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**Article:**

Walker, Ian F., Shi, Oumin, Hicks, Joseph P. et al. (2019) Analysis of loss to follow-up in 4099 multidrug-resistant pulmonary tuberculosis patients. *European Respiratory Journal*. 1800353. ISSN: 1399-3003

<https://doi.org/10.1183/13993003.00353-2018>

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

Journal:	<i>European Respiratory Journal</i>
Manuscript ID	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
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Key Words:	Tuberculosis (TB), drug resistance, adherence to therapy, epidemiology, pulmonary tuberculosis

## 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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2  
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.

13  
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).  
9  
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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27 191 Insert Fig. 3 here

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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 37 38 197 **Risk factors associated with loss-to-follow-up**

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40 198 After adjusting for all other variables in a Cox proportional hazards model, several  
41 199 risk factors were significantly associated with LFU (Table 2 and Figure 5). Those  
42 200 aged 26-35 and 36-50 years old had 20% and 28% higher incidence of LFU  
43 201 respectively (HR 1.20; 95% CI 1.04, 1.39 and HR 1.28; 95% CI 1.09, 1.49  
44 202 respectively) compared to those aged 0-25 years old. Males had a 13% higher  
45 203 incidence of LFU (HR 1.13; 95% CI 1.04, 1.23) compared to females. Those with  
46 204 HIV had a 36% higher incidence of LFU (HR 1.36; 95% CI 1.02, 1.80) compared to  
47 205 HIV negative patients. Those receiving an individualised treatment regimen had 45%  
48 206 lower incidence of LFU (HR 0.55; 95% CI 0.32, 0.93) compared with a standardised  
49 207 regimen.  
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210 Table 2 – Risk factors associated with loss-to-follow-up among all MDR-TB patients  
211 (n=5,970)

212 Insert Table 2 here

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

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

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## 222 Discussion

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

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

238 The timing of LFU in our study differs markedly from studies reporting more recent  
239 treatment cohorts, where the majority of LFU tended to be in the initial intensive  
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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45 299 Although some treatment cohorts in this dataset were from resource-constrained  
46 300 contexts, none were from low-income countries. Our findings therefore may not  
47 301 generalise to these settings. We have identified risk factors that are associated with  
48 302 LFU - further work needs to be done to explore the mechanisms that drive stubbornly  
49 303 high rates of LFU in all MDR-TB programmes including in low-income settings. For  
50 304 instance, the presence of co-morbid depression may reduce adherence in MDR-TB  
51 305 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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## 34 324 **Acknowledgements**

36 325 We would like to thank all the members of the *Collaborative Group for Meta-Analysis*  
37 326 *of Individual Patient Data* who allowed us to use their data in this study.

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40 327 Funding for this analysis was provided by COMDIS-HSD, a research consortium  
41 328 funded by UK aid from the UK government: however, the views expressed do not  
42 329 necessarily reflect the UK government's official policies. The funder had no bearing  
43 330 on the study findings nor did they approve or censor the manuscript  
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337 frontiers or boundaries.

