The impact of the stratification by degree of clinical severity and abandonment risk of tuberculosis treatment

Pedro Daibert de Navarro1,2, João Paulo Amaral Haddad3,4, Juliana Veiga Costa Rabelo5, Claudia Hermínia de Lima e Silva3, Isabela Neves de Almeida1,2, Wânia da Silva Carvalho4, Silvana Spindola de Miranda2

ABSTRACT

Objective: Evaluate the impact of the instrument of the “Stratification by Degree of Clinical Severity and Abandonment Risk of Tuberculosis Treatment” (SRTB) on the tuberculosis outcome. Methods: This study was a pragmatic clinical trial involving patients with a confirmed diagnosis of tuberculosis treated at one of the 152 primary health care units in the city of Belo Horizonte, Brazil, between May of 2016 and April of 2017. Cluster areas for tuberculosis were identified, and the units and their respective patients were divided into intervention (use of SRTB) and nonintervention groups. Results: The total sample comprised 432 participants, 223 and 209 of whom being allocated to the nonintervention and intervention groups, respectively. The risk of treatment abandonment in the nonintervention group was significantly higher than that in the intervention group (OR = 15.010; p < 0.001), regardless of the number of risk factors identified. Kaplan-Meier curves showed a hazard ratio of 0.0753 (p < 0.001). Conclusions: The SRTB instrument was effective in reducing abandonment of tuberculosis treatment, regardless of the number of risk factors for that. This instrument is rapid and easy to use, and can be adapted to different realities. Its application showed characteristics predisposing to a non-adherence to the treatment and established bases to mitigate its impact.

Keywords: Tuberculosis; Patient compliance; Risk factors; Treatment adherence.

INTRODUCTION

In recent years, the number of tuberculosis cases has decreased globally. However, this reduction has been insufficient to reach the goals of the WHO End TB Strategy worldwide. These goals will only be achieved if diagnosis, treatment, and prevention are focused on the patient and in their needs in a context of universal health care coverage.

Tuberculosis remains one of the major 10 causes of death in the world, affecting 1.3 million people; there were approximately 10 million patients with tuberculosis in 2018. Treatment success rates remain low, reinforcing the need for health care models that facilitate the adequate monitoring of people with tuberculosis.

Brazil is one of the 20 countries with the highest burden of tuberculosis, with an estimated 91,000 cases and 7,000 annual deaths. Belo Horizonte (BH) is the capital of the second most populous state in the country, with cure rates (72.5%) and treatment abandonment (11.8%) outside the recommended international parameters of at least 85% and at most 5%, respectively.

Despite the high effectiveness of the recommended therapeutic procedures for the treatment and prevention of tuberculosis, low adherence to the treatment is considered the main challenge for the global control of the disease. The inadequate treatment interruption can cause consequences individual and collectively, such as death, sequelae, appearance of drug-resistant Mycobacterium tuberculosis, increased costs for health systems, in addition providing a place for the permanence of the source of infection in the community.

International agencies have been advocating for the Directly Observed Treatment (DOT) since 1994 to strengthen treatment adherence. Its premise is to guarantee the visualization of the medication taken by the patient and to strengthen their bond with the health care team.

Various studies have shown that DOT alone does not provide greater treatment adherence and have pointed out the need for other measures.

Strengthening adherence interventions can have a greater impact on the health of the population, when compared with any other improvements in

Correspondence to:
Silvana Spindola de Miranda. Avenida Alfredo Balena, 190, Santa Efigênia, CEP 30130-100, Belo Horizonte, MG, Brasil.
Tel.: 55 31 3409-9905. E-mail: silvanaspindola@gmail.com

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medical treatment.\(^{(15,16)}\) Low adherence is a primary determinant of treatment effectiveness, because it reduces the expected clinical benefits. It is believed that its magnitude and effect are even greater, especially in developing countries, given the scarcity of resources and the inequalities in access to the health care system.\(^{(6,7)}\) The ideal care organization requires coordination of patient needs and the identification of possible barriers to treatment.\(^{(9-11,17,18)}\)

Health systems such as Primary Health Care (PHC) consider this level of care to be the preferred access to the care network. PHC uses technologies of high complexity and low technological density that should solve health problems of greater frequency and relevance in its territory,\(^{(19)}\) including tuberculosis.\(^{(4-7,9,10,20)}\)

