Prevalence of drug-resistant *Mycobacterium tuberculosis* in patients under intermittent or daily treatment*

Prevalência de *Mycobacterium tuberculosis* resistente em pacientes sob tratamento parcialmente intermitente ou sob tratamento diário

Tomás Aiza Alvarez, Marcelo Palmeira Rodrigues, Carlos Alberto de Assis Viegas

**Abstract**

**Objective:** To compare the prevalence rates of drug-resistant *Mycobacterium tuberculosis* in patients under intermittent treatment with those observed in patients under daily treatment. **Methods:** We used World Health Organization data regarding 5,138 patients with active pulmonary TB in Brazil, separated into two groups: patients in the Federal District of Brasília, treated with a one-month daily regimen followed by an intermittent thrice-weekly regimen; and patients in other parts of Brazil, treated with a daily regimen only. The resistance pattern was categorized as primary or acquired, based on the history of previous treatment. Multidrug resistance was defined as resistance to at least isoniazid and rifampin, whereas monoresistance was defined as resistance to only one drug. **Results:** The prevalence of primary resistance in the Federal District of Brasília and in the other parts of Brazil, respectively, was as follows: overall, 9.2% and 9.3% (p = 0.94); monoresistance, 6.6% and 6.9% (p = 0.89); and multidrug resistance, 1.0% and 1.2% (p = 0.85). The prevalence of acquired resistance in the Federal District of Brasília and in the other parts of Brazil, respectively, was as follows: overall, 15.8% and 26.8% (p = 0.39); monoresistance, 5.3% and 13.7% (p = 0.33); and multidrug resistance, 0.0% and 10.2% (p = 0.16). **Conclusions:** No significant differences were found between patients treated with an intermittent regimen and those treated with a daily regimen in terms of resistance rates.

**Keywords:** Tuberculosis, pulmonary; Drug resistance; Drug administration schedule; Tuberculosis, multidrug-resistant.
Introduction

Resistance of *Mycobacterium tuberculosis* to the medication typically used constitutes a relevant obstacle to the success of the treatment, regardless of whether a daily or intermittent regimen is used. Many times, resistance is established by previous contact between *M. tuberculosis* and the drug; therefore, the previous treatment is the greatest clinical indicator of the development of multidrug-resistant TB forms.[1]

The efficiency of the intermittent TB treatment has long been observed.[2-4] In a systemic review, the cure and recurrence rates have proven to be very similar between the daily and intermittent treatment.[5] The efficiency of the intermittent regimen has also been shown in patients in retreatment,[6] in pediatric patients,[7] in HIV patients[8] and in patients with clinical indicators of low adherence to treatment.[9]

Normally, when the treatment regimen is self-administered, daily use of medication is preferred, probably due to the fact that omission of a day of treatment would be less ominous. In contrast, the intermittent regimen is preferentially used in the supervised forms of treatment. Therefore, even in countries such as Brazil, in which the self-administered form is adopted, the use of the intermittent supervised form is particularly interesting in situations in which a low adherence rate is presumed, such as in alcoholic, chemically-dependent and homeless patients.

The appearance of drug resistance associated with the intermittent regimen is unclear. One group of authors observed elevated resistance rates in Burundi,[10] above the mean of other African countries, suggesting that the intermittent treatment form practiced for 11 years in this country might be implicated. In accordance with this point of view, other authors highlight a relationship between acquired resistance to rifampin (RMP) and its intermittent use during the initial phase of the treatment in HIV-infected patients.[11] Conversely, another group of authors[12] did not detect the appearance of RMP-resistant mycobacteria in the course of the fully intermittent treatment in a series of 467 cases (2 months with 3 weekly administrations of isoniazid [INH], RMP, pyrazinamide [PZA] and ethambutol [EMB]; followed by 6 months with a weekly administration of INH and EMB).

Therefore, knowing and monitoring mycobacterial resistance to the treatment regimen used is of utmost importance. Our study aims at comparing the mycobacterial resistance rates between TB patients in two communities: one which has received intermittent treatment since 1974 and another which receives daily treatment.

Methods

We used data from a worldwide survey produced by the World Health Organization together with the International Union Against Tuberculosis and Pulmonary Diseases. Between 1994 and 1997, those two organizations make efforts to establish a worldwide plan of surveillance of bacterial resistance to anti-tuberculous drugs. This project involved the measurement of the prevalence rates of this resistance in many countries worldwide and, or particular importance, using standardized measurement methods.
Isolation, culture and susceptibility testing were described in another publication. The summarized description follows. Sputum smear microscopy was carried out by the Ziehl-Neelsen technique. Positive sputum samples were maintained packed in ice until arrival at the referral laboratory, when they were decontaminated by the Petroff technique and cultivated in the Löwenstein-Jensen medium for up to 60 days. Positive cultures were submitted to first-line antituberculous drug susceptibility testing and to \textit{M. tuberculosis} identification and differential testing (niacin testing, nitrite reduction testing and catalase testing).

