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Effects of Treatment Interruption Patterns on Treatment Success Among Patients With Multidrug-Resistant Tuberculosis in Armenia and Abkhazia

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Background. The success of the current treatment regimen for multidrug-resistant (MDR) tuberculosis is poor partly owing to a high default rate. Many studies have explored predictors of poor outcomes, but very few have assessed the effects of treatment interruptions on treatment outcomes for MDR tuberculosis.

Methods. We conducted a retrospective analysis among patients with MDR tuberculosis enrolled in 2 MDR tuberculosis programs using regimens recommended by the World Health Organization under directly observed therapy. Treatment outcomes were defined as successful if the patient was cured or completed treatment and unsuccessful if the patient died or defaulted from treatment or if treatment failed. The effect of patterns of interruptions on treatment outcomes was assessed through multivariate logistic regression.

Results. A total of 393 patients with MDR tuberculosis 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%) had failed treatment, and 127 (32.3%) defaulted from treatment. In multivariate analysis, long interruptions (≥3 days) (adjusted odds ratio, 3.87; 95% confidence interval, 1.66–8.98) and short gaps (<10 days) between interruptions (3.94; 1.76–8.81) were independently associated with an unsuccessful treatment outcome.

Discussion. This study shows that in a directly observed therapy–based MDR tuberculosis program, treatment interruptions at short intervals of ≥3 days directly affect treatment outcome.

Keywords. multidrug-resistant; tuberculosis; treatment interruptions; outcomes; duration; gaps.

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

Treatment of patients with MDR tuberculosis is long and costly and has a low efficacy, resulting in very poor effectiveness in routine program conditions. In a very large meta-analysis, 54% of patients with MDR tuberculosis had a successful treatment outcome, consistent with the overall success rate for MDR tuberculosis reported by WHO in its last global report, ranging between 44% and 58% [1, 2]. One main cause of the poor outcomes is the high proportion of patients who default from treatment [2–4]. Several studies investigated factors associated with poor treatment outcomes in

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MDR tuberculosis, including social factors, advanced disease, fluoroquinolone resistance at treatment initiation or amplification during treatment, treatment duration, and number of drugs in the regimen [5–9]. Very few studies assessed the factors associated with defaulting from treatment for MDR tuberculosis. They found that treatment default was mostly associated with substance (alcohol and drug) abuse, socioeconomic 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 few consider 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 the WHO definition. We have conducted a retrospective study of data from 2 programs on DR tuberculosis to assess the effect of temporary interruptions on treatment outcomes in patients with MDR tuberculosis.

METHODS

Study Settings

We conducted a retrospective data analysis of routinely collected data in 2 drug-resistant (DR) tuberculosis programs supported by Médecins Sans Frontières, in Armenia and Abkhazia (Georgia). Patients were included in the study if baseline drug susceptibility testing (DST) confirmed MDR tuberculosis and if they started treatment ≥24 months before the administrative censoring date for the database, 31 July 2010. We excluded from the analysis patients who were transferred out or still receiving treatment at the database closing date. Patients' sociodemographic, clinical, and laboratory data at treatment initiation as well as their interruptions and adherence rate during treatment were collected in each program using the Koch6 software developed by Médecins Sans Frontières for the clinical management of patients with DR tuberculosis.

