*Original Report*

# Tuberculosis and Drug Resistance among Patients Seen at an AIDS Reference Center in São Paulo, Brazil

Walkyria Pereira Pinto, PhD;*† David Jamil Hadad, MD;† Maria A. Silva Telles;‡ Sueli Yoshino Mizuka Ueki;‡ Moisés Palaci;‡ and Maria Aparecida Basile, PhD*

## ABSTRACT

*Objectives:* To assess the frequency of resistance of *Mycobacterium tuberculosis* to antituberculosis drugs and the factors associated with it among patients with tuberculosis (TB) and acquired immunodeficiency syndrome (AIDS).

*Materials and Methods:* The medical records of TB and AIDS cases diagnosed from 1992 to 1997 in a public service for AIDS care were reviewed.

*Results:* Resistance was diagnosed in 82 (19%) of 431 cases. The mean and median values between the diagnosis of AIDS and the diagnosis of TB were 214.8 days and 70.5 days, respectively. Multidrug-resistant TB (MDR TB) occurred in 11.3% of cases. Of the 186 patients with no previous treatment, 13 (6.9%) presented primary MDR TB. Of the 90 cases with previous treatment, six (6.7%) presented monoresistance to rifampin and 27 (30%) presented MDR TB. The distribution of cases with sensitive and resistant *M. tuberculosis* strains was homogeneous in terms of the following variables: gender, age, category of exposure to human immunodeficiency virus (HIV), alcoholism, and homelessness. Multivariate analysis showed an association between resistance and the two following variables: previous treatment and duration of AIDS prior to TB exceeding 71 days. The rates of primary multiresistance and of monoresistance to rifampin were higher than those detected in HIV-negative patients in Brazil.

*Conclusions:* In this patient series, *M. tuberculosis* resistance was predominantly of the acquired type, and resistance was independently associated with previous treatment for TB and with duration of AIDS prior to TB exceeding 71 days.

Key Words: *AIDS, Brazil, drug resistance, HIV infection, MDR TB, rifampin monoresistance, multidrug resistance, tuberculosis*

*Professor of the Infectious Diseases Division of the São Paulo University School of Medicine; †Reference Center for STD/AIDS (CRTA) of the São Paulo State Health Department; ‡Scientific Researcher of the Adolfo Lutz Institute (IAL) of the São Paulo State Health Department, São Paulo, Brazil.

Address correspondence to Dr. Walkyria Pereira Pinto, Rua Girassol 584 apto 301-A, CEP 05433-001 Vila Madalena, São Paulo, São Paulo, Brazil. E-mail: walkpp@usp.br.

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Over the past few years, the drug resistance of *Mycobacterium tuberculosis* in patients with acquired immunodeficiency syndrome (AIDS) has become a topic of international interest, especially after the occurrence of hospital outbreaks of multidrug-resistant tuberculosis (MDR TB) in the United States.[1] Some studies have detected a higher prevalence of resistance in patients with AIDS than in human immunodeficiency virus (HIV)-negative patients,[2–4] whereas other studies have not detected this association.[5–8] This diversity of results may be attributable to differences in the epidemiologic situation of TB in different places and to differences in the model of care provided to patients with TB or AIDS. In Brazil, few studies have evaluated resistance to anti-tuberculosis drugs in patients with AIDS.[9–11] Co-infection with TB and HIV is of special relevance in the State of São Paulo, where the cumulative incidence of AIDS from 1980 to 1998 was 211.7 cases per 100,000 inhabitants and where TB was recorded in 33% of adult patients with AIDS.[12,13] On the basis of clinical radiographic or microbiologic data, 919 cases of coinfection with TB and AIDS were reported to the Reference and Training Center for Sexually Transmitted Diseases and AIDS (STD/AIDS) (CRTA-SP) in the city of São Paulo from 1993 to 1997 (Epidemiological Surveillance Service of CRTA. Personal communication). Since 1992, susceptibility tests have been performed in all cases of positive culture and identification of *M. tuberculosis* at the Center. The present report is a review of the experience of this reference public service for AIDS care (CRTA-SP) in terms of certain aspects of antituberculosis drug resistance in patients with AIDS.

