International Journal of Infectious Diseases 16 (2012) e391–e396

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Adjunctive surgery improves treatment outcomes among patients with multidrug-resistant and extensively drug-resistant tuberculosis

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ARTICLE INFO

Article history:
Received 22 August 2011
Accepted 13 December 2011

Corresponding Editor: William Cameron, Ottawa, Canada

Keywords:
Drug-resistant
Tuberculosis
Treatment
Outcome
Surgery

SUMMARY

Objectives: To determine risk factors for poor outcomes among patients with pulmonary multidrug- or extensively drug-resistant (M/XDR) tuberculosis (TB) in Georgia.
Methods: This was a prospective, population-based observational cohort study.
Results: Among 380 M/XDR-TB patients (mean age 38 years), 179 (47%) had a poor outcome: 59 (16%) died, 37 (10%) failed, and 83 (22%) defaulted. Newly diagnosed M/XDR-TB cases were significantly more likely to have a favorable outcome than retreatment cases (odds ratio (OR) 4.26, 95% confidence interval (CI) 1.99–9.10, $p < 0.001$). In the multivariable analysis, independent risk factors for a poor treatment outcome included previous treatment history (OR 2.92, 95% CI 1.29–6.58), bilateral disease (OR 1.90, 95% CI 1.20–3.01), body mass index (BMI, kg/m^2) ≤18.5 (OR 1.91, 95% CI 1.11–3.29), and XDR-TB (OR 2.28, 95% CI 1.11–4.71). Patients who underwent surgical resection (OR 0.27, 95% CI 0.11–0.64) and had sputum culture conversion by 4 months (OR 0.33, 95% CI 0.21–0.52) were significantly less likely to have poor treatment outcomes.
Conclusions: Adjunctive surgery appeared to be beneficial in treating patients with M/XDR-TB. Retreatment cases, XDR-TB, bilateral disease, and low BMI were associated with a poor outcome. Additional studies are needed to further define the apparent beneficial role of surgery in the treatment of M/XDR-TB.

1. Introduction

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) have emerged as serious public health problems in many countries, including Georgia, and threaten to undermine efforts to improve TB control.[1] MDR-TB is defined as *Mycobacterium tuberculosis* resistant to both isoniazid and rifampin, and as XDR by additional resistance to any fluoroquinolone and any one of three injectable agents: amikacin, capreomycin, and kanamycin. Two meta-analyses reported the average proportion of successful treatment outcomes in MDR-TB patients to be 62%, while in XDR patients it was only 42%.[2,3] Principal reasons for poor outcomes with M/XDR-TB include lengthy, costly, and inadequate treatment regimens and limited availability of second-line drugs (SLDs). In 2008, it was estimated that of the approximately 440 000 MDR-TB cases worldwide, less than 2% were treated with a World Health Organization (WHO) recommended regimen.[4] In an effort to improve SLD access, the Green Light Committee Initiative was formed in 2000 and has since made important progress in expanding access to quality-assured SLDs for M/XDR-TB patients treated within a programmatic setting. To date, more than 29 000 patients have received or are receiving care for M/XDR-TB through the Green Light Committee, with the estimated number of patients on treatment expected to double in the next year.[5]

Georgia is one of 27 high MDR-TB burden countries as designated by the WHO.[6] A 2006 population-based survey carried out by our group found 7% of all new TB cases and 27% of retreatment cases were either MDR- or XDR-TB.[7] Of particular concern is that more recent in-country surveillance data have shown the prevalence of M/XDR-TB to be >10% in newly diagnosed cases and >40% in retreatment cases. The first pilot MDR-TB treatment program in Georgia took place in 2006 in collaboration with Médecins San Frontières. Based on the success of this project and the rising prevalence of M/XDR-TB, the Georgian National TB Program (NTP) applied for and received Green Light Committee Initiative approval for quality-assured SLD access. The approval from the Green Light Committee in combination with support from The Global Fund enabled universal access to diagnosis and treatment for M/XDR-TB in Georgia beginning in 2008.

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1201-9712/$36.00 – see front matter
doi:10.1016/j.ijid.2011.12.018

The main objective of this study was to assess the clinical outcomes of the first cohort of M/XDR-TB patients treated with SLDs by the Georgian NTP and to determine risk factors for poor treatment outcome.