The DR tuberculosis programs covered the entire city of Yerevan in Armenia and the autonomous region of Abkhazia in Georgia. Treatment regimens were individualized based on DST results and included at least ≥4 effective drugs, including second-line drugs (ofloxacin, levofloxacin and moxifloxacin, kanamycin and capreomycin, para-aminosalicylic acid, ethionamide, cycloserine), for a duration of 18–24 months, according to the WHO guidelines [3, 4, 13]. Treatment administration was under direct observation during the full course of treatment 6 days a week with the patient either coming to the closest health facility or receiving the treatment at home from health personnel or a trained community member, to facilitate treatment after discharge from the hospital. Patients were hospitalized for treatment initiation and discharged after documentation of 2 smear-negative sputum samples. Patients underwent medical assessment during daily the first month of treatment and then monthly until the end of treatment, with careful management of adverse events. Psychological support was provided, individually and in group sessions, together with socioeconomic support (financial and nutrition support and transport reimbursement). 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 the patient died or defaulted from treatment or if treatment failed [13]. For second-line drugs with reliable susceptibility testing (fluoroquinolones, aminoglycosides, and glycopeptides), we defined extension of drug resistance as an increase in the number of drugs to which *Mycobacterium tuberculosis* was resistant in vitro during treatment follow-up compared with baseline. Pre–extensively drug-resistant (pre-XDR) was defined as resistance to ≥1 second-line injectable drug or to ofloxacin and extensively drug-resistant (XDR) as resistance to ofloxacin and ≥1 second-line injectable drug. For treatment interruptions, we considered their duration, the duration of the interval (gap) between 2 interruptions, and the incidence of the interruptions. We defined a treatment interruption as when a patient stopped all antituberculosis drugs for ≥2 consecutive days. Given that the overall median duration of interruption was 3 days, the pattern of the interruptions was defined as short if their median duration was ≤2 days and as long if it was >2 days. The gap between 2 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 (ie, period under treatment) was defined as short if their overall median duration was ≤10 days and as long if it was >10 days. We considered separately the incidence of treatment interruptions due to patients' decisions (eg, social reasons or refusal) and those due to clinicians' decisions (eg, adverse effects or poor tolerability, comorbid conditions, and severe clinical conditions). 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 receiving treatment, to take into account duration of treatment, which may vary according to outcome. The treatment adherence rate was calculated as the number of days that the drugs were taken divided by the number of days that they 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 medians and interquartile ranges (IQRs) for continuous variables. Only patients with ≥1 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 (long vs short) on treatment outcome. Patients with no interruptions did not fall into one of the categories because they never interrupted the treatment. Number of interruptions relative to time on treatment, median duration of interruptions, maximum duration of interruptions, time to first interruption and duration of gaps between interruptions were calculated according to 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 χ^2 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: program location, sex, age, alcohol use, known diabetes, being a former prisoner, history of

Table 1. Characteristics of Patients With MDR Tuberculosis at Treatment Initiation in Armenia and Abkhazia

Characteristic	Patients, No. (%)[a]		
	Armenia (n = 239)	Abkhazia (n = 154)	Overall (N = 393)
Sex			
Male	194 (81.2)	134 (87.0)	328 (83.5)
Female	45 (18.8)	20 (13.0)	65 (16.5)
Age, median (IQR), y	40 (29–49)	37 (30–47)	38 (30–48)
BMI, median (IQR), kg/m^2	20.4 (18.5–23.4)	19.8 (18.0–22.1)	20.1 (18.2–22.7)
BMI category			
<18.5 kg/m^2	58 (24.3)	47 (30.5)	105 (26.7)
≥18.5 kg/m^2	181 (75.7)	107 (69.5)	288 (73.3)
Alcohol use			
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			
No	203 (84.9)	142 (92.2)	345 (87.8)
Yes	36 (15.1)	12 (7.8)	48 (12.2)
Former prisoner			
No	159 (66.5)	78 (50.6)	237 (60.3)
Yes	80 (33.5)	76 (49.4)	156 (39.7)
Cavities on chest radiograph			
No	21 (8.8)	80 (51.9)	101 (25.7)
Yes	218 (91.2)	74 (48.1)	292 (74.3)
History of tuberculosis treatment			
New case	30 (12.8)	53 (34.9)	83 (21.4)
Previously treated with 1st-line drug	132 (56.2)	57 (37.5)	189 (48.8)
Previously treated with 2nd-line drug	73 (31.0)	42 (27.6)	115 (29.7)
Unknown	4	2	6
Sputum smear microscopic results			
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			
MDR without resistance to 2nd-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 (2nd-line drug not tested)	135 (56.5)	11 (7.2)	146 (37.1)

Abbreviations: BMI, body mass index; DST, drug susceptibility testing; IQR, interquartile range; MDR, multidrug-resistant; XDR, extensively drug-resistant.

