

# Treatment Outcomes and Predictive Factors for Multidrug-Resistant TB and HIV Coinfection in Rio De Janeiro State, Brazil

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## Research article

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# Abstract

**Background:** This study aims to identify and compare factors associated with the unfavorable treatment of MDR-TB patients with HIV coinfection in the State of Rio de Janeiro (RJ), Brazil.

**Methods:** A retrospective cohort study with data from TB-MDR patients notified between 2000 and 2016 in RJ. Clinical and epidemiological characteristics and treatment outcomes of patients with HIV positive, negative, and unknown were compared. Bivariate and multivariate Cox hazard regression analysis was conducted to identify factors associated with unfavorable treatment results in patients MDR-TB / HIV positive.

**Results:** Of 2,269 cases, 1,999 (88.1%) had a negative result for HIV, 156 (6.9%) positive and 114 (5.0%) unknown. The proportion of unfavourable outcomes was 43.7% among HIV negative, 52.6% among HIV positive and 43.9% among HIV unknown. Regarding MDR-TB / HIV positive cases, the unfavorable outcomes more prevalent were loss to follow up (24.4%) and death (23.1%). Previous MDR-TB treatment was associated with unsuccess and death. Illicit drugs use was a risk factor for unsuccess and loss to follow up. The six-month culture conversion was a protective factor for unsuccess and death. Administration of antiretroviral therapy was a protective factor for unsuccess, death and failure. The risk of XDR-TB cases for failure was six times higher than that of MDR-TB patients. All XDR-TB / HIV positive cases had unfavorable outcomes.

**Conclusions:** Early identification and immediate initiation of appropriate treatment are key to reducing unfavorable outcomes among MDR-TB / HIV positive. The high proportions of loss to follow-up and death may reflect difficulties in monitoring treatment, due to poor integration between the TB and HIV programs. In addition, none of XDR-TB / HIV positive patient had therapeutic success, highlighting the urgency to incorporate new drugs for the treatment of multidrug-resistant TB by Brazil's Ministry of Health.

## Background

Human Immunodeficiency Virus (HIV) infection and the growing number of drug-resistant tuberculosis (TB) patients constitute a significant challenge to the global elimination of TB. It is estimated that in 2018, 8.6% (range, 7.4–10%) of TB cases were among people living with HIV and 251 thousand deaths occurred in this group (1).

Treatment of multidrug-resistant tuberculosis (MDR-TB) (drug resistance at least isoniazid and rifampicin) and extensively drug-resistant tuberculosis (XDR-TB) (TB-MDR plus resistance to a fluoroquinolone and a second-line injectable drug) require the use of second-line drugs which are more expensive and more toxic for a longer period than drug-sensitive TB (2). In HIV-infected patients, treatment is even more challenging. There may be additional comorbidities and opportunistic infections, ingestion of more pills resulting from the co-administration of antituberculosis drugs and antiretroviral therapy (ART), potential additive side effects, and drug interactions (3).

Brazil ranks 20th worldwide in TB cases and 19th in terms of TB-HIV coinfection, being one of the 30 countries considered priority by the World Health Organization (WHO) for TB elimination in the world (1). The State of Rio de Janeiro (RJ), one of Brazil's most developed subnational units, stands out for having a poor performance in TB control. It has the second-highest incidence and mortality rates in the country, which in 2018 were 63.3 and 4.2 per 100 thousand inhabitants, respectively (4). Therefore, a better understanding of the association between HIV infection and MDR-TB is certainly needed.

That said, this work aims to identify the factors associated with the unfavorable treatment of MDR-TB in patients with HIV coinfection in RJ. The paper will also consider failure, death and loss of follow-up as specific unfavorable outcomes.

## Methods

### Research design and data

Retrospective cohort study based on secondary data of patients who started treatment for MDR-TB between 2000 and 2016. The cohort was extracted from the Special Tuberculosis Treatment Information System (SITETB). SITETB is an electronic information system of the Ministry of Health (MoH) of Brazil, used for the compulsory notification and follow-up of all TB cases unable to use the standard TB regimen (2RHZE/4RH) (5).

The CD4, CD8 cell counts and viral load copies/ml, performed before or during the first month of treatment for MDR-TB, were collected from the AIDS Laboratory Database (SISCEL) or patients' medical records. ART data were collected from the Antiretroviral Control System Database (SICLOM) or medical records. An additional file shows the data in more detail [see Additional file 1].

