

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years retrospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040862
Article Type:	Original research
Date Submitted by the Author:	26-May-2020
Complete List of Authors:	Tola, Habteyes; Tehran University of Medical Sciences, Epidemiology and Biostatistics; Ethiopian Public Health Institute, TB/HIV Research Directorate Holakouie-Naieni, K; Tehran University of Medical Sciences, Epidemiology and Biostatistics Mansournia, Mohammad; Tehran University of Medical Sciences, Epidemiology and Biostatistics Yaseri , Mehdi ; Tehran University of Medical Sciences, Epidemiology and Biostatistics Gemtesa, Dinka; Ethiopian Public Health Institute Tesfaye , Ephrem ; Ethiopian Public Health Institute Mahamed , Zemedu ; Ethiopian Public Health Institute Sisay, Million ; Ethiopian Public Health Institute
Keywords:	Tuberculosis < INFECTIOUS DISEASES, EPIDEMIOLOGY, INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, INTERNAL MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years retrospective cohort study

Habteyes Hailu Tola^{1, 2}, Kourosh Holakouie-Naieni^{1*}, Mohammad Ali Mansournia¹, Mehdi Yaseri¹, Dinka Fikadu Gamtesa², Ephrem Tesfaye², Zemedu Mahamed², Million Molla Sisay³

¹Tehran University of Medical Sciences, School of Public Health, Department of Epidemiology and Biostatistics, Tehran, Iran

²Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa, Ethiopia

³Saint Peter's Specialized Hospital, Research and Evidence Generation Directorate, Addis Ababa, Ethiopia

Habteyes H. Tola (MSc, PhD)

-Tehran University of Medical Sciences, School of Public Health
Department of Epidemiology and Biostatistics, Tehran, Iran

-Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa, Ethiopia

Email: habetola@gmail.com

P.O. Box 1242

*** Corresponding author:**

Kourosh Holakouie-Naieni* (DVM, MSc, PhD)

Tehran University of Medical Sciences, School of Public Health
Department of Epidemiology and Biostatistics, Tehran, Iran

Phone: +98 21-88950185

Fax: +98 21-88950185

P.O. Box 1416753955

Email: holakoik@hotmail.com

Mohammad Ali Mansournia (MD, PhD)

Tehran University of Medical Sciences, School of Public Health
Department of Epidemiology and Biostatistics, Tehran, Iran

Email: mansournia_ma@yahoo.com

1
2
3 P. O. Box 1416753955
4

5 **Mehdi Yaseri** (MSc, PhD)
6

7 Tehran University of Medical Sciences School of Public Health

8 Department of Epidemiology and Biostatistics, Tehran, Iran

9 Email: myaseri@gmail.com
10
11

12
13 P. O. Box 1416753955
14

15 **Dinka Fikadu Gemtesa** (BSc, MPH)
16

17 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
18 Ethiopia
19

20 Email: ejeta430@gmail.com
21
22

23
24 P. O. Box 1242
25

26 **Ephrem Tesfaye** (BSc, MSc)
27

28 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
29 Ethiopia
30

31 Email: ephremt13@gmail.com
32
33

34
35 P. O. Box 1242
36

37 **Zemedu Mahamed** (BSc, MSc)
38

39 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
40 Ethiopia
41

42 Email: zemedu2003@gmail.com
43
44

45
46 P. O. Box 1242
47

48 **Million Molla Sisay** (MD, MSc)
49

50 Saint Peter's Specialized Hospital, Research and Evidence Generation Directorate, Addis Ababa,
51 Ethiopia
52

53 Email: milishagr8@gmail.com
54
55

56
57 P. O. Box 1242
58
59
60

Abstract

Objectives: Treatment success in patients treated for multidrug-resistant tuberculosis (MDR-TB) is low, but predictors of death and treatment failure have understudied. Thus, we aimed to estimate the national proportion of treatment outcomes in past 10 years and factors that predict duration from treatment initiation to death and treatment failure in MDR-TB patients in Ethiopia.

