Evaluation of a Diagnostic Algorithm for Sputum Smear–Negative Pulmonary Tuberculosis in HIV-Infected Adults

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Background: The Revised National TB Control Program bases diagnosis of tuberculosis (TB) on sputum smear examination and response to a course of antibiotics, whereas World Health Organization recommends early chest radiography [chest x-ray (CXR)] for HIV-infected symptomatic patients. We evaluated the utility of initial CXR in the diagnostic algorithm for symptomatic HIV-infected patients with negative sputum smears.

Methods: HIV-infected ambulatory patients with cough or fever of ≥2 weeks and 3 sputum smears negative for acid-fast bacilli were enrolled in Chennai and Pune, India, between 2007 and 2009. After a CXR and 2 sputum cultures, a course of broad-spectrum antibiotics was given and patients were reviewed after 14 days. Sensitivity, specificity, positive and negative predictive values of symptoms, CXR, and various combinations for diagnosing pulmonary tuberculosis (PTB) were determined, using sputum culture as gold standard.

Results: Five hundred four patients (330 males; mean age: 35 years; median CD4: 175 cells per cubic millimeter) were enrolled. CXR had a sensitivity and specificity of 72% and 57%, respectively, with positive predictive value (PPV) of 21% and negative predictive value (NPV) of 93% to diagnose PTB. TB culture was positive in 49 of 235 patients (21%) with an abnormal initial CXR and 19 of 269 patients (7%) with a normal CXR ($P < 0.001$). Sensitivity and specificity of cough ≥2 weeks for predicting PTB was 97% and 6%, with PPV and NPV of 14% and 94%, respectively.

Conclusions: Although moderately sensitive, basing a diagnosis of TB on initial CXR leads to overdiagnosis. An absence of weight loss had a high NPV, whereas none of the combinations had a good PPV. A rapid and accurate diagnostic test is required for HIV-infected chest symptomatic.

Key Words: chest symptomatics, ambulatory HIV infected, chest radiography

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INTRODUCTION

Before the onset of the HIV epidemic, it was estimated that there were approximately 1.2 cases of smear-negative pulmonary tuberculosis (SNPTB) and extrapulmonary tuberculosis for every case of smear-positive pulmonary tuberculosis in developing countries.[1] Patients with SNPTB were found to be less infectious and to have a lower mortality, but a significant proportion (50%–70%) progressed to active disease, justifying treatment.[2] With the advent of the HIV epidemic, rates of SNPTB and extrapulmonary tuberculosis have risen.[3] While remaining less infectious than smear-positive cases, HIV-infected SNPTB patients experience significantly higher mortality rates than HIV-negative pulmonary tuberculosis (PTB) patients.[4] Delayed diagnosis, an accelerated rate of TB disease progression, and missed diagnoses of other opportunistic infections may be important contributors to this excess mortality.[5] Additionally, due to the reduced sensitivity of direct sputum examination, the lack of other sensitive and widely available diagnostic tests, and a higher frequency of atypical lesions in the chest x-ray (CXR), the diagnosis of TB is more challenging in HIV-infected individuals.[6]

In the absence of an easily applied rapid diagnostic test that can reliably detect active TB disease in HIV-infected individuals, health care workers often rely on tools such as diagnostic algorithms. Several diagnostic algorithms based on case definitions, clinical symptoms, response to antibiotic trials, repeat smear examination, and CXR have been developed to improve case detection.[7–9] In 2007, World Health Organization (WHO) published guidelines for the diagnosis of SNPTB in symptomatic individuals in HIV-prevalent

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settings.[10] The guidelines included a series of algorithms whose main aim was to assist clinical decision making in HIV-prevalent and resource-constrained settings, to expedite the diagnostic process and minimize incorrect diagnosis and mortality in adults living with HIV/AIDS (Fig. 1). In addition to stressing the critical importance of sound clinical assessment, the guidelines recommended the use of sputum culture and CXR early in the diagnostic pathway with the hope of reducing the delay in diagnosing SNPTB.

Widespread implementation of this guideline would potentially require additional policy changes (eg, HIV testing of TB suspects, rather than TB patients), training and infrastructure development (eg, culture facilities), data on the performance of the recommended algorithm in different settings, so forth. The WHO recommends early CXR and culture for ambulatory nonseriously ill HIV-infected chest symptomatics, whereas Revised National TB Control Programme (RNTCP) recommends a course of antibiotics before CXR (Fig. 2) and bases diagnosis of TB on nonresponse to antibiotics.[11] In this prospective study, we evaluated the value of adding an early CXR to the existing RNTCP protocol for the diagnosis of SNPTB among HIV-infected patients.

