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Treatment outcomes and predictive factors for multidrug-resistant TB and HIV coinfection in Rio de Janeiro State, Brazil

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SUMMARY

BACKGROUND: Brazil ranks 14th worldwide in the number of TB cases and 19th in terms of TB-HIV coinfected cases. This study aims at identifying clinical and demographic factors associated with unsuccessful treatment outcomes (loss to follow-up, treatment failure and death) of HIV-positive patients with multidrug-resistant TB (MDR-TB) in Rio de Janeiro State, Brazil.

METHODS: This was a retrospective cohort study of MDR-TB cases notified from 2000 to 2016 in RJ. Cox proportional hazard regression models were used to assess risk factors associated with unsuccessful treatment in HIV-positive patients with MDR-TB.

RESULTS: Among 2,269 patients, 156 (6.9%) were HIV-positive and had a higher proportion of unsuccessful treatment outcomes (52.6%) than HIV-negative cases (43.7%). All HIV-positive cases with extensively drug-resistant TB (XDR-TB) had unsuccessful treatment outcomes. Multivariate analysis shows that previous MDR-TB treatment (HR 1.97, 95% CI 1.22–3.18) and illicit drugs use (HR 1.68, 95% CI 1.01–2.78) were associated with a greater hazard of unsuccessful treatment outcomes, while 6-month culture conversion (HR 0.48, 95% CI 0.27–0.84) and use of antiretroviral therapy (ART) (HR 0.51, 95% CI 0.32–0.80) were predictors of reduced risk.

CONCLUSIONS: Unsuccessful treatment was higher among HIV patients with MDR-TB than among HIV-negative patients. Prompt initiation of ART and effective interventions are necessary to improve treatment adherence and prevent retreatment cases.

KEY WORDS: treatment outcome; risk factors; surveillance epidemiologic

HIV infection and the growing number of drug-resistant TB isolates in patients constitute a significant challenge to the global elimination of TB. It is estimated that in 2019, 8.2% of TB cases were among people living with HIV and 208,000 deaths occurred in this group.[1]

Treatment of multidrug-resistant TB (MDR-TB; defined as drug resistance to at least isoniazid and rifampicin) and extensively drug-resistant TB (XDR-TB; defined as MDR-TB 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-susceptible TB.[2] Treatment of HIV-infected patients is even more challenging. There may be additional comorbidities and opportunistic infections, ingestion of more pills resulting from the co-administration of anti-TB drugs and antiretroviral therapy (ART), potential additive side effects and drug interactions.[3]

Brazil ranks 14th worldwide in the number of TB cases and 19th in terms of TB-HIV coinfection, and is one of the 30 WHO priority countries for TB elimination in the world.[1] The state of Rio de Janeiro (RJ), one of Brazil's most developed states, is known for its poor performance in TB control. RJ has the second highest incidence and mortality rates in the country (respectively 63.3 and 4.2 per 100,000 population in 2018),[4] as well as the highest proportion of MDR-TB cases reported nationally.[5] Therefore, a better understanding of the association between HIV infection and MDR-TB in RJ is warranted.

This paper aims at identifying clinical and demographic factors associated with unsuccessful treatment outcomes in patients with MDR-TB and HIV in RJ.

METHODS

This work is based on previous research by Bhering et al.[6]

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Research design and data

This was a retrospective cohort study based on secondary data of patients who started treatment for MDR-TB between 2000 and 2016. Data were extracted from the Special Tuberculosis Treatment Information System (*Sistema de Informação de Tratamentos Especiais da Tuberculose*, SITETB), an electronic information system, where all TB cases unable to use the standard TB regimen (2RHZE/4RH) are notified and followed-up.[7]

Data on CD4, CD8 cell counts and viral load (copies/mL), recorded before or during the first month of treatment for MDR-TB, were collected from the AIDS Laboratory Database (*Sistema de Controle de Exames Laboratoriais*, SISCEL) or patients' medical records. Data on ART were collected from the Antiretroviral Control System Database (*Sistema de Controle Logístico de Medicamentos*, SICLOM) or medical records.

