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Analysis of loss to follow up in 5,970 multidrug-resistant pulmonary tuberculosis patients

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1 Analysis of loss to follow up in 5,970 multidrug-resistant pulmonary 2 tuberculosis patients

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28 Take home message: Loss to follow up risk is constant throughout MDRTB
29 treatment globally. ↑risk = men, HIV+, 26-50yrs & standard regime

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3 **Abstract**

4 31 Loss-to-follow-up (LFU) of two or more consecutive months contributes to the poor
5 32 levels of treatment success in multidrug-resistant tuberculosis (MDR-TB), reported
6 33 by TB programmes. We explore the timing when LFU occurs by month of MDR-TB
7 34 treatment and identify patient-level risk factors associated with LFU.

8
9 35 We analysed a dataset of individual MDR-TB patient data (5,970 patients from 23
10 36 countries). We used Kaplan-Meier survival curves to plot time to LFU and a Cox
11 37 proportional hazards model to explore the association of potential risk factors with
12 38 LFU.

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14 39 One-fifth (n=1,282) of patients were recorded as LFU. Median time to LFU was 16
15 40 months (IQR=6-18). A sharp increase in rate of LFU at month 18 of treatment was
16 41 identified as artefactual from one large cohort. Risk factors associated with LFU were
17 42 age (26-35yrs: Hazard Ratio (HR) 1.20; 95% CI 1.04, 1.39 and 36-50yrs: HR 1.28;
18 43 95% CI 1.09, 1.49 compared with age 0-25yrs), being male (HR 1.13; 95% CI 1.04,
19 44 1.23), HIV positive (HR 1.36; 95% CI 1.02, 1.80) and treatment with a standardised
20 45 regimen (individualised treatment had HR 0.55; 95% CI 0.32, 0.93 compared with
21 46 standardised regimen).

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24 47 Both patient and regimen-related factors were associated with LFU which may guide
25 48 interventions to improve treatment adherence.
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49 Introduction

50 Multidrug-resistant tuberculosis (MDR-TB) is a growing challenge to TB treatment
51 programmes globally. Treatment completion rates remain low at 50% with 16% lost
52 to follow up (LFU - previously termed “treatment default”)[1-4] – defined as MDR-TB
53 patients “whose treatment was interrupted for two consecutive months or more”. [5]
54 Patients who do not complete pulmonary MDR-TB treatment pose a public health
55 risk of ongoing transmission of resistant, infectious disease as well as a high
56 likelihood of death for the patient.

57 Current evidence from MDR-TB treatment cohorts, identifies that LFU is associated
58 with being male,[6] substance misuse,[6-11] resistance to a high number of anti-TB
59 drugs, [6, 12, 13] the absence of early culture conversion,[6, 11, 13, 14] poor patient-
60 provider relationships,[8, 10] greater disease severity,[7] HIV co-infection[15] and the
61 occurrence of drug side effects.[10, 13]

62 Several studies suggest that the majority of LFU takes place in the early stages of
63 MDR-TB treatment when patients may still be infectious. The percentage of total
64 LFU that occurred in the intensive phase (first 6-8 months) of MDR-TB treatment
65 was 77.8% in the Philippines (total sample size(N)=273, total LFU=91)),[10] 71.1% in
66 Armenia (N=381, LFU=97),[13] 72.7% in Pakistan (N=186, LFU=33)[16] and 40.8%
67 in Georgia (N=1,240, LFU=458).[11] The total LFU occurring by six months was
68 86.9% in India (N=796, LFU=153).[14] In Uzbekistan, median time to LFU was 6
69 months (N=710, LFU=142).[12]

70 Several strategies have been attempted by TB programmes to reduce LFU[17],
71 including providing directly observed treatment (DOT) throughout the course of
72 treatment,[18] providing patient education and managing smaller numbers of
73 patients.

74 To optimise the management of MDR-TB patients, national TB treatment
75 programmes would benefit from knowing who are at risk of LFU and when it is likely
76 to occur. Interventions targeted at individuals with these risk factors and these time
77 points could reduce rates of LFU and ultimately assist in controlling the epidemic.
78 Analysis to specify the time of LFU more accurately would optimise the timing of
79 such interventions. Here we are able to use the largest ever multi-country, individual

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3 80 MDR-TB dataset, to identify the timing of LFU in the treatment of pulmonary MDR-
4 81 TB and to identify patient-level risk factors associated with LFU. [1-3]
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8 83 **Methods**

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10 84 The dataset of the *Collaborative Group for Meta-Analysis of Individual Patient Data*
11 85 *in MDR-TB* was used for this analysis. This data set includes individual-level
12 86 treatment data from 9,153 pulmonary MDR-TB patients from TB clinics or
13 87 programmes from 23 countries, reported in 32 previously published observational
14 88 studies. Patients had to have received at least one month's treatment in order to be
15 89 included. The patient characteristics and definitions of the variables within the
16 90 dataset have been described elsewhere.[1] Permission was not granted for this
17 91 analysis, for one cohort of patients included in the original data set.
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24 92 For our analysis, patients were included if there was authorization of the lead
25 93 investigator for each cohort and patients were alive at the point of LFU. Patients
26 94 were defined as LFU if their outcome was recorded as 'defaulted', 'transferred out
27 95 (with unknown outcome)' or 'unknown' in the dataset, based on the outcome
28 96 definitions available at the time data were collected.[19] Time of LFU for each patient
29 97 was identified by their recorded duration of treatment in months. The treatment
30 98 cohorts included in this analysis used a variety of drug regimens and treatment
31 99 lengths, most were 20-24 months. Those with a duration of treatment longer than 24
32 100 months (n=800) were truncated at 24 months. Records were excluded if lead
33 101 investigators did not give consent for their data to be included or if there was no
34 102 record of duration of treatment. We also excluded patient records whose outcome
35 103 was death. Although it is possible that some of these patients may have chosen to
36 104 stop MDR-TB treatment before death, the dataset did not include this detail so we
37 105 decided to exclude all patients who died.
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47 106 We identified the independent variables from the dataset to include in the analysis
48 107 from previous studies where significant associations with LFU had been identified
49 108 (see introduction). Variables included in the analysis were: age, sex, HIV co-infection
50 109 status, extensive TB disease (defined as Acid Fast Bacillus (AFB) smear positive, or
51 110 cavities on chest radiography if no information about AFB-smear was available), type
52 111 of regimen (standardised v individualised), previous TB therapy (defined as
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3 112 treatment with first-line, or second-line TB drugs for 1 month or more), recorded drug
4 113 resistance to pyrazinamide, ethambutol and streptomycin, recorded serious adverse
5 114 events and AFB-smear status. We were also interested in variations by national
6 115 income and so we distinguished study cohorts from high-income and middle-income
7 116 countries within the analysis (according to World Bank classifications).[20] There
8 117 were no cohorts from low-income countries.

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13 118 The proportion of all patients who were LFU are reported. As the data were
14 119 negatively skewed we used quantile regression analysis to compare median time to
15 120 LFU for subgroups (per independent variable). We then employed Kaplan-Meier
16 121 methods to plot survival curves and estimate the unadjusted time to LFU across the
17 122 treatment period. To explore this distribution further, we undertook sensitivity
18 123 analysis by plotting timing of LFU by each cohort within the data set, comparing
19 124 middle-income and high-income countries and by removing one large cohort. Lastly,
20 125 a Cox proportional hazards model was created to assess the effects of potential risk
21 126 factors on LFU, using adjusted hazard ratios with 95% confidence intervals and the
22 127 associated (two-sided) p-values. Patient-level data were considered to be clustered
23 128 within study cohorts and so the model used a random-effects, multi-level analysis to
24 129 account for this. SAS software (SAS Institute Inc. version 9.4) was used to undertake
25 130 the statistical analysis. The original ethics approval for the analysis of anonymised
26 131 data for the *Collaborative Group for Meta-Analysis of Individual Patient Data*[1]
27 132 covered also this secondary analysis and therefore no separate ethics review was
28 133 needed.

