

Diagnosing HIV-associated tuberculosis: reducing costs and diagnostic delay

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SUMMARY

SETTING: University-affiliated hospital in South Africa.

OBJECTIVE: To assess the time to diagnosis and the yield and laboratory cost of diagnostic procedures in human immunodeficiency virus (HIV) associated tuberculosis.

DESIGN: Cohort study.

PATIENTS: Adult HIV-infected patients with newly-diagnosed tuberculosis admitted over a 2-year period.

RESULTS: A total of 141 admissions fulfilled the case definition. Sputum smear yield (43% overall) correlated strongly with chest radiograph appearance but not with CD4+ lymphocyte count. Sputum smear yield was approximately 40% per sample sent, resulting in a high cumulative yield when \geq three samples were sent. Smear of sputum or wide needle lymph node aspirates were the most cost-effective diagnostic methods. Significant diagnostic delay occurred in sputum smear-negative patients.

Most patients with sputum smear-negative tuberculosis had either pleural effusions or lymphadenopathy. Lymph node biopsy had a high diagnostic yield even in patients with symmetrical nodes, but was under-utilised in this group. There was unnecessary expenditure on cultures, with many patients having several positive cultures.

CONCLUSION: Repeated sputum smear examination produces a high cumulative yield in HIV-associated tuberculosis. Considerable savings in laboratory utilisation and bed occupancy would have been made if a streamlined diagnostic approach with greater use of lymph node aspirate and early pleural or lymph node biopsy had been followed.

KEYWORDS: HIV infection; tuberculosis diagnosis; sputum smear; needle aspirate; South Africa.

TUBERCULOSIS IS the leading cause of mortality and morbidity in human immunodeficiency virus (HIV) infected patients in Africa and Asia.¹⁻⁴ In both developing⁵ and industrialised⁶ nations, delayed or missed diagnoses of tuberculosis have important adverse consequences including nosocomial transmission, death, and wasted bed occupancy.^{5,6} Sputum smear is the preferred method of rapid diagnosis of tuberculosis due to its low cost. However, most⁷⁻⁹ but not all^{10,11} studies of HIV-infected patients with tuberculosis have found a higher rate of smear-negative sputum.

The aims of the present study were to investigate the clinical correlates of smear-negative sputum in HIV-infected in-patients with tuberculosis, to assess recent recommendations to reduce the number of sputum smears from three to two per patient-episode,¹² to examine resource utilisation in cases where sputum is smear-negative, and to propose a cost-effective approach to rapid diagnosis.

METHODS

The study was conducted in an urban university-affiliated hospital providing general in-patient ser-

vices over the period October 1994 to September 1996. During this period all patients with suspected tuberculosis were offered HIV testing and 88% accepted. During the study period the policy was to send at least one sputum specimen for mycobacterial culture for all HIV seropositive admissions. Mycobacterial culture was encouraged on biopsy material as well as other specimens. Discharge summaries of patients treated for tuberculosis were collected prospectively and cross-checked against the laboratory database and monthly records of HIV-positive admissions compiled by the hospital infection control nurse to ensure that all patients with proven or empirically treated tuberculosis were identified. Radiological and clinical data were abstracted from the medical records and the laboratory database was used to identify investigations for tuberculosis.

The case definition for tuberculosis required one of the following three criteria: 1) culture of *Mycobacterium tuberculosis* from any site; 2) an anatomical diagnosis of tuberculosis at necropsy; 3) the presence of acid-fast bacilli (AFB) on a smear or granulomas on histology with subsequent response to treatment. Patients who defaulted from treatment and presented

with early relapse were excluded. Sputum smear-negative tuberculosis was defined as negative smear on all sputum samples sent, irrespective of the number of specimens sent. Smears of sputum and aspirates from lymph nodes were examined using the fluorochrome method except when urgent processing was requested, in which case Ziehl-Neelsen staining was done. Mycobacterial cultures were performed with a radiometric system (BACTEC™). Laboratory cost data were obtained from the March 1996 unit costs supplied by the laboratory. The unit costs include reagents, staff and other costs.

Fisher's exact test and χ^2 with Yate's continuity correction were used for comparison of proportions as appropriate. The Kruskal-Wallis test was used for comparison of means.

