

HIV Infection in 567 Active Pulmonary Tuberculosis Patients in Brazil

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Summary: We studied 567 patients with active pulmonary tuberculosis (APT) in Rio de Janeiro, Brazil, by using a standardized questionnaire and by testing blood for HIV antibodies. The rate of HIV infection was 3.9% in 1987, 4.8% in 1988, and 5.2% in 1989, and did not differ by sex. It was highest (7.4%) in the 15- to 39-year age group. There was no difference between patients infected and not infected by HIV with regard to education, income, housing, or employment. Among all patients with definite HIV risk behavior, the HIV infection rate was 23.3%, rising to 31.2% among homo/bisexual men and 36.4% among intravenous drug users, and the rate was 6.5% for blood-transfusion recipients. Among patients who denied risk behavior, the rate was 1.2%. Generalized lymphadenopathy and oral candidiasis occurred with greater frequency among HIV-infected patients ($p < 0.0001$). Applying the World Health Organization 1985 clinical criteria and revised case definition for AIDS, we found, respectively, sensitivities of 34% and 76.9% and specificities of 31% and 26.3%; in the Rio de Janeiro environment, these clinical criteria without HIV serology should not be adopted for tuberculosis patients. For chest radiographs, a significant association was found between HIV infection and the occurrence of atypical images ($p = 0.0001$), and hilar and/or mediastinal adenopathy ($p = 0.0002$) and absence of cavities ($p = 0.0003$). A PPD (purified protein derivative) skin test induration of <5 mm was identified in 53% of the HIV-positive cases and in 31.3% of the HIV-negative cases. Only 11.5% of HIV-infected APT patients met the Centers for Disease Control 1987 AIDS criteria. **Key Words:** Brazil—HIV—Tuberculosis.

The pandemic of HIV disease and its impact on tuberculosis (TB) require research in various countries to understand better the association between

theses two diseases. *Mycobacterium tuberculosis* is commonly found in patients infected with HIV from areas with known TB endemicity and among intravenous drug users and inner-city populations of lower socioeconomic status in developed countries (1-3). An estimated 300,000 people are coinfecting by both microorganisms in Latin America alone (3).

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Using a case definition similar to that of the Centers for Disease Control (CDC) (4), 30,000 cases of

AIDS had been reported in Brazil by August 1992. Some 78% of these cases were in Sao Paulo and Rio de Janeiro, with cumulative incidence rates of 11/100,000 and 4/100,000 inhabitants, respectively (5). These AIDS cases were reported mainly from Infectious Disease Services or AIDS Clinics.

In Brazil, TB incidence is still high, about 57/100,000 in 1987. Although it has been falling in the rest of Brazil, it has been increasing since 1990 in both Rio de Janeiro and Sao Paulo (5). TB has been diagnosed in 21% of all AIDS cases reported in Brazil, behind only candidiasis and *Pneumocystis carinii* pneumonia (6).

TB tends to occur early in HIV infection and there are two distinct clinical patterns of TB in HIV-infected patients. Patients in the AIDS phase who have TB, often with atypical features, are commonly treated in general hospitals or in AIDS clinics (3,7). The other clinical pattern that has not received as much attention has been described in a few prospective studies of HIV-seropositive TB patients seen in chest or TB clinics (8-12). These studies more often find typical presentation of TB without signs or symptoms of AIDS (9-11), leading to a low specificity and sensitivity of the clinical case definition for AIDS in TB patients (13).

To establish the overall impact of HIV on TB, it is necessary to include general hospital patients as well as those in TB clinics or sanatoria. It is also urgent to understand the relationship between HIV infection rates and various factors such as poverty, alcohol, and intravenous drug use, associated with AIDS risk, TB, or both (14).

Here, we report the prevalence of HIV infection in active pulmonary tuberculosis (APT) inpatients and their demographics, socioeconomic and clinical features, sexual behavior, and alcohol use as seen in two sanatoria in Rio de Janeiro.

