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4 **Title:** High rates of treatment success in pulmonary multidrug-resistant tuberculosis  
5 by individually tailored treatment regimens

6 **Running title:** Optimal multidrug-resistant tuberculosis treatment outcomes

7

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53 **Abstract**

54 Rationale

55 We evaluated whether treatment outcomes for patients with multidrug-resistant and  
56 extensively drug-resistant tuberculosis can be substantially improved, when sufficient  
57 resources for personalizing medical care are available.

58 Objectives

59 To describe the characteristics and outcomes of patients with pulmonary multidrug-  
60 resistant tuberculosis from the Otto Wagner Hospital in Vienna, Austria.

61 Methods

62 Retrospective single-centre study at the Otto-Wagner-Hospital, Vienna, Austria. The  
63 records of patients with multidrug-resistant tuberculosis were reviewed for  
64 epidemiological, clinical, laboratory, treatment and outcome data.

65 Results

66 Ninety patients with pulmonary multidrug-resistant tuberculosis were identified.  
67 Median age was 30 years (interquartile range 26-37). All patients were of non-  
68 Austrian origin and 70 (78%) came from the former Soviet Union States. Thirty-nine  
69 (43%) patients had multidrug-resistant tuberculosis, 28 (31%) had additional bacillary  
70 resistance to at least one second-line injectable drug, 9 (10%) to a fluoroquinolone,  
71 14 (16%) patients had extensively drug-resistant tuberculosis. In 97.8% (n=88) of  
72 patients different drug combinations were used for treatment. Sixty-five (72.2%)  
73 patients had a successful treatment outcome, 8 (8.9%) defaulted, 3 (3.3%) died, 8  
74 (8.9%) continued treatment in another country and their outcome was unknown, and  
75 6 (6.7%) were still on therapy. None of the patients experienced treatment failure.  
76 Treatment outcome for extensively drug-resistant tuberculosis was similar to that of  
77 multidrug-resistant tuberculosis.

78 Conclusions

79 High rates of treatment success can be achieved in patients with multidrug-resistant  
80 and extensively drug-resistant tuberculosis when individualized tailored treatment  
81 regimen can be provided.

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## 86 Introduction

87 Despite Global efforts, tuberculosis (TB) remains a leading cause of morbidity and  
88 mortality representing the tenth most common cause of death worldwide (1).

89 Although the incidence of TB has registered a descending trend in recent years, the  
90 emergence and increase in multidrug-resistant (MDR) TB incidence is a cause of  
91 great concern. According to the World Health Organization (WHO), an estimated  
92 480,000 cases of MDR-TB have occurred in 2013 resulting in 210,000 deaths (2).

93 MDR-TB is defined as bacillary resistance to isoniazid and rifampicin, while  
94 extensively drug-resistant (XDR)-TB is defined by additional resistance to at least  
95 one second-line injectable drug (amikacin, kanamycin, capreomycin) and at least  
96 one fluoroquinolone (3). The WHO recommends that patients with MDR-TB receive  
97 prolonged antimicrobial treatment of at least 20 months (4), including a minimum of 4  
98 second-line drugs that are likely to be effective in the therapy plus pyrazinamide.  
99 MDR-TB treatment is frequently associated with adverse drug events (5), with high  
100 costs (6), and high rates of loss to follow-up and failure (7-11). Additionally, owing to  
101 limited possibilities to test for drug-resistance and to optimise regimens in many  
102 settings where the global burden of MDR-TB is highest, treatment for MDR-TB is  
103 often standardized irrespective of the severity of disease and the resistance pattern  
104 of the associated strain.

105 Poor treatment outcomes were reported in a meta-analysis of over 6700 patients,  
106 where MDR-TB treatment success ranged from 64% in patients with MDR-TB and  
107 no additional resistance to injectable drugs or fluoroquinolones to 40% in patients  
108 with XDR-TB (8). Additionally, according to data from the European Centre for  
109 Disease Prevention and Control (ECDC) analysing treatment outcomes, treatment  
110 success was registered in only 46% of MDR-TB and only 23.2% of XDR-TB cases

111 (10). Furthermore, access to MDR-TB treatment is often difficult with only a third of  
112 the estimated cases being enrolled on treatment in 2013 (2).

