HIV-related tuberculosis in South Africa — clinical features and outcome

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Objective. To assess the difference between human immunodeficiency virus (HIV)-infected and non-infected tuberculosis patients with regard to demographic characteristics, clinical features, case fatality rates and, particularly, compliance with therapy.

Design. Cohort study.

Setting. Hlabisa Hospital, KwaZulu-Natal, a 450-bed hospital serving a rural district containing 180 000 people.

Patients. Two hundred and ninety-seven consecutive adult patients (> 15 years) diagnosed with tuberculosis.

Main outcome measures. Age, sex, type of tuberculosis, case fatality rate and compliance with therapy.

Results. A total of 107 out of 297 (36%) adults tested HIV-positive (95% confidence interval (CI) 31 - 42%). Prevalence of HIV infection was higher in women than men (46% v. 29%, relative risk (RR) 1.6, 95% CI 1.2 - 2.2). HIV-positive patients were significantly younger than HIV-negative patients (mean age 31.2 years v. 38.7 years; $P < 0.001$). Extrapulmonary tuberculosis (EPTB) was more common in HIV-positive patients (41% v. 11%, RR 3.7, 95% CI 2.3 - 5.9). The case fatality rate was higher in HIV-positive patients (13% v. 9%, RR 1.5, 95% CI 0.7 - 3.0). Many more HIV-positive patients failed to complete treatment (21% v. 7%, RR 3.0, 95% CI 1.5 - 6.0).

Conclusions. We found that HIV-positive patients with tuberculosis were three times more likely to fail to complete treatment than HIV-negative patients. HIV infection is clearly altering the epidemiological profile of tuberculosis in rural South Africa and poses an additional challenge to tuberculosis control programmes to maintain high case-holding rates among HIV-infected tuberculosis patients.

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The epidemiology and clinical features of tuberculosis have been profoundly affected by the HIV epidemic in sub-Saharan Africa.[1]

In early 1992 the World Health Organisation estimated that 4 million people were infected with both HIV and tuberculosis and that almost 80% of them lived in sub-Saharan Africa.[1] HIV infection increases the risk of developing active tuberculosis, either from reactivation of latent infection or rapid progression of newly acquired infection.[2] The prevalence of HIV infection in tuberculosis patients has been variously reported at 20 - 67% in different sub-Saharan African countries.[3] HIV-positive tuberculosis patients are reported to be younger, to have more extrapulmonary tuberculosis (EPTB) and to experience higher mortality rates than HIV-negative tuberculosis patients.[3] Response to short-course chemotherapy is considered equally effective in the two groups, although relapse may be higher in HIV-positive patients.[1] The consequence of this dramatic change in epidemiology and clinical features is a marked increase in the incidence of active tuberculosis that threatens to overwhelm control programmes.[3]

At Hlabisa Hospital the monthly average number of patients diagnosed with tuberculosis doubled from 26 in 1991 to 52 in 1992, and increased further to 66 per month in 1993.[4] In the course of routine clinical duties, staff noted that more sick young women, more cases of EPTB, and more tuberculosis patients with HIV-associated signs (such as chronic diarrhoea, generalised lymphadenopathy and oropharyngeal candidiasis) were presenting to the hospital. The tuberculosis field staff expressed concern that known HIV-positive patients were defaulting on treatment and attending traditional healers. Over the same period the HIV seroprevalence in women attending antenatal clinics in the district rose from 4.2% to 7.9%.[5,6]

The purpose of this study was to assess the difference between HIV-infected and non-infected tuberculosis patients with regard to demographic characteristics, clinical features, case fatality rates and compliance with therapy. Particular emphasis was placed on assessment of the case-holding rates in HIV-negative and positive groups.

Methods

The study took place from May 1993 to June 1994 in the Hlabisa Health Ward, KwaZulu-Natal. This is a largely rural area and the almost exclusively black population of 180 000 people depend on subsistence farming and migrant labour. The hospital and its clinics provide most of the health care in the area. All adult patients (> 15 years) diagnosed with tuberculosis in the hospital over the 6-month period May to October 1993 were eligible for recruitment into the study. All patients with suspected tuberculosis were admitted to the hospital for diagnostic investigations, as were patients with a diagnosis of tuberculosis transferred to Hlabisa Hospital from other hospitals.