PATIENTS AND METHODS

This study was conducted in two sanatoria: Santa Maria State Hospital and Ary Parreiras State Hospital. The two sanatoria are the only hospitals for TB inpatients in Rio de Janeiro State and serve a population of 12 million. From February 1987 to December 1989, HIV antibody testing was conducted in 567 (89.4%) of 634 patients with APT who were asked to participate in this study. Only patients whose sputum examination results were positive for acid-fast bacilli within the preceding 30 days were eligible to participate. A standardized questionnaire, which covered all parts of the provisional World Health Organization (WHO) clinical case definition of AIDS (15), revised Caracas case definition of AIDS (16), and demographic features, including socioeconomic level, was applied by trained interviewers.

The questionnaire also included questions about (a) chronic diarrhea (defined as at least two stools of unusually loose consistency per day for at least 30 days during the previous 2 months), (b) weight loss >10% of body weight, (c) intermittent or constant fever for >1 month, (d) chronic progressive genital herpes (defined as a painful genital ulceration existing for >1 month), and (e) alcoholism (defined as two or more positive answers to any of the four questions of the CAGE screening test) (17). Questions about alcoholism were included because it is associated with TB (18) and may also be associated with risk factors for HIV infection (for instance, drug use). Questions about socioeconomic and alcoholism variables were added to the original questionnaire during the investigation, so fewer patients answered these questions than were enrolled in the study. Total educational status, employment status, and alcohol use were assessed in the 362 patients studied in 1988 and 1989. Data about familial monthly income were obtained from 278 of these 362 patients. Housing status was evaluated in only the 136 patients studied in 1989.

All patients had a physical examination that included a search for generalized lymphadenopathy (defined as the presence of lymph nodes >1 cm in at least two noncontiguous extrainguinal sites). Major diagnoses were recorded from hospital charts. Interviews and examinations were carried out by persons who were unaware of the HIV antibody status of the patients. Tuberculin skin tests were performed by an expert using 2 tuberculin units (TU) of purified protein derivative (PPD) Rt 23 (State Serum Institute, Denmark; equivalent in potency to 5 TU PPD-standard) and were considered positive when an induration of >10 mm was observed 72 h later. Chest radiographs were analyzed in a standard fashion by a single chest physician who was unaware of the patient's HIV status, and the images were evaluated as being typical or atypical of the reactivation form of TB in adults.

The following radiologic features were considered typical: infiltrative or nodular, low-density images with ill-defined boundaries, with or without cavitory lesion images in the upper lobe(s) and/or the apical segment of the lower lobe(s). Blood for HIV serology testing was obtained from all patients after they had signed an informed consent. Serum samples were tested for antibody to HIV by enzyme-linked immunosorbent assay (ELISA) (Organon Teknika, Boxtel, The Netherlands). All ELISA-positive samples were analyzed by using the Western blot immune assay on strips provided by Dupont (Wilmington, DE, U.S.A.). The samples were considered positive when they reacted to both the ELISA and the Western blot methods.

The chi-squared test (corrected for continuity), Fisher's exact test, and Student's *t* test were used for statistical analyses.

RESULTS

Sixty APT patients (10.6%) refused to participate, but they were demographically and clinically similar to the patients included in this study. The prevalence rate for HIV was 3.9% (8 of 205) in 1987, 4.8% (11 of 226) in 1988, and 5.2% (7 of 136) in 1989 (χ^2 trend, 0.34, $p = 0.56$). Included were 437 men and 130 women. Overall seropositivity (19 men and 7 women positive) as well as age distribution of positives were similar for both sexes. Seropositivity

was highest among patients who were ≤ 39 years of age (7.4%), 2.6% for those aged 40–59, and 0 for elderly patients (χ^2 , 10.02, $p = 0.0067$).

Intravenous drug use (IVDU), homosexuality, bisexuality, and blood transfusion, respectively, were confirmed by 2.5%, 2.1%, 1.2%, and 7.9% of the patients (Table 1). Seropositivity for HIV was 23.3% for patients with any of these recognized risk factors and 1.2% for all others. The frequency of seropositivity was also high among one of the other possible risk groups: subjects with more than five sexual partners (including female prostitutes) in the preceding 12 months.

None of the other demographic and socioeconomic variables that we measured was significantly associated with HIV infection. Alcoholism, detected in 39.0% of the 361 patients who answered all of the CAGE questions, was more common among men (48.0%) than among women (18.3%), but was not significantly associated with seropositivity.