METHODS

This prospective study was conducted at the National Institute for Research in Tuberculosis and the Government Hospital of Thoracic Medicine in Chennai and clinical sites of the National AIDS Research Institute in Pune, between 2007 and 2009. HIV-infected adults with a cough ≥2 weeks and/or fever ≥2 weeks, regardless of previous antituberculosis treatment (ATT) or antiretroviral treatment (ART) and with 3 initial sputum smear examinations negative for acid-fast bacilli (AFB) by Ziehl–Neilsen technique, were enrolled (Fig. 3). The protocol was approved by the institutional ethics committees, and written informed consent was obtained from all patients.

Two additional sputum specimens (1 spot and 1 early morning) were collected for AFB smear examination (by the Ziehl–Neilsen technique) and culture (by conventional Lowenstein–Jensen method) and a chest radiograph was performed.[12] Patients with miliary TB, pleural effusion, extensive parenchymal involvement, or cavitary disease on CXR and those seriously ill were initiated on ATT and did not participate further in the study. If the CXR showed lesions suggestive (but not confirmatory) of TB, or was

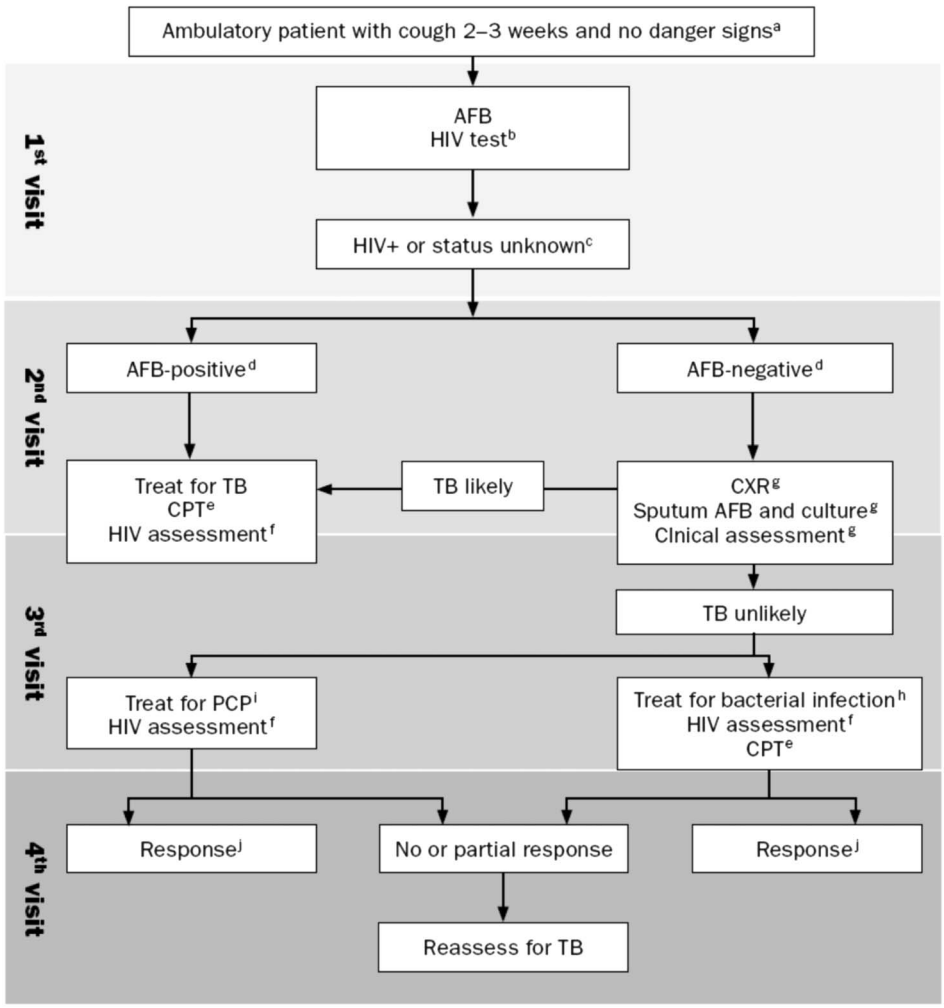