### Treatment of MDR-TB and HIV/AIDS

Brazil has a good record of treating HIV/AIDS and TB. The MoH has been distributing medicines for the prophylaxis and treatment of infections since the mid-1980s. A federal law enacted in 1996 guaranteed the right of all individuals with HIV/AIDS to receive medicines free of charge. Regarding antituberculosis drugs, since the 1960s distribution has been free in the country. TB cases diagnosed in the private sector are referrals to the public sector. Private pharmacies do not offer first or second-line TB drugs. Medicines are ordered and purchased centrally by the MoH. Since 2000 the MoH has developed specific epidemiological actions for MDR-TB, with a protocol for treatment, notification and monitoring of drug resistance cases.

HIV/Aids and MDR-TB are treated and monitored separately. In Brazil, health units are classified according to their complexity. In primary health care (PHC), patients with TB are treated using a basic regimen, as well as those with minor adverse reactions. TB-HIV cases are treated at the secondary level, along with patients with severe adverse reactions, including hepatotoxicity. Patients with drug-resistant and seriously ill TB are treated at the tertiary level, which is composed of hospitals and outpatient referral centers (6).

An HIV positive patient diagnosed with MDR-TB is referred to outpatient referral services for specialist evaluation. An anti-HIV test is performed in PHC and should be offered to every patient diagnosed with TB, regardless of its presentation (pulmonary or extrapulmonary).

Until 2014, the treatment of HIV/AIDS infection was performed mainly at the secondary level. From 2014 onwards, the treatment of HIV/AIDS with low risk began to be decentralized for PHC. For patients with MDR-TB, guidance for treatment shared among specialists remained.

In active tuberculosis, the onset of ART was indicated around 30 days after starting TB treatment, regardless of the result of the CD4 count (7,8). In 2013 patients with CD4 < 200 cells/mm<sup>3</sup> or with signs of advanced immunodeficiency have to start ART within two weeks after starting treatment for TB (9). Since 2017 this

recommendation is for patients with CD4 < 50 cells/mm. In other patients, ART should begin on the 8th week. Concomitant initiation of treatment for both conditions is not recommended (10).

### **Outcomes: definition of key terms**

Treatment outcomes were classified according to WHO recommendations (11). The former are mutually exclusive. "Cure" occurs when the patient has at least three negative cultures after the 12th month of treatment. "Complete treatment" is the case when the patient has completed the stipulated time for treatment, with favorable clinical and radiological evolution, but without the accompanying cultures. "Loss of follow-up" takes place when the treatment was interrupted for 2 consecutive months or more. "Failure" is the outcome if the patient had two or more positive cultures in three recommended ones after the 12th month of treatment or three consecutive positive cultures after the 12th month of treatment, at least 30 days apart. Failure can also be the case according to medical evaluation and decision to change treatment early due to clinical and radiological worsening. "Death" is the outcome whenever the patient died for any reason during treatment. The "unfavorable" outcome is the sum of patients who had results classified as death, failure or loss of follow-up. "Success" of treatment is the sum of patients who had the result classified as complete cure and treatment.

### **Independent variables**

The following variables were included in the regression analyses: sex, being under 37 years old, having less than 8 years of schooling, race/color, diabetes, comorbidities (viral hepatitis, renal failure, neoplasia, silicosis, transplant, mental disorder, use long-term use of corticosteroids, users of TNF alpha inhibitors, seizures and other undefined drugs, use of illicit drugs, alcohol dependence, smoking, unemployment, drug resistance category (MDR-TB or XDR-TB), treatment regimen (standardized or individualized), type of drug resistance (primary, that is, patients with no history of previous treatment; or acquired, that is, patients already treated for TB for one month or more) (12), disease extension (presence of chest cavity and/or bilateral disease), previous MDR-TB treatment, use of ART, and six-month culture conversion (defined as those patients with at least two negative cultures by the sixth month of treatment).

The standardized treatment regimen for MDR-TB is recommended and applied in Brazil and must include at least one first-line oral drug, if susceptible, a fluoroquinolone, an injectable drug along with terizidone. Individualized regimens may include other drugs, such as clofazimine, linezolid, imipenem and isoniazid in high doses. They are restricted to patients with additional resistance to first-line drugs, pre-XDR, XDR-TB, and to patients who have had adverse events with standardized regimen (7).

Patients who had more than one treatment for MDR-TB registered with SITETB were considered to have had previous treatment for MDR-TB.

Only variables that had a maximum of 10% of missing values were selected. For this reason, the results of counting CD4, CD8 and HIV viral load were only described.