Proper management of chronic health conditions imposes the need to stratify cases so that patients receive differentiated care, which is an attribute of a rational and resolving health care system. The population stratification process is central to health care models because it allows the identification of people and groups with similar health needs that must be cared for by specific technologies and resources, based on different approach of people and groups that present similar risks.\(^{(21,22)}\) Usually, without risk stratification, the services supply follows demand criteria, generating unnecessary interventions, depriving differentiated attention according to people’s needs.\(^{(16-18)}\)

Tuberculosis is considered a chronic disease, and it is extremely important to recognize the social determinants involved in the process. Patients need an individualized approach, as the frequency of associated diseases is high, as well as other vulnerabilities. Many factors are associated with adherence to the TB treatment, including patient characteristics, the relationship between the health care provider and the patient, the prolonged treatment regime and the organization of health systems.\(^{(4-10)}\)

This study aims to assess the impact of the instrument of the "Stratification by Degree of Clinical Severity and Abandonment Risk of Tuberculosis Treatment" (SRTB) on the tuberculosis outcome.

**METHODS**

This was a pragmatic clinical trial involving patients with a confirmed diagnosis of tuberculosis who were treated at one of the 152 PHC units in the city of Belo Horizonte, Brazil, between May of 2016 and April of 2017. All of the PHC units in the city were divided into two groups, taking into consideration the administrative organization of the health care network, the presence of cluster areas for tuberculosis in the territory, and social vulnerability indexes, in order to avoid selection bias in the sample.

We used a georeferencing software (https://www.mapdevelopers.com/batch_geocode_tool.php) and the addresses of the participants with the objective of determining the geographic location of 70-90\% of the cases between 2012 and 2015 in order to define the existence of possible clusters. Maps were created for each of those years, as was one for the four years as a whole, using the TerraView software (www.dpi.inpe.br/terraview). In order to assess the presence of clusters we used the SaTScan software (https://www.satscan.org/download_satscan.html), which was adopted to search for high rates with the purely spatial discrete Poisson scan model.

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (Protocol no. 43320015.4.0000.5149), and all participants agreed to participate and signed a free informed consent form.

The SRTB instrument (Chart 1) was developed considering international guidelines for the management of tuberculosis.\(^{(4,5,10,15,20,23)}\) The instrument is structured into two parts: the degree of clinical risk (low/medium/high/very high), according to disease presentation, presence of comorbidities, bacterial resistance and clinical complications, with the premise of referring the patient to the ideal level of health care (PHC, Secondary Reference - medical specialties, Tertiary Reference – emergency hospitals/health units); and the risk degree of abandoning the treatment - low/high - in order to strengthen compliance measures linking it to the PHC unit).

All of the patients diagnosed with tuberculosis who were 18 years or older and agreed to participate in the study were interviewed by trained researchers and had their home address linked to the respective PHC unit. The PHC units were divided into two groups: nonintervention and intervention. In both, a questionnaire was applied, validated for research, which contains sociodemographic characteristics (sex, race/color self declaration, education, marital status and income), individual characteristics (homeless person, freedom deprivation), clinical characteristics (signs/symptoms, comorbidities: people living with the Human Immunodeficiency Virus (HIV/AIDS), alcoholism, smoking and use of illicit drugs), characteristics of treatment (history of previous treatment for TB, adverse reaction to drugs, DOT, report of symptoms improvement after the second month of treatment) and operational characteristics of the health system (epidemiological surveillance and case monitoring). The SRTB instrument was used only in the intervention group, and the patients in this group were monitored regarding the implementation of the recommendations in the instrument. Treatment outcomes were as follows: cure (considering clinical, radiological, and/or bacteriological results), treatment abandonment (i.e., not taking the medication for a period longer than 30 consecutive days), and death.

Descriptive analyses were performed with the Stata statistical software package, version 14 (StataCorp LP, College Station, TX, USA), according to the selected characteristics stratified by group, by means of frequency of distribution and measures of central tendency and dispersion for the characteristics studied.
The impact of the stratification by degree of clinical severity and abandonment risk of tuberculosis treatment

