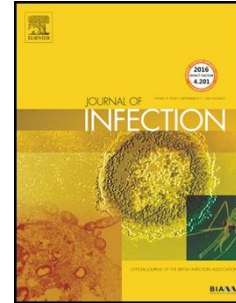


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1 **Title**

2 Management of MDR-TB in HIV co-infected patients in Eastern Europe: Results from the TB:HIV study

3 **Running Title**

4 Management of HIV-positive patients with MDR-TB in Eastern Europe

5 **Authors**

6 A.M. W. Efsen^{1,*}, A. Schultze², R.F. Miller³, A. Pantelev⁴, A. Skrahin⁵, D.N. Podlekareva¹, J.M. Miro⁶, E.
7 Girardi⁷, H. Furrer⁸, M.H. Losso⁹, J. Toibaro⁹, J. A. Caylà¹⁰, A. Mocroft², J.D. Lundgren¹, F.A. Post¹¹, O. Kirk¹,
8 for the TB:HIV study in EuroCoord[#]

9 [#]A full list of the TB:HIV Study Group investigators can be found in the acknowledgement section

10

11 **Affiliations**

12 ¹CHIP, Department of Infectious Diseases, Finsencentret, Rigshospitalet, University of Copenhagen,
13 Blegdamsvej 9, 2100 Copenhagen Ø, Denmark (Anne Marie Werlinrud Efsen (PhD), Daria N.
14 Podlekareva (MD), Jens D. Lundgren (DMSc), Ole Kirk (DMSc)).

15 ²Department of Infection and Population Health, University College London Medical School, Rowland
16 Hill Street, NW3 2PF, London, UK ((Anna Schultze (MSc), Amanda Mocroft (Professor)).

17 ³Centre for Sexual Health and HIV Research, Mortimer Market Centre, University College London,
18 London WC1E 6JB, UK (Robert F. MILLER (Professor))

19 ⁴Department of HIV/TB, TB hospital 2, Ushinskogo str 39/1 – 122, 195267 St. Petersburg, Russia
20 (Alexander Pantelev (DMSc))

21 ⁵Clinical Department, Republican Research and Practical Centre for Pulmonology and TB, Minsk,
22 Belarus (Aliaksandr Skrahin (MD))

23 ⁶Infectious Diseases Service, Hospital Clinic – IDIBAPS. University of Barcelona, Villarroel, 170, 08036
24 Barcelona, Spain (Jose M. Miro (PhD))

25 ⁷Department of Infectious Diseases INMI "L. Spallanzani", Ospedale L Spallanzani, Via Portuense, 292,
26 00149 Rome, Italy (Enrico Girardi (MD))

27 ⁸Department of Infectious Diseases, Bern University Hospital, University of Bern, CH-3010 Bern, Switzerland
28 (Hansjakob Furrer (Professor))

29 ⁹Department of immunocompromised, Hospital J.M. Ramos Mejia, Pabellón de Clínica, 2do Piso, CP
30 1221 Buenos Aires, Argentina (Marcelo H. Losso (MD), Javier Toibaro (MD))

31 ¹⁰Agencia de Salud Pública de Barcelona, Barcelona, España; Programa Integrado de Investigación
32 en Tuberculosis de SEPAR (PII-TB); Centro de Investigación Biomédica en Red de Epidemiología y Salud
33 Pública (CIBERESP) (Joan A. Caylà, (MD))

34 ¹¹Department of Sexual Health, Caldecot Centre, King's College Hospital, Bessemer Road, London SE5
35 9RS, UK (Frank A. POST (MD))

36

37 ***Corresponding Author**

38 Anne Marie Werlinrud Efsen, PhD

39 Rigshospitalet, University of Copenhagen

40 CHIP, Department of Infectious Diseases, Section 2100 (CHIP)

41 Blegdamsvej 9

42 DK-2100 Copenhagen Ø, Denmark

43 Phone: + 45 35 45 57 57

44 Fax: +45 35 45 57 58

45 E-mail: anne.marie.werlinrud.efsen@regionh.dk/

46 Web: www.chip.dk

47

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56

57

Highlights

- Management of TB/HIV co-infected patients in Eastern Europe (EE) is suboptimal
- TB/HIV co-infected patients diagnosed with MDR-TB received inferior TB treatment with limited numbers of active drugs
- Access to rapid diagnostics for TB is urgently needed
- Performance of extended DST for all patients diagnosed with MDR-TB is required
- Integration of TB and HIV clinics can potentially ensure better management of patients in EE

Abstract

Objectives

Mortality among HIV patients with tuberculosis (TB) remains high in Eastern Europe (EE), but details of TB and HIV management remain scarce.

Methods

In this prospective study, we describe the TB treatment regimens of patients with multi-drug resistant (MDR) TB and use of antiretroviral therapy (ART).

Results

A total of 105 HIV-positive patients had MDR-TB (including 33 with extensive drug resistance) and 130 pan-susceptible TB. Adequate initial TB treatment was provided for 8% of patients with MDR-TB compared with 80% of those with pan-susceptible TB. By twelve months, an estimated 57.3% (95%CI 41.5-74.1) of MDR-TB patients had started adequate treatment. While 67% received ART, HIV-RNA suppression was demonstrated in only 23%.

Conclusions

Our results show that internationally recommended MDR-TB treatment regimens were infrequently used and that ART use and viral suppression was well below the target of 90%, reflecting the challenging patient population and the environment in which health care is provided. Urgent improvement of management of

83 patients with TB/HIV in EE, in particular for those with MDR-TB, is needed and includes widespread access
84 to rapid TB diagnostics, better access to and use of second-line TB drugs, timely ART initiation with viral
85 load monitoring, and integration of TB/HIV care.

86

87 **Introduction**

88 Although rates of tuberculosis (TB) have begun to decline in recent years, simultaneous rapid increases in
89 the relative contribution of multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) are
90 worrying (1-4). Eastern Europe (EE), together with central Asia, has the worlds' highest proportions of MDR-
91 and XDR-TB with 9-35% of new TB cases and 49-77% of re-treatment cases being diagnosed with MDR-TB in
92 Belarus, Russia and Ukraine compared with 1-3% of new cases and 4-14% of re-treatment cases in Italy,
93 Switzerland and the United Kingdom (1, 5-8).