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45 137 **Results**

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48 138 Data originated from 23 countries: ten studies were from Asia (four of which were
49 139 from South Korea), six from North America, five from Europe, four from Central and
50 140 South America, four from former Soviet states, two from South Africa and one from
51 141 Iran. The exclusions from the full dataset (n=9,153) were one treatment cohort
52 142 without permission to include (n=607), patients with no follow-up time recorded
53 143 (n=1,333) or with an outcome of death (n=1,243). Our dataset therefore included

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3 144 5,970 patients, of which 1,282 (21.5%) were recorded as LFU. This LFU rate is
4 145 comparable with that reported in the full data set (23%).[1] The characteristics of the
5 146 patients in our dataset are described in table 1.
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11 149 Table 1 – Characteristics of MDR-TB patients and the median time to loss-to-follow-
12 150 up

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14 151 Insert Table 1 here

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16 152 MDR-TB: multidrug-resistant tuberculosis; LFU: lost to follow-up; IQR: inter-quartile range; HIV: human immunodeficiency virus;
17 153 AFB: acid-fast bacillus test

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20 155 After six months of treatment, 26% (n=336) of those who were recorded as LFU had
21 156 been lost (Fig. 1). At the end of the intensive stage of treatment at 8 months 35%
22 157 (n=448) had been lost. By the 12 month stage 44% (n=567) had been lost and by 18
23 158 months it was 88% (n=1124).
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27 159 Figure 1 – Cumulative percentage of LFU* for all MDR-TB patients and for LFU
28 160 patients by month of treatment

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30 161 Insert Fig.1 here

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32 162 Note: The two sets of data points show the timing of LFU among all MDR-TB patients (n=5,970) and for those that were
33 163 recorded as LFU (n=1,243). *LFU: loss to follow up

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36 165 For all patients recorded as LFU, the median time to LFU was 16 months (inter-
37 166 quartile range (IQR) 6-18 months). The median time to LFU was much lower in some
38 167 sub-groups (Table 1): for example, those over 50 years old (median time to LFU 9
39 168 months (IQR 5-18), high-income country cohorts (8 months; IQR 5-16), negative HIV
40 169 status (11 months; IQR 5-18), individualised treatment regime (7 months; IQR 3-14),
41 170 no previous TB treatment (10 months, IQR 6-18) and previous MDR-TB treatment
42 171 (12 months; IQR 5-18). Time to LFU also varied by the decade in which cohorts were
43 172 treated and the median time was much longer in patients starting treatment in the
44 173 latter decade.
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49 175 **Timing of LFU**
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3 176 For all patients recorded as LFU, the rate of LFU occurrence is steady in the first 17
4 177 months of treatment (Fig. 2). A substantial change in probability of being LFU then
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6 178 occurs around month 18 of treatment. We suspected this may have been artefactual
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8 179 and therefore conducted further analysis (see supplementary material and Fig. 3).
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10 180 From this we identified a large cohort from South Africa (n=1,789) which appeared to
11 181 contribute to this change in probability at 18 months. After removing this large cohort,
12 182 the plot of time to LFU in the reduced data set indicates it was indeed responsible
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14 183 (Fig. 4).
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18 185 Figure 2 - Time to Loss-to-Follow-Up after starting MDR-TB treatment for all patients,
19 186 using Kaplan-Meier analysis

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21 187 Insert Fig. 2 here

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24 189 Figure 3 – Time to Loss-to-Follow-Up after starting MDR-TB treatment, for patients
25 190 by national income category, using Kaplan-Meier analysis

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30 193 Figure 4 - Time to Loss-to-Follow-Up after starting MDR-TB treatment for all patients
31 194 (minus a large South African cohort), using Kaplan-Meier analysis (n=4,181)

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34 195 Insert Fig. 4 here

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36 197 **Risk factors associated with loss-to-follow-up**

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38 198 After adjusting for all other variables in a Cox proportional hazards model, several
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40 199 risk factors were significantly associated with LFU (Table 2 and Figure 5). Those
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42 200 aged 26-35 and 36-50 years old had 20% and 28% higher incidence of LFU
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44 201 respectively (HR 1.20; 95% CI 1.04, 1.39 and HR 1.28; 95% CI 1.09, 1.49
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46 202 respectively) compared to those aged 0-25 years old. Males had a 13% higher
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48 203 incidence of LFU (HR 1.13; 95% CI 1.04, 1.23) compared to females. Those with
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50 204 HIV had a 36% higher incidence of LFU (HR 1.36; 95% CI 1.02, 1.80) compared to
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52 205 HIV negative patients. Those receiving an individualised treatment regimen had 45%
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54 206 lower incidence of LFU (HR 0.55; 95% CI 0.32, 0.93) compared with a standardised
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56 207 regimen.
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7 210 Table 2 – Risk factors associated with loss-to-follow-up among all MDR-TB patients
8 211 (n=5,970)

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10 212 Insert Table 2 here

11 213 MDR-TB: multidrug-resistant tuberculosis; CI: confidence interval; HIV: human immunodeficiency virus; AFB: acid-fast bacillus
12 214 test; HIC: high-income country; MIC: middle-income country

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16 216 Figure 5 – Adjusted hazard ratios of risk factors associated with loss-to-follow-up
17 217 among all MDR-TB patients (n=5,970)

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25 222 **Discussion**

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27 223 Incomplete treatment of MDR-TB is an important driver of continued transmission
28 224 and avoidable TB morbidity and mortality worldwide. Using the largest dataset of
29 225 individual MDR-TB patients currently available, our study is the most comprehensive
30 226 assessment to date of the timing and risk factors for LFU. The overall frequency of
31 227 21.5% is similar to that reported by WHO from global TB monitoring[4]. The median
32 228 time to LFU was 16 months (IQR 6-18 months). Sub-groups with a higher risk of LFU
33 229 were 26-50 year olds, males, those with HIV+ status and those receiving a
34 230 standardised treatment regimen.

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36 231 The timing of LFU for patients in our study is predominantly in the continuation phase
37 232 of treatment (months 8–24) with a large change in LFU at 18 months. Further
38 233 analysis identified that a large cohort from South Africa (n=1,789) was mainly
39 234 responsible for this change, which is likely to be artefactual in nature. The reporting
40 235 practices of the TB programme at the time caused many patients to be assigned
41 236 LFU at 18 months, even though they may have met the criteria for LFU well before
42 237 this date (personal communication with study authors)..

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44 238 The timing of LFU in our study differs markedly from studies reporting more recent
45 239 treatment cohorts, where the majority of LFU tended to be in the initial intensive
46 240 phase of treatment (see Introduction). The treatment of all patients in our study
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3 241 predates 2008, compared with these LFU studies of MDR-TB patients which tend to
4 242 be more recent (published 2006 – 2015)[7-16]. It is possible that the distribution of
5 243 timing of LFU has changed over time. Further research on aggregated data from
6 244 more recent cohorts would help to identify if a different pattern exists for timing of
7 245 LFU compared with our older cohorts in this study.

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11 246 Some of the patient-related risk factors associated with LFU which we identify are
12 247 similar to those found in previous studies. Being male is a common risk factor for
13 248 poor adherence in many health conditions[22] and has been identified in MDR-TB
14 249 patients previously[6]. As the majority of MDR-TB patients receiving treatment
15 250 globally are male[4] this is an important driver of rates of LFU. This association with
16 251 sex is complex[23]. It is difficult to separate individual behaviours and responses to
17 252 treatment by males compared to females, from structural factors such as the social
18 253 construct of gender identities and the delivery of health care services[24]. For
19 254 example, the opening times of TB treatment centres can be incompatible with regular
20 255 access from workers in labour markets structured differentially by gender[25]. Being
21 256 male may also be associated with attitudes and behaviours shaped by cultural
22 257 factors which predispose to interruption (e.g. itinerancy, alcohol use)[24]. Further
23 258 qualitative research with MDR-TB patients (particularly men who do not complete
24 259 treatment, although they can be difficult to access) could shed light on this complex
25 260 area of treatment adherence.

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31 261 Having co-infection of HIV is a risk factor for LFU in our analysis with MDR-TB
32 262 patients. Historically, poor access to anti-retroviral treatment and the lack of co-
33 263 ordination between HIV and TB treatment programmes have been highlighted as
34 264 factors which lead to worse outcomes for those co-infected[26]. In addition, these
35 265 patients might develop some other infectious or non-infectious complication, which
36 266 precludes continuation of their MDR-TB treatment. Our analysis underlines the
37 267 importance of identifying and addressing the particular challenges faced by patients
38 268 who are co-infected with HIV, to improve their chance of a successful treatment
39 269 outcome.

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51 270 Better treatment outcomes in children compared with adults have been reported in
52 271 co-infected HIV populations[27] and non-HIV populations[28]. An increased risk of
53 272 LFU in those aged 26-50 was identified in our analysis. This could be explained by
54 273 increased family support offered to younger and older family members with MDR-TB.

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3 274 Furthermore, the competing demands of employment and dependents for individuals
4 275 in the working age groups could also be influential in their greater risk of LFU[25].
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6 276 For several variables in our Cox proportional hazards model, the 'unknown' category
7 277 was significantly associated with being LFU (resistance to pyrazinamide, resistance
8 278 to streptomycin and serious adverse events). Weaker TB treatment programmes
9 279 may be the confounding factor, where poorer recording practices and limited efforts
10 280 at following up patients are both associated with weaker programmes.
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15 281 The study has several imitations. The large number (35%) of excluded patient
16 282 records, largely as a result of missing data of time to LFU or death, may have
17 283 introduced bias in our findings. The data quality was variable, although attempts
18 284 have been made to ensure the dataset is as complete as possible. There are likely to
19 285 be other artefactual influences on our data set beyond those we identified from the
20 286 large South African cohort, which are unaccounted for in our analysis. This dataset is
21 287 largely restricted to patients who had received one month or more of treatment. This
22 288 could have led to an artefactual prolongation of LFU as patients who would have
23 289 been early interrupters were selectively removed from the cohorts. We did not have
24 290 data available for some patient variables that we were interested in, such as co-
25 291 morbid substance misuse or treatment interruptions of less than two consecutive
26 292 months. Furthermore, there are likely to be other types of programme-related or
27 293 treatment-related risk factors that are associated with LFU which we did not analyse
28 294 and which could explain LFU more fully. All datasets pre-date 2008 so these findings
29 295 may not generalise to current programme management of MDR-TB. For instance the
30 296 use of a standardised 9-11 month regimen recommended by WHO since 2016 in
31 297 selected MDR-TB patients has the potential to reduce LFU due to a substantially
32 298 shorter duration of treatment than previous MDR-TB regimens.[29]
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36 299 Although some treatment cohorts in this dataset were from resource-constrained
37 300 contexts, none were from low-income countries. Our findings therefore may not
38 301 generalise to these settings. We have identified risk factors that are associated with
39 302 LFU - further work needs to be done to explore the mechanisms that drive stubbornly
40 303 high rates of LFU in all MDR-TB programmes including in low-income settings. For
41 304 instance, the presence of co-morbid depression may reduce adherence in MDR-TB
42 305 as it does in other health conditions. [22, 30]
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3 306 Our study identifies risk factors associated with being LFU which can guide policy
4 307 makers to target interventions at those most at risk, such as men of working age.
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6 308 Treatment programmes should consider how best to maintain engagement with
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8 309 these men in an approach that is person-centred and accessible at times and in
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10 310 locations that are convenient for them. In addition, patients with a co-morbid HIV
11 311 infection are more at risk of being LFU. The policy rhetoric that highlights the need
12 312 for co-ordination of treatment between both diseases must be implemented by TB
13 313 and HIV treatment programmes.
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16 314

