Intensified Tuberculosis Case Finding Among HIV-Infected Persons From a Voluntary Counseling and Testing Center in Addis Ababa, Ethiopia

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Objective: To evaluate commonly available screening tests for pulmonary tuberculosis (TB), using sputum bacteriology as a gold standard, in HIV-infected persons attending an urban voluntary counseling and testing clinic in Addis Ababa, Ethiopia.

Design: Prospective enrollment of HIV-infected persons, all of whom underwent TB screening, regardless of symptoms, with: (1) symptom screening and physical examination, (2) 3 sputum specimens for smear microscopy, and (3) chest radiograph. One sputum was also sent for concentrated smear microscopy and mycobacterial culture. Chest radiographs were reviewed by 2 independent radiologists. A confirmed TB diagnosis was defined as 1 positive sputum smear and/or 1 positive sputum culture.

Results: We enrolled 438 HIV-infected persons: 265 (61%) females, median age 34 years (range: 18–65), median CD4 cell count 181 cells per cubic millimeter (range: 2–1185). Overall, 32 (7%) persons were diagnosed with TB, of whom 5 (16%) were asymptomatic but culture-confirmed TB cases. Screening for cough >2 weeks would have detected only 12 (38%) confirmed TB cases; screening for cough or fever, of any duration, would have detected 24 (75%) cases, with specificity of 64%. Negative predictive value of screening for these 2 symptoms was 97%. Simulation of the current Ethiopian national guidelines had a sensitivity of 63% and specificity of 83% for diagnosing TB disease among study patients.

Conclusions: Traditional symptom screening is insufficient for detecting TB disease among HIV-infected persons but may serve to exclude TB disease. More sensitive, rapid, and low-cost diagnostic tests are needed to meet the demand of resource-limited settings.

Key Words: diagnosis, Ethiopia, HIV infection, screening, tuberculosis

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INTRODUCTION

The worldwide epidemic of HIV/AIDS has contributed to a resurgence of tuberculosis (TB), now a leading cause of HIV-related morbidity and mortality.[1] TB disease has been shown to accelerate the natural course of HIV disease, and similarly, HIV infection results in more rapid progression from latent TB infection to TB disease.[2–6] However, diagnosing TB in HIV-infected persons is a major public health challenge.

The diagnosis of TB has traditionally been based on clinical and laboratory parameters, which perform poorly in HIV-infected patients. HIV-infected TB patients often lack the classic symptoms of pulmonary TB and may even be asymptomatic.[7,8] Up to 30% of HIV-infected TB patients have normal chest radiographs (CXRs).[9,10] Sputum microscopy for acid-fast bacilli (AFB), the most widely applied test for the diagnosis of TB, fails to detect nearly half of HIV-infected TB patients.[11,12] High rates of smear-negative and extrapulmonary TB occur in HIV-infected persons, presenting further diagnostic challenges.[13] Although sputum culture significantly improves detection of TB in HIV patients, it is not available in most high-burden settings. Globally, it is estimated that only 45% of TB cases are currently being diagnosed, due to either the lack of effective diagnostic tools or the inadequate health care infrastructure in which to utilize them.[1]

An integral component of the World Health Organization (WHO) strategy for reducing the burden of HIV-related TB disease is intensified case finding (ICF) for TB among HIV-infected persons.[14,15] Case finding for TB has 2 main goals: to reduce TB morbidity and mortality by early diagnosis and to reduce TB transmission. DOTS, the current global strategy for TB control, relies on passive TB case finding

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whereby the patient self-presents for diagnostic evaluation and treatment. ICF extends the DOTS strategy by proactively targeting persons with no or minimal symptoms but who are at high risk for TB disease. If used successfully, ICF has the potential to increase case detection rates and improve TB control.[16,17] In addition, excluding TB disease in HIV-infected persons is a prerequisite for initiating isoniazid preventive therapy (IPT) and is recommended before antiretroviral (ARV) therapy to reduce incidence of immune reconstitution inflammatory syndrome with TB. However, the optimal method of diagnosing or excluding TB disease has not yet been determined in HIV-infected persons.

Ethiopia is a high-burden country for TB, with an estimated incidence of 341 of 100,000 population per year in 2005.[18] In addition to high TB burden, Ethiopia has been seriously affected by HIV/AIDS, with an estimated 1.5 million HIV-infected persons currently.[19] To better inform policy and practices about screening for pulmonary TB among HIV-infected persons, the aim of this study was to determine the sensitivity, specificity, and predictive value of the routinely available TB diagnostic tests among ambulatory HIV-infected persons, using sputum smear and/or sputum culture as the gold standard.