94 The MDR-TB epidemic in EE is further complicated by high rates of HIV co-infection. Whereas most other
95 regions have reported declining rates of new HIV infections over recent years, EE has experienced an
96 increase of 30% in annual number of new HIV infections since the turn of the millennium (9, 10). The
97 TB/HIV epidemic in EE is primarily driven by injection drug users (IDU) who often access health care late,
98 are co-infected with hepatitis C (HCV), and frequently have poor treatment compliance and retention in
99 care (11-14). We recently reported a one-year mortality rate of 27% for TB/HIV co-infected patients in EE,
100 and patients diagnosed with MDR-TB had roughly three-times higher mortality compared to those with
101 drug-susceptible TB. Further, patients from EE who initiated TB treatment with three or more active drugs
102 had significantly lower risk of death compared to patients who received less than three active TB drugs
103 (13% vs 34%) (15).

104 Treatment for MDR-TB is complex in terms of pill burden, drug-interactions and toxicity, and costly (1, 16-
105 18). MDR-TB therapy is prolonged (typically at least 20 months) although the 2016 WHO guidelines include

106 an option for shorter MDR-TB regimens in specific cases (16, 19). Preliminary results with a novel six
107 months regimen (consisting of pretomanid, bedaquiline and linezolid) may be highly effective to treat MDR-
108 TB (20). For now, standard of care consists of at least five drugs including a fluoroquinolone, a second-line
109 injectable, at least two other active drugs plus pyrazinamide during the intensive phase of treatment (19).
110 Reported MDR-TB treatment success rates, however, have been generally low, in particular for HIV-positive
111 individuals, and rarely exceed 50% (18, 21).

112 Epidemiological data and detailed descriptions of the clinical management of HIV-positive patients with
113 MDR-TB in EE remain relatively scarce (22). We prospectively studied patients with TB/HIV co-infection in
114 EE and in this paper report on the management of those with MDR-TB.

115

116 **Methods**

117 **Study design and participants**

118 The TB:HIV Study is a prospective cohort study including 62 TB and HIV clinics in 19 countries in EE, Western
119 Europe, Southern Europe, and Latin America. Adult (>16 years) HIV-positive patients with a TB diagnosis
120 were consecutively enrolled between 01/01/2011 and 31/12/2013. Demographic, clinical, and laboratory
121 data were collected on standardized case report forms at baseline and month 6, 12, and 24 (12); further
122 details are available at <http://www.cphiv.dk/TBHIV>. All participating clinics obtained ethical approval in
123 accordance with local rules and legislations, and the study was performed in accordance with the strobe
124 guidelines for observational studies (23).

125 **Study definitions**

126 Patients from EE were included in the present analyses if they had definite or probable TB. A diagnosis of
127 definite TB was based on positive culture or molecular diagnostics for *Mycobacterium tuberculosis* (*Mtb*),

128 and probable TB on the presence of acid fast bacilli and/or granulomatous inflammation on sputum smear
129 or tissue biopsy specimens (12). **Baseline** was defined as the date TB treatment was initiated, and a
130 baseline culture was defined as a culture obtained within one month of baseline. All TB drugs initiated
131 within 10 days of baseline were considered to constitute initial TB treatment. Standard definitions of MDR-
132 TB, pre-XDR-TB, and XDR-TB were used (see box), and pan-susceptible TB was defined as TB without
133 documented drug resistance. TB treatment regimens were categorized in line with general
134 recommendations (16, 24): 1: Treatment regimens containing RHZ (with or without ES) targeting drug-
135 susceptible TB (24), 2: Treatment regimens containing RHZ plus a fluoroquinolone AND a second line
136 injectable, providing empiric cover for both susceptible TB and MDR-TB, 3: Five or more MDR-TB drugs
137 (including a fluoroquinolone AND a second line injectable) providing appropriate empiric cover for MDR-TB,
138 4: Regimens containing a fluoroquinolone OR a second line injectable (but not both), providing inadequate
139 cover for MDR-TB, and 5: Any other drug combination (Fig. 1). For patients with MDR-TB, the number of
140 active drugs in the TB regimen was calculated at various time points based on the susceptibility pattern of
141 isolates obtained up to the given time point. If a Drug Susceptibility Test (DST) result was not available for a
142 specific drug included in the regimen, the given *Mtb* isolate was either considered potentially susceptible to
143 this drug (**potentially** active drugs) or resistant to this drug (**known** active drugs), thus representing a “best
144 case” and “worst case” treatment scenario.

145 Antiretroviral treatment (ART) was defined as a combination of ≥ 3 antiretroviral drugs from any ART class.
146 Participants were considered **lost to follow-up** (LTFU) when no attendance was recorded at the relevant
147 time points in those who were not known to have died.

148 **Statistical analysis**

149 Descriptive statistics were used for baseline characteristics of patients. Patients were stratified into three
150 groups: MDR-TB at baseline, pan-susceptible TB at baseline, and other (no baseline DST results available or
151 the presence of non-MDR-TB resistance patterns). MDR-TB patients who had extended DST available were

152 further classified as having pre-XDR or XDR-TB. Baseline characteristics among patients who had MDR-TB,
153 those who were fully susceptible and those who did not have any baseline DST available were compared
154 using the chi-squared test or Fisher's exact test as appropriate for categorical variables, whereas the
155 Kruskal-Wallis test was used to compare continuous variables.

156 TB and HIV treatment regimens were analyzed at months 0, 3, 7, 13, and 21. Kaplan-Meier estimates were
157 used to estimate time to receiving adequate treatment for MDR-TB (category 3: five or more MDR-TB drugs
158 including a fluoroquinolone AND a second line injectable), and time to starting ART censoring at last visit
159 date (maximum 21 months) or death, whichever occurred first. Further, Kaplan-Meier estimates were also
160 used to estimate the time to starting ART. All statistical analyses were performed using SAS (Statistical
161 Analysis Software, Cary, NC, USA, version 9.3).

