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3 **Treatment responses in multidrug-resistant tuberculosis in Germany**

4
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29 **Running head:** Treatment Outcomes in M/XDR-TB

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33 **Abstract (200)**

34 Recently, excellent treatment outcomes have been reported for patients with
35 multidrug/extensively drug-resistant tuberculosis (M/XDR-TB) in settings where optimal
36 resources for individualized therapy are available. We ascertained whether differences in
37 treatment responses still exist in patients with M/XDR-TB compared to patients with non-
38 M/XDR-TB.

39 Patients with tuberculosis were prospectively enrolled between March 2013 and March
40 2016 at five hospitals in Germany. Treatment was conducted following current guidelines
41 and individualized on the basis of comprehensive drug-resistance testing. Two-months and
42 6-months sputum-smear and sputum-culture conversion rates were assessed. A clinical and
43 a radiological score were used to assess the response to anti-tuberculosis therapy.

44 Non-M/XDR-TB (n=29) and M/XDR-TB (n=46) patients showed similar rates of
45 microbiological conversion (2-months smear-conversion-rate 90% vs. 78% and culture-
46 conversion-rate 67% versus 61%, respectively; time-to-smear/culture-conversion 19 (IQR10-
47 32) vs. 31 (IQR14-56) (p=0.066), and 39 (IQR17-67) vs. 39 (IQR6-85) days (p=0.191),
48 respectively). Both clinical and radiological scores declined after the introduction of anti-
49 tuberculosis therapy. There were no significant differences of scores between the groups
50 until 6 months of therapy.

51 Under optimal clinical conditions with availability of novel diagnostics and a wide range of
52 therapeutic options for individualized therapy, patients with M/XDR-TB achieve 6 month
53 culture conversion rates that are compatible to patients with non-M/XDR-TB.

54 **Introduction**

55 Tuberculosis (TB) is the leading cause of mortality attributed to a single microbial pathogen
56 worldwide (1, 2). The World Health Organization (WHO) estimates that more than 10 million
57 people developed active TB in 2016, the highest ever-estimated number of affected patients
58 in history. The emergence of multidrug-resistant (MDR; defined by bacillary resistance
59 against rifampicin and isoniazid) and extensively drug-resistant (XDR; MDR plus resistance
60 against at least one fluoroquinolone and one second-line injectable drug) TB is especially
61 worrisome. M/XDR-TB has been related to high treatment costs, increased frequency of
62 adverse drug-events, and poor therapy outcomes (1, 3-7). At the recent meeting of the G20
63 leaders in Hamburg, Germany, combatting antimicrobial resistance, including drug-resistant
64 TB, has been identified as a global priority (8).

65

66 Currently, the World Health Organization (WHO) recommends a therapy duration for
67 M/XDR-TB patients of at least 20 months unless specific criteria allow for a standardized
68 short course MDR-TB regimen over 9-12 months (3, 9-13). Only approximately 50% of
69 M/XDR-TB patients in Europe attain favorable outcomes. In contrast, in settings where
70 individualized treatment can be provided, successful treatment outcomes are usually
71 observed (3, 4, 14-16). The concept of individualized therapy targets the special demands of
72 every host and pathogen leading to tailored treatment in every patient (17). Currently, new
73 diagnostic methods and novel drugs have been introduced that may improve treatment
74 outcomes (17-20).

75

76 Based on these observations, we aimed to compare 6-months culture conversion, as early
77 indicators of treatment outcomes, in M/XDR-TB and non-M/XDR-TB patients from settings
78 where optimal resources are available. Additionally, we evaluated a clinical and a
79 radiological scoring system (21).

80

81 **Study population and methods**

82 Between March 2013 and March 2016 patients with TB identified by sputum GeneXpert
83 MTB/RIF test (Cepheid, Sunnyvale, USA) were prospectively enrolled at the Medical Clinic,
84 Research Center Borstel; Karl-Hansen-Klinik, Bad Lippspringe; Sankt Katharinen-
85 Krankenhaus, Frankfurt; Thoraxklinik-Heidelberg, Heidelberg; Asklepios Fachkliniken
86 München-Gauting, Munich in Germany. Patients with M/XDR-TB were enrolled
87 consecutively at all centers after satisfying in- and exclusion criteria, and providing written
88 informed consent. Patients with non-MDR-TB were also recruited if inclusion criteria were
89 met or exclusion criteria were not met and they agreed with participation. Although patients
90 with non-MDR-TB were not strictly recruited consecutively at all centers, selection was not
91 based on patients characteristics but depended on staff availability. Individuals were
92 excluded if they were less than 18 years of age, not legally able to provide consent or if they
93 were infected with HIV. All patients gave written informed consent. Following approval at
94 the Ethics Committee of the University of Lübeck (AZ 12-233), Germany, the study protocol
95 was approved at the local Ethic Committees of all participating centers.

