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Impact of treatment interruption patterns on treatment success among patients with multidrug-resistant tuberculosis in Armenia and Abkhazia

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Abstract

Background

The success of the current treatment regimen for multidrug-resistant tuberculosis (MDR-TB) is poor partly due to a high defaulter rate. Many studies explored predictors of poor outcomes, but very few assessed the impact of treatment interruptions on MDR-TB treatment outcomes.

Methods

We conducted a retrospective analysis among MDR-TB patients enrolled in two MDR-TB programmes using WHO recommended regimens under directly observed therapy (DOT). Treatment outcomes were defined as successful if patient was cured or completed treatment, and unsuccessful if patient died, failed or defaulted. The effect of patterns of interruptions on treatment outcomes was assessed through multivariate logistic regression.

Results

A total of 393 MDR-TB patients were included in the study; 171 (43.5%) had a successful outcome and 222 (56.5%) an unsuccessful outcome: 39 (9.9%) died, 56 (14.3%) failed and 127 (32.3%) defaulted. In multivariate analysis, having long (>3 days) interruptions (aOR 3.87, 95% CI 1.66–8.98) and short (<10 days) gaps between interruptions (aOR 3.94, 95% CI 1.76–8.81) were independently associated with an unsuccessful treatment outcome.

Discussion

This study shows that in a DOT based MDR-TB program, treatment interruptions at short intervals of a minimum of 3 days duration directly affects treatment outcome.

Introduction

The emergence of resistance to anti-tuberculosis drugs has become a significant public health problem in a number of countries and an obstacle to effective tuberculosis (TB) control. Among all incident TB cases globally, 3.6% (95% CI 3.0–4.4) are estimated to have multidrug-resistant TB (MDR-TB). In Armenia, in 2011, the World Health Organization (WHO) estimated that among new TB cases and previously treated TB cases, the proportions of MDR-TB were 9.4% (95% CI 7.1 – 12) and 43% (95% CI 38 – 49), respectively. In Georgia, these proportions were estimated to be 11% (95% CI 9.6 – 12) and 32% (95% CI 28 – 35), respectively [1].

Treatment of MDR-TB patients is long, costly and has a low efficacy, which results in a very poor effectiveness in routine program conditions. In a very large meta-analysis, 54% of MDR-TB patients had a successful treatment outcome, which was consistent with the overall MDR-TB success rate reported by WHO in their last Global report ranging between 44 and 58% [1,2]. One of the main causes of the poor outcomes is the high proportion of patients who default from treatment [2–4]. Several studies had investigated the factors associated with poor MDR-TB treatment outcomes including social factors, advanced disease, fluoroquinolone resistance at treatment initiation or amplification during treatment, treatment duration and number of drugs used in the regimen [5–9]. Very few studies assessed the factors associated with defaulting MDR-TB treatment. They found that treatment default was mostly associated with substance abuse (alcohol and drug), socio economic factors, dissatisfaction with health services, patient mobility, number of previous treatments, poor tolerability and absence of early culture conversion [4,7,10–12].

Most of the studies focus on baseline characteristics of patients and very few take into consideration treatment adherence. In addition, to our knowledge there is no published

information on the effect of treatment interruptions that are not long enough to be defined as default according to WHO definition. We have conducted a retrospective study of data from two drug resistance TB programme to assess the effect of temporary interruptions on patients' MDR-TB treatment outcomes.

Methods

Study settings

We conducted a retrospective data analysis of routinely collected data in two drug-resistant TB (DR-TB) programmes supported by MSF in Armenia and Abkhazia (Georgia). Patients were included in the study if they had a baseline drug susceptibility testing (DST) confirming MDR-TB and if they initiated treatment at least 24 months before the administrative censoring date of the database which was 31st July 2010. We excluded from the analysis patients who were transferred out or still on treatment at the closing date of the database. Patients' socio-demographic, clinical and laboratory data at treatment initiation as well as patients' interruptions and adherence rate during treatment were collected in each programme using the Koch'6 software developed by MSF for the clinical management of patients with DR-TB.