2. Methods

2.1. Study population

All patients in Georgia aged ≥16 years with laboratory-confirmed pulmonary M/XDR-TB initiating treatment between March and December 2008 through the Georgian NTP were enrolled in a prospective observational study. The study was approved by the institutional review boards of the Georgian National Center for Tuberculosis and Lung Diseases, Georgia, and Emory University, USA.

2.2. Drug susceptibility testing

All patients had sputum culture and first- and second-line drug susceptibility testing (DST) performed at the National TB Reference Laboratory in Tbilisi, Georgia. DST to first-line drugs was performed using the absolute concentration method on Löwenstein–Jensen medium with the following drug concentrations: streptomycin 4 μg/ml, isoniazid 0.2 μg/ml, rifampin 40 μg/ml, and ethambutol 2 μg/ml. DST to second-line anti-TB drugs was performed using the proportion concentration method with the following drug concentrations: ethionamide 40.0 μg/ml, ofloxacin 2.0 μg/ml, para-aminosalicylic acid 0.5 μg/ml, capreomycin 40.0 μg/ml, and kanamycin 30.0 μg/ml.[8] Pyrazinamide testing was performed using the MGIT960 liquid broth system (concentration 100 μg/ml).[9] External quality control of the Georgian National TB Reference Laboratory was performed by the WHO-affiliated Supranational Reference Laboratory in Antwerp, Belgium.[8]

2.3. Definitions

Treatment outcomes were defined using WHO criteria.[10] Cure and treatment completion were classified as a favorable outcome; treatment failure, death during treatment, and default were classified as a poor outcome.[10]

2.4. Treatment

Treatment regimens were individualized based on DST results and guided by WHO recommendations.[10] Regimens were designed to include at least four drugs to which the patient's *M. tuberculosis* isolate was susceptible.[10] All treatment regimens included a fluoroquinolone (moxifloxacin or levofloxacin) and also an injectable agent (i.e., kanamycin or capreomycin) for at least 6 months. Treatment was continued for at least 18 months after achieving a negative sputum culture. All patients received treatment through directly observed therapy (DOT). Most patients received initial care as an inpatient before transitioning to outpatient treatment.

The decision to perform surgical resection (i.e., adjunctive surgical therapy) was made by the Georgian NTP Drug Resistance Committee. In addition, sufficient pulmonary function to tolerate resection and a localized lesion amenable to resection were required.

2.5. Data collection

Demographic and clinical information were collected from the medical records. Sputum culture and DST results were obtained from either the medical records or the National TB Reference Laboratory database. Treatment outcomes were collected as part of ongoing surveillance at the NTP using a standardized 'treatment outcomes' form.

2.6. Statistical analysis

Data analyses were performed using SAS software, version 9.1 (Cary, NC, USA). For descriptive statistics, differences in categorical variables were tested using the Chi-square test, and for continuous variables a two-sample *t*-test was used. A binary multivariable logistic regression model was used to evaluate the independent association of potential risk factors with poor outcome. Model building and selection was based on the purposeful selection of covariates strategy as previously described, based on epidemiological findings in the bivariate analysis and biological plausibility.[11] A *p*-value of <0.05 was considered significant.

3. Results

3.1. Patient characteristics

Three hundred and eighty patients in Georgia with laboratory-confirmed pulmonary M/XDR-TB were enrolled in the study. The average age was 38 years (range 16–81 years), and 109 patients (29%) were female (Table 1). Among the 380 patients with M/XDR-TB, 334 (88%) had a prior history of TB treatment ('retreatment cases') and 46 (12%) were newly diagnosed TB cases (Table 1). Compared to new cases, retreatment cases were significantly older, reported alcohol abuse more frequently, and were more likely to have bilateral radiological disease (Table 1). In addition, newly diagnosed M/XDR-TB cases had a higher rate of culture conversion at 4 months than retreatment cases (67% vs. 43%, $p = 0.002$). There was no significant difference in the rate of XDR-TB among new and retreatment cases (9% vs. 13%, $p = 0.36$).

3.2. Drug resistance

Based on DST, the average number of drugs to which *M. tuberculosis* isolates were resistant was 5.4 (range 2–10). In addition to isoniazid and rifampin resistance (100% by definition), there were high rates of drug resistance to streptomycin (92%), ethambutol (66%), and ethionamide (59%), while the proportion of patients resistant to the remainder of drugs tested by DST was lower (Table 2). Resistance to pyrazinamide was 22%. Patients who had a history of receiving treatment with SLDs had significantly higher rates of resistance to fluoroquinolones (ofloxacin, 41% vs. 17%, $p < 0.001$), kanamycin (51% vs. 35%, $p = 0.002$), and capreomycin (38% vs. 20%, $p < 0.001$) compared to newly diagnosed TB cases.