FIGURE 1. WHO recommended algorithm for the diagnosis of tuberculosis in ambulatory patient in HIV-prevalent settings. [a]The danger signs include any one of the following: respiratory rate >30/min, fever >39°C, pulse rate >120/min, and unable to walk unaided; [b]For countries with adult HIV prevalence rate ≥1% or prevalence rate of HIV among tuberculosis patients ≥5%. [c]In the absence of HIV testing, classifying HIV status unknown as HIV positive depends on clinical assessment or national and/or local policy. [d]AFB positive is defined as at least 1 positive and AFB negative as 2 or more negative smears. [e]CPT, co-trimoxazole preventive therapy. [f]HIV assessment includes HIV clinical staging, determination of CD_4 count if available and referral for HIV care. [g]The investigations within the box should be done at the same time wherever possible to decrease the number of visits and speed up the diagnosis. [h]Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered. [i]PCP, *Pneumocystis carinii* pneumonia, also known as *Pneumocystis jirovecii* pneumonia. [j]Advise to return for reassessment if symptoms recur. Source: http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.379_eng.pdf.

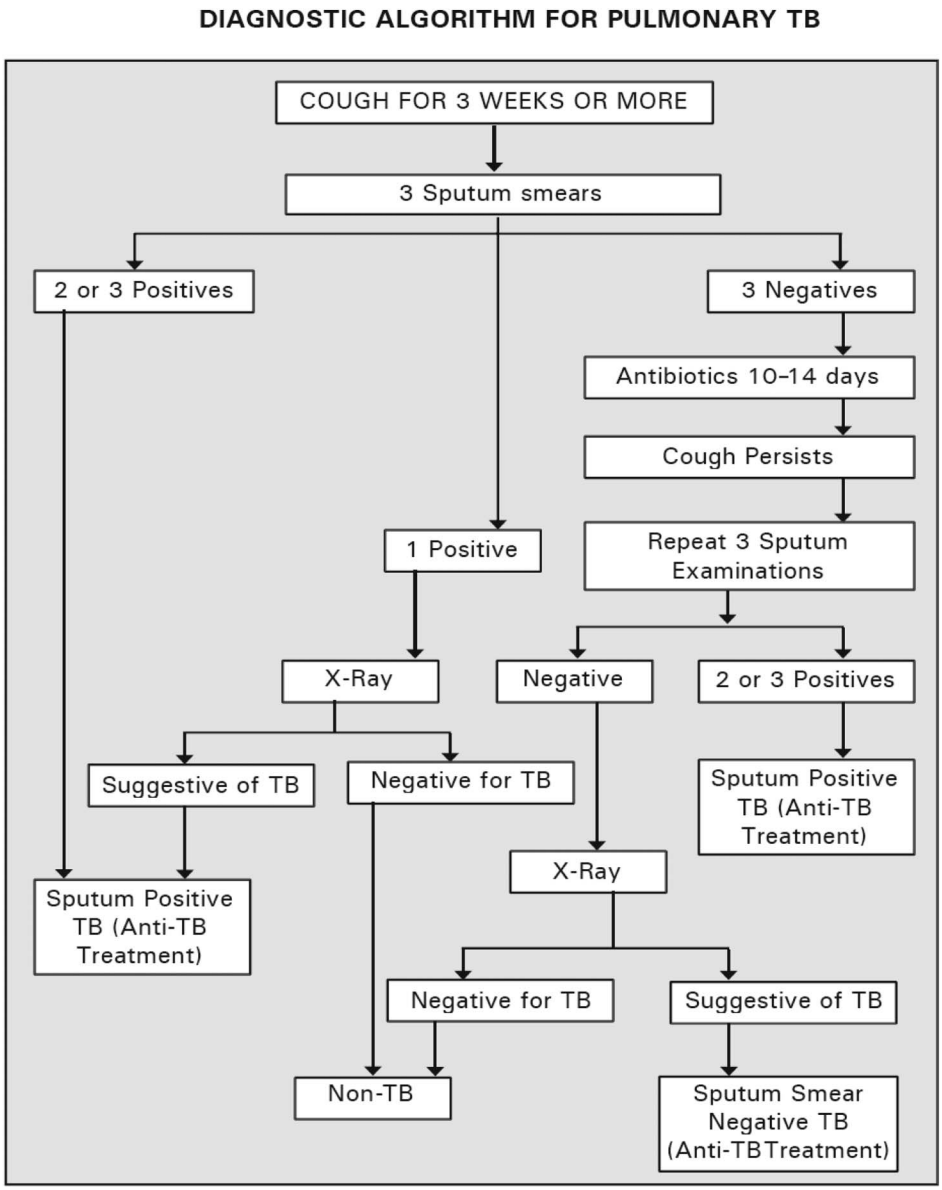

FIGURE 2. RNTCP diagnostic algorithm for pulmonary tuberculosis (This is RNTCP older algorithm. Current algorithm uses cough for 2 weeks and 2 sputum smears) for HIV-infected and uninfected individuals.

