Performance of symptom-based tuberculosis screening among people living with HIV: not as great as hoped

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Abstract

Objective—The objective of the present study was to determine the diagnostic performance of the symptom-based tuberculosis (TB) screening questionnaire recommended by WHO for people living with HIV (PLWH) in resource-limited settings, among adults off and on antiretroviral therapy (ART).

Design—Cross-sectional study at two HIV clinics in South Africa.

Methods—A total of 825 PLWH completed the screening questionnaire and underwent investigations [chest radiography (CXR) and microbiologic testing of sputa]. A positive screen was defined as presence of cough, fever, night sweats, or weight loss. Pulmonary tuberculosis (PTB) was defined as sputum smear positive for acid-fast bacilli or growth of *Mycobacterium tuberculosis*.

Results—Of 737 participants with at least one diagnostic sputum specimen, PTB was diagnosed in 31 of 522 (5.9%) on ART, and 34 of 215 (15.8%) not on ART. The questionnaire missed 15 of 31 (48.4%) PTB cases on ART, and three of 34 (8.8%) not on ART. Among participants on ART, post-test probability of PTB diagnosis (95% confidence interval) was 6.8% (4.0–10.9%) if screening positive, and 5.2% (2.9–8.4%) if screening negative, whereas among participants not on ART, post-test probabilities were 20.3% (14.2–27.5%) and 4.8% (1.0–13.5%), respectively. Among participants diagnosed with PTB, those on ART were significantly less likely to screen positive (adjusted odds ratio 0.04, 95% confidence interval: 0.01–0.39). In both groups (ART and no ART), screening was more sensitive when CXR was incorporated.

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Conclusion—For case detection and exclusion of PTB, the WHO-recommended questionnaire performed adequately among PLWH not on ART, and poorly among those on ART. Further research is needed to identify feasible and effective TB screening strategies for PLWH in resource-limited settings.

Introduction

People living with HIV (PLWH) are at increased risk of developing and dying from tuberculosis (TB). In areas where HIV-associated TB is prevalent, routine screening for TB among PLWH is recommended in order to detect cases earlier, and to exclude TB prior to initiating isoniazid preventive therapy (IPT). The latter two objectives are anticipated to result in a decrease of TB-related morbidity and mortality. The WHO recommends using a symptom-based questionnaire for TB screening among PLWH in resource-constrained settings [1]. The questionnaire categorizes patients into two groups: asymptomatic individuals in whom IPT can be initiated, and symptomatic individuals (i.e., TB suspects) requiring further evaluation to exclude TB. The recommended questionnaire was selected based on a meta-analysis of screening studies in adult PLWH [2].

In high TB and HIV burden settings, HIV-associated TB remains a significant cause of morbidity and mortality even among persons on antiretroviral therapy (ART) [3,4]. However, few data from adults on ART were included in the meta-analysis which motivated the selection of the recommended screening questionnaire [2]. Since the meta-analysis was published, two reports from South Africa have described the performance of symptom-based screening among adults on ART and arrived at disparate conclusions [5,6]. In the larger of the two studies ($N = 1429$), diagnostic performance was inferior among participants on ART compared with those not taking ART [5], whereas in the smaller study ($N = 422$), symptom-based screening was highly sensitive regardless of ART status [6]. Importantly, neither study evaluated screening strategies that incorporated chest radiography (CXR) in the screening process.

In South Africa, where both HIV and TB are highly prevalent, the number of PLWH receiving ART has increased substantially over the past decade (75% in the last 2 years) [7]. Increases in ART uptake have also been achieved elsewhere [7]. As more PLWH are receiving ART, it is critically important to define the TB screening questionnaire's performance among PLWH on ART.

Methods

Our primary objective was to compare the performance of the WHO-recommended symptom-based screening questionnaire for the diagnosis of pulmonary TB (PTB) in adult PLWH on ART and those not taking ART at two HIV clinics in South Africa. As a secondary objective, we sought to evaluate diagnostic performance of a screening strategy utilizing CXR and the questionnaire.