### **Statistical methods**

Given the nature of the dependent variable, number (frequency) and median (interquartile range [IQR] 25% -75%) were used to describe the characteristics of the patients and the treatment outcome according to coinfection status (TB-MDR HIV negative, positive and unknown). Treatment outcomes were also described according to the

drug resistance pattern (MDR or XDR-TB), and coinfection. The chi-square test ( $\chi^2$ ) or Fisher's exact test were used to compare the proportions between groups.

Cox proportional hazards models were implemented to estimate hazard rates (HR) between each of the treatment outcomes and the covariates in the MDR-TB HIV positive patient group. Variables with significance levels  $\leq 0.20$  in the bivariate analysis were included in the multivariate model. The better adjusted model was chosen using the likelihood ratio test. A significance level of 0.05 was applied to all tests. The statistical analysis was conducted with STATA version 13.1 program.

## Results

### Descriptive Analysis

Between 2000 and 2016, 2,477 cases of MDR-TB were reported in RJ, with 208 cases excluded: 8 non-residents in RJ, 11 undergoing treatment, 3 unknown results, 11 changes in diagnosis and 175 drug-susceptibility testings not indicating resistance to, at least, rifampicin and isoniazid. Of the total of 2,269 cases, 1999 (88.1%) had a negative result for HIV, 156 (6.9%) positive and 114 (5.0%) unknown. There were 1466 (64.6%) male patients. Table 1 describes the sociodemographic and clinical variables relating to MDR-TB patients with HIV positive, negative, and unknown results.

Overall, the median age was 38 (IQR 28-49) years, whereas among HIV positive patients, the median was 37 (IQR 30-45). HIV positive cases also stand out for having 14.7% of cases with extrapulmonary or pulmonary/extrapulmonary MDR-TB, while in the HIV negative and unknown group they had, respectively, 1.3% and 2.6%. In addition, HIV positive patients had a higher percentage of comorbidities (14.1% [excluding diabetes]) than patients with negative and unknown HIV (11.9% and 11.4%). The groups with negative and unknown HIV had more cases with diabetes, 9.8% and 14.9%, respectively, than the group with HIV positive, which had 3.2%. Among the 22 HIV positive patients with comorbidities, the most prevalent types were viral hepatitis, mental disorder, neoplasia, and depression.

Unemployment was frequent within the groups, with 307 cases (15.4%) within HIV negative cases, 42 (26.9%) within HIV positive and 24 (27.0%) within unknown HIV. The use of illicit drugs was reported in 30 (19.2%) HIV positive patients, a higher percentage than among HIV negative and unknown patients, 6.9% and 10.5% respectively.

Among the 156 HIV positive patients, 137 (87.8%) already had a diagnosis of HIV when they started MDR-TB treatment, 117 (75%) had a CD4 record, and 88 (56.4%) had a CD8 record available. The median of CD4 was 311 cells/mm<sup>3</sup> (IQR 141-497), while the median of CD8 was 840.5 cells/mm<sup>3</sup> (IQR 520.5-1204.5). HIV viral load was available in 65 (41.6%) records, with a median of 8166 copies/ml (IQR 903-37,000). As for ART, 85 (66.4%) had a treatment record during the treatment of MDR-TB.

Table 1. Demographic and clinical characteristics of 2,269 MDR-TB patients by HIV status

Characteristics	HIV negative (%) N=1999	HIV positive (%) N=156	HIV unknown (%) N=114	p-value*
Sex	670 (34.8)	61 (39.1)	47 (41.2)	0.226
Female	1304 (65.2)	95 (60.9)	67 (58.8)	<0.001
Male	316 (15.8)	11 (7.1)	18 (15.8)	0.155
Age Range	975 (48.7)	104 (66.7)	47 (41.2)	0.296
0 - 24	635 (31.7)	40 (25.6)	41 (36.0)	<0.001
25 - 44	74 (3.7)	1 (0.6)	8 (7.0)	0.004
45 - 64	730 (36.5)	44 (28.2)	42 (36.8)	0.399
≥65	1198 (60.0)	106 (68.0)	68 (59.6)	<0.001
Ethnical group	71 (3.5)	6 (3.8)	4 (3.5)	0.477
Caucasian	95 (4.7)	13 (8.3)	5 (4.4)	<0.001
Afro-Brazilian	379 (19.0)	31 (19.9)	20 (17.5)	0.695
Unknown	771 (38.6)	65 (41.7)	43 (37.7)	<0.001
Years of study	437 (21.9)	24 (15.4)	30 (26.3)	<0.001
None	153 (7.6)	7 (4.5)	6 (5.3)	0.725
1 a 3	164 (8.2)	16 (10.2)	10 (8.8)	0.026
4 a 7	9 (0.5)	10 (6.4)	1 (0.9)	0.098
8 a 11	1974 (98.7)	133 (85.3)	111 (97.4)	0.084
≥12	16 (0.8)	13 (8.3)	2 (1.7)	0.019
Ignored	197 (9.8)	5 (3.2)	17 (14.9)	0.037
Site of disease	243 (12.2)	14 (9.0)	16 (14.0)	
Extrapulmonary	138 (6.9)	30 (19.2)	12 (10.5)	
Pulmonary	170 (8.5)	10 (6.4)	12 (10.5)	
Both	307 (15.4)	42 (26.9)	24 (27.0)	
Other factors	237 (11.9)	22 (14.1)	13 (11.4)	
Diabetes	1586 (82.0)	99 (68.3)	87 (78.4)	
Alcohol abuse	1478 (76.4)	108 (74.5)	62 (56.4)	
Illicit Drug use	298 (14.9)	22 (14.1)	14 (12.3)	
Smoking	1701 (85.1)	134 (85.9)	100 (87.7)	
Unemployed	1550 (77.5)	118 (75.6)	76 (66.7)	
	449 (22.5)	38 (24.3)	38 (33.3)	

