ORIGINAL ARTICLE

An Algorithm for Tuberculosis Screening and Diagnosis in People with HIV

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ABSTRACT

BACKGROUND

Tuberculosis screening is recommended for people with human immunodeficiency virus (HIV) infection to facilitate early diagnosis and safe initiation of antiretroviral therapy and isoniazid preventive therapy. No internationally accepted, evidence-based guideline addresses the optimal means of conducting such screening, although screening for chronic cough is common.

METHODS

We consecutively enrolled people with HIV infection from eight outpatient clinics in Cambodia, Thailand, and Vietnam. For each patient, three samples of sputum and one each of urine, stool, blood, and lymph-node aspirate (for patients with lymphadenopathy) were obtained for mycobacterial culture. We compared the characteristics of patients who received a diagnosis of tuberculosis (on the basis of having one or more specimens that were culture-positive) with those of patients who did not have tuberculosis to derive an algorithm for screening and diagnosis.

RESULTS

Tuberculosis was diagnosed in 267 (15%) of 1748 patients (median CD4+ T-lymphocyte count, 242 per cubic millimeter; interquartile range, 82 to 396). The presence of a cough for 2 or 3 weeks or more during the preceding 4 weeks had a sensitivity of 22 to 33% for detecting tuberculosis. The presence of cough of any duration, fever of any duration, or night sweats lasting 3 or more weeks in the preceding 4 weeks was 93% sensitive and 36% specific for tuberculosis. In the 1199 patients with any of these symptoms, a combination of two negative sputum smears, a normal chest radiograph, and a CD4+ cell count of 350 or more per cubic millimeter helped to rule out a diagnosis of tuberculosis, whereas a positive diagnosis could be made only for the 113 patients (9%) with one or more positive sputum smears; mycobacterial culture was required for most other patients.

CONCLUSIONS

In persons with HIV infection, screening for tuberculosis should include asking questions about a combination of symptoms rather than only about chronic cough. It is likely that antiretroviral therapy and isoniazid preventive therapy can be started safely in people whose screening for all three symptoms is negative, whereas diagnosis in most others will require mycobacterial culture.

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Tuberculosis is a leading cause of death among adults who are infected with the human immunodeficiency virus (HIV).[1] In some countries, death occurs in up to 50% of these patients during treatment for tuberculosis, usually within 2 months after tuberculosis has been diagnosed.[2-6] Delayed diagnosis of tuberculosis is probably an important contributor to high mortality.[7] Antiretroviral therapy can substantially reduce the risk of death,[2,4] but initiating this therapy in a patient with untreated tuberculosis can lead to the immune-reconstitution inflammatory syndrome.[8-13] To reduce the risk of tuberculosis, the World Health Organization (WHO) recommends the use of isoniazid preventive therapy for people with HIV infection who do not have active tuberculosis.[14] In 2007, less than 1% of eligible patients worldwide received isoniazid preventive therapy, largely because many programs lack the ability to accurately rule out tuberculosis.[1]

To reduce mortality, increase the safety of antiretroviral therapy, and facilitate the use of isoniazid preventive therapy, the WHO recommends tuberculosis screening at the time that HIV infection is diagnosed, before the initiation of antiretroviral therapy and isoniazid preventive therapy, and regularly thereafter.[14] There are no internationally accepted, evidence-based guidelines for performing such screening. Chest radiography and microscopical examination of sputum smears for acid-fast bacilli are relatively insensitive screens for tuberculosis in people with HIV infection,[15,16] and those who have no symptoms, normal radiographs, and negative smears may still have culture-positive tuberculosis.[17,18] Multiple studies have been conducted to develop a simple method for ruling out tuberculosis in people with HIV infection,[19-23] but methodologic issues, including failure to use highly sensitive diagnostic tests, enrollment at single centers, and enrollment of highly selected populations, preclude the use of any of these studies alone as the basis for global health policy.