**Chart 1.** Stratification by degree of clinical severity and abandonment risk of tuberculosis treatment.

| STRATIFICATION BY DEGREE OF CLINICAL SEVERITY AND ABANDONMENT RISK OF TUBERCULOSIS TREATMENT | DOT (preferably at the health unit or other place to be agreed). Guidance regarding the disease and drug treatment. Involvement of the multidisciplinary team. |
|---|---|
| **1st STEP** | **2nd STEP** |
| RISK OF ABANDONMENT OF TREATMENT | RISK OF ABANDONMENT OF TREATMENT |
| I | LOW RISK | DOT (preferably at the health unit or other place to be agreed). Guidance regarding the disease and drug treatment. Involvement of the multidisciplinary team. |
| | TB without identified risk of abandonment | DOT (preferably at the health unit or other place to be agreed). Guidance regarding the disease and drug treatment. Involvement of the multidisciplinary team. |
| II | HIGH RISK | DOT (preferably at the health unit or other place to be agreed). Guidance regarding the disease and drug treatment. Involvement of the multidisciplinary team. |
| | TB with identified risk of abandonment; | DOT (preferably at the health unit or other place to be agreed). Guidance regarding the disease and drug treatment. Involvement of the multidisciplinary team. |
| | (1) Social vulnerability; | (1) Social service; |
| | (2) Abusive / harmful use of alcohol and other drugs; | (2) Mental Health Services; |
| | (3) History of previous TB treatment abandonment; | (3) Identification and intervention in previous abandonment factors; |
| | (4) Homeless situation; | (4) Social Work and Mental Health; |
| | (5) HIV infection; | (5) Teams from the Secondary Reference Centers for HIV / AIDS; |
| | (6) Freedom deprivation. | (6) Immediately report to the epidemiological surveillance service, informing the probable prison unit. |
| A | LOW RISK | Primary Health Care: |
| | - Pulmonary, ganglionic and/or pleural TB | - Basic health unit |
| B | MEDIUM RISK | Secondary Reference Clinic: |
| | - Confirmed extrapulmonary TB (except, ganglion and pleural); | - Children: Reference center for pediatric TB; |
| | - TB with severe comorbidities; | - Adults: Reference center in TB in adults; |
| | - TB with clinical complications and/or major adverse effects to treatment; | - HIV / AIDS: Reference center in TB-HIV - infectious diseases. |
| | - Treatment failure; | |
| | - TB resistant to a medication. | |
| C | HIGH RISK | Tertiary Reference Clinic or hospitalization: |
| | - TB + clinical/surgical criteria for hospitalization | - Children: Reference hospital for pediatric TB; |
| | - MDR or XDR | - Adults: Reference hospital for TB in adults; |
| | - Confirmed tuberculous meningoencephalitis | - HIV / AIDS: Reference hospital in TB-HIV - infectious diseases |
| D | VERY HIGH RISK | Emergency Health Unit |
| | - Suspected tuberculous meningitis; | |
| | - TB with signs of severity: respiratory failure (hypoxemia or tachyypnea), circulatory failure (oliguria or hypotension) and severe change in mental status; | |
| | - TB with complications that require immediate assistance intervention | |

DOT: directly observed treatment; TB: tuberculosis; MDR: multidrug resistant; and XDR: extensively drug resistant.

The magnitude of the association between the explanatory variables and the “treatment abandonment” event was estimated using odds ratio and its corresponding 95% CI for each variable, obtained by logistic regression. In the univariate analysis, variables with \( p \leq 0.20 \) in the Wald test were manually selected for the multivariate analysis. The level of significance required for inclusion in the final model was \( p < 0.05 \). The likelihood ratio test was used in order to compare the models. The goodness of fit of the final models was assessed by the Hosmer-Lemeshow test. Survival analysis was performed, according to Cox's semi parametric model, to estimate the occurrence of treatment abandonment between groups.

**RESULTS**

During the study period, 623 tuberculosis patients were identified, of whom 476 were interviewed. Of those, 44 patients were excluded from the study: a change in the diagnosis (\( n = 16 \)), place of residence other than Belo Horizonte (\( n = 6 \)); and a lack of follow up at the PHC unit (\( n = 22 \)). Therefore, the study sample comprised 432 participants, who were divided into the nonintervention (\( n = 223 \)) and intervention (\( n = 209 \)) groups.

After the similarity test between the groups and the univariate logistic regression, no significant differences were found, unless for income, presence
of comorbidities and adverse reaction, demonstrating the homogeneity of the sample.

The descriptive analysis (Table 1) revealed a predominance of male individuals, and approximately half of the total sample had a low level of education (≤ 8 years of schooling). In addition, 319 patients (73.8%) had comorbidities, 123 (28.5%) were alcoholics, 170 (39.4%) were current smokers, 69 (16.0%) made use of illicit drugs, and 203 (47.0%) presented with adverse reactions to medications in the second month of treatment (Table 1).

In the nonintervention group, in the univariate analysis, several characteristics were associated with treatment abandonment: non-white color, single marital status, low income (criteria used by the Brazilian Federal Government which considers families that have a monthly income per capita of up to half a minimum wage or a total family income up to three minimum wages), homeless person, presence of comorbidities, alcoholism, smoking, use of illicit drugs, retreatment by re-entry after abandonment, presence of one or more risk factors identified (low income, homeless person, treatment for re-entry after abandonment, alcoholism and/or use of illicit drugs). In the intervention group, none of these characteristics were associated with treatment abandonment.