RESULTS

During the review period there were 415 medical admissions of HIV-infected patients, of whom 179 were treated for tuberculosis. Mycobacterial culture of sputum was requested for 51/69 patients with respiratory conditions other than tuberculosis, and for 157/179 patients treated for tuberculosis. Of 149 admissions that fulfilled the case definition of tuberculosis, eight patients who had defaulted and presented with early relapses were excluded as the diagnosis was already available, leaving 141 admissions in 131 patients (10 patients had recurrent tuberculosis). HIV was acquired by heterosexual transmission in 122/131 (93%) patients and by homosexual transmission in the remainder. There were 91 Africans, 30 Coloureds (a mixed race community) and 10 Caucasians. CD4+ lymphocyte counts were done within a month of admission in 103 patients (median count 83/ μ l, interquartile range 37–207). In the 141 admissions the diagnosis was confirmed by culture of *M. tuberculosis* in 109 (77%), a treatment response coupled with AFB on histology or sputum smear in 21, granulomas on histology together with a treatment response in six, and on necropsy in five.

Diagnostic yield of sputum

Sputum smear was positive in 60 admissions (43%), negative in 49 and sputum could not be obtained in 32. Sputum smear was more likely to be positive if the clinical presentation suggested pulmonary involvement (cough, chest pain or focal chest signs): 59/124 (48%) had clinical evidence of pulmonary involvement compared with 1/17 (6%) who did not ($P < 0.01$). Detailed description of the chest radiograph was available for 91 of the 124 patients with clinical evidence of pulmonary involvement—the radiographic appearance correlated with the yield of sputum smear (Table 1). The yield of sputum smear was not related to the CD4+ lymphocyte count: 35/68 (51%) with pulmonary symptoms and a CD4+ lymphocyte count

Table 1 Chest radiographic appearance and yield of sputum smear (χ^2 for linear trend 13.08, $P < 0.01$)

Radiographic pattern	Smear-negative (or no sputum)	Smear-positive n (%)
Pleural effusion	11	1 (8)
Normal	12	5 (29)
Nodular infiltrate	22	14 (39)
Consolidation	7	15 (68)
Cavitation	0	4 (100)

<200/ μ l were smear-positive compared with 10/25 (40%) with higher counts (odds ratio 1.59, 95% confidence interval 0.57–4.48, $P = 0.45$).

In view of recommendations to reduce the number of sputum smears,¹² we examined the yield of smears of consecutive sputum specimens. Sputum smear yield was not significantly different for consecutive samples (45/109 [41%] for the first, 20/61 [33%] for the second, 12/32 [38%] for the third and 8/18 [44%] for the fourth; χ^2 for linear trend 0.027, $P = 0.868$). The incremental yield from repeating the smear on those patients negative on preceding smears was 8/39 for a second, 4/21 for a third and 3/12 for a fourth specimen. The yield of smear on first sputum was 17/29 (59%) in patients able to produce a sample on the day of admission compared to 22/65 (34%) when sputum was obtained after day one ($P = 0.04$).

The yield of culture of the first sputum sample was 25/34 (74%) on smear-negative patients and 37/43 (86%) on smear-positive patients ($P = 0.28$). Thirty-three patients had two sputum samples cultured with a similar yield (26/33 and 28/33), but five patients who were negative on the first specimen were positive on the second.

Resource utilisation

To reflect clinical decision-making, time to diagnosis was assessed for admissions where the diagnosis was based on specimens obtained during admission, i.e., excluding necropsy diagnoses (five patients) and diagnoses made on specimens sent from the clinic prior to admission (8 patients). Mean time to diagnosis was 13 days when sputum was smear-negative or the patient could not produce sputum, compared to 2 days for smear-positive tuberculosis ($P < 0.01$). Of smear-negative admissions, mean time to diagnosis was 11 days for patients who had a biopsy compared to 20 days for patients who did not ($P = 0.01$). For smear-negative admissions with a biopsy diagnosis, mean time to diagnosis was 3 days in patients undergoing pleural biopsy compared to 7 days for patients undergoing biopsies of other tissues ($P = 0.04$).

In patients with smear-negative sputum or no sputum, wide needle aspirate and/or biopsy was performed in 13/43 (30%) with symmetrical lymph node enlargement compared to 13/17 (76%) with lymph

nodes noted to be asymmetric in size ($P < 0.01$). Patients with negative aspirate went on to biopsy only when the nodes were noted to be asymmetric. This difference in use of investigations occurred despite no difference in yield: 6/7 biopsies of symmetrical node enlargement were positive compared to 8/10 for biopsies of asymmetrical nodes, and the corresponding figures for aspirates were 3/7 and 5/9.