96

97 Following rapid molecular identification of rifampicin resistance by GeneXpert, sputum
98 samples underwent second-line molecular drug resistance testing of *M. tuberculosis* by line-
99 probe-assays (GenoType MTBDR_{plus} and MTBDR_{s/} Hain Lifesciences, Nehren, Germany).

100 Sputum samples also underwent phenotypic drug susceptibility testing according to WHO
101 recommendations at a certified and quality controlled microbiology laboratory (WHO
102 Supranational Reference Laboratory Network). During the in-patient period, sputum samples
103 were collected for smear microscopy and culture on a weekly basis. After discharge, sputum
104 was collected as part of routine follow-up visits. Demographic information was collected on
105 study enrolment.

106

107 A novel clinical score consisting of self-reported and objectively observed items (maximum
108 score of 30 points), which is based on a published scoring system (22), was recorded by a
109 physician during the clinical visits. Self-reported items were cough, hemoptysis, dyspnea,
110 thoracic pain, night sweats, loss of weight, and inability to walk (each one point). The
111 examined score items (if not indicated differently, one point each) consisted of axillary body
112 temperature ($>37^{\circ}$ = one point, $>38^{\circ}$ = two points), impaired consciousness, focal neurologic
113 deficits, body mass index (kg/m^2 ; <20 = one point, <18 = two points, <16 = three points),
114 middle upper arm circumference (mm; <220 = one point, <200 = two points), capillary filling
115 time >2 sec., cyanosis, tachycardia (beats per minute; >100 = one point, >120 =two points),
116 blood pressure <90 mmHg systolic or <60 mmHg diastolic, lung crackles, tachypnea (per
117 minute; >20 = one point, >25 = two points, >30 = three points), oxygen saturation (%; <90 =
118 one point, <87 = 2 points), and age above 65 (one point).

119

120 Chest X-rays were performed at clinically relevant time-points during the course of
121 treatment. The extent of pulmonary TB was assessed by a validated scoring system (21). In
122 brief, the percentage of TB-associated infiltrations in chest X-rays was assessed and 40

123 points were added to the score if cavities were present (max. 140 points). An experienced
124 chest physician scored the chest X-rays.

125

126 Time to sputum culture conversion (TCC) and smear conversion (TSC) were defined as the
127 time (in days) from the initiation of effective anti-TB therapy to the date of the first negative
128 culture or sputum smear (date of collection). Therapy was deemed effective according to
129 DST results.

130

131 Individualized anti-TB drug regimens for patients with M/XDR-TB were designed using
132 current therapy recommendations, and results of molecular and phenotypic drug
133 susceptibility testing (10, 11, 23, 24). Patients with non-M/XDR TB were treated following
134 national TB guidelines (25).

135

136 Smear and culture conversion for the first six months after treatment initiation were
137 evaluated using survival analysis, and compared with survival curves for the two cohorts by a
138 logrank test. Kaplan-Meier estimates derived from the survival curves for smear and culture
139 conversion at month 2 and month 6, and the median time to smear or culture conversion
140 are reported. Measured clinical score and change in radiological score were assessed by
141 mean and 95% confidence interval at *a priori* time points. All statistical tests used a two-
142 sided alpha-value of 0.05 to assess statistical significance. Analyses were performed using
143 STATA (Version 14, StataCorp LLC, College Station, Texas, USA).

144

145 **Results**

146 Seventy-five patients were enrolled, of whom 46 were infected with non-M/XDR and 29 with
147 M/XDR-TB strains. Patients' characteristics are displayed in **table 1**. Of the 29 patients with
148 M/XDR-TB, eight patients were infected with an XDR strain of *M. tuberculosis*. Median age
149 was higher in patients with non-M/XDR-TB compared to M/XDR-TB patients (43.0 years (IQR
150 31.0 – 58.0) vs. 36.0 years (IQR 30.0 – 41.0)). Sex distribution (non-M/XDR-TB: males 30
151 (65.2%) vs. M/XDR-TB: males 16 (62.1%)) and median BMI values (non-M/XDR-TB: 21.1
152 kg/m² (IQR 18.1 – 24.8 vs. M/XDR-TB: 21.7 kg/m² (19.4 - 25.4)) were similar in both patient
153 groups.