METHODS

Setting

This study was conducted at Zewditu Memorial Hospital, a large referral hospital in Addis Ababa that serves more than 40,000 patients a year. This hospital provides inpatient and outpatient services, including care and treatment for TB and HIV/AIDS patients with ARVs and IPT, if appropriate. The voluntary counseling and testing (VCT) clinic is well-established with 5 full-time counselors and provides rapid anonymous HIV counseling and testing services.[20,21] Approximately 50–60 clients are seen each day, of whom, about 20% are HIV infected. An ARV treatment program was started at this site in July 2003. Patients being evaluated for ARV initiation undergo a routine medical examination, including symptom screening for TB disease and other opportunistic infections, and determination of eligibility for IPT.

Study Population

All newly diagnosed HIV-positive clients from the VCT clinic were offered enrollment in the TB screening study. We included all persons with documented HIV infection diagnosed at the VCT clinic, who were 18 years of age or older (based on age of consent for HIV testing in Ethiopia) and who agreed to participate in the study and the required follow-up. Persons who were unable or unwilling to complete the full diagnostic evaluation, pregnant women, persons in jail or prison, persons taking medications with antimycobacterial activity (eg, flouroquinolones, macrolides, or aminoglycosides) within the past 2 weeks, and persons currently receiving anti-TB treatment were excluded.

Data Collection

A trained physician conducted a standardized symptom screening and physical examination in a private consultation room, within the VCT clinic. Patients were asked in their native language about the presence and duration of: cough, hemoptysis, fever, weight loss, night sweats, shortness of breath, chest pain, diarrhea, appetite loss, and fatigue. Additional data were collected on basic demographics and risk factors for TB.

All patients provided 3 sputum samples for smear examinations ("spot—early morning—spot"), had blood drawn for CD4 cell count, and underwent a single full-size, posterior–anterior view CXR. The early morning sputum was split for direct smear and a portion sent to the national TB reference laboratory for concentrated smear and mycobacterial culture.

CXR findings were recorded using a standardized form that included specific radiographic patterns suspicious for active TB, such as: tuberculoma, miliary pattern, cavity in any lobe, upper or lower lobe infiltrate with hilar adenopathy, interstitial pattern, upper lobe fibrosis with nodular change, intrathoracic mass with lymphadenopathy (noncalcified), pleural effusion, and/or thickening (unilateral, $>1/2$ thoracic cavity).

Laboratory Methods

Sputum smear for AFB was performed in 2 ways for all subjects: a direct Ziehl–Neelson smear done on site at Zewditu Memorial Hospital and a concentrated smear done at the national TB reference laboratory. All sputum specimens received at the national TB reference laboratory were digested and decontaminated using the modified Petroff method, which is used routinely and has been described previously.[22] For mycobacterial culture, the resuspended sediment was inoculated in 2 tubes of Lowenstein–Jensen medium. The cultures were incubated at 37°C for 8 weeks or until growth of colonies was observed; they were first inspected after 48 hours, then weekly. If no growth was detected by 8 weeks, or in case of contamination, the cultures were discarded. In addition to growth characteristics, niacin and nitrate reductase and 68°C catalase tests were used for identification of *Mycobacterium tuberculosis*.[23]

Data Analysis

Case Definitions

For purposes of analysis, all patients were classified as a confirmed TB case or not based on results of sputum AFB smear, combined with mycobacterial culture, using the revised WHO case definitions for HIV-prevalent settings.[24] A "smear-positive pulmonary tuberculosis" (PTB^+) case was defined as TB in a patient with: (*a*) at least 1 initial sputum smear positive for AFB by direct microscopy, (*b*) 1 initial sputum smear positive for AFB by concentrated method, or (*c*) 1 initial positive culture for *M. tuberculosis*. A "smear-negative pulmonary TB" (PTB^-) case was defined as TB in a patient with 3 initial smears negative for AFB but positive by culture. "Extrapulmonary TB" was not specifically evaluated in this study, but patients with both pulmonary TB and extrapulmonary TB were classified as a case of PTB. A "non-TB" case included anyone who did not meet the above criteria.

Chest Radiographs

CXRs were categorized as normal, abnormal with pulmonary disease, or abnormal with nonpulmonary disease (eg, rib fracture). CXR findings considered abnormal with

pulmonary disease were further categorized as highly suggestive TB, probable TB, or non-TB lung disease (eg, lobar pneumonia).

Outcome Measures

The primary outcome measure was the performance of routinely available TB diagnostic tests (eg, symptom screening, physical examination, direct mycobacterial smear for AFB, and chest radiography). Each symptom was evaluated alone and in combination with other symptoms at varying durations for each symptom. We measured test performance by calculating sensitivity, specificity, positive predictive value, and negative predictive value of each test.