normal but the patient was symptomatic, a course of broad-spectrum antibiotics (amoxicillin 500 mg 6 hourly for 7 days, followed by doxycycline 100 mg twice daily for 7 days) was given and the patient reviewed after 2 weeks. They also received 1 double strength tablet of cotrimoxazole daily as prophylaxis against pneumocystis jiroveci and other opportunistic infections from the time of study entry, as per national guidelines.

Symptom status was ascertained, a repeat CXR was taken, and 2 more sputum specimens were collected for smear and culture. Patients who were diagnosed as having active pulmonary TB disease were started on ATT, as per the RNTCP guidelines (new cases: $2EHRZ_3/4RH_3$; previously treated cases: $2SEHRZ_3/1EHRZ_3/5EHR_3$), in the following situations:

1. Persistently abnormal CXR with sputum smear positive for AFB ± symptoms.
2. Persistently abnormal CXR with sputum smear negative for AFB ± symptoms.
3. Normal CXR but sputum smear or culture positive for AFB ± symptoms.
4. If the attending physician felt the need to start the patient on ATT.

Patients considered not to have TB (with none or improved symptoms, normal CXR and negative sputum smears after 14 days) were reviewed along with their culture results at the end of 2–3 months.

CXR interpretation was done by a panel of 3 doctors—TB specialists with specific training in TB radiology—2 from the same institute and 1 from an independent assessor not involved with the study, all blinded to patient information. Parenchymal infiltration, opacities, and hilar shadows/lymph nodes were considered to be consistent with TB. Consensus