162

163 **Results**

164 **Patient characteristics**

165 Of 1406 patients enrolled into the TB:HIV study, 834 received care in EE, of these 485 had definite or
166 probable TB and were included in this analysis (supplementary Fig. 1). A positive culture for *Mtb* was
167 reported in 383 (79%) patients, 302 (79%) of these were tested for resistance to any drug, 270 (70%) for
168 both R and H, and 68 (18%) for fluoroquinolone or second line injectables. Of the 485 patients, 105 (22%)
169 had MDR-TB, 130 (27%) had pan-susceptible TB at baseline and 183 (38%) had no DST results; the
170 remaining 67 (14%) had non-MDR-TB resistance patterns and were excluded from subsequent analyses.
171 Baseline characteristics are shown in Table 1. The majority of patients were male and white, with a median
172 age of 35 years. Recent incarceration was common, and previous TB, IDU, and HCV co-infection were
173 significantly more common among MDR-TB patients. The median baseline CD4 cell count was 91
174 (interquartile range [IQR] 31-230) cells/mm³, and only 82 (17%) patients were on ART.

175 DST patterns for MDR-TB patients

176 Among the 105 patients with MDR-TB at baseline, DST results (obtained at any time during TB treatment)
177 for other drugs ranged from 51-95% for group 1 drugs, 75-78% for group 2/3 drugs, and 49-69% for group 4
178 drugs (Table 2). The timing of DST testing for individual TB drugs is shown in Table 3a. Overall, 13 (12%) of
179 MDR-TB patients had XDR-TB, 20 (19%) had pre-XDR, 35 (33%) had MDR, and 37 patients had insufficient
180 data to determine pre-XDR/XDR-TB status.

181 Treatment regimen and outcomes

182 In Fig. 1, TB treatment regimens and outcomes are depicted from baseline through 21 months of follow-up.
183 WHO recommended regimens were initiated in the majority of individuals with drug-susceptible TB but
184 maintained well beyond the recommended 6 months. Despite the high population prevalence of MDR-TB,
185 very few subjects received empiric therapy that provided cover against drug-susceptible and (multi)drug
186 resistant TB (category 2). High rates of death were observed among MDR-TB patients and those without
187 DST. Loss to follow-up (from both TB and HIV care) was high, ranging from 8% of MDR-TB patients to 19-
188 20% among patients with pan-susceptible TB or no DST.

189 TB treatment for MDR-TB patients

190 Only 8 (8%) of MDR-TB patients initiated an adequate empiric MDR-TB regimen (category 3), which
191 increased to 35 (44% of patients still under follow-up) after three months. A total of 49 MDR-TB patients
192 ever received category 3 treatment after a median of 1.2 months (IQR 0.4-2.3), and by 12 months, an
193 estimated 57.3% (95%CI=41.5-74.1%) had started adequate MDR-TB treatment. Similar results were
194 obtained when excluding patients with known pre-XDR-TB or XDR-TB (data not shown).

195 Fluoroquinolones and second-line injectables were uncommon components of initial treatment and, if
196 used, commonly used without adequate companion drugs (Table 3b/c). By three months, a quarter of
197 MDR-TB patients still had not initiated a fluoroquinolone or a second-line injectable. Group 4 drugs were

198 variably used, a single patient had received linezolid (introduced late during the course of treatment), and
199 no patients had received bedaquiline or delamanide. Culture conversion was documented in 45/105 (43%)
200 of MDR-TB patients and 77/130 (59%) of patients with pan-susceptible TB after a median of 3.0 (IQR 1.8-
201 5.1) and 2.3 (IQR 1.7-4.9, $p=0.30$) months, respectively.

202 **Activity of TB treatment for MDR-TB patients**

203 Fig. 2a-c illustrates the total number of drugs and the total number of “potentially” active drugs and
204 “known” active drugs, respectively, in the MDR-TB treatment regimens. While most patients received 4 or
205 more drugs in their regimen during the first year of treatment, more than 70% received 0, 1 or 2 drugs with
206 demonstrated activity. A regimen containing 5 or more known active drugs was received by less than 15%
207 of patients and a regimen containing 5 or more potentially active drugs by less than 40% of patients.

208 **HIV treatment for MDR-TB patients**

209 Despite 77% of MDR-TB patients at the time of their TB diagnosis already having an HIV diagnosis and the
210 majority being severely immunosuppressed with a median CD4 cell count of 100 cells/mm³, only 13% were
211 on ART at baseline (Table 1). The proportion on ART among those who remained in care increased to more
212 than 60% (Figure 3). The majority of those on ART did not have regular HIV-RNA monitoring, and less than
213 20% of MDR-TB patients were documented to have had an undetectable HIV-RNA (<500 copies/mL) at any
214 stage during follow up. The Kaplan-Meier estimate of starting ART by eight weeks was only 23%; similar
215 results were observed for patients with drug-susceptible TB and those with no DST results (data not
216 shown).

217

218 **Discussion**

219 This study shows suboptimal management of MDR-TB in HIV-positive patients in EE. Despite the high
220 prevalence of MDR-TB, full DST testing was often restricted and delayed, resulting in prolonged use of
221 inappropriate or failing regimens that contained few active drugs and suboptimal intensification strategies,
222 with only half of patients ultimately receiving recommended MDR-TB therapy. In addition, we observed a
223 low uptake of ART, inadequate viral load monitoring and low rates of HIV-RNA suppression. All of these
224 factors are likely to have contributed to the mortality rate of nearly 50% at two years. These data point
225 towards opportunities to improve management of HIV-positive individuals with TB in parts of EE.

226 The similar characteristics of patients with and without MDR-TB preclude public health strategies based on
227 risk-stratification of patients and argue for routine DST in all TB patients. Rapid TB diagnostics and DST such
228 as line-probe assays or cartridge-based molecular tests for *Mtb* and rifampicin resistance (16) should be
229 introduced as a priority (25), with routine evaluation of genotypic or phenotypic DST for fluoroquinolones
230 and second line injectables of all rifampicin-resistant isolates. Thirty-nine percent of those tested for MDR-
231 TB in our cohort had MDR-TB which is consistent with other recent reports from the EE region (8, 26). Of
232 the patients with MDR-TB, approximately one-third had MDR, one-third had pre-XDR or XDR-TB, and one-
233 third did not have sufficient DST data to assess whether they had (pre-)XDR-TB. We also found common co-
234 resistance to other drugs, as described in another European multicenter study (27). Despite the setting of
235 high MDR-TB prevalence in EE, empiric therapy rarely provided cover for MDR-TB. This is also problematic
236 as selection for additional drug-resistance is more likely to occur early on when the bacillary burden is high.
237 It is worth noting, however, that four in five patients who later were shown to have fully susceptible TB,
238 initially received adequate RHZ-based treatment, as recently described (28).