Comorbidities <sup>†</sup>	1126 (56.3)	74 (47.4)	64 (56.1)
Chest radiography (n=2189)	368 (18.4)	38 (24.4)	27 (23.7)
Cavitation	295 (14.8)	36 (23.1)	16 (14.0)
Bilateral	210 (10.5)	8 (5.1)	7 (6.1)
Drug Resistance type			
Primary			
Acquired			
Previous MDR-TB treatment			
No			
Yes			
Outcomes			
Cured/Treatment completed			
Lost to follow up			
Died			
Failed			

TB: tuberculosis; MDR-TB: multidrug-resistant TB; XDR-TB: extensively drug-resistant TB;

HIV: human immunodeficiency virus.

\*Comparison between HIV negative, positive and unknown.

<sup>†</sup> Except Diabetes and HIV.

In general, 1,005 (44.3%) patients had unfavorable outcomes, being more frequent among HIV positive patients (52.6%) than in HIV negative cases (43.7%), and in HIV unknown (43.9%). The most frequent variable associated with unfavorable treatment was lost to follow up, which occurred in 38 (24.4%) cases with HIV positive, and in 395 (18.4%) with HIV negative. Death affected 36 (23.1%) of HIV positive cases, and 295 (14.8%) of HIV negative. Failure was twice as high among HIV negative patients (10.5%) as among HIV positive patients (5.1%).

### Drug resistance and treatment outcomes

Upon analysis of treatment outcomes by HIV status and drug resistance (see Table 2), MDR or XDR-TB, it was observed that MDR-TB patients, regardless of HIV serological status, have more therapeutic success. The success among XDR-TB HIV negative/unknown cases was only 20.8%, while, in the same period, there was no case of therapeutic success among XDR-TB HIV positive cases. Death was more frequent in HIV positive, especially in XDR-TB patients, while failure was practically the same among XDR-TB groups, but it was lower among MDR-TB HIV positive (2.8%) than among MDR-TB HIV negative cases (8.5%).

Table 2: Treatment outcomes among 2,269 patients with MDR-TB and XDR-TB by HIV status

Outcomes	HIV Negative/Unknown		HIV Positive			
	MDR	XDR	p-value*	MDR	XDR	p-value*
	(n= 1983)	(n= 130)		(n= 145)	(n=11)	
Cure/treatment completed	1163 (58.6)	27 (20.8)	<0.001	74 (51.0)	0 (0.0)	0.001
Lost to follow up	379 (19.1)	16 (12.3)	0.054	35 (24.1)	3 (27.3)	0.815
Died	273 (13.8)	38 (29.2)	<0.001	32 (22.1)	4 (36.4)	0.278
Failed	168 (8.5)	49 (37.7)	<0.001	4 (2.8)	4 (36.4)	<0.001

TB: tuberculosis; MDR-TB: multidrug-resistant TB; XDR-TB: extensively drug-resistant TB;

HIV: human immunodeficiency virus.

\*Comparison between MDR/XDR-TB.

Among HIV positive patients who did not undergo ART, half died within the first 180 days after starting treatment for MDR-TB, while among those who did ART, the time span was 510 days. These patients were treated with a median of 5 drugs. The most common initial regimens included amikacin (65%), streptomycin (28%), ethambutol (92%), clofazimine (25%), terizidone (95.5%), pyrazinamide (55%), ofloxacin (47%) and levofloxacin (44%).