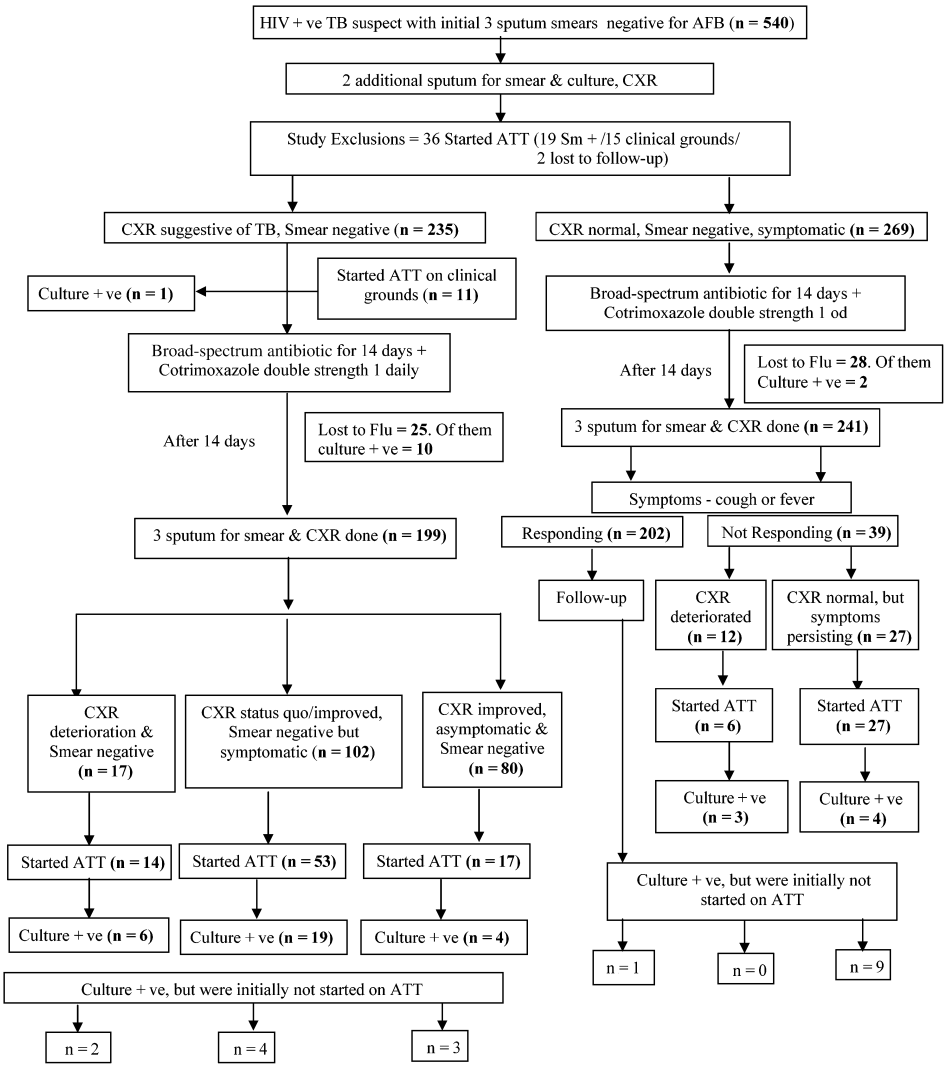

FIGURE 3. Study Design.

of 2 readers was taken as the final reading. If AFB was detected on the initial or second week sputum smear examinations, the results were immediately informed to the medical officer for initiation of ATT.

The study outcome was proportion of patients correctly identified as definite cases of TB by applying this algorithm—combining the RNTCP antibiotic algorithm with initial CXR as suggested by WHO—among HIV-infected chest symptomatics who were AFB negative on initial smear examination. This was done by determining (1) patients with initial CXR suggestive of TB who had cultured confirmed pulmonary TB disease and (2) patients started on ATT based on clinical grounds who had culture-confirmed TB.

Statistical analysis was performed using SPSS version 14 (IBM SPSS, Inc., Chicago, IL). The diagnostic performance of the WHO 2007 algorithm to diagnose SNPTB was assessed by calculating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CXR, and combination of symptoms and signs, using culture positivity for *Mycobacterium tuberculosis* as the gold standard. Patients who were initially smear positive and those without CXR or sputum culture results were excluded from the analysis. Multivariable logistic regression was performed to identify factors associated with culture-proven TB.

RESULTS

Patients enrolled at the 2 sites (Chennai and Pune) were similar in terms of general demographics and immune status (Table 1). Hence, data from both sites were combined for analysis. At the time of study enrollment, only 20 patients were on ART and 75 patients had received previous TB treatment. Of the 540 patients screened, 504 were enrolled to the study; 330 were males, mean age was 35 years (SD), mean weight of 46 ± 9 kg, and median CD4 cell count of 175 cells per cubic millimeter. The 36 patients excluded were found to be either AFB smear positive on additional sputum examination (n = 19) or did not come back for further study procedures (n = 2) or were started on TB treatment immediately by the attending physician based on their clinical condition (n = 15). Of the 504 patients enrolled, 492 were eligible for analysis (12 patients did not have data available for symptom

TABLE 1. Demographic and Clinical Characteristics of Study Participants

Characteristics	Chennai (n = 248), Mean (SD)	Pune (n = 256), Mean (SD)	*P*
Age, y	36 (8)	36 (8)	0.68
Male	166	164	0.36
Weight, kg	46.6 (9)	45.8 (9)	0.26
Height, cm	158.2 (9)	165 (8)	0.0001*
Body mass index	18.6 (3)	16.9 (3)	0.0001*
CD4 cell count in cells per cubic millimeter (median, IQR)	182 (3, 1088)	170 (4, 950)	0.12

*Statistically significant.
IQR, interquantile range.

duration). Four hundred sixty-one (94%) presented with "cough ≥2 weeks", 31 with "cough <2 weeks" but "fever ≥2 weeks" duration. Figure 3 describes the flow of patients in the 2 groups, namely those with CXR "suggestive of TB" and those with CXR normal but symptomatic, after 14 days of broad-spectrum antibiotics.

Operational Performance of the WHO-Recommended Algorithm

Two hundred thirty-five patients had an initial abnormal CXR, of whom only 49 (21%) had *M. tuberculosis* isolated in culture, whereas of the 269 with a normal CXR, 19 (7%) had a positive culture ($P < 0.001$). These 19 patients with a positive culture and normal CXR all had cough ≥2 weeks. No patient with cough <2 weeks and a normal CXR had a positive culture.

