

# Impact of HIV on tuberculosis in Zambia: a cross sectional study

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## Abstract

**Objective**—To examine the contribution of HIV infection to the apparently increasing incidence of tuberculosis in central Africa.

**Design**—Cross sectional study.

**Setting**—Outpatient clinic in teaching hospital, Lusaka, Zambia.

**Patients**—346 Adult patients with tuberculosis.

**Results**—Overall, 206 patients (60%; 95% confidence interval 54% to 65%) were positive for HIV—in one or both assays used. The peaks for both tuberculosis and HIV infection were among men aged 25-34 years and women aged 14-24 years. Of patients with confirmed pulmonary tuberculosis, 73/149 (49%; 41% to 57%) were positive for HIV; 67/83 (81%; 70% to 89%) patients with pleural disease and 16/19 (84%; 60% to 97%) patients with pericardial disease were positive. HIV positive patients with positive sputum culture were less likely to have had a positive sputum smear, and their chest x ray films less often showed classic upper zone disease or cavitation. Of 72 patients who fulfilled clinical criteria for AIDS, 17 were negative for HIV.

**Conclusions**—The high prevalence of HIV in patients with tuberculosis suggests that an epidemic of reactivating tuberculosis is arising in those who are infected with HIV. The redirection of public health priorities towards tuberculosis would focus on a major treatable and preventable complication of the AIDS epidemic.

## Introduction

Over the past few years tuberculosis has emerged as an important disease in people infected with HIV. Increases in the numbers of new cases of tuberculosis have been recorded in the United States,<sup>1</sup> Tanzania, Burundi,<sup>2</sup> and Zambia, and seroprevalence surveys have indicated a strong link between tuberculosis and HIV.<sup>3,4</sup> The activation of latent infection with organisms acquired early in life and exposed by deteriorating immune control is characteristic of AIDS.<sup>5</sup> In many developing countries latent infection with tuberculosis is present in most adults,<sup>6</sup> and in these countries the spread of HIV may cause a major secondary epidemic of active tuberculosis.

In Zambia, therefore, we have embarked on a series of studies of the interaction between the two organisms, and in this paper we present the findings of an initial cross sectional study undertaken to establish the prevalence of HIV-1 infection among patients with tuberculosis in Lusaka and to examine the impact of HIV infection on the clinical presentation of tuberculosis.

## Patients and methods

### PATIENTS

Patients with tuberculosis in Lusaka and the surrounding areas are notified and kept under review at the chest clinic of the University Teaching Hospital in Lusaka. Patients arriving at the clinic wait in line to be seen by one of three or four clinical officers or doctors.

Between November 1988 and January 1989 all the adult patients being treated for tuberculosis seen by one doctor were asked to take part in the study; they were selected on the basis simply of being next in line. A questionnaire relating to history and clinical examination was completed for each patient, radiological and laboratory results were recorded, and a blood sample was taken. Serological testing was carried out anonymously, all clinical and laboratory data being identified only by a number.

In all, 360 eligible patients were seen. Eight patients refused to take part and two (both of whom had had positive HIV antibody results) were considered too sick to be subjected to the interview. Four of the 350 patients recruited were excluded from the analysis, two because the true diagnosis was found to be other than tuberculosis and two more because the data obtained were inadequate.

### INFECTION AND TREATMENT

A rigorous diagnosis of tuberculosis is not always possible, so for the purposes of the study a case of tuberculosis was defined as a patient being treated for tuberculosis. The patient might be starting, continuing, or completing treatment on the day of recruitment. About 60% of cases of pulmonary disease were confirmed by sputum smear or culture. The remainder were diagnosed on the basis of clinical and radiological findings. Pleural tuberculosis was diagnosed clinically, sometimes by the presence of protein or high numbers of cells in the pleural fluid, and pericardial disease usually with the support of echocardiography, but bacteriological confirmation was impossible. In a number of patients more than one site was affected. Other types of tuberculosis were underrepresented because patients were recruited solely from the chest clinic.

Patients seen at the chest clinic are treated according to national guidelines. Patients with positive sputum smears and those with military and meningeal disease are treated with streptomycin, rifampicin, isoniazid, thiacetazone, and pyrazinamide for two months and then isoniazid and thiacetazone for six months. All other patients are treated with streptomycin, isoniazid, and thiacetazone for two months and then isoniazid and thiacetazone for 10 months, with the exception of pregnant women, in whom the use of streptomycin and pyrazinamide is avoided.

