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Symptom-based screening tool in ruling out active tuberculosis among HIV-infected patients eligible for isoniazid preventive therapy in Tanzania

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Abstract

OBJECTIVES We assessed the usefulness of the National TB and Leprosy Control Program (NTLP) symptom-based tuberculosis (TB) screening tool in identifying HIV-infected patients eligible for isoniazid preventive therapy in Muhimbili National Hospital, Dar es Salaam Tanzania.
METHODS Descriptive cross-sectional study. Data collected included socio-demographic and clinical data. Chest X-ray, sputum for acid-fast bacilli (AFB) microscopy, mycobacterial culture, CD4 + count and complete blood count were performed. Patients were considered not having active TB if they presented with no symptom in the screening tool, which comprised these symptoms: cough, fever and excessive night sweats for ≥2 weeks; weight loss of ≥3 kg in 4 weeks and haemoptysis of any duration. The reference standard was a negative culture for *Mycobacterium tuberculosis*.
RESULTS We enroled 373 patients, of whom 72.1% were females. Active pulmonary TB was found in 4.1% (14/338) of the participants as defined by a positive culture. The sensitivity and specificity of the NTLP screening tool were 71.4% (10/14) and 75.9% (246/324), respectively. False-negative rate was 28.6% (4/10). Cough, fever for ≥2 weeks and weight loss were independent predictors of NTLP-defined TB. Cough ≥2 weeks predicted TB when a positive culture was used to define TB.
CONCLUSION The screening tool had fairly good sensitivity and specificity for TB screening; however, there is a possibility that about 29% of the screened population will be given IPT while they are supposed to receive a full course of TB treatment.

keywords sensitivity, specificity, negative predictive value, tuberculin skin test, NTLP screening tool

Introduction

In 2012, an estimated 8.6 million people developed TB worldwide. Of these, 1.1 million (13%) were HIV infected. About 75% of these TB-HIV co-infected cases were in the African region (WHO 2013). To reduce the burden of TB among HIV-infected patients, WHO recommends provision of TB preventive therapy such as isoniazid preventive therapy (IPT) in patients with latent TB infection (LTBI) (WHO 2009). Traditionally, screening for LTBI includes an intradermal injection of purified mycobacterial protein, also known as tuberculin skin test (TST). A positive TST without symptoms of active TB or chest abnormality is an indication for TB preventive therapy (Akolo *et al.* 2010). WHO strongly recommends that in resource-constrained settings, absence of TST should not be an obstacle for initiating TB preventive therapy for people living with HIV. It recommends symptom-based screening for TB; probing the presence of current cough, night sweat, fever or weight loss. At the basis of this recommendation lies the result of an individual participant data meta-analysis of observational studies that found that at a hypothetical 5% TB prevalence among people living with HIV, the negative predictive value for these symptoms was 97.7% (Getahun *et al.* 2011). Countries have mandates to modify the WHO-proposed questionnaire aiming at increasing the sensitivity and the negative predictive value of the screening questionnaire (WHO 2011). Studies have shown great variability in terms of sensitivity and specificity of the screening tools used in different countries (Mohammed *et al.* 2004; Day *et al.* 2006; Corbett *et al.* 2010). The variability is attributable to the choice of, and the number of symptoms used, duration of the symptoms and whether symptoms were used singly or in combination. This study was conducted to provide data on diagnostic accuracy of the

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Tanzania National Tuberculosis and Leprosy Program (NTLP) symptom-based screening tool in identifying patients eligible for IPT among patients attending the Muhimbili National Hospital (MNH) HIV clinic.

Methods

Study design, site and population

This was a descriptive cross-sectional study conducted at the Muhimbili National Hospital (MNH) HIV clinic in Dar es Salaam, Tanzania. Dar es Salaam is the largest commercial city in Tanzania where majority of the government administrative authorities reside. According to the 2012 National census, this city had a population of 4 364 541 (Tanzania National Bureau of Statistics 2013).