113 While the European Region of the WHO has the highest proportion of all patients  
114 with MDR-TB identified world-wide, the vast majority of these patients live in eastern  
115 part of the European Region, especially in countries from the former Soviet Union.

116 Compared to the European Union/ European Economic Area countries, where a total  
117 of only 1255 patients with laboratory-confirmed MDR-TB were identified in 2013,  
118 there were 33,679 patients with MDR-TB identified in Eastern Europe during the  
119 same time period (10). Furthermore, an estimated 100,000 MDR-TB cases occurred  
120 in India in China (2).

121 Poor treatment outcomes that have been reported for MDR-TB may not be  
122 applicable when resources for diagnosis and treatment are readily available and  
123 MDR-TB management can be optimized. Austria has a low incidence of TB, where  
124 only 16 patients with M/XDR-TB were registered in 2013 (12), more than half (57%)  
125 of the patients diagnosed with MDR-TB from Austria are treated at the Otto-Wagner  
126 Hospital in Vienna. This hospital has a dedicated unit for the treatment of patients  
127 with M/XDR-TB, where highly specialized care can be provided under optimal  
128 circumstances. In addition to continuous and unrestricted drug-availability as well as  
129 rigorous monitoring during the course of therapy (clinical, laboratory, microbiological  
130 and radiological), the management of all patients includes regular physiotherapy and  
131 psychological counselling sessions supporting treatment adherence and coping with  
132 the adverse events of therapy. Considering the large number of patients originating  
133 from outside Austria, interpreters are present when required, to assist patients with  
134 communication issues. Furthermore social workers from the department of public  
135 health as well as an on-site fully-dedicated social worker, provide assistance with the

136 administrative and insurance-related issues and organize further care after discharge  
137 from hospital.

138 We evaluated treatment outcomes for patients with M/XDR-TB under personalized  
139 medical care.

140 Some of the results of this study have been previously reported in the form of an  
141 abstract (13).

142

143

## 144 **Methods**

### 145 *Patient population*

146 Patients with microbiologically-confirmed pulmonary MDR-TB and positive cultures  
147 for *M. tuberculosis* from respiratory samples, admitted at the Otto Wagner Hospital,  
148 Vienna for treatment between January 2003 and December 2012 were included in  
149 the study. Otto Wagner Hospital is a referral center with extensive expertise in the  
150 treatment of patients with TB from Austria.

### 151 *Data collection*

152 Patients were identified using the department patient register which included all  
153 patients with M/XDR-TB hospitalized at the site. Entries were cross-referenced with  
154 the microbiological registries to identify *M. tuberculosis* strains with rifampicin and  
155 isoniazid resistance. Patient records were reviewed for epidemiological, clinical,  
156 laboratory, treatment and outcome data and information was recorded in an  
157 anonymized database which was further analysed.

158

### 159 *Drug susceptibility testing*



160 Drug susceptibility testing was performed in a specialized laboratory at the Institute  
161 for Medical Microbiology and Hygiene, Austrian Agency of Health and Food Safety  
162 and confirmed at the National Reference Center for Mycobacteriology, Borstel,  
163 Germany, one of the WHO supranational reference laboratory for tuberculosis. All  
164 patients included in the study had a positive *Mycobacterium tuberculosis* culture  
165 available for drug susceptibility testing.

166 Susceptibility testing was performed for the following drugs: isoniazid, rifampicin,  
167 rifabutin, ethambutol, pyrazinamide, streptomycin, amikacin, capreomycin,  
168 fluoroquinolones, prothionamide, cycloserine, *para*-aminosalicylic acid (PAS), and  
169 linezolid.