Serum samples were analysed for HIV antibody by competitive recombinant enzyme linked immunosorbent assay (ELISA) (Wellcozyme; Wellcome Diagnostics, Dartford, Kent) and antiglobulin recombinant ELISA (DuPont; de Nemoirs, Belgium). Ethical approval was given by the research and ethics committee of the University Teaching Hospital, Lusaka.

### STATISTICAL METHODS

Associations were corrected for age and sex by stratified analysis, with age in five groups (14-24, 25-34, 35-44, 45-54,  $\geq 55$ ). Odds ratios and significance tests were obtained by Mantel-Haenszel methods and in the case of risk factors for HIV infection by logistic regression.<sup>7</sup> Calculations for 95%

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confidence intervals for percentages were by exact or approximate methods depending on the sample size. Where appropriate,  $\chi^2$  tests for trend were conducted by attaching successive integer scores to the categories of the variables of interest.

## Results

### AGE AND SEX DISTRIBUTION OF PATIENTS

The 346 patients with tuberculosis comprised 203 men and 143 women. Of the women the largest number (65; 45%) were in the 14-24 year age group; of the men the largest number (81; 40%) were aged 25-34 years. In the youngest age group there was only one patient under 15 years of age, a girl aged 14. Five patients did not know their age.

### HIV SEROPREVALENCE

Of the 346 patients with tuberculosis 206 (60%; 95% confidence interval 54% to 65%) were found to be positive by both assays for HIV-1. These patients were designated to HIV positive for our analysis. There were 17 discrepant results: eight serum samples were positive by Wellcozyme assay but not DuPont; nine serum samples were positive by DuPont assay but not Wellcozyme. The 17 patients positive by only one test were included in the negative group, perhaps underestimating the overall seropositivity.

There was a striking difference in prevalence of HIV according to age group (table I). Among women it was highest in the youngest age group and declined thereafter ( $\chi^2=10.61$ ,  $df=4$ ;  $p<0.05$ ). Among men it was highest in those aged 25-34 and then fell with increasing age ( $\chi^2=15.84$ ,  $df=4$ ;  $p<0.005$ ). The distribution of numbers of cases and prevalence of HIV thus followed the same pattern. Overall 92 (64%; 56% to 72%) of the women were seropositive compared with 114 (56%; 49% to 63%) of the men, but this difference was not significant even after allowing for age (Mantel-Haenszel test  $\chi^2=0.69$ ,  $df=1$ ).

The association between HIV infection and certain other variables was studied. After allowing for age and sex, a high prevalence of HIV infection was found to be significantly associated with a high number of years spent in full time education, good housing (a low number of people sharing the same bedroom), divorced or widowed marital state, and history of previous treatment for sexually transmitted diseases (table II). All these associations remained significant when joint effects between them were examined.

### TUBERCULOSIS

Table III shows the prevalence of HIV antibody according to category of tuberculosis; patients in whom more than one site was affected are included in the table under each site. A much higher prevalence of HIV antibody was found among those with pleural or pericardial disease than among those with pulmonary disease, and, although patients with pleural or pericardial disease were younger than those with pulmonary disease, the difference in HIV state was independent of age and sex. This was shown by comparing those with pleural or pericardial disease, or both, with or without pulmonary disease, with those with pulmonary disease but no pleural or pericardial disease (odds ratio corrected for age and sex=3.5 (1.7 to 5.9);  $p<0.001$ ).

Results of sputum culture were positive in 126 patients and not available for three. The results of sputum smear examinations were compared in 62 patients positive for HIV and 61 negative for HIV (table IV). Only 39 (63%; 51% to 75%) of those positive for HIV had had a positive smear compared with 50 (82%; 72% to 92%) of those negative for HIV ( $\chi^2=4.67$ ,  $df=1$ ;  $p<0.05$ ). Among patients with a positive

sputum smear there was a tendency for those who were HIV positive to show a lower count of bacilli (table IV;  $\chi^2$  for trend=3.34,  $df=1$ ;  $p=0.07$ ).