Outcomes: definitions of key terms

Treatment outcomes were classified according to WHO recommendations.[8] "Cured" is defined as at least three negative culture results after Month 12 of treatment. "Treatment completed" is defined as treatment completion with favourable clinical and radiological changes within the time stipulated for treatment, but without accompanying culture results. "Loss of follow-up" (LTFU) is defined as treatment interruption for $\geq$2 consecutive months. "Treatment failure" is defined as two or more positive culture results of three recommended ones, or three consecutive positive cultures at least 30 days apart after Month 12 of treatment. Failure may be decided on medical evaluation and decision to change treatment early due to clinical and radiological worsening. "Died" is defined as deaths due to any reason during treatment. "Success" is the sum of "cured" and "treatment completed" cases. An "unsuccessful" treatment outcome was defined as the sum of "died", "treatment failure", and "LTFU".

Independent variables

Study variables were categorised into two classes: drug resistance category (MDR-TB or XDR-TB), type of treatment regimen (standardised or individualised), type of drug resistance (primary, that is, patients with no history of previous TB treatment; or acquired, that is, patients already treated for TB for $\geq$1 month),[9] disease extension (presence of chest cavity and/or bilateral disease), and 6-month culture conversion status (defined as those patients with at least two negative cultures by Month 6 of treatment).

In Brazil, the WHO standardised treatment regimen for MDR-TB is recommended and applied. In case of drug-susceptible, the regimen includes at least one first-line oral drug, a fluoroquinolone, an injectable drug along with terizidone. For patients with additional resistance to first-line drugs, pre-XDR-TB, XDR-TB, and patients who have had adverse events with the standardised regimen, individualised regimens are recommended.[10] MDR-TB patients registered in SITETB who had had more than one treatment for MDR-TB were considered to have had previous treatment.

Only variables having a maximum of 10% of missing values were selected for analysis. For this reason, CD4 and CD8 counts and HIV viral load were only described.

Statistical methods

Number (frequency) and median (interquartile range [IQR] 25%–75%) were used to describe characteristics of dependent variables; treatment outcome in patients were described according to coinfection status (MDR-TB/HIV-negative, positive and unknown). Treatment outcomes were also described according to the drug resistance pattern (MDR- or XDR-TB), and coinfection. Cases with HIV status unknown were excluded from the analysis. χ^2 or Fisher's Exact test was used to compare proportions between groups.

Cox proportional hazards models were used to estimate hazard rates (HRs) between each of the treatment outcomes and the covariates only in the MDR-TB+HIV-positive group. Variables with significance levels $\leq$0.20 in the bivariate analysis were included in the multivariate model. The best-adjusted model was chosen using the likelihood ratio test. A significance level of 0.05 was set for all tests. Statistical analysis was conducted using STATA v13.1 (StataCorp, College Station, TX, USA).

Ethics approval and consent to participate

The Research Ethics Committee of the Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil, approved the study (CAAE 10126919.2.0000.5257).

RESULTS

Descriptive analysis

Of the 2,269 MDR-TB cases reported in RJ between 2000 and 2016, 1999 (88.1%) were HIV-negative, 156 (6.9%) were positive and 114 (5.0%) had unknown HIV status. There were 1,466 (64.6%) male patients; the median age was 38 years (IQR 28–49); among HIV-positive patients, the median age was 37 years (IQR 30–45). To note, 14.7% of HIV-positive cases had extrapulmonary or pulmonary-extrapulmonary MDR-TB, while in the HIV-negative and HIV unknown groups, this figure was respectively 1.3% and 2.6%. In addition, HIV-positive patients had a higher percentage of comorbidities (excluding DM), at 14.1%, than HIV-negative patients and those with unknown HIV status

Table 1 Demographic and clinical characteristics of MDR-TB patients by HIV status ($n = 2,269$)