[a] Unless otherwise specified, data represent No. (%) of patients.

earlier tuberculosis treatment, number of drugs previously received (before actual MDR regimen, including first- and second-line antituberculosis drugs), body mass index, presence of cavities on chest radiograph, sputum smear microscopy result, DST profile at treatment initiation, adherence to treatment, and incidence of adverse effects per month of treatment. Covariates associated with a P value of <.40 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 ($P < .05$) was assessed with the likelihood-ratio test. Sensitivity analysis excluding patients who defaulted from treatment was 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 ≥1 culture follow-up result available. Analyses were performed using Stata 12.1 software (StataCorp).

Ethical approval was sought from the ethical committee of the University of Psychology of Yerevan, the Biomedical Research Ethics Committee of the National Center for Tuberculosis and Lung Diseases in 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 patients with MDR tuberculosis who started treatment between 19 June 2002 and 29 June 2010, a total of 22 (3.5%) were excluded from analysis because they did not have an outcome assigned at the administrative censoring date for the database (12 were still receiving treatment and 10 had transferred out). Therefore, a total of 393 patients with MDR tuberculosis were included in the study, 60.8% from Armenia and 39.2% from Abkhazia. Their characteristics at treatment initiation are presented in Table 1. Most of them (83.5%) were male, their median age was 38 years (IQR, 30–48 years), and their median body mass index was 20.1 kg/m^2 (IQR, 18.2–22.7 kg/m^2). New cases accounted for 21.4% of patients, and 48.8% and 29.7% had been previously treated with first- or second-line drugs, respectively. At treatment initiation, 155 patients (80.3%) had positive sputum smears, and the DST profiles of patients was distributed as follows: 37.2% MDR without resistance to second-line drug, 21.9% pre-XDR, 3.8% XDR, and 37.1% MDR with unknown resistance to second line drugs.

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 default rate in Abkhazia ($P < .001$). Overall, the median treatment duration was 11.3 months (IQR, 4.9–19.1 months) for patients with unsuccessful outcome and 22.0 months (21.0–24.1 months) for those with a successful outcome. Patients defaulted from treatment after a median (IQR) of 8.4 months (4.5–15.7 months).

Among all patients, the median number of interruptions was 5 (IQR, 2–11) for patients with an unsuccessful outcome and 4 (1–11) for those with a successful outcome ($P = .50$). Seventy patients had no interruptions during their treatment course; 40 (57.1%) of them 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 with ≥1 interruption. In Table 3, we provide a detailed description of the interruptions. For the 2859 interruptions, the median duration of interruptions was 3 days (IQR, 2–5 days) for patients with a successful outcome and 4 days (2–9 days) for those with an unsuccessful outcome ($P < .001$). As displayed in Figure 1, the

Table 2. Treatment Duration and Outcomes in Patients With MDR Tuberculosis Treated in Armenia and Abkhazia

Treatment Durations and Outcomes	Armenia (n = 239)	Abkhazia (n = 154)	Overall (N = 393)
Treatment duration, median (IQR), mo			
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)
Treatment failure	17.3 (11.9–23.6)	22.4 (15.9–27.8)	18.1 (12.7–23.9)
Default from treatment	7.9 (4.3–13.8)	9.6 (4.8–20.7)	8.4 (4.5–15.7)
Outcome, No. (%) of patients			
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)
Treatment failure	39 (16.3)	17 (11.0)	56 (14.3)
Default from treatment	66 (27.6)	61 (39.6)	127 (32.3)

Abbreviations: IQR, interquartile range; MDR, multidrug-resistant.

Table 3. Characteristics of Treatment Interruptions and Gaps Between Interruptions in Patients With MDR Tuberculosis Stratified by Successful and Unsuccessful Outcomes[a]