18 315 **Conclusion**

20 316 The call within the global End TB strategy of patient-centred care should be pursued
21 317 to address the ongoing issue of LFU. Our findings suggest that MDR-TB treatment
22 318 programmes could offer targeted, enhanced support to prevent LFU in men, those of
23 319 working age and patients with HIV co-infection. The use of individualised treatment
24 320 regimens may also be beneficial to combat LFU. Further research examining the
25 321 timing of LFU in more recent treatment cohorts would add to our knowledge of this
26 322 important aspect of MDR-TB treatment.
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frontiers or boundaries.

338

339 References

- 340 1. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, Becerra MC, Benedetti A,
341 Burgos M, Centis R, Chan ED, Chiang CY, Cox H, D'Ambrosio L, DeRiemer K, Dung NH, Enarson D,
342 Falzon D, Flanagan K, Flood J, Garcia-Garcia ML, Gandhi N, Granich RM, Hollm-Delgado MG, Holtz TH,
343 Iseman MD, Jarlsberg LG, Keshavjee S, Kim HR, Koh WJ, Lancaster J, Lange C, de Lange WC, Leimane
344 V, Leung CC, Li J, Menzies D, Migliori GB, Mishustin SP, Mitnick CD, Narita M, O'Riordan P, Pai M,
345 Palmero D, Park SK, Pasvol G, Pena J, Perez-Guzman C, Quelapio MI, Ponce-de-Leon A, Riekstina V,
346 Robert J, Royce S, Schaaf HS, Seung KJ, Shah L, Shim TS, Shin SS, Shiraishi Y, Sifuentes-Osornio J,
347 Sotgiu G, Strand MJ, Tabarsi P, Tupasi TE, van Altena R, Van der Walt M, Van der Werf TS, Vargas
348 MH, Viiklepp P, Westenhouse J, Yew WW, Yim JJ, Collaborative Group for Meta-Analysis of Individual
349 Patient Data in M-T. Multidrug resistant pulmonary tuberculosis treatment regimens and patient
350 outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012; 9(8):
351 e1001300.
- 352 2. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox H, Holtz TH, Hollm-Delgado M-G, Keshavjee S,
353 DeRiemer K, Centis R. Resistance to fluoroquinolones and second-line injectable drugs: impact on
354 MDR-TB outcomes. *European Respiratory Journal* 2012: erj01347-02012.
- 355 3. Migliori GB, Sotgiu G, Gandhi NR, Falzon D, DeRiemer K, Centis R, Hollm-Delgado M-G,
356 Palmero D, Pérez-Guzmán C, Vargas MH. Drug resistance beyond XDR-TB: results from a large
357 individual patient data meta-analysis. *European Respiratory Journal* 2012: erj01363-02012.
- 358 4. World Health Organization. Global Tuberculosis Report 2017. Geneva: WHO; 2017.
- 359 5. World Health Organisation. Health in 2015: from MDGs, Millennium Development Goals to
360 SDGs, Sustainable Development Goals. WHO, Geneva, 2015.
- 361 6. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-
362 resistant tuberculosis: a systematic review and meta-analysis. *PloS one* 2009; 4(9): e6914.
- 363 7. Cox HS, Kalon S, Allamuratova S, Sizaire V, Tigay ZN, Rüsç-Gerdes S, Karimovich HA, Kebede
364 Y, Mills C. Multidrug-resistant tuberculosis treatment outcomes in Karakalpakstan, Uzbekistan:
365 treatment complexity and XDR-TB among treatment failures. *PloS one* 2007; 2(11): e1126.
- 366 8. Holtz T, Lancaster J, Laserson K, Wells C, Thorpe L, Weyer K. Risk factors associated with
367 default from multidrug-resistant tuberculosis treatment, South Africa, 1999–2001. *The International*
368 *Journal of Tuberculosis and Lung Disease* 2006; 10(6): 649-655.
- 369 9. Miller A, Gelmanova I, Keshavjee S, Atwood S, Yanova G, Mishustin S, Furin J, Shin S. Alcohol
370 use and the management of multidrug-resistant tuberculosis in Tomsk, Russian Federation. *The*
371 *International Journal of Tuberculosis and Lung Disease* 2012; 16(7): 891-896.
- 372 10. Tupasi TE, Garfin AM, Kurbatova EV, Mangan JM, Orillaza-Chi R, Naval LC, Balane GI, Basilio
373 R, Golubkov A, Joson ES, Lew WJ, Lofranco V, Mantala M, Pancho S, Sarol JN, Jr. Factors Associated
374 with Loss to Follow-up during Treatment for Multidrug-Resistant Tuberculosis, the Philippines, 2012-
375 2014. *Emerging infectious diseases* 2016; 22(3).
- 376 11. Kuchukhidze G, Kumar AM, de Colombani P, Khogali M, Nanava U, Blumberg HM, Kempker
377 RR. Risk factors associated with loss to follow-up among multidrug-resistant tuberculosis patients in
378 Georgia. *Public health action* 2014; 4(Suppl 2): S41-46.
- 379 12. Lalor MK, Greig J, Allamuratova S, Althomsons S, Tigay Z, Khaemraev A, Braker K, Telnov O,
380 du Cros P. Risk factors associated with default from multi- and extensively drug-resistant
381 tuberculosis treatment, Uzbekistan: a retrospective cohort analysis. *PloS one* 2013; 8(11): e78364.
- 382 13. Sanchez-Padilla E, Marquer C, Kalon S, Qayyum S, Hayrapetyan A, Varaine F, Bastard M,
383 Bonnet M. Reasons for defaulting from drug-resistant tuberculosis treatment in Armenia: a