239 In patients with MDR-TB, there were significant delays to initiate treatment for MDR-TB, and many patients
240 never received adequate MDR-TB treatment as defined by international guidelines (19). The number of
241 active drugs remained low at all time points; only one-third of patients were treated at some stage with at
242 least five potentially active drugs, and only one-sixth of patients received regimens with 5 drugs known to

243 have activity against their *Mtb* isolate. This is of concern as recent studies demonstrate improved outcomes
244 with optimal MDR-TB regimens (≥ 5 likely effective drugs) (29-31). Optimal MDR-TB treatment requires
245 continued, unrestricted access to high quality medications; in a recent survey we documented that this was
246 not the case in many clinics in EE (32). In agreement with this, linezolid, bedaquiline and delamanid were
247 generally not used although widespread use in the current context raises significant opportunities for these
248 drugs to be rapidly lost due to the emergence of resistance.

249 There is now solid evidence that ART should be initiated shortly after TB diagnosis, especially in patients
250 with MDR-TB and those with CD4 cell counts below 50 cells/mm³ (33-36). In our study, patients were
251 severely immunosuppressed, and two-thirds of those who remained under follow-up at three months had
252 initiated ART. However, less than 20% had documented suppressed viral loads at any time which is well
253 short of the WHO goal of virological suppression in 90% of patients receiving ART (37).

254 We documented a mortality rate of nearly 50% within the first two years following initiation of TB
255 treatment, which is similar to the mortality observed in a retrospective study from our group of HIV-
256 patients with MDR-TB in EE which was conducted in the period 2004-2006 (14). Retrospective African
257 studies reported mortality rates among HIV-positive patients with MDR-TB of 15-31% (38-40) and a meta-
258 analysis of outcomes found a pooled mortality rate of 38% (41). The vast majority of deaths in our
259 retrospective cohort were due to TB (42), which underscores the particular need for high-quality TB
260 management for people with HIV. Other circumstances may have played a role in determining outcome of
261 MDR-TB patients in EE. A disintegrated health care system with separated TB and HIV management remains
262 common (32) and is likely to contribute to poor coordination of care to this often very vulnerable patient
263 population. In particular, opioid substitution therapy for IDU is severely restricted or even prohibited in
264 some countries despite documented positive effects on adherence to treatment and health care in general
265 (43).

266 Our observational study has several limitations including the intrinsic risk of selection bias. The participating
267 clinics were primarily located in major cities and may not be representative of all clinics across EE. DST was
268 done locally and methods for performing DSTs varied between clinics, and when calculating the number of
269 active drugs, we counted all drugs as equally effective which is likely to be an over-simplification. A large
270 number of patients had missing DST results, CD4 cell counts and HIV-RNA measurements precluding a more
271 robust evaluation of immune-virological outcomes. Nonetheless, the circumstances described reflect the
272 difficulties for many HIV and TB clinicians working in EE, although substantial regional variability in the
273 prevalence of MDR-TB and availability of DST, TB and ART drugs, and HIV-RNA measurements exists (12).
274 Due to limited number of patients with MDR-TB we did not assess intraregional variability.

275

276 **Conclusion**

277 In EE, there is an urgent need for access to rapid diagnostics to guide initial TB treatment, to extended DST
278 to all patients diagnosed with rifamycin-resistant or MDR-TB and to provide better access to second line
279 drugs to allow the administration of optimally active MDR-TB regimens. Integration of TB and HIV services
280 can ensure better management and support for people with HIV who frequently have IDU and HCV
281 coinfection, including rapid initiation of fully suppressive ART.

282

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285 **Eastern Europe**

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289 Mitsura, E. Kozorez, O. Tumash; Gomel Region Centre for Hygiene: O. Suetnov (PI) and D. Paduto.
- 290 Estonia: East Viru Central Hospital (Kohtla-Jarve): V. Iljina (PI) and T. Kummik.
- 291 Georgia: Infectious Diseases, AIDS and Clinical Immunology Research Center (Tbilisi): N. Bolokadze (PI), K.
292 Mshvidobadze and N. Lanchava; National Center for Tuberculosis and Lung Diseases of Georgia (Tibilisi): L.
293 Goginashvili, L. Mikiashvili and N. Bablishvili.
- 294 Latvia: Infectology Centre of Latvia (Riga): B. Rozentale (PI), I. Zeltina and I. Janushkevich.
- 295 Lithuania: Centre for Communicable Diseases and AIDS (Vilnius): I. Caplinskiene (PI), S. Caplinskas, Z.
296 Kancauskiene.
- 297 Poland: Wojewodski Szpital Zakanzy/Medical University of Warsaw (Warszawa): R. Podlasin (PI), A.
298 Wiercinska-Drapalo (PI), M. Thompson and J. Kozłowska; Wojewodski Szpital Specjalistyczny/Medical
299 University Teaching Hospital (Bialystok): A. Grezesczuk (PI); Jozef Strus Multidisciplinary City Hospital
300 (Poznan): M. Bura (PI); Wroclaw University School of Medicine (Wroclaw): B. Knysz (PI) and M. Inglot;
301 Jagiellonian University Medical College (Krakow): A. Garlicki (PI) and J. Loster.
- 302 Romania: Dr. Victor Babes Hospital (Bucharest): S. Tetrarov (PI) and D. Duiculescu (†).
- 303 Russia: Botkin Hospital of Infectious Diseases (St. Petersburg): A. Rakhmanova (PI[†]), O. Panteleeva, A.
304 Yakovlev, A. Kozlov, A. Tyukalova and Y. Vlasova; City TB Hospital No. 2 (St. Petersburg): A. Panteleev (PI);
305 Center for Prevention and Control of AIDS (Veliky, Novgorod): T. Trofimov (PI); Medical University
306 Povoljskiy Federal Region.
- 307 Ukraine: Crimean Republican AIDS Centre (Simferopol): G. Kyselyova (PI).
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327 Kaiser L, Keiser O, Klimkait T, Kouyos R, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B,
328 Metzner K, Müller N, Nadal D, Nicca D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S,
329 Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schöni-Affolter F,
330 Schmid P, Schüpbach J, Speck R, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.