We conducted a prospective study to develop an evidence-based clinical algorithm for people with HIV infection in resource-limited locations — first, to rule out tuberculosis, and second, to diagnose tuberculosis among people for whom the diagnosis was not ruled out. We enrolled a broad cross-section of people with HIV infection from clinics in Cambodia, Thailand, and Vietnam; performed standardized mycobacterial testing on multiple specimens from multiple anatomical sites; and analyzed the utility of readily available symptoms, signs, and diagnostic tests in ruling out or confirming the presence of tuberculosis.

METHODS

ENROLLMENT AND SPECIMEN COLLECTION

People with HIV infection were enrolled consecutively from outpatient facilities that provide care for HIV-infected patients, including four clinics in Cambodia (two in Banteay Meanchey province, one in Battambang, and one in Phnom Penh), one in Bangkok, Thailand, and three in Ho Chi Minh City, Vietnam, from September 2006 through July 2008. All persons with HIV infection presenting to the clinics during the enrollment period were screened for eligibility, and if eligible, they were invited to participate in the study. Patients were recruited regardless of the presence or absence of symptoms or clinical suspicion that they may have had tuberculosis. Patients with documented HIV infection were eligible for the study if they were older than 6 years of age, had not been screened for tuberculosis with the use of chest radiography or sputum smears in the previous 3 months, had not received treatment for tuberculosis or isoniazid preventive therapy in the previous year, and had taken no medications with antituberculosis activity in the previous month. Since our primary objective was to derive algorithms for tuberculosis screening and diagnosis before the initiation of antiretroviral therapy, patients who were receiving antiretroviral therapy were excluded from the analysis.

The study was approved by human subjects committees at the U.S. Centers for Disease Control and Prevention and collaborating institutions in each country. After providing written informed consent, patients underwent a standardized interview and physical examination, chest radiography, and testing for a complete blood count and a count of CD4+ T lymphocytes. Patients provided three sputum specimens over the course of 2 days and one specimen each of urine, blood, and stool. If physical examination revealed peripheral lymph nodes larger than 1 cm in diameter (>2 cm for inguinal nodes), the largest palpable node was aspirated with a wide-gauge needle.

LABORATORY ASSESSMENTS

One reference laboratory was used in each country. Standardized methods, including quality assurance and efforts to avoid cross-contamination, were implemented in all three laboratories. All specimens were examined by means of concentrated Ziehl–Neelsen microscopy and were cultured on Löwenstein–Jensen medium. Specimens obtained in Thailand and Vietnam were also cultured in the Mycobacterial Growth Indicator Tube.[24] Blood specimens were inoculated directly into Myco/F-Lytic bottles and placed in automated blood-culture instruments (BACTEC 9050 and 9120 systems).[24] Positive cultures were identified as *Mycobacterium tuberculosis* by means of biochemical tests or the Accuprobe *M. tuberculosis* complex assay.[24]

STATISTICAL ANALYSIS

Patients for whom at least one of the cultured specimens tested positive for *M. tuberculosis* were considered to have tuberculosis. (Throughout this article, "tuberculosis" refers to the disease, also called active tuberculosis.) Patients for whom no cultured specimen was positive and for whom at least one cultured sputum specimen and one cultured nonsputum specimen were negative for *M. tuberculosis* were considered not to have tuberculosis.

The analysis for tuberculosis screening included only those variables that could be readily ascertained at any level of the health care system (e.g., signs, symptoms, and exposure history). The goal of tuberculosis screening is to divide the population into two groups: those who do not have tuberculosis and those who need further evaluation to confirm the presence or absence of tuberculosis. Because a missed diagnosis of tuberculosis in a person with HIV infection can have serious adverse consequences, we required the screening step to be highly sensitive. We conducted an exhaustive search using all combinations of between one and five signs, symptoms, and medical-history indicators to identify combinations with a sensitivity of 85% or more and a high specificity for a given sensitivity level.

For all patients who were considered to require further evaluation on the basis of the above screening step, our goal was to divide them into three groups: patients for whom tuberculosis was diagnosed without further need for evaluation, patients for whom tuberculosis was ruled out, and patients for whom additional clinical evaluation was needed, followed by confirmatory mycobacterial culture. In this diagnostic step, we used recursive partitioning analysis to construct a decision tree,[25] using smear microscopy for acid-fast bacilli, chest radiography, and blood tests as predictors.