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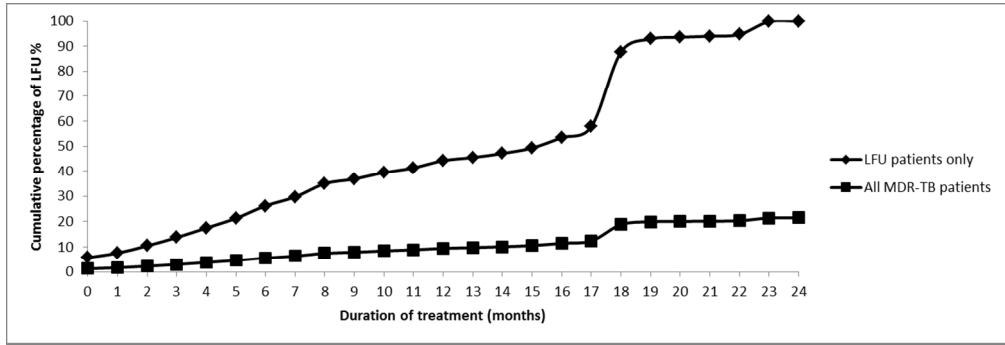
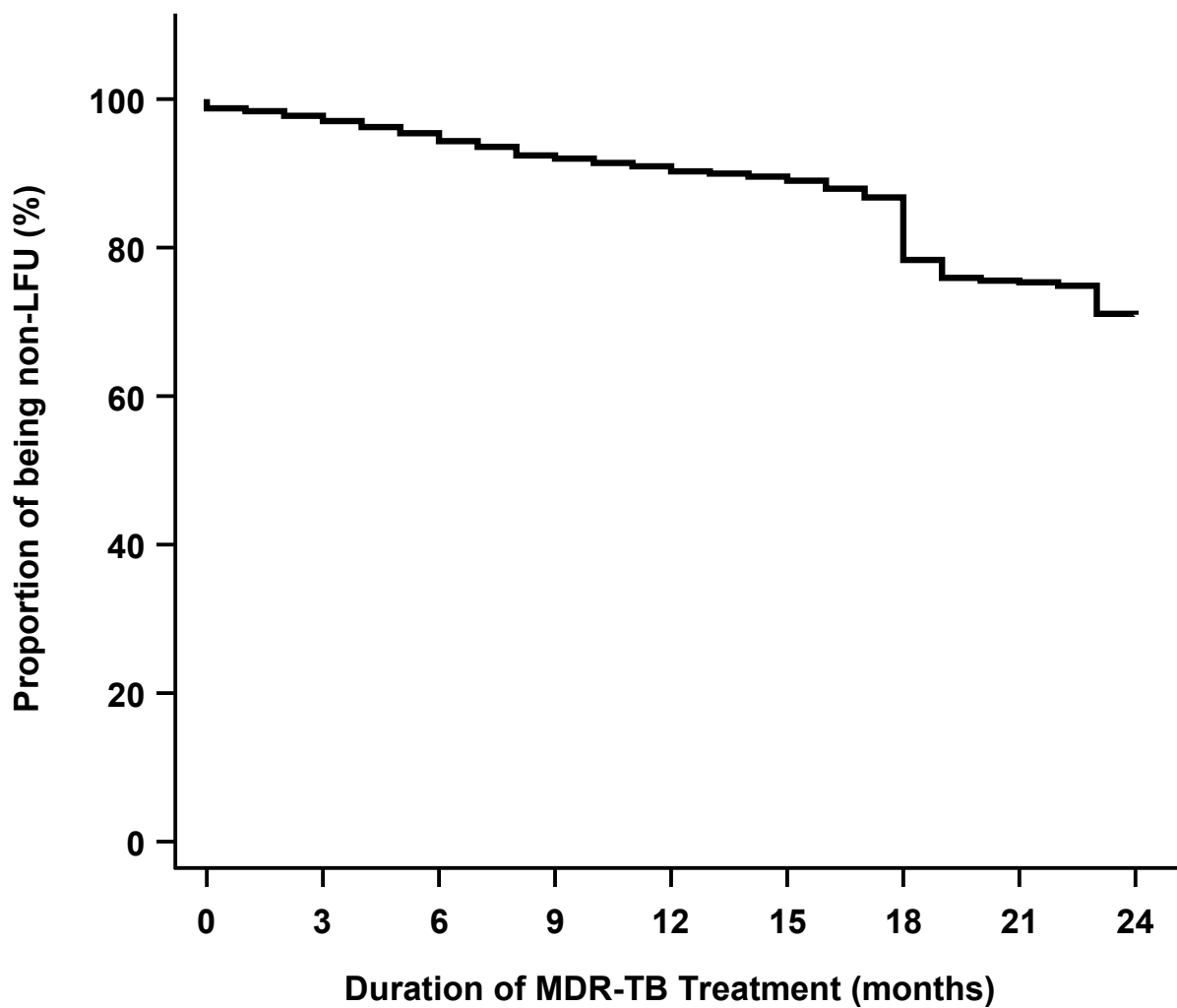
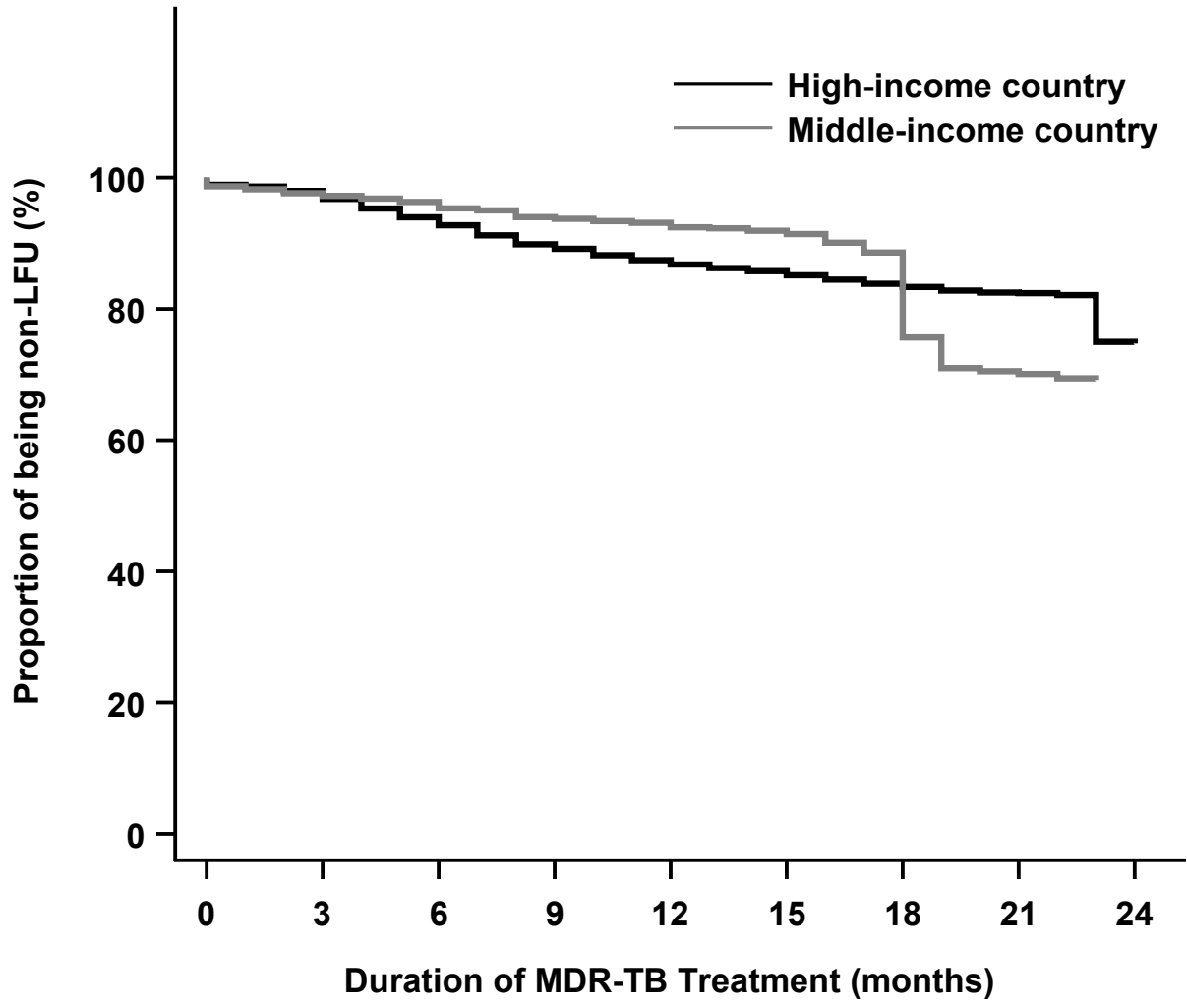