In our study, all patients included in the original project were considered, except for those diagnosed and treated in the Federal District of Brasília, although resident in other regions. Patients with infectious pulmonary TB admitted for treatment in the health care clinics of the Brazilian Tuberculosis Control Program in the period between 1995 and 1997 were included in the original project, totaling 5,138 patients. Patients were separated into two groups: with or without history of previous specific treatment. Resistance was then categorized into primary or acquired, according to absence or presence of previous treatment in the collected data.

Resistance patterns were classified in monoresistance (a single drug), multi-resistance (INH and RMP necessarily, with or without another drug) or other patterns (more than one drug, except for INH and RMP simultaneously).
Resistance is classified as acquired, when the very individual was previously submitted to treatment, or primary, when the infected individual acquired the bacillus from another individual. Therefore, higher resistance rates can be expected due to the degree of inefficiency of the treatment. Inefficiency is to be understood as factors related not only to drug efficacy, but to the system of administration and to various factors related to the use of these drugs in the community.

Regardless of any possible difference between the Federal District of Brasília and the other parts of Brazil concerning any of those factors, some authors reported a virtually identical abandonment rate: 25.7% for the Federal District of Brasília and 25.9% for the other parts of Brazil. Other factors related to a more efficient health care system, although unmeasured, seem to be inexistent, due to the fact that the same guidelines instruct the activities in the TB control clinics. Other factors related to the form of drug administration, which is self-administered throughout Brazil, also seem to be inexistent.

The development of higher rates of bacterial anti-tuberculous drug resistance, especially regarding multiple-drug resistance, is related to the contact between the microorganism and these drugs. Resistance is classified as acquired, when the very individual was previously submitted to treatment, or primary, when the infected individual acquired the bacillus from another individual. Therefore, higher resistance rates can be expected due to the degree of inefficiency of the treatment. Inefficiency is to be understood as factors related not only to drug efficacy, but to the system of administration and to various factors related to the use of these drugs in the community.

The data in the present study evidence a similarity between the resistance rates in the Federal District of Brasília and in the other parts of Brazil. First, the presence of possible biases must be questioned. Factors related to the profile of the studied patients, such as the prevalence of AIDS, alcoholism, use of illicit drugs and other morbidities in the sample, can interfere with the adherence to treatment. Regardless of any possible difference between the Federal District of Brasilia and the other parts of Brazil concerning any of those factors, some authors reported a virtually identical abandonment rate: 25.7% for the Federal District of Brasilia and 25.9% for the other parts of Brazil.

Other factors related to a more efficient health care system, although unmeasured, seem to be inexistent, due to the fact that the same guidelines instruct the activities in the TB control clinics. Other factors related to the form of drug administration, which is self-administered throughout Brazil, also seem to be inexistent.

The question of the group of drugs available for the treatment can have direct importance in relation to the appearance of resistant bacilli. The non-addition of PZA to the treatment regimen, for example, evaluated in a study in which four

### Results

In the studied period, 271 patients were diagnosed with TB in the Federal District of Brasília; of those, 35 patients were excluded for not residing in the Federal District of Brasília. Of the 236 patients included, 161 (68.2%) were male and 75 (31.8%) were female. Age ranged from 15 to 86 years, and mean according to gender was 41.5 and 36.7 years, respectively. The results observed in those 236 patients were compared to those obtained from a total of 4,867 patients studied in the other parts of Brazil.

In the Federal District of Brasilia, 214 patients (90.7%) were treatment-naïve, whereas 22 (9.3%) reported a history of previous treatment. In the other parts of Brazil, these values were 4,024 (82.7%) and 843 (17.3%), respectively. The frequency of cases with or without resistance to any drugs is shown in Table 1.

As observed in Tables 2 and 3, there was no statistically significant difference between the prevalences, regardless of the patterns, between primary and acquired resistance in the Federal District of Brasília and in the other parts of Brazil. In two analyzed situations, the “any resistance” or “monoresistance” patterns for the primary type, the prevalences showed virtually identical, translating into a minimal size difference and implying a reduced power. In the Federal District of Brasilia, no resistance to EMB was observed, nor was there resistance to PZA and ETH, in accordance with reports for the other parts of Brazil.