Chest radiographs were available for 139 of the 149 patients with pulmonary tuberculosis confirmed by sputum smear or culture, or both (table V). Of these

TABLE I—Prevalence of HIV infection in men and women with tuberculosis in Lusaka by age group. Figures are proportions (percentages) positive for HIV

Age (years)	Men	Women
14-24	15/31 (48)	48/65 (74)
25-34	55/81 (68)	32/50 (64)
35-44	32/57 (56)	8/14 (57)
45-54	9/19 (47)	3/10 (30)
≥55	2/14 (14)	
Unknown	1/1 (100)	1/4 (25)
Total	114/203 (56)	92/143 (64)

TABLE II—Relation of HIV-1 antibody state to education, housing, marital state, and history of treatment for sexually transmitted diseases

	No of patients	Odds ratio for HIV infection		$\chi^2$	p Value
		Crude	Adjusted*		
Years of full time education:					
0	30	1	1	19.29†	<0.001
1-6	72	1.67	1.46	(df=1)	
7	68	4.28	3.09		
8-12	142	5.75	5.35		
≥13	32	5.13	5.08		
Housing (No of people sharing bedroom):					
1	72	1	1	10.39†	=0.001
2	115	0.92	0.84	(df=1)	
3	91	0.68	0.50		
4	43	0.90	0.58		
≥5	23	0.28	0.17		
Marital state:					
Married	192	1	1	7.71	<0.025
Single	94	0.90	0.65	(df=2)	
Widowed or divorced	58	1.33	2.30		
History of treatment of sexually transmitted diseases:					
No	240	1	1	15.04	<0.001
Yes	99	2.83	3.09	(df=1)	

\*Adjusted odds ratios and significance tests were obtained by logistic regression allowing for age and sex.

†Test for trend.

TABLE III—Sites of tuberculosis related to HIV-1 infection

Site	Proportion (%) of patients positive for HIV (95% confidence interval)
Lung:	
Tuberculosis confirmed	73/149 (49) (41% to 57%)
Tuberculosis not confirmed	60/101 (59) (50% to 69%)
Pleura	67/83 (81) (70% to 89%)
Pericardium	16/19 (84) (60% to 97%)
Node	7/10 (70) (35% to 93%)
Other	6/12 (50) (21% to 79%)

TABLE IV—Relation between HIV-1 antibody state and results of sputum smear in patients with pulmonary tuberculosis confirmed by positive sputum culture

Bacilli per field (25× objective)	No (%) of patients positive for HIV (n=62)	No (%) of patients negative for HIV (n=61)
0	23 (37)	11 (18)
1-10	22 (35)	15 (25)
11-20	6 (10)	16 (26)
≥21	11 (18)	19 (31)

TABLE V—Relation of HIV-1 antibody state to x ray findings in patients with pulmonary tuberculosis confirmed by sputum smear or culture, or both

x Ray findings	No (%) of patients positive for HIV (n=67)	No (%) of patients negative for HIV (n=72)
Upper zones:		
Included	46 (69)	66 (92)
Not included	21 (31)	6 (8)
Cavitation	32 (48)	49 (68)

TABLE VI—Clinical features of AIDS in patients with tuberculosis

Symptom or sign	No of patients with symptom or sign	% Positive for HIV-1‡	% Of patients with symptom or sign‡		p Value*
			Positive for HIV (n=206)	Negative for HIV (n=140)	
Weight loss	114	62	34	31	NS
Symptoms lasting more than one month per year:					
Fever	90	67	29	21	NS
Diarrhoea	36	83	14	4	<0.005
Cough	169	57	47	51	NS
Lymph nodes swollen	225	72	79	44	<0.001
Candida (oral)	10	100	5		<0.05
Maculopapular rash	9	89	4	1	NS
Herpes zoster	16	100	8		<0.005
Kaposi's sarcoma	4	75†	1	1	

\*For comparison of prevalence of symptom in patients HIV positive and HIV negative; NS=not significant.

†All patients with Kaposi's sarcoma were positive by Wellcozyme assay; one was negative by the DuPont assay.