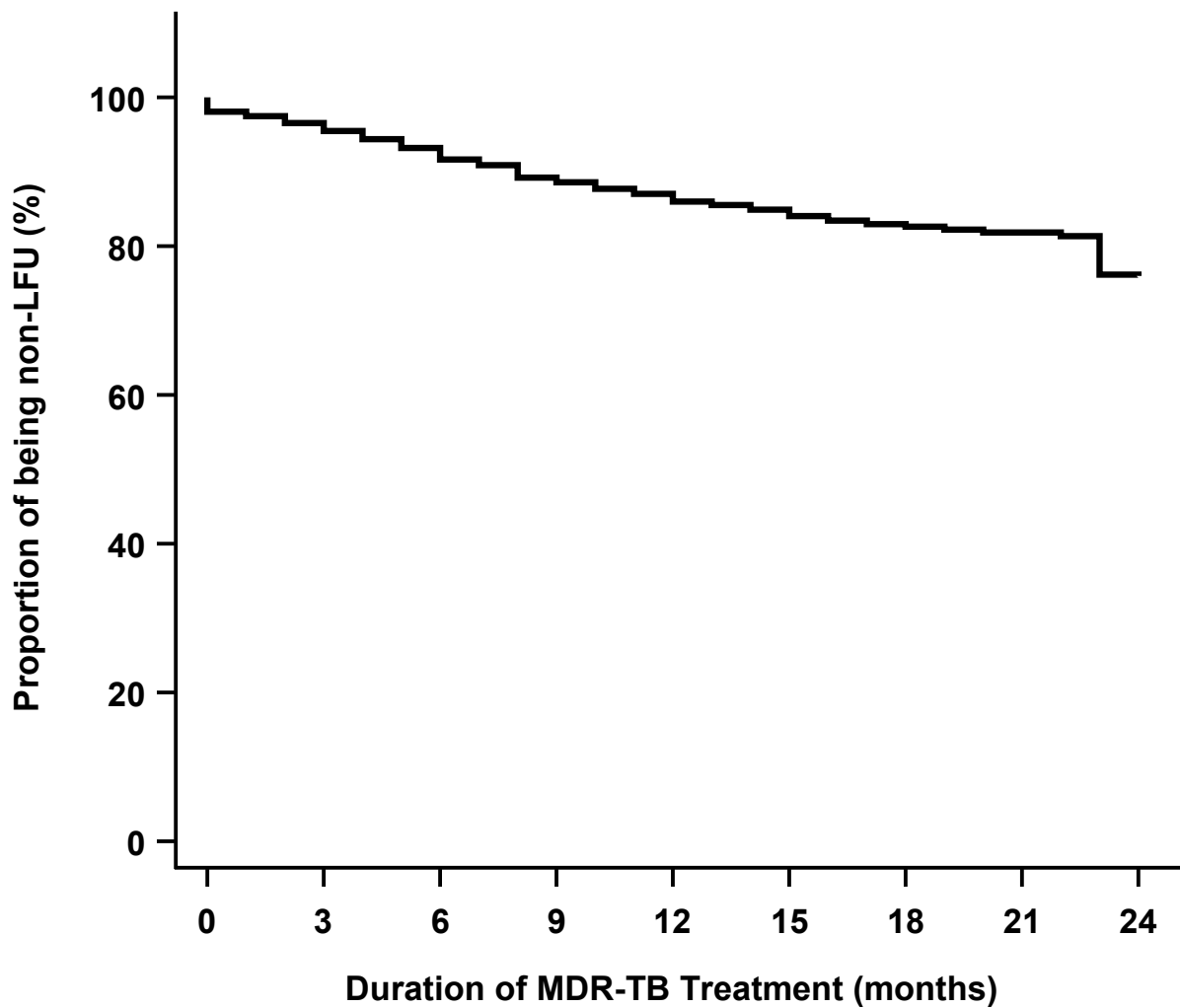
Figure 1 – Cumulative percentage of LFU\* for all MDR-TB patients and for LFU patients by month of treatment



