

HIV Infection in Patients with Tuberculosis in Kinshasa, Zaire^{1,2}

ROBERT L. COLEBUNDERS, ROBERT W. RYDER, NZILA NZILAMBI, KALUNGA DIKILU, JEAN-CLAUDE WILLAME, MULUMBA KABOTO, NKOKO BAGALA, JACQUES JEUGMANS, KALALA MUEPU, HENRY L. FRANCIS, JONATHAN M. MANN, THOMAS C. QUINN, and PETER PIOT

Introduction

Most adults in central Africa are latently infected with *Mycobacterium tuberculosis* (1), which may be reactivated because of immunosuppression (2) caused by human immunodeficiency virus (HIV) infection. In urban centers of central Africa, 5 to 20% of the sexually active population is infected with HIV (3). Therefore, if HIV and tuberculosis (TB) are associated in a sense that infection with one could favor the development of disease by the other, serious public health problems could arise.

High HIV seroprevalence rates in TB patients in Africa have been reported (4, 5). To define the relationship between HIV infection and TB more clearly and to determine the clinical characteristics of HIV-infected TB patients, we performed three HIV seroprevalence surveys of different groups of TB patients in Kinshasa, Zaire. Serologic results in TB patients were compared with seroprevalence data in healthy hospital workers from the same city.

Methods

1985 and 1987 Surveys of Sanatorium Patients

In March 1985 and May 1987, we performed cross-sectional serologic surveys of the patients hospitalized in the Makala Sanatorium in Kinshasa, Zaire. This sanatorium is a 300-bed facility integrated into a citywide TB program. Patients with clinically and/or sociologically complex disease are generally admitted for a minimum of two months to ensure adequate initial treatment. In Zaire, at the time of this study, standard antituberculosis treatment for adults consisted of a two-month regimen of streptomycin (1 g administered intramuscularly daily, 6 days a week), thiacetazone (150 mg administered orally daily), and isoniazid (300 mg administered orally daily), followed by a ten-month regimen of thiacetazone (150 mg daily) and isoniazid (300 mg daily). If, after six months of this standard antituberculosis treatment, acid-fast bacilli (AFB) were still seen in the expectorated sputum, therapy was changed to rifampin, ethambutol, and pyrazinamide (1).

SUMMARY To better define the interrelationship of infection with human immunodeficiency virus (HIV) and tuberculosis (TB), we conducted three HIV serosurveys of inpatients and outpatients with confirmed or suspected TB in Kinshasa, Zaire. HIV seroprevalence in hospitalized sanatorium patients did not change significantly in serosurveys conducted in 1985 and 1987 (92/231 [40%] versus 85/234 [36%]). These proportions were significantly higher than the 17% HIV seroprevalence observed in a 1987 serosurvey of 509 consecutive patients with an initial diagnosis of pulmonary TB seen at an outpatient TB diagnostic center in Kinshasa ($p < 0.001$). HIV seroprevalence was higher in sanatorium patients with extrapulmonary TB (22/46 [48%]) and suspected pulmonary TB (60/132 [45%]) than in patients with bacteriologically confirmed pulmonary TB (94/287 [33%]) ($p < 0.02$). *Mycobacterium* sputum isolation rates were similar in HIV-seropositive (28/34 [82%]) and HIV-seronegative patients (135/159 [85%]). All isolates were *Mycobacterium tuberculosis*. Eighteen (21%) of 84 HIV-seropositive sanatorium patients in 1987, who were followed for two months after admission, had died, compared with 11 (9%) of 128 HIV-seronegative patients ($p < 0.01$). However, clearance rates of acid-fast bacilli from sputum after standard therapy were equally good in HIV-seropositive and HIV-seronegative survivors. With the growing AIDS problem, the serious TB burden in sub-Saharan Africa may become even more onerous and may critically overload the stressed African health care systems.

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The information collected on sanatorium patients included demographic factors, current and prior history of TB, and recent medical history. Interviews and examinations were carried out by physicians unaware of the HIV-antibody status of the patients. Patients were classified into three groups: (1) those with "confirmed pulmonary TB," who had at least one sputum examination positive for AFB or a culture positive for *M. tuberculosis*; (2) patients with "suspected pulmonary TB," who had clinical symptoms and radiologic signs of TB, but no bacteriologic proof. A patient was considered to have suspected pulmonary TB if his chest X-ray showed alveolar infiltrates with or without cavitation and if these infiltrates were resistant to common antibiotic treatment. Some of the patients of this group had received antituberculosis therapy before admission to the sanatorium, but their prior sputum examination reports could not be traced. Others could not produce sputum; (3) patients with "extrapulmonary TB," who had clinical evidence of TB in the pleura, pericardium, bone, or had histologic or bacteriologic evidence of TB in a lymph node.

