Predictors of tuberculosis treatment outcomes*

Preditores dos desfechos do tratamento da tuberculose

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Abstract

Objective: To analyze tuberculosis treatment outcomes and their predictors. **Methods:** This was a retrospective longitudinal cohort study involving tuberculosis patients treated between 2004 and 2006 at the *Instituto de Pesquisa Evandro Chagas*, in the city of Rio de Janeiro. We estimated adjusted risk ratios (ARRs) for the predictors of treatment outcomes. **Results:** Among 311 patients evaluated, the rates of cure, treatment abandonment, treatment failure, and mortality were 72%, 19%, 2%, and 6%, respectively. Changes in the treatment regimen due to adverse events occurred in 8%. The factors found to reduce the probability of cure were alcoholism (ARR, 0.30), use of the streptomycin+ethambutol+ofloxacin (SEO) regimen (ARR, 0.32), HIV infection without the use of antiretroviral therapy (ART; ARR, 0.36), and use of the rifampin+isoniazid+pyrazinamide+ethamb utol regimen (ARR, 0.58). Being younger and being alcoholic both increased the probability of abandonment (ARR, 3.84 and 1.76, respectively). It was impossible to determine the ARR for the remaining outcomes due to their low prevalence. However, using the relative risk (RR), we identified the following potential predictors of mortality: use of the SEO regimen (RR, 11.43); HIV infection without ART (RR, 9.64); disseminated tuberculosis (RR, 9.09); lack of bacteriological confirmation (RR, 4.00); diabetes mellitus (RR, 3.94); and homosexual/bisexual behavior (RR, 2.97). Low income was a potential predictor of treatment failure (RR, 11.70), whereas disseminated tuberculosis and HIV infection with ART were potential predictors of changes in the regimen due to adverse events (RR, 3.57 and 2.46, respectively). **Conclusions:** The SEO regimen should not be used for extended periods. The data confirm the importance of ART and suggest the need to use it early.

Keywords: Tuberculosis; HIV; Rifampin; Drug toxicity; Risk factors; Medication adherence.

Resumo

Objetivo: Analisar os desfechos do tratamento da tuberculose e seus preditores. **Métodos:** Estudo longitudinal de coorte de pacientes com tuberculose tratados entre 2004 e 2006 no Instituto de Pesquisa Evandro Chagas, na cidade do Rio de Janeiro. As razões de risco ajustadas (RRa) dos preditores foram estimadas. **Resultados:** Foram incluídos 311 pacientes. As taxas de cura, de abandono, de mortalidade e de falha terapêutica foram, respectivamente, 72%, 19%, 6% e 2%. A troca de regime terapêutico por eventos adversos foi necessária em 8%. O alcoolismo (RRa, 0,30), uso do regime estreptomicina+etambutol+ofloxacina (SEO; RRa, 0,32), infecção por HIV sem tratamento antirretroviral (TARV; RRa, 0,36) e o uso do regime rifampicina+isoniazida+pirazinamida+etambutol (RRa, 0,58) reduziram a probabilidade de cura. A faixa etária mais jovem (RRa, 3,84) e o alcoolismo (RRa, 1,76) aumentaram a probabilidade do abandono. Não foi possível determinar as RRa para os demais desfechos devido a suas baixas prevalências. Entretanto, medidas do risco relativo (RR) identificaram os seguintes potenciais preditores do óbito: uso de esquema SEO (RR, 11,43), infecção pelo HIV sem TARV (RR, 9,64), forma clínica disseminada (RR, 9,09), ausência de confirmação bacteriológica (RR, 4,00), diabetes mellitus (RR, 3,94) e comportamento homo/bissexual (RR, 2,97). A baixa renda (RR, 11,70) foi potencial preditor para falha terapêutica, ao passo que infecção pelo HIV com uso de TARV (RR, 2,46) e forma clínica disseminada (RR, 3,57) foram potenciais preditores para troca do esquema por evento adverso. **Conclusões:** O esquema SEO deve ser utilizado transitoriamente quando possível. Os dados confirmam a importância de TARV e sugerem a necessidade de seu início precoce.

Descritores: Tuberculose; HIV; Rifampicina; Fatores de risco; Toxicidade de drogas; Adesão à medicação.