Characteristics of Treatment Interruptions and Gaps Between Interruptions	Unsuccessful Outcome (n = 182)	Successful Outcome (n = 141)	*P* Value	Overall (N = 323)
Interruptions by length of treatment, No (%) of interruptions (N = 2859)				
≤3 mo of treatment	300 (18.3)	89 (7.3)	<.001	389 (13.6)
3–6 mo of treatment	304 (18.5)	150 (12.3)		454 (15.9)
6–12 mo of treatment	494 (30.1)	310 (25.4)		804 (28.1)
>12 mo of treatment	542 (33.1)	670 (55.0)		1212 (42.4)
Overall duration of interruptions, median (IQR), d	4 (2–9)	3 (2–5)	<.001	3 (2–7)
Maximum duration of interruptions per patient, median (IQR), d	26 (15–38)	9 (5–18)	<.001	18 (8–27)
Time to first interruption, median (IQR), d	65 (29–148)	143 (64–336)	<.001	95 (42–205)
Time to first interruption, No. (%) of patients				
≤3 mo of treatment	111 (61.0)	44 (31.2)	<.001	155 (48.0)
3–6 mo of treatment	37 (20.3)	38 (27.0)		75 (22.2)
6–12 mo of treatment	25 (13.7)	25 (17.7)		50 (15.5)
>12 mo	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)	<.001	1.03 (0.39–2.05)
Incidence of interruptions due to adverse effects, median (IQR)[b]	0 (0–0.31)	0 (0–0.14)	.17	0 (0–0.17)
Duration of gaps between interruptions, median (IQR), d	10 (4–28)	19 (7–49)	<.001	13 (5–37)
Patterns of interruptions or gaps, No. (%) of patients				
Duration of interruptions[c]			<.001	
Short	16 (8.8)	35 (24.8)		51 (15.8)
Long	166 (91.2)	106 (75.2)		272 (84.2)
Duration of gaps between interruptions[d]				
Short	81 (44.5)	15 (10.6)	<.001	96 (29.7)
Long	89 (48.9)	105 (74.5)		194 (60.1)
Undefined (single interruption)	12 (6.6)	21 (14.9)		33 (10.2)
Reason for interruptions, No. (%) of interruptions (N = 2859)				
Patient absent	627 (38.2)	584 (47.9)	<.001	1211 (42.4)
Patient refused treatment	637 (38.8)	374 (30.7)		1011 (35.4)
Adverse effect/intolerance[b]	146 (8.9)	105 (8.6)		251 (8.8)
Comorbid conditions	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)

Abbreviations: IQR, interquartile range; MDR, multidrug-resistant.

[a] Seventy patients were excluded because they never interrupted treatment.

[b] The 3 most common adverse effects were gastrointestinal effect (54.6%), hepatotoxicity (16.2%), and systemic hypersensitivity reaction (13.0%).

[c] Interruptions duration were considered short if their median duration was 2 days and long if it was >2 days.

[d] Gaps between treatment interruptions were considered short if their median duration was ≤10 days and long if it was >10 days.

duration of interruptions did not vary strongly according to length of treatment. This figure was observed for both patients with a successful and those with an unsuccessful outcome. The median maximum duration of interruption was 18 days (IQR, 8–27 days) and was higher for patients with an unsuccessful outcome ($P < .001$). The first interruption occurred in the first 3 months of treatment for 48.0% of patients and after 6 months for 28.8%, and it differed according to treatment outcome ($P < .001$). Among the 2859 interruptions, the median gap between 2 consecutive interruptions was 13 days (IQR, 5–37 days), and it was lower for patients with an unsuccessful outcome ($P < .001$). Using our definitions of patterns of interruptions during treatment, we found that 84.2% of patients had a pattern of long interruptions and 29.7% had a pattern of short gaps between interruptions and that both of these patterns were more common in the unsuccessful outcome group ($P < .001$). The main reasons for interruptions were decisions made by patients themselves (treatment refusal or patient absence) followed by medical decisions (due to adverse effects or intolerance, comorbid conditions, or severe conditions).

