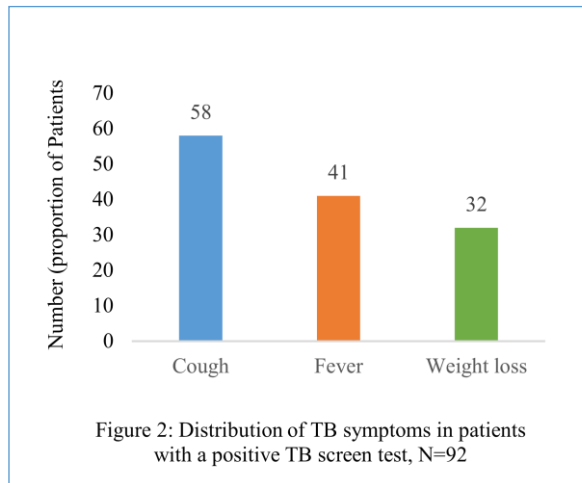
The odds of sputum ordering in patients whose general appearance was noted to be abnormal (ORa = 3.05; 95% CI, 1.07–1.67, $p = 0.036$) were 3.05 times the odds of sputum ordering in patients whose condition was described as normal. Similarly, patients with more than one symptom were over three times more likely to have a sputum order compared to those with one symptom (ORa = 3.42; 95% CI, 1.15 – 10.21, $p = 0.028$) were significantly associated with sputum ordering for patients with a positive TB screening test. The odds of sputum ordering in patients with an alternative presumptive diagnosis (ORa=0.36; 95% CI, 0.13–0.86, $p = 0.023$) were reduced by 66% compared to those with no such diagnosis, and this was significant (Table 2).

Common alternative diagnoses

The most common alternative diagnoses documented in the client folders were malaria and respiratory tract infections (RTI). Of the forty (40) patients that had

Table 1. Baseline and clinical characteristics of patients

Characteristic	No. (%)
Age	
<15	19(4.8)
15-24	15 (3.8)
25-34	102 (25.5)
35-44	119 (29.7)
45-54	90 (22.5)
≥55	55 (13.7)
Sex	
Female	271 (67.7)
Male	129 (32.3)
Visit type	
New	81 (20.2)
Continuing	319 (79.8)
WHO stage at enrollment	
I	126(31.5)
II	134(33.5)
III	107 (26.7)
IV	33(8.3)



alternative diagnoses documented, half of them were reported to have RTI. The other diagnoses included meningitis, liver disease and weight loss (figure 3).

Prevalence of chest x-ray uptake

Additionally, it may be essential to embrace the use of chest x-rays (CXR) as a screening tool for TB among PLHIV. Investigation of patients with CXR was very low, as only 3.3% ($n = 3/92$) of the patients with a positive screen test had a CXR order documented.

Barriers to sputum ordering and chest x-ray use

We further conducted qualitative interviews to seek barriers hindering HIV-infected patients' screening for TB and further testing those with a positive TB screening test. The main reasons given are presented under three broad themes based on the health system building blocks and one at the patient's level. These include; human resources for health-related factors, health financing factors, as well as leadership and governance. The Interviews were carried out with six (6) health workers who were all female.

High workload due to many patient numbers

One of the barriers identified by the health workers for failing to order sputum to conduct further assessment of

TB among PLHIV who had had a positive TB screening was due to the high patient numbers resulting in a high workload. For example, one interviewee said: "The number of patients in this clinic is high. This sometimes hinders the provision of quality services, including TB screening and evaluation (Nurse, La General Hospital)". Another health worker said: "The clients here are too many. We cannot do much. As you know, like elsewhere in Africa, the doctor/nurse to patient ratio is very low, increasing the workload and leading to failure to perform some key tasks. However, we try to ensure that all patients get tested for TB at least twice a year." (Nurse, La General Hospital)

