

Screening for tuberculosis in adults with advanced HIV infection prior to preventive therapy

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SUMMARY

It is important to exclude tuberculosis prior to preventive therapy, but this can be difficult in patients with symptomatic human immunodeficiency virus (HIV) disease. Patients with clinically advanced HIV disease were screened for active tuberculosis using a symptom questionnaire, measured weight loss, chest radiography, sputum microscopy and culture prior to receiving tuberculosis preventive therapy. Tuberculosis was diagnosed in

11 of 129 patients screened. A simple screening instrument of two or more of the symptoms measured weight loss, cough, night sweats or fever, had a sensitivity of 100% and specificity of 88.1%, and positive and negative predictive values of 44% and 100%, respectively.

KEY WORDS: tuberculosis; diagnosis; HIV infection; Africa; South Africa; screening

SCREENING FOR TUBERCULOSIS is important in human immunodeficiency virus (HIV) infected patients both prior to initiating tuberculosis preventive therapy, to prevent the development of drug resistance,¹ and in HIV testing centres in developing countries, where active case finding uncovers many new cases of tuberculosis.²⁻⁴ However, HIV-associated tuberculosis is frequently difficult to diagnose because of the increased proportion of smear-negative and extrapulmonary disease. This is particularly true of patients with clinically advanced HIV disease (World Health Organization [WHO] clinical stages 3 & 4), who are at high risk of developing tuberculosis.⁵

There is a need to develop and validate screening instruments for diagnosing active tuberculosis in HIV-infected patients prior to preventive therapy.¹ The screening instrument should be simple, so that it can be applied in developing countries where the burden is highest, and must be capable of detecting tuberculosis in patients with advanced HIV, as they frequently have constitutional symptoms. We report our experience with such an instrument in a study of patients with advanced HIV disease in an area of high tuberculosis incidence (600 per 100 000 population annually and 10.4 per 100 person-years in patients with HIV infection).⁵ The objective of the study was to calculate the test validity of various symptoms, signs and laboratory investigations for active tuberculosis in this setting.

METHODS

Patients with clinically advanced HIV disease (WHO clinical stage 3 or 4) were referred for possible participation in a randomised controlled trial of tuberculosis preventive therapy (not reported here) in three hospital-based adult HIV clinics in Cape Town, South Africa. Clinicians were asked not to refer patients with suspected tuberculosis. Exclusion criteria included treatment for tuberculosis within the last 5 years, pregnancy, active alcohol abuse, age <18 years and antiretroviral therapy (which was not available in the South African public sector at the time of the study).

A trained investigator (AM) performed Mantoux skin tests. Induration was measured with a Vernier calliper using the mean of the transverse and longitudinal diameters after marking with a ballpoint pen. Induration of ≥ 5 mm at 48–72 hours was considered positive. Screening for active tuberculosis was done using a structured symptom questionnaire administered by a nurse in the patient's home language. Sputum was either collected at the clinic visit if the patient was able to produce sputum, or a container was given to the patient to produce an early morning specimen. Sputum microscopy (auramine stain) and mycobacterial culture (radiometric Bactec[®] system) was performed in all patients. Patients returned after 4 weeks when the sputum culture result was available. Weight was measured with a beam balance scale zeroed at

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each session. Weight loss of $\geq 2.5\%$ within 4 weeks was considered significant.

A single investigator (GM) blinded to the laboratory diagnosis of tuberculosis assessed the chest radiograph. The radiographs were interpreted as normal, abnormal but not suggestive of active tuberculosis, or abnormal compatible with tuberculosis (pulmonary infiltrates, adenopathy or pleural effusions). Tuberculosis was classified as definite (culture-positive together with appropriate symptoms or radiographic appearances), probable (smear-positive) and possible (clinical diagnosis together with a response to therapy).

Signed informed consent was obtained from all patients. The Research Ethics Committees of the Universities of Cape Town and Stellenbosch approved the study.

The ability of symptoms, measured weight loss and radiographic abnormalities to predict active tuberculosis singly or in combination was assessed. Test validity characteristics and their 95% confidence intervals (95%CI) were calculated. A logistic regression model was used to assess the independent predictive effects of these measures.

RESULTS

One hundred and sixty patients were referred, of whom 20 (12.5%) were excluded (three pregnant, one HIV-seronegative, 10 not WHO stage 3 or 4, six previous tuberculosis within 5 years) and 11 (6.9%) failed to complete Mantoux testing, leaving 129 patients screened for tuberculosis. There were 69 (53.5%) females. HIV transmission was heterosexual in 124 (96.1%). There were five (3.9%) men who had sex with men and no intravenous drug users. The mean age was 38 (standard deviation ± 10.9) years. Tuberculosis was diagnosed in 11 (8.5%) patients: 10 definite and one possible (fever and meningitis with cerebrospinal fluid negative for cryptococcal antigen and negative cultures for bacteria, fungi and mycobacteria and a good response to anti-tuberculosis therapy).

The performance of the individual screening tests for these 11 cases of tuberculosis is shown in the Table. A screening instrument of two or more symptoms of weight loss, cough, night sweats or fever, had a sensitivity of 100% (lower 95%CI 67.9) and specificity of 88.1% (95%CI 80.6–93.1). In logistic regression analysis these four variables were independent predictors of tuberculosis. The positive and negative predictive values of the screening instrument (two or more of weight loss, cough, night sweats or fever) were 44% and 100%, respectively (likelihood ratio positive 8.43). In logistic regression modelling this screening instrument (two or more of weight loss, cough, night sweats or fever) provided the best fit (Wald statistic 19.64, $P < 0.001$). Adding the Mantoux or chest radiograph result did not improve the performance of the screening instrument. If only one of the four variables was used for screening, the specificity was reduced to 53.4% (95%CI 44–62.5). The sensitivity and specificity of three of the four variables was 82% and 97%, respectively, and for all four it was 27% and 100%, respectively.