The variables sex, education, DOT performance, presence of adverse reaction to medications and improvement of symptoms, assessed in the second month of treatment, as well as HIV/AIDS co-infection, did not show an association in both groups.

In the multivariate analysis, we adjusted the variables related to treatment abandonment, producing two models (Table 2): one taking into consideration the number of risk factors identified; and one using the following variables: low income, retreatment, use of illicit drugs and/or alcohol, and homeless person. In both models, adherence to DOT and the use of the SRTB instrument reduced the risk of treatment abandonment.

The impact of income on tuberculosis treatment was evident (Figure 1). Low income was associated with a greater chance of dropping out. The abandonment risk decreases when the income increases, showing an inverse relation. The income effect under the risk of abandonment practically disappears for people with an income above R$ 5,000 per month.

Treatment abandonment was more likely to occur in the nonintervention group, when compared with the intervention group (OR = 15.010; p < 0.001). The application of the SRTB instrument reduced the impact of all characteristics associated with treatment abandonment.

The number of risk factors directly increased the “abandonment” outcome in the nonintervention group. However, this outcome was not significant in the intervention group, regardless of the number of risk factors identified (Figure 2).

The Kaplan-Meier curves followed by the log-rank test (Figure 3) were statistically different (p < 0.001), showing that the intervention was effective in reducing treatment abandonment in the intervention group. The Cox proportional hazards model showed an association between the exposure factor, whether or not it was part of the intervention group (hazard ratio = 0.0753).

**DISCUSSION**

Treatment success for patients with tuberculosis at a high risk of abandonment is exceptionally difficult, requiring intense commitment and innovative approaches. The use of the SRTB instrument significantly reduced the risk of treatment abandonment (OR = 15.010; p < 0.001), even in the presence of one or more risk factors (OR: 4.376 p=0.001 to 12.240 p<0.001). Studies that promoted a set of treatment adherence interventions reported lower treatment abandonment rates.\(^\text{[6-12,14,15]}\) The greater adherence of patients to drug treatment can be achieved by combining interventions aimed at the identified risk factors. Even considering that these measures have a cost, it is still less than the consequences of the abandonment.\(^\text{[6-7,14,24]}\) Due to the set of interventions performed, a reduction in abandonment was observed in intervention group (with SRTB it was 92.5% more slow at any time of follow-up - HR:0.0753) when compared to nonintervention group, showing a strong association between the occurrence of abandonment and the proposed strategy by SRTB.

Abandonment among non-white patients may be associated with social issues evidenced in the present study, because low income is more common in that population in Brazil.\(^\text{(19)}\) Therefore, poverty is one of the main reasons for patients not to understand the benefit of clinical treatment. Other studies\(^\text{[2,20,25-27]}\) corroborate the connection between social capital and health: as the family income increased, treatment abandonment significantly decreased. Poor people generally have less access to health care services or have access to health care facilities with fewer resources. In addition, that population is exposed to social determinants of tuberculosis, which indicates the need for further government actions in order to promote equity.\(^\text{[2,20,25-27]}\)

The present study showed that DOT reduced the risk of treatment abandonment when associated with other measures, but only in the intervention group. The effectiveness of DOT, a globally recommended strategy to strengthen treatment adherence, is questioned in some studies,\(^\text{[26,27]}\) being especially directed at vulnerable groups.\(^\text{[28,29]}\) Other authors have demonstrated that DOT reduced dropout, especially when other support measures are involved, such as educational and psychological support programs.\(^\text{[14,30]}\)

It is evident that good health care services are necessary to ensure that patients benefit from the treatment, but this alone is insufficient; the autonomy...
The impact of the stratification by degree of clinical severity and abandonment risk of tuberculosis treatment of patients, who choose whether they will take their medication or not, should be considered. This point of view emphasizes that a health care system should be targeted to the needs of patients and not only to mechanisms for monitoring behavior, such as DOT; usually, patients with chronic diseases have difficulty in adhering to the recommended protocols.¹⁹,²¹ Other characteristics showed a strong association with treatment abandonment in the nonintervention group: people on the street,¹⁷,²⁷ presence of comorbidities,⁴,²⁰