### Discussion

The development of higher rates of bacterial anti-tuberculous drug resistance, especially regarding multiple-drug resistance, is related to the contact between the microorganism and these drugs. Resistance is classified as acquired, when the very individual was previously submitted to treatment, or primary, when the infected individual acquired the bacillus from another individual. Therefore, higher resistance rates can be expected due to the degree of inefficiency of the treatment. Inefficiency is to be understood as factors related not only to drug efficacy, but to the system of administration and to various factors related to the use of these drugs in the community.

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**Table 3 - Prevalence of acquired resistance in the Federal District of Brasilia and in the other parts of Brazil.**

<table>
<thead>
<tr>
<th>Type of resistance</th>
<th>FDB, %</th>
<th>Brazil, %</th>
<th>p</th>
<th>W effect size</th>
<th>Power, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>15.8</td>
<td>21.9</td>
<td>0.59</td>
<td>0.1634</td>
<td>99</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>0.0</td>
<td>11.7</td>
<td>0.13</td>
<td>1.0000</td>
<td>100</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15.7</td>
<td>9.1</td>
<td>0.38</td>
<td>0.2650</td>
<td>100</td>
</tr>
<tr>
<td>Any resistance</td>
<td>15.8</td>
<td>26.8</td>
<td>0.39</td>
<td>0.2580</td>
<td>100</td>
</tr>
<tr>
<td>Monoresistance</td>
<td>5.3</td>
<td>13.7</td>
<td>0.33</td>
<td>0.4444</td>
<td>100</td>
</tr>
<tr>
<td>Multidrug</td>
<td>0.0</td>
<td>10.2</td>
<td>0.16</td>
<td>1.0000</td>
<td>100</td>
</tr>
<tr>
<td>Other patterns</td>
<td>10.5</td>
<td>2.9</td>
<td>0.07</td>
<td>0.5730</td>
<td>100</td>
</tr>
</tbody>
</table>

FDB: Federal District of Brasilia.
intermittent regimens were compared to a daily one, was capable of resulting in a recurrence rate four times higher in a year, compared to that in which PZA was present.\(^{(16)}\) Again, in the Federal District of Brasília the same recommendations regarding the drugs used are followed, differing only in the intermittent form starting on the second month of treatment.

Indeed, in a recent systematic review, the intermittent regimen consisting of three administrations per week following a continuous initial phase, such as it is conducted in the Federal District of Brasília, seems to reach the lowest recurrence rates together with the daily administration regimen. The odds ratio in these two regimens was significantly lower than in those fully intermittent or with lower weekly frequency.\(^{(16)}\)

Although the intermittent treatment used for more than 20 years in the Federal District of Brasília has not resulted in different bacterial resistance rates from the other Brazilian regions, caution is necessary in its extrapolation. Some authors\(^{(17)}\) have observed a relation between the acquisition of RMP resistance and the low count of CD4 cells in HIV-infected patients. In the same study, these authors pointed out a tendency to the association between the RMP resistance and the intermittent treatment with two weekly administrations in the initial phase \((p = 0.15)\) and also with the non-use of antiretroviral treatment in the 2 first months of TB treatment \((p = 0.05)\).

Considering the level of plasma concentration of the drugs in the treatment with two weekly administrations,\(^{(18)}\) these authors have postulated that in a context of immunosuppression, low concentrations of RMP at the end of long intervals can allow the selective replication of resistant mycobacteria.\(^{(17)}\)

In this sense, some authors\(^{(15)}\) have also studied TB and HIV infected patients, and observed a relative risk of 6.4 for RMP-acquired resistance, when it was administered intermittently since the treatment was initiated.

Given the multiplicity of factors involved, it is difficult to impute, through observational studies, the intermittent form of treatment as exclusively responsible for the failure, recurrence or the appearance of resistance. In Burundi,\(^{(10)}\) a sample of 496 new cases evidenced 16.1\% resistance to any drug (2\% to RMP). The study was carried out 11 years after the implementation of the directly observed treatment, short-course program, using an intermittent regimen. These are levels above the African means. A possible bias regards the prevalence of HIV-infected patients. Conversely, in India,\(^{(12)}\) in a fully intermittent controlled clinical assay, there was no appearance of primary RMP resistance.

In our study, a similarity in the population group, in the abandonment rate, health care system and group of drugs used in the treatment gathers a unique opportunity to observe the effect of the intermittent form, used since 1974 in the Federal District of Brasília, on the mycobacterial resistance, compared to the daily treatment. Our data allow the conclusion that the resistance rates are similar between the two groups.

References


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