#### **Factors associated with treatment outcomes in MDR-TB patients with HIV coinfection in the bivariate model**

Bivariate analyses of the factors associated with unsuccessful, loss to follow up, death and failure for HIV-positive MDR-TB patients are displayed in table 3. Unsuccessful was more likely among illicit drug users (HR 1.64, 95% CI 1.01-2.70), the unemployment (HR 1.73, 95% CI 1.08-2.75), and patients with previous MDR-TB treatment (HR 1.97, 95% CI 1.22-3.19). Six-month culture conversion (HR 0.50, 95% CI 0.29-0.87) and receiving ART (HR 0.61, 95% CI 0.39-0.95) were protective factors for unsuccessful. The loss to follow up was associated with the use of illicit drugs (HR 3.59, 95% CI 1.87-6.90), alcohol abuse (HR 2.30, 95% CI 1.05-5.05), and being unemployed (HR 2.08, 95% CI 1.07-4.01). Risk factors for treatment failure were previous MDR-TB treatment (HR 5.13, 95% CI 1.23-21.41), and being XDR-TB (HR 6.47, 95% CI 1.49-28.0), while ART (HR 0.16, 95% CI 0.03-0.80) was a protective factor. For death, six-month culture conversion (HR 0.19, 95% CI 0.05-0.63) and ART (HR 0.37, 95% CI 0.18-0.73) were protective factors.

Table 3. Bivariate analysis: Predictors of unsuccessful, default and death among 156 MDR-TB HIV positive patients

Predictors	Unsuccess	Loss to follow up	Death	Failure
	HR (95% CI) <i>p</i> -value			
Sex	1.0	1.0	1.0	1.0
Female	0.89 (0.57–1.39) 0.621	0.84 (0.44-1.62) 0.622	1.05 (0.53-2.10) 0.875	0.62 (0.15-2.50) 0.508
Male	1.0	1.0	1.0	1.0
<40 years	1.35 (1.07-3.52) 0.186	1.66 (0.86-3.29) 0.127	2.16 (0.83-5.59) 0.112	2.78 (0.34-22.6) 0.339
No	1.0	1.0	1.0	1.0
Yes	1.0	1.0	1.0	1.0
Years of schooling	1.16 (0.63-2.13) 0.619	1.10 (0.47-2.53) 0.819	1.19 (0.45-3.16) 0.717	1.64 (0.19-13.7) 0.646
≥ 8	1.0	1.0	1.0	1.0
< 8	1.22 (0.73-2.01) 0.438	1.39 (0.66-2.96) 0.381	0.91 (0.44-1.89) 0.811	3.66 (0.44-30.0) 0.227
Afro-Brazilian	1.0	—	1.0	—
No	1.0	—	1.0	—
Yes	0.26 (0.03-1.91) 0.188	1.0	0.63 (0.08-4.68) 0.656	—
Diabetes	1.0	1.39 (0.61-3.17) 0.431	1.0	1.0
No	1.12 (0.60-2.07) 0.717	1.0	1.09 (0.42-2.84) 0.849	1.79 (0.35-8.99) 0.476
Yes	1.0	3.59 (1.87-6.90) <0.001	1.0	1.0
Comorbidities	1.64 (1.01-2.70) 0.048	1.0	0.40 (0.12-1.36) 0.142	1.91 (0.22-16.08) 0.548
No	1.0	2.30 (1.05-5.05) 0.037	1.0	—
Yes	1.0	1.0	1.0	1.0
Illicit drug use	1.26 (0.67-2.37) 0.468	1.0	0.42 (0.10-1.81) 0.251	1.87 (0.44-7.86) 0.390
No	1.0	1.90 (0.74-4.89) 0.182	1.0	1.0
Yes	1.12 (0.48-2.58) 0.788	1.0	0.45 (0.06-3.31) 0.434	0.25 (0.03-2.05) 0.198
Alcohol abuse	1.0	2.08 (1.07-4.01) 0.029	1.0	1.0
No	1.73 (1.08-2.75) 0.020	1.0	1.28 (0.61-2.70) 0.498	1.0
Yes	1.0	0.92 (0.46-1.83) 0.820	1.0	0.18 (0.03-0.91) 0.038
Smoking	1.0	1.0	1.0	1.0
No	0.50 (0.29-0.87) 0.015	1.0	0.19 (0.05-0.63) 0.007	1.30 (0.16-10.63) 0.803
Yes	1.0	1.31 (0.64-2.66) 0.446	1.0	1.0
Unemployed	1.05 (0.66-1.67) 0.823	1.0	1.24 (0.60-2.55) 0.551	0.86 (0.20-3.62) 0.841
No	1.0	1.0	1.0	1.0
Yes	1.0	1.0	1.0	1.0