The secondary outcome measures were as follows: (1) "TB risk factors": we compared demographic and clinical factors among confirmed TB cases with those without confirmed disease. Factors examined included sex, age, body mass index, TB history, contact with a TB case, history of incarceration, modified Karnofsky performance scale, and CD4 cell count; (2) "CXR reliability": we compared the final interpretation (based on categories above) of each radiologist to determine the reliability of CXR readings (ie, interrater agreement); and (3) "Simulated performance and cost of diagnostic algorithms": we compared the performance and direct costs of the current Ethiopian TB screening guidelines with an alternative approach.

Management of Patients

All HIV-positive clients, including pregnant women, regardless of participation in this study were screened for TB symptoms based on Ethiopian national guidelines.[25] Persons with confirmed TB received TB treatment according to the National TB Control guidelines. HIV-infected persons who did not have evidence of TB disease were referred for routine medical care, including evaluation for ARV therapy, IPT, treatment of opportunistic infections, and any other therapy deemed appropriate by physicians and health care staff at the antiretroviral therapy clinic. Persons with negative sputum smear and CXR but with positive culture for *M. tuberculosis* were followed up and registered for TB treatment.

Statistical Methods

We calculated simple proportions for all analyses of sensitivity, specificity, and predictive value. For categorical variables, we compared proportions using χ^2 tests and, when appropriate, Fisher's exact test. For continuous variables, we compared medians using the Wilcoxon rank sum test. To calculate the agreement of CXR readings between the expert radiologist and the TB program, we used the kappa statistic (κ). We used multivariate logistic regression to determine adjusted odds ratios for TB risk factors. Variables with *P* values less than 0.2 from bivariate analysis were included in the model. We assessed model fit using the maximum likelihood test.

We simulated the performance of various screening algorithms using the results of symptom screening, sputum smear microscopy (concentrated and direct), and chest radiography. Cost of each strategy was estimated based on public sector actual costs per test. All data were entered and cleaned at one central site using Microsoft Access. Data were analyzed by a team of investigators from participating institutions using Statistical Package for Social Services version 14.0 (SPSS, Inc., Chicago, IL).

Ethical Considerations

The Ethiopian Science and Technology Commission, the national ethics review board, reviewed this protocol and provided ethical approval. The protocol was also reviewed by the US Centers for Disease Control and Prevention and found to be a public health program evaluation not requiring oversight by a human subjects' research institutional review board.

RESULTS

Patients

From November 2005 to June 2006, we evaluated 498 HIV-positive clients for enrollment in the study. Forty-five persons were excluded because of pregnancy or suspected pregnancy (n = 31), treatment with antibiotics with anti-TB activity in the past 2 weeks (n = 6), unwillingness or inability to complete follow-up tests (n = 6), and current anti-TB therapy (n = 2). An additional 15 patients were excluded because of missing or incomplete sputum smear and culture results. The remaining 438 patients were enrolled in the study (Fig. 1).

Of the 438 HIV-infected persons enrolled, 265 (61%) were female and median age was 34 years (range: 18–65 years, Table 1). Few subjects reported TB risk factors such as exposure to a known TB case (n = 30, 7%), history of incarceration (n = 31, 7%), or prior history of TB diagnosis (n = 59, 13%). The median CD4 cell count was 181 cells per

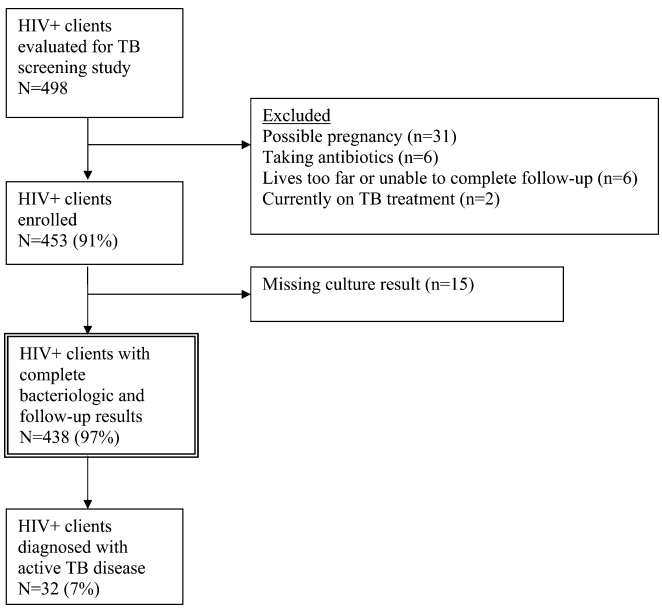


FIGURE 1. Study sample selection from HIV-positive clients attending a VCT clinic in Addis Ababa, Ethiopia.