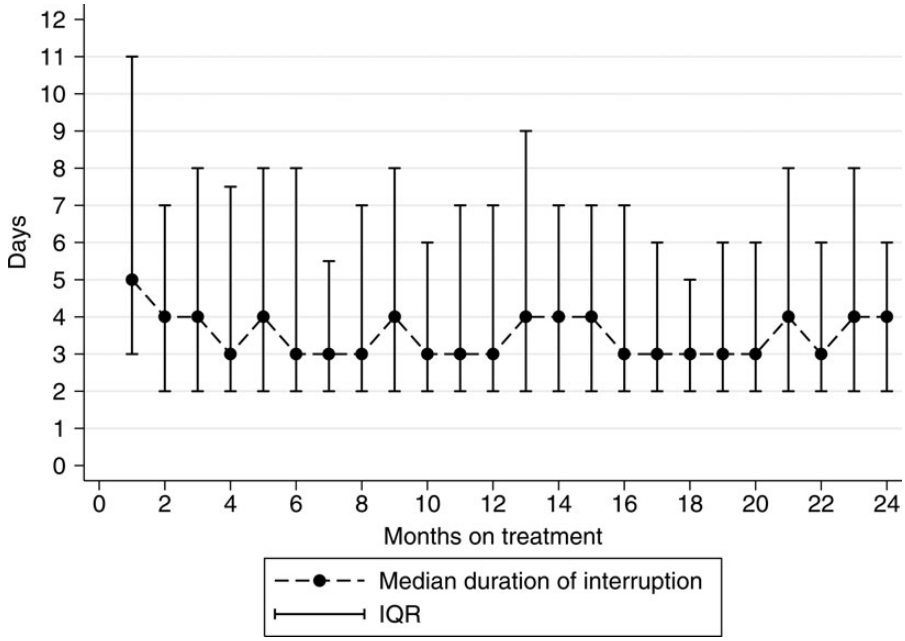

Figure 1. Median duration of treatment interruptions according to length of treatment. Abbreviation: IQR, interquartile range.

Results of univariate and multivariate analysis are presented in Table 4. After univariate analysis, the following potential confounders were included in the initial multivariate model: program, sex, being an former prisoner, history of tuberculosis treatment, sputum smear microscopy result, DST profile at initiation, adherence to treatment and incidence of adverse effects during treatment. The final multivariate model showed that having a pattern of long interruptions (adjusted odds ratio [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. The incidence of interruptions due to adverse effects (aOR, 3.93; 95% CI, 1.12–13.85) was also independently associated with an unfavorable outcome, whereas the incidence of interruptions based on a patient's decision was not. This meant that for each additional interruption due to adverse effects in a 3-month period, we observed a 4-fold increase in the odds of unfavorable outcome. Finally, treatment adherence <80% (aOR, 6.93; 95% CI, 3.54–13.61) was strongly associated with an unfavorable outcome. However, we found no significant association between DST profile at admission and treatment outcomes ($P = .20$), including when we grouped MDR without resistance to second-line drug and MDR second-line drug not tested.

When defaulters were excluded in the sensitivity analysis and after adjustment for the same confounders, a pattern of long interruptions (aOR, 3.02; 95% CI, 1.16–7.90) and the incidence of interruptions due to adverse effects (aOR, 6.01; 95% CI, 1.60–22.55) remained independently associated with unsuccessful outcome. The pattern of short gaps between interruptions (aOR, 2.11; 95% CI, .85–5.24) had borderline a borderline effect.

Extension of drug resistance could be determined among 286 of 323 patients (88.5%) and occurred in 45 (15.7%). Among patients with a pattern of long duration of interruptions, drug resistance was extended in 18.3%, whereas this percentage fell to 2.2% among those with a pattern of short duration of interruptions ($P = .006$). However, no difference was found according to patterns of the duration of gaps between interruptions (Table 5).

DISCUSSION

The proportion of patients who successfully completed treatment was low in the 2 programs, with a high proportion of patients who defaulted from treatment. This is consistent with the overall treatment success (48%) and default rate (28%) reported in the 2013 WHO report on tuberculosis [15]. The WHO recommends the use of direct treatment observation for treatment of DR tuberculosis and assigns a final treatment outcome of treatment defaulter to a patient who interrupts treatment for ≥2 consecutive months. However, we have shown that interruptions at short intervals of ≥3 days 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 in the duration of treatment interruptions were significantly associated with the extension of drug resistance to either fluoroquinolones or second-line injectables.

