

## Co-infection with *Mycobacterium tuberculosis* and human immunodeficiency virus: an epidemiological analysis in the city of Taubaté, Brazil\*

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### ABSTRACT

**Objective:** To discuss the main aspects of co-infection with *Mycobacterium tuberculosis* and human immunodeficiency virus in the city of Taubaté (located in the state of São Paulo, Brazil) in 2001 and 2002. **Methods:** This study presents epidemiological data on tuberculosis cases occurring in Taubaté in 2001 and 2002. **Results:** Of the 250 cases of tuberculosis analyzed, 70 (28%) presented human immunodeficiency virus seropositivity, 95 (38%) presented human immunodeficiency virus seronegativity, and 85 (34%) were patients who had not been submitted to serological testing. In the first group (tuberculosis and human immunodeficiency virus seropositivity), males from 30 to 40 years of age predominated, the most common clinical presentation of tuberculosis was pulmonary (65.71%), and the cure rate was 59.38%. In the group of tuberculosis patients presenting human immunodeficiency virus seronegativity, males from 30 to 40 years of age also predominated, the most common clinical presentation of tuberculosis was also pulmonary (70.55%), and the cure rate was 81.63%. **Conclusion:** We conclude that the human immunodeficiency virus plays an important role in the epidemiology of tuberculosis. Therefore, serological testing for human immunodeficiency virus should be carried out when a diagnosis of tuberculosis is made.

**Keywords:** Tuberculosis/epidemiology; HIV infections; HIV; Prevalence

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## INTRODUCTION

Tuberculosis (TB) is an ancient disease whose incidence was high in the twentieth century. It was expected to be eradicated by 2000 in developed countries. However, the occurrence of human immunodeficiency virus (HIV) infection provoked a change in the epidemiological trend of TB, which, as a result, regained its importance as an opportunistic infection, especially when occurring in combination with acquired immunodeficiency syndrome (AIDS). In developing countries, TB has always been a public health problem due to the great social inequality that exists in such countries. In recent years, HIV-*Mycobacterium tuberculosis* co-infection has exacerbated this situation and returned TB to its position of great importance in the global context.<sup>(1-2)</sup>

The worldwide incidence of TB is estimated to be 8 million cases, double the number of reported cases. It is estimated that 80% of all cases of TB are concentrated in 22 countries, one of which is Brazil. In 2002, a total of 81,034 new cases were reported in Brazil, the rates of incidence and mortality being higher in the state of Rio de Janeiro than in any other state.<sup>(3)</sup> In 2004, there were 17,993 new cases of TB reported in the state of São Paulo, of which 33% presented HIV seropositivity, 53% presented HIV seronegativity. The HIV status was unknown in 34% of the cases. Of the patients contracting TB in the state of São Paulo in the preceding year (2003), 76% were cured, 10% abandoned the treatment, 6% died, 5% were transferred to other facilities, and 3% were unaccounted for.<sup>(4)</sup> It is estimated that, within the next ten years, TB will kill 30 million people worldwide.<sup>(5)</sup>

Infection with HIV is currently considered one of the main risk factors for the development of active TB due to the decreased immune response of the patient.<sup>(1)</sup> Susceptibility to TB depends on cytokine production by T-helper (Th) lymphocytes. The Th1 lymphocytes are responsible for the production of interferon-gamma and, therefore, for the main immune response to the *Mycobacterium*. However, Th2 lymphocytes produce interleukin-4 and interleukin-10, which do not confer immunity against the TB bacillus. In HIV-positive patients, there is a reduction in the number of Th1 lymphocytes themselves, and such patients are

therefore much more susceptible to TB than are HIV-negative patients.<sup>(6)</sup>

In the initial phase of the infection, HIV-positive patients typically present CD4 cell counts greater than 200/mm<sup>3</sup>. In such patients, TB presents clinical characteristics similar to those presented by TB in HIV-negative patients. In the advanced phases of the infection (AIDS), these patients tend to present CD4 cell counts lower than 200/mm<sup>3</sup>, different clinical characteristics (such as negative tuberculin test results and negative sputum testing results), TB in extrapulmonary sites (ganglia, pleura, and pericardium), and (in the pulmonary presentations) there are atypical radiographic findings, such as the infiltrates found in other lung diseases. Therefore, the diagnosis becomes more difficult, increasing the risk of TB transmission. As a consequence, TB-related morbidity and mortality are more common in this patient population.<sup>(6-7)</sup>