TABLE 1. Demographic and Clinical Characteristics of HIV-Positive Clients Screened for TB Disease (N = 438)

Characteristic	Total, N = 438	TB Case, n = 32	Non-TB Case, n = 406	*P**	Bivariate RR (95% CI)
Sex					
Male	173 (39.5)	19 (11)	154 (89)	0.023	2.24 (1.14 to 4.41)†
Female	265 (60.5)	13 (4.9)	252 (95.1)	—	Referent
Age, median yrs (range)	34 (18–65)	39 (19–50)	33.5 (18–65)	0.08	—
15–24 yrs	44 (10.1)	5 (11.4)	39 (88.6)		Referent
25–44 yrs	334 (76.3)	20 (6.0)	314 (94)	0.19	0.53 (0.21 to 1.33)
45–64 yrs	59 (13.5)	7 (11.9)	52 (88.1)	0.82	1.04 (0.35 to 3.07)
≥65+ yrs	1 (0.2)	0	1 (100)	NA	NA
Body mass index, median (range)	21 (13–34)	—	—	—	—
<18.5	70	6	64	—	1.22 (0.51 to 2.93)
≥18.5	270	19	251	—	Referent
Performance scale					
Normal activity level	297 (68.4)	20 (6.7)	277 (93.3)	—	Referent
Not at normal activity level	137 (31.6)	12 (8.8)	125 (91.2)	0.44	1.3 (0.65 to 2.58)
Symptoms with normal activity	127 (92.7)	11	116	NA	NA
Bedridden with 50% activity	7 (5.1)	1	6	NA	NA
Bedridden with <50% activity	3 (2.2)	0	3	NA	NA
Exposed to known TB case					
Yes	30 (6.9)	4 (13.3)	26 (86.7)	0.26	1.93 (0.73 to 5.15)
No	406 (93.1)	28 (6.9)	378 (93.1)	—	Referent
History of incarceration					
Yes	31 (7.1)	3 (9.7)	28 (90.3)	0.48	1.39 (0.45 to 4.33)
No	403 (92.6)	28 (6.9)	375 (93)	—	Referent
History of TB diagnosis					
Yes	59 (13.5)	2 (3.4)	57 (96.6)	0.29	0.43 (0.10 to 1.74)
No	378 (86.5)	30 (7.9)	348 (92.1)	—	Referent
CD4 cell count, median (range)	181 (2–1185)	110 (18–633)	186 (2–1185)	0.047†	—
mean	—	175.9	238	—	—
<250 cells/mm^3	273 (63.3)	24 (8.8)	249 (91.2)	0.48	1.74 (0.80 to 3.77)
≥250 cells/mm^3	158 (36.7)	8 (5.1)	150 (94.9)	—	Referent
Sputum smear and culture results					
Smear positive, culture positive	9 (28.1)	9 (28.1)	NA	NA	NA
Smear negative, culture positive	18 (56.2)	18 (56.2)			
Smear positive, culture negative	5 (15.6)	5 (15.6)			

NA RR and *P* value not calculated for exceedingly small cell sizes or where not appropriate.
*The *P* value determined by χ^2 test.
†Statistically significant at $P < 0.05$ level.

cubic millimeter, with 273 (63.3%) subjects having CD4 cell counts less than 250 cells per cubic millimeter.

Overall, 32 (7%) HIV-positive clients were diagnosed with confirmed TB disease: of those, 9 (28%) were smear positive and culture positive (sm+cx+), 18 (56%) were smear negative but culture positive (sm−cx+), and 5 (16%) were smear positive but culture negative (sm+cx−, Table 1). Direct smear microscopy by Ziehl–Neelson method detected 3 of 32 TB cases (9%). When combined with the sputum concentration method, 14 cases were AFB smear positive.

Descriptive and clinical characteristics of 32 TB cases were compared with 406 non-TB cases in bivariate analysis. TB cases were more likely to be male [relative risk (RR) = 2.24, confidence interval (CI) = 1.14 to 4.41] but were not more likely to have other common risk factors for TB disease (eg, contact with TB case, history of incarceration, prior TB; Table 1). TB cases had a lower median CD4 cell count compared with non-TB cases. On clinical evaluation, TB cases were more likely to report symptoms of cough (RR = 2.32, CI = 1.19 to 4.51), fever (RR = 4.31, CI = 2.17 to 8.55), or night sweats (RR = 2.63, CI = 1.34 to 5.15), of any duration (Table 2). In multivariable analysis, controlling for sex, age, CD4 cell count, and TB symptoms, only fever (adjusted odds ratio = 5.13, CI = 1.66 to 15.90) remained a significant predictor of TB disease.