Table 2 displays for each investigation the diagnostic yield and cost per diagnosis. Due to the large numbers of positive results obtained after a previous positive result, diagnostic yield is shown both as number of positive results and number of occasions when the positive result was the first evidence of tuberculosis. Cost per diagnosis is calculated as total cost (number of investigations multiplied by the March 1996 unit costs) divided by the number of occasions when the positive result was the first evidence of tuberculosis. One diagnosis was made on culture of a skin biopsy¹³ but, as this was the only investigation of this type, it is excluded from Table 2 along with five cases diagnosed at autopsy and eight on samples sent prior to admission.

Given the high cost per diagnosis of many investigations and frequent delay in obtaining diagnoses, we modelled laboratory utilisation using the diagnostic yield data from the 127 admissions in Table 2. Sputum smear-negative patients fell into three groups—those with pleural effusions, those with lymph nodes >1 cm and those with neither. Investigations for

patients with pleural effusions could be limited to histology of pleural biopsy followed by trial of therapy pending results of pleural fluid culture. The laboratory cost for the 22 patients with pleural effusion would have decreased from US\$1015 to US\$570 (44% reduction), but three patients would have been empirically treated instead of confirmed as tuberculosis. Investigations for patients with lymph nodes >1 cm can be limited to wide-needle aspirate followed by excision biopsy if the aspirate smear is negative. The laboratory cost for the 40 sputum smear-negative patients with nodes >1 cm would have decreased from US\$1615 to US\$445 (72% reduction), but four patients (10%) would have required further investigations to confirm the diagnosis of tuberculosis. Only 10 patients were smear-negative or unable to produce sputum and had neither effusion nor nodes >1 cm.

DISCUSSION

Tuberculosis in patients co-infected with HIV is associated with more extra-pulmonary disease and, as immunity declines, more non-cavitating pulmonary tuberculosis.¹⁴ This presents diagnostic difficulties as sputum is often unobtainable or smear-negative. This is reflected in the present study, where 23% of patients were unable to produce sputum and the overall yield of sputum smear was 43%. As we have shown, negative sputum smears are associated with diagnostic delays. The most important resource used in the diagnosis of tuberculosis is bed occupancy, and the time to diagnosis is critical.¹⁵ A more rapid diagnosis would also reduce morbidity and mortality in HIV-infected patients.⁶

The yield of sputum smear in our study was approximately 40% per sample sent. We believe this is an accurate reflection of HIV-associated tuberculosis in in-patients, as a large number of sputum samples were assessed and the diagnosis of tuberculosis was unlikely to be missed in our extensively investigated cohort. The incremental yield of sputum smear depends on the yield per sample sent. If this is 80%, then $>95\%$ of cases who are sputum-smear positive will be detected on two smears (80% positive on the first smear and 80% positive on the remaining 20%—i.e., 96%). This was the finding of an out-patient study in Tanzania of patients of unknown HIV status.¹² That study has influenced policy to the extent that the South African National Tuberculosis Programme requires only two sputum samples be sent from clinics. In our in-patient HIV cohort with a sputum smear yield of 40% per sample sent, six specimens would need to be sent in order to detect $>95\%$ of cases. However, it would waste bed occupancy to wait for six sputum samples before embarking on other tests. With a yield of 40% per sample, three smears will detect almost 80% of cases—it would thus be reasonable to proceed to invasive diagnostic

Table 2 Laboratory cost per diagnosis (calculated as the total cost for each investigation divided by the number of occasions when the positive result was the first diagnostic result)

Specimen type	Yield (%)	First diagnostic result	Cost per diagnosis (US\$)
Sputum			
Smear	85/220 (39)	54	\$9
Culture	116/142 (82)	17	\$78
Lymph node			
Aspirate	8/16 (50)	8	\$5
Biopsy	14/17 (82)	13	\$20
Pleura			
Histology	15/21 (71)	15	\$20
Culture	6/9 (67)	1	\$82
Pleural fluid			
Smear	2/20 (10)	2	\$26
Culture	12/20 (60)	4	\$45
Bone marrow			
Histology	5/19 (26)	3	\$103
Culture	6/16 (38)	2	\$67
Urine			
Smear	1/26 (4)	1	\$67
Culture	11/26 (42)	3	\$74
Liver			
Histology	3/4 (75)	1	\$112*
Blood			
Culture	19/45 (42)	3	\$267

* Includes cost of liver function tests and tests of coagulation function.

tests after three negative sputum smears. Further smears can still be sent, but the additional yield will be progressively lower and no more than six in total should be sent.

