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When is Tb-Aids Co-Infection Treatment Discontinued? an Analysis of the Situation in Brazil

ORIGINAL

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Abstract

Introduction: Brazil has high levels of TB-AIDS co-infection.

Objective: To analyse differences and similarities, with respect to each State in Brazil and to the Federal District, concerning the stage at which TB-AIDS co-infection treatment is discontinued. The study period was 2008-13.

Methods: Cross-sectional, quantitative study, using data from the Diseases and Notification Information System administered by the Brazilian Health Ministry. The data were analysed using the statistics program R, and the results are represented graphically by dotplots and dendrograms.

Results: 58,704 cases of tuberculosis-AIDS co-infection were recorded. Rates of cure were under 30%. In the States of Paraíba and Pernambuco, treatment dropout was almost 50%.Mortality levels were high, at 70-90% in some States. Multiresistant TB was observed in less than 20%of cases. The rate of non-treated/non-resolved cases was 70% in Bahia. Transfer rates varied widely, with the highest level being recorded in Alagoas (80% of cases).

Conclusion: Global goals are far from being met. There is considerable operational diversity in the public health policies of the different States. TB-AIDS co-infection should be monitored continuously and the epidemiological information system regularly updated in order to control this double epidemic.

Keywords

Co-infection; Epidemiological Surveillance; Public Health.

Introduction

Tuberculosis (TB) is an infectious disease that has been known since antiquity It has a major impact on public health worldwide. By the mid-1980s, the global epidemiological situation had been brought under control, but with the appearance of human immunodeficiency virus (HIV) infection and of acquired immunodeficiency syndrome (AIDS), there has been a resurgence of TB [1]. Nowadays, it is considered the second main cause of death by infectious disease in the world, after AIDS, and the first cause of death among AIDS patients [2, 3].

One third of the world's population is infected by the TB bacillus, and 30 million of them may die of this cause in the next ten years. HIV-AIDS is one of the main obstacles to controlling the disease [2, 4]. Individuals infected by HIV are 50 times more likely to contract TB than those who are not infected [5]. This co-infection is reciprocal and generates a vicious circle, accelerating the pathogenic course of the microorganisms involved and favouring the appearance of drug-resistant strains [6].

HIV infection accelerates latent TB activation by depressing the immune system, and favours the rapid reproduction of the bacillus. In turn, TB further accentuates immune depression and accelerates the evolution of HIV infection into AIDS, activating and destroying macrophages and T lymphocytes infected by the virus. The probability of death and of contracting other diseases is higher in co-infected patients than in those with either disease alone [3].

The global strategy to combat TB, established by the WHO in 2006, aimed to eliminate it as a public health problem by 2015, reducing the global incidence by 50%, detecting 70% of cases, curing at least 85% of new cases, reducing treatment dropout, reducing death rates to under 5% and preventing the rise of drug-resistant bacilli and co-infection by HIV-AIDS [7, 8].

In Brazil, access to antiretroviral and TB treatment has extended throughout the population in the last two decades. Since 1999, in view of the widespread presence of TB-HIV co-infection, the National Plan for Tuberculosis Control has recommended anti-HIV tests should be performed for all TB patients. The Plan also stresses the importance of monitoring HIV-AIDS patients to identify symptoms of TB and of detecting the disease at the earliest possible stage, providing adequate treatment and preventing opportunistic diseases [7].

Ensuring that the necessary diagnostic tests are carried out should be a joint commitment entered into by patients and the health system, and health service managers must provide the necessary conditions for this to take place [9].

Although the importance of testing anti-HIV in TB patients is well known, studies have highlighted the low frequency of requests for such tests in Brazil, and this shortcoming limits our perceptions of the real occurrence of TB-HIV co-infection [10, 11].

In view of the above considerations regarding the TB-AIDS epidemic and the lack of information about its distribution and treatment in Brazil, the aim of the present study is to analyse the situation in the individual States and in the Federal District, in relation to TB-AIDS co-infection and the conclusion of treatment, during the period 2008-2013.