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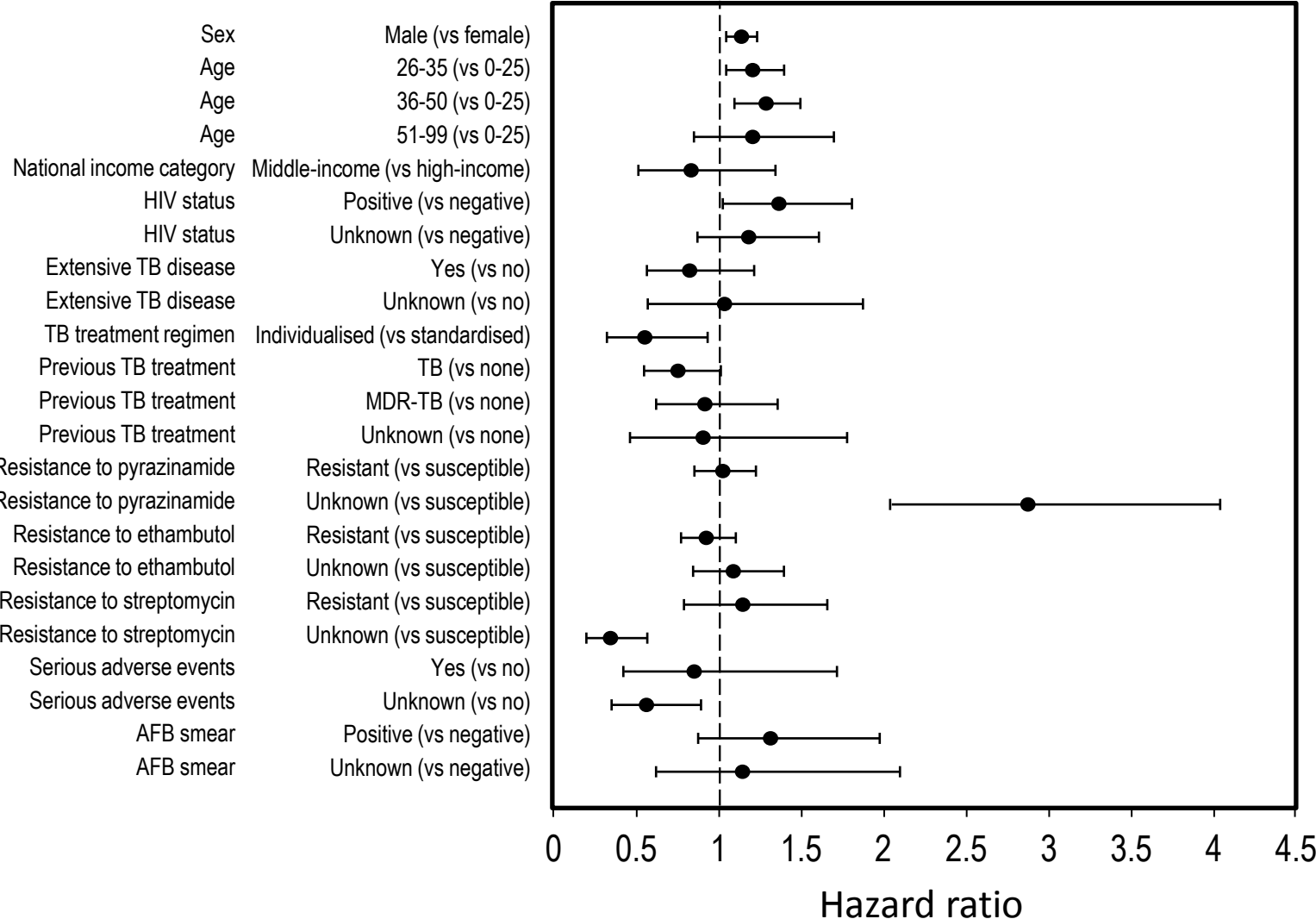


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Characteristic		Number of patients in group (% of total)	Those recorded as LFU (% of total LFU)	Percentage of each category that were LFU	Median time to LFU in months (IQR)
<b>Total</b>	All patients	5,970 (100%)	1,282 (100 %)	21.5%	16 (6-18)
<b>Sex</b>	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)
<b>Age</b>	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)
<b>National income category</b>	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)
<b>HIV status</b>	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)
<b>Extensive TB disease</b>	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)
<b>Treatment regimen</b>	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)
<b>Previous TB treatment</b>	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)
<b>Resistance to Pyrazinamide</b>	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)
<b>Resistance to Ethambutol</b>	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)
<b>Resistance to Streptomycin</b>	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)
<b>Serious adverse events</b>	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)
<b>AFB smear</b>	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)
<b>Years of study for included cohorts</b>	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)