The DR-TB programs covered the entire city of Yerevan in Armenia and the autonomous region of Abkhazia in Georgia. Treatment regimens were individualised based on drug susceptibility testing results using at least 4 to 5 effective drugs including second line drugs (ofloxacin, levofloxacin and moxifloxacin, kanamycin and capreomycin, PAS, ethionamide, cycloserine) for a duration of 18 to 24 months according to the WHO guidelines [3,4,13]. Treatment administration was under direct

observation during the full course of treatment six days a week with either the patient coming to the closest health facility or receiving the treatment at home by a health personnel or a trained community person in order to facilitate the intake of treatment after discharge from the hospital. Patients were hospitalised for treatment initiation and discharged after documentation of two smear-negative sputum samples. Patients had daily medical assessment during the first month of treatment and then monthly until the end of treatment with careful management of adverse events. Psychological support, individually and in group sessions, together with socioeconomic support (financial and nutrition support, transport reimbursement) were provided. The Armenian and Abkhazia programs were approved by the WHO Green Light Committee in 2006 and 2004, respectively.

Definitions

Treatment outcomes followed the WHO 2008 guidelines and were defined as successful if patient was cured or completed treatment, and unsuccessful if patient died, failed or defaulted from treatment [13]. For second line drugs with reliable susceptibility testing (fluoroquinolons, aminoglycosides, and glycopeptides), we defined extension of drug resistance as an increase in the number of drugs towards which *Mycobacterium tuberculosis* (*MTB)* was resistant *in vitro* during treatment follow-up compared with baseline. Pre-XDR was defined as resistance to at least one second line injectable drug or to ofloxacin and XDR as resistance to ofloxacin and at least one second line injectable drug. For treatment interruptions, we considered their duration, the duration of the interval (gap) between two interruptions and the incidence of the interruptions. We defined a treatment interruption when a patient stopped all anti-tuberculosis drugs for at least two consecutive days. Given that the overall median duration of interruption was 3 days, the pattern of duration of the interruptions was defined as short if the median duration of all the

interruptions was 2 days and as long if the median was more than 2 days. The gap between two consecutive interruptions for a patient was calculated as the time between the end of the previous interruption and the beginning of the next one. The pattern of gaps between interruptions (i.e. period under treatment) was defined as short if the median duration of all the gaps was 10 days (overall median of gaps) or less, and as long if higher than 10 days. We considered the incidence of treatment interruptions due to patients' decision (social reasons, refusal…) and due to clinician's decision (side-effects or poor tolerability, comorbidities, and severe clinical condition) separately. For each patient, the incidence was calculated as the total number of interruptions divided by the number of trimesters (3-month period) that the patient was on treatment, to take into account duration of treatment which may vary according to patients' outcome. Treatment adherence rate was calculated as the number of days that the drugs were taken divided by the number of days that the drugs were prescribed and was categorized using a threshold of 80% [14].

Statistical analysis

Patients' characteristics at treatment initiation were summarized using frequencies and percentages for categorical variables, and median and interquartile range (IQR) for continuous variables.

Only patients with at least one interruption of treatment were included in further analyses. Patients with no interruptions were excluded because in this study, we were interested in the effect of the different patterns of interruptions on treatment outcome (long vs. short). Therefore, these patients did not fell into one the categories because they never interrupted the treatment. Number of interruptions over time on treatment, duration of interruptions, maximum duration on interruptions, time to first interruption and duration of gaps between interruptions were calculated according to patients' outcome. We also plotted the evolution of the duration of

interruptions during treatment. In addition, we described the different patterns of interruptions per patient. Comparison between successful and unsuccessful outcome were made using Chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous variables. Univariate and multivariate logistic regression were fitted to explore the link between the different patterns of interruption and patient outcomes. The following potential confounders were included in the analysis: programme location, gender, age, alcohol use, known diabetes, being ex-prisoner, past history of TB treatment, number of drugs previously received (prior to actual MDR regimen including first line and second line antiTB drugs), body mass index (BMI), presence of cavities on chest X-ray, sputum smear-microscopy result and DST profile at treatment initiation, adherence to treatment and incidence of side effects per month of treatment. Covariates associated with a p-value < 0.4 in univariate analysis were included in the initial multivariate model and we used a backward stepwise approach to obtain the final multivariate model. Statistical significance (p-value < 0.05) was assessed with the likelihood-ratio test. Sensitivity analysis excluding patients who defaulted from treatment was also carried out. We also explored and described the effect of patterns of interruptions on extension of drug resistance to injectables and/or fluoroquinolones for patients with at least one culture follow-up result available. Analyses were performed using Stata 12.1 software (Stata Corporation, College Station, Texas, USA).