Symptom Screening

Individual Symptoms

The sensitivity, specificity, and predictive value of each of the 8 symptoms, if screened individually, are presented in Table 3. Cough of any duration had a sensitivity of 44% and

TABLE 2. Symptoms Reported Among HIV-Positive Clients Undergoing Screening for TB Disease, by TB Disease Status (N = 438)

Symptom*	Total, N = 438	TB Case, n = 32	Non-TB Case, n = 406	P†	Bivariate RR (95% CI)‡
Cough	110	14	96	0.012	2.32 (1.19 to 4.51)§
Fever	121	20	101	<0.001	4.31 (2.17 to 8.55)§
Night sweats	122	16	106	0.004	2.63 (1.34 to 5.15)§
Weight loss	211	19	192	0.168	1.70 (0.79 to 3.66)
Fatigue	201	20	181	0.057	1.93 (0.97 to 3.85)
Loss of appetite	141	14	127	0.164	1.61 (0.82 to 3.13)
Shortness of breath	43	4	39	0.513	1.46 (0.53 to 4.01)
Chest pain	20	2	18	0.646	1.42 (0.36 to 5.57)

*Patients could report presence of more than one symptom.
†The P value determined by χ^2 test.
‡Compared with patients without this symptom.
§Statistically significant result with $P < 0.05$.

specificity of 76%. In addition, 96 non-TB patients reported cough, so the positive predictive value of cough was only 13% (ie, "How many patients with cough actually have TB disease?"). However, the negative predictive value was 95% (ie, "How many patients without a cough are free of TB disease?"). Single-symptom screening for fever (of any duration) would detect 63% of TB cases, weight loss would detect 68%, and fatigue 63%. Negative predictive values were above 95% for single-symptom screenings that used fever (96%), weight loss (95.5%), or night sweats (95%).

Symptoms in Combination

Screening for cough or fever in all HIV-positive clients identified 24 (75%) TB cases, with a specificity of 64% (Table 3). Negative predictive value was 97% for clients who reported no cough and no fever. Screening for any 1 of cough, fever, or night sweats would identify 25 (78%) TB cases, but specificity was low at 56%. Screening for any 1 of cough, fever, or weight loss would identify more TB cases (n = 26, 87%), but specificity is lowered to 34%.

Stratification by Immune Status

Among 273 subjects with known CD4 cell count <250 cells per cubic millimeter, we identified 24 (9%) TB cases. Of these, 22 (92%) reported at least 1 TB symptom. The sensitivity of screening for any 1 of 8 symptoms in the group was 91%, with a specificity of 19%. Among 158 subjects with CD4 ≥250 cells per cubic millimeter, 8 (5%) TB cases were identified, of which 5 (63%) reported at least 1 TB symptom. The sensitivity of screening for any symptoms in subjects with CD4 ≥250 cells per cubic millimeter was 63%, with a specificity of 31%. Overall, subjects with CD4 <250 cells per cubic millimeter were 1.34 times more likely to present with any TB symptom compared with subjects with CD4 ≥250 cells per cubic millimeter, though this did not reach statistical significance ($P = 0.12$, CI 0.83 to 2.16).

Chest Radiography

Of 88 abnormal CXRs with findings suspicious for TB disease, 19 (22%) had confirmed TB disease, for a sensitivity of 60% and specificity of 83% (Table 3). Reliability of chest radiography results between the 2 radiologists showed 92% agreement overall (kappa = 0.61, CI = 0.48 to 0.73). Agreement was lower among CXRs of active TB cases (75%, kappa = 0.53, CI = 0.26 to 0.79).

Simulated Performance of Current TB Screening Algorithm

If HIV-infected persons in our study were evaluated according to the current TB screening guidelines for Ethiopia (adapted from WHO guidelines, Fig. 2A), 5 of 32 confirmed TB cases (16%) would have been missed from the outset because they were asymptomatic. Three of 32 (9%) would have been detected by symptom screening and sputum smear microscopy (using direct Ziehl-Neelson smear only), with an additional 9 (28%) detected if concentrated sputum smear methods were used. Three hundred twenty-three of 326 symptomatic persons (99%) had negative direct AFB smear results and thus may have received a trial of antibiotics; this would have resulted in a delay in TB diagnosis for 24 of 27 symptomatic persons (89%) with TB disease. With chest radiography, an additional 86 persons would have been considered as "clinical" TB cases and thus initiated on TB treatment. However, only 17 of 86 (20%) were proven cases of TB, whereas the remaining 69 (80%) were not. With the current algorithm, 7 of 27 symptomatic TB cases (22%) would not have been detected. Overall, this algorithm based on routinely available diagnostic tests has a sensitivity of 63% and specificity of 83%.