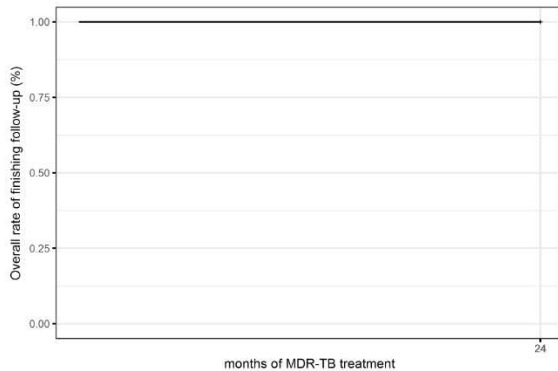
Variable		Unadjusted Hazard Ratio (95% CI)	p value	Adjusted Hazard Ratio (95% CI)	p value
Sex	Female	reference	-	reference	-
	Male	1.20 (1.03, 1.40)	0.02	1.13 (1.04, 1.23)	<0.01
Age	0-25	reference	-	reference	-
	26-35	1.35 (1.04, 1.74)	0.02	1.20 (1.04, 1.39)	0.01
	36-50	1.47 (1.00, 2.17)	0.05	1.28 (1.09, 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

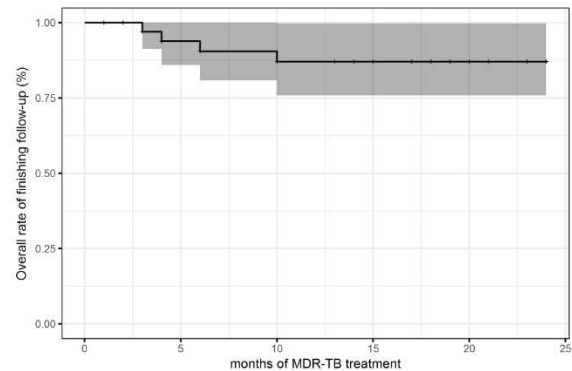
Ian F. Walker, Oumin Shi, Joseph Hicks, Helen Elsey, Xiaolin Wei, Dick Menzies, Dennis Falzon, Giovanni Battista Migliori, Carlos Pérez-Guzmán, Mario H. Vargas, Lourdes García-García, José Sifuentes Osornio, Alfredo Ponce-De-León, Martie van der Walt and James N. Newell

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

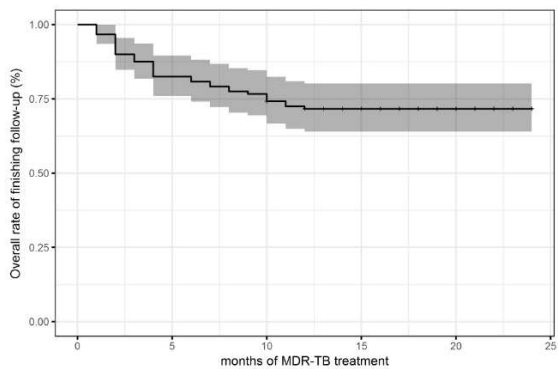
Cohort i – Canada (n=70)



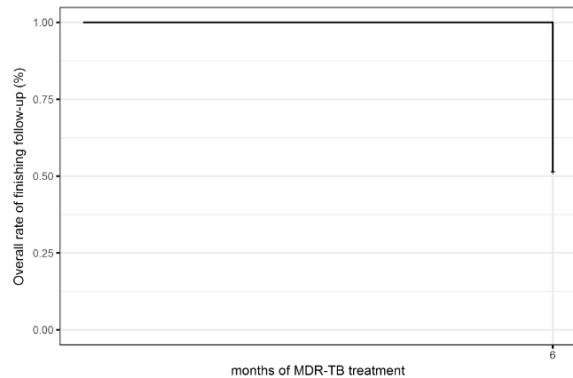
Cohort ii – USA (n=35)



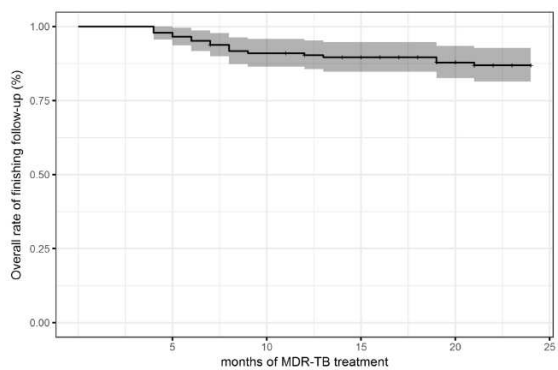
Cohort iii – Taiwan (n=120)



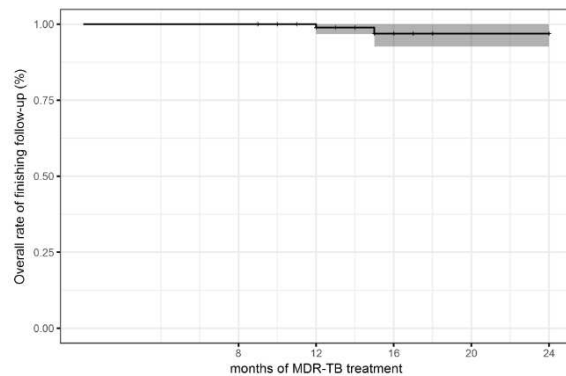
Cohort iv – Mexico (n=35)