Ethical approval was sought from the ethical committee of the University of Psychology of Yerevan, the bio-medical Research Ethics Committee of the national center for tuberculosis and lung disease of Georgia, the *Comité Consultatif de Protection des Personnes* in Saint Germain en Laye, France, the health authorities of Abkhazia and the Ministry of Health of Georgia.

Results

Among the 415 MDR-TB patients who initiated treatment between 19th June 2002 and 29th June 2010, 22 (3.5%) were excluded from the analysis because they did not have an outcome assigned at the administrative censoring date of the database (12 were still on treatment and 10 were transfer out). Therefore, a total of 393 MDR-TB patients, were included in the study, 60.8% from Armenia and 39.2% from Abkhazia. Characteristics of patients at treatment initiation are presented in Table 1. The majority of them were male (83.5%), median age was 38 years old [30 – 48] and median BMI was 20.1 kg/m^2 [IQR 18.2 – 22.7]. New cases represented 21.4% of patients and 48.8% and 29.7% were previously treated with first and second line drugs, respectively. At treatment initiation, 155 patients (80.3%) were sputum-smear positive, and the DST profile of patients was distributed as follow: 37.2% MDR without resistance to second line drug , 21.9% pre-XDR, 3.8% XDR and 37.1% MDR but without second line drugs tested.

Outcomes per project are presented in Table 2. Among the 393 patients included in the study, 171 (43.5%) had a successful outcome and 222 (56.5%) had an unsuccessful outcome. These rates differed according to project, showing a higher success rate in Armenia and a higher defaulter rate in Abkhazia (p<0.001). Overall, median treatment duration was 11.3 months [IQR 4.9 – 19.1] for patients with unsuccessful outcome and 22.0 months [21.0 – 24.1] for those with a successful outcome. Patients defaulted from treatment in a median [IQR] time of 8.4 months [4.5 – 15.7].

Among all patients, the median number of interruptions was 5 [IQR 2 – 11] for patients with unsuccessful outcome and 4 [IQR 1 – 11] for patients with successful outcome (p=0.500). Seventy patients had no interruptions during their treatment course, among them 40 (57.1%) had an unsuccessful outcome and 30 (42.9%) had a successful outcome. A total of 2859 interruptions were registered in the database for the 323 patients presenting at least one interruption. In Table

3, we provided a detailed description of the interruptions. Among the 2859 interruptions, the median duration of interruptions was 3 days [IQR 2 – 5] for patients with a successful outcome and 4 days [IQR 2 – 9] amongst those with an unsuccessful outcome (p<0.001). As displayed in Figure 1, the duration of interruptions did not vary strongly over time on treatment. This figure was observed both for patients with a successful and an unsuccessful outcome. The median maximum duration of interruption was 18 days [IQR 8 -27] and was higher for patients with an unsuccessful outcome (p<0.001). The first interruption occurred in the first 3 months of treatment for 48.0% of patients and for 28.8% after 6 months, and it differed according to treatment outcome (p<0.001). Among the 2859 interruptions, the median gap between two consecutive interruptions was 13 days [IQR 5 – 37] and was lower for patients with an unsuccessful outcome (p<0.001). Using our definitions of patterns of interruptions during treatment, we found that 84.2% of patients had a pattern of long duration of interruptions and that 29.7% of patients had a pattern of short gap between interruptions ,and both these patterns were more common among the unsuccessful outcome group (p<0.001). Main reasons for interruptions were related to decisions taken by patients themselves (treatment refusal or patient absence) followed by medical decisions (side-effects or intolerance, comorbidity or severe condition).