## MATERIALS AND METHODS

The cases were selected by a survey of the records of the Adolfo Lutz Institute (IAL) referring to patients of the CRTA-SP whose strains were isolated and identified as *M. tuberculosis* from January 1992 to June 1997 and had been submitted to susceptibility tests. Individuals with a positive anti-HIV test (by enzyme-linked immunosorbent assay [ELISA] and Western blot) and

with clinical signs and symptoms of AIDS according to the 1992 criteria of the Health Ministery and of the Centers for Disease Control and Prevention (CDC) were included in the study.[14,15] The patients' medical records were reviewed and adapted to a standardized form. The following data were recorded: gender, age, date at TB diagnosis (date of collection of the first specimen from which *M. tuberculosis* was identified and which was submitted to the susceptibility tests), date of AIDS diagnosis, category of exposure to HIV infection, history of alcoholic drink consumption, homelessness, treatment with antituberculosis drugs, clinical form (considering the origin of *M. tuberculosis*-positive specimens), the number of days the patient had AIDS prior to tuberculosis, follow-up time, and survival. The laboratory tests for TB investigation were requested at the outpatient clinic, the day hospital, and the ward of the CRTA during routine visits and were performed in the laboratories of CRTA-SP and IAL. The susceptibility tests were all performed at IAL, based on the proportion method and on the resistance ratio method.[16,17] Using the proportion method, strains were considered to be resistant when they presented growth at the proportion of 1% or more in tubes containing the following drug concentrations: isoniazid (H), 0.2 μg/mL; rifampin (R), 40.0 μg/mL; streptomycin (S), 4.0 μg/mL; ethambutol (E), 2.0 μg/mL; and 10% growth with 100 μg/mL pyrazinamide (Z).[16] Using the resistance ratio method, the strains were considered to be resistant to H, R, S, or E when they grew in tubes containing drug concentrations that resulted in ratios of 4:1 or more compared to the concentrations in the control tubes. Strains were considered to be resistant to pyrazinamide when they grew in tubes containing this drug at the concentration of 200 μg/mL. Primary resistance (PR), acquired resistance (AR), and MDR TB (characterized by resistance to at least isoniazid and rifampin) were defined according to the criteria of the World Health Organization.[18] In cases in which no information was available about previous treatment, resistance was classified as "indeterminate resistance" (IR).

Simple linear regression was used for the analysis of the tendency of resistant cases over time. The series was stratified into two groups: patients with strains sensitive to all drugs tested and patients with strains resistant to one or more drugs. The possibility of correlation between *M. tuberculosis* resistance and other variables was studied by univariate analysis, using the chi-squared and odds ratio tests to determine the presence of significant associations ($P < 0.05$). The logistic regression model was used for the multivariate analysis test, considering the occurrence of resistance as the dependent variable and all variables that had been associated with resistance in univariate analysis at $P < 0.20$ as independent variables.[19] To assess the survival time of patients with sensitive strains and those with resistant ones, the initial time was considered to be the date of collection of the first specimen from which *M. tuberculosis* was isolated and submitted to the susceptibility tests (date of TB diagnosis). The date of death was recorded, and for the patients who did not die, the time of observation was considered (i.e., the follow-up time until the last medical visit during the study period, which was concluded on June 30, 1997). The same procedure was used with the date of AIDS diagnosis considered to be the initial time. The microcomputer Stata statistical software 4.0 (Statacorp, College Station, Texas, USA) was used.