- 1
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3 384 quantitative and qualitative study. *The International Journal of Tuberculosis and Lung Disease* 2014:
4 385 18(2): 160-167.
- 5 386 14. Shringarpure KS, Isaakidis P, Sagili KD, Baxi RK. Loss-To-Follow-Up on Multidrug Resistant
6 387 Tuberculosis Treatment in Gujarat, India: The WHEN and WHO of It. *PloS one* 2015: 10(7): e0132543.
- 7 388 15. Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, Weyer K, Lancaster J, Van der
8 389 Walt M. Outcomes of Multi-Drug Resistant Tuberculosis (MDR-TB) among a Cohort of South African
9 390 Patients with High HIV Prevalence. *PloS one* 2011: 6(7): e20436.
- 10 391 16. Javaid A, Shaheen Z, Shafqat M, Khan AH, Ahmad N. Risk factors for high death and loss-to-
11 392 follow-up rates among patients with multidrug-resistant tuberculosis at a programmatic
12 393 management unit. *American journal of infection control* 2017: 45(2): 190-193.
- 13 394 17. Toczek A, Cox H, du Cros P, Cooke G, Ford N. Strategies for reducing treatment default in
14 395 drug-resistant tuberculosis: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2013: 17(3):
15 396 299-307.
- 16 397 18. Yin J, Yuan J, Hu Y, Wei X. Association between Directly Observed Therapy and Treatment
17 398 Outcomes in Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis. *PloS one*
18 399 2016: 11(3): e0150511.
- 20 400 19. Laserson K, Thorpe L, Leimane V, Weyer K, Mitnick C, Riekstina V, Zarovska E, Rich M, Fraser
21 401 H, Alarcón E. Speaking the same language: treatment outcome definitions for multidrug-resistant
22 402 tuberculosis. *The International Journal of Tuberculosis and Lung Disease* 2005: 9(6): 640-645.
- 23 403 20. The World Bank. South Asia Region. 2016 [cited; Available from:
24 404 <http://www.worldbank.org/en/region/sar>
- 25 405 21. Institute of Medicine. The New Profile of Drug Resistant Tuberculosis in Russia: A Global and
26 406 Local Perspective: Summary of a Joint Workshop. The National Academies Press, Washington DC,,
27 407 2011.
- 28 408 22. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of
29 409 systematic reviews. *Front Pharmacol* 2013: 4: 91.
- 30 410 23. Diwan VK, Thorson A. Sex, gender, and tuberculosis. *The Lancet*: 353(9157): 1000-1001.
- 31 411 24. Munro SAL, S.A. Smith, H.J. Engel, M.E. Fretheim, A. Volmink, J. Patient Adherence to
32 412 Tuberculosis Treatment: A Systematic Review of Qualitative Research. *PLoS Med* 2007: 4(7): e238.
- 33 413 25. Deshmukh RD, Dhande DJ, Sachdeva KS, Sreenivas A, Kumar AMV, Satyanarayana S, Parmar
34 414 M, Moonan PK, Lo TQ. Patient and Provider Reported Reasons for Lost to Follow Up in MDRTB
35 415 Treatment: A Qualitative Study from a Drug Resistant TB Centre in India. *PloS one* 2015: 10(8):
36 416 e0135802.
- 37 417 26. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, Castro KG, Weyer K. HIV
38 418 infection and multidrug-resistant tuberculosis—the perfect storm. *The Journal of infectious diseases*
39 419 2007: 196(Supplement_1): S86-S107.
- 40 420 27. Isaakidis P, Casas E, Das M, Tseretopoulou X, Ntzani E, Ford N. Treatment outcomes for HIV
41 421 and MDR-TB co-infected adults and children: systematic review and meta-analysis. *The International*
42 422 *Journal of Tuberculosis and Lung Disease* 2015: 19(8): 969-978.
- 43 423 28. Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes for children with
44 424 multidrug-resistant tuberculosis: a systematic review and meta-analysis. *The Lancet Infectious*
45 425 *Diseases*: 12(6): 449-456.
- 46 426 29. Khan FA, Salim MH, du Cros P, Casas EC, Khamraev A, Sikhondze W, Benedetti A, Bastos M,
47 427 Lan Z, Jaramillo E. Effectiveness and safety of standardised shorter regimens for multidrug-resistant
48 428 tuberculosis: individual patient data and aggregate data meta-analyses. *European Respiratory*
49 429 *Journal* 2017: 50(1): 1700061.
- 50 430 30. Walker IF, Baral SC, Wei X, Huque R, Khan A, Walley J, Newell JN, Eley H. Multidrug-resistant
51 431 tuberculosis treatment programmes insufficiently consider comorbid mental disorders. *The*
52 432 *International Journal of Tuberculosis and Lung Disease* 2017: 21(6): 603-609.
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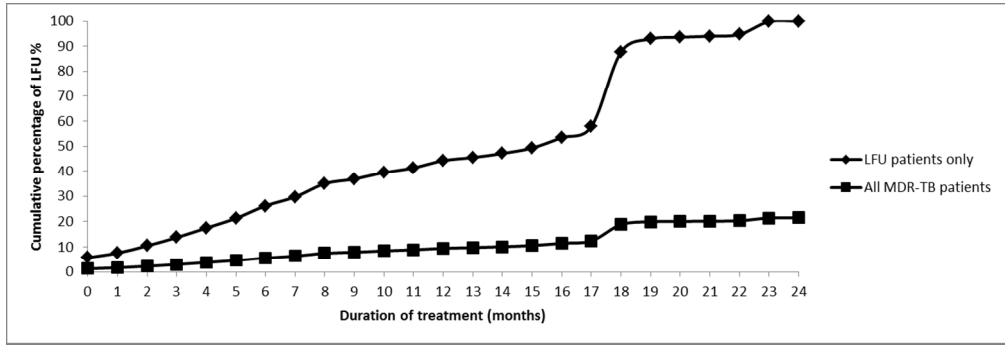
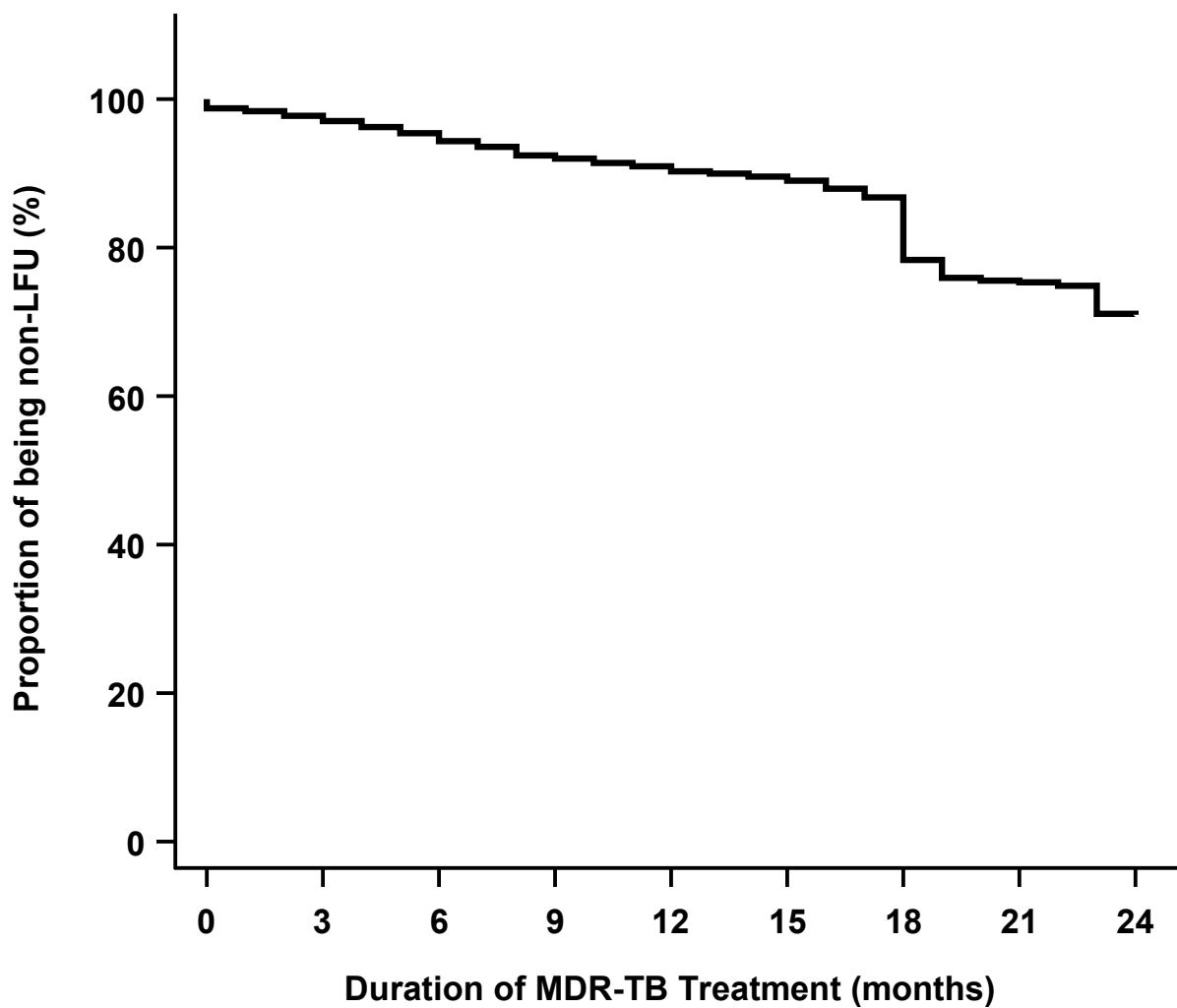
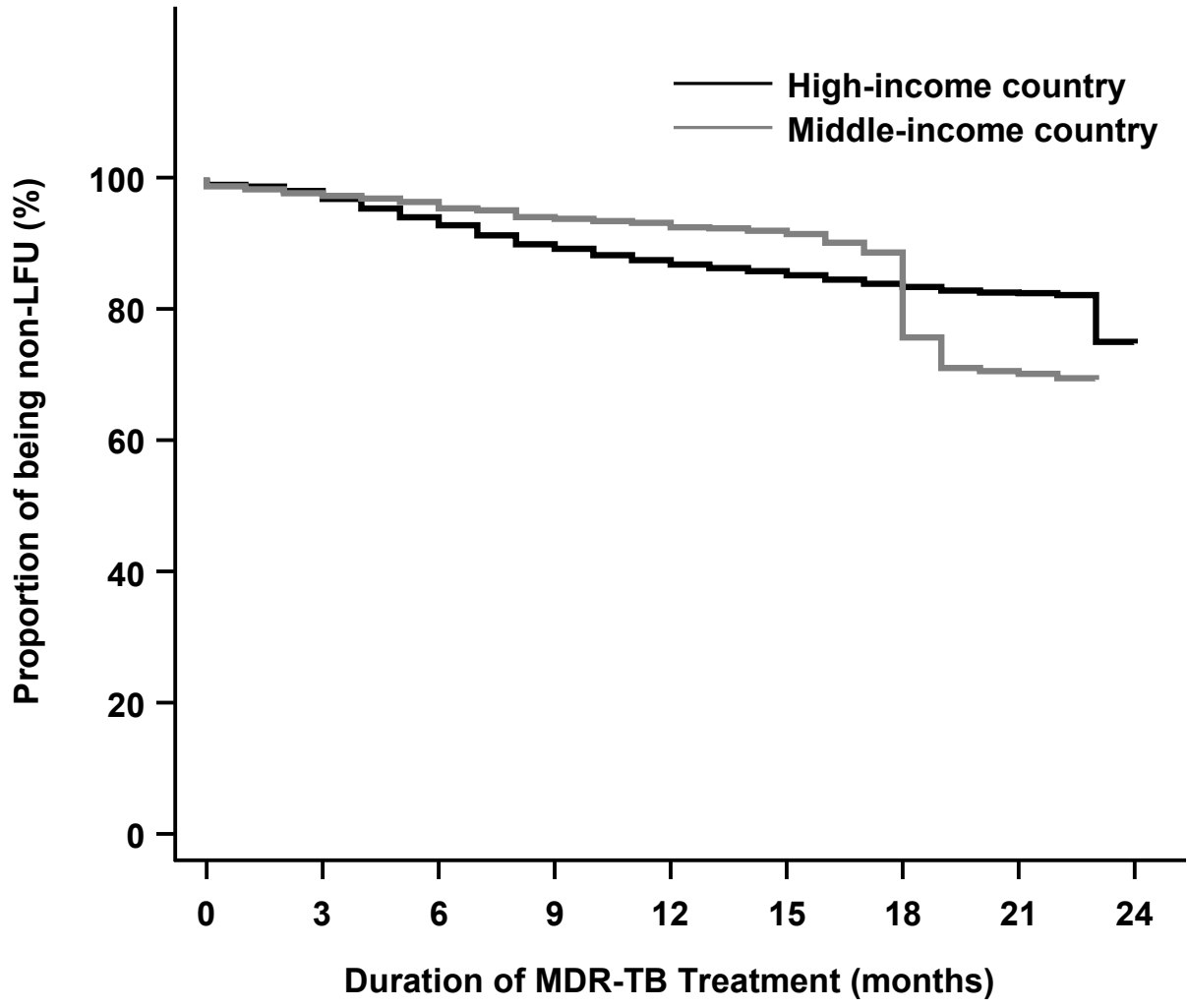