We used data from our study to compare the performance of the algorithm we developed with that of the current algorithm recommended by the WHO for diagnosing smear-negative tuberculosis[26] and with that of an approach that uses chest radiography and two sputum smears for all patients. We determined the number and characteristics of patients who were misclassified. For additional details about the clinical sites, laboratory methods, and statistical analysis, see the Supplementary Appendix, available with the full text of this article at NEJM.org.

RESULTS

PATIENTS

A total of 1836 patients with HIV infection who were not yet receiving antiretroviral therapy were screened for eligibility at participating sites (for details on enrollment, see the Supplementary Appendix). Of these patients, 1771 were eligible for enrollment and 1768 were enrolled; 20 patients could not be classified as having or not having tuberculosis on the basis of our definitions and were excluded from the study. Tuberculosis was diagnosed in 267 (15%) of the remaining 1748 patients.

The median age of enrolled patients was 31 years (range, 7 to 72), and 921 patients (53%) were male. The median CD4+ cell count was 242 per cubic millimeter (interquartile range, 82 to 396). Other characteristics are presented in Table 1.

PERFORMANCE CHARACTERISTICS FOR INDIVIDUAL PREDICTORS

Symptoms were commonly reported by the patients enrolled in the study (Table 2). Among the symptoms patients reported having in the 4 weeks before enrollment, those with the highest sensitivity for the detection of tuberculosis were fatigue (75%), fever (74%), weight loss (73%), and cough (71%). A cough lasting 2 or 3 weeks or more, a symptom that clinicians commonly rely on for tuberculosis screening, was not sensitive

Table 1. Characteristics of Patients with HIV Infection According to Whether Tuberculosis Was Diagnosed.

Characteristic	All Patients (N=1748)	Tuberculosis Diagnosed (N=267)	Tuberculosis Not Diagnosed (N=1481)
Median age (range) — yr	31 (7–72)	31 (19–72)	31 (7–65)
Male sex — no. (%)	921 (53)	173 (65)	748 (51)
Country — no. (%)			
Cambodia	847 (48)	126 (47)	721 (49)
Thailand	501 (29)	31 (12)	470 (32)
Vietnam	399 (23)	109 (41)	290 (20)
Median CD4+ cell count (interquartile range) — per mm^3	242 (82–396)	104 (33–261)	266 (101–419)
Documented HIV risk factors — no. (%)*			
Sex with opposite-sex partner	1519 (87)	231 (87)	1288 (87)
Sex with same-sex partner	235 (13)	15 (6)	220 (15)
Sex with sex worker	459 (26)	82 (31)	377 (25)
Receipt of money, gifts, or favors for sex	98 (6)	9 (3)	89 (6)
Current HIV-infected sexual partner	583 (33)	61 (23)	522 (35)
Injection-drug use	236 (14)	77 (29)	159 (11)
Blood transfusion	74 (4)	16 (6)	58 (4)
Currently taking trimethoprim–sulfamethoxazole — no. (%)	54 (3)	9 (3)	45 (3)
Currently receiving antifungal treatment — no. (%)	20 (1)	6 (2)	14 (1)
Any lymphadenopathy — no. (%)†	222 (13)	81 (30)	141 (10)
Chest radiograph — no. (%)			
Normal findings	1314 (75)	85 (32)	1229 (83)
Abnormal findings consistent with tuberculosis	317 (18)	160 (60)	157 (11)
Abnormal findings not consistent with tuberculosis	73 (4)	13 (5)	60 (4)
Missing data	44 (3)	9 (3)	35 (2)
Abnormalities			
Cavity	35 (2)	27 (10)	8 (1)
Infiltrate or consolidation	243 (14)	123 (46)	120 (8)
Pleural effusion	35 (2)	25 (9)	10 (1)
Hilar or paratracheal adenopathy	66 (4)	37 (14)	29 (2)
Median Karnofsky score (interquartile range)‡	90 (80–90)	90 (80–90)	90 (90–100)