Table 2 shows the relationship between the symptoms and signs included in the World Health Organization (WHO) and revised Caracas case definition criteria for AIDS. Only the occurrence of generalized lymphadenopathy, oral candidiasis, herpes zoster, and genital ulceration within the previous 5 years showed a high rate of specificity for HIV infection. Only oral candidiasis had a positive predictive value of $>20\%$.

Examining the WHO 1985 clinical criteria and re-

TABLE 1. HIV risk groups and HIV test results among 567 active pulmonary tuberculosis patients seen in two sanatoria in Rio de Janeiro, 1987–1989

	HIV +	HIV -	Total	% HIV +
Recognized risk groups	17	56	73	23.3
Male homo/bisexual	5	11	16	31.2
Blood transfusion	3	37	40	7.5
IVDU	4	7	11	36.4
IVDU and homo/bisexual	1	—	1	—
Homo/bisexual and blood transfusion	2	1	3	—
IVDU and blood transfusion	2	2	2	—
Other possible risk groups	4	75	79	5.1
Sexual contact in the last 12 months with				
IVDU	0	1	1	—
Female prostitute	0	19	19	—
More than 5 different partners with or without female prostitute	4	55	59	6.8
No risk identified	5	410	415	1.2
Total	26	541	567	4.6

IVDU, intravenous drug use.

TABLE 2. Specificity, sensitivity, and positive predictive value of symptoms and signs for HIV infection in active pulmonary tuberculosis patients in Rio de Janeiro, 1987–1989

Symptoms and signs	Sensitivity	Specificity	PPV
Weight loss $<10\%$	80.7	25.8	5.1
Diarrhea >1 month	16.0	93.0	9.5
Fever >1 month	46.1	64.3	5.9
Asthenia >1 month	78.9	37.1	4.6
Cough >1 month	73.1	25.8	4.5
Oral candidiasis	26.9	98.7	50.0
Herpes zoster in previous 5 years	8.0	97.6	13.3
Generalized lymphadenopathy	30.8	93.9	20.0
Genital ulceration in previous 5 years	8.0	97.6	13.3

PPV, positive predictive value.

vised Caracas case definition for AIDS, we found, respectively, sensitivities of 34% and 76.9% and specificities of 31% and 26.3% (Table 3). Using the CDC 1987 criteria for AIDS diagnosis, only three (11.5%) of 26 APT patients infected with HIV met the criteria for AIDS.

Negative tuberculin skin tests were significantly associated with HIV seropositivity. Atypical images on chest radiographs were also more common among patients infected with HIV, but typical TB images were still seen in 22 (86.4%) of the HIV-infected TB patients. Cavitation was seen in the radiographs of 19 (73.1%) of the HIV-positive patients compared with 381 (92.7%) of the HIV-negative patients. Mediastinal and/or hilar lymphadenopathy were seen more frequently in HIV-infected patients (19.2%) than in those not infected (5.1%).

DISCUSSION

HIV is thought to result in activation and dissemination of dormant bacilli or to increase the risk of

TABLE 3. Clinical criteria for AIDS in active pulmonary tuberculosis in two sanatoria in Rio de Janeiro, 1987–1989

Clinical criteria for AIDS	HIV +	HIV -	Total
WHO, 1985 ^a			
Classified as AIDS	9	157	166
Classified as non-AIDS	17	384	401
Revised Caracas ^b			
Classified as AIDS	20	232	252
Classified as non-AIDS	6	399	405

^a WHO clinical criteria: sensitivity, 34.6%; specificity, 71.0%; positive predictive value, 5.4%; and negative predictive value, 95.7%.

^b Revised Caracas criteria: sensitivity, 76.9%; specificity, 73.7%; positive predictive value, 7.9%; and negative predictive value, 98.5%.

progressive disease from new infection (1-3). In Rio de Janeiro, ~40% of the adult population is PPD positive. This increases to 70% in some slums (5). We found that HIV seropositivity among APT patients was ~35 times higher than that observed in first-time blood donors from the same geographic area. This is similar to results in other countries (8,19,20). We observed a higher HIV infection rate than in a recent survey of outpatients with TB in Rio de Janeiro, whose authors found a seroprevalence of 0.6% in pulmonary and 3.8% in extrapulmonary cases (21). Others have also documented a higher seroprevalence of HIV among TB inpatients than among TB outpatients (8,22), probably because the disease is more severe when patients are admitted to the hospital. The difference that we observed in HIV prevalence according to age group also matches results described by others (8-12,19,22-26).

