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

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

Abstract

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

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

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

Both patient and regimen-related factors were associated with LFU which may guide interventions to improve treatment adherence.

Introduction

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

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

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

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

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

MDR-TB dataset, to identify the timing of LFU in the treatment of pulmonary MDR-TB and to identify patient-level risk factors associated with LFU. [1-3]

Methods

The dataset of the *Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB* was used for this analysis. This data set includes individual-level treatment data from 9,153 pulmonary MDR-TB patients from TB clinics or programmes from 23 countries, reported in 32 previously published observational studies. Patients had to have received at least one month's treatment in order to be included. The patient characteristics and definitions of the variables within the dataset have been described elsewhere.[1] Permission was not granted for this analysis, for one cohort of patients included in the original data set.

For our analysis, patients were included if there was authorization of the lead investigator for each cohort and patients were alive at the point of LFU. Patients were defined as LFU if their outcome was recorded as 'defaulted', 'transferred out (with unknown outcome)' or 'unknown' in the dataset, based on the outcome definitions available at the time data were collected.[19] Time of LFU for each patient was identified by their recorded duration of treatment in months. The treatment cohorts included in this analysis used a variety of drug regimens and treatment lengths, most were 20-24 months. Those with a duration of treatment longer than 24 months (n=800) were truncated at 24 months. Records were excluded if lead investigators did not give consent for their data to be included or if there was no record of duration of treatment. We also excluded patient records whose outcome was death. Although it is possible that some of these patients may have chosen to stop MDR-TB treatment before death, the dataset did not include this detail so we decided to exclude all patients who died.

We identified the independent variables from the dataset to include in the analysis from previous studies where significant associations with LFU had been identified (see introduction). Variables included in the analysis were: age, sex, HIV co-infection status, extensive TB disease (defined as Acid Fast Bacillus (AFB) smear positive, or cavities on chest radiography if no information about AFB-smear was available), type of regimen (standardised v individualised), previous TB therapy (defined as

treatment with first-line, or second-line TB drugs for 1 month or more), recorded drug resistance to pyrazinamide, ethambutol and streptomycin, recorded serious adverse events and AFB-smear status. We were also interested in variations by national income and so we distinguished study cohorts from high-income and middle-income countries within the analysis (according to World Bank classifications).[20] There were no cohorts from low-income countries.

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

Results

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

5,970 patients, of which 1,282 (21.5%) were recorded as LFU. This LFU rate is comparable with that reported in the full data set (23%).[1] The characteristics of the patients in our dataset are described in table 1.

Table 1 – Characteristics of MDR-TB patients and the median time to loss-to-follow-up

Insert Table 1 here

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

After six months of treatment, 26% (n=336) of those who were recorded as LFU had been lost (Fig. 1). At the end of the intensive stage of treatment at 8 months 35% (n=448) had been lost. By the 12 month stage 44% (n=567) had been lost and by 18 months it was 88% (n=1124).

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

Insert Fig.1 here

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 recorded as LFU (n=1,243). *LFU: loss to follow up

For all patients recorded as LFU, the median time to LFU was 16 months (inter-quartile range (IQR) 6-18 months). The median time to LFU was much lower in some sub-groups (Table 1): for example, those over 50 years old (median time to LFU 9 months (IQR 5-18), high-income country cohorts (8 months; IQR 5-16), negative HIV status (11 months; IQR 5-18), individualised treatment regime (7 months; IQR 3-14), no previous TB treatment (10 months, IQR 6-18) and previous MDR-TB treatment (12 months; IQR 5-18). Time to LFU also varied by the decade in which cohorts were treated and the median time was much longer in patients starting treatment in the latter decade.

Timing of LFU

For all patients recorded as LFU, the rate of LFU occurrence is steady in the first 17 months of treatment (Fig. 2). A substantial change in probability of being LFU then occurs around month 18 of treatment. We suspected this may have been artefactual and therefore conducted further analysis (see supplementary material and Fig. 3). From this we identified a large cohort from South Africa (n=1,789) which appeared to contribute to this change in probability at 18 months. After removing this large cohort, the plot of time to LFU in the reduced data set indicates it was indeed responsible (Fig. 4).

Figure 2 - Time to Loss-to-Follow-Up after starting MDR-TB treatment for all patients, using Kaplan-Meier analysis

Insert Fig. 2 here

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

Insert Fig. 3 here

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

Insert Fig. 4 here

Risk factors associated with loss-to-follow-up

After adjusting for all other variables in a Cox proportional hazards model, several risk factors were significantly associated with LFU (Table 2 and Figure 5). Those aged 26-35 and 36-50 years old had 20% and 28% higher incidence of LFU respectively (HR 1.20; 95% CI 1.04, 1.39 and HR 1.28; 95% CI 1.09, 1.49 respectively) compared to those aged 0-25 years old. Males had a 13% higher incidence of LFU (HR 1.13; 95% CI 1.04, 1.23) compared to females. Those with HIV had a 36% higher incidence of LFU (HR 1.36; 95% CI 1.02, 1.80) compared to HIV negative patients. Those receiving an individualised treatment regimen had 45% lower incidence of LFU (HR 0.55; 95% CI 0.32, 0.93) compared with a standardised regimen.

Table 2 – Risk factors associated with loss-to-follow-up among all MDR-TB patients (n=5,970)

Insert Table 2 here

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

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

Insert Fig. 5 here

Discussion

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

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

The timing of LFU in our study differs markedly from studies reporting more recent treatment cohorts, where the majority of LFU tended to be in the initial intensive phase of treatment (see Introduction). The treatment of all patients in our study

predates 2008, compared with these LFU studies of MDR-TB patients which tend to be more recent (published 2006 – 2015)[7-16]. It is possible that the distribution of timing of LFU has changed over time. Further research on aggregated data from more recent cohorts would help to identify if a different pattern exists for timing of LFU compared with our older cohorts in this study.

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

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

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

Furthermore, the competing demands of employment and dependents for individuals in the working age groups could also be influential in their greater risk of LFU[25].

For several variables in our Cox proportional hazards model, the 'unknown' category was significantly associated with being LFU (resistance to pyrazinamide, resistance to streptomycin and serious adverse events). Weaker TB treatment programmes may be the confounding factor, where poorer recording practices and limited efforts at following up patients are both associated with weaker programmes.