170

#### 171 *Treatment and outcome*

172 Patients were considered to receive an appropriate MDR-TB treatment-regimen  
173 once they received at least 4 drugs in combination therapy that were thought to be  
174 effective according to the results of drug susceptibility testing, including a second-  
175 line injectable drug for the intensive phase of treatment (14). TB treatment was  
176 directly observed during the whole course of therapy. To ascertain the  
177 microbiological response to treatment, sputum cultures were collected on a monthly  
178 basis during hospitalization and every 1-2 months onwards until the end of therapy.  
179 Outcome was ascertained using the revised WHO definitions (3). Patients were  
180 considered to have a favourable outcome if they were either cured or had completed  
181 the treatment or an unfavourable outcome in the case of default, treatment failure or  
182 death.

183

#### 184 *Statistical analysis*

185 Data processing and analysis were performed using SPSS v17.0 (SPSS Inc.,  
186 Chicago, IL, USA). Mann-Whitney U test was used to test for differences between  
187 continuous variables and chi-square test or Fisher's exact test were used for  
188 categorical variables. The level of significance was set at  $\alpha=0.05$ . Multivariate  
189 analysis using backward stepwise logistic regression was then used to predict  
190 treatment outcome when the p-value from the univariate analysis was  $<0.20$ .

191

### 192 *Ethics*

193 The study was approved by the ethics committee of the city of Vienna  
194 (Ethikkommission der Stadt Wien: EK 14-240-VK).

195

196

## 197 **Results**

### 198 *Patient characteristics*

199 A total of 94 patients with M/XDR-TB who were admitted during the study period  
200 were identified. Four patients had extrapulmonary M/XDR-TB, and were excluded  
201 from the analysis. Median patient age at diagnosis was 30 years (interquartile range  
202 (IQR) 26-37). Male to female ratio was 1.5:1. All patients were of non-Austrian origin  
203 and came from the Russian Federation (n=55, 61.1%), Georgia (n=11, 12.2%),  
204 Romania (n=11, 12.2%) or other countries (13, 14.4%). Fifty of the patients from the  
205 Russian Federation were from Chechnya. Seventeen patients were intravenous drug  
206 users, and 52 (58%) were active smokers. All patients were tested for HIV infection,  
207 but none were HIV-seropositive. The characteristics of the patients included in the  
208 study are presented in Table 1.

209

210 *Drug susceptibility testing*

211 Thirty-nine (43%) patients had MDR-TB only, 28 (31%) had additional resistance to  
212 at least one second-line injectable drug, 9 (10%) to a fluoroquinolone, while 14  
213 (16%) of patients had XDR-TB. The patients with XDR-TB were originally from  
214 Chechnya (n=9), Romania (n=3), Georgia (n=1) and China (n=1). Resistance to at all  
215 first-line drugs was recorded in 40 (44%) of patients. The results of the drug  
216 susceptibility testing are shown in Figure 1. Of note is that 8 (8.9%) *M. tuberculosis*  
217 strains were susceptible to rifabutin.

218

219 *Management and treatment outcome*

220 Median time from hospital admission to the start of an appropriate M/XDR-TB  
221 treatment was 23.5 days (IQR 0.8-45).

222 Eighty-eight different drug combinations were used for the treatment of the 90  
223 patients (97.8%) treatment. The drug regimens according to their composition are  
224 represented in Figure 2. The intensive phase contained a median of 5 drugs (IQR 5-  
225 6), while in the continuation phase, a median of 3 drugs (IQR 3-4) were used.

226 Smear conversion occurred after a median 61 days (IQR 22-135) following the  
227 initiation of adequate treatment while culture conversion occurred after a median of  
228 62 days (34-112.8 days). Only 3 (3.3%) patients did not experience a culture  
229 conversion. Figure 3 shows smear and culture conversion during anti-TB treatment.  
230 Culture conversion occurred in 40 (46%) patients within the first 2 months of effective  
231 M/XDR-TB therapy, and in 72 (82.8%) patients within 6 months.