An alternate strategy whereby all HIV-positive clients would undergo screening first by chest radiography, followed by sputum smear only for those with negative CXRs, was evaluated (Fig. 2B). With this approach, sputum smear would be performed for 350 clients, 24 (7%) more than the 326 clients tested with sputum smear using the current Ethiopian guidelines (Fig. 2A). Overall, 22 of 32 (69% sensitivity) TB cases would be detected. Specificity of this strategy is similar to the current Ethiopian guidelines.

Comparing costs of strategy A (Ethiopian national guidelines) vs. strategy B (Table 4) reveals a 10% increase in case detection (22 cases vs. 20 cases) with strategy B for a 17% greater cost per case detected ($42.16 vs. $36.10). More sputum smears and CXRs would be done using strategy B.

DISCUSSION

We identified confirmed TB disease among 7% of newly diagnosed HIV-infected persons presenting to an urban VCT clinic in Ethiopia. We found that routinely available TB screening tests have limited sensitivity for detecting active TB disease among HIV-infected persons. Symptom screening using the most widely recommended criteria of cough for more than 2 weeks would have failed to detect 62% of TB cases. Screening for the combined symptoms of cough, fever, or night sweats of any duration would detect 78% of cases but

TABLE 3. Test Performance of Symptom Screening and Chest Radiography for TB Disease Among HIV-positive Clients (N = 438)

Test	Total*	TB cases	Non-TB cases	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Total enrolled	438	32	406				
Individual symptoms (of any duration)†							
Cough	110	14	96	43.8	76.4	12.7	94.5
Fever (missing 4 non-TB cases)	121	20	101	62.5	74.9	16.5	96.2
Night sweats (missing 1 TB case; 14 non-TB)	122	16	106	51.6	73.0	13.1	95.0
Weight loss (missing 4 TB cases; 53 non-TB)	211	19	192	67.9	45.6	9.0	94.7
Fatigue (missing 4 non-TB cases)	201	20	181	62.5	55	10.0	94.8
Loss of appetite (missing 6 non-TB cases)	141	14	127	43.8	68.3	9.9	93.8
Shortness of breath (missing 4 TB cases; 14 non-TB)	43	4	39	14.3	90.1	9.3	93.6
Chest Pain (missing 2 TB cases; 17 non-TB)	20	2	18	6.7	95.4	10.0	93.0
Combination of symptoms (of any duration)§							
Cough or fever (missing 1 TB case; 4 non-TB)	170	24	146	75.0	64.0	14.1	97.0
Cough or night sweats (missing 1 TB case; 6 non-TB)	177	20	157	64.5	60.8	11.3	95.7
Cough or weight loss (missing 2 TB cases; 43 non-TB)	249	24	225	80.0	38.0	9.6	95.8
Cough or fatigue (missing 2 non-TB cases)	242	23	219	71.9	45.8	9.5	95.4
Fever or night sweats (missing 11 non-TB cases)	168	24	144	75.0	63.5	14.3	96.9
Fever or weight loss (missing 3 TB cases; 41 non-TB)	247	23	224	79.3	38.6	9.3	95.9
Fever or fatigue (missing 4 non-TB cases)	245	25	220	78.1	45.3	10.2	96.3
Cough or fever or night sweats (missing 7 non-TB cases)	202	25	177	78.1	55.6	12.4	96.9
Cough or fever or weight loss (missing 2 TB cases; 34 non-TB)	272	26	246	86.7	33.9	9.6	96.9
Cough or fever or fatigue (missing 3 non-TB cases)	263	26	237	81.3	41.2	9.9	96.5
Any 1 symptom present	326	27	299	84.4	26.4	8.3	95.5
At least 3 symptoms present	172	22	150	68.8	63.1	12.8	96.2
Chest radiography							
Suspicious for TB (missing 2 TB; 6 non-TB)	88	19	69	59.4	83.0	21.6	96.3

*Total number of patients who reported presence of symptom(s).