331 United Kingdom: Mortimer Market Centre (London): R. Miller (PI) and N. Vora; St. Mary's Hospital: G.
332 Cooke (PI) and S. Mullaney; North Manchester General Hospital: E. Wilkins (PI) and V. George; Sheffield
333 Teaching Hospitals: P. Collini (PI) and D. Dockrell; King's College Hospital (London): F. Post (PI), L. Campbell,

334 R. Brum, E. Mabonga and P. Saigal. Queen Elizabeth Hospital: S. Kegg (PI); North Middlesex University
335 Hospital: J. Ainsworth (PI) and A. Waters. Leicester Royal Infirmary: J. Dhar (PI) and L. Mashonganyika.

336 **Southern Europe:**

337 Italy: IRCCS - Ospedale L. Spallanzani (Rome): E. Girardi (PI), A Rianda, V. Galati, C. Pinnetti and C. Tommasi;
338 AO San Gerardo (Monza): G. Lapadula (PI); IRCCS AOU San Martino – IST di Genoa (Genova): A. Di Biagio (PI)
339 and A. Parisini; Clinic of Infectious Diseases, University of Bari (Bari): S. Carbonara (PI), G. Angarano and M.
340 Purgatorio; University of Brescia Spedali Civili: A. Matteelli (PI) and A. Apostoli.

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352 **Latin America**

353 The CICAL Cohort: Cohorte administration: M. Losso (PI), J. Toibaro and L. Gambardella. Participating
354 Centers and Physicians: Argentina: Hospital J. M. Ramos Mejía (Buenos Aires): J. Toibaro and L. Moreno
355 Macias; Hospital Paroissien (BA): E. Warley (PI) and S. Tavella; Hospital Piñero (BA): O. Garcia Messina and
356 O. Gear; Hospital Nacional Profesor Alejandro Posadas: H. Laplume; Hospital Rawson (Cordoba): C. Marson
357 (PI); Hospital San Juan de Dios (La Plata): J. Contarelia and M. Michaan; Hospital General de Agudos

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360 (México DF): B. Crabtree (PI); Hospital General Regional de Leon- CAPACITS: JL Mosqueda Gomez; Hospital
361 Civil de Guadalajara: A. Villanueva and LA Gonzalez Hernandez.

362

363 **TB:HIV Steering Committee**

364 H. Furrer, E. Girardi, J. A. Caylá, M. H. Losso, J. D. Lundgren, A. Panteleev (co-chair), R. Miller, J.M. Miro, Å.
365 B. Andersen, S. Tetradov, F. A. Post (co-chair), A. Skrahin and J. Toibaro.

366

367 **Statistical centre**

368 A. Schultze, A. Mocroft.

369

370 **Coordinating centre**

371 AM. W. Efsen, M. Mansfeld, B. Aagaard, B. R. Nielsen, A H. Fisher, E.V. Hansen, D. Raben, D. N. Podlekareva,
372 O. Kirk.

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379

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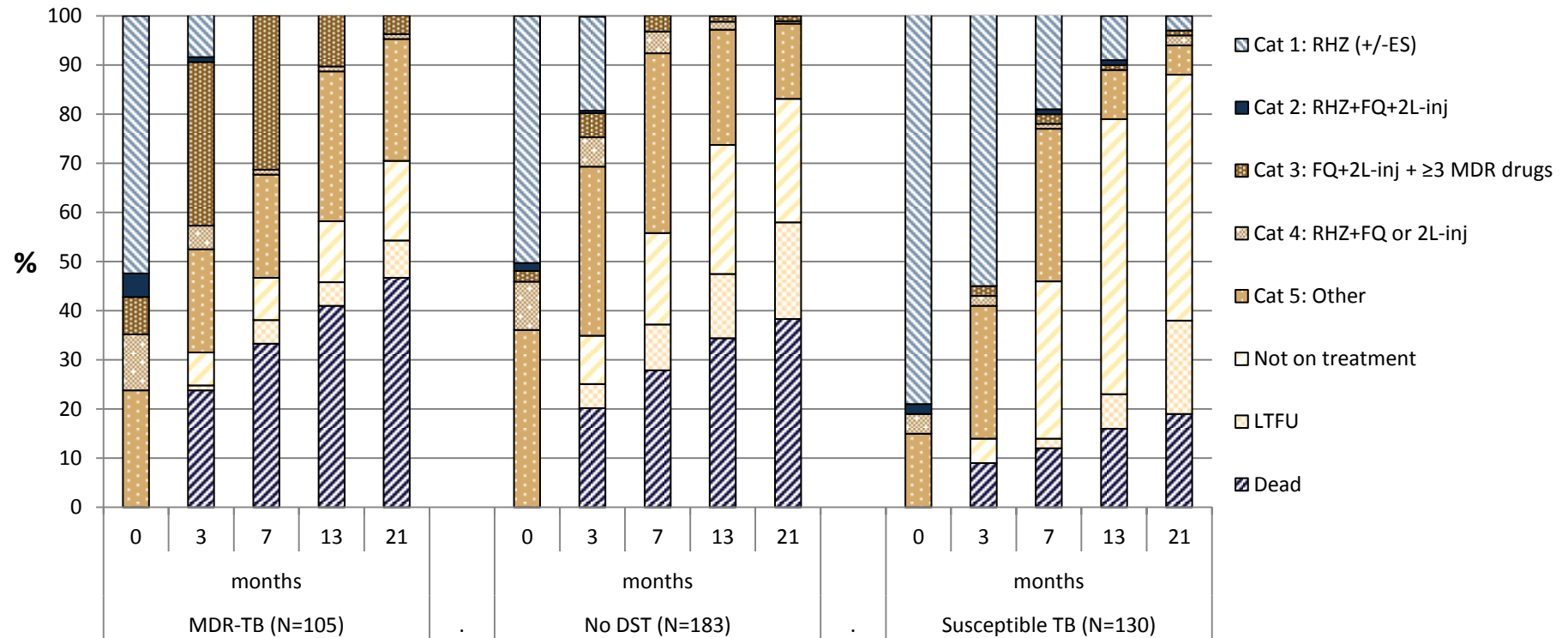
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504 **Figure 1: TB treatment and outcomes over time among 105 patients with MDR-TB (left), 183 with no DST (middle) and 130 patients with**
 505 **susceptible TB (right) from time of start of TB treatment.**