Six-month culture conversion	1.0	1.52 (0.54-4.31) 0.424	1.0	—
No	1.34 (0.67-2.70) 0.400	1.0	1.22 (0.42-3.49) 0.705	1.0
Yes	1.0	1.53 (0.72-3.27) 0.264	1.0	5.13 (1.23-21.41) 0.025
Treatment regimen	1.09 (0.67-1.75) 0.719	1.0	0.89 (0.44-1.80) 0.755	1.0
Individualized	1.0	0.91 (0.44-1.90) 0.815	1.0	6.47 (1.49-28.0) 0.013
Standardized	1.17 (0.68-2.05) 0.558	1.0	1.21 (0.52-2.80) 0.652	1.0
Drug Resistance type	1.0	1.75 (0.87-3.51) 0.110	1.0	0.16 (0.03-0.80) 0.026
Primary	1.97 (1.22-3.19) 0.005	1.0	1.73 (0.81-3.67) 0.154	
Acquired	1.0	1.10 (0.34-3.61) 0.864	1.0	
Chest radiography	1.60 (0.83-3.08) 0.156	1.0	1.24 (0.43-3.61) 0.683	
No cavitation	1.0	1.04 (0.52-2.07) 0.909	1.0	
Cavitation	0.61 (0.39-0.95) 0.029		0.37 (0.18-0.73) 0.004	
Unilateral				
Bilateral				
Previous MDR-TB Treatment				
No				
Yes				
Categories of drug resistance				
MDR-TB				
XDR-TB				
ART				
No				
Yes				

TB: tuberculosis; MDR-TB: multidrug-resistant TB; XDR-TB: extensively drug-resistant TB

HR: hazard rates; CI: confidence interval

HIV: human immunodeficiency virus

ART: antiretroviral therapy

† Except Diabetes and HIV

**The multivariate model: Factors associated with treatment outcomes in MDR-TB patients with HIV coinfection**

In the final model, having previous MDR-TB was associated with unsuccessful (HR 1.91 CI 95% 1.18-3.09 p = 0.008), and death (HR 2.99 CI 95% 1.22-7.31 p = 0.016). Use of illicit drugs was associated with unsuccessful (HR 1.63 CI 95% 0.98-2.71 p = 0.055) and had three times more risk of loss to follow up (HR 3.25 CI 95% 1.67-6.31 p = 0.001). Being XDR-TB had six times more risk than MDR-TB for failure (HR 6.11 CI 95% 1.41-26.32 p = 0.015). Six-month culture conversion was a protective factor for unsuccessful (HR 0.46 CI95% 0.26-0.80 p = 0.007) and death (HR 0.30 CI95% 0.08-1.03 p = 0.056), while ART was a protective factor for unsuccessful (HR 0.58 CI95% 0.37-0.91), death (HR 0.38 CI95% 0.16-0.92 p = 0.034), and failure (HR 0.15 CI 95% 0.03-0.78 p = 0.024) (Table 4).

Table 4. Multivariate analysis: Predictors of unsuccessful, default and death among 157 patients with HIV positive.

Predictors	Unsuccess	Loss to follow up	Death	Failure
	HR (95% CI) <i>p</i> -value			
Illicit drug use	1.0	1.0	1.0	1.0
No	1.83 (1.10-3.04) 0.019	3.25 (1.67-6.31) 0.001	0.29 (0.85-0.99) 0.050	6.11 (1.41-26.32) 0.015
Yes	1.0		1.0	1.0
Six-month culture conversion	0.49 (0.28-0.85) 0.012		3.14 (1.26-7.77) 0.013	0.15 (0.03-0.78) 0.024
No	1.0		1.0	
Yes	1.81 (1.11-2.95) 0.016		0.38 (0.15-0.93) 0.035	
Previous MDR-TB Treatment	1.0			
No	0.58 (0.37-0.91) 0.018			
Yes				
Categories of drug resistance				
MDR-TB				
XDR-TB				
ART				
No				
Yes				

TB: tuberculosis; MDR-TB: multidrug-resistant TB; XDR-TB: extensively drug-resistant TB;

HR: hazard rates; CI: confidence interval

HIV: human immunodeficiency virus.