We did not find a difference in HIV infection rate between men and women. This is similar to what has been described in TB patients in Haiti and in African countries (8-11,14,19). In the United States, the seroprevalence of HIV was higher in male TB patients (2,9,12,24,25). Our results were more typical of regions where the heterosexual transmission of HIV predominates, which may be an ominous sign indicating a shift toward heterosexual transmission of HIV in Brazil (27).

In Brazilian TB sanatoria, only patients with clinically and/or sociologically complex disease are generally admitted. We observed that the socioeconomic level of typical TB inpatients is low, regardless of whether they are infected with HIV, and their alcoholism, homelessness, and unemployment rates are all high. In New York City, this description also frequently applies to TB patients infected with HIV (24,25,28). Although anti-TB therapy can be effective in most patients with HIV infection, the main barrier to successful therapy is patient non-compliance. Alcoholism, poverty, and IVDU are all strongly linked to poor compliance (28), and these same factors may complicate interventions to reduce AIDS risk behavior in this population (29,30).

TB leads to chronic ill health and wasting. We could not distinguish symptoms and physical findings caused by *M. tuberculosis* from those caused by HIV infection. Some of the following variables have been described as differentiating TB patients who are or are not infected by HIV: fever, cough, weight loss, chronic diarrhea, genital ulceration, herpes zoster, oral candidiasis, and polyadenopathy

(8,11,26). In our study, only oral candidiasis and, to a lesser degree, polyadenopathy were strongly associated with HIV infection.

Our APT patients infected with HIV tend to be more anergic to the PPD skin test than are those who are not infected. Similar studies have demonstrated that a substantial proportion of HIV-infected TB patients will have PPD anergy (8-10,12,19,25).

The radiographic appearance of TB in HIV disease may vary with the degree of immunodeficiency (2,7). In our study, chest radiographic findings of atypical TB were more likely to occur in HIV-seropositive patients. One possible explanation may be that some HIV-infected patients lack sufficient cellular immunity to form granulomas and cavitory lesions in response to TB. As described by others, intrathoracic adenopathy, diffuse pulmonary infiltrates, and focal consolidation in the lower lobes were more common in HIV-seropositive patients, who were less likely to have cavitory lesions (8,9,11,12,18,25,26,31,32).

We found that only 11.5% of APT patients with HIV infection fulfill the criteria for a diagnosis of AIDS (CDC, 1987), similar to findings in other TB services (13-18.2%) (9,10,12), but lower than that observed in TB patients in general hospitals (50.5-70.0%) (24,25). The APT patients infected with HIV seen in our sanatoria usually have clinical, radiologic, and laboratory features that are more characteristic of standard pulmonary TB. This complicates the management of individual TB cases and public health strategies for TB and AIDS control.

We found low sensitivity and specificity for the WHO clinical case definition of AIDS in our APT patients, as has been described by others (11,13,22). Without HIV serology, the revised Caracas case definition was also not very useful with these patients.

Clinical criteria wrongly labeled many TB patients as AIDS cases. Many symptoms used in the AIDS clinical case definitions (for example, cough, fever, and weight loss) overlap with TB symptoms. It may be impossible to design a clinical AIDS case definition that would be specific enough to be useful in TB patients. Probably, in countries like Brazil, serologic screening for HIV should become part of the initial evaluation of persons who develop TB, especially those who belong to an HIV risk group or who have oral candidiasis, generalized lymphadenopathy, a negative PPD test, and/or atypical chest radiographs.

The importance of identifying HIV infection in APT patients cannot be overemphasized. Not only is this important clinical information for the management of anti-TB treatment, but to ignore the problem of HIV infection would be to focus on only its acute manifestation rather than the underlying cause. Treatment of HIV infection (where possible) and counseling to reduce the likelihood of transmission of HIV to others (always possible) are just as important for these patients as the treatment of TB. This problem, which is likely only to increase with time, must be dealt with squarely by TB control programs.

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