154

155 The results of available DST results are shown in **table 2**. Among the 46 patients with non-
156 M/XDR-TB two patients had isoniazid mono-resistance. No further drug-resistances to first-
157 line drugs (ethambutol and pyrazinamide tested in 44 strains) nor second-line drugs
158 (prothionamide, ofloxacin, and capreomycin tested in 11 strains) were detected in this
159 group. Strains from patients with M/XDR-TB showed high frequencies of first-line drug
160 resistance; 18/27 (66.7%) for ethambutol, 22/27 (81.5%) pyrazinamide. Additionally,
161 resistance was present in M/XDR-TB strains to capreomycin 10/29 (34.5%), amikacin 7/29
162 (24.1%), ofloxacin 9/27 (33.3%), prothionamide 14/27 (51.9%), para-amino-salicylic acid 1/27
163 (3.7%) and linezolid 1/27 (3.7%). None of the M/XDR-TB strains were resistant to
164 terizidone/cycloserin.

165

166 The starting therapy regimens are shown in **table 3**. Most M/XDR-TB patients receiving
167 fluoroquinolones were treated with moxifloxacin 18/22 (81.8%) and only 4/22 (18.2%)
168 received levofloxacin. Of 21/29 (72.4%) M/XDR-TB patients who were treated with second-
169 line injectable drugs 14/21 (66.7%) patients were given capreomycin and 7/21 (33.3%)

170 amikacin. Only 3/29 (10.4%) M/XDR-TB patients were treated with regimens containing
171 bedaquiline or delamanid.

172 Patients with M/XDR-TB had a slightly lower Kaplan-Meier estimate for smear conversion
173 compared to patients with non-M/XDR-TB at month two (78% versus 90%, respectively), and
174 at month six (93% and 96%, respectively, $p=0.004$; **table 4** and **figure 1A**). Such a difference
175 was not seen for culture conversion (**figure 1B** and **table 4**), where Kaplan-Meier estimates
176 were 61% and 67%, respectively at month two, and 95% and 97%, respectively, at month six
177 ($p = 0.191$). The median time to smear conversion was 31 days (IQR: 14-56) and 19 days
178 (IQR: 10-32) for patient with non-M/XDR-TB and M/XDR-TB respectively. Time to culture
179 conversion was with 39 days, identical in both groups.

180 The mean clinical scores before treatment initiation were higher in patients with non-
181 M/XDR-TB TB than in patients with M/XDR-TB (5.8 (95%CI 3.5–7.4) vs. 4.8 (95%CI 3.6–5.6))
182 with a decline of mean scores in both cohorts after therapy initiation (**online appendix table**
183 **1** and **figure 2**). There were no obvious differences in the development of the clinical score
184 between treatment initiation and month 6.

185 The radiological extent of disease evaluated using the Ralph score at baseline showed similar
186 values in both groups (mean 58.8 vs. 52.1 points; **online appendix table 1** and **figure 3**).
187 Although there was a slight increase of pulmonary infiltrations in the non-M/XDR-TB cohort
188 after treatment start, the score values declined over the time of treatment. Here, the
189 radiological scores of patients with M/XDR-TB remained at higher values, which was mainly
190 explained by a higher frequency of the persistence of cavitary lesions in the chest X-rays. A
191 higher proportion of patients with M/XDR-TB previously had TB and thus prior lung damage,
192 which would explain more extensive infiltrations.

193 **Discussion**

194 We compared early treatment response in a prospective cohort of patients with M/XDR-TB
195 and patients with non-M/XDR-TB in Germany, a country where unrestricted diagnostic and
196 therapeutic resources for the management of patients with M/XDR-TB are available. Six-
197 months culture conversion was similar for patients with non-MDR-TB and M/XDR-TB, which
198 could suggest a high chance of cure for patients with M/XDR-TB.

199

200 Our findings are in line with published data showing that the 6-months culture conversion
201 status is indicative for sustained treatment response in patients with M/XDR-TB (14, 26).
202 Using 6-months culture conversion status and a one-year follow-up after therapy completion
203 as markers for therapy outcome has also been suggested in a recently published study (14).
204 Although the 2-months culture conversion status has been evaluated as a surrogate for
205 treatment response in clinical trials evaluating novel anti-TB drugs, such as bedaquiline and
206 delamanid (27, 28), treatment outcomes are better correlated to the 6-months culture
207 conversion status (29). Six-months culture-conversion status was similar in both groups
208 (table 4). In the present study, the 2-months culture conversion rates of our M/XDR-TB
209 patients undergoing tailored treatment regimens on the basis of comprehensive drug
210 susceptibility testing exceeded the rates from trials presenting promising novel drugs with
211 excellent therapy results (27, 28, 30).