## RESULTS

Tests of susceptibility of the *M. tuberculosis* strains isolated from the specimens obtained from 452 patients were performed during the study period. Twenty-one of these patients were excluded from analysis, three because of negative anti-HIV serology and 18 because of the lack of information in their medical records. Thus, the study was conducted on 431 patients with TB and AIDS. Age ranged from 16.3 years to 66.3 years (mean = 33.6 y; median = 32.5 y), and 368 subjects (85.4%) were males. With respect to the categories of exposure to HIV, there was a predominance of homosexuals (35.7%) and of drug users (32.5%). The most frequent clinical form was the pulmonary form (58.0% of cases), followed by the disseminated form (20.0%) and the lymphatic form (16.2%). In 307 patients (71.2%) there was pulmonary involvement, in 101 (23.4%) there was lymphonodal involvement, in 28 (6.5%) meningeal involvement, and in 23 patients (5.3%) lesions in other organs or systems were diagnosed separately (renal, pleural, pericardic, cutaneous, and testicular TB) or in parallel to pulmonary, lymphonodal, and meningeal lesions (disseminated forms). Previous treatment for TB was reported by 90 patients (20.9%), was denied by 186 (43.2%), and for 155 patients (36.0%) there was no information about this variable; 72 (16.7%) patients reported alcohol consumption and 30 (7.0%) were homeless. Among the 431 patients, the time elapsed between the diagnoses of AIDS and TB was not available for nine. Taking into account this time, the other 422 patients were divided in three groups. At first, based on the median value of this sample, the patients were divided in two groups: 211 with less than 71 and the others with more than 71 days. This second group was again divided in two groups based on the median value of 241 days. A total of 395 patients (91.6%) were followed-up for a period ranging from 1 to 1832 days (5 y) and 36 cases (8.4%) were lost to follow-up after the diagnosis of TB.

In 82 cases (19.0%), the *M. tuberculosis* strains were resistant, 31 of them (7.2%) being monoresistant and 51 (11.8%) being resistant to two or more drugs. Monoresistance corresponded to 2.6% of resistance to H, 2.1% to

**Table 1.** Distribution of 82 Cases of TB Caused by Resistant *Mycobacterium tuberculosis* in Relation to the Total Series of 431 Cases, according to the Type of Resistance to Antituberculosis Drugs*

| *Type of Resistance* | *AR n = 37 (8.5%)* | *PR n = 24 (5.5%)* | *IR n = 21 (4.8%)* | *Total n = 82 (19.0%)* |
|---|---|---|---|---|
| H | 1 (0.2) | 5 (1.2) | 5 (1.2) | 11 (2.6) |
| R | 6 (1.4) | 1 (0.2) | 2 (0.5) | 9 (2.1) |
| Z | 3 (0.7) | 0 (–) | 2 (0.5) | 5 (1.2) |
| S | 0 (–) | 4 (0.9) | 2 (0.5) | 6 (1.4) |
| H, R | 18 (4.2) | 12 (2.8) | 4 (0.9) | 34 (7.9) |
| H, R, Z | 7 (1.6) | 1 (0.2) | 4 (0.9) | 12 (2.8) |
| H, R, E | 0 (–) | 0 (–) | 1 (0.2) | 1 (0.2) |
| H, R, S | 1 (0.2) | 0 (–) | 0 (–) | 1 (0.2) |
| H, R, Z, E, S | 1 (0.2) | 0 (–) | 0 (–) | 1 (0.2) |
| H, Z | 0 (–) | 1 (0.2) | 0 (–) | 1 (0.2) |
| H, Z, E | 0 (–) | 0 (–) | 1 (0.2) | 1 (0.2) |

*CRTA-SP 1992–1997.
AR = acquired resistance; PR = primary resistance; IR = indeterminate resistance; H = isoniazid; R = rifampin; Z = pyrazinamide; S = streptomycin; E = ethambutol.

R, 1.2% to Z, and 1.4% to S; resistance to the H-R combination was the most frequent type of multiresistance, occurring in 34 (7.9%) cases. In the total series, the frequency of AR (8.5%) was higher than the frequency of PR (5.5%), with acquired monoresistance in 2.3%, acquired multiresistance in 6.2%, primary monoresistance in 2.3%, and primary multiresistance in 3.2% of cases. In the cases monoresistant to S, there was a predominance of PR, and in the cases monoresistant to R, there was a predominance of AR. Resistance to at least the H-R combination was observed in 49 patients (11.3%), being characterized as AR in 6.2% (27/431), PR in 3.0% (13/431), and IR in 2.0% (9/431) of cases. The rates of primary monoresistance to H (1.2%) and to S (0.9%) were similar to one another and higher than those observed for R (0.2%). No primary resistance to E was observed (Table 1). Information about the previous use of antituberculosis drugs was obtained for 64% (276/431) of the patients. Of the 90 patients who reported previous use of these drugs, 37 (41.1%) presented AR; of the 186 patients with no previous treatment, 24 (12.9%) presented PR (Table 2). Simple linear regression analysis among the variable number of individuals with multiresistant *M. tuberculosis* and year of diagnosis revealed no trends toward an increase or a decrease in the number of resistant cases ($t = -0.31$, $P = 0.774$) during the study period.