Among the 461 patients with cough ≥2 weeks, sputum culture was positive in 65 patients (14%), whereas among the 31 patients with cough <2 weeks, 2 (7%) were culture positive. Both these patients had abnormal CXR. When the culture results became available, one was already on ATT, whereas the other had been lost to follow-up. Among the 75 patients with previous exposure to ATT, CXR was abnormal in 43 patients, whereas the culture was positive in only 5 patients.

After Antibiotic Trial (RNTCP Algorithm)

After 14 days of antibiotics, 199 (85%) of the 235 patients with an initial abnormal CXR returned for follow-up. A repeat CXR showed improvement in 80 patients (40%), deterioration in 17 (9%), and no significant change in the rest (51%). Two hundred forty-one of the 269 chest symptomatics (90%) with an initial normal CXR returned for follow-up. Two hundred two patients (84%) became asymptomatic, 27 (11%) had persistent symptoms, whereas 12 (5%) showed CXR deterioration. Twenty patients (5%) showed sputum smear positivity on repeat examination for AFB after the course of broad-spectrum antibiotics.

ATT was started in 128 patients for the following reasons: persistence of symptoms after a course of antibiotics (44); persistence or deterioration of CXR abnormality (73); and clinical deterioration before completion of antibiotic course and repeat CXR (11). However, of those started on ATT, only 37 (29%) had a positive culture.

At 8 weeks, *M. tuberculosis* was isolated in 68 patients. When the culture results became available, 37 patients (57%) were already on ATT based on CXR/persistent symptoms. Nineteen patients (29%) who were not on ATT were contacted and started on treatment after the culture results became available, whereas another 12 patients were lost to follow-up.

Sensitivity and Specificity of Individual Factors for Active TB Disease

Among individual symptoms, cough of ≥2 weeks of duration, fever ≥2 weeks, and weight loss were highly sensitive, but not specific for culture-proven PTB (Table 2). Specificity of cough increased with increasing duration of cough to ≥3 weeks but still remained low at 25%. Weight loss, CD4 cell count of <200 cells per cubic millimeter, or

TABLE 2. Diagnostic Performance of Individual and Combination of Clinical and Radiographic Characteristics With Culture as the Gold Standard

Characteristics	TB Positive	Non-TB	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
H/o cough ≥ 2 wk	63/65	398/427	97 (89–99)	6 (5 to 7)	14 (13 to 14)	94 (78 to 99)
H/o cough ≥ 3 wk	55/65	322/427	85 (70 to 90)	25 (20 to 30)	15	92
H/o fever ≥ 2 wk	48/54	281/327	89 (78 to 95)	14 (12 to 15)	15 (13 to 16)	88 (77 to 95)
H/o weight loss	48/48	253/268	100	5.6 (4 to 6)	16 (15 to 16.5)	99 (75 to 100)
CXR "suggestive of TB"	49/68	186/436	72 (60 to 82)	57 (55 to 59)	21 (17 to 24)	93 (90 to 95)
CD4 < 200 cells/mm^3	43/62	218/407	69 (57 to 80)	46 (45 to 48)	17 (14 to 19)	91 (87 to 94)
CXR "suggestive of TB" or cough ≥ 2 wk	65/65	183/427	99 (93 to 99)	6 (4 to 7)	26 (24 to 27)	99 (97 to 100)
CXR "suggestive of TB" or cough ≥ 3 wk	58/61	169/402	95 (86 to 99)	58 (57 to 59)	25 (23 to 27)	98 (96 to 99)
Cough ≥ 2 wk or fever ≥ 2 wk or weight loss	37/38	199/200	97 (95 to 99)	5	16 (15 to 17)	50
CXR "suggestive of TB" or cough ≥ 2 wk or CD4 < 200	61/61	216/402	98 (91 to 99)	46 (45 to 47)	22 (20 to 23)	100

H/o, history of.

a CXR interpreted by treating physician as suggestive of active TB were also sensitive but not specific for TB. The presence of either cough ≥2 weeks or abnormal CXR was highly sensitive and the absence of both had a NPV of 99%. Other clinical features, including dyspnea, hemoptysis, and appetite loss, were neither sensitive nor specific for active TB disease (data not shown). Similarly, the sensitivity, specificity, NPV, and PPV did not change significantly when the 20 patients on ART were excluded from the analysis (CXR "suggestive of TB"—sensitivity 71%, specificity 57%, PPV 20%, and NPV 93%).