212

213 Standardized therapy regimens as presented by the “Bangladesh” regimen have yielded
214 excellent outcomes in specific settings with low frequencies of second-line drug resistance
215 (30). Based on these results the WHO made a conditional recommendation for a “shorter
216 course regimen” for the treatment of MDR-TB (9). However, only very few patients from the
217 European region may be eligible for this regimen due to high frequencies of second-line drug

218 resistance (13, 31, 32), which may lead to treatment failure and acquisition of additional
219 drug resistance (33). The low eligibility of patients from this setting is also reflected by our
220 study where high frequencies of first and second-line drug resistance were identified. This
221 strongly indicates that standard treatment regimens could lead to the emergence of
222 additional drug resistance due to inadequate therapy.

223

224 This study also showed that tailored treatment regimens in our study were highly variable. In
225 fact, such individualized therapy regimens were shown to lead to very high frequencies of
226 favorable treatment outcomes in an Austrian cohort (15). In contrast to patients who
227 received standardized treatment regimens, higher frequencies of cure for patients with
228 MDR-TB from the European region were found with individualized treatment regimens in a
229 large European multicenter cohort (Günther et al. submitted). Higher frequencies of
230 treatment success in patients receiving individualized therapy were also shown by large
231 meta-analyses comparing treatment results of patients with MDR-TB under standardized or
232 individualized regimens (16, 34).

233

234 We also evaluated the performance of an existing radiological score using chest X-rays and a
235 novel clinical score to further characterize the effect of treatment on an individual basis (21,
236 35). The items included in the clinical score were based on a published scoring system, which
237 was shown to predict mortality and treatment response in African cohorts (22, 36, 37).
238 Although we were able to show declining clinical and radiological scores after therapy
239 initiation (figure 3 and 4, online appendix table 1), our intention to correlate the scores'
240 trajectories with the established markers such as time to culture or to smear conversion, and
241 2- or 6 month culture conversion status failed, given the almost uniformly high frequency of
242 conversion in a relatively small cohort. Unfortunately, the small number of patients

243 precluded data reduction strategies like principal component analysis to evaluate the clinical
244 score. The decline in radiological score observed in our study was slow probably due to
245 persistence of cavitary lesions, which are slower to resolve, and in the presence of an
246 adequate clinical and microbiological response. Nevertheless, these or other clinically
247 derived scores may serve as alternative end-points for future biomarker validation and
248 should be reconsidered in future studies (38).

249
250 Although the relatively low number of patients evaluated limits our study, a very close
251 microbiological and clinical monitoring and the observations from clinical and radiological
252 scores strengthens our findings.

253

254 In conclusion, under optimal clinical conditions with availability of novel diagnostics and
255 individualized therapy, patients with M/XDR-TB can achieve 6-months culture conversion,
256 the frequency of which is similar to that of to patients with non-M/XDR-TB. This personalized
257 approach to therapy may have the potential to yield high frequencies of cure. The clinical
258 and radiological scores should be further evaluated with the aim to identify and validate
259 markers to individualize the duration of therapy.

260

261 **Acknowledgements**

262 We thank Cordula Ehlers, Jessica Hofmeister, Franziska Daduna, Nelleke Smitsmann, and
263 Dagmar Schaub for the study management and data entry. The study is funded by the
264 German Center for Infection Research (DZIF).

266 **Table 1.** Clinical characteristics of patients with non-MDR-TB and M/XDR-TB.

	Non-M/XDR*		M/XDR		Total	
	N = 46		N = 29		N = 75	
	n	%	n	%	n	%
Sex						
Male	30	65.2	18	62.1	48	64.0
Age, median (IQR)	43.0	31.0 – 58.0	36.0	30.0 – 41.0	39.0	31.0 – 56.0
BMI, median (IQR)	21.1	18.1 – 24.8	21.7	19.4 - 25.4	21.2	18.3 – 25.4
TB contact						
No	21	45.7	9	31.0	30	40.0
Yes	6	13.0	4	13.8	10	13.3
missing	19	41.3	16	55.2	35	46.7
BCG						
Yes	13	28.3	16	55.2	29	38.7
missing	28	60.9	12	41.4	40	53.3
TB type						
not previously treated for TB	35	76.1	18	62.1	53	70.7
Relapse	6	13.0	6	20.7	12	16.0
Failure	0	0.0	1	3.4	1	1.3
Return from default	1	2.2	1	3.4	2	2.7
missing	4	8.7	3	10.3	7	9.3
Previous TB						
Yes	7	15.2	10	34.5	17	22.7
missing	14	30.4	4	13.8	18	24.0
Diabetes						
Yes	4	8.7	2	6.9	6	8.0
missing	19	41.3	5	17.2	24	32.0
Hepatitis B						
Yes	3	6.5	1	3.4	4	5.3
missing	25	54.3	12	41.4	37	49.3
Hepatitis C						
Yes	2	4.3	3	10.3	5	6.7
missing	25	54.3	11	37.9	36	48.0