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Introduction

Tuberculosis treatment outcomes in Brazil continue to fall far short of the goals established by the Brazilian National Ministry of Health. In 2009, the mortality and treatment abandonment rates in Brazil were 2.5/100,000 population (3.5/100,000 in the state capitals) and 9.1%, respectively.[1] Since 1979, the Brazilian National Ministry of Health has recommended, for the treatment of new cases of tuberculosis, a regimen consisting of rifampin, isoniazid, and pyrazinamide (known in Brazil as regimen 1 or the RHZ regimen).[2] The recommendation of the RHZ regimen as a priority is due to its greater efficacy and effectiveness. Currently, however, the need for alternative regimens without these drugs has been increasing, especially in cases of tuberculosis and HIV co-infection. In cases of intolerance to rifampin and isoniazid due to hepatotoxicity or a history of liver disease, a regimen consisting of streptomycin, ethambutol, and ofloxacin (known in Brazil as regimen SEO) is indicated.[3] In individuals living with HIV/AIDS, the clinical severity of the disease[4] and the increasing need for regimens without rifampin because of interactions with antiretroviral therapy (ART) make treatment more complex.[5,6] Since rifampin is the most potent tuberculostatic drug, these regimens might produce unfavorable outcomes. The objective of the present study was to analyze tuberculosis treatment outcomes, including changes in the treatment regimen due to adverse events, as well as outcome predictors, among which are the different treatment regimens used.

Methods

This was a retrospective longitudinal cohort study involving tuberculosis patients treated between 2004 and 2006 at the Oswaldo Cruz Foundation *Instituto de Pesquisa Clinica Evandro Chagas* (IPEC, Evandro Chagas Clinical Research Institute), located in the city of Rio de Janeiro, Brazil.

Data were collected in accordance with previously established clinical protocols and were systematically recorded on charts during the medical visits, from diagnosis to the end of treatment. Those protocols elicited detailed information about signs and symptoms, simple ancillary tests, income, level of education, smoking habits, alcohol consumption (CAGE questionnaire), comorbidities (among which are HIV, HBV, and HCV infection), clinical presentations, diagnosis of tuberculosis, treatment, adverse effects, and outcomes. For the patients who used rifampin, data were collected at the treatment initiation visit, as well as at 15, 30, 60, 120, and 180 days thereafter. For the patients who did not use rifampin, data were collected at 180 days after treatment initiation and every two months thereafter, for one year. After the end of treatment, the patients were evaluated annually for two years.

The diagnostic investigation of tuberculosis included smear microscopy, culture from all clinical samples (sputum, biopsy specimens, blood) for mycobacteria, mycobacterial identification and antimicrobial susceptibility testing in all positive cultures, chest X-ray, ultrasound (in cases of pleural or abdominal tuberculosis), and pleural or lymph node biopsy, when indicated. The clinical presentations of tuberculosis were classified as pleuropulmonary (when involvement was limited to the lung or pleura), extrapulmonary (when only one extrapulmonary site was involved), or disseminated (there was hematogenous dissemination to or involvement of at least two noncontiguous sites).[4,5]

We included all patients who started treatment at the IPEC and gave written informed consent to participate in the study, and in whom the diagnosis of tuberculosis was confirmed by a positive smear or culture from a clinical specimen. In cases without bacteriological confirmation, the diagnosis was established by histopathological examination, together with clinical findings suggestive of or signs and symptoms consistent with tuberculosis and therapeutic response. We excluded those who discontinued follow-up during the first 15 days of treatment for any reason, including death, and those with other differential diagnoses that could explain the clinical profile.

Treatment abandonment was defined as voluntary treatment discontinuation by the patient for 30 consecutive days.[2] Cure was defined as the presence of a negative sputum culture or two negative sputum smears. In the absence of expectoration, cure was defined by clinical and radiological improvement. In cases of extrapulmonary or pleuropulmonary tuberculosis with initially negative smears, cure was defined as treatment completion with clinical and radiological improvement and satisfactory results in other ancillary tests.[7] Death from tuberculosis was

defined as the reporting of tuberculosis as one of the direct causes of death on the death certificate. Multidrug-resistant tuberculosis was defined as joint resistance to rifampin and isoniazid.[2] The regimen that the patient used for the longest period during treatment was defined as the one responsible for the outcome.

All patients included in the study received self-administered treatment and initiated therapy with the RHZ regimen, except those with formal contraindications to its use. For ART-naïve individuals living with HIV/AIDS, except for those with contraindications, a regimen containing zidovudine, lamivudine, and efavirenz was prescribed and was preferably initiated after the first 30 days of tuberculosis treatment. For patients with a history of ART, regimens containing ritonavir and saquinavir were prescribed in combination with two nucleoside analogue reverse transcriptase inhibitors, selected on the basis of the history of ART or by genotyping.[7]

Medians and interquartile ranges for continuous variables were compared with the rank sum test. Absolute risks and relative risks (RRs) for categorical variables, as well as hypothesis tests for RRs (null hypothesis, RR = 1), were estimated with mid-P via Monte Carlo simulation. Multivariate analysis with a logistic regression model was conducted to adjust ORs. Variables were selected for the final model by comparing nested models using the Wald test. Each model was subjected to penalization at the intercept and tilting on the basis of the penalty estimated by resampling (bootstrapping, 100 repeats). On the basis of the ORs of the final models, adjusted risk ratios (ARRs) were calculated by the logit-log transformation method. All analyses were performed by the program R, version 2.12 (The R Foundation for Statistical Computing, Vienna, Austria).