Table 4. Univariate and Multivariate Logistic Regression to Assess the Effects of Patterns of Treatment Interruptions on Unsuccessful Treatment Outcome (N = 323)

Predictor of Unsuccessful Treatment	Unsuccessful Outcome, No. (%)	Univariate Analysis			Multivariate Analysis		
		OR	95% CI	*P* Value	aOR	95% CI	*P* Value
Sex							
Male	162/271 (59.8)	Reference	. . .	. . .	. . .	. . .	. . .
Female	20/52 (38.5)	0.42	.23–.77	.005	. . .	. . .	. . .
Age (10-y increase)[a]	. . .	1.03	.87–1.21	.74	. . .	. . .	. . .
BMI							
<18.5 kg/m^2	46/81 (56.8)	Reference	. . .	. . .	. . .	. . .	. . .
≥18.5 kg/m^2	136/242 (56.2)	0.98	.59–1.62	.93	. . .	. . .	. . .
Alcohol use							
None	91/164 (55.5)	Reference	. . .	. . .	. . .	. . .	. . .
Moderate	78/138 (56.5)	1.04	.66–1.64	.86	. . .	. . .	. . .
Excessive	13/21 (61.9)	1.30	.51–3.31	.58	. . .	. . .	. . .
Diabetes							
No	162/286 (56.6)	Reference	. . .	. . .	. . .	. . .	. . .
Yes	20/37 (54.1)	0.90	.45–1.79	.76	. . .	. . .	. . .
Former prisoner							
No	98/193 (50.8)	Reference	. . .	. . .	. . .	. . .	. . .
Yes	84/130 (64.6)	1.77	1.12–2.80	.01	. . .	. . .	. . .
Cavities on chest radiograph							
No	42/71 (59.1)	Reference	. . .	. . .	. . .	. . .	. . .
Yes	140/252 (55.6)	0.86	.51–1.47	.59	. . .	. . .	. . .
History of tuberculosis treatment							
New case	42/72 (58.3)	Reference	. . .	. . .	. . .	. . .	. . .
Previously treated with 1st-line drug	75/148 (50.7)	0.73	.42–1.30	.29	. . .	. . .	. . .
Previously treated with 2nd-line drug	64/97 (66.0)	1.38	.74–2.60	.31	. . .	. . .	. . .
Unknown	1/6 (16.7)	0.14	.02–1.29	.08	. . .	. . .	. . .
Drugs previously received[a]	. . .	1.15	.89–1.48	.27	. . .	. . .	. . .
Sputum smear microscopic results							
Negative	14/29 (48.3)	Reference	. . .	. . .	. . .	. . .	. . .
Positive	75/126 (59.2)	1.58	.70–3.54	.27	. . .	. . .	. . .
Unknown	93/168 (55.4)	1.33	.60–2.92	.48	. . .	. . .	. . .
DST profile at admission							
MDR without resistance to 2nd-line drug	59/116 (50.9)	Reference	. . .	. . .	. . .	. . .	. . .
Pre-XDR	40/61 (65.6)	1.84	.97–3.49	.06	. . .	. . .	. . .
XDR	10/11 (90.9)	9.66	1.20–77.92	.03	. . .	. . .	. . .
MDR (2nd-line drug unknown)	73/135 (54.1)	1.14	.69–1.87	.61	. . .	. . .	. . .
Adherence to treatment							
≥ 80%	30/127 (23.6)	Reference	. . .	. . .	Reference	. . .	. . .
<80%	150/193 (77.7)	11.28	6.63–19.19	<.001	6.93	3.54–13.61	<.001
Unknown	2/3 (66.7)	0.31	.20–.47	.13	4.22	.29–62.88	.19
Incidence of interruptions due to patient[a,b]	. . .	2.04	1.60–2.60	<.001	1.13	.82–1.57	.46
Incidence of interruptions due to adverse effects[a,b]	. . .	4.32	1.69–11.07	.002	3.93	1.12–13.85	.03
Incidence of interruptions due to comorbid and severe conditions[a,b]	. . .	2.62	1.05–6.53	.04	1.80	.60–5.42	.29
Pattern of interruptions or gaps							
Duration of interruptions							
Short	16/51 (31.8)	Reference	. . .	. . .	Reference	. . .	. . .
Long	166/272 (61.0)	3.42	1.81–6.49	<.001	3.87	1.66–8.98	.002
Duration of gaps between interruptions							
Long	89/194 (45.9)	Reference	. . .	. . .	Reference	. . .	. . .
Short	81/96 (84.4)	6.37	3.43–11.83	<.001	3.94	1.76–8.81	.001
Unknown	12/33 (36.4)	0.67	.31–1.45	.31	1.05	.40–2.77	.92

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; DST, drug susceptibility testing; IQR, interquartile range; MDR, multidrug-resistant; OR, odds ratio; XDR, extensively drug-resistant.