There was no significant difference between the patient group with sensitive strains and the group with resistant ones with respect to the distribution of cases of the pulmonary, lymphatic, and disseminated forms of TB ($\chi^2 = 4.33$; $P = 0.11$).

There was no significant difference between patient groups with sensitive and resistant strains in terms of patient distribution by gender ($\chi^2 = 1.917$; $P = 0.166$), age range ($\chi^2 = 5.999$; $P = 0.112$), category of exposure to HIV infection ($\chi^2 = 3.986$; $P = 0.408$), a history of alcohol consumption ($\chi^2 = 3.295$; $P = 0.070$), or homelessness ($\chi^2 = 2.579$; $P = 0.108$). The proportion of patients submitted to previous treatment was significantly higher in the patient group with resistant strains ($\chi^2 = 28.03$; $P < 0.001$).

For the comparison of patient groups with sensitive and resistant strains in relation to the time elapsed between the diagnoses of AIDS and TB, the median values of 71 and 241 days were considered as limits. These

**Table 2.** Distribution of 431 Cases of Co-infection with TB and AIDS, according to Profile of Sensitivity to *Mycobacterium tuberculosis* and a History of Previous TB Treatment*

| *Sensitivity Profile* | *With Treatment n = 90 (100%)* | *Without Treatment n = 186 (100%)* | *No Information n = 155 (100%)* | *Total n = 431 (100%)* |
|---|---|---|---|---|
| Sensitive | 53 (58.9) | 162 (87.1) | 134 (86.5) | 349 (80.97) |
| Resistant | 37 (41.1) | 24 (12.9) | 21 (13.5) | 82 (19.0) |
| H | 1 (1.1) | 5 (2.7) | 5 (3.2) | 11 (2.6) |
| R | 6 (6.7) | 1 (0.5) | 2 (1.3) | 9 (2.1) |
| Z | 3 (3.3) | 0 (0.0) | 2 (1.3) | 5 (1.2) |
| S | 0 (0.0) | 4 (2.2) | 2 (1.3) | 6 (1.4) |
| H, R | 18 (20.0) | 12 (6.4) | 4 (2.6) | 34 (7.9) |
| H, R, Z | 7 (7.8) | 1 (0.5) | 4 (2.6) | 12 (2.8) |
| H, R, E | 0 (0.0) | 0 (0.0) | 1 (0.6) | 1 (0.2) |
| H, R, S | 1 (1.1) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| H, R, Z, E, S | 1 (1.1) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| H, Z | 0 (0.0) | 1 (0.5) | 0 (0.0) | 1 (0.2) |
| H, Z, E | 0 (0.0) | 0 (0.0) | 1 (0.6) | 1 (0.2) |

*CRTA-SP 1992–1997.
H = isoniazid; R = rifampin; Z = pyrazinamide; S = streptomycin; E = ethambutol.