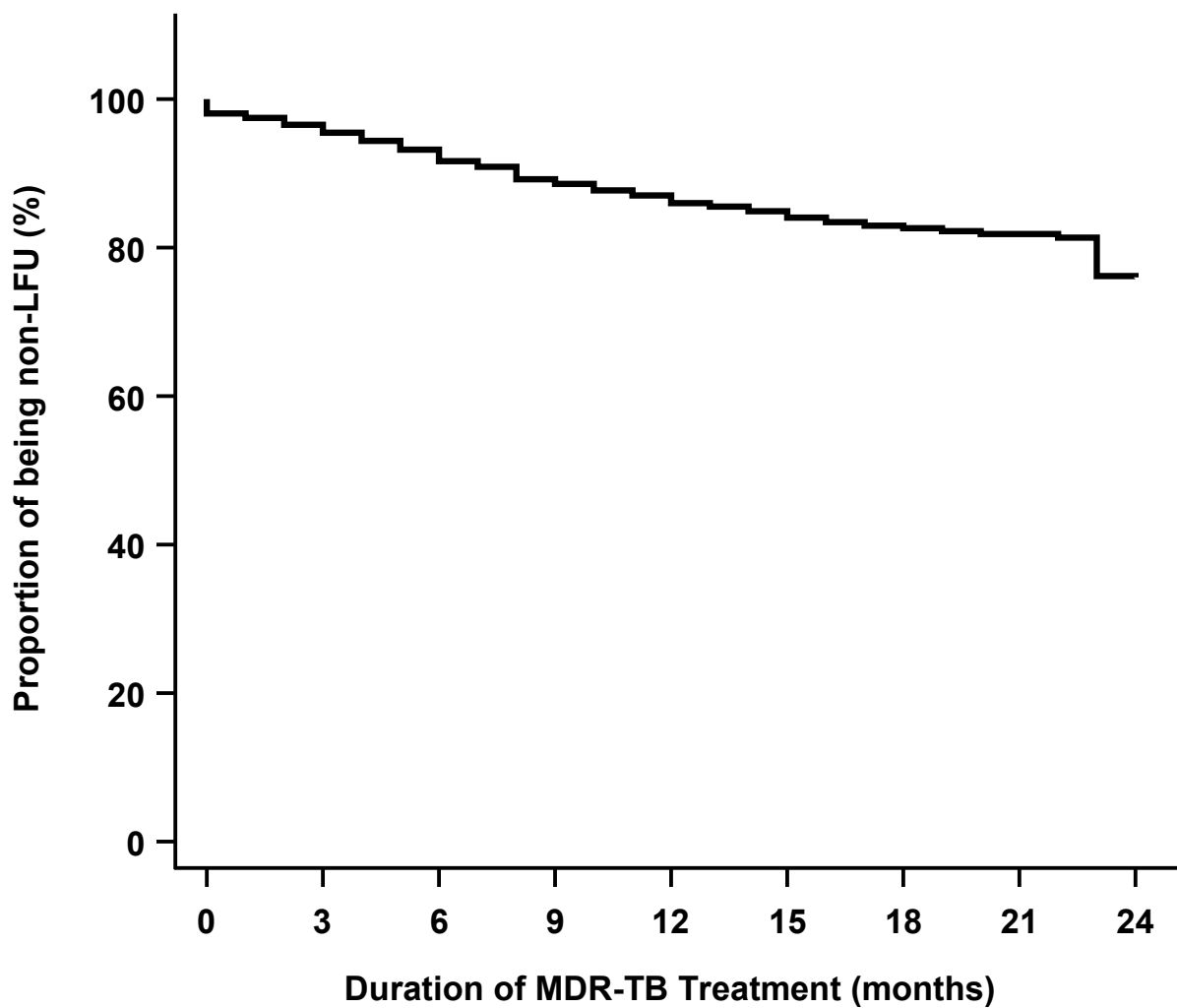
Figure 1 – Cumulative percentage of LFU* for all MDR-TB patients and for LFU patients by month of treatment



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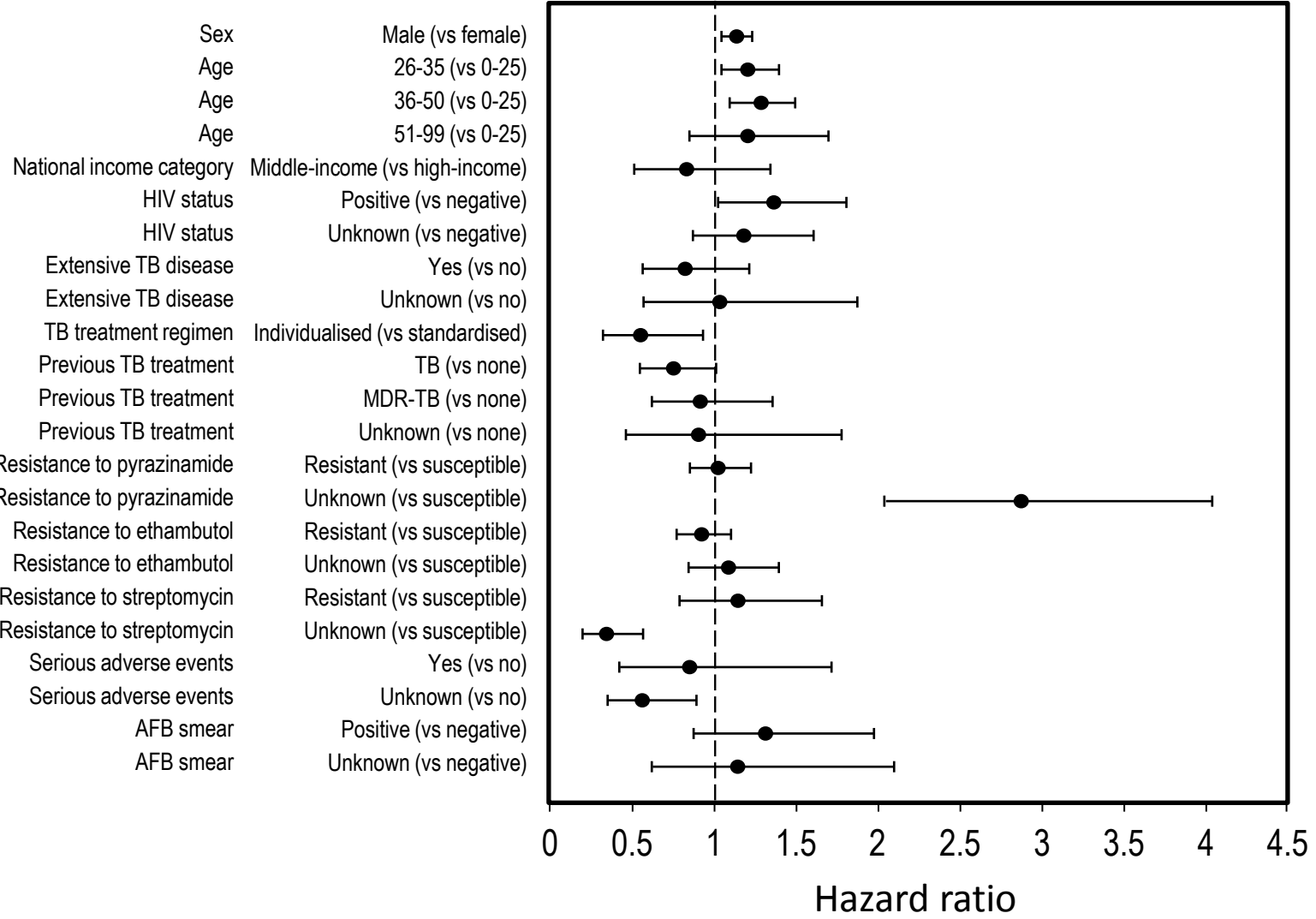