Setting: A retrospective cohort study with 10 years follow up period was conducted in 42 treatment centers in Ethiopia.

Participants: A total of 3,553 adult MDR-TB patients who had final treatment outcome and treated under nation TB programme were included. Data was collected from clinical charts, registration books and laboratory result reports. Competing risk survival analysis model with robust standard error was used to determine predictors of duration from treatment initiation to death and treatment failure.

Primary and secondary outcomes: Treatment outcome was a primary outcome while predictors of death and treatment failure were a secondary outcome.

Results: The proportion of treatment success was 75.7%, while death 12.8%, treatment failure 1.7% and lost to follow up 9.7%. Older age (Adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); $p < 0.001$), being HIV sero-reactive (AHR = 2.0; 95% CI (1.6–2.4); $p < 0.001$) and presence of any grade of anemia (AHR = 1.7; 95% CI (1.4–2.0); $p < 0.001$) were significantly predicted duration from treatment initiation to death. However, all variables included to multivariable model were not significantly associated with duration from treatment initiation to treatment failure.

Conclusion: In past ten years, MDR-TB treatment success in Ethiopia is well achieved. However, the proportion of patients who died is considerable. Death could be reduced through providing special attention to old age, HIV-infected and anemic patients. Further prospective cohort study is necessary to explore predictors of duration from treatment initiation to death and treatment failure.

Keywords: Tuberculosis, Multidrug resistance, Refampin resistance, Treatment outcome

Strengths and Limitations of this study

- ❖ National multidrug resistance tuberculosis (MDR-TB) treatment outcomes proportions in past ten years were estimated using MDR-TB treatment programme data.
- ❖ Although MDR-TB treatment outcome is low across the world, predictors of time to death and treatment failure have underreported.
- ❖ This study was determined the predictors of duration from treatment initiation to death and treatment failure using competing risk survival analysis model with robust standard error.
- ❖ Retrospective nature of the study design leads to key variables such as sociodemographic, behavioural, adverse drug reactions, key laboratory variables and treatment adherence status missing.

Background

The emergency of drug resistance tuberculosis (TB) has been undermining the global TB control programme and continues to cause severe morbidity and mortality among millions across the world. World health organization (WHO) estimated that nearly half a million rifampin-resistant new TB cases occurred in 2018 across the world.¹ The treatment of multidrug resistance (MDR) and extensively drug resistance (XDR) TB has been challenging the global TB control efforts due to difficulty related to diagnosis, long duration treatment, less effective and toxic drugs used for the treatment, and limitation they impose on the available treatment options.²⁻⁴ MDR-TB is defined as a *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin, whereas XDR-TB is refers to a *Mycobacterium tuberculosis* resistance at least to rifampin and isoniazid plus resistance to any fluoroquinolone and at least one of the three injectable anti-TB drugs (capreomycin, kanamycin or amikacin).⁵

The current MDR-TB treatment success rate (the sum of cured and treatment completed) is considerably low.^{1,3,6} The WHO recent global estimation indicates that only 56% of MDR-TB patients were successfully treated in 2018.¹ This indicates that nearly half of MDR-TB patients who were diagnosed and treated have succumbed unsuccessful treatment outcome which is the main obstacle to achieve WHO End TB treatment success target of $\geq 90\%$ at 2035.¹ According to more recent studies, the treatment success rate of MDR-TB is 54% in Russia⁶, 53.4% in Morocco⁷ and 60% in India.⁸ In contrast, a recent studies indicated that, relatively high treatment success rates in certain settings.⁹⁻¹² For example, 82.4% of MDR-TB patients treated successfully in Taiwan⁹, and 75.7% in Tanzania.¹⁰ Moreover, 78.8% of MDR-TB patients are successfully treated in Ethiopia¹¹, and 75.8% in Pakistan.¹² A review studies are also indicated that about 60%^{13,14} of MDR-TB patients treated successfully.