Infrequent training to improve health workers

The interviewees noted inadequate staff training on TB diagnosis and management among HIV/AIDS patients. They said that the frequency of the training was low, especially on the change of policy on TB and management for PLHIV. Newly qualified health workers were particularly singled out for not being well trained in TB management and were not helped by the lack of on-the-job training. This affected the quality of care, especially for workers, since health workers were not kept abreast with the changes in the TB treatment policies that had been brought on board. The following quotations represent the issue of low training frequency. "Once in a blue moon, we have workshops. The (DOTS) coordinator organizes training once in a blue moon" (Physician Assistant, Tema General Hospital). Another interviewee noted the limited knowledge among trainee students and newly qualified health workers who sometimes participated in the treatment of patients. This was pointed out as an additional reason for the need to have frequent job-based training to fill knowledge gaps among these health workers. "Training are few here. We have not had any in the last three months. They should increase the number of training. Aside from the staff, there are sometimes students assisting whose knowledge may be limited" (Physician Assistant).

The cost associated with a chest x-ray

The chest x-ray is one of the tests recommended as part of the workup of PLHIV. However, its use was very low. A common view among interviewees was that the cost associated with the x-ray services was the main barrier to its use. One health worker commented: "Unlike sputum, a chest x-ray is not free. When the patients do x-rays, they have to pay. This limits the uptake of the service as part of TB workup" (Nurse). Other responses to this question included that when patients had accepted to have a chest X-ray done where its cost was to be met under the national health insurance scheme for NHIS subscribed members, the fact that they were to pay for the report generated out-of-pocket became a detriment to accepting the investigation to be carried out. Talking about this issue, one interviewee said: "Although the chest X-ray is covered under the National Health Insurance Scheme

(NHIS), patients have to pay money for the radiologist report to accompany the x-ray. This also makes the x-rays services unaffordable for most of the patients." (Nurse)

Lack of integration of TB services into HIV care

Good practice necessitates that both TB and HIV services for PLHIV should be integrated, where services for both diseases are handled in the same clinic under the same roof. This is necessary to avoid patients dropping out of the cascade of care because of having to move to different places for the services. In one of the hospitals in this study, the interviewees expressed an existing lack of integration of TB services into HIV care and treatment services. While patients attended the HIV clinic for HIV care, they were expected to proceed to another clinic handling chest infections to receive TB services. Many patients were lost out in the process, failing to have a further assessment for TB, even when they had been screened and found positive. An interviewee said about this issue: "There is a chest clinic that takes care of TB patients where patients with TB are sent for treatment and further evaluation. Even TB medicines for TB/HIV co-infected patients are not provided here but at the chest clinic." (Physician)

The inability of the patients to produce sputum

It was also mentioned that sometimes when PLHIV presenting in HIV clinics were asked to produce sputum that would be used for further testing of TB, they failed to do so. In such cases, nothing else would be done. The comment below illustrates this feeling: "Sometimes a patient comes, and you ask them to provide sputum, but he/she says I can't produce sputum, I have failed. So, in that case, no test will be done". On the other hand, some patients were uncooperative in providing the sputum as much as they would be able to produce it. This was especially practised by PLHIVs, who perceived that they were well. One interviewee mentioned: "Patients who do not want to provide sputum, they don't see the need for doing many tests. We cannot force them. However, those who are sick try their best to provide the sputum for testing." (Nurse)

DISCUSSION

TB screening in PLHIV in this study was fairly high at 78% (n = 312), though lower than the required target of 100%. The proportion of patients with a positive TB symptom screen test was 29.5% (n = 92), out of which 57.6% (n = 53) had evidence of a sputum order. In both bivariate and multivariate analysis, the patient's general appearance was described as abnormal, with more than one TB symptom and an alternative diagnosis significantly associated with sputum ordering among patients with a positive TB symptom screen. The findings from this study indicate that TB screening in PLHIV in Ghana was extremely lower than that noted in four other Sub-Saharan African countries with a high TB burden. For

example, the prevalence of TB screening was noted to be at 89.6%, 98%, 95.7% and 93% in South Africa, Kenya, Tanzania and Uganda, respectively [14-16,27]. In all the studies cited above, the TB screening rate was far higher than what was found in this study. This difference could be due to the fact that all the studies cited above assessed TB screening of new patients at enrollment into HIV/TB care. However, the data in this study patients recorded and reviewed for those with the most recent patient visit. The majority was obtained from routine patients but not exclusively from the initial visit, as was in the other studies. It must be noted that high TB screening levels in PLHIV tend not to be sustained along the course of care [28].