* All risk factors were self-reported and, with the exception of current sex partner with HIV infection, could have been relevant at any time during the patient's life.
† Lymphadenopathy was defined as any peripheral lymph node measuring 1 cm or more in diameter in a noninguinal region or any inguinal node measuring 2 cm or more in diameter.
‡ Scores range from 10 to 100, with lower scores indicating more severe clinical illness or impairment.

for the disease (sensitivity of 33% for a cough lasting more than 2 weeks and 22% for a cough lasting more than 3 weeks). Microscopical examination of two sputum specimens for acid-fast bacilli was the best predictor of tuberculosis on the basis of a positive likelihood ratio, but its sensitivity was only 38%.[27] Chest radiography was the best single predictor for ruling out a diagnosis of tuberculosis; with a negative likelihood ratio of 0.41, however, it was a relatively weak predictor when used alone.[27]

SCREENING ALGORITHM

We evaluated the performance characteristics of more than 80 million unique combinations of one to five predictors of tuberculosis. Many combinations performed similarly well. The best-performing combinations of four or five predictors

Table 2. Performance Characteristics of Indicators in Predicting Tuberculosis in All 1748 Patients.

Indicator	Prevalence	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value	Likelihood Ratio*	
						Negative	Positive
	no. (%)	%	%	%	%		
Cough							
In previous 24 hr	622 (36)	58	68	90	25	0.61	1.83
In previous 4 wk							
Any	890 (51)	71	53	91	21	0.55	1.50
Lasting ≥2 wk	355 (20)	33	82	87	25	0.82	1.83
Lasting ≥3 wk	241 (14)	22	88	86	25	0.88	1.84
Lasting ≥4 wk	194 (11)	17	90	86	24	0.92	1.72
With sputum production	688 (39)	52	63	88	20	0.76	1.40
Fever							
In previous 24 hr	374 (21)	42	82	89	30	0.70	2.40
In previous 4 wk							
Any	867 (50)	74	55	92	23	0.48	1.63
Lasting ≥2 wk	297 (17)	39	87	89	35	0.71	2.95
Lasting ≥3 wk	199 (11)	25	91	87	34	0.82	2.88
Lasting ≥4 wk	165 (9)	21	93	87	33	0.86	2.78
Hemoptysis in previous 4 wk	56 (3)	4	97	85	20	0.99	1.35
Diarrhea in previous 4 wk	510 (29)	35	72	86	18	0.90	1.25
Drenching night sweats							
In previous 24 hr	285 (16)	33	87	88	31	0.77	2.52
In previous 4 wk							
Any	490 (28)	48	75	89	26	0.69	1.94
Lasting ≥2 wk	188 (11)	20	91	86	28	0.88	2.18
Lasting ≥3 wk	141 (8)	16	93	86	30	0.90	2.35
Lasting ≥4 wk	118 (7)	11	94	85	25	0.94	1.89
Weight loss in previous 4 wk	879 (50)	73	54	92	22	0.50	1.58
Loss of appetite							
In previous 24 hr	445 (25)	51	79	90	31	0.61	2.47
In previous 4 wk	591 (34)	58	71	90	26	0.59	1.99
Fatigue in previous 4 wk	993 (57)	75	46	91	20	0.54	1.40
Difficulty sleeping in previous 4 wk	761 (44)	58	59	89	20	0.72	1.41
Previous treatment for tuberculosis	26 (1)	2	99	85	23	0.99	1.67
Household contact with tuberculosis in previous 2 yr	205 (12)	14	89	85	19	0.97	1.26
Body-mass index <18.5†‡	492 (28)	50	76	89	27	0.66	2.05
Temperature >38°C†	119 (7)	20	96	87	45	0.83	4.61
Lymphadenopathy†							
Any	222 (13)	30	90	88	36	0.77	3.19
Head and neck	175 (10)	27	93	88	42	0.78	3.97
CD4+ cell count <200/mm^3	743 (43)	68	61	91	24	0.52	1.76
Either of first 2 sputum smears positive for acid-fast bacilli	120 (7)	38	99	90	84	0.63	29.55
Abnormal chest radiograph	390 (22)	65	85	93	44	0.41	4.42

* The negative likelihood ratio is calculated as (1 − sensitivity) ÷ specificity; the positive likelihood ratio is calculated as sensitivity ÷ (1 − specificity).[27] Small differences in percentages may be due to rounding.
† This evaluation was made on physical examination at enrollment.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 3. Performance Characteristics of Combinations of Predictors.