High rates of TB-HIV co-infection have been observed in recent years. In the state of Rio Grande do Sul, this combination was seen in 30% of the cases diagnosed with TB.<sup>(3)</sup> In the city of Campinas (located in the state of São Paulo), in 2004,<sup>(8)</sup> TB-HIV co-infection was found in 55.1% of the TB patients who later died. Therefore, TB-HIV co-infection affects TB control. Consequently, preventing and treating HIV infection must be prioritized.<sup>(9)</sup>

Resistance of micro-organisms also seems to be related to co-infection. This resistance results from the incorrect use of medications and from noncompliance with treatment. In this group of patients, the rates of noncompliance with treatment and irregular treatment tend to increase. This occurs because the use of injection drugs is higher among HIV-positive patients, and drug users are more refractory to treatment. In addition, these patients are on a treatment regimen that includes many medications, making compliance more difficult.<sup>(10)</sup>

Based on these findings, it is obvious that the incidence of TB remains high. The increased incidence of TB in recent years, principally due to the occurrence of TB-HIV co-infection, has worsened the situation and returned TB to its position as a public health problem of great importance.

The objective of the present study was to investigate the main aspects of TB-HIV co-infection in the city of Taubaté (located in the state of São Paulo, Brazil) in 2001 and 2002 based on the data

provided by the Taubaté Municipal Epidemiological Surveillance Unit.

## METHODS

We carried out an epidemiological survey of the TB cases occurring in 2001 and 2002 based on the data provided by the Taubaté Municipal Epidemiological Surveillance Unit. The data used were obtained from the Epidemiological Surveillance Unit database and analyzed according to gender, age, level of education, clinical form, place of diagnosis, type of diagnosis, and cure rate.

## RESULTS

In the two years studied, a total of 250 TB cases were reported. Of those, 169 occurred in males. In 70 (42.4%) of the 165 cases submitted to HIV testing, TB-HIV co-infection was identified (Table 1). It is important to highlight that 85 (34%) of the patients were not submitted to this testing.

In the group of patients presenting TB-HIV co-infection, there was a considerable predominance of males (48 of the 70 cases), and the greatest number of cases occurred among males from 30 to 50 years of age (Table 2). Among the co-infected patients, 37 had seven or less years of schooling,

TABLE 1

Distribution of tuberculosis cases in 2001 and 2002

Year	HIV+	HIV-	HIV testing not performed	Total
2001	38	43	45	126
2002	32	52	40	124
Total	70	95	85	250

HIV: human immunodeficiency virus

TABLE 2

Distribution of cases presenting co-infection with tuberculosis and human immunodeficiency virus according to age

Age bracket	Male	Female	Total
< 10 years	2	0	2
10-20 years	2	2	4
20-30 years	6	8	14
30-40 years	24	6	30
40-50 years	13	4	17
50-60 years	1	1	2
Undetermined	0	1	1

and 6 were illiterate.

We observed that, in the various groups of patients studied, the pulmonary presentation of TB predominated. Among the patients presenting HIV seronegativity, no concomitance between the pulmonary and extrapulmonary clinical presentations of TB was observed. However, such concomitance occurred in 20% of the co-infected patients (Table 3).

The outcomes of the TB cases can be seen in Table 4, where it can also be seen that the cure rate was lower among the co-infected patients. However, the cure rate was even lower among the patients who were not submitted to HIV testing.

The diagnosis of TB was primarily made in public health care facilities, which were responsible for more than 80% of the diagnoses of all TB cases in the city of Taubaté. The principal health service was the emergency room or the public hospital. Table 5 shows the principal types of health care facilities in which a diagnosis of TB was made, collectively accounting for 83.6% of all reported cases.

TABLE 3

Distribution of tuberculosis cases by clinical presentation

Form	HIV +		HIV -		HIV testing not performed	
	n	%	n	%	n	%
Pulmonary	46	65.71	70	73.68	57	67.06
Extrapulmonary	10	14.29	25	26.32	15	17.65
Pulmonary + extrapulmonary	14	20.0	0	0.0	13	15.24

HIV: vírus da imunodeficiência humana.