Sensitivity and Specificity of Combination of Factors for Active TB Disease

On combining individual factors, the specificity of TB diagnosis increased considerably, although the sensitivity decreased. On adding an abnormal CXR with cough >2 weeks duration, the specificity increased from 6% to 60%, which further increased to 76% on adding CD4 of <200 cells per cubic millimeter (Table 3). A combination of factors, namely cough ≥2 weeks and fever ≥2 weeks and an abnormal CXR, had a sensitivity of 69% and a high negative predictive value (93%) in diagnosing culture-proven TB; the specificity increased when duration of cough was >3 weeks (Table 3). Using a multivariable logistic prediction model, lower baseline CD4 count (odds ratio = 1.9, $P = 0.03$) and abnormal CXR (odds ratio = 2.7, $P = 0.001$) were associated with culture-proved TB. The remaining variables namely weight loss, fever, breathlessness, hemoptysis, so forth were not statistically significant.

DISCUSSION

In this prospective cohort study of HIV-infected SNPTB suspects at 2 sites in India, neither radiographic abnormalities nor symptoms were sensitive and specific for diagnosing active PTB disease. A CXR read as "suggestive of TB" by 2 physicians had a sensitivity of 72% and specificity of 57% for the diagnosis of active TB disease. CXR, although an important component of the diagnostic algorithm, is on its own unreliable for the diagnosis of active PTB disease, both due to inherent difficulties in the interpretation and the wide differential diagnosis of abnormal CXR findings among HIV+ persons.[13] The immune status of the patient, intrareader and interreader variation, and variable quality of the x-ray film itself make use of CXR alone unreliable for TB diagnosis in resource poor settings.[13–16] Because of its low specificity, if diagnosis among HIV-infected TB suspects was to be based on CXR alone, this would lead to a substantial overdiagnosis.[13,17,18]

Koole et al[18] assessed the operational performance of WHO 2007 algorithm for the diagnosis of SNPTB in HIV-infected patients and observed a good agreement between readers for distinguishing normal from abnormal x-rays, but only a fair agreement for distinction between TB and non-TB. Taking into account the difficulties in interpreting x-rays in HIV-infected patients, they suggested further simplification of the algorithm by commencing TB treatment in any HIV-infected patient with an abnormal CXR. According to them, this would increase the sensitivity of the algorithm in HIV-positive TB suspects to 64.7% but with a decreased specificity of 72.9%. However, only 17% of our patients with an initial abnormal CXR had culture-confirmed PTB disease. A further 28% were initiated ATT on clinical grounds at the treating physician's discretion while awaiting sputum culture results. Few of them had worsening CXR, whereas about half of them had unchanged CXR but persistent symptoms. These patients could have had other types of respiratory opportunistic infections related to HIV. CXR as a screening tool is often considered cost-effective. However, if large number of patients were to be overdiagnosed and incorrectly placed on treatment, other costs will go up that will reduce the cost-effectiveness of the diagnostic algorithm.[19] The challenge is to increase the specificity of CXR and diminish the proportion of overdiagnosis of smear-negative cases. Clinical review and repeat CXR after a course of broad-spectrum antibiotics improves performance and can minimize overdiagnosis by more than 60%.[19] However, 7% of the TB suspects who had an initial normal CXR in our study had culture-confirmed TB, reaffirming the fact that radiologic changes are not always obvious in HIV-infected TB patients and that it should not be used to exclude disease.[14,20,21]

Previous studies have shown that symptom screening is adequate to effectively exclude active PTB disease in people living with HIV.[22–24] A recent meta-analysis showed that the absence of current cough, fever, night sweats, and weight loss can be used to screen people living with HIV to identify those who have a very low probability (2%) of having active TB

TABLE 3. Diagnostic Performance of Combination of Clinical and Radiographic Features Against Culture as the Gold Standard