267 *44 patients with pan-drug susceptible TB and 2 patients with isoniazid mono-resistance

268

269 **Table 2.** Results of *Mycobacterium tuberculosis* phenotypic drug susceptibility testing from
 270 patients with non-M/XDR and M/XDR.

Drug	Non M/XDR*				M/XDR			
	N = 46				N = 29			
	Tested		Resistant		Tested		Resistant	
	N	%	N	%	N	%	N	%
H	45	97.8	2	4.4	27	93.1	27	100
R	46	100	0	0.0	29	100	29	100
E	44	95.7	0	0.0	27	93.1	18	66.7
Z	44	95.7			27	93.1	22	81.5
L					10	34.5	9	90.0
M					16	55.2	9	56.3
O	11	23.9	0	0.0	27	93.1	9	33.3
S					16	55.2	12	75.0
A					29	100	7	24.1
C	11	23.9	0	0.0	29	100	10	34.5
K					8	27.6	2	25.0
P	11	23.9	0	0.0	27	93.1	14	51.9
T					26	89.7	0	0.0
c					1	3.4	1	100
l					27	93.1	1	3.7
p					27	93.1	1	3.7
m					1	3.4	1	100
a					1	3.4	1	100

271 *44 patients with pan-drug susceptible TB and 2 patients with isoniazid mono-resistance

272 H: isoniazid; R: rifampicin; Z: pyrazinamid; E: ethambutol; O: ofloxacin; M: moxifloxacin; L: levofloxacin; S:
 273 streptomycin; C: capreomycin; A: amikacin; K: kanamycin; P: protionamide; T: terizidone/cycloserin; l: linezolid;
 274 c: clofazamin; p: para-amino-salicylic acid; m: meropenem; a: amoxicillin/clavulanic acid.

275

276 **Table 3.** Starting regimens in patients with non-MDR-TB and M/XDR-TB.

Drugs	Non-M/XDR*	M/XDR
HRZE - OML - SCAK - PTlc - BD - pma		
XXXX - ... - - - .. - ...	34	0
XXXX - ... - - ..X. - .. - X..	1	0
XXX. - ... - - - .. - ...	6	0
XX.X - ... - X... - - .. - ...	2	0
XX.X - ... - - - .. - ...	1	0
X..X - ... - - - .. - ...	1	0
.XXX - .X. - - - .. - ...	1	0
.X.. - .X. - .X.. - XX.. - .. - ...	0	1
..XX - .X. - .X.. - XX.. - .. - ...	0	1
..XX - .X. - .X.. - XX.. - .. - ...	0	1
..XX - .X. - ..X. - XX.. - .. - ...	0	1
..XX - ..X - ..X. - .XX. - .. - ...	0	1
..X. - .X. - .X.. - XXX. - .. - ...	0	1
..X. - .X. - .X.. - XX.. - .. - ...	0	2
..X. - .X. - .X.. - .X.. - .. - ...	0	1
..X. - .X. - ..X. - ..XX - .. - ...	0	1
..X. - ..X - ..X. - .XXX - .. - ...	0	1
..X. - ... - .X.. - .XX. - .. - ...	0	1
..X. - ... - ..X. - .X.X - .. - XXX	0	1
..X. - ... - - .X.X - .. - XXX	0	1
...X - .X. - .X.. - XX.X - .. - ...	0	1
...X - .X. - .X.. - XX.. - .. - ...	0	1
...X - .X. - .X.. - X.. - .. - ...	0	1
...X - ..X - - XXX. - .. - ...	0	1
.... - .X. - .X.. - .XXX - .. - X..	0	1
...X - ... - ..X. - .XX. - X. - ...	0	1
.... - .X. - .X.. - .XX. - .. - X..	0	1
.... - .X. - ..X. - .XX. - .. - X..	0	1
.... - .X. - - XXXX - .. - ...	0	1
.... - ..X - - .XX. - X. - ...	0	1
.... - ... - - .XXX - X. - .XX	0	2
.... - ... - - .XXX - .. - XXX	0	1
.... - ... - - .XX. - .. - ...	0	1