The study has several imitations. The large number (35%) of excluded patient records, largely as a result of missing data of time to LFU or death, may have introduced bias in our findings. The data quality was variable, although attempts have been made to ensure the dataset is as complete as possible. There are likely to be other artefactual influences on our data set beyond those we identified from the large South African cohort, which are unaccounted for in our analysis. This dataset is largely restricted to patients who had received one month or more of treatment. This could have led to an artefactual prolongation of LFU as patients who would have been early interrupters were selectively removed from the cohorts. We did not have data available for some patient variables that we were interested in, such as co-morbid substance misuse or treatment interruptions of less than two consecutive months. Furthermore, there are likely to be other types of programme-related or treatment-related risk factors that are associated with LFU which we did not analyse and which could explain LFU more fully. All datasets pre-date 2008 so these findings may not generalise to current programme management of MDR-TB. For instance the use of a standardised 9-11 month regimen recommended by WHO since 2016 in selected MDR-TB patients has the potential to reduce LFU due to a substantially shorter duration of treatment than previous MDR-TB regimens.[29]

Although some treatment cohorts in this dataset were from resource-constrained contexts, none were from low-income countries. Our findings therefore may not generalise to these settings. We have identified risk factors that are associated with LFU - further work needs to be done to explore the mechanisms that drive stubbornly high rates of LFU in all MDR-TB programmes including in low-income settings. For instance, the presence of co-morbid depression may reduce adherence in MDR-TB as it does in other health conditions. [22, 30]

Our study identifies risk factors associated with being LFU which can guide policy makers to target interventions at those most at risk, such as men of working age. Treatment programmes should consider how best to maintain engagement with these men in an approach that is person-centred and accessible at times and in locations that are convenient for them. In addition, patients with a co-morbid HIV infection are more at risk of being LFU. The policy rhetoric that highlights the need for co-ordination of treatment between both diseases must be implemented by TB and HIV treatment programmes.

Conclusion

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

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References

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

quantitative and qualitative study. *The International Journal of Tuberculosis and Lung Disease* 2014: 18(2): 160-167.

14. Shringarpure KS, Isaakidis P, Sagili KD, Baxi RK. Loss-To-Follow-Up on Multidrug Resistant Tuberculosis Treatment in Gujarat, India: The WHEN and WHO of It. *PloS one* 2015: 10(7): e0132543.

15. Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, Weyer K, Lancaster J, Van der Walt M. Outcomes of Multi-Drug Resistant Tuberculosis (MDR-TB) among a Cohort of South African Patients with High HIV Prevalence. *PloS one* 2011: 6(7): e20436.

16. Javaid A, Shaheen Z, Shafqat M, Khan AH, Ahmad N. Risk factors for high death and loss-to-follow-up rates among patients with multidrug-resistant tuberculosis at a programmatic management unit. *American journal of infection control* 2017: 45(2): 190-193.

17. Toczek A, Cox H, du Cros P, Cooke G, Ford N. Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2013: 17(3): 299-307.

18. Yin J, Yuan J, Hu Y, Wei X. Association between Directly Observed Therapy and Treatment Outcomes in Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis. *PloS one* 2016: 11(3): e0150511.

19. Laserson K, Thorpe L, Leimane V, Weyer K, Mitnick C, Riekstina V, Zarovska E, Rich M, Fraser H, Alarcón E. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease* 2005: 9(6): 640-645.

20. The World Bank. South Asia Region. 2016 [cited; Available from: http://www.worldbank.org/en/region/sar

21. Institute of Medicine. The New Profile of Drug Resistant Tuberculosis in Russia: A Global and Local Perspective: Summary of a Joint Workshop. The National Academies Press, Washington DC,, 2011.

22. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. *Front Pharmacol* 2013: 4: 91.

23. Diwan VK, Thorson A. Sex, gender, and tuberculosis. *The Lancet*: 353(9157): 1000-1001.

24. Munro SAL, S.A. Smith, H.J. Engel, M.E. Fretheim, A. Volmink, J. Patient Adherence to Tuberculosis Treatment: A Systematic Review of Qualitative Research. *PLoS Med* 2007: 4(7): e238.

25. Deshmukh RD, Dhande DJ, Sachdeva KS, Sreenivas A, Kumar AMV, Satyanarayana S, Parmar M, Moonan PK, Lo TQ. Patient and Provider Reported Reasons for Lost to Follow Up in MDRTB Treatment: A Qualitative Study from a Drug Resistant TB Centre in India. *PloS one* 2015: 10(8): e0135802.

26. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, Castro KG, Weyer K. HIV infection and multidrug-resistant tuberculosis—the perfect storm. *The Journal of infectious diseases* 2007: 196(Supplement_1): S86-S107.

27. Isaakidis P, Casas E, Das M, Tseretopoulou X, Ntzani E, Ford N. Treatment outcomes for HIV and MDR-TB co-infected adults and children: systematic review and meta-analysis. *The International Journal of Tuberculosis and Lung Disease* 2015: 19(8): 969-978.

28. Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *The Lancet Infectious Diseases*: 12(6): 449-456.

29. Khan FA, Salim MH, du Cros P, Casas EC, Khamraev A, Sikhondze W, Benedetti A, Bastos M, Lan Z, Jaramillo E. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. *European Respiratory Journal* 2017: 50(1): 1700061.

30. Walker IF, Baral SC, Wei X, Huque R, Khan A, Walley J, Newell JN, Elsey H. Multidrug-resistant tuberculosis treatment programmes insufficiently consider comorbid mental disorders. *The International Journal of Tuberculosis and Lung Disease* 2017: 21(6): 603-609.