Study population

The study was conducted at two HIV care and treatment clinics in Eastern Cape Province, supported by ICAP-Columbia University. Xhosa-speaking or English-speaking PLWH at least 18 years old and able to provide informed consent were eligible for enrollment, irrespective of ART status. Patients on TB treatment or awaiting results of TB investigations were ineligible.

Study procedures

Between March 2011 and January 2012, a TB screening questionnaire was administered to all PLWH attending routine clinic visits. The questionnaire was available in English as part of the provincial Adult Clinical Record and administered by clinic providers, as per routine practice, in the patient's preferred language. Patients interested in study participation were assessed for eligibility and enrolled by trained research assistants. After providing written informed consent in English or Xhosa, participants submitted three sputum specimens (spot/morning/spot) for microbiologic testing (three smears and one mycobacterial culture) and underwent CXR regardless of questionnaire responses. Spot sputa were induced using nebulized hypertonic saline with adherence to infection control protocols to minimize transmission risk.

Induced sputa were examined onsite using direct smear microscopy (Kinyoun staining for light microscopy at Hospital A; fluorescence microscopy at Hospital B). Within 48 h after collection, early morning sputa were refrigerated and transported to a referral laboratory where, after decontamination, fluorescence microscopy and liquid mycobacterial cultures were performed (BACTEC MGIT 960). Laboratories had established quality assurance programs.

At each study site, radiographs were interpreted by a designated physician trained to read CXR in a standardized fashion and blinded to screening results.

Age, sex, height, weight, HIV care enrollment date, ART initiation date, ART regimen, history of previous TB, use of IPT, CD4+ cell count, screening questionnaire responses, and results of TB investigations were abstracted from medical charts using a standardized form.

The protocol was approved by Institutional Review Boards of the University of Cape Town and Columbia University Medical Center, the research review committees of the Eastern Cape Department of Health and of the East London Hospital Complex.

Statistical analysis

Because symptoms could change with time, we excluded smear and culture results from sputa submitted more than 14 days after the questionnaire was administered. Our analyses excluded participants not submitting sputa and those submitting all specimens more than 14 days after enrollment.

As per South African guidelines [8], PTB was defined as presence of at least one sputum smear positive for acid-fast bacilli or for growth of *Mycobacterium tuberculosis* in culture.

A positive screen was defined as presence of at least one symptom (fever, cough, night sweats, or weight loss) at study enrollment (determined using the questionnaire) [1]. For our secondary objective, a positive screen was defined as presence of at least one symptom or any abnormal CXR finding.

We described participant characteristics stratified by ART status. Statistical significance was assessed with Mann–Whitney U-tests, continuity-adjusted x^2, or Fisher's exact tests, with significance threshold of $P < 0.05$.

For both the screening questionnaire and the screening strategy including the questionnaire and CXR, we calculated point estimates and 95% confidence intervals (CIs) of the following operating characteristics: sensitivity, specificity, positive predictive value, negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio.

To assess for effect modification by ART use on the questionnaire's sensitivity and specificity, we performed regression analyses stratified by presence or absence of PTB in which the dependent variable was the result of the screening questionnaire [9]. In the analysis restricted to participants with PTB (to determine whether ART modified sensitivity), possible outcomes for the questionnaire were 'true-positive' or 'false-negative,' and the odds ratio (OR) for ART status compared the odds of a true-positive screen among participants on ART to odds of a true-positive screen among those not taking ART. In the model restricted to participants without PTB (for effect modification on specificity), the possible outcomes were 'true-negative' or 'false-positive.'

Crude and adjusted ORs were calculated using logistic regression. Covariates included study site, sex, age, history of previous TB, duration of enrollment in HIV care, BMI, $CD4^+$ cell count, and abnormal CXR findings. Model fit was assessed using the Hosmer–Lemeshow statistic.

In post-hoc sensitivity analyses, we restricted our definition of PTB to growth of *M. tuberculosis* in culture.