Heterogeneous and interrelated factors are associated with poor MDR-TB treatment outcome. Infection with Human immunodeficiency Virus (HIV)¹⁵⁻²¹, diabetes mellitus^{19,22,23}, malnutrition^{24,25}, anemia^{19,21,26} are co-morbidities that associated with poor treatment outcome in patients treated for MDR-TB. Moreover, treatment interruption^{21,27,28}, medication regimens²⁹, Antiretroviral therapy (ART) timing³⁰, time to MDR-TB treatment initiation after diagnosis³¹ and previous TB treatment history^{15,25,32} are treatment related factors that associated with poor treatment outcome in MDR-TB patients. Being smear positive at diagnosis^{15,25}, occurrence of XDR-TB^{12,18,25,32}, socioeconomic factors^{26,33}, presence of cavity on chest X-ray^{10,16,30} and lack of Directly Observed Therapy (DOT) programme³⁴ are also among factors that associated with poor treatment outcome in MDR-TB patients.

Ethiopia is among the 30 high TB and MDR-TB prevalent countries with an estimated TB incidence of 165 per 100,000 population in 2018.¹ Despite an improving TB control programme and treatment success rate, the burden of MDR-TB in Ethiopia remains high which accounts 2.2% in new and 21.1% in previously treated TB cases.³⁵ However, WHO recent estimate indicated that 0.71% of MDR-TB in new cases and 16% in previously treated cases were developed in 2018 in Ethiopia.¹ Although there is no national level report on MDR-TB treatment outcome, studies reported from local data indicated variable treatment success which ranges from 63%–78.8% in Ethiopia^{11,16,26}

Although evidence indicates low treatment success rate among MDR-TB patients, there is less information on the factors that predicting duration from treatment initiation to death and treatment failure in different setups. Beside evidence limitation, available studies are focused in the determination of predictors of unsuccessful treatment outcome which comprises the sum of death, treatment failure and lost to follow up in one category. Categorization of death, treatment

1
2
3 failure and lost to follow up in one category could cover the actual predictors of death and
4 treatment failure. To that extent, there is no study that reported the predictors of death and
5 treatment failure separately using robust standard competing risk survival analysis model.
6
7 Ethiopia is among the countries lack such evidence at national level to plan effective intervention
8 that could decrease death and treatment failure in MDR-TB patients. Thus, we aimed to estimate
9 the national level treatment outcome rate in past 10 years and factors that predict duration from
10 treatment initiation to death and treatment failure in MDR-TB patients in Ethiopia.
11
12
13
14
15
16
17
18

19 **Materials and methods**

20 **Study setting, population and design**

21
22 We conducted a retrospective cohort study on adult patients aged ≥ 15 years old, diagnosed
23 either biologically or clinically for both pulmonary and extra-pulmonary TB, and enrolled to
24 MDR-TB treatment at 42 treatment initiating centers (TICs) in Ethiopia from February 2009–
25 February 2019. MDR-TB treatment was started in February 2009 in one hospital in Addis
26 Ababa, Ethiopia.¹⁶ During this study period there were a total of 53 TICs and several treatment
27 follow up centers (TFCs) in the country. The majority of MDR-TB patients initiate their
28 treatments in TICs while stable patients follow the treatment under directly observed therapy
29 (DOT) programme in nearby TICs or TFCs as ambulatory outpatients. However, all information
30 on the patients registered for MDR-TB treatment has been documented at TICs where the patient
31 started the treatment. We included a total of 42 TICs to this study, due to the remaining 11 TICs
32 had no patients who completed their treatment during the study period.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Inclusion and exclusion criteria

We included all adult patients who were aged 15 years and older, diagnosed either bacteriologically or clinically for MDR-TB and enrolled to the treatment from February 2009. However, we excluded patients who had no final treatment outcome (transferred out or still on treatment or treatment outcome missed from data sources).