Demographic and clinical data were gathered as part of normal clinical practice. Sputum smears were prepared with Ziehl-Neelsen stain and examined for acid-fast bacilli in the Hlabisa Hospital laboratory. Specimens for histological assessment were stored and transported in formalin to the regional laboratory for examination by a specialist histopathologist. After counselling and with informed consent, blood was drawn for HIV testing; serum was separated the same day and stored at 4°C until transported to the regional laboratory. All sera were subjected to a third-

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generation enzyme-linked immunosorbent assay (ELISA) for anti-HIV antibodies (HIV 1/2 Recombinant ELISA, Abbott). Reactive sera were confirmed with a second ELISA (Core HIV 1/2 ELISA, Roche-Cobus).

Smear-positive tuberculosis was defined as a typical clinical and radiological picture with at least a single sputum smear positive for acid-fast bacilli (culture was not available). Smear-negative tuberculosis was defined as a typical clinical and radiological picture and at least three negative sputum smears. EPTB was histologically defined whenever possible (e.g. lymph node biopsy), or by typical clinical picture (pleural effusion with lymphocytic exudate), in accordance with WHO and the International Union against Tuberculosis and Lung Disease guidelines.[7,8]

In accordance with Department of Health policy at that time all patients were initially treated with four drugs given daily while in hospital (isoniazid, rifampicin, pyrazinamide and ethambutol). As soon as patients were considered fit for discharge, all were offered twice-weekly drug treatment under full supervision in the community. This supervised intermittent ambulatory treatment (SIAT) started on average 2 - 3 weeks after diagnosis. The same four drugs were given twice-weekly in high dosages. Supervision was either by a health worker or a lay person such as a storekeeper.[9] The only patients not managed on SIAT were those too sick to be discharged. Tuberculosis field staff visited supervisors monthly and traced any absconders by visiting their homes immediately. When the patient was found to have left the area no further tracing was attempted, but relatives were asked to send the patient to the hospital should he return. When the patient was reported to be in the area, further tracing efforts were made, either directly or via family members.

Statistical analysis was done using the Epi-Info statistical software package (Centers for Disease Control, Atlanta, Georgia, USA, 1990). Associations were corrected for age and sex by stratified analysis. Relative risks (RRs) and significance tests were obtained by Mantel-Haenszel methods for categorical data. Kruskal-Wallis non-parametric tests were used for continuous variables. The study was approved by the KwaZulu AIDS Programme.

Results

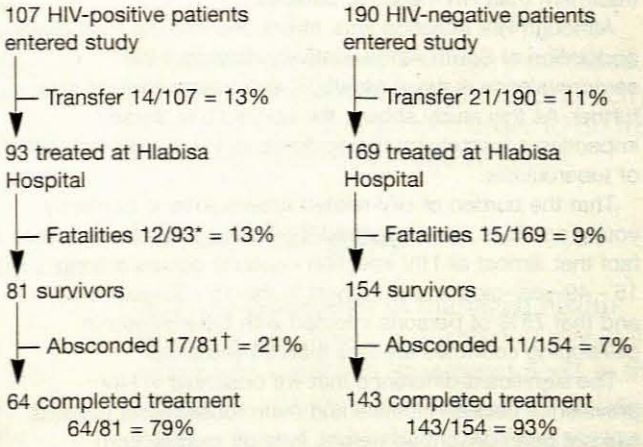
Of 307 adults diagnosed with tuberculosis during the study period, 10 (3%) declined HIV testing. One hundred and seven patients (36%, 95% CI 31 - 42%) tested HIV-positive. In all, 57 women (46%) tested HIV-positive compared with 50 men (29%) (RR 1.6, 95% CI 1.2 - 2.2). This association remained significant after adjustment for the different age distributions. The mean age (interquartile range) of HIV-negative men was 39.5 (28 - 50) years compared with 33.6 (27 - 38) years for HIV-positive men ($P = 0.04$). The mean age (interquartile range) of HIV-negative women was 37.2 (24 - 42) years compared with 29.1 (23 - 35) years for HIV-positive women ($P = 0.02$).

Type of tuberculosis. Pulmonary tuberculosis was the commonest diagnosis in both HIV-positive (63/107; 59%) and HIV-negative patients (169/190; 89%). The proportion with a negative sputum smear was the same in both groups (18%). EPTB was more common in HIV-positive than HIV-negative patients (RR 3.7, 95% CI: 2.3 - 5.9). This association remained significant after adjustment for age and sex. The site of EPTB is shown in Table I.