Results

We enrolled 825 participants. While enrollment was ongoing and prior to analysis, data from the first 73 enrolled at one of the sites were removed because of concerns about data integrity. Fifteen participants were excluded because sputa were submitted more than 14 days after enrollment. Supplement Figure S1, http://links.lww.com/QAD/A511 describes recruitment, enrollment, and exclusion.

Participant characteristics

Table 1 describes characteristics of the 737 participants, of whom 522 (70.8%) were on ART at study enrollment. Participants on ART were more likely to have a history of previous TB and had higher median $CD4^+$ cell count, BMI, and duration of enrollment in care compared with those not taking ART ($P < 0.001$ for all). Among participants on ART, 8.2% ($N = 43$) had been on ART for less than 3 months. All questionnaire symptoms were less common among PLWH on ART ($P < 0.001$).

Three smears and one culture were performed for 78.4% ($N = 578$) of participants, and culture results were available for 82.9% ($N = 611$), with no differences noted by ART status. CXR was performed in 95.7% ($N = 705$) of participants.

Pulmonary tuberculosis

Sixty-five participants (8.8%) were diagnosed with PTB, 31 of 522 (5.9%) on ART and 34 of 215 (15.8%) not on ART (Table 2). Compared with those not diagnosed with PTB, participants with PTB were significantly less likely to be on ART ($P < 0.001$) and to have a history of previous TB ($P < 0.001$), and had lower median CD4$^+$ cell count ($P = 0.01$), BMI ($P < 0.001$), and duration of enrollment in care ($P = 0.02$).

Most PTB was smear-negative and culture-positive [ART: 48.4% ($N = 15$); no ART: 64.7% ($N = 22$)], followed in frequency by smear-positive and culture-positive [ART: 32.3% ($N = 10$); no ART: 32.4% ($N = 11$)]. Five participants on ART (16.1%) and one not on ART (2.9%) were smear-positive and culture-negative. Culture results were missing for one smear-positive participant on ART.

Performance of the screening questionnaire

Sensitivity was lower, and specificity higher, among participants on ART as compared with those not on ART (Table 3). NPV was similar in both groups. In the ART group, the questionnaire was not useful for distinguishing between participants with and without PTB diagnosis: post-test probability of PTB was 6.8% (95% CI: 4.0–10.9%) after a positive screen and 5.2% (95% CI: 2.9–8.4%) after a negative screen. In the no ART group, post-test probability of PTB was 20.3% (95% CI: 14.2–27.5%) and 4.8% (95% CI: 1.0–13.5%) among those screening positive and negative, respectively.

In both ART and no ART groups, the questionnaire identified most PTB cases among the minority – that is, 21 of 65 – that were both smear-positive and culture-positive [ART: 90.0% ($N = 9$); no ART: 100% ($N = 11$)]. In the no ART group, the questionnaire identified most smear-negative culture-positive, or smear-positive culture-negative/missing PTB [86.9% ($N = 20$)]; however, few of these cases were identified among those on ART [33.3% ($N = 7$)].

Table 4 summarizes the operating characteristics of the screening strategy in which a positive screen was defined as the presence of any symptom or an abnormal CXR. Among participants on ART, compared with the use of the questionnaire alone, this strategy's sensitivity was higher (76.7 vs. 51.6%) and specificity lower (27.4 vs. 55.8%), whereas among those not on ART, the predominant effect was a lower specificity (15.5 vs. 32.6%). In both ART and no ART groups, post-test probabilities of PTB were similar to those using the questionnaire alone. As shown in Supplement Table S1 (see Supplemental Digital Content, http://links.lww.com/QAD/A511), sensitivities were unchanged, and specificities slightly higher if CXR criterion for a positive screen was an abnormality suggestive of TB instead of any abnormality.

Participant characteristics associated with sensitivity and specificity of the screening questionnaire

The questionnaire's sensitivity was significantly lower among participants on ART in both bivariable and multivariable analyses (Table 5). Conversely, the questionnaire's specificity was significantly higher among persons on ART. In multivariable analyses, both abnormal CXR and BMI were associated with specificity; the former was also associated with sensitivity.