A cutaneous delayed hypersensitivity reaction was tested by intradermal skin test (Mantoux) with two T.U. tuberculin P.P.D. (Institut Pasteur du Brabant, Brussels, Belgium) or multitest (IMC Merieux, Lyon, France). Skin tests were performed on all sanatorium patients and on a group of healthy HIV-seronegative health care workers and were read after 48 to 72 h. A patient was consid-

ered anergic to tuberculin if induration at the injection site was less than 2 mm.

All 1987 study participants were followed in the hospital for a maximum of two months. Patients' weights, examination of sputum for AFB, a chest radiograph, and erythrocyte sedimentation rates (ESR) were obtained before discharge.

Serologic results in TB patients were compared with age- and sex-specific seroprevalence data obtained in 1986 from 2,193 healthy adults working at Mama Yemo Hospital in Kinshasa (6).

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¹ From the Project SIDA, Department of Public Health, the Belgian Zairian Medical Cooperation, the National Tuberculosis Program, Tuberculosis Diagnostic Center, and the Makala Sanatorium, Kinshasa, Zaire; the Institute of Tropical Medicine, Antwerp, Belgium; the Center for Infectious Diseases, Centers for Disease Control, Atlanta, Georgia; Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; Special Programme on AIDS, World Health Organization, Geneva, Switzerland.

² Correspondence and requests for reprints should be addressed to Robert L. Colebunders, M.D., Department of Microbiology, Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium.

TABLE 1

HIV SEROPOSITIVITY OF SANATORIUM AND AMBULATORY TB PATIENTS BY AGE AND SEX, KINSHASA, ZAIRE

Age	Sanatorium Patients, 1985 and 1987 No. HIV Positive/No. Tested (%)			Outpatients, 1987 No. HIV Positive/No. Tested (%)		
	Men	Women	Total	Men	Women	Total
< 20	1/17 (6)	4/20 (20)	5/37 (14)	0/31	1/33 (3)	1/64 (2)
20-29	27/95 (28)	46/105 (44)	73/200 (37)	7/126 (6)	27/108 (25)	34/234 (16)
30-39	33/78 (42)	27/50 (54)	60/128 (47)	24/103 (23)	17/41 (41)	41/144 (28)
40-49	15/31 (48)	7/19 (36)	22/50 (44)	6/30 (20)	2/18 (11)	8/48 (17)
> 50	10/34 (29)	7/16 (44)	17/50 (34)	1/15 (7)	0/4	1/19 (5)
Total	86/255 (34)	91/210 (43)	177/465 (38)	38/305 (12)	47/204 (23)	85/509 (17)

1987 Survey of TB Outpatients

To ascertain the prevalence of HIV infection in less severely ill TB patients, from January to April 1987, we tested the serum of all patients diagnosed for the first time with confirmed pulmonary TB (sputum examination positive for AFB) for HIV at an outpatient TB diagnostic center (Centre de Dépistage de la Tuberculose [CDT]). The CDT is the reference outpatient TB diagnostic facility in Kinshasa.

Laboratory Methods

HIV serology. HIV serology was conducted with ELISA (Organon Teknika, Oklahoma City, OK or Wellcozyme, Burroughs Wellcome, Dartford, UK). Serum samples that were repeatedly HIV-positive by ELISA were confirmed by Western blot (DuPont de Nemours, Wilmington, DE) or indirect immunofluorescence. A Western blot was considered positive if a reaction against the protein bands p24 and gp41 or gp120/160 was observed.

Mycobacterium cultures. In the 1987 survey of sanatorium patients, every patient with pulmonary TB who had been on antituberculosis therapy for fewer than 14 days had one sputum sample cultured for mycobacteria. In the 1987 survey of TB outpatients, sputum of a random sample of patients was obtained for mycobacteria culture before antituberculosis treatment was started. Mycobacteria were cultured on Lowenstein-Jensen and Ogawa medium and identified with standard procedures (7), including a paperstrip method for niacin (Difco, Detroit, MI) (8).