277 *44 patients with pan-drug susceptible TB and 2 patients with isoniazid mono-resistance

278 “.” indicates if drug was not used and “X” if drug was used; H: isoniazid; R: rifampicin; Z: pyrazinamid; E:
 279 ethambutol; O: ofloxacin; M: moxifloxacin; L: levofloxacin; S: streptomycin; C: capreomycin; A: amikacin; K:
 280 kanamycin; P: protionamide; T: terizidone/cycloserin; I: linezolid; c: clofazamin; B: bedaquiline; D: delamanid; p:
 281 PAS; m: meropenem; a: amoxicillin/clavulanic acid.

282

283

284 **Table 4.** Percentage of patients with *M. tuberculosis* culture and smear conversion at month
 285 2 and 6 after therapy initiation and median time to conversion with interquartile range for
 286 patients with non-M/XDR-TB and M/XDR-TB.

	Non-M/XDR*				M/XDR				p-value#
	KM estimate (%)		Time conversion to		KM estimate (%)		Time conversion to		
	Month 2	Month 6	Median	IQR	Month 2	Month 6	Median	IQR	
	%	%	Days	Days	%	%	Days	Days	
Smear conversion	90	96	19	10 - 32	78	93	31	14 - 56	0.044
Culture conversion	67	97	39	17 - 67	61	95	39	6 - 85	0.191

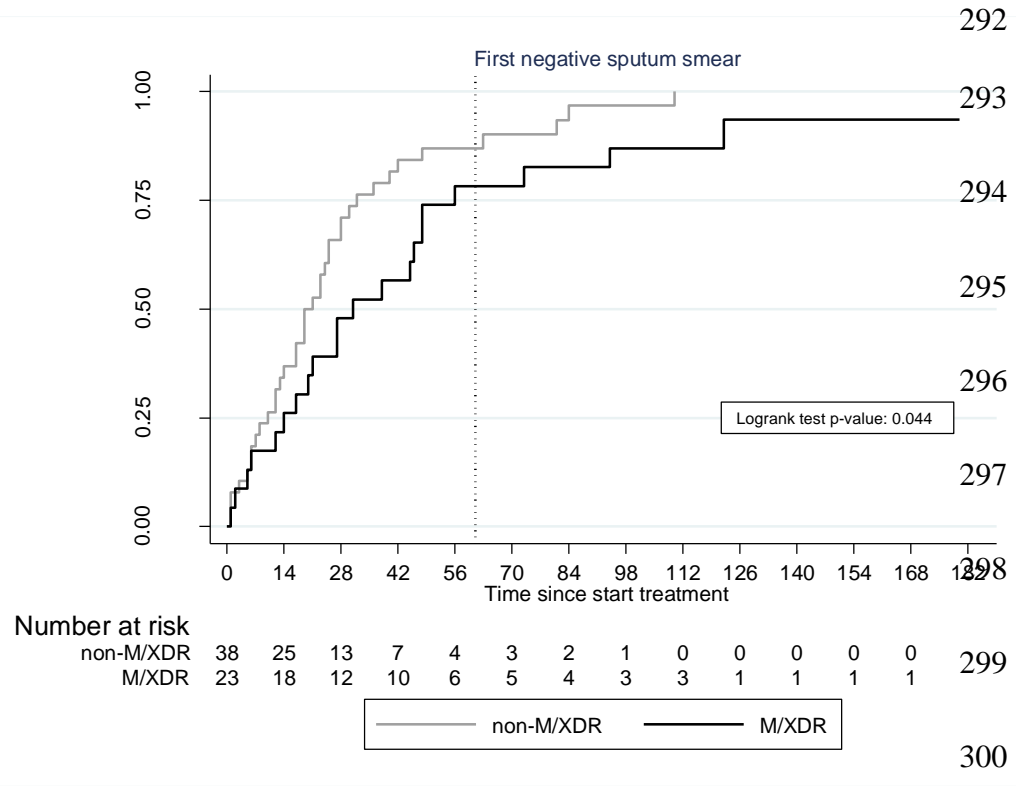
287 *44 patients with pan-drug susceptible TB and 2 patients with isoniazid mono-resistance

288 #Derived from Log-rank test.