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Characteristic		Number of patients in group (% of total)	Those recorded as LFU (% of total LFU)	Percentage of each category that were LFU	Median time to LFU in months (IQR)
Total	All patients	5,970 (100%)	1,282 (100 %)	21.5%	16 (6-18)
Sex	Female	1,933 (32.4)	384 (30.0)	19.9%	17 (7-18)
	Male	4,037 (67.6)	898 (70.0)	22.2%	15 (6-18)
Age	0-25	1,041 (17.4)	184 (14.4)	17.7%	16 (6-18)
	26-35	1,755 (29.4)	385 (30.0)	21.9%	17 (8-18)
	36-50	2,107 (35.3)	500 (39.0)	23.7%	16 (7-18)
	51-99	1,067 (17.9)	213 (16.6)	20.0%	9 (5-18)
National income category	High-income country	2,266 (38.0)	438 (34.2)	19.3%	8 (5-16)
	Middle-income country	3,704 (62.0)	844 (65.8)	22.8%	18 (8-18)
HIV status	Negative	4,509 (75.5)	881 (68.7)	19.5%	11 (5-18)
	Positive	504 (8.4)	154 (12.0)	30.6%	18 (17-18)
	Unknown	957 (16.0)	247 (19.3)	25.8%	18 (15-18)
Extensive TB disease	No	1,587 (26.6)	317 (24.7)	20.0%	17 (6-18)
	Yes	4,273 (71.6)	939 (73.2)	22.0%	15 (6-18)
	Unknown	110 (1.8)	26 (2.0)	23.6%	18 (17-18)
Treatment regimen	Standardised	2,166 (36.3)	614 (47.9)	28.3%	18 (17-18)
	Individualised	3,804 (63.7)	668 (52.1)	17.6%	7 (3-14)
Previous TB treatment	None	1,132 (19.0)	240 (18.7)	21.2%	10 (6-18)
	First line TB drugs	3,644 (61.0)	806 (62.9)	22.1%	18 (8-18)
	Second line TB drugs	743 (12.4)	144 (11.2)	19.4%	12 (5-18)
	Unknown	451 (7.6)	92 (7.2)	20.4%	10 (4-17)
Resistance to Pyrazinamide	Susceptible	1,202 (20.1)	211 (16.5)	17.6%	10 (6-17)
	Resistant	1,664 (27.9)	289 (22.5)	17.4%	9 (5-16)
	Unknown	3,104 (52.0)	782 (61.0)	25.2%	18 (8-18)
Resistance to Ethambutol	Susceptible	1,604 (26.9)	322 (25.1)	20.1%	8 (4-15)
	Resistant	2,431 (40.7)	429 (33.5)	17.6%	8 (4-16)
	Unknown	1,935 (32.4)	531 (41.4)	27.4%	18 (17-18)
Resistance to Streptomycin	Susceptible	984 (16.5)	204 (15.9)	20.7%	7 (4-12)
	Resistant	2,896 (48.5)	536 (41.8)	18.5%	8 (4-13)
	Unknown	2,090 (35.0)	542 (42.3)	25.9%	18 (18-18)
Serious adverse events	No	2,254 (37.8)	606 (47.3)	26.9%	18 (10-18)
	Yes	1,335 (22.4)	280 (21.8)	21.0%	16 (8-18)
	Unknown	2,381 (39.9)	396 (30.9)	16.6%	8 (4-15)
AFB smear	Negative	1,278 (21.4)	272 (21.2)	21.3%	18 (8-18)
	Positive	3,583 (60.0)	830 (64.7)	23.2%	16 (6-18)
	Unknown	1,109 (18.6)	180 (14.0)	16.2%	10 (6-18)
Years of study for included cohorts	1980+ (4 cohorts)	100 (1.7)	9 (0.7)	9.0%	8 (4-13)
	1990-99 (10 cohorts)	910 (15.2)	234 (18.3)	25.7%	8 (4-12)
	1990-2008 (5 cohorts)	404 (6.8)	56 (4.4)	13.9%	6 (6-8)
	2000-2008 (12 cohorts)	4,556 (76.3)	983 (76.7)	21.6%	18 (8-18)

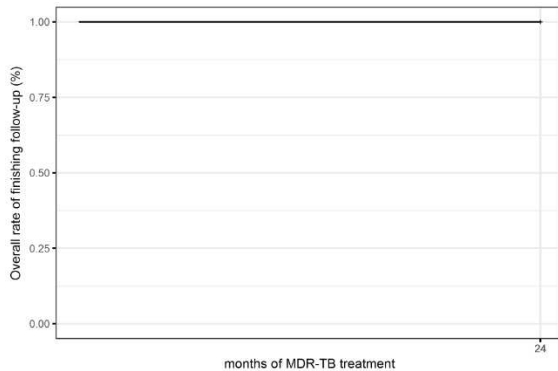
Variable		Unadjusted Hazard Ratio (95% CI)	p value	Adjusted Hazard Ratio (95% CI)	p value
Sex	Female	reference	-	reference	-
	Male	1.20 (1.03, 1.40)	0.02	1.13 (1.04, 1.23)	<0.01
Age	0-25	reference	-	reference	-
	26-35	1.35 (1.04, 1.74)	0.02	1.20 (1.04, 1.39)	0.01
	36-50	1.47 (1.00, 2.17)	0.05	1.28 (1.09, 1.49)	<0.01
	51-99	1.29 (0.75, 2.22)	0.37	1.20 (0.85, 1.69)	0.30
National income category	HIC	reference	-	reference	-
	MIC	1.33 (0.69, 2.57)	0.40	0.83 (0.51, 1.34)	0.45
HIV status	Negative	reference	-	reference	-
	Positive	1.64 (1.21, 2.22)	<0.01	1.36 (1.02, 1.80)	0.04
	Unknown	1.34 (1.06, 1.70)	0.01	1.18 (0.87, 1.60)	0.29
Extensive TB disease	No	reference	-	reference	-
	Yes	1.07 (0.81, 1.42)	0.65	0.82 (0.56, 1.21)	0.32
	Unknown	1.21 (0.53, 2.75)	0.65	1.03 (0.57, 1.87)	0.92
TB Treatment regimen	Standardised	reference	-	reference	-
	Individualised	0.55 (0.35, 0.85)	<0.01	0.55 (0.32, 0.93)	0.03
Previous TB treatment	None	reference	-	reference	-
	TB	1.08 (0.72, 1.64)	0.71	0.75 (0.55, 1.01)	0.06
	MDR-TB	0.75 (0.33, 1.74)	0.51	0.91 (0.62, 1.35)	0.64
	Unknown	1.24 (0.53, 2.91)	0.62	0.90 (0.46, 1.77)	0.75
Resistance to Pyrazinamide	Susceptible	reference	-	reference	-
	Resistant	0.95 (0.79, 1.14)	0.59	1.02 (0.85, 1.22)	0.87
	Unknown	1.93 (1.38, 2.70)	<0.01	2.86 (2.03, 4.02)	<0.01
Resistance to Ethambutol	Susceptible	reference	-	reference	-
	Resistant	0.77 (0.58, 1.04)	0.09	0.92 (0.77, 1.10)	0.36
	Unknown	1.21 (0.81, 1.82)	0.36	1.08 (0.84, 1.39)	0.56
Resistance to Streptomycin	Susceptible	reference	-	reference	-
	Resistant	1.05 (0.64, 1.71)	0.85	1.14 (0.79, 1.65)	0.49
	Unknown	1.38 (0.73, 2.61)	0.32	0.34 (0.20, 0.57)	<0.01
Serious Adverse Events	No	reference	-	reference	-
	Yes	0.77 (0.44, 1.34)	0.36	0.85 (0.42, 1.71)	0.64
	Unknown	0.48 (0.28, 0.83)	<0.01	0.56 (0.35, 0.89)	0.01
AFB Smear	Negative	reference	-	reference	-
	Positive	1.11 (0.82, 1.51)	0.51	1.31 (0.87, 1.97)	0.20
	Unknown	0.71 (0.40, 1.27)	0.24	1.14 (0.62, 2.09)	0.68

Analysis of loss to follow up in 5,970 multidrug-resistant pulmonary tuberculosis patients

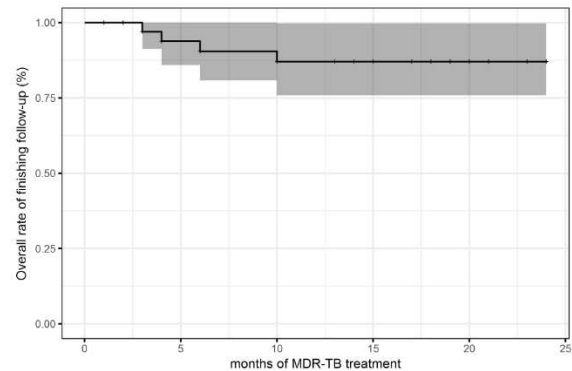
Ian F. Walker, Oumin Shi, Joseph Hicks, Helen Elsey, Xiaolin Wei, Dick Menzies, Dennis Falzon, Giovanni Battista Migliori, Carlos Pérez-Guzmán, Mario H. Vargas, Lourdes García-García, José Sifuentes Osornio, Alfredo Ponce-De-León, Martie van der Walt and James N. Newell

Supplementary Data – Kaplan-Meier plots by cohort (Combined sample size N=5,970) Shaded areas are confidence intervals.