Laboratory test

All laboratory tests were performed according to WHO and national TB programme recommendations in quality assurance TB laboratories.^{36,37} Culture tests were carried out with solid (Löwenstein-Jensen (LJ)) and a fluorometric BACTEC MGIT960 at one national TB reference laboratory and nine regional laboratories. In addition, Xpert MTB/RIF assay is a rapid, sensitive and specific technique that has been widely using to detect *M. tuberculosis* and rifampin resistant at each level in the national health system. Drug susceptibility test (DST) for first-line drugs was performed by indirect proportional method based on WHO recommended critical concentrations, for rifampicin (1.0 µg/ml), isoniazid (0.1 µg/ml), streptomycin (1.0 µg/ml), ethambutol (5µg/ml) and pyrazinamide (100 µg/ml). DST for second-line has been recently started in the country and rarely performed. Data on second-line DST not included to this study because very few DST results for SLDs obtained in the records. Quality assurance for DST was regularly performed by Milan WHO's Supranational Reference Laboratory in Rome, Italy.

Treatment

Previously, all MDR-TB patients were treated as inpatient model of care for the first few months at treatment centers until the patient become clinically stable and *M. tuberculosis* culture conversion. However, according to the recent edition of national TB treatment guideline, all

1
2
3 patients with MDR-TB need to be treated under clinic-based ambulatory model of care, unless
4
5 the patient unstable or developed sever adverse drug reaction during the course of treatment.
6
7 Patients either with serious medical or social conditions could be admitted with the decision of
8
9 the treatment panel. Standardized long treatment regimens were used to treat MDR-TB patients
10
11 in Ethiopia. The long treatment regimen contained at least four oral drugs which used daily
12
13 during full course of treatment and one injectable drug until *M. tuberculosis* culture conversion.
14
15 Treatment with injectable drugs continues at least for eight months based on clinical,
16
17 microbiological and radiographic examination results. The minimum treatment duration was 20
18
19 months for long regimen which is at least 18 months after bacteriological conversion, whereas
20
21 nine to 11 months for short treatment regimen.³⁷ All patients included to this study were on long
22
23 treatment regimens. Laboratory tests, chest X-ray and clinical investigations are used to monitor
24
25 response to the treatment and to identify treatment related complications in patients on MDR-TB
26
27 treatment in Ethiopia. Clinical investigations only are used to monitor response to the treatment,
28
29 while laboratory tests are used to identify treatment related complications for extra-pulmonary
30
31 TB patients. MDR-TB treatment is free of any const in Ethiopia and there is full access to all
32
33 categories of drugs to treat MDR-TB patients.
34
35
36
37
38
39

40 **Data collection**

41
42 We collected data on socio-demographic variables such as sex, age and regional state. We also
43
44 collected TB related data such as anatomical site of TB (pulmonary vs extra pulmonary), drug
45
46 resistance type (RR vs MDR), previous treatment (new vs previously treated), diagnosis method
47
48 (bacteriologically vs clinically), HIV sero-status (reactive vs non-reactive) and Antiretroviral
49
50 Therapy (ART) status (on ART vs not applicable vs not on ART). In addition, we collected
51
52 information on bacteriological status (smear, Xpert MTB/RIF, culture or first-line drugs DST
53
54
55
56
57
58
59
60

1
2
3 results) at treatment initiation. All data were extracted from patients' clinical charts, registration
4 books and laboratory result reports. Data were collected by health professionals familiar with
5 MDR-TB treatment after two days practical training on data collection tool.
6
7
8
9

10 **Definitions**

11
12
13 In this study, we used standard WHO and national treatment guidelines definitions for laboratory
14 confirmations, patient categories and treatment outcomes.^{36,37} Clinically diagnosed MDR-TB
15 refers to those cases with no documented drug susceptibility test (DST) results but treated
16 empirically with a course of treatment including SLDs based on clinical criteria and contact
17 history.³⁷ However, bacteriologically confirmed MDR-TB refers to those cases with documented
18 DST results. All patients were categorized into new patients (never treated for TB or has treated
19 for less than one month) and patients previously treated for tuberculosis. The final treatment
20 outcomes of MDR-TB were cured, treatment completed, death, treatment failed and lost to
21 follow up. Cured is refers to a patient initially bacteriologically confirmed and completed the
22 treatment without the evidence of treatment failure and three or more consecutive cultures taken
23 at least 30 days apart are negative after the intensive phase. Treatment completed is defined as a
24 patient who completed the treatment without the evidence of treatment failure but there is no
25 record that indicates three or more consecutive cultures taken at least 30 days apart are negative
26 after the intensive phase. A patient whose treatment is terminated or need for permanent regimen
27 change of at least two anti-TB drugs is categorized as treatment failure. Lost to follow up is also
28 refers to a patient whose treatment is interrupted for two consecutive months or more. Successful
29 treatment outcome was the sum of cured and treatment completed, whereas unsuccessful was the
30 combination of death, treatment failed and lost to follow up.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Data analysis