DISCUSSION

We found active tuberculosis in 8.5% of adults with clinically advanced HIV disease. The proportion of tuberculosis cases found in other settings where tuberculosis is endemic is similar to ours.^{2–4,6} A simple screening instrument of symptoms and documented weight loss was capable of ruling out tuberculosis. A high sensitivity and negative predictive value, i.e., avoiding false negatives, is more important in a screening instrument for tuberculosis prior to initiating tuberculosis preventive therapy in order to prevent the development of drug resistance.¹ The 88% specificity of the screening instrument means that 12% of patients without tuberculosis would not be immediately eligible for preventive therapy, but could always be considered for it after tuberculosis had been excluded. As in our study, nurses could apply the screening instrument. Kimerling et al. found symp-

Table Performance of screening tests for tuberculosis in 129 patients with advanced HIV disease

Screening test	Sensitivity %	Specificity %	Odds ratio (95% CI)*	P†
Observed weight loss				
$\geq 2.5\%$ in 4 weeks	81.8	78.8	12.6 (2.9–55.3)	<0.01
Cough >2 weeks	81.8	88.1	20.7 (4.8–89.7)	<0.01
Night sweats >2 weeks	72.7	88.1	12.9 (3.7–45.1)	<0.01
Fever >2 weeks	72.7	83.1	9.6 (2.7–33.9)	<0.01
Mantoux (≥ 5 mm induration)	54.5	83.1	4.8 (1.6–14.4)	0.01
Chest X-ray suggestive	27.3	95.8	5.7 (1.9–17.3)	0.02
Sputum smear	54.5	100	N/A	N/A
Sputum culture	90.9	100	N/A	N/A

* Odds ratios adjusted after logistic regression.

† Fisher's exact 2-tailed test.

HIV = human immunodeficiency virus; CI = confidence interval; N/A = not applicable.

toms had a lower positive predictive value;⁶ this may be due to their different patient population (all in home care) or because weight loss was not measured. Nevertheless, 95% of their tuberculosis cases had symptoms.⁶

A single sputum culture specimen appears sufficient to establish the diagnosis of pulmonary tuberculosis in HIV-infected patients.⁷ However, patients with extra-pulmonary disease alone, as in one of our cases, would clearly not be detected using sputum culture, and it is possible that we underdiagnosed tuberculosis. A further limitation of the study is the inherently biased patient selection process, as it was hospital-based, consisted only of patients with advanced HIV disease, and clinicians were selecting patients whom they presumed not to have tuberculosis.

The WHO and the US Centers for Disease Control and Prevention recommend chest radiograph as part of the screening process to exclude tuberculosis prior to preventive therapy in HIV infection.^{1,8} We found that chest radiographs were not sensitive. It is possible that the investigator who reviewed the radiographs may have introduced observer bias by underreporting abnormalities. However, another South African study at voluntary counselling and testing centres found that only 44% of patients with pulmonary tuberculosis discovered during screening prior to preventive therapy had suggestive findings on chest radiographs.⁹ Chest radiographs should be limited to symptomatic patients, and probably only to patients whose sputum is smear-negative.¹⁰

Active tuberculosis case finding should be an integral component of HIV management at primary care and voluntary counselling and testing centres.⁹ We have demonstrated that a simple screening instrument can effectively exclude tuberculosis in patients with advanced HIV disease. Once tuberculosis has been excluded, tuberculin skin testing can be done to assess eligibility for preventive therapy.

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RÉSUMÉ

Il est important d'exclure une tuberculose-maladie avant une thérapie préventive. Ceci peut être difficile chez les patients atteints d'une maladie due au virus de l'immunodéficience humaine (VIH) déjà symptomatique. Nous avons dépisté la tuberculose active chez les patients atteints d'une maladie VIH cliniquement avancée en utilisant un questionnaire sur les symptômes, en mesurant la perte de poids et en pratiquant l'examen radiographique du thorax ainsi que la bacilloscopie et la culture des

expectorations, avant de commencer une thérapie préventive de la tuberculose. Sur les 129 patients examinés, une tuberculose a été découverte chez 11 sujets. Un instrument simple de dépistage comportant deux ou plus des éléments suivants : perte de poids mesurée, toux, sueurs nocturnes et fièvre, a une sensibilité de 100%, une spécificité de 88,1% et des valeurs prédictives positive et négative respectivement de 44% et de 100%.

RESUMEN

Es importante excluir la tuberculosis antes de aplicar la terapia preventiva, pero esto puede ser difícil en los pacientes con enfermedad por el virus de la inmunodeficiencia humana (VIH) sintomática. Se realizó una detección de la tuberculosis en pacientes con enfermedad VIH clínicamente avanzada utilizando un cuestionario de síntomas, la medición de la pérdida de peso, la radiografía de tórax y la baciloscopia y el cultivo de esputo, antes de

aplicar la terapia preventiva de la tuberculosis. Se diagnosticó una tuberculosis en 11 de los 129 sujetos sometidos a la detección. Un instrumento simple de detección que incluye dos o más síntomas, medición de la pérdida de peso, tos, sudores nocturnos o fiebre, tenía una sensibilidad de 100% y una especificidad de 88,1% y valores predictivos positivos y negativos de 44% y 100%, respectivamente.