MNH is the country's largest tertiary hospital and a teaching hospital for the Muhimbili University of Health and Allied Sciences (MUHAS). The MNH HIV clinic was the 1st established HIV clinic in the city and thus has patients from all the three municipalities that make up the city of Dar es Salaam. The clinic also receives patients who are discharged from the MNH medical wards. Inpatients come from all over the country and are seen in the clinic for varied lengths of time before they can be discharged to continue with care at HIV clinics in the districts or regions where they came from. The MNH clinic operates 5 days a week. Patients are seen once monthly for clinical evaluation and refill of antiretroviral drugs (ARV). About 70–100 patients are seen daily in the clinic. This study site was chosen because it is one of the 14 NTLP pilot sites in the country for provision of isoniazid preventive therapy (IPT). Participants to this study were all outpatients attending this clinic, both ARV naïve and those on ARV treatment.

Data collection and procedures

From September to November 2011, three doctors consecutively recruited about 15 patients on every Monday, Tuesday and Friday from 9:00 am to 12:30 noon. The inclusion criteria included consenting adults aged 18 years or older attending the MNH HIV clinic, both ARV naïve and experienced. We excluded patients with active TB or those who had received TB treatment within the past 2 years, patients who were already on IPT, alcohol abusers and pregnant women. Pregnancy was excluded by asking female patients about their last normal menstrual period, whereas alcohol abusers self-reported this.

A structured questionnaire, which included the NTLP TB screening tool, was used to collect socio-demographic and clinical data. The NTLP TB screening tool comprised five questions, namely, presence of cough ≥2 weeks, fever ≥2 weeks, haemoptysis of any duration, excessive night sweat ≥2 weeks and noticeable weight loss or weight loss of ≥3 kg within 4 weeks (Tanzania Ministry of Health & Social welfare (MoHSW) 2008). Patients who presented with none of the symptoms were considered free of active TB and were to start TB preventive therapy. Patients who presented with any of the five symptoms were considered active TB suspects and were further investigated for presence or absence of active TB.

Clinical examination included a thorough examination of the respiratory system, lymphatic system, skin and mucous membranes, gastrointestinal tract (GIT), cardiovascular, central nervous system and musculoskeletal systems. Abnormalities were recorded as present or absent. Weight was measured using an analogue scale (SECA) without shoes and in light clothing and was recorded to the nearest 0.5 kg. Height was measured using a measuring rod without shoes and cap and was recorded to the nearest centimetre. Temperature was measured in degrees Celsius using a digital thermometer.

All participants underwent pretreatment with 200 μg of inhaled salbutamol from a standard metered-dose inhaler. All participants then underwent sputum induction 10 min after a dose of inhaled salbutamol. Sputum induction was carried out by an Omron NE-U17 ultrasonic nebulizer in an open space. The nebulizer had a maximum air volume of 17 l/min, a spraying speed of 0–3 ml/min and a particle size of 4.4 μ mass median aerodynamic diameter (MMAD). A volume of 10 ml of 3% hypertonic saline was put in the nebulizer to induce each patient (Paggiaro *et al.* 2002). Nebulization time ranged from 0 to 5 min. If the patient could not produce sputum in the first attempt, we repeated the procedure to a maximum of four attempts (Castagnaro *et al.* 1999), but the three subsequent attempts were carried out without repeating pretreatment with salbutamol inhaler. The induced sputum was collected in a 50-ml falcon tube and was transported in cool boxes to the NTLP TB reference laboratory at the Central Pathology Laboratory (CPL) within MNH.