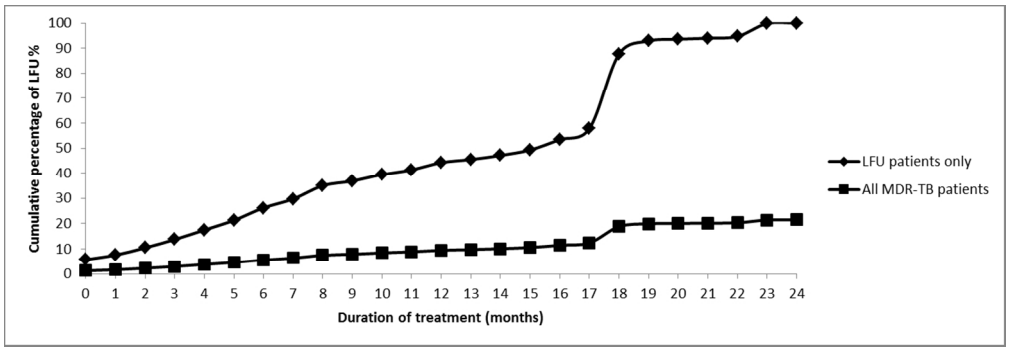
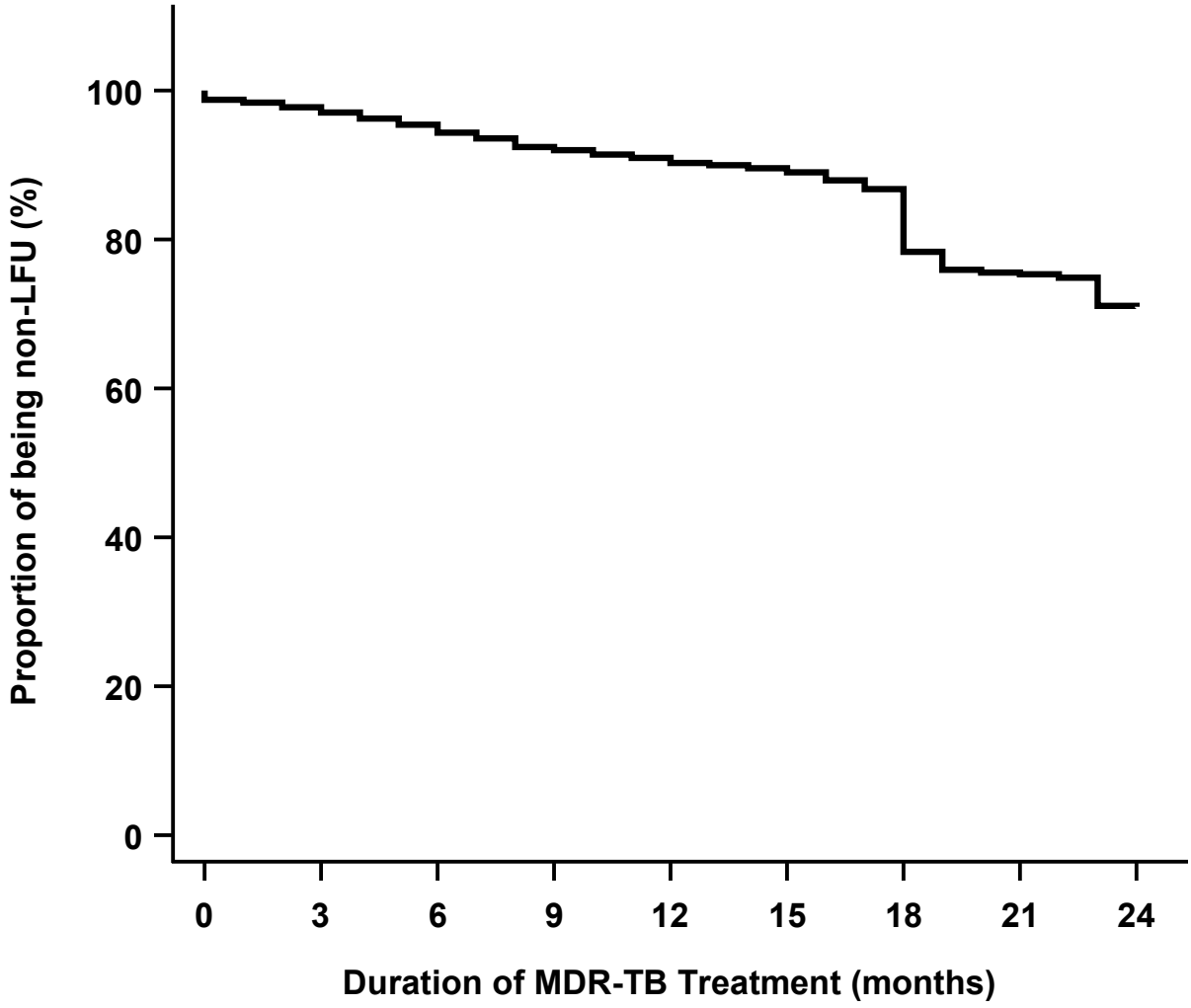
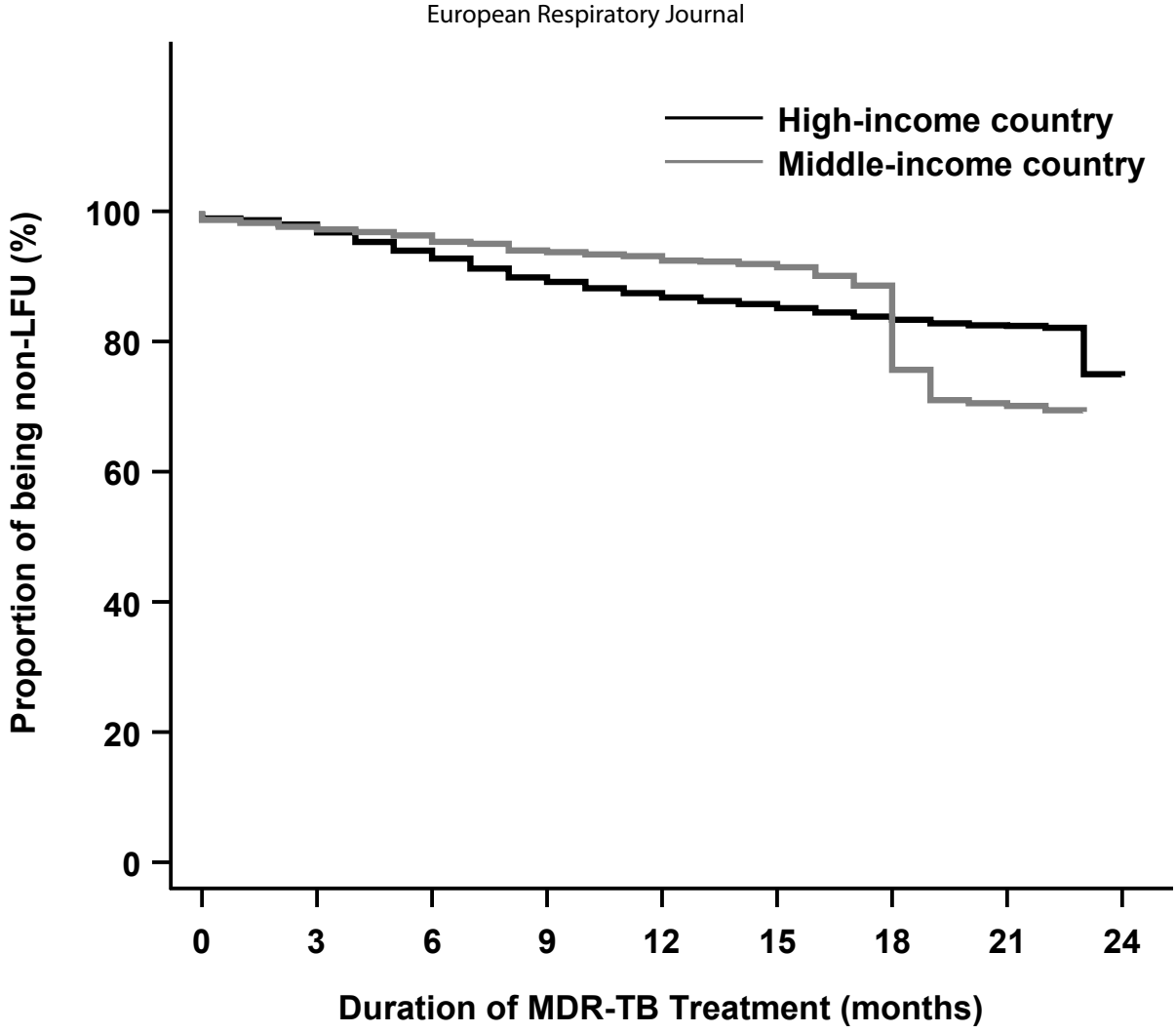