### Table 1. Characteristics of the sample of patients diagnosed with tuberculosis in the nonintervention and intervention groups, Belo Horizonte, Brazil (N = 432).*  

| Characteristic                          | Nonintervention (n = 223) | Intervention (n = 209) | p*  |
|----------------------------------------|---------------------------|------------------------|-----|
| **Sociodemographic**                   |                           |                        |     |
| Sex                                    |                           |                        |     |
| Male                                   | 162 (72.65)               | 141 (67.46)            | 0.240 |
| Female                                 | 61 (27.35)                | 68 (32.54)             |     |
| Self-reported race/skin color          |                           |                        |     |
| White                                  | 47 (21.08)                | 39 (18.66)             | 0.530 |
| Non-White                              | 176 (78.92)               | 170 (81.34)            |     |
| Level of education                     |                           |                        |     |
| > 8 years of schooling                 | 96 (43.05)                | 92 (44.02)             | 0.847 |
| ≤ 8 years of schooling                 | 127 (56.95)               | 117 (55.98)            |     |
| Marital status                         |                           |                        |     |
| Not single                             | 109 (48.88)               | 120 (57.42)            | 0.076 |
| Single                                 | 114 (51.12)               | 89 (42.58)             |     |
| Income†                                |                           |                        |     |
| Not low                                | 110 (49.33)               | 125 (59.81)            | 0.033 |
| Low                                    | 113 (50.67)               | 84 (40.19)             |     |
| **Clinical**                           |                           |                        |     |
| Comorbidities                          |                           |                        |     |
| No                                     | 71 (31.84)                | 42 (20.10)             | 0.006 |
| Yes                                    | 152 (68.16)               | 167 (79.90)            |     |
| HIV                                    |                           |                        |     |
| No                                     | 206 (92.38)               | 190 (90.91)            | 0.581 |
| Yes                                    | 17 (07.62)                | 19 (09.09)             |     |
| Alcoholism                             |                           |                        |     |
| No                                     | 155 (69.51)               | 154 (73.68)            | 0.336 |
| Yes                                    | 68 (30.49)                | 55 (26.32)             |     |
| Smoking status                         |                           |                        |     |
| Never smoker                           | 100 (44.84)               | 95 (45.45)             | 0.318 |
| Former smoker                          | 40 (17.94)                | 27 (12.92)             |     |
| Smoker                                 | 83 (37.22)                | 87 (41.63)             |     |
| Illicit drug use                       |                           |                        |     |
| No                                     | 188 (84.68)               | 173 (83.17)            | 0.670 |
| Yes                                    | 34 (15.32)                | 35 (16.83)             |     |
| Monitoring                             |                           |                        |     |
| Why did you seek a health care unit?   |                           |                        |     |
| Physician or family referral           | 87 (39.01)                | 96 (45.93)             | 0.146 |
| Self-referral                          | 136 (60.99)               | 113 (54.07)            |     |
| Adverse reactions to medications in the 2nd month |           |                        |     |
| No                                     | 151 (69.59)               | 71 (34.13)             | < 0.001 |
| Yes                                    | 66 (30.41)                | 137 (65.87)            |     |
| Treatment outcome                      |                           |                        |     |
| Cure                                   | 183 (82.06)               | 206 (98.56)            | > 0.001 |
| Abandonment                            | 40 (17.94)                | 3 (1.44)               |     |

*Values expressed as n (%). †In accordance with the Brazilian Federal Government criteria, families that have a monthly income per capita of up to half the minimum wage or a total family income up to three minimum wages are considered as having low income (minimum wage: R$1,045 [US$209 on 2020/01/07]). *Qui-square test.
alcohol abuse and/or illicit drugs use,\(^{(14,17)}\) smoking,\(^{(14,26)}\) and re-entry into treatment.\(^{(20,26)}\) Thus, the identification of these characteristics provides more precise strategies for reducing initial risks with the use of the SRTB instrument.

The interaction between people on the street and abusive use of alcohol and/or illicit drugs was evidenced, revealing a ten times greater chance of abandoning treatment (OR:10.769 \(p=0.002\)); being five times greater than the presence of only the variable abuse of alcohol and/or illicit drugs. Homeless people are recognized as one of the groups with the highest prediction of abandonment, especially when the use of associated licit and/or illicit drugs are identified.\(^{(27,31)}\) The SRTB mitigated the impact of all these interactions by targeting strategic interventions and organized in order to promote greater adherence to treatment, such as social support and care with a multidisciplinary team.