Methods

A cross-sectional, quantitative study was performed. The study population was composed of all the TB-AIDS cases notified from 2008 to 2013 in the 27 States of Brazil, namely Acre (AC), Alagoas (AL), Amapá (AP), Amazonas (AM), Bahia (BA), Ceará (CE), Espírito Santo (ES), Goiás (GO), Maranhão (MA), Mato Grosso (MT), Mato Grosso do Sul (MS), Minas Gerais (MG), Pará (PA), Paraíba (PB), Paraná (PR), Pernambuco (PE), Piauí (PI), Rio de Janeiro (RJ), Rio Grande do Norte (RN), Rio Grande do Sul (RS), Rondônia (RO), Roraima (RR), Santa Catarina (SC), São Paulo (SP), Sergipe (SE), Tocantins (TO) together with the Federal District (DF).

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2015
Vol. 8 No. 239
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The study data were obtained in June 2015, from the Diseases and Notification Information System, online version, available at the website of the Brazilian Ministry of Health [12]. Statistical analysis was performed using the statistics program R, version 3.2.0 [13].

The variables addressed described all situations in which TB-AIDS co-infection treatment was ended: non-treated/non-resolved cases, cure, dropout, death by TB, death by other causes, transfer and multi-drug-resistant TB (MDR-TB). The data obtained were analysed using a dot plot (a one-dimensional graph of dispersion).

In our analysis, the *dotplot* shows the distribution of the variables and their degree of dispersion. The values are represented by dots along a line, distributed according to a specific scale. When the data are homogeneous, the dots are closely grouped, and when they are dispersed, the dots are dispersed [14].

In order to analyse the degree of similarity among the States, regarding the distribution of TB-AIDS cases, the hierarchical clustering method (dendrogram) was applied, in which distances between pairs of States were determined by the nearest-neighbour method; thus, an element was associated with a given cluster if there was a similarity with any other element in that cluster. The first two cases combined are those with the shortest distance or the maximum similarity.

The distance between two clusters was calculated as follows: $d'(b_{i,} b_j \cup b_k) = \min(d(b_{j,} bi), d(b_{k,} b_i))$, in which i, j and k are the States and the Federal District for $i \neq j$. A is a cluster of the 27 States, from which a Euclidean distance was calculated, and $D=(\delta_{ij})_{1 \leq i,j \leq n}$ is the matrix of distance between these States. The aim of the cluster analysis is to achieve a non-supervised classification of A elements, that is, to group the elements into disjoint classes. If these classes group successively in higher-level classes, the result is a hierarchical structure of clusters, which can be graphically represented by a dendrogram.

The cophenetic correlation coefficient was then calculated. This is a simple test to validate a group by measuring the degree of preservation of parallel distances in the dendrogram obtained from the association of States, compared to the original distances [15, 16, 17].

The silhouette mean is an indicator of the maximisation of a partition. The peak of the silhouette mean marks the point at which the data clustering determined by the algorithm is appropriate.

We also used the Rand index, showing the proportion of all pairs of States in which two different partitions may be correlated, i.e. whether a pair of States is assigned to the same group in both situations or is assigned to different groups [18].

This study was approved by the research ethics committee of the Universidade Estadual da Paraíba (Register No. 45954315.5.0000.5187), in accordance with Resolution 466/2012 of the National Health Council, the regulatory body for research with human beings in Brazil.

Results

During the study period, 526,561 cases of TB were registered in Brazil, of which 58,704 cases were TB-AIDS co-infections. The reasons for ending TB treatment are shown in **Figure 1**, by proportions, for each State.

In most States, TB was cured in less than 15% of cases, but in RR and AP this value was approximately 20% and in AC it was 33% **(Figure 1)**.

In 14 States, the rate of treatment dropout was below5%, and in most of the rest it ranged from 8% to 20%. However, PE and PB recorded almost 50% **(Figure 1)**.

Death rates by TB varied considerably. In most cases, the level was below 5% but in SE, RN, TO and AC it rose to 10%, in GO and MT to 20%, in PB and AP to 30%, in MA and TO to approximately 50% and in PA to 70% of all cases recorded.