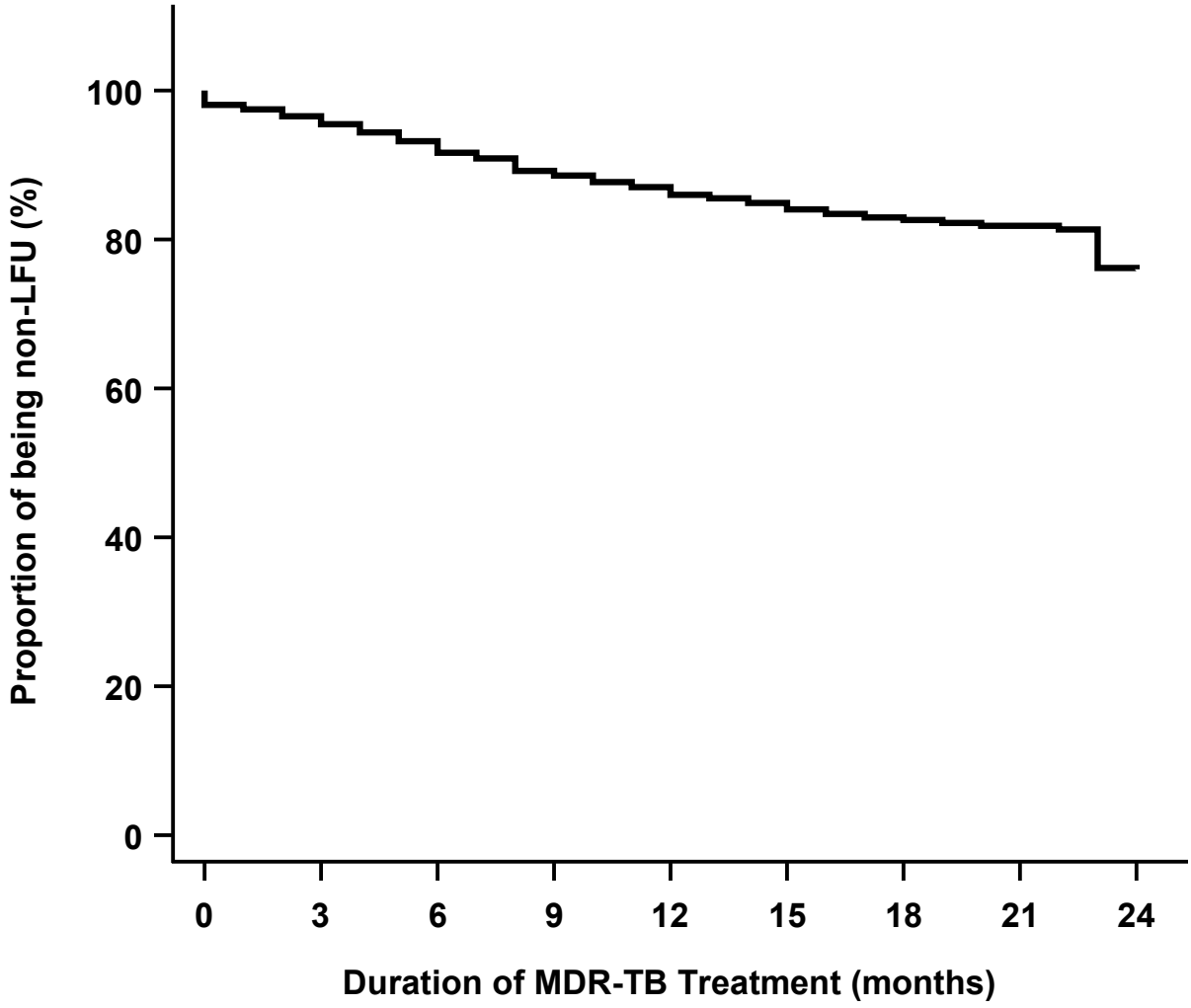
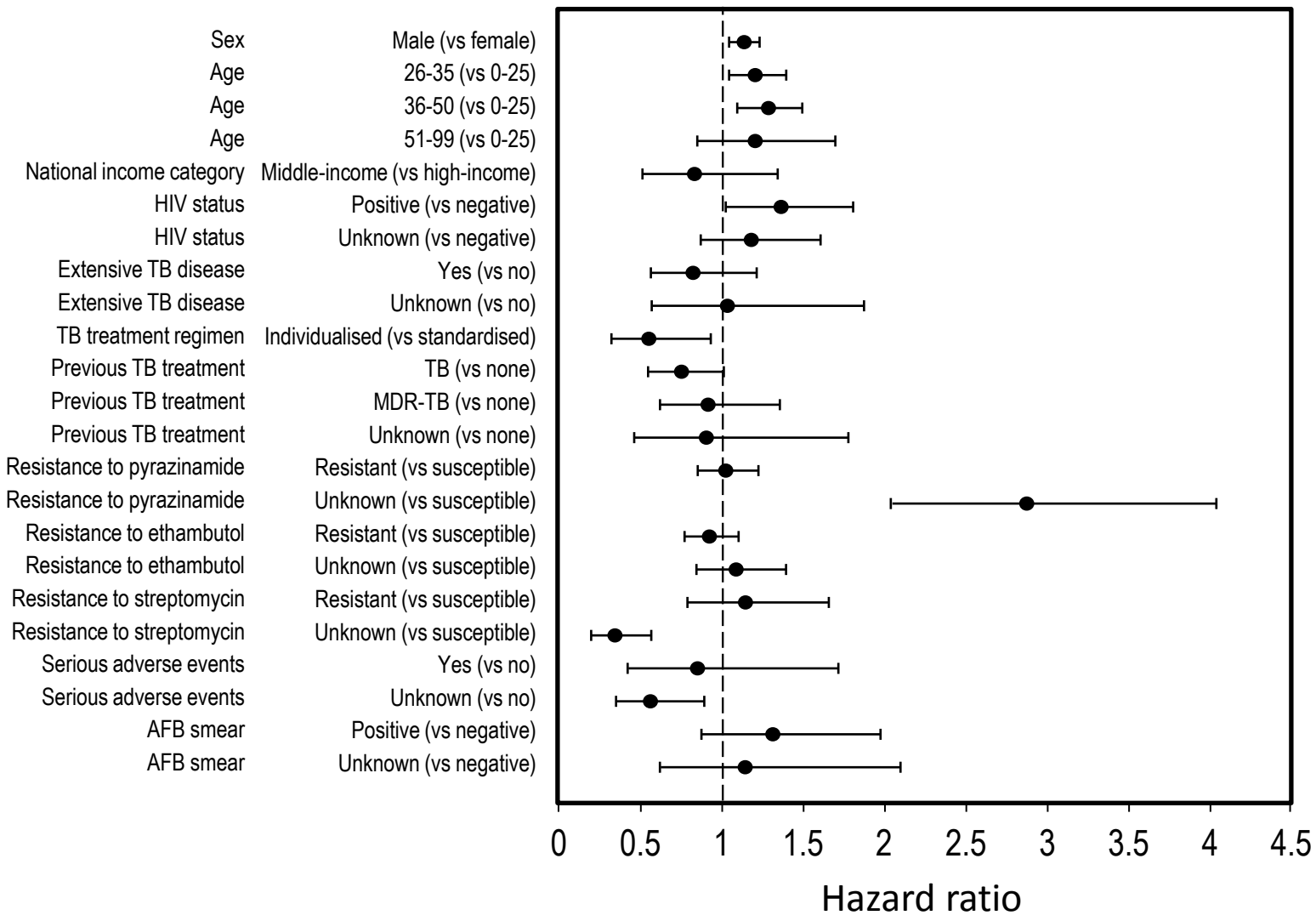