Results of univariate and multivariate analysis were presented in Table 4. After univariate analysis, the following potential confounders were included in the initial multivariate model: programme, gender, being an ex-prisoner, history of TB treatment, sputum-smear microscopy result, DST profile at initiation, adherence to treatment and incidence of side-effects during treatment. The final multivariate model showed that having a pattern of long duration of interruptions (aOR 3.87, 95% CI 1.66 – 8.98) and a pattern of short gaps between interruptions (aOR 3.94, 95% CI 1.76 – 8.81) remained independently associated with an unsuccessful treatment outcome. Incidence of interruptions due to side-effects (aOR 3.93, 95% CI 1.12 – 13.85) was also independently

associated with an unfavourable outcome whereas incidence of interruptions based on patient's decision was not. This meant that for each additional interruption due to side-effect in a 3-month period, we observed a fourfold increase in the odds of unfavourable outcome. Finally, treatment adherence below 80% (aOR 6.93, 95% CI 3.54 – 13.61) was strongly associated with an unfavourable outcome. However, we found no significant association between DST profile at admission and treatment outcomes (p=0.205), also when we grouped MDR without resistance to second line drug and MDR second line not tested.

When defaulters were excluded in the sensitivity analysis and after adjustment for the same confounders, a pattern of long interruptions duration (aOR 3.02, 95% CI 1.16 – 7.90) and incidence of interruptions due to side-effects (aOR 6.01, 95% CI 1.60 – 22.55) remained independently associated with unsuccessful outcome. The effect of the pattern short gaps between interruptions (aOR 2.11, 95% CI 0.85 – 5.24) was borderline.

Extension of drug resistance could be determined among 286/323 patients (88.5%) and occurred in 45 (15.7%) patients. Among patients having a pattern of long duration of interruptions, 18.3% extended drug resistance whereas this percentage fell to 2.2% among those having a pattern of short duration of interruptions (p=0.006). However, no difference was found according to the pattern of duration of gaps between interruptions (Table 5).

Discussion

The proportion of patients who successfully completed treatment was low in the two programs with a high proportion of patients who defaulted from treatment. This is consistent with the overall treatment success (48%) and defaulter rate (28%) reported in the 2013 WHO TB report [15]. WHO recommends the use of direct treatment observation for treatment of drug resistance

TB and assigns a final treatment outcome of treatment defaulter to a patient who interrupts treatment for 2 consecutive months or longer. However, we have shown that interruptions at short intervals of at least 3 days duration and low adherence (<80%) increased the risk of treatment failure or death. The effect seems to be more pronounced when the interruptions occurred during the first months of treatment.

In addition, patterns of duration of treatment interruption was significantly associated with the extension of drug-resistance to either fluoroquinolones or second-line injectables. This is consistent with the results of a previous study in MDR-TB patients, which showed an association between the cumulative number of months with less than 80% adherence and the development of XDR-TB [16]. This is particularly important since several studies have shown that amplification of resistance to second line drugs during treatment of MDR-TB were significantly associated with poor treatment response [3,5]. This association between treatment interruptions and acquired resistance questions the assumption, based on preclinical models, that acquired anti-tuberculosis drug resistance is due to between-patient pharmacokinetic variability and not to non-compliance [17].

Our results also highlight the poor tolerability of the current MDR-TB regimens and the effect on the treatment outcomes [18–21]. More than one third of treatment interruptions were due to patients' refusal to take the treatment. In another study in the same program in Armenia, poor treatment tolerability was also independently associated with the risk of defaulting treatment [4]. This highlights the needs to improve the early detection and management of mild side-effects, before they result in treatment interruption, especially during the ambulatory phase of the treatment. The absence of patient was also one of the main reasons of interruption of treatment. As shown in the previous study in Armenia and due to the length of treatment, patients may stop treatment in order to travel for professional or family reasons. A good communication between

the program and the patients is very important for the program to be informed in advance about patient's leave to adapt the treatment delivery and avoid interruption.