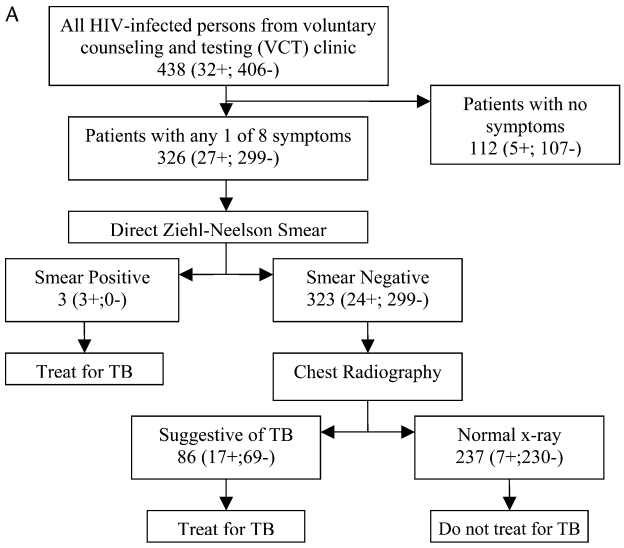
†Sensitivity, specificity, positive predictive value and negative predictive value are calculated only among the subset of patients who have complete data for the individual symptom being evaluated.

§Patients reporting presence of at least one symptom in the combination are included in the calculation of test performance. Patients with missing responses to both (or all 3) symptoms in the combination are not included in calculations of sensitivity, specificity, positive predictive value and negative predictive value.

would have low positive predictive value (12%). Predictive value will vary based on the prevalence of TB disease in the screened population, but the 7% rate in our study is similar to that found in other studies evaluating TB screening algorithms among HIV-infected persons.[26–28] Nonetheless, HIV care and treatment settings must consider TB disease prevalence when estimating the likely performance of any screening algorithm.

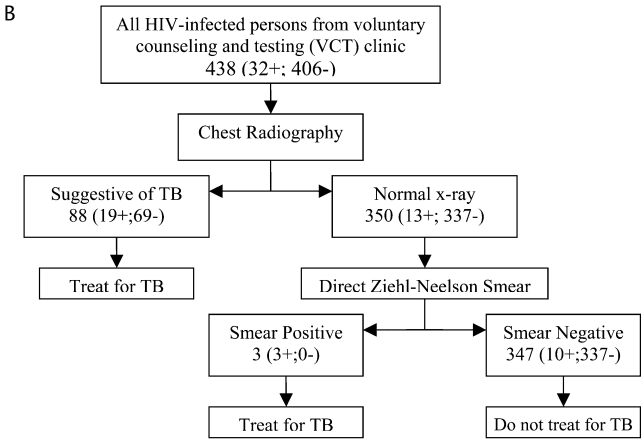
Although symptom screening fails to detect all culture-positive TB cases, our results demonstrate that it can serve as an effective means for ruling out active TB; patients who report no cough and no fever are very unlikely to have TB disease (specificity 64%, negative predicitive value 97%). Thus, symptom screening may be a useful tool for HIV care and treatment programs to use for excluding active TB in patients being considered for ARV therapy or IPT. A strategy that combines symptom screening with sputum smear microscopy and chest radiography (eg, current Ethiopian national guidelines) would detect up to 62% of TB cases, with a specificity of 82% and high negative predictive value. In the absence of widespread availability of culture technology, this 3-step approach may offer an acceptable balance as an algorithm that misses the fewest number of TB cases, while minimizing overdiagnosis and overtreatment.

Of note, in this study, 15% of confirmed cases reported no TB symptoms and had negative sputum smear for AFB. These rates are similar to results from other recent studies that identified cases of subclinical TB only detected by sputum mycobacterial culture.[7,8] The paucibacillary nature of TB disease in immunocompromised patients reduces the performance of sputum smear microscopy, which requires 5000–10,000 bacilli for detection. Sputum culture is 10 times more sensitive, but is generally reserved for TB treatment failures, retreatment cases, or others considered "high risk" for drug-resistant TB in WHO guidelines,[29] largely because of limited resources and the high cost and complexity of culture technology. However, our study and others challenge this notion and provide support for earlier more widespread use of sputum culture for TB diagnosis among HIV-infected patients. Moreover, emerging reports of rapidly fatal drug-resistant TB among HIV-infected persons underscore the need for scale-up of laboratory capacity for *M. tuberculosis* detection and drug resistance testing.[30] Reducing diagnostic and treatment delays may help reduce TB transmission, slow the progression of HIV



		Gold standard tests for TB		
Diagnostic Method:		+	-	**Total**
Symptom screen,	+	20	69	89
then sputum smear,	-	12	337	349
then chest x-ray	**Total**	32	406	438

Sensitivity = 62.5 %
Specificity = 83.0%
Positive Predictive Value = 22.5%
Negative Predictive Value = 92.7%



		Gold standard tests for TB		
		+	-	**Total**
Diagnostic Method: Chest x-ray then sputum smear	+	22	69	91
	-	10	337	347
	Total	32	406	438

Sensitivity = 68.8 %
Specificity = 83.0%
Positive Predictive Value = 24.2%
Negative Predictive Value = 97.1 %

FIGURE 2. A, Simulation of TB screening using current Ethiopian national guidelines: symptom screening, followed by direct sputum smear on positives, and chest radiography only for smear-negative patients. B, simulation of TB screening using chest radiography for all HIV-positive clients as the entry point, followed by sputum smear on all positives (N = 438). Parenthesis contain number of TB cases (+) and non-TB cases (−) in each step of the algorithm.