232 The median duration of the intensive phase was 123 days (IQR 82-228) and  
233 continuation phase was 494 days (IQR 388-599 days). The overall median duration  
234 of therapy was 21 months (IQR 18-24 months); in patients with a favourable

235 outcome, the median duration of therapy was 23 months (IQR 19-24 months) while  
236 in patients who experienced an unfavourable outcome it was 4 months (IQR 3-18  
237 months,  $p < 0.001$ ). One patient defaulted before therapy could be initiated.  
238 The median duration of inpatient stay was 141 days (IQR 96.5-230.3 days) while the  
239 median duration of treatment in the out-patient setting was of 15 months (IQR 12-23  
240 months).. Patients with smear positive tuberculosis had a significantly longer hospital  
241 stay with a median duration of 191 days (IQR 108.5-243) compared to smear  
242 negative patients - median duration 102.5 days (IQR 67.5-134.8,  $p < 0.001$ ).  
243 Additionally, the median length of hospital stay was longer in patients with XDR-TB  
244 in comparison to patients with non-XDR-TB (335 vs. 128 days,  $p < 0.001$ ).  
245 Surgery was performed in 10 (11.1%) of patients. Of the nine patients with a known  
246 outcome, 6/9 (66.7%) had a favourable outcome. For facilitating the administration of  
247 parenteral therapy, 48 (53.3%) of patients received a totally implantable central  
248 venous access system (port-a-cath).  
249 As shown in Table 2, 65 (72.2%) patients had a favourable treatment outcome (56  
250 fulfilled the criteria for cure and 9 completed treatment), 8 (8.9%) defaulted, 3 (3.3%)  
251 died, 8 (8.9%) continued the treatment in their home-country after hospital discharge  
252 and their outcome was therefore unknown, and 6 (6.7%) were still on therapy. One  
253 of the patients who died had concomitant central nervous system TB. If only the  
254 cases with a known outcome are considered, then 85.5% of patients had a  
255 successful outcome. Out of 14 patients with XDR-TB, nine (64%) were cured, one  
256 (7%) died and four (29%) were still on treatment. None of the patients included in the  
257 study experienced treatment failure. Of the seven patients who were treated with  
258 bedaquiline, five were still on treatment when the data were analysed, one was  
259 transferred to another treatment facility and one died. All patients treated with

260 bedaquiline, who had a prolonged culture positivity, achieved culture conversion. Of  
261 the 14 patients who had received fusidic acid, 13 had a favourable outcome, while  
262 one died ( $p=0.68$ ). In the univariate analysis the duration of therapy ( $p < 0.01$ ),  
263 treatment with cycloserine ( $p < 0.01$ ), not receiving treatment with pyrazinamide  
264 ( $p=0.04$ ) and a negative culture status at six months ( $p=0.04$ ) were associated with a  
265 favourable treatment outcome. In the multivariate analysis the duration of therapy  
266 (OR 0.66, 95%CI 0.51-0.86;  $p=0.002$ ) and culture status at 6 months (OR 0.04,  
267 95%CI 0.02-0.70;  $p=0.03$ ) were associated with a favourable outcome.

268

### 269 *Adverse events*

270 Gastrointestinal adverse events occurred in 74 (82.2%) patients, polyneuropathy in  
271 48 (53.3%), ototoxicity in 31 (34.4%), psychiatric adverse effects in 44 (48.9%), and  
272 liver enzymes were elevated during therapy in 44 (48.9%) of patients. Treatment with  
273 linezolid was more frequently associated with polyneuropathy (62.3% versus 34.5%,  
274  $p=0.023$ ), while ototoxicity was associated with amikacin therapy (52.2% versus  
275 28.4%,  $p=0.046$ ). Ototoxicity was present in 25% of patients who had received  
276 capreomycin versus 42% of patients without capreomycin treatment,  $p=0.92$ .