Predictors	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value	Likelihood Ratio*	
					Negative	Positive
			percent			
Combination of 2 predictors						
Cough or fever of any duration in previous 4 wk	91	37	96	21	0.23	1.44
Cough in previous 24 hr or fever of any duration in previous 4 wk	88	44	95	22	0.27	1.58
Combination of 3 predictors						
Cough or fever of any duration or drenching night sweats for ≥3 wk in previous 4 wk	93	36	97	21	0.19	1.45
Cough, drenching night sweats, or loss of appetite of any duration in previous 4 wk	93	35	97	21	0.19	1.44
Cough in previous 24 hr or fever of any duration or drenching night sweats for ≥3 wk in previous 4 wk	90	43	96	22	0.23	1.58
Cough in previous 24 hr or drenching night sweats or loss of appetite of any duration in previous 4 wk	89	44	96	22	0.24	1.60
Combination of 4 predictors						
Cough of any duration or fever for ≥2 wk or drenching night sweats in previous 24 hr or loss of appetite of any duration in previous 4 wk	93	37	97	21	0.18	1.48
Cough or drenching night sweats or loss of appetite in previous 24 hr or lymphadenopathy of the head or neck in previous 4 wk	88	50	96	24	0.25	1.76

* The negative likelihood ratio is calculated as (1 − sensitivity) ÷ specificity, and the positive likelihood ratio as sensitivity ÷ (1 − specificity).[27]

performed similarly to the best-performing combinations of three predictors. In all cases, requiring two or more predictors for a positive result yielded insufficient sensitivity as compared with requiring one or more predictors. Selected combinations are presented in Table 3. The best combinations of two predictors included fever of any duration in the previous 4 weeks plus either cough of any duration in the previous 4 weeks (91% sensitivity and 37% specificity) or cough in the previous 24 hours (88% sensitivity and 44% specificity). The best algorithms with three predictors included either cough of any duration in the previous 4 weeks or cough in the previous 24 hours, either drenching night sweats for 3 weeks or more or drenching night sweats of any duration in the previous 4 weeks, and either fever of any duration in the previous 4 weeks or loss of appetite of any duration in the previous 4 weeks. As compared with the two-predictor combination of cough or fever of any duration in the previous 4 weeks, a three-predictor combination that added night sweats for 3 weeks or more reduced by 5 the number of patients with false negative screens but increased by 18 the number of patients requiring diagnostic evaluation — that is, for each additional patient correctly classified as having tuberculosis, an additional 3.6 patients had to undergo diagnostic testing. The performance of this algorithm with the addition of chest radiography, along with performance of the algorithm in particular subgroups (e.g., according to CD4+ cell count, sex, and country), is described in the Supplementary Appendix.

DIAGNOSTIC ALGORITHM

The diagnostic algorithm is used to evaluate patients requiring further evaluation for tuberculosis after the screening step — that is, patients who reported having at least one of the three screening symptoms (Fig. 1). We found that microscopical examination of two sputum smears for acid-fast bacilli was the best first step. Among patients with at least one positive sputum smear, 87% had tuberculosis. Among patients with two negative sputum smears, chest radiography was

the next best step. At this point in the evaluation, the prevalence of tuberculosis in the group of patients with a normal chest radiograph was 8%, as compared with 33% in the group with an abnormal chest radiograph. Among patients with a normal chest radiograph, the prevalence of tuberculosis among patients with a CD4+ cell count of 350 or more per cubic millimeter was 5%, as compared with a prevalence of 10% among those with a CD4+ cell count of less than 350 per cubic millimeter.