The study has some limitations. The analysis included only data from two programs in South Caucasus, which limits the reproducibility of the study results to other regions of the world. Sample size was not big enough to further assess in multivariate analysis the effect of treatment interruption on the extension of drug resistance. It was a retrospective analysis of observational data, which explains the amount of missing data. However, because both programs were using the same data collection system, there was a good homogeneity of the collected data. Excluding the 70 patients with no interruptions did not introduce a bias in our analysis and in the estimates of our primary variables of interest since they could not be classified with having short or long interruptions duration and short or long gap between interruptions.

These results highlight the weaknesses of the current regimen for the treatment of MDR-TB, which is very long, poorly tolerated and results in frequent treatment interruptions and poor outcomes. These results point out the importance of maximising the efforts to maintain patients on treatment. In addition to individual social and adherence support to patients, this would also imply very close monitoring of the frequency and duration of interruption. Contrary to HIV, there is need for more research to assess the best indicators or thresholds of treatment adherence to monitor in drug resistance TB. The use of new technologies to improve the quick detection of adherence problems and tolerability in order to rapidly help patients to cope with their treatment should be further investigated [22].

However ultimately, these results highlight the urgent needs for shorter, more efficacious and better tolerated drug regimens for the treatment of MDR TB, which could be anticipated with the advent of new drugs such as bedaquiline and delamanid [23–25].

Footnote Page

The authors have no conflicts of interest to disclose.

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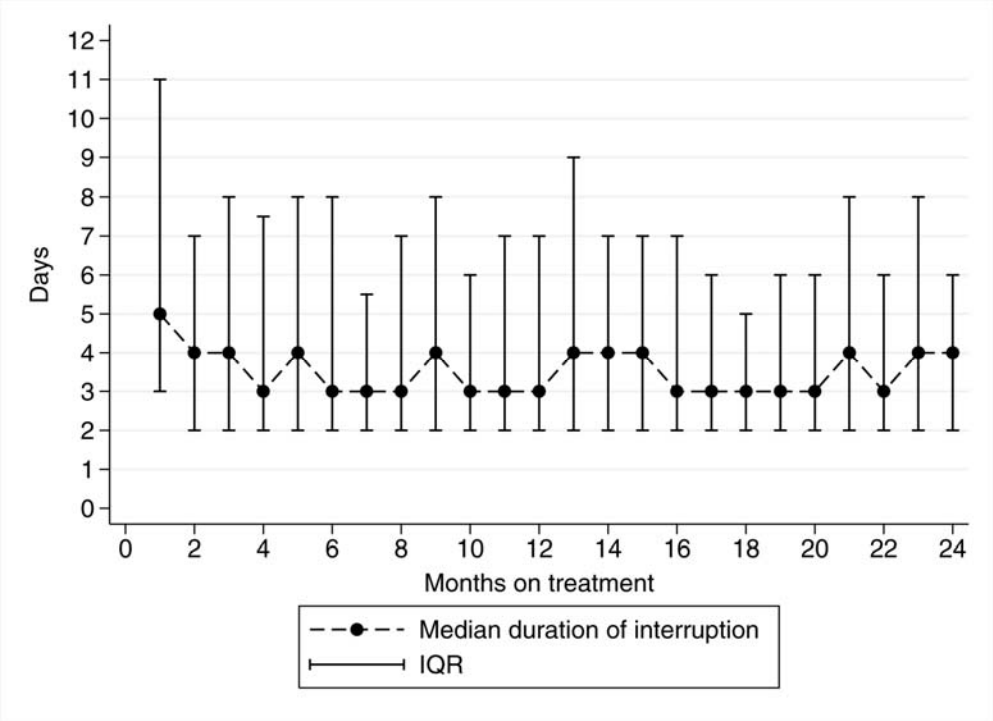

Tables

Table 1. Characteristics of MDR-TB patients at treatment initiation in Armenia and Abkhazia.