277

278

## 279 **Discussion**

280 While treatment outcome for patients with M/XDR-TB in Europe are frequently  
281 reported to be poor (15), we are able to show that treatment outcomes for pulmonary  
282 M/XDR-TB can be substantially improved in a setting where patient management is  
283 individualized. By using tailored drug regimen, treatment success rates close to the  
284 target proposed by the WHO (13) can be achieved. In this study from a single

285 referral centre in Austria treatment success rates were over 72%, (and over 85% in  
286 patients with a definite outcome) which contrasts with the ECDC data which reports  
287 a successful treatment outcome in only 46% of patients from Europe (10). One  
288 explanation for this large difference might be the incomplete reporting of treatment  
289 outcomes to the ECDC and a larger proportion of lost to follow-up due to migration,  
290 as well as an offsetting contribution by countries with a large number of MDR-TB  
291 patients and low treatment success rates such as Romania and Lithuania (10).  
292 Furthermore, individualized therapy is also likely to have played an important  
293 contribution to achieving high rates of treatment success, considering that in this  
294 study 88 different drug-combinations were used.

295 With the advent of two new drugs for the treatment of MDR-TB and XDR-TB,  
296 treatment outcomes may improve substantially. As 6 of the 7 patients receiving a  
297 bedaquiline based treatment regimen experienced sustained culture conversion it is  
298 hoped that treatment outcomes may improve in general in the European region,  
299 when these drugs will become universally available. Recently it has been reported,  
300 that 28 of 29 (97%) patients with culture-positive pulmonary M/XDR-TB who were  
301 treated with a bedaquiline containing regimen, experienced culture conversion at 6  
302 months of treatment (16). Furthermore, the 6 months culture status is a very good  
303 approximation for achieving a successful treatment outcome in patients treated for  
304 MDR-TB (17).

305 While analyses of large patient cohorts describe unfavourable outcomes in more  
306 than half of patients with MDR-TB, studies from individual countries or specialized  
307 centres report significantly higher rates of treatment success. For example, studies  
308 on selected patient cohorts from other European countries, describe treatment  
309 success rates of 59% in Germany (18), 68% in Belgium (19), 71% in the United

310 Kingdom (20), 76% in Switzerland (21), and 79% in the Netherlands (22).

311 Interestingly, the overall and MDR-TB treatment success rates in Austria were lower  
312 than the ones from this study, of 66% and 65%, respectively, emphasizing the  
313 importance of highly- specialized management (10).

314 All patients with M/XDR-TB in this study are not of Austrian origin. The ECDC TB  
315 report also suggests that over half of patients with TB in a lot of the countries of  
316 Western Europe are of foreign origin (10). This underscores the importance of  
317 migration in the epidemiology of MDR-TB. While in the countries of Western Europe  
318 most patients with MDR-TB have access to appropriate treatment, in other countries  
319 such as Russia less than half of the estimated 44,000 patients with MDR-TB were  
320 enrolled on treatment in 2011 (23), while in Ukraine, a country with a high-burden of  
321 MDR-TB due to conflict and population displacement many patients have difficulties  
322 in accessing treatment (24). More than half of the patients with M/XDR-TB in this  
323 study were from Chechnya. This might be because Austria has the second largest  
324 Chechen diaspora in Europe with a large proportion of refugees (25) and in  
325 Chechnya about a half of TB cases are MDR (26).

326 Another factor that contributes to treatment accessibility and success is the cost of  
327 MDR-TB therapy. While a full course of MDR-TB treatment costs 70 times more than  
328 for pan-susceptible TB, costs for XDR-TB might be as 280-fold higher making it a  
329 considerable burden on countries where M/XDR-TB are prevalent (6).

330 Interestingly, almost a tenth of the *M. tuberculosis* strains isolated were still  
331 susceptible to rifabutin. This underscores the importance of drug susceptibility  
332 testing for rifabutin, and if susceptible, including it in the therapy regimen which, due  
333 to its effectiveness, could potentially lead to a shorter duration of therapy and  
334 improved treatment outcomes.