TABLE 4

Outcomes of tuberculosis cases

Outcome	HIV+	HIV-	HIV testing not performed
	%	%	%
Cure	56.36	91.46	53.57
Treatment noncompliance	7.27	1.22	5.95
Transfer	10.91	2.44	22.62
Change in diagnosis	1.82	1.22	9.53
Death from TB	0.0	1.22	1.19
Death from other causes	23.64	2.44	7.14

HIV: human immunodeficiency virus; TB: tuberculosis

TABLE 5

Distribution of cases according to the type of health care facility where tuberculosis was diagnosed

Health care facility	HIV+	HIV-	HIV testing not performed
Public outpatient clinic	16	37	24
University outpatient clinic	11	10	6
ER or public hospital	24	22	28
ER or university hospital	14	10	7

HIV: human immunodeficiency virus; ER: emergency room

## DISCUSSION

In the city of Taubaté, it was observed that many TB patients also presented HIV seropositivity: 70 (42.4%) of the 165 patients submitted to HIV testing. This is higher than the rates of co-infection found in other studies, such as the 9.3% found in the city of Belo Horizonte (located in the state of Minas Gerais),<sup>(11)</sup> and the 18% found in the city of Sorocaba (located in the state of São Paulo).<sup>(12)</sup> It is also higher than the levels of co-infection in the state of São Paulo as a whole, where the rate of such co-infection has been reported to be 13%.<sup>(4)</sup> This high rate of TB-HIV co-infection in the city of Taubaté could be related to various factors, such as the location of the city. Taubaté is located in the Middle Valley of the Paraíba do Sul River, a major circulation axis between the states of São Paulo and Rio de Janeiro, which are the centers presenting the highest productivity and greatest population density in the country. This results in a great number of people migrating to this city. The great number of inhabitants, together with the fact that many students (having different habits and customs) live in this city, might favor an increase in the incidence of AIDS. Another important fact to be considered is that, since 2001, when the Taubaté Municipal Program for the Prevention of Sexually Transmitted Diseases and Acquired Immunodeficiency Syndrome was reorganized and began working in conjunction with the Municipal Epidemiological Surveillance Unit, there has been an increase in the number of reported cases of AIDS, making Taubaté an important referral center for the treatment of the disease. The dimension, as well as the socioeconomic and cultural significance, of this city - within the context of its geographic location (in the Vale do Paraíba) - should also be considered. These and other factors have

increased the number of diagnoses made and treatments prescribed in the city, which might explain the high rates of co-infection found in the present study.

Co-infection with TB and HIV alters the epidemiological trend of the disease, since TB presents different characteristics when it occurs in patients with co-infection. In such individuals, the extrapulmonary presentations are the most common, and the patient is more likely to develop multidrug-resistant TB.<sup>(2)</sup> In the 2004 II Consenso Brasileiro de Tuberculose (Second Brazilian Consensus on Tuberculosis), the duration of the treatment recommended for these patients is six months, the same as for those who do not present co-infection with HIV.<sup>(13)</sup> This differs from the recommendation made in the 1997 First Brazilian Consensus on Tuberculosis, which was that co-infected patients should be treated for nine months, a policy that made noncompliance more likely.<sup>(7)</sup> It is important to highlight that infection with *M. tuberculosis* accelerates the HIV replication process, and this can result in greater mortality among co-infected patients.<sup>(1)</sup>

It is of note that 85 (34%) of the patients were not submitted to HIV testing. This is a high number considering that it is important to determine whether there is co-infection in order to adopt appropriate therapeutic measures that can prevent resistance to antituberculosis drugs, in addition to the fact that the lack of these data impedes the epidemiological analysis of the disease.

In a study<sup>(14)</sup> analyzing the TB cases in the region of Botucatu (a city located in the state of São Paulo) from 1993 to 1998, it was found that 73.8% of the patients had not been submitted to HIV testing. Another study<sup>(15)</sup> revealed that serological testing was requested in only 25.8% of the cases in the state of Rio de Janeiro, which is a cause for concern. This is believed to occur because many patients consider HIV testing discriminatory, which places the physician in a complicated situation, since, although HIV testing is recommended by the Ministry of Health, patient consent is necessary, and the patient has the constitutional right to refuse. This fact is alarming because studies show that a considerable percentage of individuals presenting TB also present HIV. In addition, there is negligence on the part of health professionals, who very often do not request the exams.<sup>(2,11)</sup>