Characteristics	HIV-negative ($n = 1999$) *n* (%)	HIV-positive ($n = 156$) *n* (%)	HIV unknown ($n = 114$) *n* (%)	*P* value
Sex				0.226
Female	670 (34.8)	61 (39.1)	47 (41.2)	
Male	1304 (65.2)	95 (60.9)	67 (58.8)	
Age range, years				<0.023
0–17	45 (2.3)	0 (0.0)	1 (0.9)	
18–32	685 (34.7)	54 (34.6)	34 (29.8)	
33–41	392 (19.6)	48 (30.8)	23 (20.2)	
≥42	877 (43.9)	54 (34.6)	56 (43.5)	
Ethnical group				0.155
Caucasian	730 (36.5)	44 (28.2)	42 (36.8)	
Afro-Brazilian	1198 (60.0)	106 (68.0)	68 (59.6)	
Unknown	71 (3.5)	6 (3.8)	4 (3.5)	
Years of study				0.296
None	95 (4.7)	13 (8.3)	5 (4.4)	
1–3	379 (19.0)	31 (19.9)	20 (17.5)	
4–7	771 (38.6)	65 (41.7)	43 (37.7)	
8–11	437 (21.9)	24 (15.4)	30 (26.3)	
≥12	153 (7.6)	7 (4.5)	6 (5.3)	
Not known	164 (8.2)	16 (10.2)	10 (8.8)	
Site of disease				<0.001
Extrapulmonary	9 (0.5)	10 (6.4)	1 (0.9)	
Pulmonary	1974 (98.7)	133 (85.3)	111 (97.4)	
Both	16 (0.8)	13 (8.3)	2 (1.7)	
Other factors				
Diabetes mellitus	197 (9.8)	5 (3.2)	17 (14.9)	0.004
Alcohol use	243 (12.2)	14 (9.0)	16 (14.0)	0.399
Illicit drug use	138 (6.9)	30 (19.2)	12 (10.5)	<0.001
Smoking	170 (8.5)	10 (6.4)	12 (10.5)	0.477
Unemployed	307 (15.4)	42 (26.9)	24 (27.0)	<0.001
Comorbidities*	237 (11.9)	22 (14.1)	13 (11.4)	0.695
Chest radiography ($n = 2189$)				
Cavitation	1586 (82.0)	99 (68.3)	87 (78.4)	<0.001
Bilateral	1478 (76.4)	108 (74.5)	62 (56.4)	<0.001
Drug resistance type				0.725
Primary	298 (14.9)	22 (14.1)	14 (12.3)	
Acquired	1701 (85.1)	134 (85.9)	100 (87.7)	
Previous MDR-TB treatment				0.026
No	1550 (77.5)	118 (75.6)	76 (66.7)	
Yes	449 (22.5)	38 (24.3)	38 (33.3)	
Outcomes				
Cured/treatment completed	1126 (56.3)	74 (47.4)	64 (56.1)	0.098
Lost to follow-up	368 (18.4)	38 (24.4)	27 (23.7)	0.084
Died	295 (14.8)	36 (23.1)	16 (14.0)	0.019
Failed	210 (10.5)	8 (5.1)	7 (6.1)	0.037

* Except diabetes mellitus and HIV.
MDR-TB = multidrug-resistant TB.

(respectively 11.9% and 11.4%). The HIV-negative and unknown HIV groups had more cases with DM (respectively 9.8% and 14.9%) than the HIV-positive group (3.2%). Among the 22 HIV-positive patients with comorbidities, the most prevalent comorbidities were viral hepatitis, mental disorder, neoplasia and depression.

The use of illicit drugs was reported by 30 (19.2%) HIV-positive patients, a higher proportion than among HIV-negative and HIV-unknown patients (respectively 6.9% and 10.5%) (Table 1).

A total of 1,005 (44.3%) patients had unsuccessful treatment outcomes; rate of unsuccessful treatment was higher in HIV-positive patients (52.6%) than in HIV-negative (43.7%), or in HIV-unknown cases (43.9%). The most frequent outcome associated with unsuccessful treatment outcomes was LTFU (HIV-positive: 38, 24.4%; HIV-negative: 395, 18.4%). Thirty-six (23.1%) HIV-positive cases and 295 (14.8%) HIV-negative died. Treatment failure rates were twice as high among HIV-negative patients than among HIV-positive patients (10.5% vs. 5.1%).