The research project was approved by the IPEC Research Ethics Committee (Protocol no. 0025.0.009.000-09).

Results

According to the study inclusion criteria, 356 patients were eligible. Of those, 45 were excluded: 23 (51.1%) because there was a change in diagnosis during treatment; 11 (24.4%) because they died within the first 15 days of treatment; 8 (17.8%) because they failed to return to the hospital after treatment initiation; and 3 (6.7%) because they were transferred to another institution within the first 15 days of treatment. The reasons for a change in diagnosis were as follows: atypical mycobacterial disease, in 11; cryptococcosis, in 2; histoplasmosis, in 2; lymphoma, in 2; collagenosis, in 2; nontuberculous uveitis, in 2; leprosy, in 1; and extrinsic alveolitis, in 1. Therefore, 311 patients were included in the analyses. Of those, 131 were individuals living with HIV/AIDS, 105 of whom were on ART.

The mean age of the 311 study participants was 39 years. Of those 311 patients, 193 (62.1%) had an income lower than three times the national minimum wage, 197 (63.4%) received the RHZ regimen, 56 (18.0%) received the RHZ regimen+ethambutol, and 13 (4.2%) received regimens containing rifampin in combination with other medications (isoniazid, pyrazinamide, streptomycin, ethambutol, ofloxacin, levofloxacin, and/or terizidone). Regimens without rifampin were used by 42 patients (13.5%), of whom 14 (4.5%) received the SEO regimen and 28 (9.0%) received varying regimens (various combinations of isoniazid, pyrazinamide, ofloxacin, ethambutol, streptomycin, ethionamide, levofloxacin, and amikacin). There were no patients with primary liver disease; all patients who received the SEO regimen had had hepatic intolerance to the RHZ regimen and could not tolerate its reintroduction. A total of 260 patients (83.6%) remained on the same initial treatment throughout the follow-up period.

The cure rate was 72.0%. Among the 224 patients who were considered cured, there were 7 cases of recurrence, of which 6 occurred in the first semester and 1 occurred in the second semester. Absolute risks and RRs for the predictors of cure are shown in Tables 1-4. In the final model, four variables were found to reduce the probability of cure: alcoholism (ARR = 0.30); use of the SEO regimen (ARR = 0.32); HIV infection without the use of ART (ARR = 0.36); and use of the RHZ regimen+ethambutol (ARR = 0.58). Being younger—treatment abandonment increases with decreasing age—and being alcoholic both increased the probability of abandonment (ARR = 3.85 and 1.76, respectively; Table 5).

The tuberculosis mortality rate was 6.1%. It was impossible to determine the ARR for death because of its low frequency. However, using RRs, we identified the following potential predictors of mortality: use of the SEO regimen (RR = 11.43); disseminated tuberculosis (RR = 8.71);

Table 1 - Absolute risks and relative risks for the demographic and socioeconomic data on the 311 patients included in the study, by outcome.[a]

Outcome	Patients	Gender		Race		Marital status			Type of housing		Family income, n of times the NMW			Years of schooling		
	n	M	F	White	Non-White	Single	Married	Other	Brick	Wood	0-3	[3-5[	> 5	≤ 9	[9-12[	> 12
Cure	224															
R		0.72	0.73	0.74	0.70	0.69	0.74	1.00	0.73	0.86	0.72	0.70	0.88	0.71	0.71	0.78
RR		1.00	1.02	1.00	0.94	1.00	1.08	1.45	1.00	1.18	1.00	0.97	1.23	0.91	0.91	1.00
p			0.80		0.37		0.29	0.08		0.50		0.71	0.04	0.42	0.46	
Abandonment	58															
R		0.19	0.19	0.17	0.20	0.21	0.17	0.00	0.18	0.00	0.21	0.15	0.03	0.22	0.16	0.06
RR		1.00	1.00	1.00	1.24	1.00	0.80	0.00	1.00	0.00	1.00	0.71	0.14	3.58	2.64	1.00
p			1.00		0.38		0.36	0.20		0.25		0.29	0.01	0.03	0.15	
Death	19															
R		0.07	0.04	0.06	0.07	0.06	0.07	0.00	0.06	0.14	0.05	0.08	0.06	0.05	0.07	0.09
RR		1.00	0.58	1.00	1.20	1.00	1.10	0.00	1.00	2.35	1.00	1.62	1.26	0.54	0.77	1.00
p			0.29		0.70		0.84	0.66		0.43		0.38	0.73	0.36	0.68	
Failure	6															
R		0.02	0.03	0.02	0.02	0.03	0.01	0.00	0.02	0.00	0.01	0.06	0.03	0.01	0.03	0.06
RR		1.00	1.64	1.00	0.87	1.00	0.24	0.00	1.00	0.00	1.00	11.70	5.68	0.09	0.49	1.00
p			0.56		0.87		0.19	0.81		0.89		0.02	0.30	0.06	0.46	
Adverse event	26															
R		0.06	0.12	0.06	0.10	0.07	0.10	0.00	0.08	0.00	0.07	0.15	0.06	0.07	0.09	0.12
RR		1.00	1.91	1.00	1.65	1.00	1.42	0.00	1.00	0.00	1.00	2.09	0.81	0.58	0.74	1.00
p			0.09		0.21		0.36	0.60		0.54		0.07	0.83	0.34	0.60	