COMPARISON OF THE STUDY ALGORITHM WITH ALTERNATIVE APPROACHES

Of the 1748 patients tested, 549 (31%) reported having none of the three predictive symptoms in our screen; 18 (3%) actually had tuberculosis and thus received false negative results. The diagnostic step led to an additional 13 false negative results — that is, tuberculosis was ultimately found to be present despite two negative sputum smears, a normal chest radiograph, and a CD4+ cell count of 350 or more per cubic millimeter. The total number of false negative results in the screening and diagnostic steps combined was 31, which is fewer than the number seen with other common approaches to screening and diagnosis. Asking patients only if they have had a cough for more than 2 or 3 weeks, as recommended by the WHO for tuberculosis screening in people with HIV infection, produced 179 false negative results, whereas an approach that relies on the findings of chest radiography and culture of two sputum smears produced 75 false negative results — that is, 75 patients who had tuberculosis also had normal chest radiographs and negative smears for *M. tuberculosis* from two sputum specimens. In addition, the patients who had false negative results with the algorithm used in this study tended to have higher CD4+ cell counts than did the patients who had false negative results with the use of alternative approaches and rarely had positive smears. Many ultimately received a diagnosis of tuberculosis on the basis of liquid culture alone (Table 4).

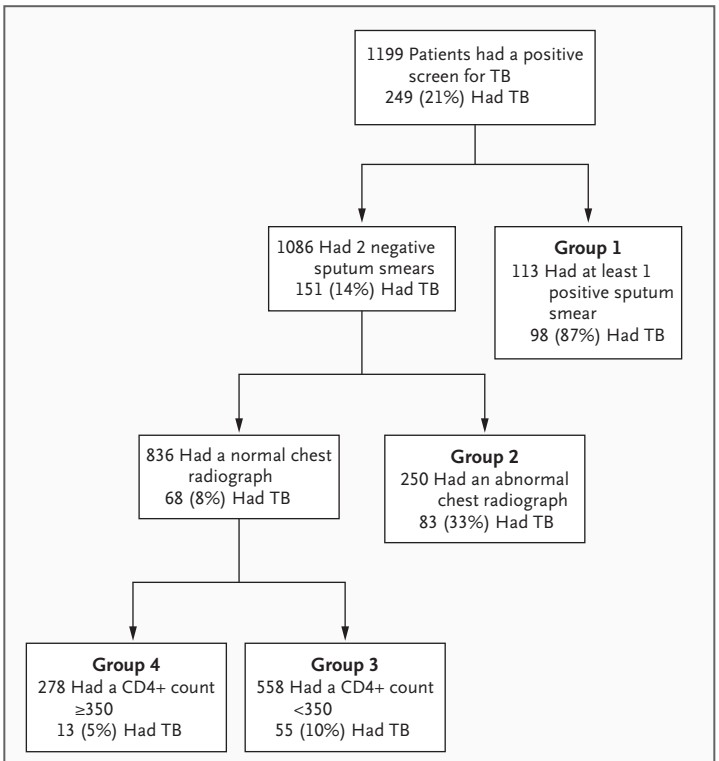

Figure 1. Diagnostic Algorithm for Tuberculosis in Patients with HIV Infection.
Eligibility for diagnostic screening required a history of cough of any duration, fever of any duration, or night sweats lasting 3 weeks or more in the preceding 4 weeks and includes the 1199 patients who reported one or more of these symptoms. For patients in group 1, treatment for tuberculosis (TB) is in most cases indicated immediately. For those in groups 2 and 3, clinical judgment should be used to determine whether immediate treatment is needed, followed by confirmatory mycobacterial culture. For patients in group 4, the best course of action is unclear. Ideally, mycobacterial culture would be obtained, but this group has a lower priority than group 2 or group 3. Reevaluation of group 4 at a later date might be a safe alternative to immediate culture, but this strategy has not been tested.

DISCUSSION

In this study of persons with HIV infection living in Southeast Asia, we found that asking patients about the presence or absence of three symptoms was an effective approach to ruling out a diagnosis of tuberculosis. As compared with other, commonly used approaches to screening for tuberculosis, our approach improves the sensitivity of screening and identifies patients who require further evaluation with the use of specific diagnostic tests.