Drug resistance and treatment outcomes

MDR-TB patients, regardless of HIV status, had greater therapeutic success. All XDR-TB+HIV-positive cases had unsuccessful treatment outcomes, while the treatment success rate among XDR-TB cases who were HIV-negative was only 19.7% in the same period. Death was more frequent in HIV-positive,

Table 2 Treatment outcomes among patients with MDR- and XDR-TB by HIV status ($n = 2,155$)

	HIV-negative			HIV-positive		
Outcomes	MDR-TB ($n = 1877$)	XDR-TB ($n = 122$)	*P* value*	MDR-TB ($n = 145$)	XDR-TB ($n = 11$)	*P* value*
Cure/treatment completed	1102 (58.7)	24 (19.7)	<0.001	74 (51.0)	0 (0.0)	0.001
Lost to follow-up	354 (18.9)	14 (11.5)	0.041	35 (24.1)	3 (27.3)	0.815
Died	258 (13.7)	37 (30.3)	<0.001	32 (22.1)	4 (36.4)	0.278
Failed	163 (8.7)	47 (38.5)	<0.001	4 (2.8)	4 (36.4)	<0.001

* Comparison between MDR/XDR-TB.
MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB.

especially in XDR-TB patients, while treatment failure was similar among XDR-TB groups, but was lower among MDR-TB+HIV-positive cases (2.8%) than among MDR-TB cases who were HIV-negative (8.7%) (Table 2).

Of 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 count, and 88 (56.4%) had a CD8 count available. The median CD4 count was 311 cells/mm^3 (IQR 141–497), while the median CD8 count was 840.5 cells/mm^3 (IQR 520.5–1204.5). HIV viral load was available for 65 (41.6%) cases; the median HIV viral load was 8,166 copies/mL (IQR 903–37,000). Ninety-six (61.5%) were on ART during MDR-TB treatment.

Of the 60 HIV-positive patients who did not undergo ART, 22 (36.7%) died, 13 (59.1%) of whom died within the first 180 days after starting MDR-TB treatment; 14/96 (14.6%) patients who had undergone ART died within a mean period of 459 days.

There was no statistically significant association between unsuccessful treatment outcomes and year of treatment initiation ($P = 0.337$).

Factors associated with treatment outcomes in MDR-TB patients with HIV coinfection

Table 3 gives the factors associated with unsuccessful treatment outcomes in patients with MDR-TB + HIV-positive in bivariate and multivariate analyses. In the final multivariate Cox regression model, previous MDR-TB treatment (HR 1.97, 95% CI 1.22–3.18; $P = 0.005$), and illicit drug use (HR 1.68, 95% CI 1.01–2.78; $P = 0.044$) were found to be statistically significant risk factors for unsuccessful treatment outcomes, while 6-month culture conversion (HR 0.48, 95% CI 0.27–0.84; $P = 0.010$) and ART use (HR 0.51, 95% CI 0.32–0.80; $P = 0.003$) were protective factors.

DISCUSSION

This study found a therapeutic success rate of 56.3% among MDR-TB cases who were HIV-negative and 47.4% among those who were HIV-positive. A recent meta-analysis with nine studies including 3,368 MDR-TB+HIV-positive participants from sub-Saharan Africa reported a treatment success rate of 44.8%.[11]

With regard to poor treatment outcomes, LTFU was higher among HIV-positive cases than among HIV-negative cases (24.4% vs. 18.4%). According to the WHO, the Americas has the highest proportion of LTFU cases, with 26% among MDR- and rifampicin-resistant TB cases, while at the global level this is 14%.[12]

Among the 2,269 cases analysed, the proportion of MDR-TB+HIV coinfection was 6.9%. In 2016, 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] Data on MDR-TB+HIV coinfection in Brazil are limited. In a nationwide study conducted in MDR-TB patients, coinfection was found to be 9%,[14] while another study carried out in a reference hospital in the city of São Paulo found 4%.[15]