The observed lack of relation of CD4+ lymphocyte count to sputum smear result is in keeping with one previous study by Smith et al.¹¹ but contrasts with another by Jones et al.,¹⁶ and requires further study. This was a surprising finding given that there was a good correlation of the CD4+ lymphocyte count with the chest radiographic appearance, which, as we have previously shown, correlates well with the CD4+ lymphocyte count.¹⁴

Based on our finding that most patients with sputum smear-negative tuberculosis have either pleural effusions or lymphadenopathy, we suggest a streamlined diagnostic approach which would result in considerable savings in laboratory utilisation and bed occupancy (Figure). Early pleural biopsy and aspiration should be done in patients with pleural effusions. The combined yield of these two procedures is very high. Most clinicians would be comfortable continuing anti-tuberculosis treatment even if histology and cultures are negative if there is a satisfactory response. Lymphadenopathy is significantly associated with tuberculosis in HIV-infected patients presenting with respiratory disease.¹⁷ Lymph node aspirates have a high yield in HIV-associated tuberculosis,^{18,19} and were under-utilised in our cohort. This was the most cost-effective diagnostic test. Our finding that lymph node biopsy was often diagnostic even when the nodes were symmetrically enlarged, in contrast with tuberculous lymphadenitis in HIV seronegative patients, is in agree-

ment with a large central African study performed by Bem.²⁰ Provided that the clinical picture suggests tuberculosis, clinicians should not hesitate to biopsy nodes that are symmetrically enlarged. Despite the aggressive approach to diagnosis in our patients, three patients died without treatment and without investigation, all with symmetrical lymph node enlargement.

Patients who are sputum smear-negative and have neither effusion nor lymph nodes (only 8% in this study), together with those with a negative lymph node biopsy, could have a trial of therapy pending culture results if the clinical picture is strongly suggestive of tuberculosis. The specimen with the highest culture yield in our study was sputum, whilst urine, blood and bone marrow had a similar yield. Culture of bone marrow aspirate or blood should be performed wherever atypical mycobacteria are common.^{21,22} The yield of the two investigations is similar, but the bone marrow trephine biopsy provides an opportunity to make a rapid diagnosis if granulomas or AFB are found (26% yield in the present study). Blood culture was an expensive diagnostic test in our study largely because it was slow and other cultures were often positive first. In addition, a reasonable yield of blood cultures can only be assured by case selection on CD4+ lymphocyte count (modest yield with counts 100–200 × 10⁶/l and high yield with counts under 100),¹⁶ adding to expense. Urine culture is valuable even in the absence of pyuria.²³ Sending two or three specimens for mycobacterial culture prior to a trial of therapy should be sufficient—reducing the number of specimens cultured has been identified by others as an important area for cost savings.²⁴

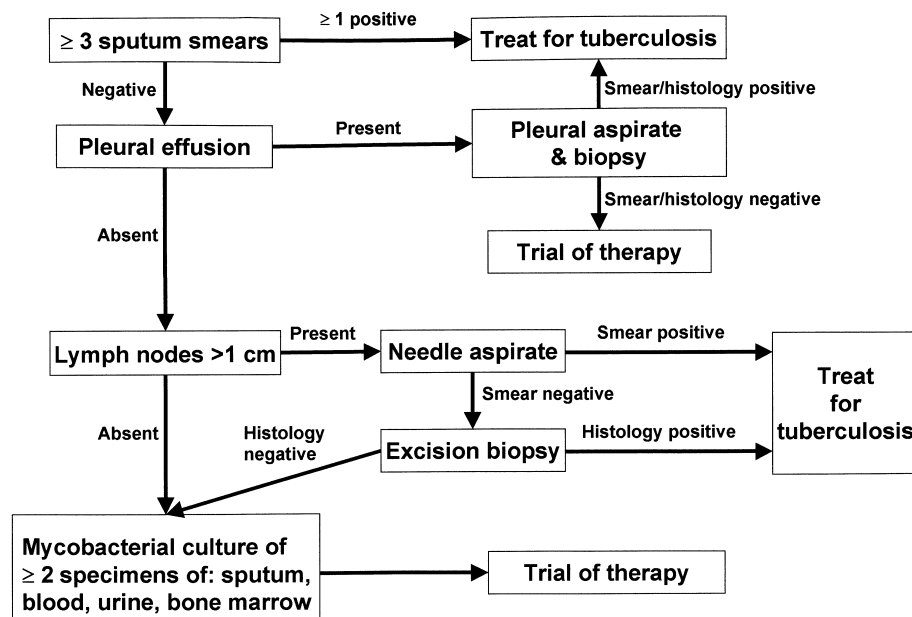


Figure Proposed diagnostic algorithm for HIV-infected patients with suspected tuberculosis. Trial of therapy should only be undertaken if other diagnoses are excluded or unlikely.