Figure 1 – Cumulative percentage of LFU* for all MDR-TB patients and for LFU patients by month of treatment


Proportion of being non-LFU (%)
100
80
60
40
20
0
0
3
6
9
12
15
18
21
24
Duration of MDR-TB Treatment (months)


High-income country
Middle-income country
Proportion of being non-LFU (%)
100
80
60
40
20
0
0
3
6
9
12
15
18
21
24
Duration of MDR-TB Treatment (months)


Proportion of being non-LFU (%)
100
80
60
40
20
0
0
3
6
9
12
15
18
21
24
Duration of MDR-TB Treatment (months)


Sex
Male (vs female)
Age
26-35 (vs 0-25)
Age
36-50 (vs 0-25)
Age
51-99 (vs 0-25)
National income category
Middle-income (vs high-income)
HIV status
Positive (vs negative)
HIV status
Unknown (vs negative)
Extensive TB disease
Yes (vs no)
Extensive TB disease
Unknown (vs no)
TB treatment regimen
Individualised (vs standardised)
Previous TB treatment
TB (vs none)
Previous TB treatment
MDR-TB (vs none)
Previous TB treatment
Unknown (vs none)
Resistance to pyrazinamide
Resistant (vs susceptible)
Resistance to pyrazinamide
Unknown (vs susceptible)
Resistance to ethambutol
Resistant (vs susceptible)
Resistance to ethambutol
Unknown (vs susceptible)
Resistance to streptomycin
Resistant (vs susceptible)
Resistance to streptomycin
Unknown (vs susceptible)
Serious adverse events
Yes (vs no)
Serious adverse events
Unknown (vs no)
AFB smear
Positive (vs negative)
AFB smear
Unknown (vs negative)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
Hazard ratio

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)

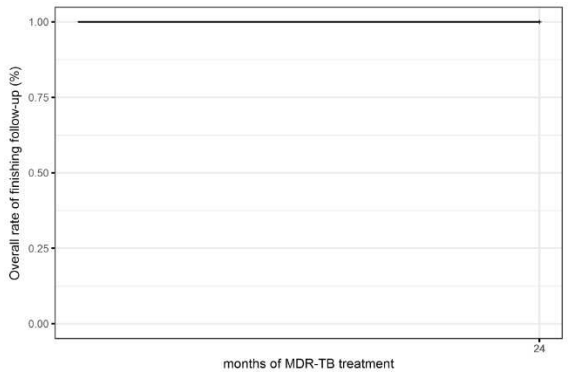
Variable		Unadjusted Hazard Ratio (95% CI)	p value	Adjusted Hazard Ratio (95% CI)	p value
Sex	**Female**	reference	-	reference	-
	Male	1.20 (1.03, 1.40)	0.02	1.13 (1.04, 1.23)	<0.01
Age	**0-25**	reference	-	reference	-
	26-35	1.35 (1.04, 1.74)	0.02	1.20 (1.04, 1.39)	0.01
	36-50	1.47 (1.00, 2.17)	0.05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