The epidemiological investigation of TB is impeded by the under-reporting that occurs worldwide. According to the World Health Organization, the estimated number of new TB cases in Brazil in 2001 was 110,511, corresponding to an incidence rate of 64 cases/100,000 inhabitants. However, only 74,466 new TB cases were actually reported in 2001, translating to an incidence rate of 43 cases/100,000 inhabitants.<sup>(16)</sup> In 2002, the estimate was for 116,000 new TB cases (68 cases/100,000 inhabitants) to occur. However, the actual number of cases reported was only 80,000. Nevertheless, the World Health Organization has ranked Brazil 15th in the world in terms of annual TB incidence.<sup>(17)</sup> In 2002, the city of Taubaté had an estimated population of 251,992 inhabitants, and the incidence of new TB cases was 49.2 cases/100,000 inhabitants.<sup>(18)</sup>

In Brazil, there are a greater number of new TB cases among individuals from 20 to 39 years of age (32,061 new cases in 2001). In the southeast region of the country, the same is true (15,236 new cases in the 20-39 age bracket).<sup>(19)</sup> In the city of Taubaté, 125 of the 250 reported cases occurred among individuals in the 30-49 age bracket. We observed that, in the city of Taubaté, males predominated in the three study groups (individuals presenting HIV seropositivity, individuals presenting HIV seronegativity, and individuals who were not submitted to serological testing). Of the new cases of TB, 169 were among males, and 81 were among females. This is in accordance with the data obtained in other studies,<sup>(1,20-21)</sup> in which males also predominated. It is important to highlight that among patients from 30 to 39 years of age presenting HIV seropositivity, males were even more over-represented. This might be related to the fact that more individuals test positive for HIV in their thirties than in any other decade of life. This correlation was also found by the authors of a study carried out in Taipei, Taiwan.<sup>(22)</sup>

We observed that, among the patients presenting HIV seronegativity, the pulmonary clinical presentation of TB was the most common (seen in 73.68%). Among those patients, we found no cases in which the pulmonary and extrapulmonary presentations were concomitant. Among the patients presenting HIV seropositivity, the most common presentation was also pulmonary (65.71%). However, concomitance of the two clinical

presentations was observed in 20% of the cases. Other studies have shown that the extrapulmonary presentation can be seen in up to 50% of cases, as occurred in a study analyzing HIV infection in patients who were hospitalized for TB in the city of Belo Horizonte.<sup>(11)</sup> These prevalence rates are high, since, in patients receiving appropriate treatment for HIV and in compliance with the HIV treatment regimen, the extrapulmonary form of TB can be prevented through early diagnosis. In addition, empirical treatment for TB is recommended for patients presenting a tuberculin test response (induration) equal to or greater than 5 mm. All patients diagnosed with HIV should be submitted to tuberculin tests, regardless of CD4 count and viral load.<sup>(13)</sup>

The cure rate, in the present study as well as in the other studies analyzed, was lower among patients presenting co-infection. Among the groups studied, a satisfactory cure rate was achieved only in the group consisting of patients presenting HIV seronegativity. Another important observation is that the cure rate was lower in the group of patients who were not submitted to HIV testing than in the group of patients with TB-HIV co-infection. This might indicate that there are a great number of co-infected patients who have not, however, been diagnosed with HIV infection. These data underscore the importance of submitting all TB patients to HIV testing so that the treatment can be more efficacious.<sup>(1,21)</sup>

The analysis of TB diagnosis revealed that more than 80% of the cases were diagnosed in public health facilities rather than in private ones, public outpatient clinics, emergency rooms, and public hospitals being the most common. This might indicate that individuals of lower socioeconomic status are infected with TB more often than are those in the middle and upper socioeconomic strata. This datum can be confirmed by the lower level of education of the co-infected patients. In another study,<sup>(14)</sup> it was determined that 88.8% of TB patients had had less than eight years of schooling. Therefore, poor living conditions, poverty, and malnutrition are important factors for the onset of the disease, which means that TB is not only an important chronic disease but also a serious public health problem.<sup>(1-2,12)</sup>

The present study showed how important HIV is to the epidemiology of TB, since 42.4% of the

TB patients who were submitted to HIV testing presented co-infection. Consequently, it is essential that HIV testing be performed so that co-infected patients can be made aware of that fact, which, ideally, will lead them to be more rigorous in their use of the medications and to comply with the treatment in order to prevent the risk of developing resistance to antituberculosis drugs.

Brazilian studies, as well as international studies, show that there has been a significant increase in the number of TB cases due to the occurrence of HIV infection. Therefore, a solution to this public health problem must be found so that the situation will not become more critical in the years to come. In view of this, it is important that programs aimed at achieving more efficient TB control focus on improving quality of life and providing the populace with more detailed information about AIDS.

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