**Table 3.** Univariate Analysis of the Correlation between Resistance and the Other Variables

| Variable | Patient Groups | | Odds Ratio | 95% Confidence Interval | $\chi^2$ | P-Value |
|---|---|---|---|---|---|---|
| | RG | SG | | | | |
| Previous treatment | | | | | | |
| No (n = 186) | 24 | 162 | 1 | | | |
| Yes (n = 90) | 37 | 53 | 4.71 | 2.60–8.55 | 28.03 | 0.000 |
| Duration of AIDS prior to TB* | | | | | | |
| < 71 d (n = 211) | 20 | 191 | 1 | | | |
| 71–241 d (n = 106) | 23 | 83 | 2.65 | 1.39–5.05 | | |
| > 241 d (n = 105) | 39 | 66 | 5.77 | 3.00–11.13 | 34.74 | 0.000 |
| Alcohol consumption | | | | | | |
| No (n = 201) | 38 | 163 | 1 | | | |
| Yes (n = 72) | 21 | 51 | 1.77 | 0.96–3.27 | 3.29 | 0.070 |
| Homeless | | | | | | |
| No (n = 398) | 72 | 326 | 1 | | | |
| Yes (n = 30) | 9 | 21 | 1.94 | 0.87–4.34 | 2.58 | 0.108 |
| Age (y) | | | | | | |
| <25 (n = 46) | 10 | 36 | 1 | | | |
| 25–35 (n = 242) | 45 | 197 | 0.82 | 0.38–1.78 | | |
| 36–45 (n = 114) | 17 | 97 | 0.63 | 0.26–1.51 | | |
| >46 (n = 29) | 10 | 19 | 1.89 | 0.67–5.35 | 6.0 | 0.112 |
| Gender | | | | | | |
| Male (n = 368) | 74 | 294 | 1 | | | |
| Female (n = 63) | 8 | 55 | 0.58 | 0.27–1.25 | 1.92 | 0.1662 |

*Average number of days in the 3 groups: 35, 156.5, 1342.5.
RG = resistant strains; SG = sensitive strains.

values delimited three groups of patients who had on average 35.0, 156.5, and 1342.5 days of AIDS evolution at the time of TB diagnosis. The proportion of patients with duration of AIDS prior to TB exceeding 71 days was significantly higher in the patient group with resistant strains ($\chi^2$ = 34,74; P < 0.001). Multivariate analysis showed an increased chance of drug resistance among patients with previous treatment and among those with a time of AIDS evolution exceeding 71 days (Tables 3 and 4).

Survival among the patient group with resistant strains was lower than that of those with sensitive ones, with a significant difference (P < 0.01) when the patients with sensitive strains were compared to patients with TB caused by monoresistant and multiresistant *M. tuberculosis*. The median survival time after the diagnosis of TB was 434 days for the patient group with sensitive strains, 251 days in cases with monoresistance, and 100 days in cases with multiresistance. There was no significant difference (P = 0.74) in survival time after the diagnosis of AIDS between the two patient groups.

## DISCUSSION

The presence of some type of resistance in 19% of these patients demonstrates the relevance of this problem in the present series. Case distribution by gender, age range, and category of exposure to HIV was close to that recorded for AIDS cases during the same period in the state and in the municipality of São Paulo.[20] The frequency of 58% for the isolated pulmonary form and of 71.2% for pulmonary involvement as well as the frequency of the lymphatic and localized forms were similar to those observed in other studies.[21-24]

Tuberculosis occurred within the first 2 to 3 months after the diagnosis of AIDS in 50% of cases and within up to 8 months in 75% of cases, showing that TB occurs early in relation to other opportunistic infections in most patients with AIDS.[25-28] The survival of approximately 14 months after the diagnosis of TB in the patient group with sensitive strains was lower than that observed in other countries.[29] Although, resistance is considered to have played a role in reducing the survival; the magnitude

**Table 4.** Analysis of the Correlation between Resistance and the Remaining Variables*

| Variable | Odds Ratio | 95% Confidence Interval | z | P-Value |
|---|---|---|---|---|
| Previous treatment | | | | |
| No | 1 | | | |
| Yes | 3.396 | 1.740–6.629 | 3.585 | 0.000 |
| Duration of AIDS prior to TB | | | | |
| < 71 d | 1 | | | |
| 71–241 d | 2.883 | 1.213–6.854 | 2.397 | 0.017 |
| > 241 d | 4.348 | 1.960–9.641 | 3.617 | 0.000 |

*Results of multivariate analysis, final model.

of other important factors related to this issue could not be evaluated. There was a lack of information about treatment adherence and the immunologic status of the patients (CD4 cell count).