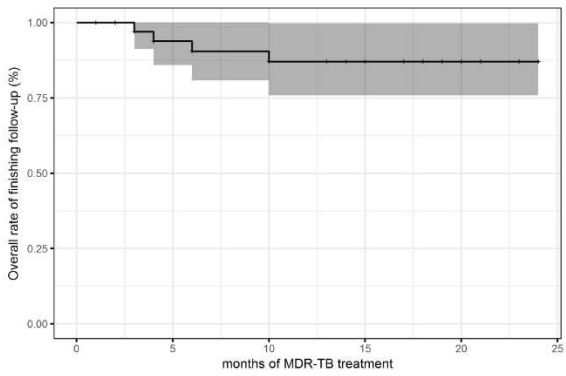
Ian F. Walker, Oumin Shi, Joseph Hicks, Helen Elsey, Xiaolin Wei, Dick Menzies, Dennis Falzon, Giovanni Battista Migliori, Carlos Pérez-Guzmán, Mario H. Vargas, Lourdes García-García, José Sifuentes Osornio, Alfredo Ponce-De-León, Martie van der Walt and James N. Newell

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

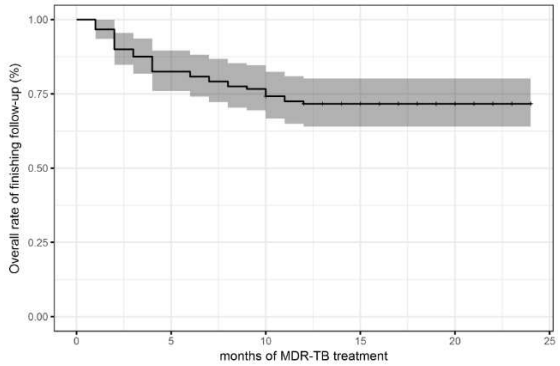
Cohort i – Canada (n=70)



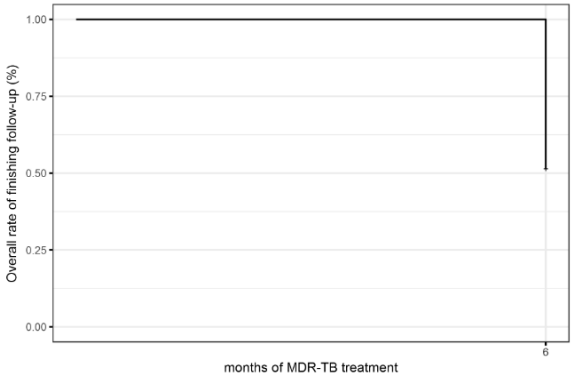
Cohort ii – USA (n=35)



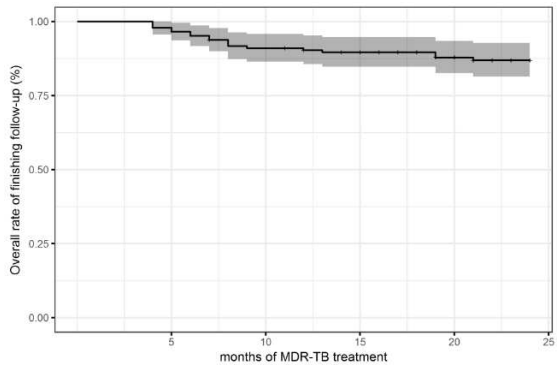
Cohort iii – Taiwan (n=120)



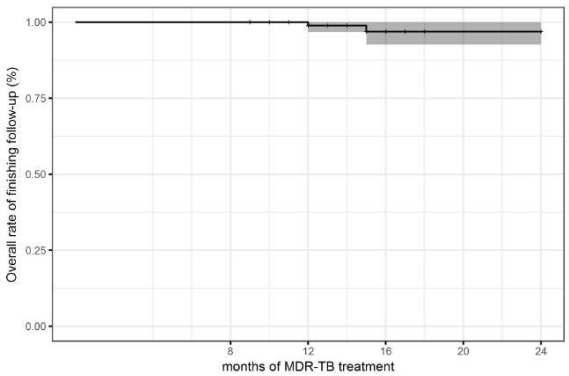
Cohort iv – Mexico (n=35)



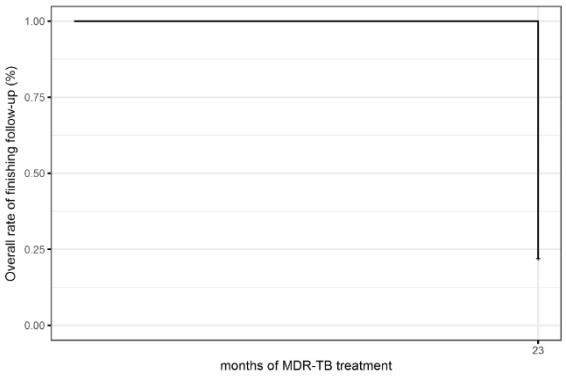
Cohort v - South Korea (n=145)



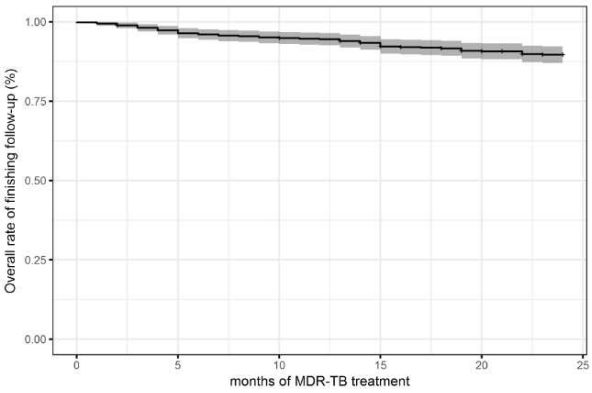
Cohort vi – Hong Kong (n=96)



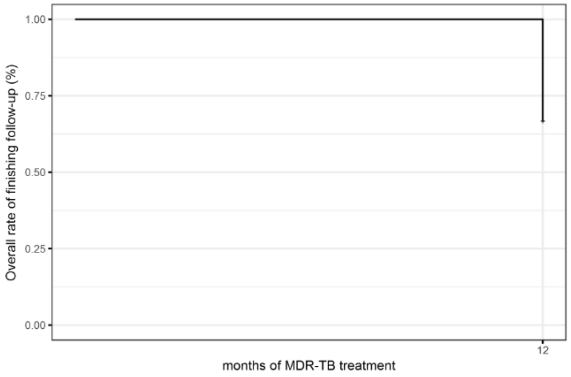
Cohort vii - Italy (n=82)