ART: antiretroviral therapy

## Discussion

In the present study, unfavorable outcomes were more frequent among HIV positive patients (52.6%) than among HIV negative cases (43.7%), and HIV unknown (43.9%). Lost to follow up (24.4%) and death (23.1%) were the unfavorable outcomes more frequently found among patients MDR-TB HIV positive. The use of illicit drugs and previous MDR-TB treatment were risk factors for unsuccess. ART and six-month culture conversion were protective factors. All of XDR-TB/HIV positive cases had an unfavorable outcome.

Among the 2,269 cases analyzed, the proportion of MDR-TB/HIV coinfection was 6.9%. In 2016, according to MoH, the national rate of HIV coinfection among new TB cases was 9.4%. In the same year, the proportion for the state of RJ was 8.7% (13). There is little data on MDR-TB/HIV coinfection in Brazil. In a study conducted with MDR-TB patients from all over the country, 9% of coinfection was observed (14), while another study conducted in a reference hospital in the city of São Paulo found 4% (15).

In general, in the present study, it was observed a therapeutic success rate of 56.3% among MDR-TB HIV negative cases and 47.4% among HIV positive cases. Recently, in a meta-analysis with 271 publications, including 3,368 MDR-TB HIV positive participants from Sub-Saharan Africa, treatment success was 44.8% (16).

Regarding unfavorable treatment outcomes, loss of follow-up was higher among HIV positive cases (24.4%) than among HIV negative cases (18.4%). According to WHO, the Americas has the highest proportion of cases with loss of follow-up, with 26% among MDR and rifampicin-resistant TB cases, while at the global level it is 14% (17). Although treatment is free of charge for both TB and HIV/AIDS in Brazil, the treatment generates extra costs such as food and access to services that consume a significant percentage of the income of the poorest patients (18). In addition, the scenario is aggravated by the barriers encountered by TB patients in accessing social protection measures. A study conducted with patients at a referral center for the MDR-TB treatment showed that only 38% of the participants reported being beneficiaries of social protection (19). A meta-analysis of low- and middle-income countries showed that social protection measures are associated with successful treatment and reduced lost of follow-up, in addition to being associated with a lower risk of impoverishment (20).

In our study, being an illicit drugs user (IDU) was a risk factor for treatment failure (HR 1.83 95% CI 1.10-3.04  $p = 0.019$ ), and generated three times more risk for loss of follow-up (1.67-6.31  $p = 0.001$ ). Although there is no specification on the type of drug, several studies have described the association between TB, HIV, and the illicit drugs use, whether injectable or not (21-25). Illicit drug use is often associated with other risk factors for TB, such as smoking, alcohol abuse, and incarceration (26). Thus, important additional barriers remain in the treatment of TB in this group. Therefore, Illicit drug users have more difficulty completing medical evaluations or adhering to Treatment for TB (3) and, when symptomatic, tend to wait longer to start appropriate treatment (27). A study conducted in the United States of America showed that, at the time of AIDS diagnosis, patients with a history of injecting drugs were 3.5 times more likely (95% CI 1.3-10.2) to have an opportunistic infection, including TB (28). This suggests that there is a lower demand for health care among IDUs, which, by its turn, can lead to more severe illnesses and contribute to an increase in TB transmission rates (29).

The challenge of maintaining high levels of adherence among IDUs highlights the current challenges facing TB elimination, which may require the provision and coordination of TB and Mental Health services with experience in handling illicit drug users, including targeted testing and treatment (30).

The proportion of death among MDR-TB HIV positive patients (23.1%) was also higher than among HIV negative cases (14.8%). Several studies report higher mortality and lower mean survival among MDR-TB HIV positive patients as compared to those without infection (31-34). A meta-analysis that included 22 studies showed that MDR-TB HIV positive patients had 1.6 times (95% CI: 1.38–1.99; I<sup>2</sup> = 74%, p <0.001) more risk of death than HIV negative. The same study also showed that unfavorable outcome among people living with HIV is greater in low-income regions (RR 2.23, 95% CI 1.60-3.11) than in high-income regions (RR 1.22, 95% CI 0.97-1.53) (30). This indicates that socio-environmental issues and lack of access to health care can increase the vulnerability of this group.

In this study, the median of CD4 had a lower count than 350 cells/mm<sup>3</sup>. This suggests late access for these patients to health services, reflecting on a greater chance of death. The late diagnosis of TB, inadequate management of MDR-TB, and limitations on access to ART are factors that contribute to a higher mortality rate in this group (35). However, early identification and the immediate initiation of appropriate anti-TB treatment and ART can reduce unfavorable outcomes among MDR-TB HIV positive patients (36). In the present study, ART was a protective factor against unsucces (HR 0.58 CI95% 0.37-0.91), death (HR 0.38 CI95% 0.16-0.92 p = 0.034), and especially for failure (HR 0.15 CI 95% 0.03-0.78 p = 0.024), showing that ART contributes to the reduction of unfavorable outcomes in patients with MDR-TB living with HIV.