3.3. Treatment outcomes

Among 380 patients with M/XDR-TB, 201 (53%) had a favorable outcome and 179 (47%) had a poor treatment outcome, including 59 (16%) who died, 37 (10%) with treatment failure, and 83 (22%) who defaulted from treatment (Table 3). Newly diagnosed M/XDR-TB cases were significantly more likely to have a favorable outcome than retreatment cases (37/46 (80%) vs. 164/334 (49%); odds ratio (OR) 4.26, 95% confidence interval (CI) 1.99–9.10; $p < 0.001$).

3.4. Prognostic factors for a poor outcome

In univariable analysis, factors that were associated with a poor treatment outcome included older age, body mass index (BMI, kg/m^2) ≤18.5, bilateral disease on chest radiograph, being a

Table 1
Clinical characteristics of 380 patients with multidrug- or extensively drug-resistant tuberculosis (M/XDR-TB)

Patient characteristics	Number of patients, *n* (%) (*N* = 380)	New cases, *n* (%) (*n* = 46)	Retreatment cases, *n* (%) (*n* = 334)	*p*-Value[a]
Female sex	109 (29)	21 (46)	88 (26)	0.007
Age (years), mean (range)	38 (16–81)	33 (16–81)	39 (16–77)	0.004[b]
Married	258 (68)	29 (63)	229 (69)	0.45
Employed	52 (14)	10 (22)	42 (13)	0.09
Current smoker	152 (40)	14 (30)	138 (41)	0.16
Alcohol use	94 (25)	6 (13)	88 (26)	0.05
History of injection drug use	14 (4)	0	14 (4)	0.16
History of incarceration	51 (13)	4 (9)	47 (14)	0.31
Diabetes mellitus	35 (9)	4 (9)	31 (9)	0.90
HIV infection	5 (1)	1 (2)	4 (1)	0.52
BMI $\leq$18.5 kg/m^2	92 (24)	8 (17)	84 (25)	0.25
Bilateral lesions on X-ray	198 (52)	17 (37)	181 (54)	0.02
Drug resistance pattern: XDR	49 (13)	4 (9)	45 (13)	0.36
Treatment characteristics				
4-month culture conversion	173 (46)	31 (67)	142 (43)	0.002
Adjunctive surgical resection	37 (10)	5 (11)	32 (10)	0.78

XDR, extensively drug-resistant; BMI, body mass index.
[a] *p*-Value for Chi-square test unless otherwise stated.
[b] *p*-Value for two-sided, unpaired *t*-test.

Table 2
Drug resistance at start of treatment by patient category (*N* = 380)

	New cases, *n* (%)	Prior first-line anti-TB drug treatment, *n* (%)	Prior second-line anti-TB drug treatment, *n* (%)	Total, *n* (%)
First-line drugs				
Isoniazid	46 (100)	253 (100)	81 (100)	380 (100)
Rifampin	46 (100)	253 (100)	81 (100)	380 (100)
Streptomycin	39 (85)	235 (93)	74 (91)	348 (92)
Ethambutol	28 (61)	171 (68)	53 (65)	252 (66)
Pyrazinamide	14 (30)	57 (23)	14 (17)	85 (22)
Second-line drugs				
Ofloxacin	8 (17)	43 (17)	33 (41)	84 (22)
Kanamycin	16 (35)	80 (32)	41 (51)	137 (36)
Capreomycin	9 (20)	49 (19)	31 (38)	89 (23)
Ethionamide	24 (52)	150 (59)	51 (63)	225 (59)
Cycloserine	2 (4)	10 (4)	5 (6)	17 (4)
PAS	7 (15)	39 (15)	12 (15)	58 (15)

TB, tuberculosis; PAS, para-aminosalicylic acid.

retreatment case, and the presence of XDR-TB (Table 4). Female gender, having had adjunctive surgical therapy, and sputum culture conversion at 4 months were all associated with better outcomes (i.e., a reduced risk of a poor outcome) (Table 4).