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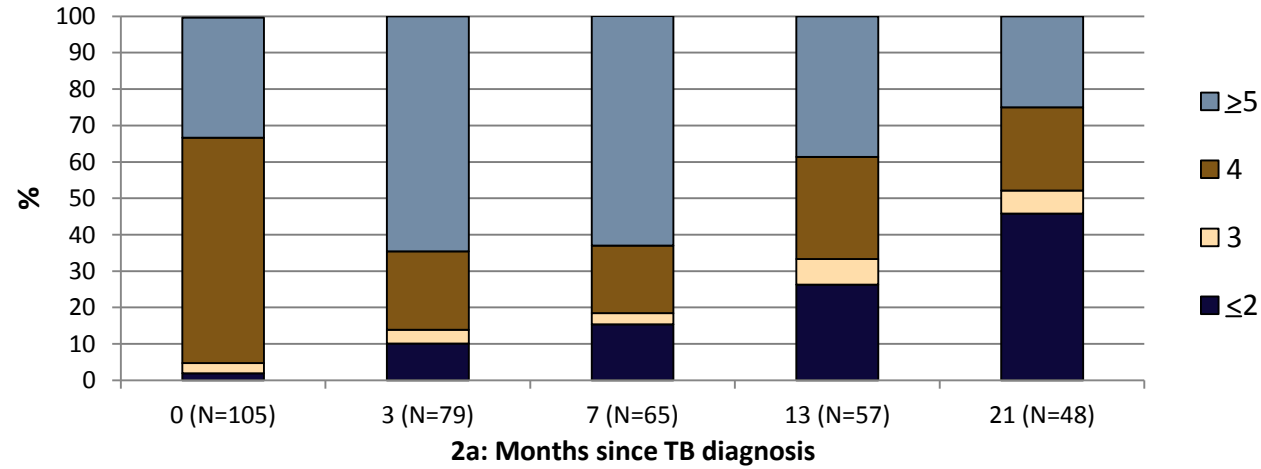
507 *R = Rifampicin*508 *H = Isoniazid*509 *Z = Pyrazinamide*510 *E = Ethambutol*511 *S = Streptomycin*512 *FQ = Fluoroquinolone*513 *2L-inj = Second-line injectables*514 *LTFU = Loss to follow-up*515 *DST = Drug-susceptibility test*

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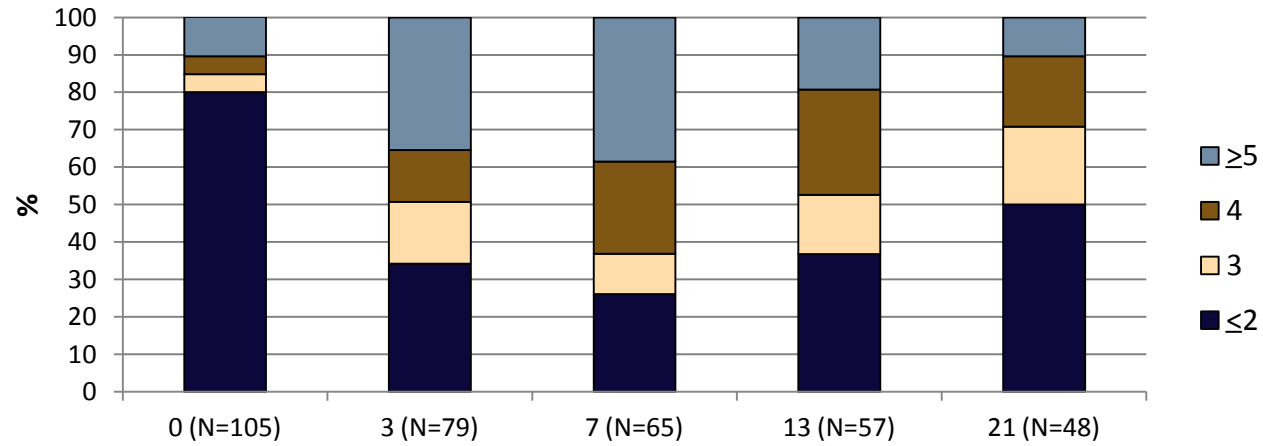
517 **Figure 2a-c: Number of *total* TB drugs (a), *potentially active** (b), and *known active*** (c) TB drugs at each time point for 105 MDR-TB**
 518 **patients under follow-up.**

519 *Potentially active: Assuming susceptibility where DST for a specific drug was missing.

520 **Known active: Only including known DST results and not assuming susceptibility for missing DST.

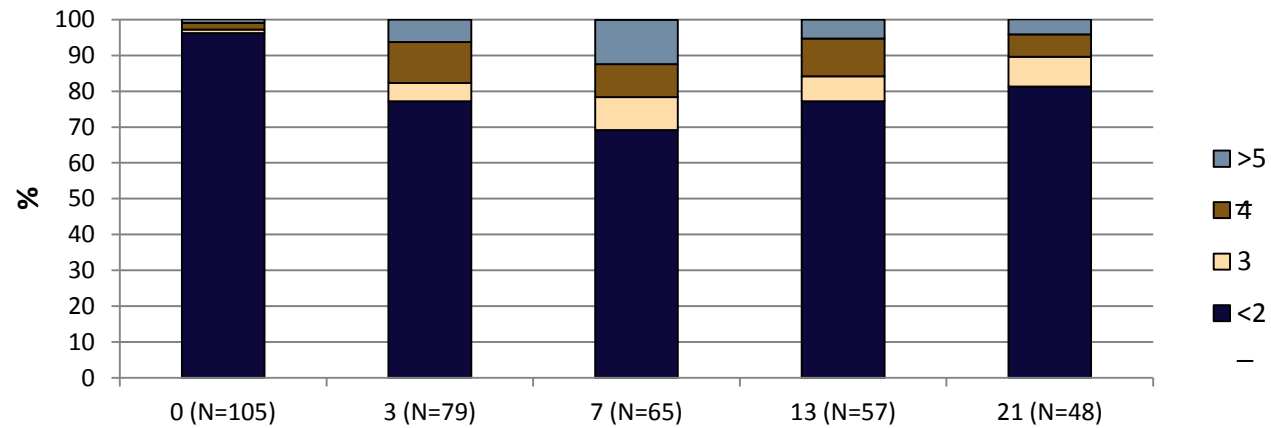


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2b: Months since TB diagnosis