[a] Continuous variable.

[b] Incidence represents the total number of interruptions divided by the number of trimesters that the patient received treatment.

Table 5. Characteristics of Treatment Interruptions and Gaps Between Interruptions in Patients with MDR Tuberculosis According to Extension of Drug Resistance on Fluoroquinolones, Aminoglycosides, and Glycopeptides

Characteristics of Treatment Interruptions and Gaps Between Interruptions	Extension of Drug Resistance (n = 45)	No Extension of Drug Resistance (n = 241)	*P* Value	Overall (N = 323)
Overall duration of interruptions, median (IQR), d	4 (3–8)	3 (2–7)	<.001	3 (2–7)
Maximum duration of interruptions, median (IQR), d	24 (11–27)	17 (7–27)	.38	18 (7–27)
Time to first interruption during treatment, median (IQR), d	128 (57–207)	105 (45–210)	.83	105 (45–210)
Duration of gaps between interruptions, median (IQR), d	15 (6–41)	13 (5–37)	.10	14 (5–38)
Pattern of interruptions or gaps, No. (%) of patients				
Duration of interruptions[a]				
Short	1 (2.2)	45 (18.7)	.006	46 (16.1)
Long	44 (97.8)	196 (81.3)		240 (83.9)
Duration of gaps between interruptions[b]				
Short	10 (22.2)	64 (86.5)	.63	74 (25.9)
Long	32 (71.1)	154 (63.9)		186 (65.0)
Undefined (single interruption)	3 (6.7)	23 (9.5)		26 (9.1)

Abbreviations: IQR, interquartile range; MDR, multidrug-resistant.

[a] Interruptions duration were considered short if their median duration was 2 days and long if it was >2 days.

[b] Gaps between treatment interruptions were considered short if their median duration was ≤10 days and long if it was >10 days.

This is consistent with the results of a previous study in patients with MDR tuberculosis, which showed an association between the cumulative number of months with <80% adherence and the development of XDR tuberculosis [16]. This is particularly important because several studies have shown that amplification of resistance to second-line drugs during treatment of MDR tuberculosis were significantly associated with poor treatment response [3, 5]. This association between treatment interruptions and acquired resistance challenges the assumption, based on preclinical models, that acquired resistance to antituberculosis drugs is due to between-patient pharmacokinetic variability and not to noncompliance [17].

Our results also highlight the poor tolerability of the current MDR tuberculosis 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 from treatment [4]. This highlights the needs to improve the early detection and management of mild adverse effects, before they result in treatment interruption, especially during the ambulatory phase of the treatment. The absence of the patient was also a main reason for treatment interruption. As shown in the previous study in Armenia and owing to the length of treatment, patients may stop treatment to travel for professional or family reasons. Good communication between program and patients is essential; the program should be informed in advance about patients' travel plans in order to adapt treatment delivery and avoid interruption.

Our study has some limitations. The analysis included data from only 2 programs in South Caucasus, which limits the reproducibility of the study results to other regions of the world. The sample size was not big enough to further assess in multivariate analysis the effect of treatment interruption on the extension of drug resistance. The study 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 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 because they could not be classified as having short or long interruptions and short or long gaps between interruptions.

These results highlight the weaknesses of the current regimen for the treatment of MDR tuberculosis, which is very long, poorly tolerated, and results in frequent treatment interruptions and poor outcomes. These results point out the importance of maximizing the efforts to maintain patients on treatment. In addition to individual social and adherence support to patients, this also implies very close monitoring of the frequency and duration of interruptions. Unlike with human immunodeficiency virus, more research is needed to assess the best indicators or thresholds of treatment adherence to monitor in DR tuberculosis. The use of new technologies to improve the quick detection of adherence problems and tolerability and thus respond rapidly to help patients to cope with their treatment should be further investigated [22]. Ultimately, however, these results highlight the urgent needs for shorter, more efficacious and better tolerated drug regimens for the treatment of MDR tuberculosis,

which could be anticipated with the advent of new drugs such as bedaquiline and delamanid [23–25].

Notes

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