The variable 'Death by other causes' also varied widely **(Figure 1)**. In MT, ES, SE, AL, RN and RR, this

2015
Vol. 8 No. 239
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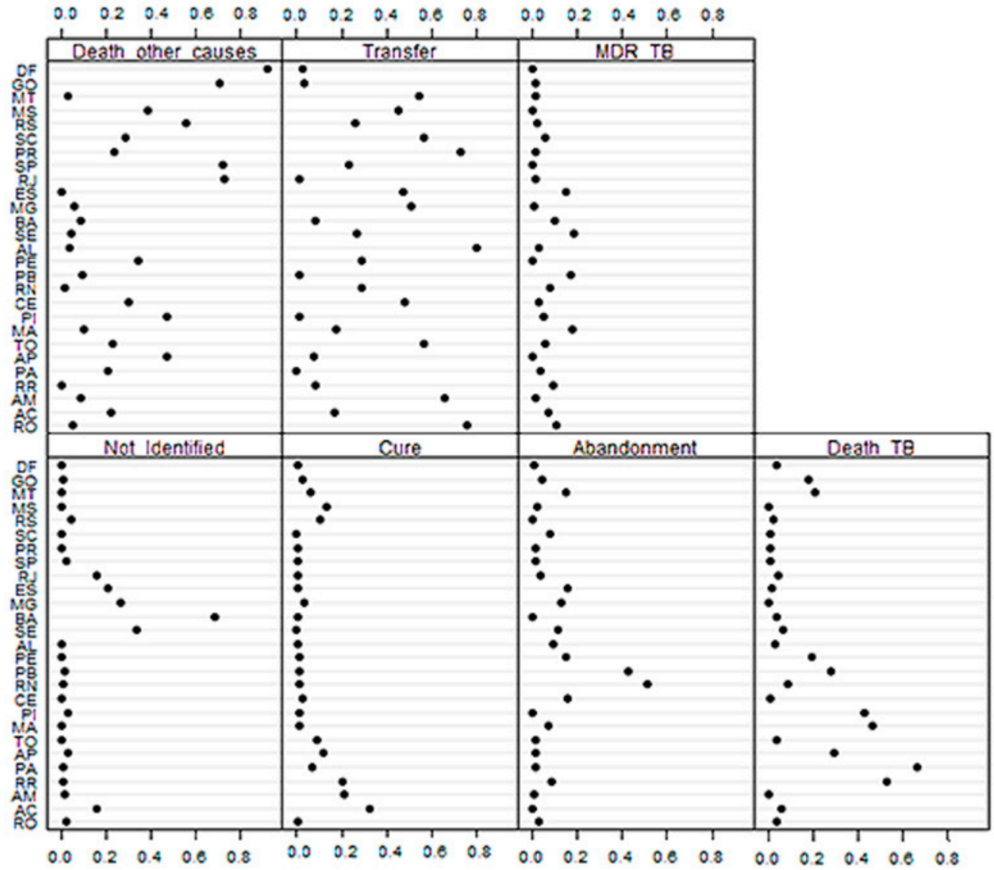
Figure 1: Death by other causes, Transfer, MDR-TB, Not identified, Cure, Abandonment, death by TB.



level was below 5% while GO, SP and RJ reported almost 70% of cases under this description, and in DF the value rose to 90% of all cases.

Regarding the transfer of TB cases, the values recorded ranged from 0% in RJ, PB, PI and PA to 80% in AL.

In all the States, MDR-TB was present at levels of less than 20%, with most States recording around 5% and the highest levels being found in BA, PB and MA.

Situations in which TB was non-treated/non-resolved were recorded in less than 5% of cases in most States, with the highest levels being registered in RJ, AC, SP, ES and MG with up to 30% and in BA with approximately70% (see **Figure 1**).

With respect to the similarity of distribution of TB-AIDS co-infection cases, **Figure 2** illustrates the formation of three large clusters, among which cluster SP has the highest number of cases and

Figure 2: Distribution of TB-AIDS cases in the States and the Federal District, 2008-2013.