Characteristics	TB Positive	Non-TB	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Cough ≥ 2 wk and fever ≥ 2 wk	46/52	268/323	89 (77 to 95)	17 (15 to 18)	15 (13 to 16)	90 (81 to 96)
Cough ≥ 3 wk and fever ≥ 3 wk	36/52	216/323	69 (56 to 80)	33 (31 to 35)	14 (12 to 17)	87 (81 to 92)
CXR "suggestive of TB" and cough ≥ 2 wk	44/65	171/427	68 (56 to 78)	60 (58 to 62)	20 (17 to 24)	92 (90 to 95)
CXR "suggestive of TB" and cough ≥ 3 wk	40/65	143/427	62 (50 to 73)	67 (65 to 68)	22 (18 to 26)	92 (89 to 94)
Cough ≥ 2 wk and CD4 < 200	41/61	203/402	67 (55 to 78)	50 (48 to 51)	17 (14 to 20)	91 (87 to 94)
CXR "suggestive of TB" and cough ≥ 2 wk and fever ≥ 2 wk	36/52	114/323	69 (56 to 80)	65 (63 to 67)	24 (19 to 28)	93 (90 to 96)
CXR "suggestive of TB" and cough ≥ 3 wk and fever ≥ 3 wk	29/52	95/323	6 (43 to 68)	71 (68 to 73)	23 (18 to 29)	91 (88 to 94)
CXR "suggestive of TB" and cough ≥ 2 wk and CD4 < 200	29/41	96/158	48 (36 to 60)	76 (74 to 780	23 (17 to 29)	91 (88 to 93)
CXR "suggestive of TB" and cough ≥ 3 wk and CD4 < 200	28/61	86/402	46 (34 to 58)	79 (77 to 80)	25 (18 to 31)	91 (88 to 93)

disease.[25] In this study, the NPV of absence of cough ≥2 weeks was 94% and of cough ≥2 weeks with a normal CXR was 99%. Hence, addition of CXR only slightly improved the NPV of symptom screening alone. Replacing chronic cough with a history of current cough and using a combination of symptoms instead of individual symptoms, including CD4 cell counts and hemoglobin, have been shown to be more efficient in screening for TB in people living with HIV.[9,25,26] However, the low specificity of the combination of symptom screen limits their utility in the detection of TB.[27] It has also been suggested that WHO symptom screen has poor sensitivity (23.8%) but higher specificity (94.4%) among patients on ART resulting in inadvertent initiation of isoniazid monotherapy.[28]

Although chronic cough has been reported to be relatively insensitive for TB disease in PLWH, we found that increasing the duration of current cough from 2 to 3 weeks increased the specificity of the diagnostic algorithm, especially in combination with an initial abnormal CXR.

Our findings suggest that the 2007 WHO algorithm to diagnose SNPTB, using either CXR "suggestive of TB" or cough ≥2 weeks in ambulatory HIV-infected adults, is a good screening, but not a good diagnostic tool. The delay in receiving a diagnosis due to an additional antibiotic trial of 14 days seems acceptable given the fact that in our study, 40% of patients with an abnormal CXR improved with a course of antibiotics. In the absence of an antibiotic trial, even patients with non-TB bacterial lung infections could respond favorably to ATT given the antibiotic effect of rifampicin. The downside of this approach is that some patients with TB would potentially be lost to follow-up and hence to treatment.

Sputum culture resulted in an additional yield of TB diagnosis, but this was offset by the delay inherent to solid culture examination. Fourteen percent (9) of the TB patients identified by culture alone had been lost to follow-up by the time the results became available. Rapid molecular diagnostics like the Xpert MTB/Rif and Line Probe assays would help to improve case finding, shorten the detection time, and probably reduce mortality from delayed or misdiagnosis.[29,30] Xpert shows particular promise for smear negative and extrapulmonary specimens as well may prove useful in HIV coinfection.[31] RNTCP is in the process of scaling up the capacity for the rapid diagnosis of M/XDR TB and HIV-associated TB using liquid culture, line probe assay, or cartridge-based nucleic acid amplification tests in India.[32]

In conclusion, algorithms that are both highly sensitive and specific for confirming TB among HIV-infected symptomatic patients are currently lacking, and immediate treatment initiation based on 2007 WHO guideline lacks sufficient evidence to validate its widespread implementation. Chest radiography is helpful especially if it can be repeated at the end of a course of antibiotics, along with clinical evaluation. However, whether it is feasible to implement high-quality routine CXR in the screening process in those places that have the highest burden of HIV-associated TB is unclear. Symptom screening algorithms can be used as a trigger for further active TB screening especially among patients on ART. Rapid, robust, and accurate point-of-care diagnostic tests for TB disease and an increase in laboratory capacity are urgently needed to reduce delay in diagnosis and inadvertent initiation of isoniazid preventive therapy among ambulatory HIV-infected adults in TB endemic settings.

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