When the types of resistance were compared to those observed in surveys carried out in different parts of the world, no substantial differences were observed.[30] The AR rate was higher than the PR rate, multiresistance was more frequent as AR than as PR, the rates of primary monoresistance to H and S were similar to each other and higher than those observed for R, and primary monoresistance to E was absent. However, there was a high frequency of monoresistance to R, a feature not observed among the *M. tuberculosis* strains isolated in Brazil.[31]

Most cases with strains monoresistant to R were classified as cases of AR, as also reported in the literature.[32-35] Brazilian studies in which *M. tuberculosis* susceptibility was assessed in HIV-infected patients dealt with significantly smaller patient series and did not mention the criteria used for patient selection,[10,11] thus preventing comparison with the present series.

The percentage of primary multiresistance was higher than the values reported for HIV-negative patients in São Paulo and in other parts of Brazil.[31,36] The rates of primary resistance to each drug were higher for H and R, lower for S, and similar for E when compared with those obtained in a recent Brazilian survey.[31] The frequency of acquired multiresistance was also higher than that observed in the same survey.

A high prevalence of primary resistance to the H-R combination has been reported for HIV-positive patients in other countries.[4] In the present study, 6.9% of previously untreated patients presented primary multiresistance. This highly significant value may be explained by the nosocomial transmission of multiresistant strains, although there are no reports of nosocomial outbreaks of MDR TB in the country.

It is important to emphasize the greater use of day-hospital beds and of wards for the care of these patients during the period of specimen collection in the present study, which preceded the recent phase of reduction in AIDS morbidity attributed to combined antiretroviral therapy.[37] It is also important to point out the possibility of transmission in outpatient clinics or in the community.

No correlation was detected between AR and factors considered to predispose to treatment default, such as drug dependence.[38] The absence of a correlation between resistance and homelessness may be explained by the fact that most homeless patients were not street dwellers but patients sheltered in care facilities. Thus, it can be seen that, although the proportion of patients with previous treatment was significantly higher among those who presented resistance, it was not possible to identify, in these cases, factors other than treatment itself as being correlated with resistance. The possibility should also be considered that some of these cases were attributable to exogenous reinfection and, therefore, were cases of primary and not acquired resistance. Reinfection with resistant bacilli may occur during or after the treatment of TB caused by sensitive *M. tuberculosis* strains.[39] These strains can only be differentiated using DNA fingerprinting methodology. This result indicates the need to redefine the concept of acquired resistance in patients with AIDS. Among patients in the present study, a longer duration of AIDS prior to TB was significantly correlated with resistance, as also reported in the literature in some studies of the case-control type in nosocomial outbreaks of MDR TB.[40,41] Exogenous infection or reinfection with the development of primary progressive TB is usually associated with the most advanced phase of AIDS. In some studies there was a longer duration of AIDS prior to TB among patients with MDR TB compared to patients with susceptible TB, a fact that was not discussed by the authors.[40,41] The relation between resistance, extent of immunosuppression, and HIV infection was indirectly suggested in a study on African patients with TB. In that series, there was a higher proportion of individuals with resistant strains among patients with CD4 lymphocyte counts lower than 200 cells/m$^3$. In most of those cases, resistance was characterized as primary.[6]

## CONCLUSION

The hypothesis should be considered that, as is the case for patients with AIDS in other countries, the group of patients with primary multiresistance in the present series contributed to the observed significant association between resistance and longer duration of AIDS prior to TB.

There is the possibility that acquired resistance is more prevalent among patients in more advanced stages of AIDS owing to irregular treatment, either because of factors related to the attitude of patients with a long time of evolution or to the concomitance of upper digestive alterations, diarrhea, and malabsorption.

The results of the susceptibility tests observed in these cases indicate the need to rediscuss the diagnostic and therapeutic approach to co-infected patients with TB and HIV. The use of a four-drug schedule until the results of susceptibility tests are obtained could be evaluated in a prospective study of patients with previous treatment and with a longer time of AIDS evolution. Furthermore, it is imperative to propose the validation of a predictive model for the occurrence of resistance in these patients. To obtain conclusive results, these cases should be extensively studied, with the identification of factors related to the psychosocial aspects of the patients as well as to the epidemiology and pathogenesis of co-infection with MDR TB and AIDS. Sequential immunologic evaluation will be needed for this program, as well as resources of molecular biology that will permit differentiation between primary and acquired resistance.

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