Table I. Site of EPTB in relation to HIV status

	HIV-positive		HIV-negative		
	No.	%	No.	%	Total
Pleural	20	46	11	52	31
Disseminated	13	29	3	13	16
Lymph node	5	12	2	10	7
Pericardial	3	7	2	10	5
Genito-urinary	1	2	2	10	3
Bone	0		1	5	1
Tuberculosis meningitis	1	2	0		1
Peritoneal	1	2	0		1
Total	44	100	21	100	65

Outcome. Of the 262 patients managed in Hlabisa, 238 (91%) were managed on SIAT and 24 were managed as inpatients (Fig. 1). Twenty-seven patients (10%) died while on treatment. The case-fatality rate was 13% (12/93 in HIV-positive patients and 9% (15/169) in HIV-negative patients (RR 1.5, 95% CI 0.7 - 3.0). Adjustment for age and sex increased this difference (RR 2.4, 95% CI 1.0 - 5.7).



* Adjusted RR = 2.45; 95% CI 1.0 - 5.70.
† RR = 3.0; 95% CI 1.5 - 6.0.

Fig. 1. Outcomes of 297 HIV-positive and HIV-negative tuberculosis patients.

The HIV-positive patients who died were of a similar age to those who survived (mean age 34.9 and 30.8 years, respectively; $P = 0.4$). Five patients died in the ward but 7 died while on SIAT, having been discharged well and improving. In contrast, the HIV-negative patients who died were significantly older than those who survived (mean age 54.9 and 37.2 years, respectively; $P = 0.004$). Six died in the ward and the 2 who died on SIAT were 80 and 85 years old, respectively.

Loss from treatment. Of the 154 surviving HIV-negative patients, only 11 (7%) failed to complete treatment. Nine absconders were men, and the ages of the absconders were

similar to those who completed treatment. In contrast 17 (21%) of the 81 surviving HIV-positive patients were lost (RR 3.0, 95% CI 1.5 - 6.0). This significant difference remained after adjustment for age, sex and type of tuberculosis. Ten of the HIV-positive absconders were men, and the ages of the absconders were similar to those who completed treatment.

Although 28 patients failed to complete treatment, 39 defaulted on treatment at least once (all were on SIAT). Of the 16 (10%) HIV-negative patients who absconded, 11 left the area and were lost, 2 returned of their own accord and 3 were traced. Of the 23 (28%) HIV-positive patients who absconded, 17 left the area and were lost, 3 returned and 3 were traced. In most cases relatives reported that the patient had left the area in search of work, but it was not possible to confirm this. Some admitted that the absconding patients were attending a traditional healer because of their HIV status.

Discussion

In our study, HIV-positive tuberculosis patients were younger, more likely to be female, presented with EPTB more commonly, and had a higher case-fatality rate than HIV-negative tuberculosis patients. Importantly, HIV-positive tuberculosis patients were more likely to default on treatment than HIV-negative patients.

Although HIV infection was introduced into the rural black population of South Africa relatively recently.[10] the seroprevalence is rising rapidly,[6,11] and seems likely to rise further. As this study shows, the epidemic is already impacting adversely on the epidemiology and management of tuberculosis.

That the burden of HIV-related tuberculosis is borne by young adults is well-described.[12-14] This is a reflection of the fact that almost all HIV infection in adults occurs among 15 - 49-year-olds and is highest in the 15 - 35-year-olds, and that 75% of persons infected with tuberculosis in developing countries are less than 50 years old.[3]

The significant difference that we observed in HIV prevalence between female and male tuberculosis patients has not been described before. In large studies from Zambia,[15] Nairobi,[12] the Ivory Coast[13] and Zimbabwe[14] no significant gender-related difference was found. It has been shown that the prevalence of HIV infection in women in KwaZulu-Natal is 3.2 times that in men.[11] The higher prevalence of HIV in women with tuberculosis described here is therefore likely to be due in large part to the background epidemiology of HIV infection in the area.