NMW: national minimum wage; R: absolute risk; and RR: relative risk. [a]Patients per variable (n)—totals vary because of missing data: male gender (193); female gender (118); being White (145); being non-White (166); being single (167); being married (137); other (7); living in brick housing (296); living in wood housing (7); earning 0-3 times the NMW (193); earning [3-5[times the NMW (66); earning > 5 times the NMW (34); having had ≤ 9 years of schooling (179); having had [9-12[years of schooling (97); and having had > 12 years of schooling (32).

Table 2 - Absolute risks and relative risks for the comorbidities, history of hospitalization, and history of tuberculosis treatment in the 311 patients included in the study, by outcomes.[a]

Outcome	Patients	SAH		DM		HBV		HCV		HIV			COPD		Alcoholism		Smoking		History of hospitalization		History of TB treatment	
	n	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes		No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
											without ART	with ART										
Cure	224																					
R		0.70	0.92	0.73	0.64	0.74	0.60	0.75	0.64	0.75	0.38	0.75	0.73	0.67	0.76	0.58	0.74	0.72	0.73	0.72	0.78	0.57
RR		1.00	1.31	1.00	0.88	1.00	0.81	1.00	0.86	1.00	0.51	1.01	1.00	0.92	1.00	0.77	1.00	0.97	1.00	0.98	1.00	0.73
p			< 0.01		0.48		0.14		0.24		< 0.01	0.95		0.73		0.01		0.68		0.82		< 0.01
Abandonment	58																					
R		0.20	< 0.01	0.18	0.07	0.18	0.20	0.17	0.18	0.18	0.31	0.16	0.18	< 0.01	0.15	0.32	0.17	0.19	0.18	0.17	0.15	0.29
RR		1.00	< 0.01	1.00	0.39	1.00	1.14	1.00	1.03	1.00	1.67	0.88	1.00	< 0.01	1.00	2.13	1.00	1.09	1.00	0.96	1.00	1.93
p			< 0.01		0.31		0.74		0.91		0.16	0.64		0.30		< 0.01		0.72		0.90		0.01
Death	19																					
R		0.06	0.05	0.05	0.21	0.05	0.12	0.05	0.14	0.03	0.27	0.07	0.06	0.17	0.06	0.05	0.05	0.07	0.05	0.09	0.05	0.07
RR		1.00	0.86	1.00	3.94	1.00	2.34	1.00	2.92	1.00	9.64	2.39	1.00	2.80	1.00	0.81	1.00	1.43	1.00	1.97	1.00	1.37
p			0.90		0.05		0.20		0.08		< 0.01	0.14		0.37		0.77		0.45		0.16		0.52
Failure	6																					
R		0.02	< 0.01	0.02	0.07	0.01	0.08	0.02	< 0.01	0.03	0.04	< 0.01	0.02	0.17	0.02	< 0.01	0.03	0.01	0.03	< 0.01	0.01	0.04
RR		1.00	< 0.01	1.00	4.20	1.00	5.46	1.00	< 0.01	1.00	1.38	< 0.01	1.00	10.07	1.00	< 0.01	1.00	0.18	1.00	< 0.01	1.00	2.73
p			0.46		0.27		0.09		0.60		0.73	0.10		0.12		0.26		0.10		0.18		0.24
Adverse event	26																					
R		1.00	< 0.01	1.00	4.20	1.00	5.46	1.00	< 0.01	1.00	1.38	0.12	0.08	0.17	0.10	< 0.01	0.10	0.07	0.08	0.11	0.09	0.06
RR			0.46		0.27		0.09		0.60		0.73	2.46	1.00	2.01	1.00	< 0.01	1.00	0.67	1.00	1.37	1.00	0.65
p			0.57		0.13		0.54		0.39		0.08	0.03		0.50		< 0.01		0.30		0.44		0.38

SAH: systemic arterial hypertension; DM: diabetes mellitus; TB: tuberculosis; ART: antiretroviral therapy; R: absolute risk; and RR: relative risk. [a]Patients per variable Yes/No (n/n)—total vary because of missing data: SAH (271/37); DM (294/14); HBV (273/25); HCV (266/28); HIV (179/131); HIV+ART (26/105); COPD (302/6); alcoholism (242/60); smoking (146/160); history of hospitalization (232/75); and history of TB treatment (227/83).