In multivariable analysis, factors that were independently associated with a poor treatment outcome included BMI $\leq$18.5, bilateral pulmonary disease on chest radiograph, being a retreatment case, and the presence of XDR-TB (Table 4). In the multivariable analysis, sputum culture conversion to negative for *M. tuberculosis* by 4 months (OR 0.33, 95% CI 0.21–0.52) and having had an adjunctive surgical resection (OR 0.27, 95% CI 0.11–0.64) were associated with a reduced risk of a poor outcome (i.e., associated with a more favorable treatment outcome) (Table 4).

Two additional multivariable logistic models were run to further explore the relationship of prior TB treatment and drug resistance with poor outcomes (Table 5). Compared to patients with MDR-TB, patients with MDR-TB plus fluoroquinolone resistance (OR 4.41, 95% CI 1.82–10.70) or XDR-TB (OR 3.02, 95% CI 1.37–6.64) were significantly more likely to have a poor treatment outcome. In the second alternative model, increasing total drug resistance was associated with an increasing likelihood of a poor outcome. In both alternative models, prior treatments were significantly associated with poor outcomes.

Table 3
Treatment outcomes of 380 multidrug- or extensively drug-resistant tuberculosis (M/XDR-TB) patients by patient category

	New cases, *n* (%) (*n* = 46)	Prior first-line treatment, *n* (%) (*n* = 253)	Prior second-line treatment, *n* (%) (*n* = 81)	Total, *n* (%) (*N* = 380)
Favorable outcome	37 (80)	133 (53)	31 (38)	201 (53)
Cure	27 (59)	101 (40)	25 (31)	153 (40)
Completed	10 (22)	32 (13)	6 (7)	48 (13)
Poor outcome	9 (20)	120 (47)	50 (62)	179 (47)
Death	2 (4)	33 (13)	24 (30)	59 (16)
Failure	2 (4)	19 (8)	16 (20)	37 (10)
Default	5 (11)	68 (27)	10 (12)	83 (22)

Table 4
Predictors of poor outcome among patients with multidrug- or extensively drug-resistant tuberculosis (M/XDR-TB)

Variable	Favorable outcome ($n=201$)	Poor outcome ($n=179$)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	p-Value[a]	OR (95% CI)	p-Value
Age, years, mean	36.6	40.3	1.02 (1.01–1.04)	0.003	1.01 (1.00–1.03)	0.16
Female sex	68 (34)	41 (23)	0.58 (0.37–0.92)	0.02	-	-
Married	129 (64)	129 (72)	1.44 (0.93–2.23)	0.10	-	-
Employed	34 (17)	18 (10)	0.55 (0.30–1.01)	0.06	-	-
Current smoker	79 (39)	73 (41)	1.06 (0.71–1.60)	0.77	-	-
Alcohol use	43 (21)	51 (28)	1.42 (0.89–2.30)	0.16	-	-
IDU	5 (2)	9 (5)	1.99 (0.65–6.07)	0.23	-	-
Prison history	23 (11)	28 (16)	1.44 (0.79–2.60)	0.23	-	-
Diabetes	19 (9)	16 (9)	0.94 (0.47–1.89)	0.86	-	-
HIV	3 (1)	2 (1)	0.75 (0.12–4.56)	0.75	-	-
BMI $\leq$18.5 kg/m^2	34 (17)	58 (32)	2.35 (1.45–3.82)	0.001	1.91 (1.11–3.29)	0.02
X-ray findings						
Bilateral disease	86 (43)	112 (63)	2.24 (1.48–3.38)	<0.001	1.90 (1.20–3.01)	0.006
Treatment category						
New	37 (18)	9 (5)	1.00		-	-
Prior first-line	133 (66)	120 (67)	3.71 (1.72–8.00)	<0.001	-	-
Prior first- and second-line	31 (15)	50 (28)	6.63 (2.82–15.59)	<0.001	-	-
All retreatment cases	164 (82)	170 (95)	4.26 (1.99–9.10)	<0.001	2.92 (1.29–6.58)	<0.001
Drug resistance categories						
XDR	17 (8)	32 (18)	2.36 (1.26–4.41)	<0.001	2.28 (1.11–4.71)	0.03
Non-XDR	184 (92)	147 (82)				
Adjunctive surgery	29 (14)	8 (4)	0.28 (0.12–0.62)	0.002	0.27 (0.11–0.64)	0.003
4-month culture conversion	120 (60)	53 (30)	0.28 (0.19–0.44)	<0.001	0.33 (0.21–0.52)	<0.001

OR, odds ratio; CI, confidence interval; IDU, injection drug use; BMI, body mass index; XDR, extensively drug-resistant.
[a] p-Value for Chi-square test unless otherwise stated.