At the laboratory, a laboratory technologist divided the sample into two aliquots. One aliquot was processed for growth in Lowenstein–Jensen (LJ) culture media, and another one was used to make a smear on a glass slide which was then stained with Ziehl-Nielsen stain for microscopic examination of acid-fast bacilli (AFB). While other TB culture media are expensive and available in big research studies only, LJ culture media are relatively cheap and readily available in referral hospitals in the country. Sputum smear for microscopy was quantified as

+1 when 10–99 AFB were seen per 100 immersion fields in a smear, +2 when 1–10 AFB were seen per 1 immersion field in a smear and +3 when more than 10 AFB were seen per 1 immersion field in a smear (NTLP of The United Republic of Tanzania 2006). Samples that could not be processed on the same day were kept at −4 °C awaiting processing.

Under aseptic procedure, 10 ml of blood was collected from the median cubital vein and put into three tubes. Two tubes contained an anticoagulant EDTA, and these two were sent for haematological analysis of CD4+ cell counts by flow cytometry using Becton Dickson Facs count machine, determination of peripheral blood counts using an automated counter Cell Dyn System 1200 (Abbott Diagnostics division) and erythrocyte segmentation rate (ESR) which was obtained using the Westergreen method. One bottle contained no anticoagulant, and this was sent to the laboratory for determination of alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) using direct spectrophotometric measurement. ALAT and ASAT were used only to give guidance on whether to start IPT or not. Samples were analysed at the central pathology laboratory (CPL) of the Muhimbili National Hospital.

Chest radiographs were obtained from all participants. A radiologist who was blinded to the HIV status of the participants reported whether the radiograph was suggestive or not suggestive of TB.

TB case definitions

We defined pulmonary TB in two ways: in accordance with the gold standard (positive sputum culture results) and with the NTLP definition. The NTLP TB definition requires the presence of two of the following: (i) Symptoms of tuberculosis (cough, fever, night sweats, loss of weight for more than 2 weeks), (ii) AFB visible by direct Ziehl-Nielsen staining of sputum specimen or *M. tuberculosis* cultured from sputum in Lowenstein–Jensen media, (iii) Chest radiograph independently interpreted as highly suggestive of tuberculosis, (iv) a clinical response to antituberculosis medication in patients with culture-negative TB (NTLP of The United Republic of Tanzania 2006). However, in the present study, we did not use the clinical response to antituberculosis medication in patients with culture-negative TB to define active TB because we did not follow-up these patients.

Subjects with active TB as per the two definitions were commenced on anti-TB as per Tanzania NTLP guidelines. Patients considered free of active TB were counselled for commencement of IPT with daily 300-mg isoniazid (INH) tablets after counselling.

Ethical issues

Ethical clearance to conduct the study was obtained from the MUHAS Institutional Review Board. Permission to do the study in the clinic was obtained from the hospital management. All patients consented to participate through written informed consent. Patients who screened positive to the screening tool were full worked up to diagnose or rule out active TB. We used the NTLP TB definition to decide which patients should receive a full course of anti-TB treatment. Upon diagnosis of active TB, a patient was started on a full course of anti-TB treatment as per Tanzania guidelines. Patients' data were handled with high confidentiality.

Statistical analysis

Data analysis was performed using SPSS version 18. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the screening tool were calculated as percentages. Two-sided 95% confidence intervals were calculated for sensitivity, specificity, negative predictive value and positive predictive value of the screening tool. Multivariate analysis was carried out to determine predictors of TB from the various symptoms used in the screening tool. *P*-value of ≤ 0.05 was taken as significant.

Results

We screened 474 patients between September and November 2011. A total of 101 patients were excluded: four patients were due to pregnancy, 19 patients were on anti-TB treatment, 23 patients were on isoniazid preventive therapy (IPT), and 55 patients who did not consent or who were unable to come for investigations scheduled on a day other than the recruitment day. A total of 373 patients were recruited and underwent screening by the NTLP screening tool.

The baseline characteristics of the study populations are summarised in Table 1. The majority 269/373 (72.1%) were women; the age group 35–44 years had the highest proportion of patients: 46.1% (172/373). The mean (SD) age was 41 (±9.6) years, 44.4 (±10.32) years for males and 36.7 (±8.99) years for females. 57% (213/273) of the patients were married or cohabiting; 42.1% (157/373) were petty traders, and 63% (235/373) had attained primary level education.