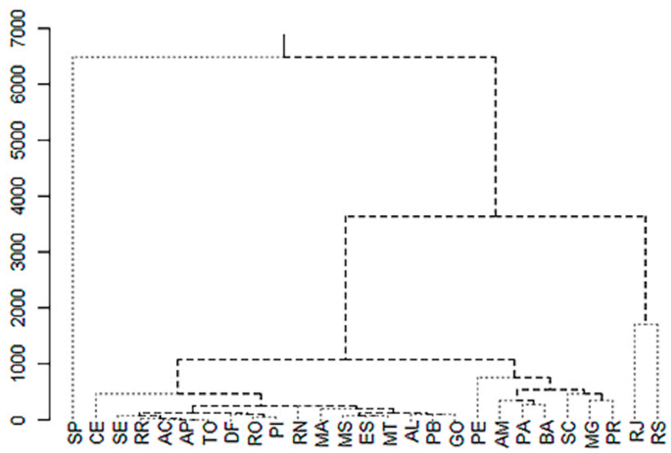


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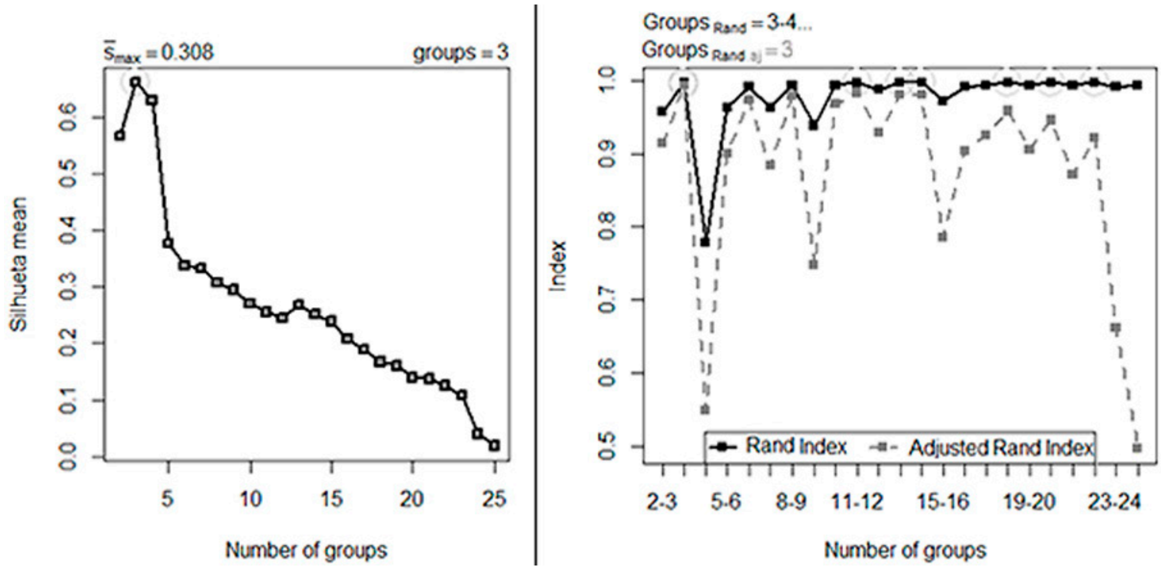
Figure 3: Rand index and number of groups



incorporates all the other States; RJ and RS present the greatest distance from the others, except SP, which shows that the largest numbers of TB-AIDS cases are recorded in the south-east of the country.

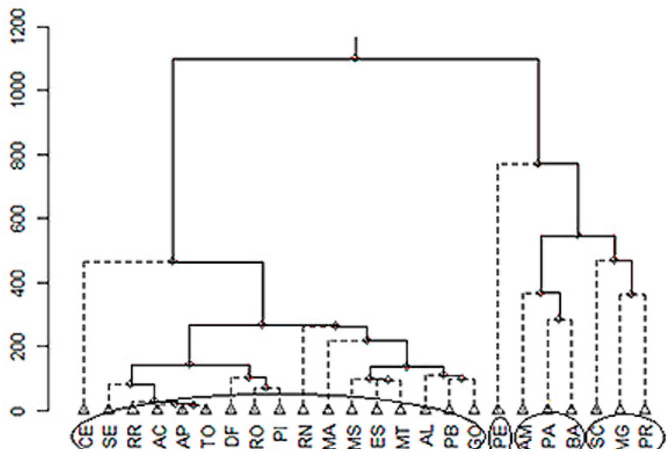
The cophenetic coefficient was fairly high (0.789), which reflects the good quality of the group.