Table 5
Alternative logistic multivariable regression models for poor outcomes among 380 multidrug- or extensively drug-resistant tuberculosis (M/XDR-TB) patients

	Adjusted OR (95% CI)	p-Value
Alternative model 1		
Age	1.02 (1.00–1.04)	0.06
BMI $\leq$18.5 kg/m^2	1.96 (1.12–3.44)	0.02
Bilateral X-ray lesions	1.89 (1.18–3.02)	0.008
Adjunctive surgery	0.24 (0.10–0.60)	0.002
4-month culture conversion	0.34 (0.21–0.55)	<0.001
Drug resistance pattern		
MDR	1.00	
MDR + FQ resistance	4.41 (1.82–10.70)	0.001
MDR + AG resistance	1.64 (0.94–2.86)	0.08
XDR	3.02 (1.37–6.64)	0.006
Treatment category		
New	1.00	
Prior first-line treatment	2.92 (1.27–6.76)	0.01
Prior second-line treatment	3.37 (1.30–8.73)	0.01
Alternative model 2		
Age	1.02 (1.00–1.03)	0.10
BMI $\leq$18.5 kg/m^2	1.92 (1.10–3.37)	0.02
Bilateral X-ray lesions	1.94 (1.22–3.10)	0.006
Adjunctive surgery	0.29 (0.12–0.68)	0.005
4-month culture conversion	0.31 (0.19–0.49)	<0.001
Total number of resistant drugs		
0–3	1.00	
4–6	2.77 (1.36–5.67)	0.005
$\geq$7	3.71 (1.68–8.21)	0.001
Treatment category		
New	1.00	
Prior first-line treatment	2.80 (1.21–6.48)	0.005
Prior second-line treatment	3.87 (1.52–9.88)	0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; MDR, multidrug-resistant; FQ, fluoroquinolone; AG, aminoglycoside; XDR, extensively drug-resistant.

4. Discussion

Georgia is one of only a few low- and middle-income countries that has had a rapid scale-up of treatment for M/XDR-TB. In less than 2 years, Georgia has achieved universal access to diagnosis and treatment of M/XDR-TB. This current study examined treatment outcomes among the first cohort of patients with pulmonary M/XDR-TB to undergo treatment in the country of Georgia.[10] The large majority (88%) of patients in this cohort were retreatment cases, likely reflecting the large pool of patients with chronic TB in Georgia who did not have access to diagnosis and treatment of M/XDR-TB until 2008. The overall proportion of favorable treatment outcomes in our study was similar to previously published studies,[12,13] but somewhat lower than that reported in a recent meta-analysis, which estimated an average successful outcome proportion for MDR-TB of 62% (95% CI 58–67%).[2] Some differences that may have accounted for a lower success rate in Georgia were the high proportion of retreatment cases and a relatively high treatment default rate (22%). Retreatment cases were older, more likely to have bilateral disease, had increasing drug resistance, and many had chronic TB disease for which they received multiple treatment regimens prior to the availability of diagnosis and treatment of M/XDR-TB in Georgia. Retreatment may be a surrogate marker for more severe disease, and these patients may be less responsive to treatment. Other studies have similarly found a higher proportion of poor outcomes in retreatment cases.[14–17] This finding emphasizes both the importance of proper detection of M/XDR-TB and access to quality-assured SLDs.

XDR-TB was an independent risk factor for a poor treatment outcome in our study, a finding that has been noted in previous studies.[18,19] The treatment success rate among those with XDR-TB (35%) in our study was in the lower range of that previously reported – 32% to 55%.[3] In our study, the presence of fluoroquinolone resistance was an independent risk factor associated with a poor treatment outcome and highlights the need for new agents that can be employed in the treatment of M/XDR-TB.

A relatively high prevalence (13%) of XDR-TB was found among patients with MDR-TB in Georgia. XDR-TB emerged at a time when SLDs were not available through the Georgian NTP. In Georgia, SLDs including the fluoroquinolones and injectable drugs were, and still are, available in pharmacies for over-the-counter purchase.[20] We suspect that their inappropriate use under non-program conditions has led to the development of XDR-TB in Georgia.