Table 3 - Absolute risks and relative risks for the behavioral characteristics/habits of the 311 patients included in the study, by outcome.[a]

Outcome	Patients	Non-injection drugs		Injection drugs		Blood transfusion		Sex without a condom		Homosexual/ bisexual		Heterosexual	
	n	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Cure	224												
R		0.75	0.67	0.74	0.25	0.74	0.66	0.73	0.74	0.73	0.73	0.71	0.79
RR		1.00	0.89	1.00	0.34	1.00	0.89	1.00	1.01	1.00	1.00	1.00	1.12
p			0.20		0.01		0.29		0.89		0.98		0.14
Abandonment	58												
R		0.16	0.26	0.17	0.38	0.18	0.18	0.19	0.17	0.20	0.09	0.20	0.12
RR		1.00	1.67	1.00	2.15	1.00	1.03	1.00	0.87	1.00	0.47	1.00	0.60
p			0.06		0.20		0.91		0.61		0.09		0.10
Death	19												
R		0.06	0.06	0.05	0.25	0.05	0.11	0.06	0.06	0.05	0.14	0.06	0.04
RR		1.00	0.98	1.00	4.66	1.00	2.13	1.00	1.02	1.00	2.97	1.00	0.58
p			0.99		0.08		0.20		1.00		0.04		0.40
Failure	6												
R		0.03	0.00	0.02	0.00	0.02	0.03	0.01	0.02	0.02	0.02	0.02	0.02
RR		1.00	0.00	1.00	0.00	1.00	1.38	1.00	2.12	1.00	1.19	1.00	1.35
p			0.21		0.85		0.73		0.54		0.82		0.71
Adverse event	26												
R		0.09	0.07	0.08	0.25	0.08	0.11	0.09	0.08	0.07	0.16	0.09	0.06
RR		1.00	0.82	1.00	3.10	1.00	1.26	1.00	0.96	1.00	2.19	1.00	0.64
p			0.70		0.16		0.64		0.89		0.08		0.37

R: absolute risk; and RR: relative risk. [a]Patients per variable No/Yes (n/n)—total vary because of missing data: non-injection drugs (237/69); injection drugs (298/8); blood transfusion (263/38); sex without a condom (90/212); homosexual/ bisexual (261/44); and heterosexual (222/82).

HIV infection without ART (RR = 9.64); lack of bacteriological confirmation (RR = 4.00); diabetes mellitus (RR = 3.94); and homosexual/bisexual behavior (RR = 2.97).

The rate of treatment failure was 1.9%. As was observed for mortality, it was impossible to perform the analysis to determine the ARR for the predictors. Only low income seemed to be a potential predictor of treatment failure.

Changes in the treatment regimen due to adverse events were necessary in 26 patients (8.4%), and this was the main reason for discontinuation of treatment. The most common adverse events were hepatotoxicity, in 5.8%, and skin rash and pruritus, in 1.9%. Bacterial resistance explained changes in the treatment regimen in 4.5% of the cases: 2.3% were resistant to isoniazid alone; 1.0% was resistant to rifampin alone; and 1.3% was resistant to more than two drugs. Chief among the predictors of need for changes in the regimen due to adverse events were disseminated tuberculosis (RR = 3.56); HIV infection with ART (RR = 2.46); bacteriologically confirmed diagnosis (RR = 0.40); and histopathologically confirmed diagnosis (RR = 0.16).

Discussion

In this cohort of 311 patients followed for two years after the end of tuberculosis treatment, we found high rates of mortality and treatment abandonment, which affected the cure rate. These data are in contrast to data for 2004 from the Brazilian Case Registry Database,[8] which reported a 70.4% cure rate, a rate that was much more affected by treatment abandonment than by mortality, which reached 3.7%. Our findings might be explained by the high proportion of individuals living with HIV/AIDS in our sample.