Statistical Analysis

Chi-square, Fisher's exact test, Student *t* test, and logistic regression analyses were used. Statistical significance was designated at $p < 0.05$.

Results*1985 and 1987 Survey of Sanatorium Patients*

Seroprevalence data. In the 1985 serosurvey, completed questionnaires, physical examinations, and serum samples were collected from 231 (84%) of the 274 sanatorium patients (some of the results of

this study have been reported [4]). In the 1987 serosurvey, we studied 234 (85%) of the 276 patients (table 1). Patients who were not enrolled in the surveys (refusal, incomplete history or examination, inadequate serum for testing) were similar to the study participants regarding demographic factors and TB classification. Pooled data from the 1985 and 1987 surveys will be presented because no differences were observed between the two studies.

Among sanatorium patients, men were older than women (mean age, 34 versus 30 yr; $p < 0.01$). The prevalence of HIV seropositivity was similar in 1985 (92/231 [40%]) and 1987 (85/234 [36%]). The rate was higher for women than for men ($p = 0.04$). HIV-seropositive men were older than HIV-seropositive women (mean age, 35 versus 31 yr; $p < 0.01$). HIV seroprevalence was significantly higher for patients 30 to 49 yr of age than for patients of all other age groups ($p < 0.01$). According to age/sex-specific rates derived from healthy hospital workers in Kinshasa, we would have expected 19 rather than the observed 73 of the 200 patients 20 to 29 yr of age to be HIV seropositive ($p < 0.001$).

HIV infection was more common in patients with extrapulmonary TB and

suspected pulmonary TB than for patients with confirmed pulmonary TB ($p < 0.01$) (table 2).

Clinical Characteristics of the Sanatorium Patients, 1987 Survey

Twenty-six (31%) of the 85 HIV-seropositive patients reported previous antituberculosis treatment within the past five years, compared with 27 (18%) of the 149 HIV-seronegative patients ($p = 0.04$). However, when only the patients with confirmed pulmonary TB were considered, differences were no longer significant.

Symptoms and signs significantly more common in HIV-seropositive patients than in HIV-seronegative patients included weight loss greater than 20% of body weight, persistent diarrhea and fever, dysphagia, papulopruritic eruption, oral candidiasis, polyadenopathy, and a history of herpes zoster (table 3). HIV-seropositive patients treated with thiacetazone reported higher rates of skin eruptions or pruritus during antituberculosis treatment (including Stevens-Johnson syndrome in two patients) than did HIV-seronegative patients (10/50 [20%] versus 7/95 [7%]) ($p = 0.05$).

HIV-seropositive patients had significantly lower mean hematocrits than HIV-seronegative patients ($p = 0.001$) (table 3). Twenty-two (26%) HIV-seropositive patients had a hematocrit less than 20%, compared with seven (5%) HIV-seronegative patients ($p < 0.0001$).

Radiographic examination showed that 55 (59%) of the 85 HIV-seropositive and 107 (72%) of the 149 HIV-seronegative patients had lesions predominantly involving the superior segments of the lungs ($p = 0.06$). Pulmonary cavitation was noted in 29 (34%) HIV-seropositive patients and in 66 (44%) HIV-seronegative patients ($p = 0.1$). Mediastinal enlargement and/or hilar lymphadenopa-

TABLE 2
HIV SEROPREVALENCE BY TB CATEGORY, KINSHASA, ZAIRE

Category	No. HIV Positive/No. Tested (%)		p Value
	Hospitalized Patients 1985 and 1987	Outpatients 1987	
Confirmed pulmonary TB	94/287 (33)		
First episode of confirmed pulmonary TB	43/129 (33)	85/509 (17)	$< 10^{-6}$
Suspected pulmonary TB	60/132 (45)		
Extrapulmonary TB*	22/46 (48)		
Total TB patients	176/465 (38)	85/509 (17)	$< 10^{-3}$

* Patient without pulmonary TB.