Characteristics	Armenia N=239	Abkhazia N=154	Overall N=393
Gender, n(%)			
Male	194 (81.2)	134 (87.0)	328 (83.5)
Female	45 (18.8)	20 (13.0)	65 (16.5)
Age (years)			
Median [IQR]	40 [29 – 49]	37 [30 – 47]	38 [30 – 48]
BMI (kg/m^2), n(%)			
Median [IQR]	20.4 [18.5 – 23.4]	19.8 [18.0 – 22.1]	20.1 [18.2 – 22.7]
< 18.5	58 (24.3)	47 (30.5)	105 (26.7)
≥ 18.5	181 (75.7)	107 (69.5)	288 (73.3)
Alcohol use, n(%)			
None	120 (50.2)	74 (48.0)	194 (49.4)
Moderate	107 (44.8)	68 (44.2)	175 (44.5)
Excessive	12 (5.0)	12 (7.8)	24 (6.1)
Diabetes, n(%)			
No	203 (84.9)	142 (92.2)	345 (87.8)

Yes	36 (15.1)	12 (7.8)	48 (12.2)
Ex-prisoner, n(%)			
No	159 (66.5)	78 (50.6)	237 (60.3)
Yes	80 (33.5)	76 (49.4)	156 (39.7)
Presence of cavities, n(%)			
No	21 (8.8)	80 (51.9)	101 (25.7)
Yes	218 (91.2)	74 (48.1)	292 (74.3)
History of TB treatment, n(%)			
New case	30 (12.8)	53 (34.9)	83 (21.4)
Previously treated first line	132 (56.2)	57 (37.5)	189 (48.8)
Previously treated second line	73 (31.0)	42 (27.6)	115 (29.7)
Unknown	4	2	6
Sputum smear-microscopy, n(%)			
Negative	21 (19.6)	17 (19.8)	38 (19.7)
Positive	86 (80.4)	69 (80.2)	155 (80.3)
Unknown	132	68	200
DST profile at admission, n(%)			
MDR without resistance to second line drug	67 (28.0)	79 (51.3)	146 (37.2)
Pre-XDR	31 (13.0)	55 (35.7)	86 (21.9)
XDR	6 (2.5)	9 (5.8)	15 (3.8)
MDR second line not tested	135 (56.5)	11 (7.2)	146 (37.1)

Table 2. Treatment duration and outcomes and of MDR-TB patients treated in Armenia and Abkhazia.

	Armenia N=239	Abkhazia N=154	Overall N=393
Treatment duration (months), Median [IQR]			
Cure	21.6 [21.0 – 22.5]	24.3 [23.0 – 29.7]	21.9 [21.0 – 24.0]
Treatment completed	21.1 [20.4 – 22.2]	24.4 [22.1 – 29.2]	22.0 [21.0 – 24.5]
Death	9.2 [2.3 – 15.0]	6.0 [2.6 – 17.2]	8.5 [2.6 – 16.1]
Failure	17.3 [11.9 – 23.6]	22.4 [15.9 – 27.8]	18.1 [12.7 – 23.9]
Defaulter	7.9 [4.3 – 13.8]	9.6 [4.8 – 20.7]	8.4 [4.5 – 15.7]
Outcome			
Cure	80 (33.5)	25 (16.2)	105 (26.7)
Treatment completed	35 (14.6)	31 (20.1)	66 (16.8)
Death	19 (8.0)	20 (13.0)	39 (9.9)
Failure	39 (16.3)	17 (11.0)	56 (14.3)
Defaulter	66 (27.6)	61 (39.6)	127 (32.3)

Table 3. Description and duration of interruptions and gaps between interruptions of MDR-TB patients during treatment stratified by successful and unsuccessful outcome (70 patients were excluded because they never interrupted treatment).