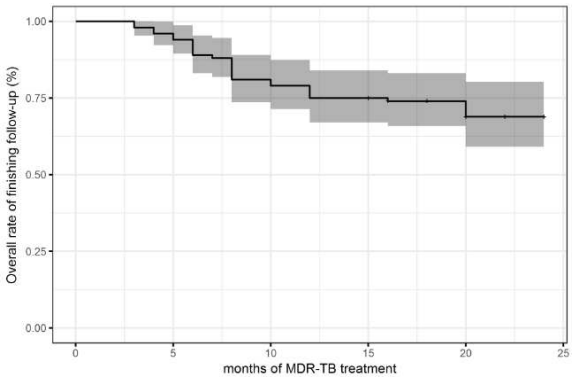
Cohort viii – Peru (n=529)



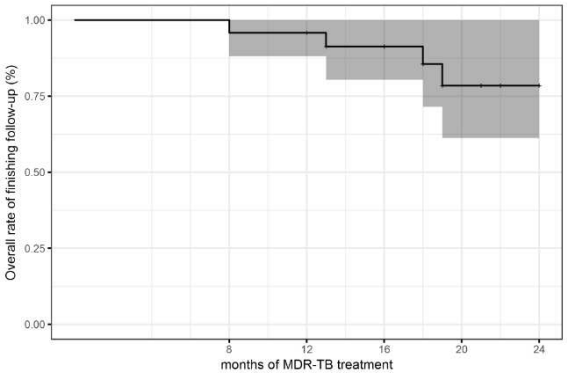
Cohort ix - Mexico (n=33)



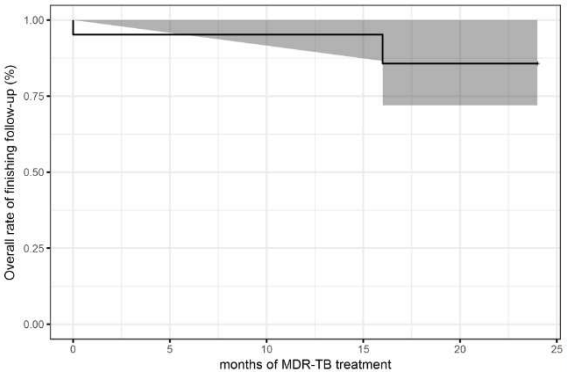
Cohort x – Argentina (n=100)



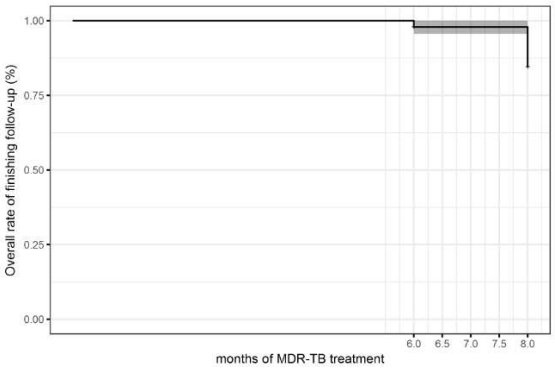
Cohort xi - UK (n=24)



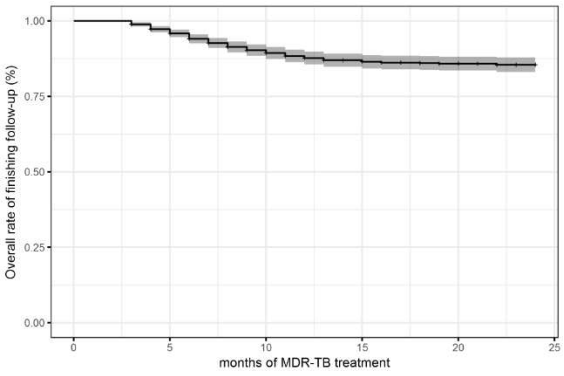
Cohort xii – Spain (n=21)



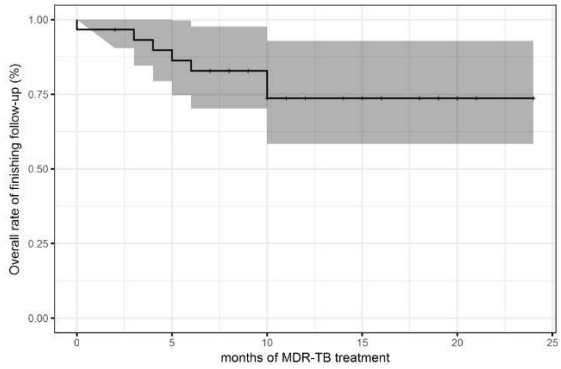
Cohort xiii – Vietnam (n=144)



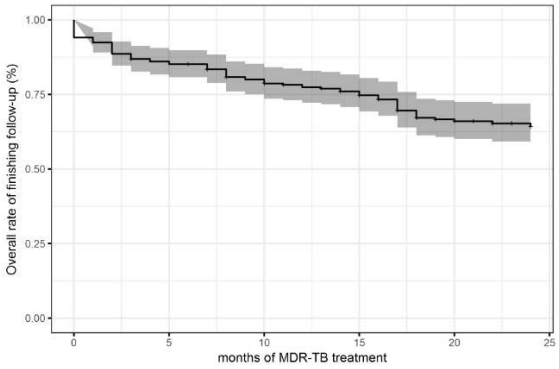
Cohort xiv – Latvia (n=949)



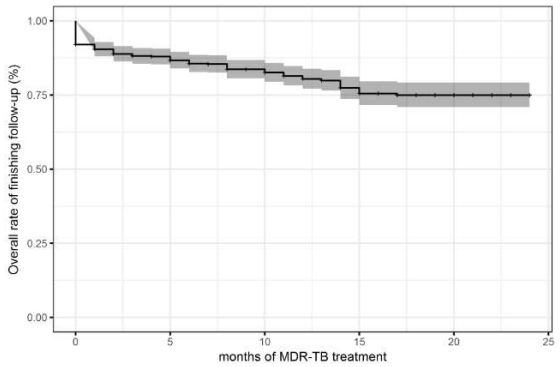
Cohort xv - France (n=30)



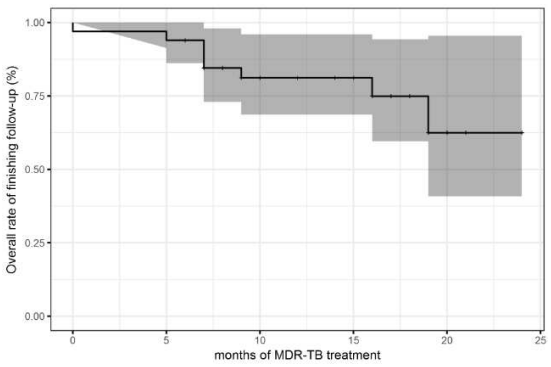
Cohort xvi – USA (n=236)