Figure 3 shows the variation of the adjusted Rand index, comparing several pairs of clusters; in this case, the variation of 2 or 3 clusters reached a satisfactory level (from 0.9 to 1.0), which suggests there is a strong degree of correspondence in each cluster.

To better visualise the subgroups in the third cluster, a cutoff was performed at point 1200 on the distance axis of the dendrogram (see **Figure 2**), as a result of which SP, RJ and RS were eliminated. The Rand index was calculated again and four clusters were formed.

Again, the cophenetic correlation coeficient value was fairly high (0.78), reflecting the good quality of the group. The adjusted Rand index was also satisfactory, ranging from 0.87 to 1, considering the four clusters (see **Figure 4**).

Figure 4: Dendrogram for all the States except SP, RJ and RS.



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Discussion

In this study, we show that the goals set by the WHO regarding the control of TB are not being met in Brazil. Although the country guarantees universal access to TB and antiretroviral drugs, free of charge, and despite the therapeutic and diagnostic advances that have been made, the incidence of TB-AIDS co-infection remains unacceptably high [19, 20]. Thus it remains necessary to expand the screening programme to detect HIV in TB patients and vice versa, to ensure early treatment and reduce co-infection [7].

However, these strategies in themselves are not enough to reduce the level of TB-AIDS in Brazil; it is also necessary to design and implement actions to reduce social inequalities, to extend access to health services and to strengthen policies of social inclusion, taking into account that this epidemic has a major effect on the poorest groups within society [21, 22].

It is also necessary to increase our epidemiological knowledge of TB-AIDS co-infection, so that both infections can be treated specifically, as this patient group is three times more vulnerable to therapeutic failure than are non co-infected patients [23, 24].

Rates of cure in Brazil are below the level recommended by the WHO (85%), a situation that may contribute to the transmission of drug-resistant bacilli and increase the time and cost of treatment [7].

Results for treatment dropout were generally poor, although some States reached the global goal, of 5% or less; furthermore, levels of cure were low and mortality rates were high. A high level of treatment dropout is associated with greater spread of the disease and with the appearance of bacilli that are resistant to TB drugs, and is considered a major factor in death from TB [7, 25, 26, 27].

In line with previous research, we found that co-infected patients presented high levels of mortality, reaching 50-90% in MA, TO, PA, GO, Spain, RJ and DF. Thus, it is evident that TB is one of the main causes of mortality in patients with AIDS. Apart from treatment dropout, immune depression and multi-resistant TB aggravate the probability of mortality [4, 23, 28].

In this context, the monitoring and periodic updating of TB and AIDS information systems are essential to enable a proper evaluation of the interventions carried out, so that appropriate public health actions to control these diseases can be implemented, and to reveal which population groups are most vulnerable to co-infection [23, 29].

The situation in BA is especially significant because this State failed to identify the reasons for ending treatment in 70% of TB cases. In this respect, too, AL reported 80% of transfer cases, and did not report precise information about the reasons for ending TB treatment. These shortcomings greatly limit the value of the data reported, making it impossible to determine exactly how these TB cases are concluded, and hampering the planning of control policies [30].

In Brazil, there are large variations in the incidence of TB-AIDS cases and in the treatment provided in the States, due to major differences between the regions and in the public health policies applied. The States of RJ and SP contain the highest levels of TB in the country, while RS has extremely high levels of patients co-infected by TB-AIDS [10, 30, 31, 32, 33].

Further studies are needed to determine the specific characteristics of each State in order to achieve a synergy of health actions and to enhance the treatment and control of these two diseases.

Detailed epidemiological knowledge about the situations in which the treatment of TB-AIDS co-infection is concluded is essential so that health service managers and personnel can recognise cases and take prompt action to remedy low rates of access to treatment and to improve strategies to control the disease. This study shows that the present situation regarding the reporting of reasons for the conclusion of treatment is unsatisfactory, and that Brazil is failing to meet the WHO targets for reducing the impact of TB. Variations among the States can be explained by regional differences and by the diversity of local policies applied.

There is a need for continuous monitoring of cases of TB and AIDS by health services, and for data obtained from epidemiological surveillance information systems in each Brazilian city and State to be regularly updated, in order to reflect the real extension of this comorbidity and its particularities, nationwide, so that health actions can be improved and the best use made of available resources.

Conclusion

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