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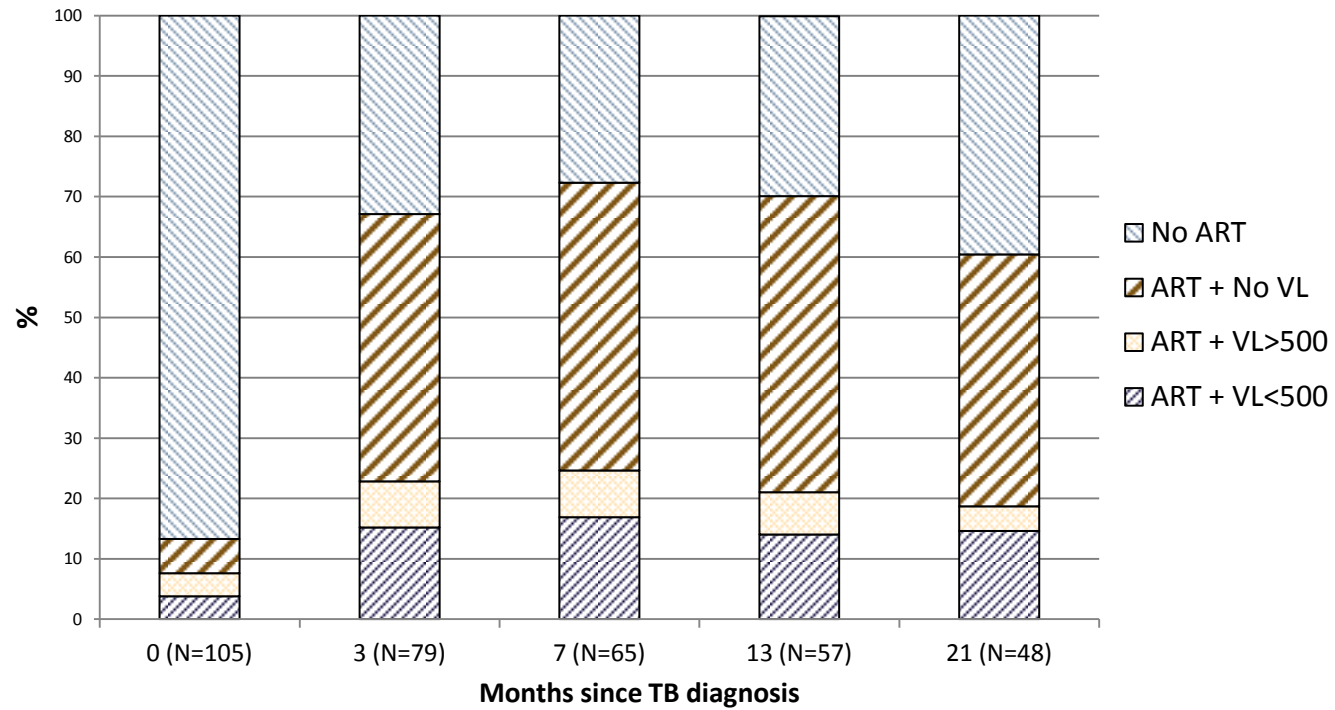
2c: Months since TB diagnosis

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526 Figure 3. Antiretroviral (ART) status over time for MDR-TB patients (N=105)*

Figure 3: Antiretroviral (ART) status over time for MDR-TB patients (N=105)*



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*ART and viral load (VL) was calculated +/- 1 month of the various time-points.

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531 Table 1. Baseline characteristics of the included individuals (N=485)

		Total N (%)	MDR-TB* N (%)	All other groups N (%)	p ⁷
Total		485	105	380	
Gender	<i>Male</i>	374 (77)	84 (80)	290 (76)	0.43
Ethnicity¹	<i>White</i>	442 (94)	98 (96)	344 (94)	0.42
Previous TB²	<i>Yes</i>	64 (13)	24 (23)	40 (11)	<0.01
TB risk factors	<i>Prison</i>	91 (19)	22 (21)	69 (18)	0.52
	<i>Alcohol</i>	128 (26)	30 (29)	98 (26)	0.57
	<i>Family</i>	41 (8)	12 (11)	29 (8)	0.22
	<i>Travel</i>	0	0	0	N/A
Injection drug use (ever)	<i>Yes</i>	327 (67)	80 (76)	247 (65)	0.03
OST (ever)	<i>Yes</i>	6 (1)	0 (0)	6 (2)	0.32
Hepatitis C³	<i>Yes</i>	254 (52)	59 (56)	195 (51)	0.03
TB type	<i>Pulmonary</i>	176 (36)	45 (43)	131 (34)	0.27
	<i>Extra pulmonary</i>	24 (5)	4 (4)	20 (5)	
	<i>Disseminated</i>	285 (59)	56 (53)	229 (60)	
HIV+ >3 months before TB diagnosis	<i>Yes</i>	354 (73)	81 (77)	273 (72)	0.28
ART⁷	<i>Yes</i>	82 (17)	14 (13)	68 (18)	0.27
		Median (IQR)			
Age	<i>Year</i>	35 (31-40)	35 (31-40)	35 (31-40)	0.75
Weight⁴	<i>Kg</i>	60 (53-68)	63 (55-68)	59 (53-68)	0.29
CD4 cell count⁵	<i>(cells/mm³)</i>	91 (31-230)	100 (32-267)	89 (31-220)	0.59
HIV-RNA⁶	<i>Log₁₀ copies/ml</i>	5.25 (4.40-5.75)	5.42 (4.46-5.91)	5.22 (4.35-5.70)	0.13

532 1. 9 individuals had missing data on previous TB.

533 2. 17 individuals had missing data on ethnicity.

534 3. 148 individuals had missing data on hepatitis C.

535 4. 300 individuals had missing weight at baseline.

536 5. 87 individuals had missing baseline CD4.

537 6. 211 individuals had missing baseline HIV-RNA.