Several other factors are associated with non-adherence to TB treatment, such as ignorance about the disease and its treatment, stigma, absence of a psychosocial approach; interventions are recommended to address these determinants in the routine of services.\(^{(4,5,14,27)}\) Another predisposing cause of treatment abandonment is the improvement of...
The impact of the stratification by degree of clinical severity and abandonment risk of tuberculosis treatment symptoms in the second month of treatment, but this factor showed no associations with treatment abandonment in the present study, corroborating the findings of other authors.

In addition, no associations were found related to adverse reactions to medications, sex, or level of education. Patients monitored at other levels of care have lower adherence to treatment, in addition to the poor-quality health care services that enhance abandonment.

The limitations of the present study were the impossibility of interviewing patients with severe tuberculosis who died prior to the interview and the impossibility of interviewing those coinfected with HIV/AIDS, whose follow-up was carried out in secondary/tertiary referral centers.

In conclusion, the SRTB instrument was effective in reducing abandonment of tuberculosis treatment, even in the presence of one or more risk factors. The implementation of the SRTB instrument and the monitoring of the process of the explained recommendations and its application not only showed characteristics predisposing to non-adherence to treatment, but also established bases to mitigate its impact. The SRTB instrument organizes the levels of care by stratifying the cases, as well as demonstrating the need for a set of person-centered interventions to achieve greater treatment success. It is an instrument of easy and quick applicability that can be adapted to different realities, considering the potential of the local health network and available resources.

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Table 2. Multiple analysis of the characteristics related to the treatment dropout among the groups studied, Belo Horizonte, Minas Gerais, Brazil.

| Description                              | Number of risk factors | According to risk factors |
|------------------------------------------|------------------------|---------------------------|
|                                          | P-value                | OR (95% CI)               | P-value | OR (95% CI)               |
|                                          | 1 (reference)          | 1 (reference)             |         | 1 (reference)             |
| Group                                    |                        |                          |         |                          |
| A (non-intervention)                     | < 0,001                | 0,07 (0,02 - 0,23)       | < 0,001 | 0,07 (0,09 - 0,22)       |
| B (intervention)                         | 0,016                  | 6,52 (1,41 - 30,13)      | 0,068   | 4,07 (0,90 - 19,40)      |
| Self-reported race / skin color          |                        |                          |         |                          |
| White                                    | 1 (reference)          | 1 (reference)             |         | 1 (reference)             |
| Not white                                | 0,025                  | 0,42 (0,20 - 0,90)       | 0,009   | 0,34 (0,15 - 0,77)       |
| Directly Observed Treatment              |                        |                          |         |                          |
| Not                                      | 1 (reference)          | 1 (reference)             |         | 1 (reference)             |
| Yes                                      | 0,025                  | 0,42 (0,20 - 0,90)       | 0,009   | 0,34 (0,15 - 0,77)       |
| Number of risk factors                   |                        |                          |         |                          |
| None                                     | 1 (reference)          | 1 (reference)             |         | 1 (reference)             |
| 1 (one)                                  | 0,001                  | 4,38 (1,78 - 10,75)      |         | 0,015                    | 2,71 (1,22 - 6,05) |
| 2 (two)                                  | < 0,001                | 11,80 (3,80 - 36,79)     |         | 0,002                    | 10,77 (2,32 - 50,04) |
| ≥ 3 (three or more)                     | < 0,001                | 12,24 (3,84 - 39,02)     |         | 0,002                    | 12,24 (3,84 - 39,02) |
| Interaction: use of illicit drugs and/or alcohol and homeless | | 1 (reference) | | 1 (reference) |
| does not use illicit drugs and/or alcohol and is not homeless | | | | | |
| does not use illicit drugs and/or alcohol and is homeless | | | | | |
| uses illicit drugs and/or alcohol and is not homeless | | | | | |
| uses illicit drugs and/or alcohol and is homeless | | | | | |
| Income                                   |                        |                          |         |                          |
| Not low                                  | 1 (reference)          | 1 (reference)             |         |                          |
| Low                                      | 0,020                  | 0,99 (0,98 - 0,99)       |         | 0,018                    | 3,08 (1,21 - 7,80) |
| Retreatment for re-entry after abandonment|                      |                          |         |                          |
| Not                                      | 1 (reference)          | 1 (reference)             |         | 1 (reference)             |
| Yes                                      | 0,018                  | 3,08 (1,21 - 7,80)       |         | 0,018                    | 3,08 (1,21 - 7,80) |

(§) Two final models have been proposed. (***) In the study, none of the patients were on the street without using illicit drugs and/or alcohol, which is why it is not possible to estimate the OR of this class.
AUTHOR CONTRIBUTIONS

PDN: main author, study design and execution; analysis of results; scientific writing of the manuscript; and approval of the final version. JPAM: statistical analysis; scientific review of the article; and approval of the final version. JVR: study execution; analysis of results; scientific writing of the manuscript; and approval of the final version. CHLS: study execution; scientific review of the article; and approval of the final version. INA: study execution; analysis of results; scientific review of the article; and approval of the final version.