	Unsuccessful outcome N=182	Successful outcome N=141	p-value	Overall N=323
Number of interruptions per period of treatment (N=2859)			<0.001	
≤ 3 months of treatment	300 (18.3)	89 (7.3)		389 (13.6)
3 – 6 months of treatment	304 (18.5)	150 (12.3)		454 (15.9)
6 – 12 months of treatment	494 (30.1)	310 (25.4)		804 (28.1)
> 12 months of treatment	542 (33.1)	670 (55.0)		1212 (42.4)
Overall interruptions duration (N=2859, days)				
Median [IQR]	4 [2 – 9]	3 [2 – 5]	<0.001	3 [2 – 7]
Maximum duration of interruptions per patient (days)				
Median [IQR]	26 [15 – 38]	9 [5 – 18]	<0.001	18 [8 – 27]

Time to first interruption during treatment, n(%)				
Median [IQR]	65 [29 – 148]	143 [64 – 336]	<0.001	95 [42 – 205]
≤ 3 months	111 (61.0)	44 (31.2)		155 (48.0)
3 – 6 months	37 (20.3)	38 (27.0)		75 (22.2)
6 – 12 months	25 (13.7)	25 (17.7)		50 (15.5)
> 12 months	9 (5.0)	34 (24.1)		43 (13.3)
Incidence of interruptions due to patient				
Median [IQR]	1.41 [0.76 – 2.68]	0.68 [0.15 – 1.30]	<0.001	1.03 [0.39 – 2.05]
Incidence of interruptions due to side-effects				
Median [IQR]	0 [0 – 0.31]	0 [0 – 0.14]	0.172	0 [0 – 0.17]
Duration of gap between treatment interruption (days)				
Median [IQR]	10 [4 – 28]	19 [7 – 49]	<0.001	13 [5 – 37]
Pattern of interruptions duration[†], n(%)			<0.001	
Short	16 (8.8)	35 (24.8)		51 (15.8)
Long	166 (91.2)	106 (75.2)		272 (84.2)

Pattern of gaps between treatment interruptions [‡], n(%)		<0.001	
Short	81 (44.5)	15 (10.6)	96 (29.7)
Long	89 (48.9)	105 (74.5)	194 (60.1)
Undefined (only 1 interruption)	12 (6.6)	21 (14.9)	33 (10.2)
Reasons for interruptions (N=2859)		<0.001	
Patient absent	627 (38.2)	584 (47.9)	1211 (42.4)
Patient refused to take treatment	637 (38.8)	374 (30.7)	1011 (35.4)
Side-effect / intolerance	146 (8.9)	105 (8.6)	251 (8.8)
Comorbidity	66 (4.0)	57 (4.7)	123 (4.3)
Severe conditions	36 (2.2)	22 (1.8)	58 (2.0)
Other	128 (7.9)	77 (6.3)	205 (7.1)

[†] Pattern of interruptions duration: short if median duration of interruptions of 2 days; long if > 2 days

[‡] Pattern of gaps between treatment interruptions: short if median gaps between interruptions ≤ 10 days; long if > 10 days

Note: The three most common side-effects were gastrointestinal effect (54.6%), hepatotoxicity (16.2%) and systemic Hypersensitivity reaction (13.0%).

Table 4. Univariate and multivariate logistic regression to assess the impact of patterns of treatment interruptions on unsuccessful treatment outcome (N=323).

Predictors of unsuccessful treatment	Unsuccessful outcome (%)	Univariate			Multivariate		
		OR	95% CI	p-value	aOR	95% CI	p-value
Gender							
Male	162/271 (59.8)	ref					
Female	20/52 (38.5)	0.42	0.23 – 0.77	0.005			
Age (10 years increase)‡	-	1.03	0.87 – 1.21	0.744			
BMI (kg/m^2)							
< 18.5	46/81 (56.8)	ref					
≥ 18.5	136/242 (56.2)	0.98	0.59 – 1.62	0.926			
Alcohol use							
None	91/164 (55.5)	ref					

Moderate	78/138 (56.5)	1.04	0.66 – 1.64	0.857
Excessive	13/21 (61.9)	1.30	0.51 – 3.31	0.578
Diabetes				
No	162/286 (56.6)	ref		
Yes	20/37 (54.1)	0.90	0.45 – 1.79	0.765
Ex-prisoner				
No	98/193 (50.8)	ref		
Yes	84/130 (64.6)	1.77	1.12 – 2.80	0.014
Presence of cavities				
No	42/71 (59.1)	ref		
Yes	140/252 (55.6)	0.86	0.51 – 1.47	0.589
History of TB treatment				
New case	42/72 (58.3)	ref		
Previously treated first line	75/148 (50.7)	0.73	0.42 – 1.30	0.286
Previously treated second line	64/97 (66.0)	1.38	0.74 – 2.60	0.310
Unknown	1/6 (16.7)	0.14	0.02 – 1.29	0.083