The proportion of HIV patients with at least one TB symptom (positive TB screen test) in this study was 29.5%. This finding is comparable to the findings from other countries, such as South Africa at 8%, Tanzania at 3.7%, and 4% in Kenya [15,16,27]. The proportion of having any TB symptoms was higher in a study that considered only PLHIV who were not on antiretroviral therapy [29]. In this study, more than half, 57.6% (n =) of all patients with a positive TB screen test had evidence of a sputum order for evaluation of TB. This is an improvement from a previous study conducted in Ghana that evaluated the impact and feedback on TB suspicion and investigation in PLHIV among healthcare providers, which found that only 27.5% of all PLHIV with a positive TB screen test were referred for a sputum test [30]. This proportion, however, increased to 50.7% after an intervention where health workers were given feedback about their performance after being audited on prior performance.

The proportion of PLHIV who had a positive symptom-based screening of TB and later sputum ordered for further TB evaluation was very low compared to the desired target of 100% and given the high burden of TB/HIV in Ghana. It has been reported that low investigation rates contribute to the high annual mortality due to TB in PLHIV [14]. Low sputum ordering for further TB assessment in PLHIV with a positive TB screen test has been reported in a number of studies. In other similar studies, sputum ordering in PLHIV with a positive TB screen test was found to be less than 50% [13,16,27]. Suboptimal evaluation of persons with a positive TB screen test results in missed opportunities for early TB diagnosis with a resultant increase in TB-related mortality in PLHIV [3,31]. There appears to be a selective application of the guidelines for intensified TB case detection in PLHIV observed in this study. PLHIV with more than one TB symptom and those whose general appearance was described as abnormal were over three times more likely to have a sputum order compared to patients with neither of the conditions. This may imply that health workers' attitude to further investigating patients with a positive TB screen is influenced by the

general condition or appearance of the patient. This is consistent with findings from other studies [14,30]. It has been suggested that this selective evaluation of patients with a positive TB screen test is likely to be a result of trying not to overburden the already challenged TB diagnostic laboratories [32]. Consistent with the previous literature, the inability of patients to produce sputum, low-risk perception in some patients, and high patient numbers that constrained the few available health workers leading to non-adherence to national guidelines were some of the reasons for failure to order sputum from PLHIV who had screened positive for TB [33,34]. The prohibitive costs associated with some TB tests, such as CXR, were other reasons given for this low sputum ordering. However, what was astonishing in some hospitals that led to low sputum ordering was the need to pay for laboratory investigation reports, even for patients covered by the national health insurance scheme.

Conclusion

TB screening in PLHIV is still lower than recommended, and almost half of PLHIV with a positive TB screen test did not have a sputum test documented. Sputum testing was likely to be done in patients with a general abnormal appearance (more than one TB symptom) and unlikely in those with an alternative presumptive diagnosis. High workload, high costs of TB tests, lack of training for health workers and inability to produce sputum by patients were the barriers to sputum testing highlighted by the health workers.

DECLARATIONS

Ethical considerations

Ethical clearance for the study (Approval No: GHS-ERC068/02/19) was obtained from the Ghana Health Service Ethical Review Board (GHS-ERC). Permission was also sought from the regional director of the Greater Accra Ghana Health Service, the district health directorates and the participating facilities to conduct the study. The data used in the analyses did not involve personal identifiers, but confidentiality was nevertheless maintained.

Consent to publish

All authors agreed to the content of the final paper.

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None

Competing Interests

No potential conflict of interest was reported by the authors.

Author contributions

DEK conceptualized and drafted the original paper. PG, SPK and BS reviewed the study design. DEK, PG and BS undertook the statistical analysis. DEK, PG and SPK contributed to drafting the manuscript

while BS reviewed it. All authors approved the final manuscript.

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Availability of data

Data is available upon request to the corresponding author.

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