Eight percentage (31/373) were underweight, 41.3% (154/373) were overweight or obese. About 53% (197/373) were in WHO HIV stage II, and 27.1% (101/373) were in WHO stage III or IV. Twenty-nine patients

Table 1 Socio-demographic and clinical characteristics of the study participants (N = 373)

Variable	Frequency	Percentage
Gender: Female	269	72.1
Age (years)		
18–24	10	2.7
25–34	80	21.4
35–44	172	46.1
45–54	78	20.9
≥55	33	8.8
Marital status		
Single	109	29.2
Married/cohabiting	213	57.1
Divorced	26	7
Widowed	25	6.7
Occupation		
Unemployed	87	23.3
Civil servant	29	7.8
Healthcare worker	17	4.6
Petty business	157	42.1
Large-scale business	7	1.9
Others	76	20.4
Education level		
No formal education	39	10.5
Primary school	235	63
Secondary school	94	25
Post secondary	5	1.3
Body mass index (BMI) kg/m^2		
<18.5	31	8.3
18.5–24.9	188	50.4
≥25	154	41.3
WHO HIV stage		
I	75	20.1
II	197	52.8
III	86	23.1
IV	15	4
CD4 count (cells/μl) n = 344		
≤50	5	1.5
51–199	59	17.2
200–349	83	24.1
≥350	197	57.3
ARV treatment (n = 333)*		
AZT+3TC+EFV	151	45.3
AZT+3TC+NVP	110	33.0
d4T+3TC+NVP	28	8.4
d4T+3TC+EFV	22	6.6
TDF+FTC+EFV	13	3.9
ABC+ddI+L/r	9	2.7
Jaundice	2	0.5
Peripheral neuropathy	109	29.2

*AZT, zidovudine; 3TC, lamivudine; EFZ, efavirenz; NVP, nevirapine; d4T, stavudine; TDF, tenofovir; FTC, emtricitabine; ABC, abacavir; ddI, didanosine; L/r, ritonavir-boosted lopinavir.

(7.8%) had no CD4+ count results. Of the 344 patients with available CD4 results, 147 (42.7%) had CD4 count <350 cells/μl.

Eighty-nine percentage (333/373) were on ARV treatment. Of the patients on ARV, 45.3% (151/333) were on zidovudine, lamivudine and efavirenz (AZT+3TC+EFV) and 2.7% (9/373) on second-line ARV which included either ritonavir-boosted lopinavir, abacavir and lamivudine; or ritonavir-boosted atazanavir, abacavir and lamivudine; or ritonavir-boosted atazanavir, tenofovir and emtricitabine; or ritonavir-boosted atazanavir, abacavir and lamivudine. Peripheral neuropathy was reported by 29.2% (109/373) of the study participants, whereas jaundice was found in 0.5% (2/373; Table 1).

The NTLP symptom-based tool identified 96 patients with suspected active TB. Sputum culture results available for 88 active TB suspects, and 250 TB unsuspected patients was positive in 10 and four patients, respectively. We did not obtain sputum culture results for 35 patients; eight TB suspects and 27 TB unsuspected patients due to contamination. The prevalence of TB by sputum culture (gold standard) was 4.1% (14/338). Using the NTLP TB definition, the prevalence of TB was 9.5% (32/338; Figure 1).

The NTLP symptom-based TB screening tool had a sensitivity of 71.4% (10/14) and a specificity of 75.9% (246/324). The positive predictive value (PPV) was 11.4% (10/88), whereas the negative predictive value (NPV) was 98.4% (246/250). The false-negative rate was 28.6%. Four participants (4/250, 1.6%) with no symptoms for TB had a positive sputum culture for *M. tuberculosis* (Table 2).