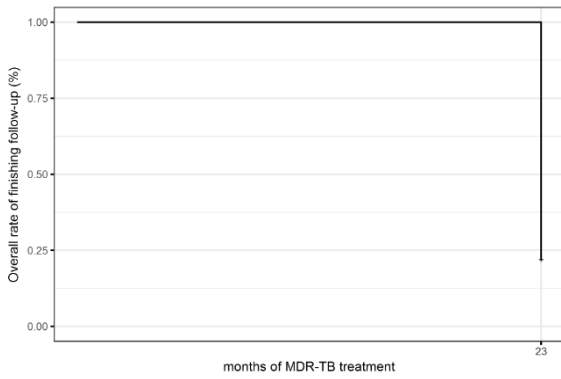
Cohort v - South Korea (n=145)



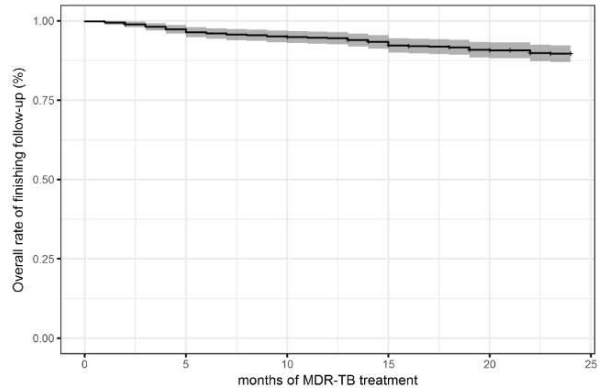
Cohort vi – Hong Kong (n=96)



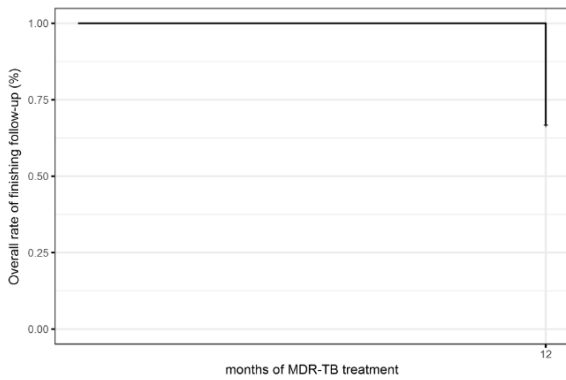
Cohort vii - Italy (n=82)



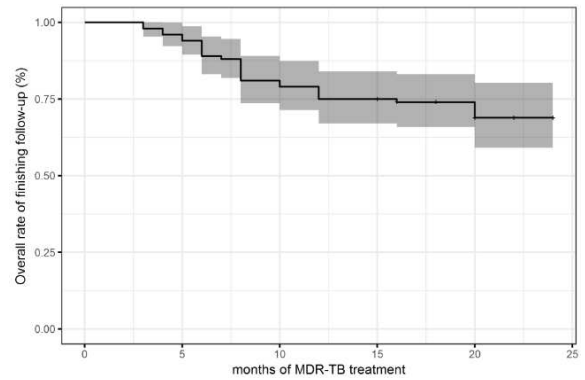
Cohort viii - Peru (n=529)



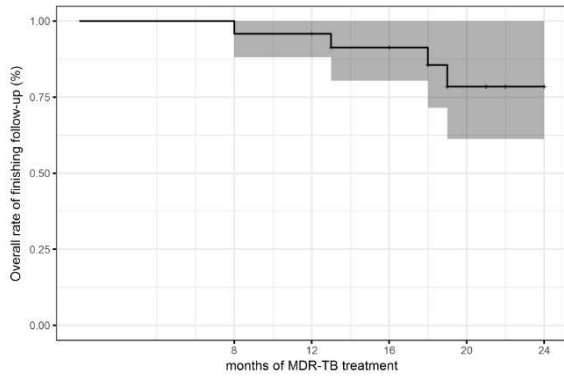
Cohort ix - Mexico (n=33)



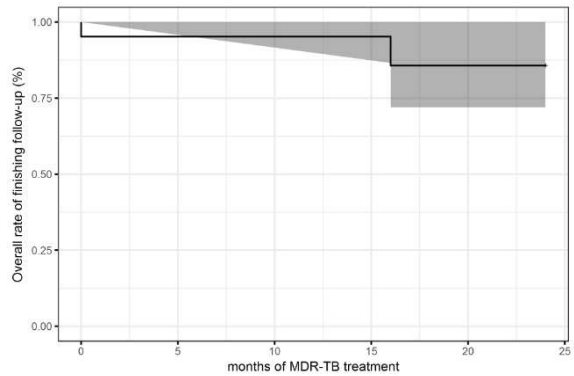
Cohort x - Argentina (n=100)



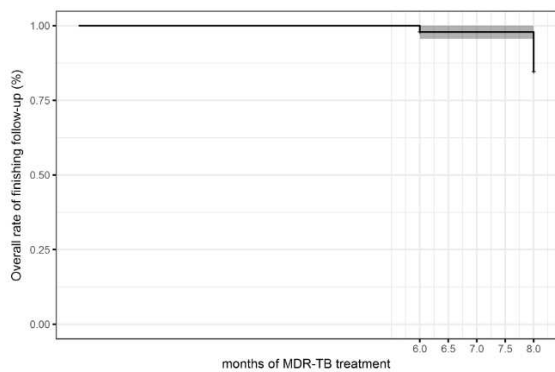
Cohort xi - UK (n=24)