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2015 [cited 2020 Dec 2]. Implementing the End TB Strategy: The Essentials. [Adobe Acrobat document, 130p.]. Available from: https://www.who.int/tp/publications/2015/end_tb_essential.pdf

2. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [cited 2020 Dec 01]. Global tuberculosis report 2019. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-report-2019

3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Brasil Livre da Tuberculose: evolução dos cenários epidemiológicos e operacionais da doença. Brasília: Ministério da Saúde; 2019.

4. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [cited 2020 Dec 1]. Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). Available from: https://www.who.int/tb/publications/2017/guideline_2017/en/

5. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):e147-e195. https://doi.org/10.1093/cid/ciw276

6. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2003 [cited 2020 Dec 1]. Adherence to long-term therapies: evidence for action. Available from: https://www.who.int/chp/knowledge/publications/adherence_report/en/

7. Volmink J, Garner P. Interventions for promoting adherence to tuberculosis management. Cochrane Database Syst Rev. 2000;(4):CD000010. https://doi.org/10.1002/14651858.CD000010

8. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev. 2007;(4):CD003343. https://doi.org/10.1002/14651858.CD003343.pub3

9. Wurie FB, Cooper V, Horne R, Hayward AC. Determinants of non-adherence to treatment for tuberculosis in high-income and middle-income settings: a systematic review protocol. BMJ Open. 2018;8(11):e021927. https://doi.org/10.1136/bmjopen-2017-021927

10. Hopewell PC, Pai M, Maher D, Uplekar M, Raviglione MC. Patient adherence to tuberculosis treatment. Bull World Health Organ. 2007;85(5):404-406. https://doi.org/10.2165/10071200-000000000-00000

11. Oloso JCN, Reis-Santos B, Locatelli RL, Sales CMM, da Silva Filho WG, da Silva KC, et al. Effect of the Bolsa Família Programme on the outcome of tuberculosis treatment: a prospective cohort study. Lancet Glob Health. 2019;7(2):e219-e226. https://doi.org/10.1016/S2214-109X(18)30047-9

12. Madeira de Oliveira S, Altmayer S, Zanon M, Alves Sidney-Filho L, Schneider Moreira AL, de Tarso Dalcin P, et al. Predictors of noncompliance to pulmonary tuberculosis treatment: An insight from South America. PLoS One. 2018;13(9):e0202593. https://doi.org/10.1371/journal.pone.0202593

13. Casaburi SC, Soares EC, Pacheco AG, Chaisson RE, Durovni B; DOTS Expansion Team. Community DOT for tuberculosis in a Brazilian favela: comparison with a clinic model. Int J Tuberc Lung Dis. 2002;6(4):307-312. https://doi.org/10.1016/S1473-3099(06)70628-4

14. Migliori GB, Zelwege JP, Abukarim I, Eramo Camerino JA, De Vries G, et al. European union standards for tuberculosis care. Eur Respir J. 2012;39(4):807-819. https://doi.org/10.1183/09031994.00038111

15. Zhang H, Ehri J, Yang H, Tang S, Li Y. Impact of Community-Based DOT on Tuberculosis Treatment Outcomes: A Systematic Review and Meta-Analysis. PLoS One. 2016;11(2):e0147744. https://doi.org/10.1371/journal.pone.0147744

16. Pasipanodya JG, Gumbo T. A meta-analysis of self-administered vs directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients [published correction appears in Clin Infect Dis. 2013 Oct;57(8):1223]. Clin Infect Dis. 2013;57(1):21-31. https://doi.org/10.1093/cid/cit167

17. Toccó A, Cox H, du Cros P, Cooke G, Ford N. Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis. Int J Tuberc Lung Dis. 2013;17(3):299-307. https://doi.org/10.5888/ijtld.12.0537

18. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev. 2002;2:CD000011. https://doi.org/10.1002/14651858.CD000011

19. Loig KR, Sobel DS, Stewart AL, Brown BW, Jr, Bandura A, Ritter P, et al. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. Med Care. 1999;37(1):5-14. https://doi.org/10.1097/00005650-199901000-00003

20. Munro SA, Levin SA, Smith H, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med. 2007;4(7):e238. https://doi.org/10.1371/journal.pmed.0040238

21. Garner P, Smith H, Munro S, Volmink J. Promoting adherence to tuberculosis treatment. Bull World Health Organ. 2007;85(5):404-406. https://doi.org/10.2165/10071200-00000

22. Starfield B. Atenção Primária: Equilíbrio Entre Necessidades de Saúde, Serviços e Tecnologia. Brasília: UNESCO e Ministério da Saúde; 2002.

23. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Manual de Recomendações para o Controle da Tuberculose no Brasil. Brasília: Ministério da Saúde; 2018.

24. Mendes EV. As redes de atenção à saúde. 2nd ed. Brasília: Organização Pan-Americana de Saúde—Representação Brasili; 2011.

25. Sög D, Ham C. Improving Care for People with Long-term Conditions. A review of UK and International Frameworks. Birmingham: University of Birmingham (HSMC, Institute for Innovation and Improvement (NHS)); 2006.

26. Silva CHL. Proposta de implantação de um novo modelo de atenção ao paciente com tuberculose, estruturado em redes, como estratégia para fortalecer a estratégia dots - “directly observed therapy short-course” [dissertation] Lisbon: Instituto Universitário de Lisboa; 2010. Available from: http://hdl.handle.net/10071/2633

27. Fitzpatrick C, Floyd K. A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis [published correction appears in Pharmacoconomics. 2012 Jan;30(1):81]. Pharmacoconomics. 2012;30(1):63-80. https://doi.org/10.2165/1195340-000000000-00000

28. Silva CHL. Proposta de implantação de um novo modelo de atenção ao paciente com tuberculose, estruturado em redes, como estratégia para fortalecer a estratégia dots - “directly observed therapy short-course” [dissertation] Lisbon: Instituto Universitário de Lisboa; 2010. Available from: http://hdl.handle.net/10071/2633

29. Cavalcante SC, Soares EC, Pacheco AG, Chaisson RE, Durovni B; DOTS Expansion Team. Community DOT for tuberculosis in a Brazilian favela: comparison with a clinic model. Int J Tuberc Lung Dis. 2002;6(4):307-312. https://doi.org/10.1016/S1473-3099(06)70628-4

30. Snyder RE, Marlow MA, Phuphanich ME, Riley LW, Maciel EL. Risk factors for differential outcome following directly observed treatment (DOT) of slum and non-slum tuberculosis patients: a retrospective cohort study. BMC Infect Dis. 2016;16:494. https://doi.org/10.1186/s12879-016-1835-1

31. Cavalcante SC, Soares EC, Pacheco AG, Chaisson RE, Durowni B; DOTS Expansion Team. Community DOT for tuberculosis in a Brazilian favela: comparison with a clinic model. Int J Tuberc Lung Dis. 2007;11(5):544-549.

32. Müller AM, Ostrolo CS, Silva DR, Sbruzzi G, de Tarso P, Dalcin R. Interventions to improve adherence to tuberculosis treatment: systematic review and meta-analysis. Int J Tuberc Lung Dis. 2007;11(5):544-549.
31. Viegas AM, Miranda SS, Haddad JP, Ceccato MDG, Carvalho WDS. Association of outcomes with comprehension, adherence and behavioral characteristics of tuberculosis patients using fixed-dose combination therapy in Contagem, Minas Gerais, Brazil. Rev Inst Med Trop Sao Paulo. 2017;59:e28. https://doi.org/10.1590/s1678-9946201759028

32. Jenkins HE, Ciobanu A, Plesca V, Crudu V, Galusca I, Soltan V, et al. Risk factors and timing of default from treatment for non-multidrug-resistant tuberculosis in Moldova. Int J Tuberc Lung Dis. 2013;17(3):373-380. https://doi.org/10.5588/ijtld.12.0464

33. Kruk ME, Schwalbe NR, Aguiar CA. Timing of default from tuberculosis treatment: a systematic review. Trop Med Int Health. 2008;13(5):703-712. https://doi.org/10.1111/j.1365-3156.2008.02042.x

34. Rosser A, Richardson M, Wiselka MJ, Free RC, Woltmann G, Mukamolova GV, et al. A nested case-control study of predictors for tuberculosis recurrence in a large UK Centre. BMC Infect Dis. 2018;18(1):34. https://doi.org/10.1186/s12879-017-2933-4

35. Mhimbira FA, Cuevas LE, Dacombe R, Mkopi A, Sinclair D. Interventions to increase tuberculosis case detection at primary healthcare or community-level services. Cochrane Database Syst Rev. 2017;11(11):CD011432. https://doi.org/10.1002/14651858.CD011432.pub2