Chief among the factors that increased the probability of a favorable outcome and reduced the probability of unfavorable outcomes were the treatment regimen used and the absence of ART. The higher cure rate of regimens containing rifampin has been well documented, in other countries,[9] as well as in Brazil.[10] Although

Table 4 - Absolute risks and relative risks for the methods of diagnostic confirmation, clinical presentation, and effective treatment of tuberculosis in the 311 patients included in the study, by outcome.[a]

Outcome	Patients	Type of diagnosis			Clinical presentation				Effective treatment[b]				
	n	Clinical	Smear microscopy/no culture[c]	Culture	Histopathological	Pleuropulmonary	Extrapulmonary	Disseminated	RHZ	RHZE	With R[d]	SEO	Without R[e]
Cure	224												
R		0.68	0.86	0.71	0.71	0.72	0.78	0.62	0.78	0.61	0.77	0.40	0.67
RR		1.00	1.25	1.04	1.04	1.15	1.25	1.00	1.00	0.78	0.99	0.51	0.85
p			0.16	0.70	0.79	0.20	0.07			**0.01**	0.89	**< 0.01**	0.21
Abandonment	58												
R		0.13	0.10	0.20	0.23	0.22	0.14	0.12	0.16	0.29	0.15	0.07	0.22
RR		1.00	0.72	1.51	1.74	1.77	1.10	1.00	1.00	1.73	0.93	0.40	1.35
p			0.72	0.35	0.30	0.14	0.86			**0.05**	0.97	0.35	0.46
Death	19												
R		0.18	0.05	0.05	0.03	0.03	0.04	0.23	0.04	0.05	< 0.01	0.40	0.11
RR		1.00	0.26	0.25	0.16	0.11	0.18	1.00	1.00	1.53	< 0.01	11.43	3.17
p			0.16	**0.01**	**0.04**	**< 0.01**	**< 0.01**			0.53	0.64	**< 0.01**	0.12
Failure	6												
R		< 0.01	< 0.01	0.03	< 0.01	0.02	0.03	0.02	0.02	0.05	< 0.01	< 0.01	< 0.01
RR		1.00	N	Inf	N	0.76	1.32	1.00	1.00	3.57	< 0.01	< 0.01	< 0.01
p			1.00	0.38	1.00	0.78	0.87			0.14	0.83	0.80	0.68
Adverse event	26												
R		0.18	0.10	0.07	0.03	0.05	0.10	0.19	0.01	< 0.01	0.31	0.67	0.37
RR		1.00	0.52	0.40	0.16	0.28	0.51	1.00	1.00	< 0.01	30.77	66.67	37.04
p			0.40	**0.05**	**0.04**	**0.01**	0.16			0.61	**< 0.01**	**< 0.01**	**< 0.01**

R: rifampin; H: isoniazid; Z: pyrazinamide; E: ethambutol; S: streptomycin; O: ofloxacin; R: absolute risk; and RR: relative risk. [a]Patients per variable (n)—totals vary because of missing data: clinical diagnosis (38); smear microscopy without culture (21); culture (217); histopathological diagnosis (35); pleuropulmonary tuberculosis (190); extrapulmonary tuberculosis (73); disseminated tuberculosis (48); RHZ regimen (200); RHZE regimen (56); other regimens with R (13); SEO (15); and other regimens without R (28). [b]Effective treatment was defined as the regimen used for the longest period during treatment. [c]Positive sputum smears without confirmation by culture. [d]Other treatment regimens with rifampin. [e]Other treatment regimens without rifampin.

Table 5 - Adjusted risk ratios and adjusted ORs estimated for cure and for treatment abandonment.

Outcome	Variable	ARR (95% CI)	AOR (95% CI)
Cure	Alcoholism	0.30 (0.19-0.44)	0.43 (0.23-0.8)
	HIV[a]		
	Yes without ART	0.36 (0.13-0.80)	0.28 (0.11-0.69)
	Yes with ART	1.14 (0.70-1.44)	1.21 (0.66-2.22)
	Treatment regimen[b]		
	RHZE	0.58 (0.29-0.98)	0.49 (0.25-0.96)
	Others with R	0.88 (0.25-1.64)	0.84 (0.21-3.33)
	Others without R	0.56 (0.21-1.10)	0.47 (0.18-1.19)
	SEO	0.32 (0.10-0.88)	0.25 (0.08-0.81)
Abandonment	Age	3.84 (2.17-8.33)	2.85 (1.26-7.14)
	Alcoholism	1.76 (1.13-1.75)	2.39 (1.15-4.95)
	Treatment regimen[b]		
	RHZE	1.40 (0.79-1.62)	1.63 (0.77-3.46)
	Others with R	1.19 (0.28-1.84)	1.28 (0.25-6.53)
	Others without R	1.65 (0.74-1.83)	2.14 (0.71-6.42)
	SEO	0.71 (0.90-1.78)	0.65 (0.08-5.36)