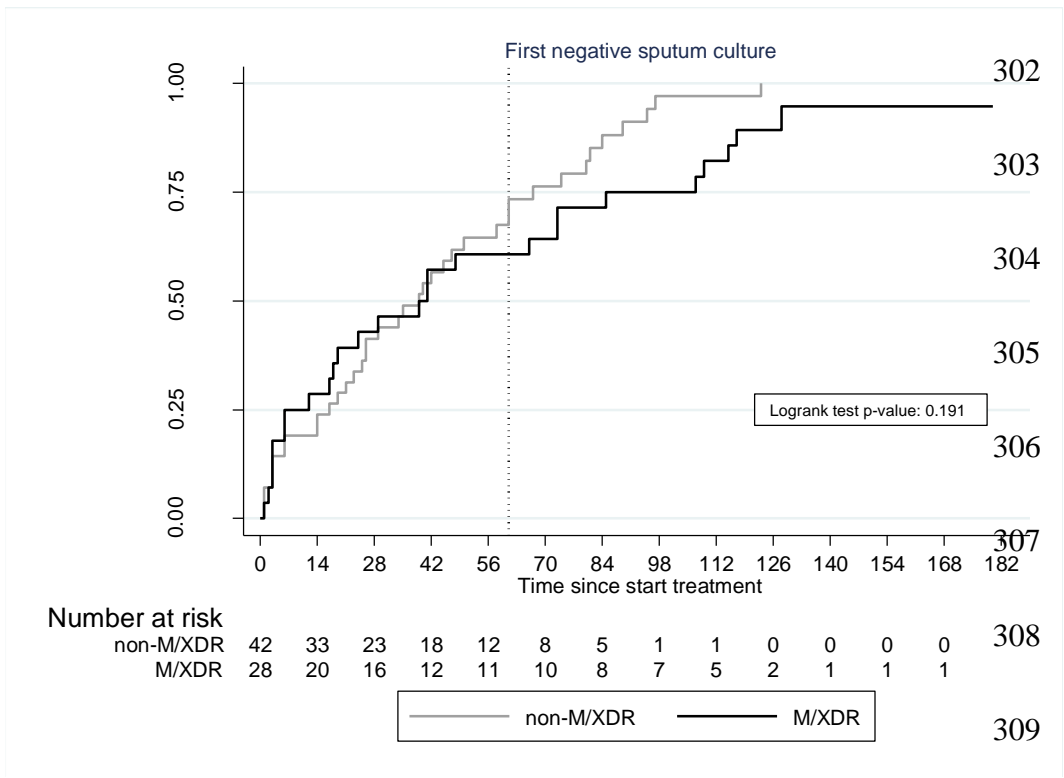
289

290 **FIGURES**

291 **A**



301 **B**

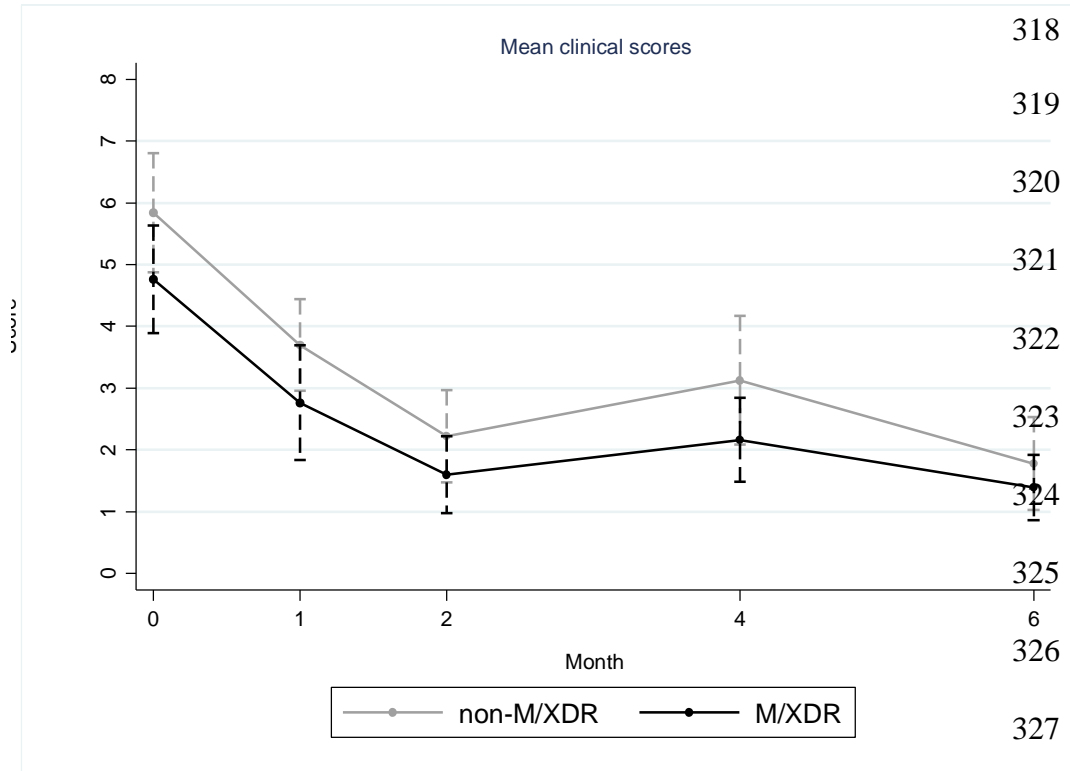


310 **Figure 1A and 1B.**

311 **A.** Kaplan-Meier estimates for the first negative sputum smear microscopy in patients with
312 non-M/XDR-TB (grey line) and M/XDR-TB (black line) after therapy initiation. Below the X-
313 axis, the number at risk is shown. **B.** Kaplan-Meier estimates for the first negative sputum
314 culture (liquid and solid) in patients with non-M/XDR-TB (grey line) and M/XDR-TB (black
315 line) after therapy initiation. Below the X-axis, the number at risk is shown.