Performance of questionnaire for the diagnosis of culture-confirmed pulmonary tuberculosis

When PTB was defined as growth of *M. tuberculosis* in culture, six smear-positive culture-negative participants were categorized as not having PTB (five on ART and one not on ART). This analysis excluded one smear-positive participant because of missing culture results (on ART) and 124 smear-negative participants for whom sputa for culture were not submitted, submitted more than 14 days after enrollment, or nondiagnostic. In the ART group ($N = 424$), questionnaire sensitivity was 60.0% (95% CI: 38.7–78.9%); and post-test probability of PTB was 7.7% (95% CI: 4.4–12.4%) among those screening positive, and 4.3% (95% CI: 2.1–7.8%) among those screening negative. In the no ART group ($N = 188$), sensitivity was 93.9% (95% CI: 79.8–99.3%), and post-test probabilities 22.5% (95% CI: 15.8–30.3%) and 4.0% (95% CI: 0.5–13.7%) for a positive and negative screen, respectively. ART status remained strongly associated with sensitivity and specificity in multivariable analyses. Supplemental Tables S2 and S3, http://links.lww.com/QAD/A511 report the full results of this analysis.

Discussion

In this study of TB screening among adult PLWH in South Africa, the diagnostic performance of the WHO-recommended symptom-based questionnaire was limited and varied by ART status. Among participants on ART, the questionnaire had low sensitivity and was not useful for differentiating those with and without PTB. Among participants not taking ART, the questionnaire was highly sensitive and diagnostically useful. Sensitivity was improved, particularly for those on ART, with incorporation of CXR in the screening strategy. An association between ART status and diagnostic performance was also observed after controlling for potential confounders, and in post-hoc analyses in which only culture-confirmed cases were categorized as PTB.

Our findings have major implications for the utility of the WHO-recommended TB screening questionnaire. In the meta-analysis used to derive the questionnaire, in which nearly all data came from PLWH not on ART, the authors reported important between-study heterogeneity in diagnostic performance [2]. The questionnaire's diagnostic performance among PLWH not on ART in our study is consistent with that reported in the meta-analysis [2], but conflicts with recent reports of poor sensitivity in the same population [10] and in antenatal clinics [11]. Between-study heterogeneity is now also evident for the questionnaire's performance among PLWH on ART. For culture-confirmed TB, the questionnaire's sensitivity was lowest in the study by Rangaka *et al.* (23.8%), followed by

our study (60%), and highest in the study by Kufa *et al.* (100%). The converse was true for specificity, which was highest in the study by Rangaka *et al.* (94.4%), followed by our study (55.1%), and the study by Kufa *et al.* (18.1%). This diagnostic heterogeneity was seen despite similar settings and reported participant characteristics, raising the question of what factors (such as viral load, opportunistic infections, or language) could explain these differences, and underscoring the need for further research.

There are a number of possible explanations for the observed association between ART use and the questionnaire's diagnostic performance. First, it is possible that a greater proportion of TB cases on ART were in an early, and hence asymptomatic, phase of TB, compared with cases not on ART. Second, ART use may have affected the diagnostic performance by promoting immune reconstitution, thereby preventing other opportunistic illnesses (including extrapulmonary TB) that could cause a positive screen. The lower sensitivity and greater specificity of the questionnaire among those on ART support this hypothesis. Finally, sensitivity may have been lower among participants on ART if they were more likely to have been previously screened for TB than those not on ART [2,12,13]. However, such differential TB screening is unlikely, as all PLWH should have been screened for TB at enrollment into HIV care and at each routine clinic visit as per national guidelines.

It is possible the questionnaire's sensitivity is higher during the initial months of ART when immune reconstitution 'unmasks' TB that was prevalent, but asymptomatic prior to ART [14]. There were too few participants on ART for less than 3 months in our study ($N = 43$, 8.2%) to permit meaningful exploration of this hypothesis. Our findings are thus most generalizable to PLWH who have been on ART for more than 3 months. Further studies are needed to establish the questionnaire's diagnostic performance during the early phase of ART use.