The sensitivity and specificity of the screening tool as measured against the NTLP PTB definition was 90.3% (28/31) and 80.5% (247/307), respectively. The PPV was 31.8% (28/88), and the NPV was 98.8% (247/250; Table 3). Four patients without TB symptoms had a positive sputum culture results. Chest radiography showed abnormalities in three of them.

Symptoms in the screening tool that predicted the presence of active TB were as follows: cough for two or more weeks when a positive sputum culture was used to define a TB case, OR (95% CI) = 13.4 (3.9–46.5), P-value <0.001. Cough for two or more weeks OR (95% CI) = 8.1 (3.0–21.7); P-value <0.001, fever for two or more weeks OR (95% CI) = 4.6 (1.7–12.5); P-value 0.003, and weight loss OR (95% CI) = 4.7 (1.8–12.2); P-value 0.002 predicted the presence of active TB when the NTLP TB definition was used to define a TB case (Table 4).

Discussion

In this study, the sensitivity and specificity of the NTLP symptom-based screening tool tested against culture in LJ

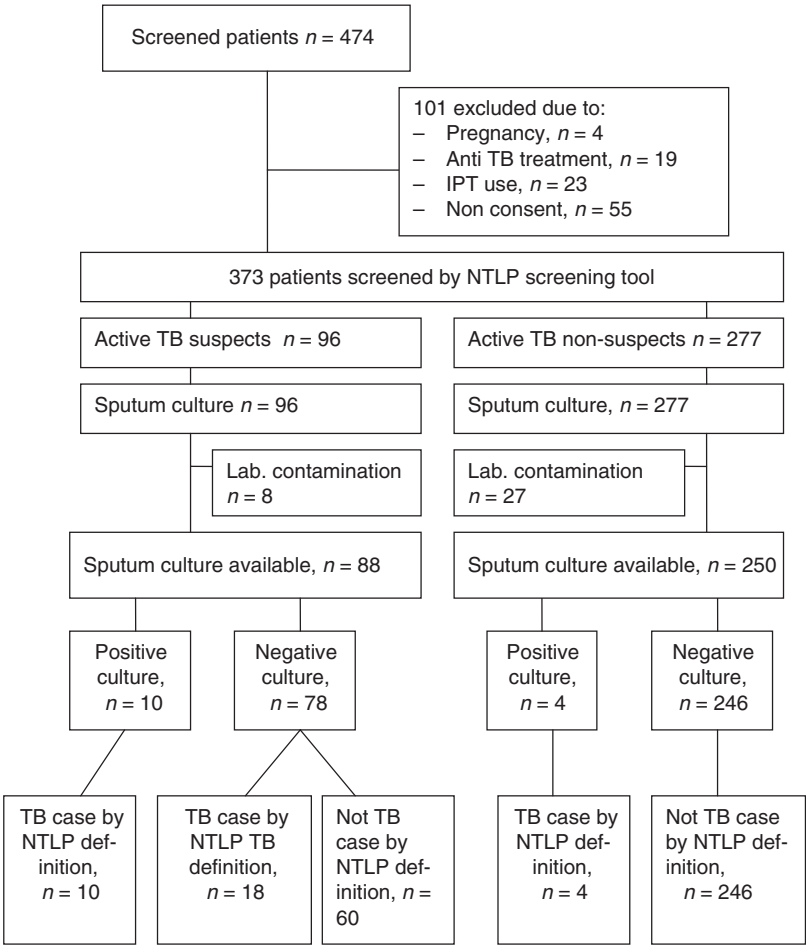

Figure 1 Flow chart of patients' recruitment and evaluation.