This study confirms previous findings that EPTB accounts for a much higher proportion of the cases of tuberculosis in HIV-positive people.[3] Disseminated tuberculosis (2 or more sites affected) is more common in HIV-positive patients and is a result of a deteriorating immune system.[3] However, pulmonary tuberculosis remains the most common form of tuberculosis in HIV-positive patients. Most cases are sputum smear-positive with typical granuloma, relatively few tubercle bacilli and a typical cavitatory picture seen on chest radiograph.[3] However, as the level of CD4 lymphocytes declines, the clinicopathological picture of pulmonary tuberculosis changes; there is less necrosis and cavitation, bacilli become abundant and the chest radiograph shows infiltration. Such cases are less often sputum smear-positive.[16]

This study found that 18% of HIV-positive and HIV-negative tuberculosis patients with pulmonary tuberculosis were sputum smear-negative. It seems unlikely that HIV-positive sputum-negative patients were underdiagnosed as standard guidelines[7,8] were followed and the level of awareness among clinicians was high. However, as the prevalence of HIV infection in tuberculosis patients rises, the proportion of cases of pulmonary tuberculosis that are smear-negative can be expected to rise and this may pose diagnostic problems.[16,17]

Prior to the HIV era the mortality rate in tuberculosis patients was 4 - 6%.[18] The 9.0% case-fatality rate for HIV-negative patients reported here is higher than expected and this may be due in part to the exclusion of children. Risk of death increased with age in HIV-negative patients, as expected, and most died in the ward; this was a reflection of their poor clinical condition. The case-fatality rate of 13.0% for HIV-positive tuberculosis patients is consistent with other reports.[3,18] Risk of death did not increase with age in this group. It is now recognised that much of this excess mortality is due to non-tuberculous AIDS-related conditions such as bacteraemia and toxoplasmosis.[19,20] This is presumably what happened to 7 of our patients who died on SIAT after having been discharged well and improving. It will be important to develop strategies to improve the access of HIV-positive patients to care during (and after) treatment for tuberculosis to detect and treat such infections, and thus reduce mortality. The reputation of tuberculosis treatment programmes, which rely on community acceptance, is also at stake here.

Compliance with, and completion of, tuberculosis treatment is the key to individual cure and public health control of tuberculosis.[21] Although treatment is recognised to be as important and as effective in HIV-positive tuberculosis patients,[17] there are no previous reports of increased defaulting on treatment by HIV-positive tuberculosis patients in Africa. Therefore our finding in this study that the risk of HIV-positive patients' defaulting was three times that of HIV-negative patients is particularly important. It is noteworthy that field staff had suspected this. It seems that many of these patients leave the area to consult traditional healers who advertise that they are able to cure HIV infection.[22] Several of our HIV-positive patients readily admitted to attending traditional healers and were convinced they would be cured.

There are three main implications of this study. One is the need to be aware of the changing clinical features of tuberculosis as HIV prevalence rises, particularly the increase in EPTB and the changing picture of pulmonary tuberculosis. Secondly there is the need to reduce mortality on treatment. This may be possible with more aggressive early management, including investigation for concomitant bacterial infection and the use of broad-spectrum antibiotics in addition to tuberculosis treatment. Finally, there is the urgent need to improve compliance in HIV-positive tuberculosis patients.

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A blood-result turn-around time survey to improve congenital syphilis prevention in a rural area

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The results of a turn-around time study of blood specimens for syphilis serology in antenatal clinic attenders between 19 rural clinics and their base hospital, including a follow-up survey to assess the impact of interventions, are described. The objective of the study was to determine how long blood samples took to get from the clinic to the laboratory and back again. The time between each phase was recorded by inclusion of a dating system on the documentation that routinely accompanies the blood samples. The longest delay was the time at the laboratory. The results were reported to the various sectors involved in the handling of the blood samples. The solution was to make all divisions of the health service aware of the needs of the clinic staff and clinic service users, and to change laboratory routine.

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Management of health services, with the aim of improving health care, is a challenge to any health administrator. Managerial weakness at the local level has been cited as one of the reasons for poor functioning in some rural health care services.[1] Inertia in the health service and resistance to change on the part of individuals are common problems. Health workers who have done research into health service evaluation have emphasised the need to define objectives of a particular health service and then to evaluate whether these objectives have been met and the use of epidemiology in health service management and planning has been discussed in the literature.[2-5] While there is currently much work on policy development, the majority of health service managers operate at a much lower level. Their concerns are more mundane but as important to effective and efficient health service delivery. Measurement of outcome change is seldom quick and, in addition, a multiplicity of factors usually contributes to the change seen.[6] A systems approach to management has drawn our attention to the need to look at process as well as outcome in health service research.[7] Against this background, the apparently poor identification of pregnant women with positive syphilis serological tests in a rural area of South Africa was investigated.

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