TABLE 3
CLINICAL FINDINGS IN SANATORIUM PATIENTS, KINSHASA, ZAIRE, 1987

Clinical Findings	HIV Positive (n = 85) (%)	HIV Negative (n = 149) (%)	p Value
Weight loss > 10%	74 (87)	121 (81)	
Weight loss > 20%	23 (27)	16 (11)	< 0.01
Diarrhea > 1 month	9 (11)	1 (1)	< 0.001
Fever > 1 month	30 (35)	24 (16)	< 0.001
Cough > 1 month	48 (56)	74 (50)	
Dysphagia	17 (20)	13 (9)	< 0.03
Pruritic papular eruption	10 (12)	6 (4)	< 0.04
Oral candidiasis	9 (11)	2 (1)	< 0.01
Polyadenopathy*	9 (11)	4 (3)	0.03
Painful genital ulceration > 1 month	2 (2)	2 (1)	
History of herpes zoster	10 (12)	1 (1)	< 0.001
Mean hematocrit (SE)	28 (0.8)	32 (0.5)	< 0.001

* Defined as presence of lymphadenopathy > 1 cm in diameter in at least two noncontiguous sites.

thy was observed in 28 (33%) HIV-seropositive and 31 (21%) HIV-seronegative patients ($p = 0.06$). Chest X-ray findings of patients with suspected TB and confirmed pulmonary TB were not significantly different.

Cutaneous anergy to tuberculin was observed more often in HIV-seropositive patients (12/36 [33%]) than in HIV-seronegative patients with confirmed TB (5/71 [7%]) and in healthy control subjects (3/34 [9%]) ($p < 0.001$).

Clinical Course of the Sanatorium Patients, 1987 Survey

Two hundred and one (86%) of the 234 study participants were followed during two months of hospitalization. Eighteen (25%) of 73 HIV-seropositive patients and 11 (9%) of 128 HIV-seronegative patients died during the observation period ($p < 0.01$). AFB were not detected in four HIV-seropositive and two HIV-seronegative patients with direct sputum examinations performed within two weeks before death. The following factors were predictors of a fatal clinical course in logistic regression analysis: fever > 1 month ($p = 0.001$), weight loss > 20% ($p = 0.01$), and HIV-seropositivity ($p = 0.04$). Only 30 (35%) of the HIV-seropositive patients gained weight during antituberculosis treatment, compared with 86 (58%) of 149 HIV-seronegative patients ($p < 0.01$). Clearance of AFB in sputum during the two-month follow-up period was similar for both HIV-seropositive patients (48/52 [92%]) and HIV-seronegative patients (93/98 [95%]) who survived.

Chest radiographs showed improvement in 30 (58%) of 52 HIV-seropositive patients and in 76 (68%) of 112 HIV-seronegative patients. Although ESR for HIV-seropositive and HIV-seronegative

patients were similar at study enrollment, in 40% of seronegative patients, the ESR decreased during therapy, compared with 15% of seropositive patients ($p = 0.001$).

1987 Survey of TB Outpatients

We studied 509 outpatients with smear-positive pulmonary TB, including 305 (60%) men and 204 (40%) women. The men were slightly older than the women (mean age, 32 versus 29 yr, $p = 0.02$).

Eighty-five (17%) of all 509 patients were HIV seropositive. Women were more frequently HIV-seropositive than were men (47/204 [23%] versus 38/305 [12%], $p < 0.01$). The mean age of HIV-seropositive men (35 yr) was significantly higher than that of women (30 yr) ($p < 0.01$). Ages of HIV-seronegative men and women were similar. HIV-seropositivity was higher in patients 30 to 39 yr of age than in all other age groups ($p < 0.001$).

TB outpatients were in general less severely ill than TB inpatients; the mean body weight of the TB outpatients was significantly higher than that of hospitalized TB patients (51 kg versus 46 kg, $p < 0.01$).

Bacteriologic Results

The 1987 survey of sanatorium patients. Thirty-four (42%) of 81 HIV-seropositive patients had a positive AFB sputum stain, compared with 79 (60%) of 132 HIV-seronegative patients ($p = 0.04$). Forty (69%) of the 58 sputum cultures obtained were positive. Thirteen (72%) of 18 HIV-seropositive patients had positive cultures, compared with 27 (68%) of 40 HIV-seronegative patients.

The 1987 survey of TB outpatients. Mycobacterial sputum cultures were performed on 135 patients. Mycobacteria were isolated from sputum from 15 (94%)

of the 16 HIV-seropositive patients and 108 (91%) of the 119 HIV-seronegative patients.

In both surveys, combined *Mycobacterium* sputum isolation rates were similar in HIV-seropositive (28/34 [82%]) and HIV-seronegative patients (135/159 [85%]). All isolates were *M. tuberculosis*.