‡Data presented as percentages as figures unavailable.

patients, 67 were positive for HIV and 72 were negative. There was no association between the total number of zones seen to be affected in the radiograph and HIV state, but 56 (92%; 83% to 97%) of the patients negative for HIV had disease that included upper zones compared with only 43 (69%; 58% to 80%) of those positive for HIV ( $\chi^2=10.32$ ,  $p<0.001$ ). Cavitation was seen in the radiographs of 42 (68%; 57% to 79%) patients negative for HIV compared with 30 (48%; 36% to 60%) of those positive for HIV ( $\chi^2=5.07$ ,  $p<0.05$ ).

#### TUBERCULOSIS AND AIDS

Seventy two of the 346 patients fulfilled the World Health Organisation clinical criteria for AIDS on the day of recruitment. Seventeen of these patients were negative for HIV-1 by both Wellcozyme and DuPont assays, and 10 of the 17 were confirmed positive for tuberculosis by sputum culture.

Table VI shows the relation between the symptoms and signs included in the WHO criteria and HIV antibody state. Diarrhoea for more than a month, generalised lymphadenopathy, oral candidiasis, and evidence of herpes zoster all showed a significant link. Weight loss did not discriminate well between tuberculosis alone and tuberculosis with HIV; nor did body mass index (weight/height<sup>2</sup>).

#### DRUG REACTIONS

Records and histories indicated that eight patients had developed Stevens-Johnson syndrome in reaction to drugs; all of these were positive for HIV ( $\chi^2=3.97$ ,  $p<0.05$ ). A further 12 had developed a lesser but generalised rash, and seven of these patients were positive for HIV.

#### RELAPSE

We found no association between previous history of treatment for tuberculosis and HIV antibody state. Thirty patients had had previous courses of treatment, more than 20 of them within the past five years; 18 (60%) were HIV positive, a proportion identical with that in the whole group. Seven of 10 patients who had received completed courses and 10 of 19 who had received previous incomplete courses were positive for HIV. One seropositive patient was unable to give details of the previous treatment.

#### Discussion

The strong link between tuberculosis and HIV has been shown in seroprevalence surveys in places as diverse as Burundi, the United States, Tanzania, and Haiti,<sup>2</sup> and in our study the prevalence of HIV-1 antibody in patients with tuberculosis in Lusaka, at 60%, was found to be considerably higher than the 10% found in blood donors from the same area over the

period from June 1987 to December 1988.<sup>8</sup> Screening patients at any stage of treatment indicates the prevalence of HIV infection in patients being treated for tuberculosis and may lead to an overestimate or an underestimate of the prevalence of HIV infection in newly diagnosed patients.

Both *Mycobacterium tuberculosis* and HIV have their impact on young adults at the beginning, or in the prime, of their productive lives; the largest numbers of cases of tuberculosis and the highest percentage of patients with HIV antibody were women aged 14 to 24 and men aged 25 to 34 years. Half of the patients screened were from the better educated sector of the population (eight or more years in full time education); in this group the prevalence of HIV antibody was higher than that in those with less education.

The seriousness of these observations need not be emphasised. There is evidence from several sources, however, that tuberculosis may respond well to treatment, even in the presence of HIV infection.<sup>9,10</sup> It is therefore essential that the diagnosis should be made and appropriate treatment given.

The classic form of tuberculosis, with cavitating, upper zone, pulmonary lesions, is known to be determined by the interaction between the bacillus and the host's immune system, so that in the presence of immune deficiency a different outcome may be expected. The link between extrapulmonary tuberculosis and HIV is well established.<sup>11</sup> We found a close association between pleural and pericardial disease and the presence of HIV, other forms of extrapulmonary tuberculosis being underrepresented in our group of patients. Tuberculosis is recognised as an important agent of pleural and pericardial disease. Our study has shown, however, that when pulmonary tuberculosis occurs in the presence of HIV the doctor may be misled both by sputum smear results and by radiological findings.

Sputum smear examination has long been a cornerstone in the diagnosis of tuberculosis, particularly in rural areas, where culture of the bacillus and chest radiography are seldom available. We found that among patients proved to have pulmonary tuberculosis by sputum culture 37% of those positive for HIV had had negative sputum smears compared with only 18% of those negative for HIV, a finding suggesting that, in the presence of HIV infection, the sputum smear must be regarded as an unreliable tool. This finding of a low bacillary load in the sputum of HIV positive patients with pulmonary tuberculosis also suggests that they may be less infectious than those negative for HIV. When a chest x ray film is available the findings can be expected to differ between patients with tuberculosis positive and negative for HIV. Our findings confirmed those of other studies<sup>12</sup>; a higher proportion of HIV positive patients showed atypical middle and lower zone disease and absence of cavitation.