Table 2 Sensitivity and specificity of the NTLP TB screening tool using sputum culture for *M. tuberculosis* in LJ media as a standard for the diagnosis of tuberculosis (N = 338)

		Sputum culture in LJ medium†		
		Positive	Negative	Total
*NTLP screening tool	TB suspect	10 (71.4%)	78 (24.1%)	88 (26%)
	Not TB suspect	4 (28.6%)	246 (75.9%)	250 (74%)
Total		14 (100%)	324 (100%)	338 (100%)

*The sensitivity (95% CI) is 71.4% (47.8–95.1).
The specificity (95% CI) is 75.9% (71.3–80.6).
The NPV (95% CI) is 98.4% (96.8–100.0).
The PPV (95% CI) is 11.4% (4.7–18.0).
†LJ, Lowenstein–Jensen.

Table 3 Sensitivity and specificity of the screening tool measured against the NTLP TB definition

		NTLP TB definition		
		TB	Not TB	Total
*NTLP screening tool	TB suspect	28 (90.3%)	60 (19.5%)	88 (26%)
	Not TB suspect	3 (9.7%)	247 (80.5%)	250 (74%)
Total		31 (100%)	307 (100%)	338 (100%)

*The specificity (95% CI) is 80.5% (76.0–85.0).
The NPV (95% CI) is 98.8% (97.5–100.0).
The PPV (95% CI) is 31.8% (22.1–41.6).
The sensitivity (95% CI) is 90.3% (80.0–100).

medium were 71.4% and 75.9%, respectively. The positive predictive value was 11.4%, and the negative predictive value was 98.4%. The sensitivity and specificity of the screening tool improved to 90.3% and 80.5%, respectively, when the tool was tested against the NTLP TB definition. Using the NTLP TB definition, the PPV improved to 31.8% but the NPV remained almost the

Table 4 Symptoms predicting active TB by sputum culture and by NTLP TB definition ($N = 338$)

*Symptoms	Total patients with symptom	TB case by positive sputum culture				TB case by NTLP TB definition			
		Univariate		Multivariate		Univariate		Multivariate	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Cough ≥ 2 wks	28	10.3 (3.3–32.3)	<0.001	13.4 (3.9–46.5)	<0.001	9.4 (3.9–22.7)	<0.001	8.1 (3.0–21.7)	<0.001
Hemoptysis	3	0 (0)	0.999	0.0 (0)	0.999	5.1 (0.5–57.7)	0.190	1.5 (0.1–33.1)	0.802
Fever ≥ 2 wks	33	1.6 (0.3–7.4)	0.564	1.4 (0.2–7.9)	0.716	5.9 (2.5–14.0)	<0.001	4.6 (1.7–12.5)	0.003
Night sweats	14	1.8 (0.2–15.1)	0.571	1.9 (0.2–20.5)	0.600	2.9 (0.8–11.0)	0.120	1.3 (0.3–6.5)	0.722
Weight loss	40	1.3 (0.3–5.8)	0.772	0.6 (0.1–3.3)	0.554	6.3 (2.8–14.3)	<0.001	4.7 (1.8–12.2)	0.002

*Participants could report presence of more than one symptom.

same, 98.8%. The prevalence of TB was 4.1% and 9.5% using culture and NTLP TB definition, respectively.

A study carried out in Ethiopia in 2005 had comparable values with a sensitivity of 78%, a PPV of 12%, specificity of 56% when TB screening based on presence of any one of cough, fever, or night sweats. A search for the presence of cough or fever had a sensitivity of 75%, specificity of 64% and NPV of 97%. However, in the Ethiopian study, cough, fever and night sweats of any duration were used in the screening questionnaire. The TB prevalence was found to be 7% (Shah *et al.* 2009). In a study to evaluate the TB screening algorithm among HIV-infected person in South Africa, Day *et al.* (2006) found a TB prevalence of 4.9% and a sensitivity as high as 91% when night sweats, new or worsening cough, weight loss >5% and abnormal chest radiograph were used for active TB screening. The NPV was calculated for each symptom separately, and it was approximately 96% in each. Again as for the Ethiopian study, Day *et al.* used a combination of fever and cough of any duration in the previous 4 weeks instead of fever and/or cough of 2 weeks or more used in the present study. Another study in Cape Town in 2003 found a TB prevalence of 8.5%. In this study, TB was classified as definite (culture-positive together with appropriate symptoms or radiographic appearances), probable (smear-positive) and possible (clinical diagnosis together with a response to therapy). Using a screening tool of two or more of the symptoms of measured weight loss, cough, night sweats or fever, a sensitivity of 100% and specificity of 88.1% were obtained with PPV and NPV of 44% and 100%, respectively (Mohammed *et al.* 2004).