To our knowledge, ours is the first study to report performance of CXR in TB screening among PLWH on ART. Because prevalence of abnormal findings on CXR was high irrespective of PTB diagnosis, incorporation of CXR into the screening strategy increased sensitivity and decreased specificity of TB screening for participants on ART. Similar results have been reported among ART-naive populations [10,12,15,16], with sensitivity reaching over 90% in three studies [10,15,16]. Further research is warranted to verify our findings, as we were unable to assess inter-reader variability.

In high HIV and TB burden settings, PLWH remain at increased risk of TB even after several years of ART [3]. In such settings, routine TB screening among PLWH is expected to lower morbidity and mortality through earlier case detection, and by expediting the exclusion of TB prior to IPT [1]. The questionnaire's poor sensitivity among participants on ART is concerning – it suggests the questionnaire is not useful for active case finding in this group. However, the questionnaire mostly failed to identify TB cases that were smear-negative culture-positive, and smear-positive culture-negative, the majority of cases. Some have questioned the clinical relevance of identifying these cases prior to symptom onset, arguing that a false-negative screen will result in poor treatment outcomes only if TB becomes substantially more extensive before it is diagnosed [17], a situation that could arise with infrequent follow-up or screening. However, even if initiation of PTB treatment in the

early stages of disease as opposed to once disease is symptomatic does not improve treatment outcomes, it may be important for preventing transmission in household, community, and healthcare settings [18–20].

Fear of generating isoniazid-resistant TB is often cited as a reason for not prescribing IPT [21,22], although proponents of IPT note that a meta-analysis and recent cluster randomized trials have shown the risk of developing isoniazid-resistant TB following IPT is minimal [23–25]. However, none of the studies in the meta-analysis, nor the cluster randomized trials, relied solely on symptom-based screening to exclude TB prior to IPT initiation. In the meta-analysis, which pooled results from six studies of IPT in PLWH, five studies used both symptom-based screening and CXR to exclude TB prior to IPT, and two studies also used sputum smear and culture [23]. In the two cluster randomized trials, participants were screened with both symptoms and CXR prior to IPT [24,25]. With the use of a less sensitive tool such as the screening questionnaire, the risk of developing isoniazid-resistant TB may be higher in populations in whom TB is common (as a greater proportion of those starting IPT will already have TB).

In our study, if only the symptom-based questionnaire was used to exclude TB prior to IPT, then among persons receiving isoniazid, 3.0% on ART and 1.6% not on ART would be cases of asymptomatic TB exposed to isoniazid monotherapy, roughly the same proportions expected to benefit from nontuberculin skin test (TST)-targeted IPT [26,27]. Screening with tests more sensitive than the questionnaire alone, and targeting IPT to TST-positive patients [25,28], will help ensure the probability of benefit from IPT outweighs the risk of inadvertent isoniazid monotherapy among PLWH, both on and off ART.

Our study has a number of strengths. First, the study included a large number of participants, both on and off ART. Second, use of sputum induction is likely to have increased the proportion of participants with TB who were identified by smear status. Third, our study was conducted under programmatic conditions in a resource-constrained area and our results are generalizable to settings in which the questionnaire is used.

Our study also has limitations. First, if smear-positive culture-negative specimens were due to laboratory error rather than PTB, then classification of participants with these results as having PTB spuriously lowered the sensitivity among those taking ART. Second, 17.1% of participants did not have culture results, which could have resulted in missed cases of PTB. However, results in post-hoc analysis addressing both limitations were similar to the primary analysis. Third, the routinely collected data used for some participant characteristics were incomplete or may not have reflected values at the time of study enrollment. Fourth, we did not assess inter-reader reliability for CXR interpretation. Fifth, each hospital used a different method to read smears; however, the proportion of positive smears was not significantly different between the hospitals (data not shown) and all multivariable models adjusted for site. A final limitation is that we were unable to determine whether using the questionnaire as the sole method of TB screening increases the risk of poor outcomes.