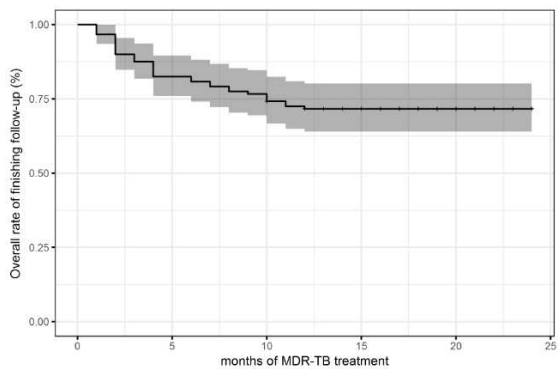
Cohort i – Canada (n=70)



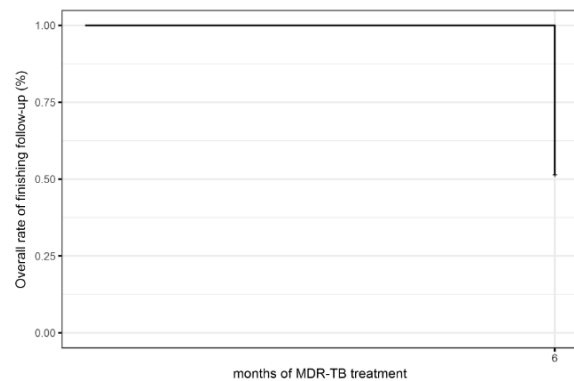
Cohort ii – USA (n=35)



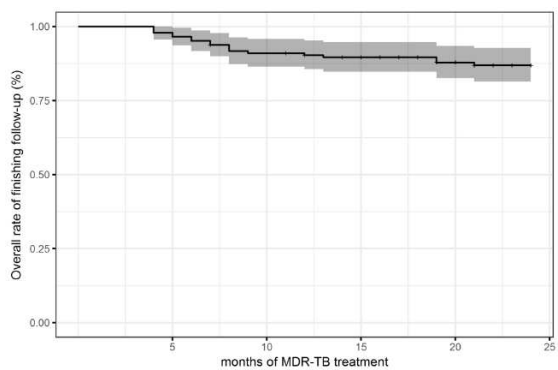
Cohort iii – Taiwan (n=120)



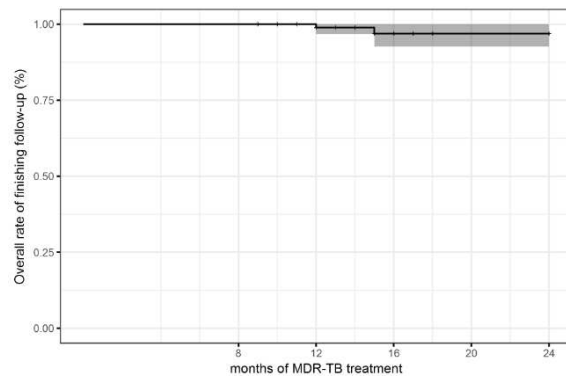
Cohort iv – Mexico (n=35)



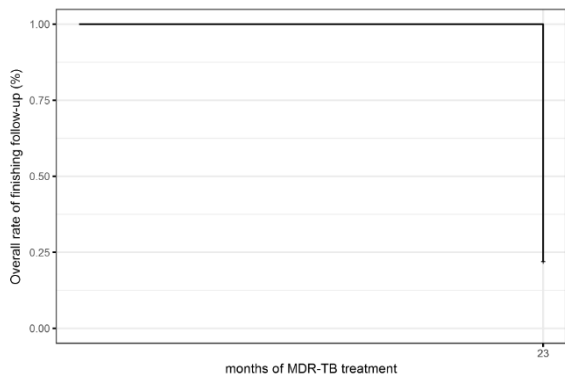
Cohort v - South Korea (n=145)



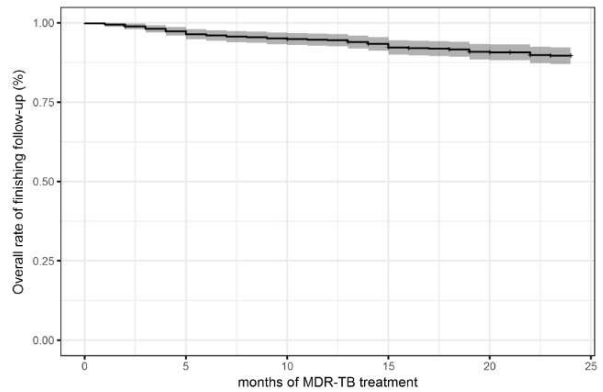
Cohort vi – Hong Kong (n=96)



Cohort vii - Italy (n=82)



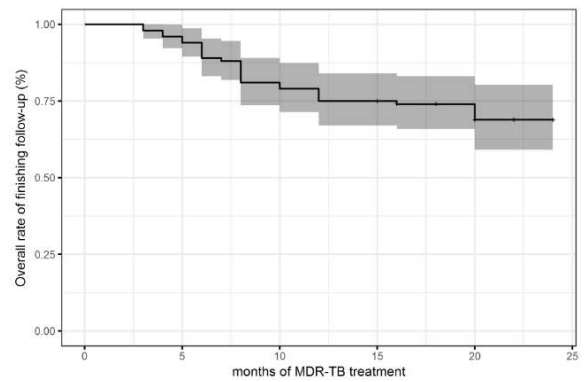
Cohort viii - Peru (n=529)



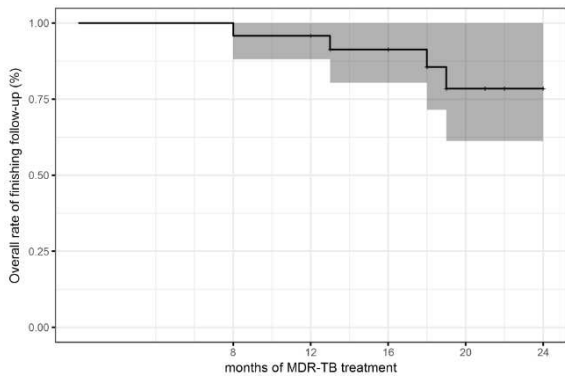
Cohort ix - Mexico (n=33)



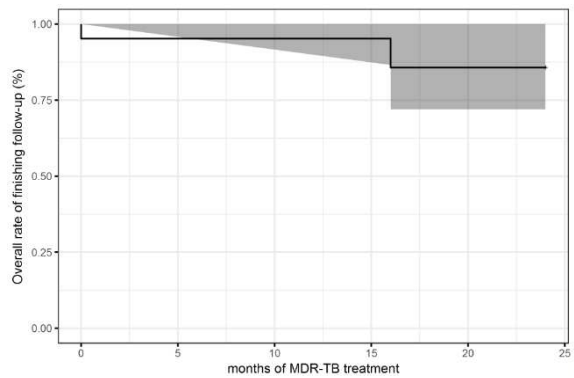
Cohort x - Argentina (n=100)



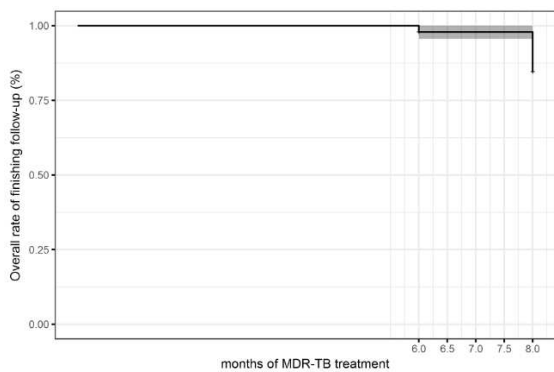
Cohort xi - UK (n=24)



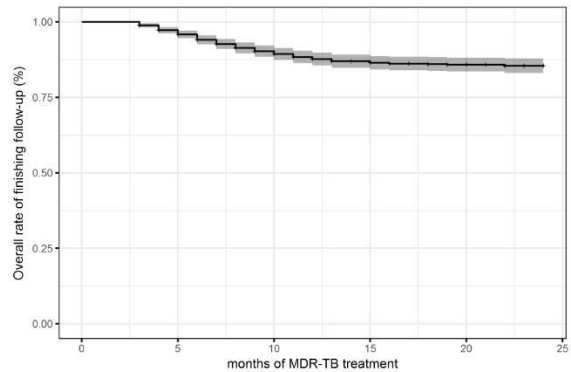
Cohort xii - Spain (n=21)