538 7. P-values compare the characteristics between individuals with MDR-TB and all other individuals included in the study. The chi-squared test, fisher's exact test, or Mann-Whitney u
539 test was used as appropriate.

540 OST = Opioid substitution therapy.

541 ART = antiretroviral therapy.

542 Table 2. Results from drug susceptibility test performed at any time point in follow-up among all patients with
 543 MDR-TB (N=105)

<u>Drug</u>	<u>N (%) with data</u>	<u>N (% of those tested) with resistance</u>
Group 1		
Pyrazinamide	54 (51)	30 (56)
Ethambutol	100 (95)	72 (72)
Streptomycin	75 (71)	72 (96)
Group 2		
Fluoroquinolones	79 (75)	22 (28)
Group 3		
Second-line injectables	82 (78)	35 (43)
Group 4		
Ethionamide/Prothionamide	72 (69)	23 (32)
Cycloserine/Terizidone	51 (49)	8 (16)
Para-Aminosalicylic Acid (PAS)	61 (58)	10 (16)

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547 **Table 3. DST performance and TB drug use among patients with MDR-TB (N=105)**

3a: N (%) of patients who had DST performed per drug up to the indicated time point among those under follow-up at given time point

	N	R	H	Z	E	FQ	2L-inj	PT/ET	CS/TZ	PAS	BDQ	DLM	LNZ
0	105	49 (47)	49 (47)	27 (26)	46 (44)	35 (33)	37 (35)	32 (30)	16 (15)	24 (23)	0	0	0
1 month	88	88 (100)	88 (100)	47 (53)	82 (93)	63 (72)	66 (75)	57 (65)	40 (45)	47 (53)	0	0	0
2 months	79	79 (100)	79 (100)	44 (56)	74 (94)	58 (73)	64 (81)	54 (68)	40 (51)	45 (57)	0	0	0
3 months	72	72 (100)	72 (100)	40 (56)	68 (94)	54 (75)	61 (85)	51 (71)	37 (51)	41 (57)	0	0	0
7 months	56	56 (100)	56 (100)	42 (57)	53 (95)	43 (77)	47 (84)	40 (71)	30 (54)	33 (59)	0	0	0
13 months	44	44 (100)	44 (100)	25 (57)	42 (95)	35 (80)	37 (84)	30 (70)	22 (50)	26 (59)	0	0	0
21 months	31	31 (100)	31 (100)	16 (52)	29 (94)	23 (74)	25 (81)	23 (74)	16 (52)	22 (71)	0	0	0

3b: N (%) of patients under follow-up who received selected anti-TB medications at the indicated time point

	N	R	H	Z	E	FQ	2L-inj	PT/ET	CS/TZ	PAS	BDQ	DLM	LNZ
0	105	86 (82)	89 (85)	90 (86)	84 (80)	16 (15)	23 (22)	14 (13)	10 (10)	4 (4)	0	0	0
1 month	88	57 (65)	59 (67)	76 (86)	68 (77)	32 (36)	38 (43)	31 (35)	23 (26)	17 (19)	0	0	0
2 months	79	39 (49)	37 (47)	66 (84)	53 (67)	43 (54)	46 (58)	40 (51)	30 (38)	29 (34)	0	0	0
3 months	72	23 (32)	23 (32)	55 (76)	37 (51)	51 (71)	48 (67)	49 (68)	39 (54)	33 (46)	0	0	0
7 months	56	6 (11)	5 (9)	42 (75)	21 (38)	50 (89)	39 (70)	47 (84)	37 (66)	31 (55)	0	0	1 (2)
13 months	44	5 (11)	4 (9)	34 (77)	14 (32)	39 (89)	15 (34)	33 (75)	27 (61)	20 (45)	0	0	0
21 months	31	2 (6)	1 (3)	20 (65)	7 (23)	25 (81)	8 (26)	19 (61)	22 (71)	15 (48)	0	0	0

3c: N (%) of patients under follow-up who had ever received selected TB medications at the indicated time point

	N	R	H	Z	E	FQ	2L-inj	PT/ET	CS/TZ	PAS	BDQ	DLM	LNZ
0	105	86 (82)	89 (85)	90 (86)	84 (80)	16 (15)	23 (22)	14 (13)	10 (10)	4 (4)	0	0	0
1 month	88	76 (86)	75 (85)	81 (92)	76 (86)	33 (38)	40 (45)	32 (36)	23 (26)	17 (19)	0	0	0
2 months	79	68 (86)	66 (84)	72 (91)	68 (86)	45 (60)	49 (62)	41 (52)	31 (39)	29 (37)	0	0	0
3 months	72	62 (86)	61 (85)	66 (92)	61 (85)	54 (75)	55 (76)	51 (71)	40 (56)	36 (50)	0	0	0
7 months	56	47 (84)	47 (84)	53 (95)	51 (91)	51 (91)	49 (88)	48 (86)	40 (71)	33 (59)	0	0	1 (2)
13 months	44	39 (89)	39 (89)	42 (95)	42 (95)	40 (91)	38 (86)	37 (84)	31 (70)	24 (55)	0	0	0
21 months	31	27 (87)	27 (87)	29 (94)	30 (97)	29 (94)	28 (90)	26 (84)	23 (74)	20 (65)	0	0	0

548 *DST = Drug Susceptibility Test*549 *R = Rifampicin*

- 550 *H = Isoniazid*
- 551 *Z = Pyrazinamide*
- 552 *E = Ethambutol*
- 553 *FQ = Fluoroquinolone*
- 554 *2L-inj = Second-line injectables*
- 555 *PT/ET = Prothionamide/Ethionamide*
- 556 *CS/TZ = Cycloserine/Terizidone*
- 557 *PAS = Para-aminosalicylic acid*
- 558 *BDQ = Bedaquiline*
- 559 *DLM = Delamanide*
- 560 *LNZ = Linezolid*
- 561

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563 **Definitions of tuberculosis resistance**

	Definition
Multidrug-resistant tuberculosis (MDR-TB)	Tuberculosis resistant to rifampicin and isoniazid
Pre-extensively drug-resistant tuberculosis (pre-XDR-TB)	MDR-TB plus additional resistance against a fluoroquinolone <i>or</i> a second-line injectable
Extensively drug-resistant tuberculosis (XDR-TB)	MDR-TB plus additional resistance against a fluoroquinolone and a second-line injectable

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