Six-month culture conversion was also a protective factor against unsucces (HR 0.46 CI95% 0.26-0.80 p = 0.007) and death (HR 0.30 CI95% 0.08-1.03 p = 0.056). In studies with MDR-TB patients, it was observed that conversion status at six-month was significantly associated with treatment success as compared to failure or death. Among patients with successful treatment, the median time to culture conversion was significantly less than among those who had unfavorable results (37).

Finally, being XDR-TB HIV positive had six times more risk for failure (95% CI 1.41-26.32 p = 0.015) than MDR-TB. None of the XDR-TB/HIV cases was successfully treated. The high rates of failure and death (36.4% each) within this group also reflect therapeutic limitations. This shows us the urgent need of the incorporation of new drugs by the MoH for the treatment of multidrug resistance. Likewise, issues related to the treatment and monitoring of patients must also be addressed.

In RJ, MDR-TB and HIV treatments are carried out in different health units, and the surveillance systems of the two diseases are not linked. This makes it difficult to monitor treatment and adverse events. Given the long duration of MDR/XDR treatment (18–24 months) and the large number of pills needed for concomitant treatment, close monitoring by healthcare professionals is necessary. Co-management of patients using ART and MDR/XDR drugs is complex and, therefore, it is essential that health professionals are trained to recognize potential and additive toxicity due to concomitant regimens.

In addition, measures at health services must be taken in order to promote the patient's commitment and adherence. Careful monitoring of patients is necessary to ensure that adverse effects are recognized quickly.

Finally, the present study has some limitations. As data were collected retrospectively, there was a lot of missing data on CD4, CD and HIV viral load. Besides, it was not possible to determine the period for starting ART. Also, due to the reduced number of records, it was not possible to assess the adverse events within the group of MDR/XDR HIV positive and their possible relationship with unfavorable outcome. Another fact that needs to be highlighted is that in the SITETB database, until 2015, variables related to diabetes, comorbidities, illicit drugs use, alcohol

dependence, and smoking, whenever classified as "no," can also mean an absence of information. There is also no standardization for the classification of alcohol dependence, smoking, and mental health disorders. At any rate, the statistical findings reported here are robust due to the large sample size on which they are based.

## Conclusion

The unfavorable results for MDR-TB HIV positive patients in RJ in 2000-2016 were associated with the illicit drugs use and previous treatment for MDR-TB. Six-month culture conversion and use of ART were protective factors. This shows, on the one hand, that early identification and immediate initiation of appropriate treatment can reduce unfavorable outcomes among MDR-TB HIV positive patients. On the other, the high proportions of loss to follow-up (24.4%) and death (23.1%) may reflect difficulties in monitoring treatment, given the lack of integration between the TB and HIV programs. In addition, the fact that none of XDR-TB HIV patient had therapeutic success reflects the limitation of treatment options, and the urgency of Brazil's health system to incorporate new drugs in the treatment of multidrug resistance.

## Abbreviations

HIV: Human Immunodeficiency Virus

TB: tuberculosis

MDR-TB: multidrug-resistant tuberculosis

XDR-TB: extensively drug-resistant tuberculosis

CI: confidence interval

ART: antiretroviral therapy

WHO: World Health Organization

RJ: State of Rio de Janeiro

SITETB: Special Tuberculosis Treatment Information System

MoH: Ministry of Health

SISCEL: AIDS Laboratory Database

SICLOM: Antiretroviral Control System Database

PHC: primary health care

IQR: interquartile

HR: hazard rates

IDU: illicit drugs user

# Declarations

## Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee of the Federal University of Rio de Janeiro (CAAE 10126919.2.0000.5257), which granted permission for the use of the data appropriate for the purposes of the study, and waived the participants' written informed consent because the study was based on secondary data. All patients had an identification number and, to protect patients' confidentiality, only one investigator had access to the identified codes and prepared the anonymous database used in this study.

## Consent for publication

Not applicable.

## Availability of data and materials

The dataset supporting the conclusions of this article is included within the article and its Additional file 1.

## Competing interests

The authors declare that they have no competing interests.

## Funding

Not applicable.

## Authors' contributions

MB and AF conceptualized and designed the study; RD contributed to the study methodology and interpretation of results; MB did the analysis and wrote the manuscript. All authors critically reviewed it. All authors read and approved the final manuscript.

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