The false-negative rate of about 29% suggests that a reasonably big number of patients might be labelled by the screening tool as TB free although they actually have active TB. These will be given INH monotherapy, which cannot cure their TB, but might give them unnecessary INH adverse events. They are also at increased risk for developing INH resistance. It is therefore mandatory to continue screening patients already on IPT using the same clinical screening tool on each visit to the hospital in order to identify those with active TB and switch them to full course anti-TB treatment (WHO 2011).

Symptoms in the screening tool that predicted the presence of active TB were cough for two or more weeks when a positive sputum culture was used to define a TB case, and cough for two or more weeks, fever for two or more weeks and weight loss when the NTLP TB definition was used to define a TB case. This means that in HIV-infected patients, weight loss, cough and fever of two or more weeks are likely to be due to TB.

Haemoptysis as a symptom was rare in the present study, found in 3/373 subjects (0.01%). Its addition in the NTLP TB screening tool in the present study did not make the sensitivity or specificity of the screening tool superior to other TB screening tools elsewhere. A meta-analysis found that indeed hemoptysis is rare among HIV-infected patients and has the lowest sensitivity for TB (Getahun *et al.* 2011).

In the present study, CXR abnormalities identified three of the four participants who were missed by the screening tool but tested TB positive by culture. A study conducted in Ethiopia showed that chest radiography screening for HIV-infected clients diagnosed 10% more TB cases (Shah *et al.* 2009). In another study conducted among gold miners in South Africa, the addition of CXR abnormalities compatible with TB reduced the proportion of TB cases that would have been missed from 40.9% to 5.1%. In the gold miners study, the CXR was in combination with symptoms that would have missed the smallest proportion of active TB (i.e. any one of night sweats, new or worsening cough and measured weight loss of

≥5%) and had a NPV of 92.6% (Day *et al.* 2006). If not for economical constrains, adding a CXR to the screening tool may improve the sensitivity and specificity of the screening tool. The negative predictive value of the NTLP symptom-based TB screening tool was high, making it acceptably good for ruling out active TB; however, the high false-negative rate poses risks of suboptimal treatment, unnecessary INH toxicities and drug resistance to patients with active TB who will receive INH monotherapy. In the present study, we did not use response to TB treatment to define TB as it is stipulated in the NTLP TB definition. Response to anti-TB treatment would possibly increase the proportion of patients who would have been labelled as having active TB. However, some of these patients might not be true TB patients, but having other bacterial infections of the chest. Rifampicin, being a broad-spectrum antibiotic is capable of curing infections other than mycobacterial ones.

The findings of this study can only be generalizable to other parts of Tanzania that have a similar prevalence of TB to that of Dar es Salaam, because sensitivity, specificity, negative and positive predictive values are all dependent on the prevalence. However, the screening tool remains useful in the absence of any other means of excluding active TB among patients with HIV in need of IPT. The strengths of this study are sputum induction in all participants and the use of mycobacterial culture as a gold standard. Failure to obtain culture results for 35 patients is its weakness.

Conclusions

The NTLP screening tool was fairly sensitive and specific in identifying active TB in patients presenting with any TB-related symptom. The false-negative rate is high; consequently, about a third of patients screened by the screening tool might be initiated on IPT instead of a full course of anti-TB treatment. Addition of a CXR to the screening tool may reduce the false-negative rate, and therefore, whenever possible, a CXR should be part of the screening tool.

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