Conclusion

We found the WHO-recommended TB screening questionnaire performs adequately among PLWH not taking ART, and poorly among those on ART. This has important implications as the population of PLWH on ART is growing rapidly and their TB risk remains elevated in high TB burden areas. Research is needed to better understand the determinants of diagnostic heterogeneity of symptom-based TB screening in PLWH, both within and between populations on and off ART. There is also a need for prospective implementation studies, which follow PLWH screened with the WHO-recommended questionnaire to determine subsequent TB incidence, drug resistance, and treatment outcomes. Finally, there remains a need to identify inexpensive TB screening strategies for PLWH in resource-limited settings with higher sensitivity and less diagnostic heterogeneity. The increasing availability of the Xpert MTB/RIF assay provides an opportunity to operationally explore its role in routine TB screening in resource-limited settings.

Our study also has implications for screening policies in settings in which TB is common among PLWH. To lower risks of exposing PLWH on ART with unrecognized TB to isoniazid monotherapy, it may be prudent to combine the screening questionnaire with CXR or perform sputum cultures regardless of symptom status. It may be safer to use one of these more sensitive screening strategies even among PLWH who are not on ART, particularly if IPT is not targeted to TST-positive persons. The resources required to implement such screening are unavailable in many places where TB is prevalent among PLWH. The limited effectiveness of symptom-based screening in our study, and results of an analysis demonstrating the cost–effectiveness of TB screening with GeneXpert or sputum culture regardless of symptoms in South Africa [29], support scale-up of TB diagnostic capacity in areas burdened by TB-HIV coinfection.

In settings where the questionnaire remains the sole method of TB screening prior to IPT initiation, implementing the WHO recommendation that PLWH be screened for TB during every follow-up visit regardless of IPT status [1], and performing drug susceptibility testing in all PLWH who develop TB on IPT, may help avoid important delays in TB treatment initiation and detection of drug-resistant TB among those with an initial negative screen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Table 1

Participant characteristics and symptoms stratified by antiretroviral therapy status $(N = 737)$[a,b].

Characteristics	ART, N (%)	No ART, N (%)
	522 (71)	215 (29)
Study site		
Hospital A	278 (53)	112 (52)
Hospital B	244 (47)	103 (48)
Sex		
Male	123 (24)	52 (24)
Female	399 (76)	163 (76)
Median age, years (IQR)	36.9 (31.4–45.2)	35.6 (29.7–44.1)
Previous TB[c]	232 (44)	52 (24)
Median CD4$^+$ cell count (cells/μl) (IQR)[c]	365 (229–510)	200 (85–303)
Median BMI (kg/m^2) (IQR)[c]	24.4 (21.2–28.3)	23.1 (20.4–27.6)
Median duration of enrollment in HIV care (days) (IQR)[c]	1150 (592–2031)	76 (7–653)
Median duration of ART (days) (IQR)	786 (433–1455)	–
Symptoms[c]		
Fever, N(%)	36 (7)	32 (15)
Cough, N(%)	156 (30)	99 (46)
Night sweats, N(%)	100 (19)	65 (30)
Weight loss, N(%)	89 (17)	108 (50)
Positive screen (any symptom), N(%)[c]	233 (45)	153 (71)

[a] ART, antiretroviral therapy; IQR, interquartile range; TB, tuberculosis.

[b] Data missing for duration of enrollment in HIV care (ART: $n = 1$; no ART: $n = 2$), ART ($n = 1$), and BMI (ART: $n = 27$; no ART $n = 17$).

[c] $P < 0.05$ for comparison between participants on ART and not on ART.

Table 2

Participant characteristics stratified by presence or absence of pulmonary tuberculosis diagnosis[a,b].