ARR: adjusted risk ratio; AOR: adjusted OR; ART: antiretroviral therapy; R: rifampin; H: isoniazid; Z: pyrazinamide; E: ethambutol; S: streptomycin; and O: ofloxacin. [a]Reference: being HIV-negative. [b]Reference: RHZ regimen.

rifampin exhibits the greatest bactericidal potency among the drugs used, the inclusion of rifampin in the regimen makes it possible to shorten treatment duration to six months, accelerating conversion to smear-negative status, and is associated with lower rates of treatment failure, recurrence, and mortality.[11-13] In contrast, the use of the RHZ regimen+ethambutol was a predictor of a lower probability of cure, of a higher risk of treatment abandonment, and of changes in the treatment regimen due to adverse events. The patients in the study period were under tuberculosis retreatment, often because of prior abandonment and, therefore, being at increased risk of abandoning treatment again, as has been described in the literature.[14-16] In these cases, the regimen is a consequence of treatment abandonment rather than a predictor. The use of the SEO regimen was also found to reduce the probability of cure because it produced increases in the rates of mortality and treatment abandonment, which is in contrast to the good results found by other authors, who investigated the cure rate among liver disease patients treated with the SEO regimen (cure rate: 85%; abandonment rate: 7.5%; and mortality rate: 7.5%). The difference between the results might be attributable to the study samples. Our sample had a high prevalence of HIV-infected patients, and intolerance was the main reason for the use of the SEO regimen, possibly because of drug interactions rather than because of a history of liver disease, unlike other studies.

In addition to treatment regimen, alcoholism was also found to reduce the probability of cure by increasing abandonment. This finding corroborates those of a study conducted in the state of Pernambuco, Brazil, which observed that excessive alcohol consumption, HIV co-infection, and tuberculosis retreatment are risk factors for treatment failure.[14] Alcoholism is a known risk factor for unfavorable outcomes in tuberculosis patients, and, in these cases, efforts toward a multidisciplinary approach should be made in order to overcome their adherence and tolerance difficulties.[17,18]

Although HIV infection alone was not a risk factor for cure or treatment failure, it was associated with changes in the treatment regimen due to adverse events. All of the other factors associated with intolerance—disseminated tuberculosis, negative sputum smears, and histopathologically confirmed diagnosis—might be associated with HIV infection. Since it was impossible to adjust the model, it is impossible to know whether these are independent factors. However, the use of ART increased the probability of cure and had a protective effect against mortality, although it was probably responsible, in part, for intolerance to the RHZ regimen.[19] The initiation of ART still during tuberculosis treatment increases survival in individuals living with HIV/

AIDS.[1] There remains, however, controversy over the best timing for the initiation of ART. There is a benefit in starting it early (15 vs. 45 days) [20] in patients with CD4 cell counts < 50 cells/mm^3. Another relevant problem is the toxicity of concomitant medications that prevents the use of ART. Although HIV immunosuppression alone did not change the probabilities of outcome, diabetes mellitus increased the risk of death. Diabetes mellitus, in addition to increasing mortality, has been described as being related to delayed sputum conversion, increased chances of recurrence, and increased chances of developing multidrug-resistant tuberculosis.[21]

Socioeconomic factors also increased the probability of unfavorable outcomes. Among the patients with a lower income and a lower level of education, the rate of treatment abandonment was higher, as was the rate of treatment failure, which might be associated with poor treatment adherence even without abandonment. These factors might be related to knowledge or understanding of the disease, its treatment, and the importance of treatment adherence, as well as to the costs of treatment for patients and their families.[21]

The present study has some limitations. The reduced number of some exposures and some outcomes did not allow the evaluation of factors independently predictive of outcomes. In addition, the lack of information on CD4 lymphocyte counts in individuals living with HIV/AIDS did not allow the evaluation of 'being immunosuppressed' as one of the predictor variables. However, the study confirms, in an underprivileged population, the relevance of the treatment regimen for tuberculosis and AIDS, as well as the relevance of social determinants in tuberculosis treatment outcomes in Brazil.

In summary, the data presented suggest that the SEO regimen should not be used for extended periods in cases of toxicity and, as soon as possible, a more potent regimen should be prioritized. We also confirm the importance of ART during tuberculosis treatment in HIV-infected patients, even if it increases the probability of adverse effects, because of its impact on mortality.