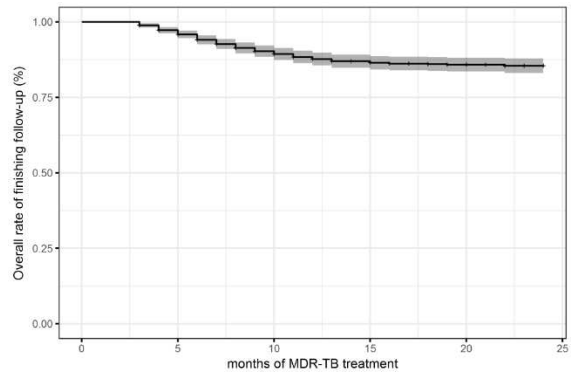
Cohort xii - Spain (n=21)



Cohort xiii - Vietnam (n=144)

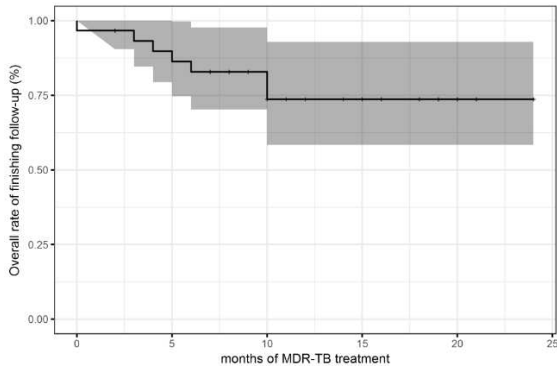


Cohort xiv - Latvia (n=949)

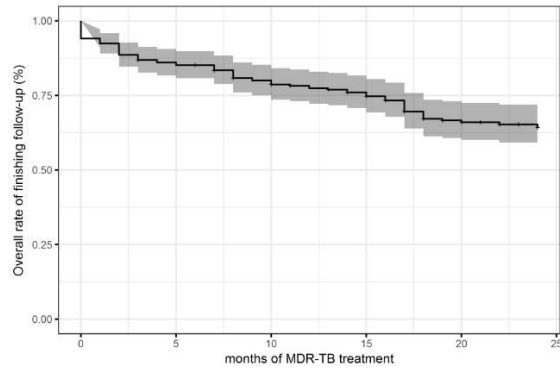


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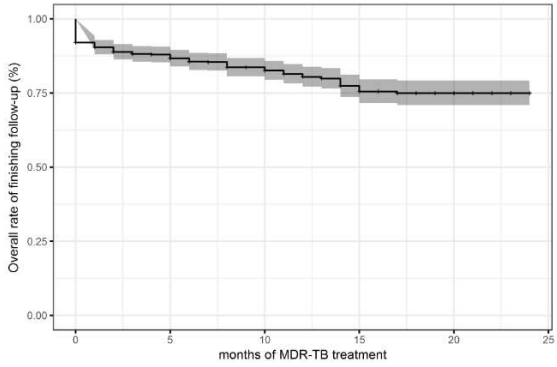
Cohort xv - France (n=30)



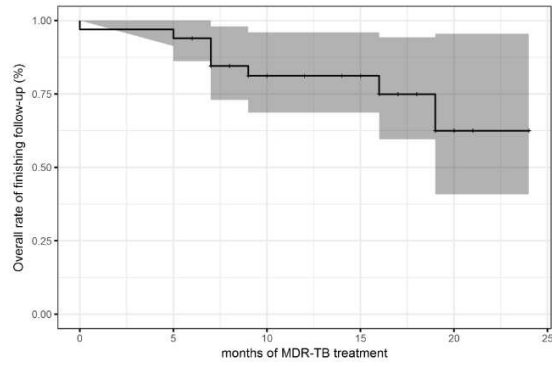
Cohort xvi – USA (n=236)



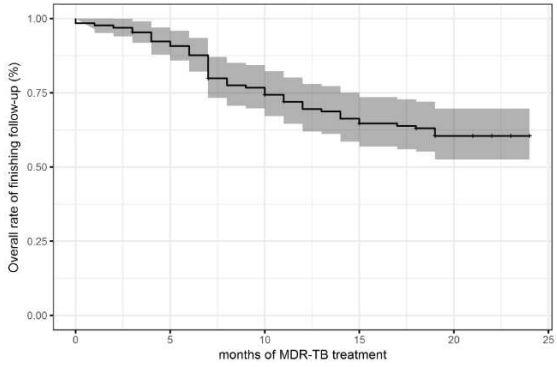
Cohort xvii - Russian Federation (n=577)



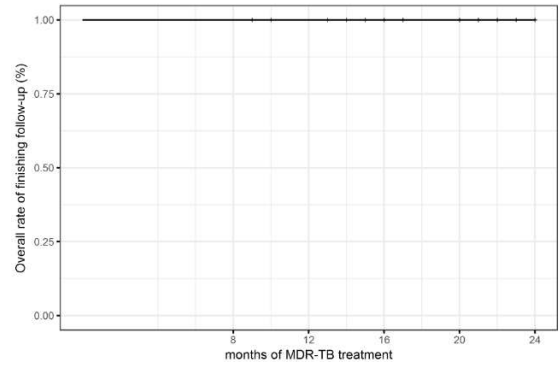
Cohort xviii – South Africa (n=33)