335 A number of drugs of unclear efficacy against *M. tuberculosis* were used for the  
336 treatment of MDR-TB. Fusidic acid, an antibiotic which works via protein synthesis  
337 inhibition and active on gram-positive bacteria, was used as part of the drug regimen  
338 in almost a fifth of patients in the study. There was a trend showing a higher rate of  
339 favourable outcome in patients receiving fusidic acid, but the difference was not  
340 significant. *In vitro* studies have shown that fusidic acid has an inhibitory effect on *M.*  
341 *tuberculosis* growth (27, 28). As this drug has not been evaluated in early  
342 bactericidal activity studies or in clinical trials fusidic acid should be explored as a  
343 repurposed drug for the treatment of MDR-TB.

344 Over two thirds of patients in this study were treated with linezolid, which has been  
345 shown to be effective in patients with M/XDR-TB (18, 29). A recently published meta-  
346 analysis on linezolid-containing regimens reported favourable outcomes in 83% of  
347 patients treated with linezolid (30), however most of the studies were retrospective  
348 and had no control arm. Unfortunately, linezolid therapy is associated with frequent  
349 and sometimes severe adverse events requiring treatment discontinuation (30, 31).  
350 In the present study, linezolid therapy was also significantly associated with  
351 polyneuropathy in over 60% of patients.

352 The multivariate analysis showed that a longer total duration of therapy, and the  
353 status of sputum culture at 6 months were associated with a favourable outcome.

354 The *M. tuberculosis* strains from the patients included in the study had high rates of  
355 additional resistance to anti-tuberculosis drugs other than rifampicin and isoniazid..

356 Over 44% of strains had resistance to all first-line drugs, 49% had resistance to  
357 prothionamide, 46% had resistance to at least one second-line injectable drug and  
358 over a quarter had resistance to fluoroquinolones. These findings are in line with  
359 other recent observations on the level of bacillary drug resistance of MDR- *M.*



360 *tuberculosis* in the region (32, 33). This represents higher rates of resistance than  
361 that reported in studies using standardized treatment regimens for MDR-TB (34) and  
362 suggests that a standardized treatment approach should not be followed in the  
363 European Region as patients may be treated with second line antituberculosis drugs  
364 that are not effective. Standardized treatment could lead to further acceleration of  
365 drug-resistance development. It is important to notice that with an individualize  
366 treatment approach high treatment success rates could be achieved despite the  
367 “MDR-TB plus” scenario in patients treated for M/XDR-TB in Vienna.

368 MDR-TB requires a prolonged duration of therapy and is associated with an  
369 increased length of hospital stay, frequent and sometimes irreversible adverse  
370 events and extremely high costs. Due to the physical and psychological difficulties  
371 experienced by patients during the course of treatment, specialized support is of  
372 great value. It is very likely that the regular psychological counselling and social  
373 support given to the patients from this study, played an important contribution to  
374 improve treatment adherence and attain high rates of treatment success in this  
375 setting.

376 Although this study is retrospective and lacks a direct comparison to other  
377 management strategies, it provides unique information on a large number of patients  
378 with pulmonary M/XDR-TB from a single-centre from a Western European country of  
379 a low tuberculosis-incidence.

380 In conclusion this study shows that high rates of successful treatment outcome can  
381 be achieved in patients with M/XDR-TB in Europe when the drug regime is  
382 individualized to the results of 2<sup>nd</sup> line drug susceptibility testing and 2<sup>nd</sup> line drugs  
383 are available for the treatment without restrictions. Additionally, the adequate  
384 funding to provide medications, appropriate testing and supportive care, treatment

385 adherence due to prolonged hospitalization and effective management of adverse  
386 events also played an important role in the high rates of treatment success. The  
387 results also underscore the importance of a multidisciplinary treatment approach  
388 comprising individualized patient care, as well as psychological and social support to  
389 improve adherence to therapy and for the early detection and management of  
390 treatment-related adverse events (35). With these combined efforts, treatment  
391 outcomes for patients with M/XDR-TB can be substantially improved.

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564

565 **Tables and figures**

566

567 **Figure 1.** Spectrum of first- and second line anti-tuberculosis drug-resistance in 90  
568 strains of *M. tuberculosis* from patients with M/XDR-TB at Otto-Wagner Hospital,  
569 Vienna (Austria) admitted between 2003 and 2012.