Characteristics	PTB, N (%)	No PTB, N (%)
	65 (8.8)	672 (91.2)
On ART[c]	31 (47.7)	491 (73.1)
Site		
Hospital A	27 (41.5)	363 (54.0)
Hospital B	38 (58.5)	309 (46.0)
Sex		
Male	18 (27.7)	157 (23.4)
Female	47 (72.3)	515 (76.6)
Median age (years) (IQR)	38.3 (30.6–46.6)	36.3 (31.0–44.6)
Previous TB[c]	10 (15.4)	274 (40.8)
Median CD4$^+$ cell count (cells/µl) (IQR)[c]	263 (98–412)	323 (187–473)
Median BMI (kg/m^2) (IQR)[c]	21.3 (19.3–23.8)	24.2 (21.2–28.5)
Median duration of enrollment in HIV care (days) (IQR)[c]	548 (30–1500)	875 (327–1772)
Median duration of ART (days) (IQR)[d]	642 (360–1681)	800 (435–1413)
Abnormal chest radiograph	43 (69.4)	370 (57.5)

[a]ART, antiretroviral therapy; IQR, interquartile range; PTB, diagnosis of pulmonary tuberculosis.

[b]Data missing for duration of enrollment in HIV care (PTB: $n = 2$; No PTB: $n = 1$); duration of ART 9PTB: $n = 0$; No PTB: $n = 1$); BMI (PTB: $n = 6$; No PTB: $n = 38$); and CXR (PTB: $n = 3$; no PTB: $n = 29$).

[c]$P < 0.05$ for comparison between PTB and No PTB groups.

[d]Among participants on ART.

Table 3

Operating characteristics of the WHO-recommended, symptom-based screening questionnaire.

N	Positive screen, N (%)	PTB, N (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	PLR (95% CI)	NLR (95% CI)	PTB cases missed, N (%)
All participants									
737	386 (52.4)	65 (8.8)	72.3 (59.8–82.7)	49.6 (45.7–53.4)	12.2 (9.1–15.6)	94.9 (92.0–96.9)	1.4 (1.2–1.7)	0.6 (0.4–0.8)	18 (27.7)
ART									
522	233 (44.6)	31 (5.9)	51.6 (33.1–69.9)	55.8 (51.3–60.3)	6.8 (4.0–10.9)	94.8 (91.6–97.1)	1.2 (0.8–1.7)	0.9 (0.6–1.3)	15 (48.4)
No ART									
215	153 (71.2)	34 (15.8)	91.2 (76.3–98.1)	32.6 (25.8–40.0)	20.3 (14.2–27.5)	95.2 (86.5–99.0)	1.4 (1.2–1.6)	0.3 (0.1–0.8)	3 (8.8)

Criteria for positive screen: any of fever, cough, night sweats, or weight loss. ART, antiretroviral therapy; CI, confidence interval; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; PTB, diagnosis of pulmonary tuberculosis.

Table 4

Operating characteristics of the screening strategy of either a positive symptom screen or positive chest radiography findings [a].

N	Positive screen, N (%)	PTB, N (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	PLR (95% CI)	NLR (95% CI)	PTB cases missed, N (%)
All participants									
705	540 (76.6)	62 (8.8)	85.5 (74.2–93.1)	24.3 (21.0–27.8)	9.8 (7.4–12.6)	94.6 (89.9–97.5)	1.1 (1.0–1.3)	0.6 (0.3–1.1)	9 (14.5)
ART									
505	368 (72.9)	30 (5.9)	76.7 (57.7–90.1)	27.4 (23.4–31.6)	6.3 (4.0–9.2)	94.9 (89.8–97.9)	1.1 (0.9–1.3)	0.9 (0.4–1.7)	7 (23.3)
No ART									
200	172 (86.0)	32 (16.0)	93.8 (79.2–99.2)	15.5 (10.4–21.9)	17.4 (12.1–24.0)	92.9 (76.5–99.1)	1.1 (1.0–1.2)	0.4 (0.1–1.6)	2 (6.3)

Criteria for positive screen: any of fever, cough, night sweats, weight loss, or any abnormality on chest radiography (CXR). ART, antiretroviral therapy; CI, confidence interval; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; PTB, diagnosis of pulmonary tuberculosis.