References

1. Portal da Saúde [homepage on the Internet]. Brasília: Ministério da Saúde. [cited 2011 Jun 1]. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Situação da Tuberculose no Brasil. [Adobe Acrobat document, 33p.] Available from: http://portal.saude.gov.br/portal/arquivos/pdf/apres_padrao_pnct_2011.pdf
2. Ministério da Saúde. Fundação Nacional de Saúde. Tuberculose – guia de vigilância epidemiológica. Brasília: Ministério da Saúde, Fundação Nacional de Saúde; 2002.
3. Sociedade Brasileira de Pneumologia e Tisiologia. II Consenso Brasileiro de Tuberculose - Diretrizes Brasileiras para Tuberculose 2004. J Bras Pneumol. 2004;30(1):S4-S56.
4. Nunn P, Brindle R, Carpenter L, Odhiambo J, Wasunna K, Newnham R, et al. Cohort study of human immunodeficiency virus infection in patients with tuberculosis in Nairobi, Kenya. Analysis of early (6-month) mortality. Am Rev Respir Dis. 1992;146(4):849-54.
5. Schmaltz CA, Sant'Anna FM, Neves SC, Velasque Lde S, Lourenço MC, Morgado MG, et al. Influence of HIV infection on mortality in a cohort of patients treated for tuberculosis in the context of wide access to HAART, in Rio de Janeiro, Brazil. J Acquir Immune Defic Syndr. 2009;52(5):623-8.
6. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. JAMA. 2004;291(8):238.
7. Programa Nacional de Doenças Sexualmente Transmissíveis/AIDS. Recomendações para terapia anti-retroviral em adultos infectados pelo HIV: 2008. Brasília: Programa Nacional de DST e AIDS; 2008.
8. Biblioteca Virtual em Saúde [homepage on the Internet]. Brasília: Ministério da Saúde. [cited 2011 Jun 1]. Sistema Nacional de Vigilância em Saúde - Relatório de Situação - Rio de Janeiro. [Adobe Acrobat document, 25p.] Available from: http://bvsms.saude.gov.br/bvs/publicacoes/caderno_rj_2007.pdf
9. Campos HS, Melo FA. Efetividade do esquema 3 (3sSZEEt/9EEt) no retratamento da tuberculose na rotina das unidades de saúde. Bol Pneum Sanit. 2000;8:7-14.
10. Pozniak AL, Miller R, Ormerod LP. The treatment of tuberculosis in HIV-infected persons. AIDS. 1999;13(4):435-45.
11. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167(4):603-62.
12. Albuquerque MF, Leitão CC, Campelo AR, de Souza WV, Salustiano A. Prognostic factors for pulmonary tuberculosis outcome in Recife, Pernambuco, Brazil [Article in Portuguese]. Rev Panam Salud Publica. 2001;9(6):368-74.
13. Portal da Saúde [homepage on the Internet]. Brasília: Ministério da Saúde. [cited 2011 Jun]. Brasil. Ministério da Saúde. [cited 2011 May 16]. Boletim Eletrônico Epidemiológico. [Adobe Acrobat document, 10p.] Available from: http://portal.saude.gov.br/portal/arquivos/pdf/boletim_epi_n11_tb_dez2010_atual2.pdf
14. Szklo A, Mello FC, Guerra RL, Dorman SE, Muzy-de-Souza GR, Conde MB. Alternative anti-tuberculosis regimen including ofloxacin for the treatment of patients with hepatic injury. Int J Tuberc Lung Dis. 2007;11(7):775-80.
15. Ribeiro SA, Amado VM, Camelier AA, Fernandes MM, Schenkman S. Estudo caso-controle de indicadores de abandono em doentes com tuberculose. J Pneumol. 2000;26(6):291-6.

16. Natal S, Valente J, Gerhardt G, Penna ML. Modelo de predição para o abandono do tratamento da tuberculose pulmonar. Bol Pneumol Sanit. 1999;7(1):65-78.
17. Breen RA, Miller RF, Gorsuch T, Smith CJ, Schwenk A, Holmes W, et al. Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. Thorax. 2006;61(9):791-4.
18. National Aids Treatment Advocacy Project [homepage on the Internet]. New York: National Aids Treatment Advocacy Project. [cited 2011 May 16]. Significant enhancement in survival with early (2 weeks) vs. late (8 weeks) initiation of highly active antiretroviral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis: "34% Reduction in Mortality in Early Arm". Available from: http://www.natap.org/2010/IAS/IAS_91.htm
19. Leite AA, Barros RA, Branco BP, Carneiro SD, Andrade Filho AT, Facundo MK. Tuberculose e diabete melito: 40 casos observados no Hospital Universitário Lauro Wanderley. Pulmão RJ. 1999;8(4):365-7.
20. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg. 2009;80(4):634-9.
21. Steffen R, Menzies D, Oxlade O, Pinto M, de Castro AZ, Monteiro P, et al. Patients' costs and cost-effectiveness of tuberculosis treatment in DOTS and non-DOTS facilities in Rio de Janeiro, Brazil. PLoS One. 2010;5(11):e14014

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