In our study, the default rate (22%) was relatively high. This finding is concerning because patients defaulting therapy have been found to have high rates of subsequent mortality and pose a

risk for subsequent transmission of highly drug-resistant TB.[21] This high level of treatment interruption occurred despite all patients receiving intensive case management, including psychological evaluation and care and DOT. Further investigations into the reasons for patient default and efforts to improve patient adherence, especially among retreatment patients, should improve overall M/XDR-TB treatment outcomes in Georgia and are important to enhance TB control efforts in Georgia.

In our study, independent risk factors for poor treatment outcomes also included low BMI ($\leq$18.5). Low BMI has been shown to be associated with an increased risk of TB and also worse outcomes in MDR-TB patients.[14,22] Our data are consistent with previous studies that have emphasized the importance of nutritional support for M/XDR-TB patients. Additional independent risk factors found to be significantly associated with favorable treatment outcomes included adjunctive surgical therapy and sputum culture conversion at 4 months. Our study suggests that surgical resection may be an important adjunctive measure in enhancing treatment cure among patients with M/XDR-TB.

Our findings are similar to previous reports suggesting that surgical resection may improve M/XDR-TB outcomes.[15,23,24] Also, the WHO recommends surgery be considered for the management of M/XDR-TB patients failing therapy and with a localized lesion, emphasizing surgical expertise and experience. Thus our findings support the important role of adjunctive surgical resection in the management of pulmonary M/XDR-TB patients who meet the criteria for surgery. The role of early culture conversion in predicting treatment outcomes has been suggested.[25] However our study is the first to demonstrate that a lack of culture conversion by 4 months is a predictor of poor treatment outcome, an outcome that highlights the importance of monitoring M/XDR-TB patients based on regular culture results. Further studies are needed to validate the use of the sputum 4-month culture conversion as a predictor of poor treatment outcome, which may be analogous to the use of 2-month culture conversion to assess the risk of relapse among drug-susceptible patients.[22]

There are a few limitations to our study. First, given that this is the first cohort of patients to ever receive treatment for M/XDR-TB in Georgia through the Georgian NTP, we suspect that many retreatment cases had undergone multiple courses of treatment for TB, but the exact number of prior courses of therapy among retreatment cases was not known. Second, although it was the policy to perform monthly sputum cultures, 38 (10%) patients missed more than two cultures.

The findings from our study have several implications for TB control activities in Georgia. First, given newly diagnosed cases had a more favorable treatment outcome, special attention is needed to detect M/XDR-TB cases early. To help enhance MDR-TB case detection, the use of a rapid molecular diagnostic test, a line probe assay called MTBDRplus, has been implemented in Georgia.[26] Second, one of the independent risk factors for a poor treatment outcome was the presence of XDR-TB. It is crucial to strengthen activities for effective use and control of SLDs to prevent the further emergence of XDR-TB. This includes advocacy and public education in order to gain support for health policy changes to limit access to key SLDs, which are currently readily available through Georgian pharmacies without a prescription, in an effort to reduce the further emergence of M/XDR-TB.

In conclusion, there was a rapid scale-up of M/XDR-TB treatment in Georgia beginning in 2008. In multivariable analyses, independent risk factors for a poor treatment outcome included prior treatment, the presence of XDR-TB, BMI $\leq$18.5, and bilateral infiltrates on chest radiograph. Sputum culture conversion by 4 months and adjunctive surgery for pulmonary TB were independent factors associated with a favorable outcome. Additional investigations are needed to further define the role of surgery in the treatment of M/XDR-TB and to validate the use of the 4-month culture conversion as a predictor of a successful treatment outcome among patients with highly drug-resistant TB.

Acknowledgements

This study was supported in part by a grant from the US National Institutes of Health (NIH) Fogarty International Center (D43TW007124 and D43TW007124-06S1). The authors thank Drs J. Boring, M. Klein, and A. Brzozowski for review of the manuscript and Dr J. Furin for assistance with the study design. We also thank Drs P. Macharashvili, N. Bablishvili, N. Tadumadze, M. Maka Akhalaia, N. Lomtadze, L. Goginashvili, and T. Chakhaia for logistical field support.

Conflict of interest: The authors have no conflict of interest.

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