We believe that our findings are relevant to settings with different resource constraints from ours. In more resource-rich settings, more cultures could be sent and procedures such as bronchoscopy could be used. We obtained diagnostic confirmation of tuberculosis without resorting to bronchoscopy (which was difficult to arrange during the study period); this is in keeping with the finding of Daley et al. that bronchoscopy is of little value in areas where tuberculosis is endemic.²⁵ In more resource-poor settings, where mycobacterial cultures are often unavailable, the early use of lymph node aspirate followed by biopsy or pleural aspirate and biopsy would yield the diagnosis in most cases. In resource-poor settings algorithms for empirical treatment based on symptoms can be used for the remaining cases.¹⁷

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RÉSUMÉ

CADRE : Hôpital d'Afrique du Sud affilié à l'Université.
OBJECTIF : Déterminer la durée nécessaire au diagnostic, le rendement et le coût en laboratoire des procédés de diagnostic dans la tuberculose associée au virus de l'immunodéficience humaine (VIH).

SCHEMA : Etude de cohorte.

PATIENTS : Sujets adultes infectés par le VIH et admis au cours d'une période de deux ans pour une tuberculose récemment diagnostiquée.

RÉSULTATS : 141 admissions ont répondu à la définition des cas. Le rendement du frottis d'expectoration (globalement 43%) est en étroite collaboration avec l'aspect

du cliché thoracique, mais non avec les décomptes de lymphocytes CD4+. Le rendement du frottis d'expectoration fut d'environ 40% par échantillon, ce qui entraîne un rendement cumulatif élevé de l'envoi de trois échantillons ou davantage. Les méthodes de diagnostic dont le rapport coût-efficacité est le meilleur sont le frottis d'expectoration ou la ponction-aspiration ganglionnaire au moyen d'une grosse aiguille. Un délai significatif de diagnostic existe chez les patients dont l'expectoration est négative à la bacilloscopie. La plupart des patients atteints d'une tuberculose à bacilloscopie négative dans l'expectoration souffraient soit d'épanchements pleu-

raux, soit d'adénopathies. La biopsie ganglionnaire a un rendement diagnostic élevé même chez les patients dont les adénopathies sont symétriques, mais elle a été sous-utilisée dans cette étude. L'on a fait des dépenses inutiles pour des cultures chez beaucoup de patients dont plusieurs cultures se sont avérées positives.

CONCLUSION : La répétition de frottis d'expectoration

entraîne un rendement cumulatif élevé dans les tuberculoses associées au VIH. D'importantes économies en matière d'utilisation du laboratoire et d'occupation des lits auraient pu être faites si une approche de diagnostic rationnelle avait été suivie, faisant appel aux ponctions ganglionnaires et aux biopsies pleurales ou ganglionnaires précoces.

RESUMEN

MARCO DE REFERENCIA : Hospital afiliado a la Universidad de Sud África.

OBJETIVO : Evaluar el tiempo de diagnóstico, el rendimiento y el costo de laboratorio de los métodos de diagnóstico en la tuberculosis asociada con VIH.

MÉTODO : Estudio de cohorte.

PACIENTES : Pacientes adultos infectados por el VIH con tuberculosis reciente, hospitalizados en un período de dos años.

RESULTADOS : En total, 141 pacientes hospitalizados cumplieron los requisitos del objetivo. El rendimiento del examen de esputos (43% del total) se relacionaba fuertemente con las imágenes radiográficas pero no con el recuento sérico de linfocitos TCD4. El rendimiento del examen de esputo fue aproximadamente del 40% por cada muestra enviada y aumentó fuertemente con el envío de ≥ 3 muestras. El examen de esputos o la aspi-

ración con aguja de los ganglios fueron los métodos de más alto rendimiento costo-beneficio. Existió una demora diagnóstica significativa en los pacientes con esputo negativo. La mayoría de los pacientes con tuberculosis y esputo negativo tenían una pleuresía o adenopatías. La biopsia ganglionar tuvo un gran rendimiento aún en pacientes con ganglios simétricos, pero fue poco utilizada en este grupo. Existió un gasto innecesario con los cultivos.

CONCLUSIÓN : Los análisis repetidos de esputos producen un alto rendimiento acumulativo en la tuberculosis asociada al SIDA. Se hubieran logrado ahorros considerables en el uso del laboratorio y ocupación de las camas si se hubiera recurrido más a la aspiración ganglionar, a la aspiración pleural temprana o a la biopsia ganglionar.