Discussion

HIV infections have substantial potential for complicating both the management of individual cases of TB and public health strategies for TB control. An estimated 2% of the Zairians develop active TB during their adult lives, and probably all have been asymptotically infected (1). With the recent onset of the HIV epidemic, there has been a concern that a growing number of persons with asymptomatic *M. tuberculosis* infection will develop clinical TB as a result of HIV infection.

When HIV seroprevalence in the general adult population of Kinshasa was estimated at 4 to 9% (6), HIV prevalence in patients with confirmed pulmonary TB was 17% in outpatients and 33% in inpatients. The marked difference between HIV seroprevalence in inpatients and outpatients can be attributed to selective admission to the Makala sanatorium of the most severely ill patients who, as our mortality data show, are more likely to be infected with HIV.

Studies performed in Kinshasa with health care workers in 1985 to 1986 showed an incidence of HIV infection of 1.6% per year (6). The seroprevalence of HIV infection in hospitalized TB patients was not significantly different from 1985 (40%) to 1987 (36%). However, inferences regarding the incidence of HIV infection cannot be made on the basis of these prevalence data. Prevalence of HIV infection in hospitalized TB patients depends on many factors that may have changed over time, such as HIV-specific mortality rates and criteria for hospital admission and discharge. Also, the number of patients in this study was too small to detect small to modest differences in the incidence of HIV infection.

In our study in Zaire, patients with extrapulmonary TB were significantly more likely to be HIV seropositive than were patients with pulmonary TB, similar to findings in the United States (9-13). However, in contrast to the United States, where pulmonary cavitation is observed more often in HIV-seronegative patients compared with HIV-seropositive TB patients (9-13), pulmonary cavitation was

nearly as common in HIV-seropositive patients (34%) as in HIV-seronegative Zairian TB patients (44%). Patients with pulmonary cavitation were probably overrepresented in our study because patients with extrapulmonary TB may remain undiagnosed and therefore not referred to the sanatorium. HIV seroprevalence was significantly higher in sanatorium patients with suspected pulmonary TB than in those with confirmed pulmonary TB. The most likely explanation is that patients with suspected pulmonary TB included patients without tuberculosis whose TB-like symptoms were in fact manifestations of progressive HIV illness: e.g., some patients may have had *Pneumocystis carinii* infection despite chest X-ray findings suggesting TB. A less likely explanation is that AFB may be harder to isolate from sputa of HIV-seropositive TB patients.

In the United States, infections with *M. avium* complex are more prevalent than infections with *M. tuberculosis* in AIDS patients (14). In this study, no nontuberculous mycobacteria were isolated in any of the patients. This may be because cultures for mycobacteria were performed only on sputum. Mycobacterium sputum isolation rates were similar in HIV-seropositive and HIV-seronegative TB patients. This suggests that the infectiousness of pulmonary tuberculosis in HIV-seropositive and HIV-seronegative patients may be of the same order of magnitude.

A larger percentage of HIV-seropositive than HIV-seronegative patients died during antituberculosis treatment. We could not determine whether death was related to resistance of the patients to standard antituberculosis treatment or to progression of their HIV-related illness. As noted in other studies, most HIV-seropositive TB patients responded as well to standard antituberculosis therapy as did HIV-seronegative TB patients (10, 11). HIV-seropositive patients report-

ed a previous episode of antituberculosis treatment more often than did HIV-seronegative patients. However, we do not know whether this was related to inadequate antituberculosis treatment or to TB reactivation after an adequate antituberculosis treatment. Long-term prospective studies of large numbers of HIV-seropositive and HIV-seronegative TB patients are needed to define TB treatment guidelines in populations in which HIV is prevalent.

Because of relatively high HIV seroprevalence, TB patients could be used as sentinel populations to detect HIV-related illnesses in selected regions. However, the marked differences in HIV seroprevalence observed between inpatients versus outpatients and between patients with confirmed pulmonary TB versus those with extrapulmonary TB should be taken into account.

In central Africa, all TB patients should be screened for HIV infection whenever possible and, if seropositive, should be properly counseled. Also all HIV-infected patients should be examined carefully for TB.

Tuberculosis has always been an important public health problem in the developing world (5), and financial resources for implementing efficient tuberculosis control programs have generally been insufficient. With the growing AIDS problem, the serious TB burden in sub-Saharan Africa may become even more onerous and it may critically overload the stressed African health care systems.

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