316

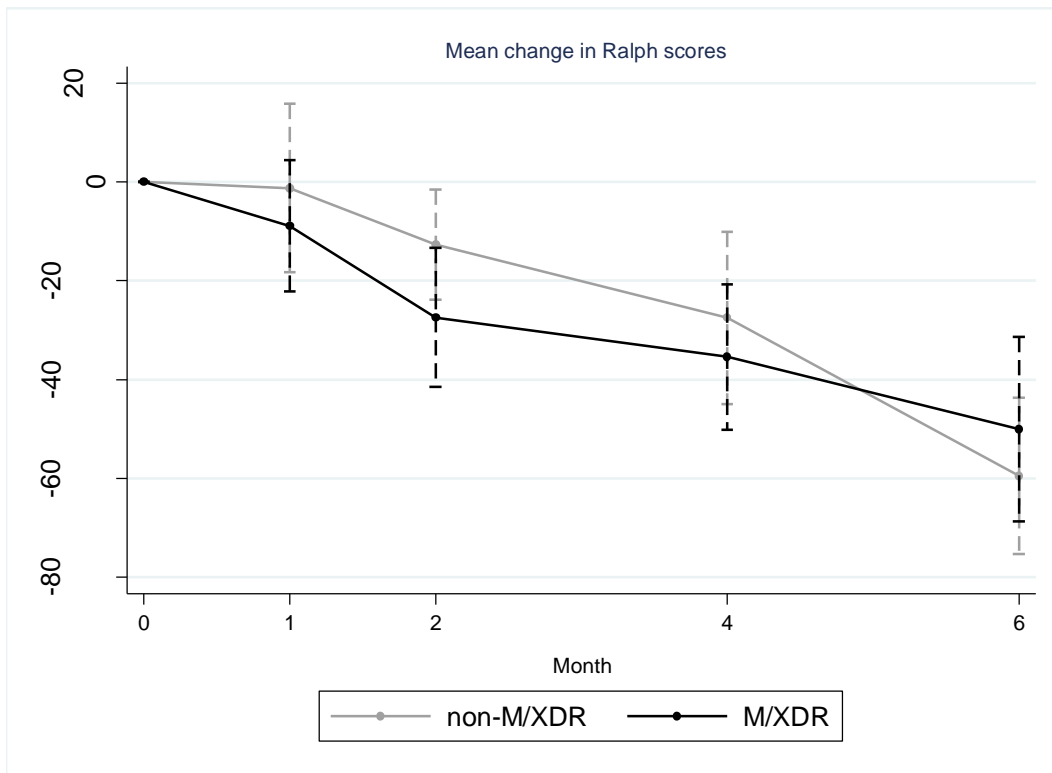
317



328

329 **Figure 2.** Mean clinical scores (Y-axis) during the course of therapy (X-axis, months) for
330 patients with susceptible (gray line) and M/XDR-TB (black line) with 95% confidence interval
331 (dashed lines).

332



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334 **Figure 3.** Mean change of radiological (Ralph) scores (Y-axis, %) in the course of therapy (X-
 335 axis, months) for patients with susceptible (grey line) and M/XDR-TB (black line) with 95%
 336 confidence interval (dashed lines).

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