Cohort xiii - Vietnam (n=144)

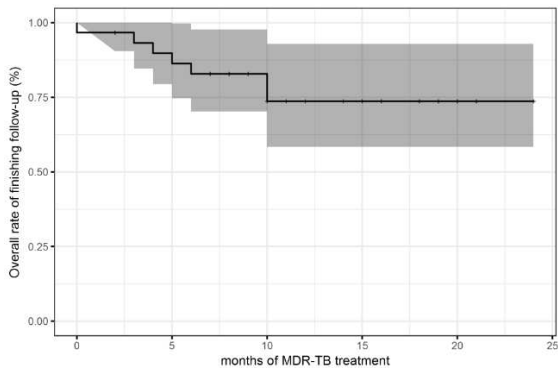


Cohort xiv - Latvia (n=949)

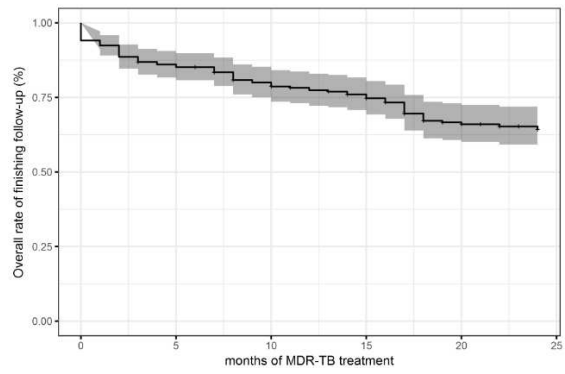


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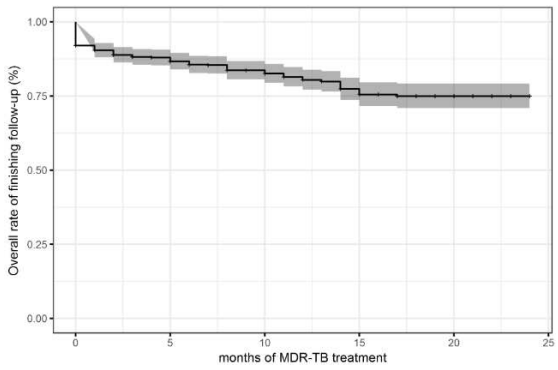
Cohort xv - France (n=30)



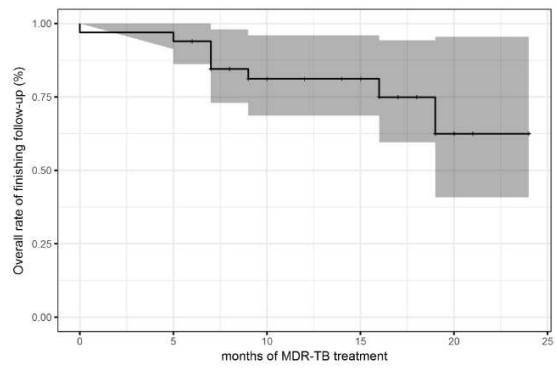
Cohort xvi – USA (n=236)



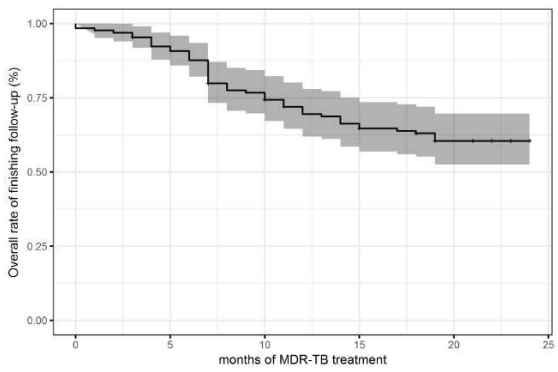
Cohort xvii - Russian Federation (n=577)



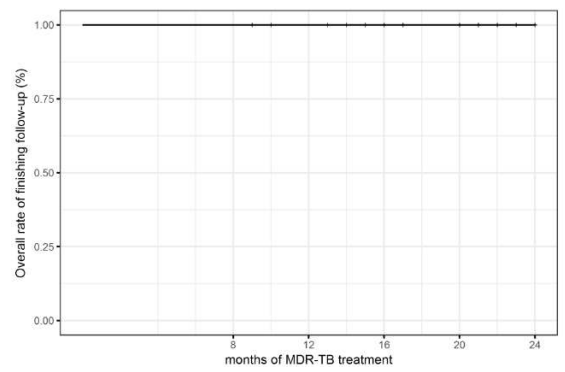
Cohort xviii – South Africa (n=33)



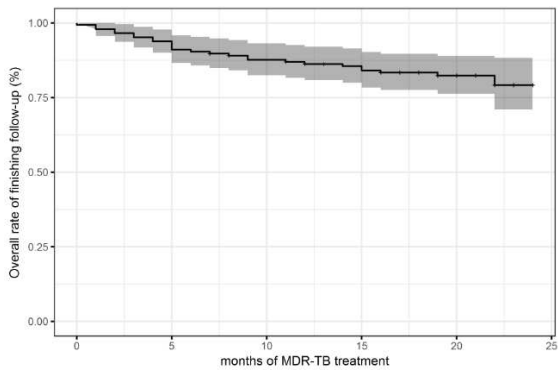
Cohort xix – South Korea (n=130)



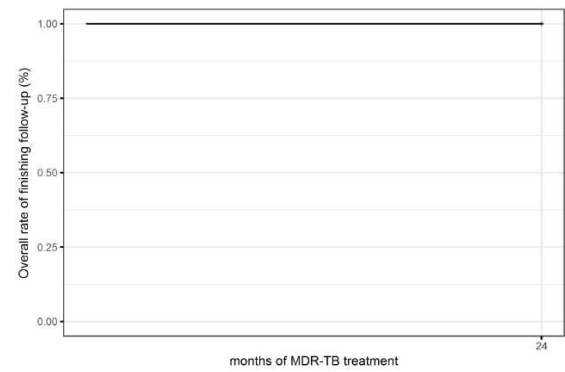
Cohort xx – Japan (n=59)



Cohort xxi – Philippines (n=146)



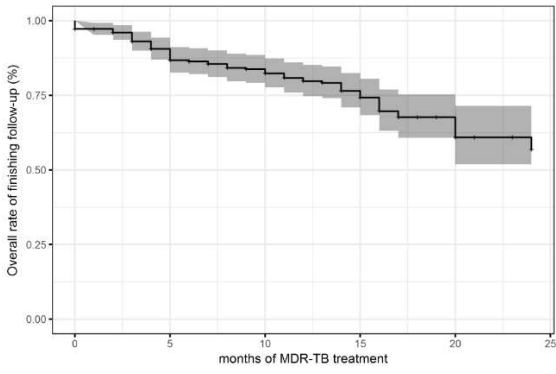
Cohort xxii – Iran (n=35)



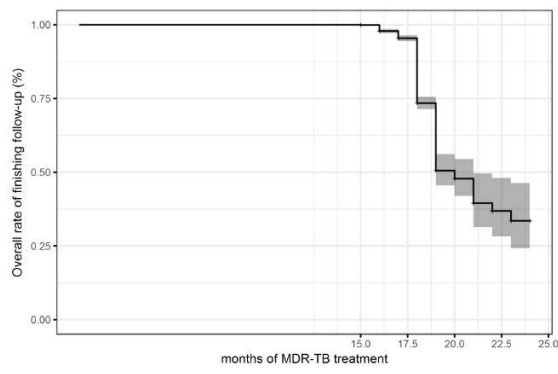
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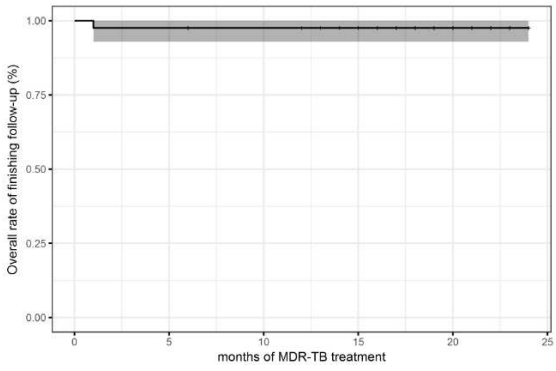
Cohort xxiii – Estonia (n=253)



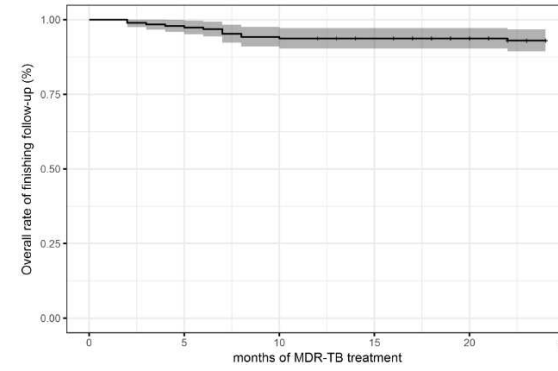
Cohort xxiv – South Africa (n=1,789)



Cohort xxv – The Netherlands (n=41)



Cohort xxvi – South Korea (n=191)



Cohort xxvii – Uzbekistan (n=67)