Drugs previously received[‡]	-	1.15	0.89 – 1.48	0.272			
Sputum smear-microscopy							
Negative	14/29 (48.3)	ref					
Positive	75/126 (59.2)	1.58	0.70 – 3.54	0.272			
Unknown	93/168 (55.4)	1.33	0.60 – 2.92	0.481			
DST profile at admission							
MDR without resistance to second line drug	59/116 (50.9)	ref					
Pre-XDR	40/61 (65.6)	1.84	0.97 – 3.49	0.062			
XDR	10/11 (90.9)	9.66	1.20 – 77.92	0.033			
MDR second line not tested	73/135 (54.1)	1.14	0.69 – 1.87	0.611			
Adherence to treatment							
≥ 80%	30/127 (23.6)	ref			ref		
<80%	150/193 (77.7)	11.28	6.63 – 19.19	<0.001	6.93	3.54 – 13.61	<0.001
Unknown	2/3 (66.7)	0.31	0.20 – 0.47	0.133	4.22	0.29 – 62.88	0.190
Incidence of interruptions due to	-	2.04	1.60 – 2.60	<0.001	1.13	0.82 – 1.57	0.455

patient[†‡]							
Incidence of interruptions due to side-effects[†‡]	-	4.32	1.69 – 11.07	0.002	3.93	1.12 – 13.85	0.033
Incidence of interruptions due to comorbidities and severe conditions[†‡]	-	2.62	1.05 – 6.53	0.039	1.80	0.60 – 5.42	0.292
Pattern of interruptions duration							
Short	16/51 (31.8)	ref			ref		
Long	166/272 (61.0)	3.42	1.81 – 6.49	<0.001	3.87	1.66 – 8.98	0.002
Pattern of gaps between treatment interruptions							
Long	89/194 (45.9)	ref			ref		
Short	81/96 (84.4)	6.37	3.43 – 11.83	<0.001	3.94	1.76 – 8.81	0.001
Unknown	12/33 (36.4)	0.67	0.31 – 1.45	0.311	1.05	0.40 – 2.77	0.925

† Incidence=total number of interruptions/number of trimester that patient received treatment

‡ Continuous variable

Table 5. Description and duration of interruptions and gaps between interruptions of MDR-TB patients during treatment according to extension of drug resistance on fluoroquinolons, aminoglycosides and glycopeptides.

	Extension of drug resistance N=45	No extension of drug resistance N=241	p-value	Overall N=323
Overall interruptions duration (days)				
Median [IQR]	4 [3 – 8]	3 [2 – 7]	<0.001	3 [2 – 7]
Maximum duration of interruptions (days)				
Median [IQR]	24 [11 – 27]	17 [7 – 27]	0.378	18 [7 – 27]
Time to first interruption during treatment, n(%)				
Median [IQR]	128 [57 – 207]	105 [45 – 210]	0.877	105 [45 – 210]
Duration of gap between treatment interruption (days)				
Median [IQR]	15 [6 – 41]	13 [5 – 37]	0.101	14 [5 – 38]
Pattern of interruptions duration[†], n(%)			0.006	
Short	1 (2.2)	45 (18.7)		46 (16.1)

Long	44 (97.8)	196 (81.3)	240 (83.9)
Pattern of gaps between treatment interruptions [‡], n(%)		0.630	
Short	10 (22.2)	64 (86.5)	74 (25.9)
Long	32 (71.1)	154 (63.9)	186 (65.0)
Undefined (only 1 interruption)	3 (6.7)	23 (9.5)	26 (9.1)

[†] Pattern of interruptions duration: short if median duration of interruptions of 2 days; long if > 2 days

[‡] Pattern of gaps between treatment interruptions: short if median gaps between interruptions ≤ 10 days; long if > 10 days