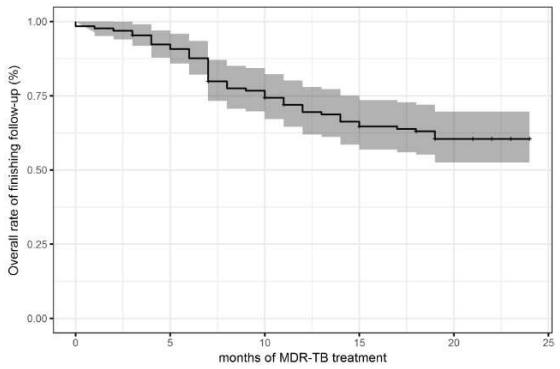
Cohort xvii - Russian Federation (n=577)



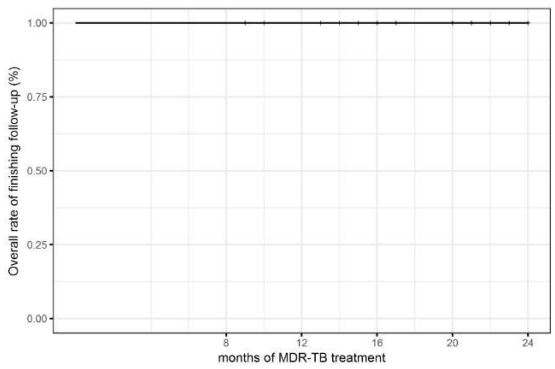
Cohort xviii – South Africa (n=33)



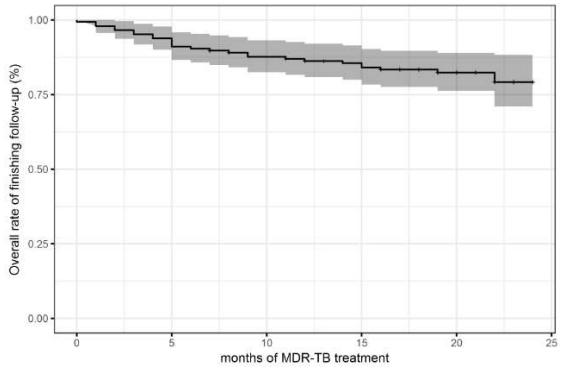
Cohort xix – South Korea (n=130)



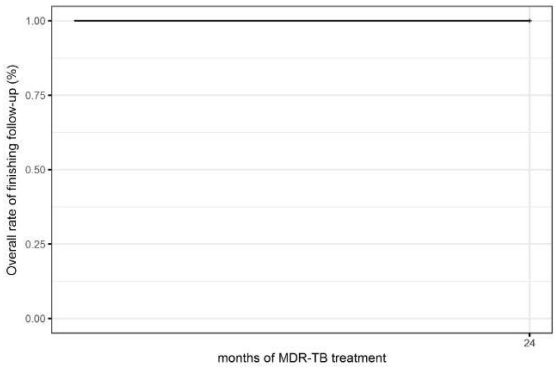
Cohort xx – Japan (n=59)



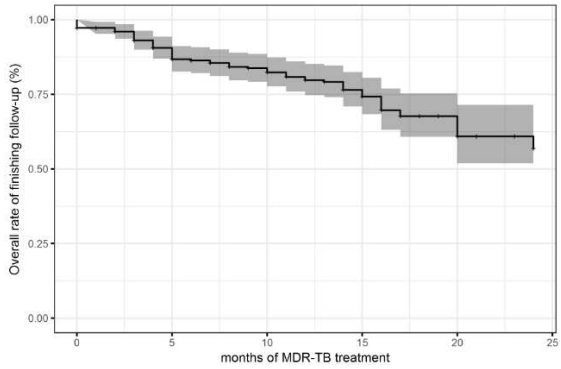
Cohort xxi – Philippines (n=146)



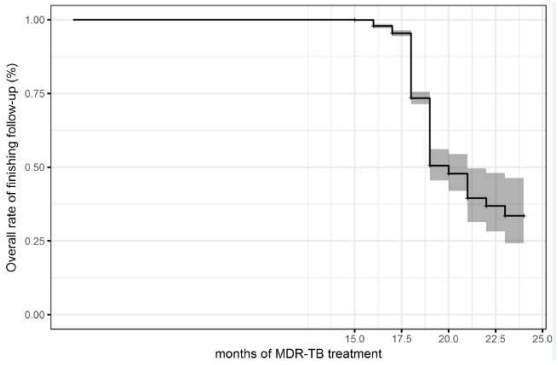
Cohort xxii – Iran (n=35)



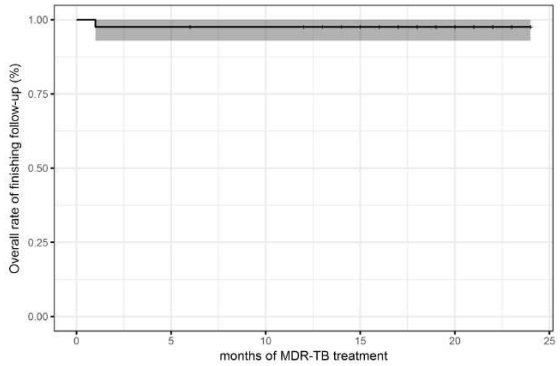
Cohort xxiii – Estonia (n=253)



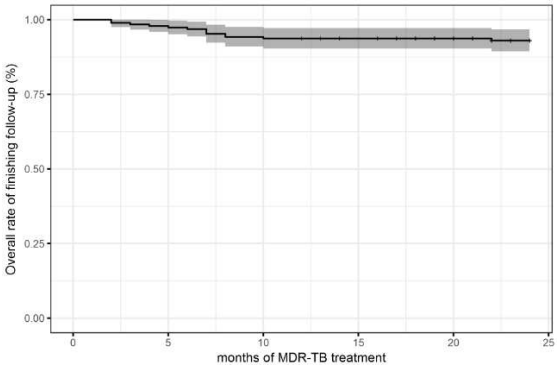
Cohort xxiv – South Africa (n=1,789)



Cohort xxv – The Netherlands (n=41)



Cohort xxvi – South Korea (n=191)



Cohort xxvii – Uzbekistan (n=67)