Like other investigators in similar studies,[20,23] we found that for patients with HIV infection, asking them only about chronic cough was an insensitive approach to screening for tuberculosis. In contrast, asking about combinations of symptoms was effective in ruling out a diagnosis of tuberculosis. We found that the optimal number of predictors, or questions asked, was three. Additional predictors added complexity without

Table 4. Comparison of Study Algorithm with Other Approaches to Tuberculosis Screening and Diagnosis.*

Variable	Study Algorithm (N=1748)†	WHO Approach (N=1748)‡	Chest Radiography and Smears of Two Sputum Specimens (N=1748)§
Tuberculosis ruled out by symptom screening — no.	549	1393	NA
False negative results in screening step — no.	18	179	NA
Sputum smear microscopy needed — no.	1199	355	1748
Chest radiography needed — no.	1086	300	1748
Culture needed — no.	808¶	300	NA
False negative results in diagnostic step — no.	13‖	Unknown	75
Characteristics of patients with false negative results — total no.	31	179	75
Disease site — no.			
Pulmonary	19	89	38
Extrapulmonary	6	19	16
Pulmonary and extrapulmonary	6	71	21
Sputum or nonsputum smear positive on microscopy	3	62	7**
Sputum smear positive on microscopy	3††	51	2
Smear negative on microscopy; LJ culture positive	18	95	49
Smear negative on microscopy, LJ culture negative, MGIT positive	10	23	19
Median CD4+ count (interquartile range) — per mm³	398 (283–577)	112 (39–283)	146 (43–319)

* The table shows what would have been the outcome for the patients enrolled in our study if one of three strategies had been followed. We defined a false negative result as a finding in a patient who had tuberculosis but neither received a diagnosis of tuberculosis by means of a given algorithm nor had specimens evaluated by means of mycobacterial culture. LJ denotes Löwenstein–Jensen medium, MGIT Mycobacterial Growth Indicator Tube, NA not applicable, and WHO World Health Organization.

† In the screening step of the study algorithm, all patients were asked whether, in the previous 4 weeks, they had had cough of any duration, fever of any duration, or night sweats lasting 3 weeks or more. Patients who reported having had at least one of these symptoms were considered to have a positive screening result for tuberculosis and underwent diagnostic evaluation, which included smear microscopy of two sputum specimens, chest radiography, and a CD4+ count.

‡ In the WHO approach, all patients are asked whether they have had a cough for 2 weeks or more. Patients who respond in the affirmative are considered to have a positive screening result for tuberculosis. In the diagnostic step, two sputum smears are examined for acid-fast bacilli. If the smears are negative, chest radiography is performed and sputum specimens are cultured.[26]

§ In this approach to tuberculosis screening, all patients undergo chest radiography and have two sputum smears examined for acid-fast bacilli; there is no screening of symptoms. Patients with a normal chest radiograph and two negative smears are considered not to have tuberculosis.

¶ We considered culture to be necessary for patients who had negative sputum smears and either an abnormal chest radiograph or a CD4+ count of less than 350 per cubic millimeter.

‖ In the diagnostic step, patients with negative sputum smears, a normal chest radiograph, and CD4+ counts of 350 or more were classified as not having tuberculosis.

** Five patients had a positive extrapulmonary smear and two had a third sputum smear that was positive after two negative sputum smears.

†† In the study algorithm, it is possible to get false negative results in patients with a positive sputum smear for two reasons: the patient did not report cough of any duration, fever of any duration, or night sweats lasting 3 weeks or more in the previous 4 weeks, and therefore smears were never evaluated, or two smears were evaluated but were determined to be negative for tuberculosis.

improving performance. The combination of predictors — cough of any duration, fever of any duration, or night sweats lasting 3 weeks or more during the previous 4 weeks — accurately rules out tuberculosis in the vast majority of patients. This finding may in turn allow for safe initiation of isoniazid preventive therapy and antiretroviral therapy, if indicated, in people who reported having none of the three predictive symptoms. In our study population, in which the prevalence of tuberculosis was 15%, the algorithm had a negative predictive value of 97%. As compared with

screening based solely on the presence or absence of chronic cough, our algorithm reduced the number of false negative results by 83% (from 179 to 31). As compared with the effectiveness of an approach in which microscopical examination of sputum smears and chest radiography were performed for every person with HIV infection, our algorithm reduced the number of false negative results by more than half while also decreasing the number of patients requiring chest radiography and sputum-smear microscopy.