There is a further matter for concern. Both tuberculosis and HIV infection lead to chronic ill health and wasting, and both are associated with persistent cough and fever. These similarities, compounded by difficulties in diagnosis, suggest that patients with tuberculosis, with or without HIV infection, might be diagnosed as having AIDS alone and might therefore fail to receive appropriate treatment. This danger is illustrated by our finding that serum samples were negative for HIV antibody in a quarter of the 72 patients being treated for tuberculosis who fulfilled the WHO's clinical criteria for AIDS<sup>13</sup> on admission to our study. We found that a severe degree of wasting is unlikely to be a good indicator of concurrent HIV infection, whereas diarrhoea, generalised lymphadenopathy, the presence of thrush in the mouth, and signs of previous or current infection with herpes zoster showed a significant association with HIV infection.

A real impediment to the successful treatment of tuberculosis is the development of severe adverse drug reactions, and patients with concurrent HIV infection seem to be particularly at risk. This is shown in our study by the occurrence of Stevens-Johnson syndrome exclusively in patients positive for HIV. It has been widely speculated that thiacetazone is the drug responsible for most of these serious rashes,<sup>14,15</sup> but this is not yet proved. Hypersensitivity to any antituberculous drug may cause a rash, and studies in which treatment did not include thiacetazone have also shown a greater incidence of adverse drug reactions among patients positive for HIV.<sup>9,16</sup> If, however, it is true that one drug is responsible for most drug reactions then it should be clearly identified so that its use in patients positive for HIV may be avoided.

Another outstanding practical question regarding the management of tuberculosis in the presence of HIV infection is whether, as seems likely, the immune deficiency caused by the virus leads to a greater danger of relapse. Current evidence is preliminary and conflicting.<sup>9,10,17</sup> No difference in HIV prevalence was observed in our study between relapsed and new cases. A more appropriate comparison, however, is between patients who have had tuberculosis and have or have not relapsed; further studies of this kind are needed. As well, prospective studies are needed to discover whether tuberculosis causes an increased rate of progression to AIDS and whether the prophylactic use of antituberculous drugs in asymptomatic patients positive for tuberculin and HIV can increase their span of healthy life.

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## Terminal cancer care and patients' preference for place of death: a prospective study

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### Abstract

**Objective**—To assess the preference of terminally ill patients with cancer for their place of final care.

**Design**—Prospective study of randomly selected patients with cancer from hospital and the community who were expected to die within a year. Patients expected to live less than two months were interviewed at two week intervals; otherwise patients were interviewed monthly. Their main carer was interviewed three months after the patient's death.

**Setting**—District general hospital, hospices, and patients' homes.

**Main outcome measure**—Stated preferred place of final care; actual place of death; reason for final hospital admission for those in hospital; community care provision required for home care.

**Results**—Of 98 patients approached, 84 (86%) agreed to be interviewed, of whom 70 (83%) died during the study and 59 (84%) stated a preferred place of final care: 34 (58%) wished to die at home given existing circumstances, 12 (20%) in hospital, 12 (20%) in a hospice, and one (2%) elsewhere. Their own home was the preferred place of care for 17 (94%) of the patients who died there, whereas of the 32 patients who died in hospital 22 (69%) had stated a

preference to die elsewhere. Had circumstances been more favourable 67% (41) of patients would have preferred to die at home, 16% (10) in hospital, and 15% (9) in hospice.

**Conclusion**—With a limited increase in community care 50% more patients with cancer could be supported to die at home, as they and their carers would prefer.

### Introduction

Place of death and quality of final care are important components of terminal cancer care for both the patient and the family. The proportion of patients with cancer dying at home has fallen steadily in the United Kingdom, from 37% in 1965 to 27% in 1987.<sup>1</sup> In Edinburgh and Western Australia, however, the provision of cancer care services has enabled as many as 41% and 70% respectively of patients with cancer to die at home.<sup>2,3</sup> There are no studies in the United Kingdom reporting patient preferences about place of terminal care.

This study was therefore undertaken to determine prospectively the needs and wishes of patients who were dying from cancer, their symptoms and symptom

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