570

571 **Figure 2.** Drugs regimens for the treatment of M/XDR-TB.

572 Regimens are represented according to their composition. In the central square it is  
573 shown how many patients received fluoroquinolones, aminoglycosides, both or none.  
574 Drugs are added along the lines. The number in the circle represents the number of  
575 the patients who go through that particular node. The black point (•) represents the  
576 number of patients ending the regimen in that node. AMC amoxicillin clavulanic acid;  
577 BDQ bedaquiline; CFZ clofazimine; CLA clarithromycin; CS cycloserine; DDS  
578 dapsone; EMB ethambutol; FQ fluoroquinolones; FUS fusidic acid; IMP imipenem;  
579 INJ second-line injectable drugs; LZD linezolid; PAS para aminosalicylic acid; PTO  
580 prothionamide; PZA pyrazinamide; RFB rifabutin; SXT trimethoprim-  
581 sulfamethoxazole.

582

583 **Figure 3.** Smear (A) and culture (B) conversion during anti-tuberculosis treatment.  
584 Smear conversion is shown only for patients with a positive smear at treatment  
585 initiation.

586

587

588 **Table 1.** Characteristics of 90 patients with M/XDR-TB admitted between 2003 and  
 589 2012 at the Otto-Wagner Hospital, Vienna (Austria)

Variable	MDR-TB N = 76	XDR-TB N = 14	p-value
Male gender, n (%)	45/76 (59.2)	9/14 (64.3)	0.722
Age (years), median (IQR)	30 (25.3-35.3)	33.5 (28.8-42.3)	0.101
Country of birth, n (%)			
Former Soviet Union	60/76 (78.9)	10/14 (71.4)	0.503
Other	16/76 (21.1)	4/14 (28.6)	
Previous TB treatment, n (%)	38/69 (55.1)	10/13 (76.9)	0.142
Cavitary disease, n (%)	50/76 (65.8)	12/14 (85.7)	0.211
Smear positive at diagnosis, n (%)	50/75 (66.7)	11/14 (78.6)	0.535
Resistance to all first-line drugs, n (%)	31/76 (40.8)	9/14 (64.3)	0.104
Resistance to fluoroquinolones, n (%)	9/75 (12)	14/14 (100)	NA
Resistance to second-line injectable drugs, n (%)	28/76 (36.8)	14/14 (100)	NA
Number of drugs in the intensive phase, median (IQR)	5 (5-6)	6 (6-6.3)	0.021

Number of drugs in the continuation phase, median (IQR)	3 (3-4)	4 (3-4)	0.051
Linezolid treatment, n (%)	49/76 (64.5)	12/14 (85.7)	0.177
Bedaquiline treatment, n (%)	3/76 (3.9)	4/14 (28.6)	0.010
Days in hospital, median (IQR)	128 (89.8-212.5)	335 (190.5-436.5)	<0.001
Duration of treatment (months), median (IQR)	19.5 (17.8-24)	24 (22.3-24.8)	0.012
Culture conversion, n (%)	71/65 (95.9)	14/14 (100)	1.00
Time to smear conversion (days), median (IQR)	56.5 (21-119.5)	128 (56-269.5)	0.024
Time to culture conversion (days), n (%)	61 (30.8-96)	110 (54.8-288.8)	0.010

590

591

592 **Table 2.** Treatment outcomes in patients with M/XDR-TB

	MDR-TB N = 76	XDR-TB N = 14
Favourable outcome (cured + completed)	56 (73.7)	9 (64.3)
Cured	47 (61.8)	9 (64.3)
Completed	9 (11.8)	0 (0)
Unfavourable outcome (died + failure)	2 (2.6)	1 (7.1)
Died	2 (2.6)	1 (7.1)
Failure	0 (0)	0 (0)
Unknown outcome (default + transferred out)	16 (21)	0(0)
Default	8 (10.5)	0 (0)
Transferred out	8 (10.5)	0 (0)
Still on treatment	2 (2.6)	4 (28.6)

593