As shown in the Supplementary Appendix, adding chest radiography to symptom screening further improves its sensitivity. Whether it is feasible to implement high-quality, routine chest radiography in the screening process in places that have the highest burden of HIV-associated tuberculosis is not known.

The clinical algorithm that we propose achieves a balance between limited resource availability and the risk of false negative results. We hypothesize that patients with a false negative result on screening would have a favorable prognosis. In our study, the median CD4+ cell count among patients with false negative results was nearly 400 per cubic millimeter, placing these patients at a reduced risk of death, as compared with patients who have lower CD4+ cell counts.[2] The facts that a high proportion of these patients had negative sputum smears and positive results for *M. tuberculosis* only with the use of liquid cultures suggest a low bacillary burden, favoring survival and reducing the risk of the development of isoniazid resistance during isoniazid preventive therapy. Initiating this therapy in patients with undiagnosed tuberculosis can lead to isoniazid resistance, although the overall risk of resistance in patients receiving isoniazid preventive therapy is reportedly low.[28] In patients with undiagnosed tuberculosis, initiation of antiretroviral therapy may be followed by the development of the immune reconstitution inflammatory syndrome, but the frequency and severity of the syndrome are lower in patients with higher CD4+ cell counts.[11]

Among patients with positive results of symptom screening, tuberculosis could be reliably diagnosed only in the small subgroup of patients with positive sputum smears. No approach, other than mycobacterial culture, was optimally effective in diagnosing tuberculosis in patients with negative sputum smears. Tuberculosis is relatively uncommon in patients with positive results of symptom screening if they have two negative smears, a normal chest radiograph, and a CD4+ cell count of 350 or more per cubic millimeter. Prospective research is needed to determine whether this group can be safely reassessed for tuberculosis at a follow-up visit or whether mycobacterial culture should be performed immediately. For patients with an abnormal chest radiograph or a CD4+ cell count of less than 350 per cubic millimeter, clinicians must decide whether or not to initiate empirical treatment for tuberculosis, and specimens should be obtained for immediate culture. In a separate analysis, we found that the best-performing diagnostic approach is to obtain at least two, and ideally three, sputum specimens for culture on liquid mediums, with the possible addition of lymph-node aspiration with smear and culture for patients with an enlarged peripheral node.[29] To meet this need, the availability of facilities capable of performing mycobacterial culture must be scaled up, and access to those facilities for people with HIV infection must be improved. In the interim, screening can be implemented, and this diagnostic algorithm can be used to help clinicians assess the risk of tuberculosis in people with HIV infection.

These results can be interpreted in light of the strengths and limitations of this study. The multiple specimens we cultured have documented diagnostic value in patients with HIV infection and required minimally invasive procedures. Although culturing specimens from other sources, such as bone marrow or enlarged intraabdominal lymph nodes, might have helped establish the diagnosis, these procedures would not have been feasible in the settings where the study was conducted. Although we found chest radiography to be useful, this finding was based on our use of experienced, independent readers. Maximizing the usefulness of chest radiography requires ensuring the quality of the reading. Since the clinical characteristics of tuberculosis in young children differ from those in adults, we did not enroll children younger than 7 years of age. Future studies should address tuberculosis screening and diagnosis in young children with HIV infection. We cannot be certain of the generalizability of this algorithm outside Southeast Asia. Factors that favor its generalizability include enrollment of a broad cross-section of people with HIV infection from varied clinical settings in three countries and the consistent performance

of the algorithm across subgroups. Prospective evaluation of this algorithm is needed in Asia, Africa, and other parts of the world to validate the findings of this study and to measure the effect of this algorithm on mortality. In view of the absence of high-quality data from other locations, the limitations of current international guidelines, and the persistently high rate of tuberculosis-associated morbidity and mortality among patients infected with HIV, we believe that policy changes should be considered.

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