TABLE 4. Comparative Costs of Strategies for Screening for Pulmonary TB Among HIV-Positive Clients*

	Strategy A†		Strategy B‡	
	Number	**Cost (USD)**	**Number**	**Cost (USD)**
Sputum smears	326	$182.56	350	$196.00
CXRs	323	$539.41	438	$731.46
Total cost		$721.97		$927.46
No. cases diagnosed	20	—	22	—
Cost per diagnosed case	—	$36.10	—	$42.16

*Cost estimates based on charges for each test in the public sector: sputum smear (5 Ethiopian birr = $0.56), CXR (15 Ethiopian birr = $1.67).

†Strategy A, Ethiopian national guidelines: screening all symptomatic HIV-positive clients with sputum smear, followed by chest radiography for smear-negative TB suspects.

†Strategy B, alternative strategy: chest radiography screening for all HIV-positive clients, regardless of symptoms, followed by sputum smear for patients with normal chest x-ray.

infection, and lower the high early mortality rate among HIV-infected TB patients.[4]

We found that sputum concentration improved the case detection rate by more than 4 times that of direct microscopy. However, even concentrated smear methods failed to detect 18 (56%) culture-confirmed cases. This is likely due to the paucibacillary nature of TB disease in HIV-infected persons and the known limits of detection for smear microscopy. Sputum smear (by either method) did diagnose 5 TB cases not detected by culture. Smear-positive, culture-negative TB cases are known to occur as mycobacteria may be killed during transport or processing of sputum specimens. Smear may still detect dead bacilli, whereas culture requires live replicating mycobacteria for growth and detection. The Petroff method used by the national TB reference laboratory is known to be more harsh than other decontamination methods and may have contributed to the high rate of culture-negative, smear-positive cases.[22]

Chest radiography is an attractive diagnostic tool for TB, but use of chest radiography may be limited by extensive interobserver and intraobserver variability in interpretation of the films.[31] Coinfection with HIV further challenges the reliability of chest radiography because radiographic patterns in patients with pulmonary TB are atypical or even normal.[10] In addition, there is skepticism about the cost-effectiveness of CXR screening in resource-limited countries.[32,33] In our study, we found excellent agreement among independent radiologists blinded to patient symptoms and to each other. In a simulated strategy of chest radiography screening for all HIV-positive clients, we found that 10% more cases would be diagnosed at an additional cost of $6 per case identified. Nonetheless, this strategy may be preferable if it avoids use of an "antibiotic trial" that can lead to delays in diagnosis and has limited utility in resource-limited settings with high HIV prevalence.[24]

Our study has a number of limitations that must be considered. Patients with symptoms, who were smear negative and culture negative, were not followed longitudinally or reevaluated for subsequent development of TB disease. These patients may be true TB cases whom we failed to detect using solid media culture but who may have been detected with a more sensitive technique (eg, liquid culture). This may lead to an underestimate of TB prevalence in this study and reduce the calculated sensitivity of symptom screening. Although liquid culture is known to be a more sensitive diagnostic method, it was not available in Ethiopia at the time of our study. HIV-infected patients are known to develop disseminated TB disease at a higher rate than HIV-uninfected persons, but an evaluation of an algorithm for extrapulmonary TB was beyond the scope of the present study. Last, symptom screening may vary by provider and health care setting, so performance of this tool may differ across settings.

Despite these limitations, our study provides a critical, prospective evaluation of routinely available TB diagnostic tools compared with sputum mycobacterial culture as a gold standard. That we screened all HIV-positive clients, regardless of symptoms, is a major strength of our study. Indeed, 15% of TB cases were asymptomatic in our study and were only detected by sputum culture. These patients may have initiated ARVs or IPT and would be at risk for developing immune reconstitution syndrome or isoniazid resistance, respectively. The limited availability of more sensitive diagnostic tests for TB must be addressed. Laboratories must be strengthened in high TB burden and HIV prevalence settings. Without investing in better diagnostic modalities, patients with TB and HIV coinfection are at high risk of misdiagnosis, delayed diagnosis with poor treatment outcomes, TB drug resistance, and community spread of their disease.

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