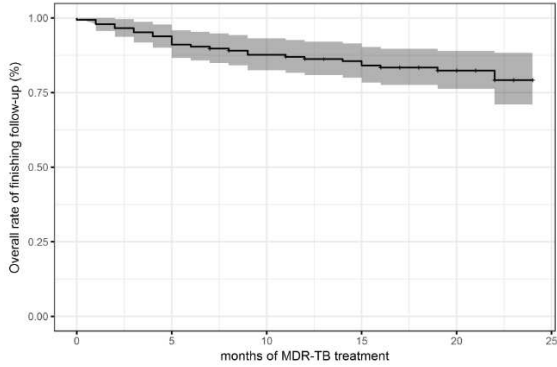
Cohort xix – South Korea (n=130)



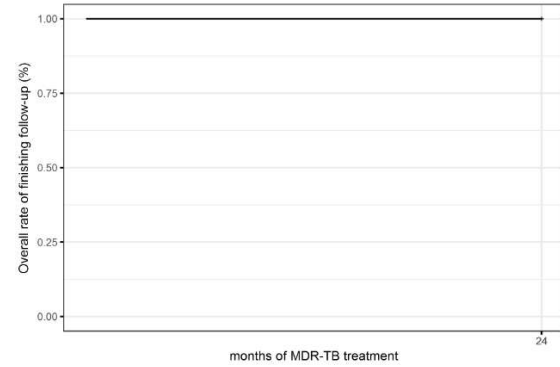
Cohort xx – Japan (n=59)



Cohort xxi – Philippines (n=146)

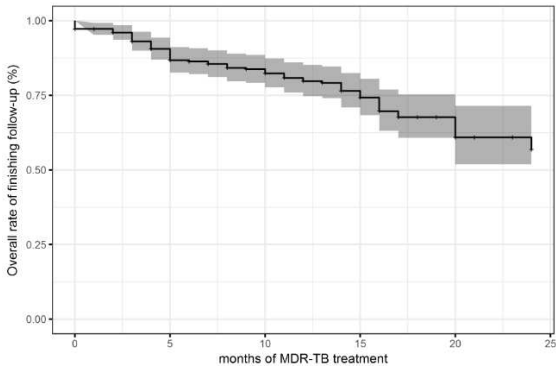


Cohort xxii – Iran (n=35)

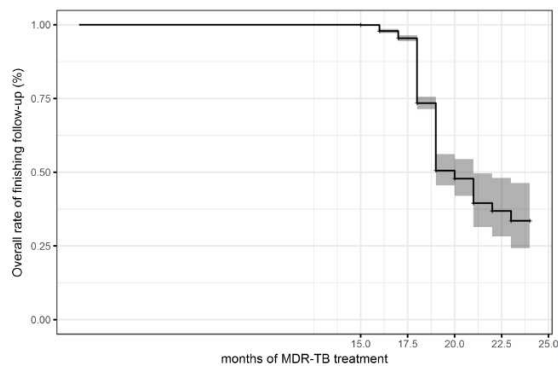


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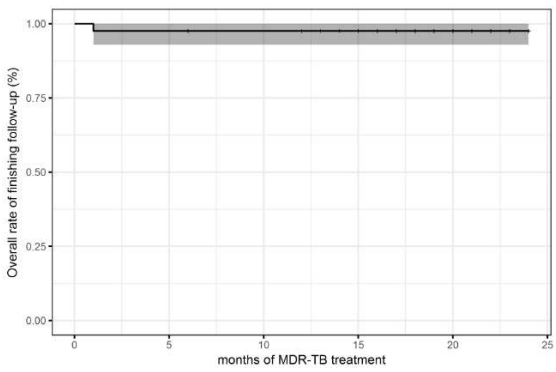
Cohort xxiii – Estonia (n=253)



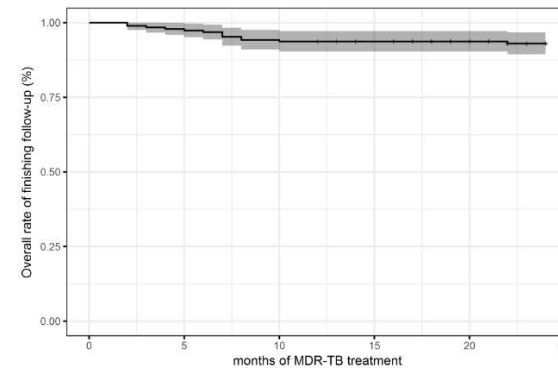
Cohort xxiv – South Africa (n=1,789)



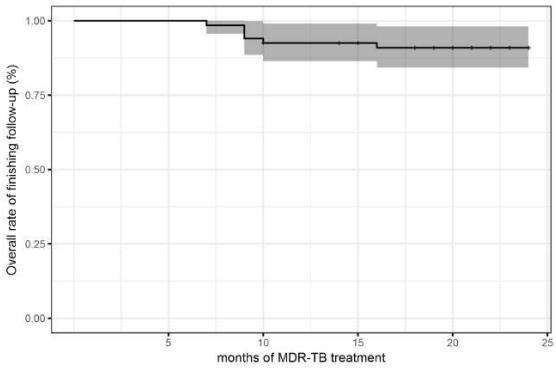
Cohort xxv – The Netherlands (n=41)



Cohort xxvi – South Korea (n=191)



Cohort xxvii – Uzbekistan (n=67)



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