[a] Excludes participants with no CXR performed.

Table 5

Crude and adjusted associations between participant characteristics and performance of the tuberculosis screening questionnaire.

Participant characteristics	Sensitivity				Specificity			
	OR[a] (95% CI)	P value	aOR[b] (95% CI)	P value	OR[c] (95% CI)	P value	aOR[d] (95% CI)	P value
ART status								
ART	**0.10 (0.03–0.41)**	**0.001**	**0.04 (0.01–0.39)**	**0.005**	**2.61 (1.83–3.74)**	**<0.001**	**2.44 (1.57–3.79)**	**<0.001**
No ART	ref		ref		ref		ref	
Sex								
Female	1.46 (0.45–4.74)	0.53	0.82 (0.12–5.43)	0.84	**1.54 (1.07–2.21)**	**0.02**	1.11 (0.72–1.71)	0.64
Male	ref		ref		ref		ref	
Age								
37 years	**0.27 (0.08–0.96)**	**0.04**	0.39 (0.04–3.39)	0.39	**0.68 (0.50–0.92)**	**0.01**	0.80 (0.56–1.15)	0.22
18–37 years	ref		ref		ref		ref	
Previous TB								
Previous TB	1.64 (0.31–8.59)	0.56	2.83 (0.20–39.33)	0.44	**0.71 (0.52–0.97)**	**0.03**	0.70 (0.48–1.02)	0.06
No previous TB	ref		ref		**ref**		ref	
CD4+ cell count (cells/μl)								
<200	**3.98 (1.14–13.88)**	**0.03**	0.51 (0.06–4.00)	0.52	**0.51 (0.36–0.73)**	**<0.001**	0.80 (0.51–1.24)	0.31
200	ref		ref		**ref**		ref	
BMI (kg/m²)								
18.5	0.43 (0.08–2.19)	0.31	0.36 (0.04–3.47)	0.37	**7.62 (3.18–18.27)**	**<0.001**	**5.92 (2.40–14.61)**	**<0.001**
<18.5	ref		ref		ref		ref	
Duration of enrollment in HIV care								
<1 year	**4.0 (1.14–14.05)**	**0.03**	1.87 (0.16–22.27)	0.62	**0.56 (0.40–0.80)**	**0.001**	0.84 (0.52–1.36)	0.48
1 year	ref		ref		ref		ref	
CXR								
Any abnormality	**3.94 (1.21–12.86)**	**0.02**	**8.31 (1.15–60.27)**	**0.04**	**0.59 (0.43–0.81)**	**0.001**	**0.65 (0.45–0.94)**	**0.02**
Normal	ref		ref		ref		ref	

Multivariable models include all variables listed in the table as well as study site. Estimates in bold have a *P* value less than 0.05. For sensitivity, the OR is the ratio of the odds of having a true-positive screening test vs. a false-negative screening test between strata of the participant characteristics, among those with PTB. For example, in the multivariable model, among participants with PTB, the odds of a positive screen were 0.04 times lower among persons on ART compared with persons not on ART. For specificity, the OR is the ratio of the odds of having a true-negative screening test vs. a false-positive screening test between strata of the participant characteristics, among those without PTB. For example, in the multivariable model, among participants without PTB, the odds of a negative screen were 2.44

times higher among persons on ART compared with persons not on ART. aOR, adjusted odds ratio; ART, antiretroviral therapy; CXR, chest radiography; OR, odds ratio; PTB, diagnosis of pulmonary tuberculosis.

[a] $N = 65$, except for duration of HIV care ($N = 63$); BMI ($N = 59$); and chest radiography ($N = 62$).

[b] $N = 54$.

[c] $N = 672$, except for duration of HIV care ($N = 671$); BMI ($N = 634$); and chest radiography ($N = 643$).

[d] $N = 605$.