In our study, illicit drugs use (IDU) was a risk factor for unsuccessful treatment (HR 1.83 95% CI 1.10–3.04; $P = 0.019$). Several studies have described the association between TB, HIV and IDU, whether injectable or not.[16–20] IDU is often associated with other risk factors for TB, such as smoking, alcohol abuse and incarceration.[21] Thus, important additional barriers remain in the treatment of TB in this group. Illicit drug users find it more difficult to complete medical evaluations or adhere to TB treatment,[3] and, when symptomatic, tend to wait longer to start appropriate treatment.[22] A study conducted in the United States showed that patients with a history of injecting drugs were 3.5 times more likely (95% CI 1.3–10.2) at the time of AIDS diagnosis to have an opportunistic infection, including TB.[23] This suggests that there is a lower demand for healthcare among illicit drug users, which in turn, can lead to more severe illnesses and contribute to an increase in TB transmission rates.[24]

It is well-known that previous TB treatment significantly increases the risk of poor treatment outcomes in MDR-TB patients.[25] In the present study, patients with previous MDR-TB treatment had nearly two-fold (95% CI 1.11–2.95) likely to have an unsuccessful treatment outcome. It is therefore important to provide optimal care at first

Table 3 Bivariate and multivariate analysis: predictors of treatment failure, default and death among HIV-positive patients with MDR-TB ($n = 156$)

	Treatment failure			
Predictors	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Sex		0.621		
Female	1			
Male	0.89 (0.57–1.40)			
Age, years		0.056		
≥37	1.54 (0.98–2.40)			
<37	1			
Years of schooling		0.561		
≥8	1			
<8	1.19 (0.65–2.18)			
Afro-Brazilian		0.258		
No	1			
Yes	1.33 (0.80–2.20)			
Other factors			1.68 (1.01–2.78)	0.044
Diabetes mellitus	0.24 (0.03–1.76)	0.163		
Comorbidities*	1.08 (0.58–2.01)	0.791		
Illicit drug use	1.66 (1.00–2.75)	0.046		
Alcohol abuse	1.29 (0.67–2.46)	0.437		
Smoking	1.11 (0.48–2.57)	0.8		
Unemployed	1.57 (0.99–2.49)	0.052		
6-month culture conversion		0.008		0.01
No	1		1	
Yes	0.47 (0.27–0.82)		0.48 (0.27–0.84)	
Treatment regimen		0.953		
Individualised	1			
Standardised	1.01 (0.64–1.59)			
Drug resistance type		0.343		
Primary	1			
Acquired	1.39 (0.69–2.80)			
Chest radiography				
No cavitation	1			
Cavitation	1.16 (0.72–1.88)	0.535		
Unilateral	1			
Bilateral	1.19 (0.69–2.05)	0.521		
Previous MDR-TB treatment		0.007		0.005
No	1		1	
Yes	1.93 (1.20–3.10)		1.97 (1.22–3.18)	
Categories of drug resistance		0.329		
MDR-TB	1			
XDR-TB	1.41 (0.70–2.81)			
ART		0.003		0.003
No	1		1	
Yes	0.51 (0.33–0.80)		0.51 (0.32–0.80)	

* Except diabetes and HIV.
MDR-TB = multidrug-resistant TB; HR = hazard rate; CI = confidence interval; aHR = adjusted HR; XDR-TB = extensively drug-resistant TB; ART = antiretroviral therapy.

treatment initiation to prevent unsuccessful treatment outcomes.

The proportion of death among HIV-positive patients with MDR-TB (23.1%) was also higher than among HIV-negative cases (14.8%). Some studies report higher mortality and lower mean survival in HIV-positive patients with MDR-TB than in those without infection.[26,27] A meta-analysis including 22 studies showed that HIV-positive patients with MDR-TB had 1.6 times (95% CI 1.38–1.99; $I^2 = 74\%$, $P < 0.001$) higher risk of death than HIV-negative cases, and that unsuccessful treatment among people living with HIV is lower in high-income than in low-income regions (risk ratio [RR] 1.22, 95% CI 0.97–1.53 vs. RR 2.23, 95% CI 1.60–3.11).[28] This indicates that socio-environmental issues and lack of access to healthcare can increase the vulnerability of this group.

In this study, the median of CD4 count was <350 cells/mm^3. This suggests late access to health services by these patients, which may have resulted in greater risk of death. In addition, about 60% of HIV-positive patients who had not undergone ART died within the first 180 days after starting treatment for MDR-TB. The late diagnosis of TB, inadequate management of MDR-TB and limited access to ART are factors that contributed to a higher mortality rate in this group.[16,29,30] Early identification and the immediate initiation of appropriate anti-TB treatment and ART can prolong survival among HIV-positive patients

with MDR-TB and reduce unsuccessful treatment outcomes.[31–33] In the this study, ART (HR 0.58, 95% CI 0.37–0.91) was a protective factor against unsuccessful treatment outcomes in patients with MDR-TB and HIV.

Six-month culture conversion (HR 0.49, 95% CI 0.28–0.85) was also a protective factor against unsuccessful treatment outcomes. Previous studies in MDR-TB patients reported that the 6-month conversion status was significantly associated with successful treatment.[34,35] The median time to culture conversion among patients with successful treatment was significantly shorter than among those who had unsuccessful treatment outcomes.[36]

None of the XDR-TB+HIV-positive cases was successfully treated. The high rates of failure and death (36.4% each) in this group also reflect therapeutic limitations. This highlights the urgent need for the inclusion of new drugs by the Ministry of Health for the treatment of multidrug resistance. Also, MDR-TB and HIV treatments in RJ are carried out in different health units, and the surveillance systems of the two diseases are not linked, which makes it difficult to monitor treatment and adverse events.[16]

This study had some limitations. As data were collected retrospectively, there were several missing data on CD4 and CD8 counts and HIV viral load. Moreover, it was not possible to determine the time of ART start. Finally, due to the reduced number of records, it was not possible to perform a statistical analysis specifically for death, LTFU and failure.

CONCLUSION

Unsuccessful treatment outcome was higher among HIV-positive patients with MDR-TB than among HIV-negative patients. Prompt initiation of ART and effective interventions are necessary to improve treatment adherence and prevent retreatment cases. In addition, the fact that none of the XDR-TB+HIV-positive patients experienced therapeutic success reflects the dearth of treatment options in Brazil. This highlights the need to include new drugs in the treatment regimen for MDR-TB.

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RÉSUMÉ

CONTEXTE : Le Brésil se situe au 14è rang mondial pour les cas de TB et au 19è range en termes de coinfection TB-VIH. Cette étude vise à identifier les facteurs cliniques et démographiques associés à l'échec du traitement (perte de vue, échec et décès) de patients atteints de TB multirésistante (MDR-TB) et positifs au VIH dans l'état de Rio de Janeiro (RJ).

MÉTHODES : Etude rétrospective de cohorte de cas de MDR-TB notifiés de 2000 à 2016 dans le RJ. Des modèles de régression aléatoires proportionnels de Cox ont été mis en œuvre pour évaluer les facteurs de risque associés à un échec du traitement des patients MDR-TB et positifs au VIH.

RÉSULTATS : Sur 2269 patients, 156 (6,9%) ont été VIH positifs et ont eu une proportion plus élevée d'échec du traitement (52,6%) que les cas VIH négatifs (43,7%). Tous les cas de TB ultrarésistante (XDR-TB) et positifs at VIH ont eu un résultat défavorable du traitement. L'analyse multivariée montre qu'un traitement préalable de MDR-TB (HR 1,97 ; IC 95% 1,22–3,18) et l'utilisation de drogues (HR 1,68 ; IC 95% CI 1,01–2,78) ont été associés à un risque plus élevé d'échec du traitement, tandis qu'une conversion de culture à 6 mois (HR 0,48 ; 95% CI 0,27–0,84) et le recours à un traitement antirétroviral (ART) (HR 0,51 ; IC 95% 0,32–0,80) ont été prédictifs d'une réduction du risque.

CONCLUSION : Un échec du traitement a été plus élevé parmi les patients MDR-TBet de VIH par rapport aux patients négatifs au VIH. Une mise en route rapide de l'ART et des interventions efficaces sont nécessaires pour améliorer l'adhérence au traitement et éviter les cas de retraitement.