We entered data into CPro software version 6.1 and analyzed by STATA version 14 (StataCorp, College Station, TX, USA). The data were confirmed from each data source and cleaned for errors before main analysis. We described participants' demographic and clinical characteristics using descriptive statistics. The proportions of MDR-TB treatment outcomes were frequency weighed by the total number of patients registered from February 30, 2009–February 30, 2019 in each TIC.

We used a competing risk survival analysis model with robust standard error to assess the effects of different variables on the duration from treatment initiation to death and treatment failure. Effect levels were reported by Hazard Ratio (HR) with 95% Confidence Intervals (CIs). We included variables scored p-values less than or equal to 0.2 during Univariate analysis and clinically or epidemiologically relevant. We considered death as failure event to estimate the effects of different variables on duration from treatment initiation to death, while treatment failure and success considered as competing risks. Similarly, we considered treatment failure as failure event to estimate the effects of different variables on the duration from treatment enrolment to treatment failure, whereas death and treatment success considered as competing risks. Lost to follow up was considered as censored across the fitted models. Level of significance was set at 5% for all analysis.

Patient and public involvement: Both patient and public were not involved in this study.

Results

Participants' characteristics

A total of 4,419 patients were enrolled to MDR-TB treatment in 42 of 53 (79.2%) treatment initiating centers (TICs) in Ethiopia from February, 2009 to February, 2019 [Fig 1]. Of 4,419

patients, 3,395 (76.8%) were fulfilled our inclusion criteria and enrolled to this study analysis [Fig 1].

The highest proportion of patients was enrolled into the treatment in 2015 (667 patients), while the lowest number of patients registered in 2019 (only 4 patients) [Fig 2].

Of 3,395 patients included to this study analysis 1,870 (55.1%) were male, and the mean age was 31.6 (SD \pm 11.7) years with the age range of 15 to 85 years. Seventy two percent of the patients were in the age category of 15 to 35 years [Table 1]. More than 50% of the patients were infected with TB bacilli resistant to rifampin (isonizid susceptibility status unknown), and 3,171 (93.4%) were pulmonary TB patients [Table 1]. Eighty six percent of patients had previous TB treatment history and drug resistance status of 3,242 (95.5) isolates were bacteriologically confirmed at treatment enrolment [Table 1]. The main drug resistant diagnosis method was GeneXpert MTB/RIF (57.9%) and 1,421 (41.9%) patients had previous exposure to second line drugs [Table 1]. Of the 3,395 patients, 767 (22.6%) were HIV infected [Table 1], and of 767 patients whose HIV sero-status were known, 686 (89.4%) were on ART. Only 6.0% of the patients had previous MDR-TB patient contact history and 1,831 (53.9%) of patients were hospitalized at the treatment initiation [Table 1]. Of the patients who were hospitalized at the treatment initiation the mean duration of hospitalization was 81.7 (\pm 47.4) days.

Table 1: Demographic and clinical characteristics of the patients (n = 3,395)

Variable		n (%)
Sex	Male	1,870 (55.1)
	Female	1,525 (44.9)
Age (in year)	15–25	1,268 (37.3)
	26–35	1,186 (34.9)
	36–45	529 (15.6)
	\geq 46	412 (12.1)
Drug resistance type	RR/INH status unknown	1,810 (53.3)
	MDR-TB	1,585 (46.7)
Anatomical site of TB	Pulmonary	3,171 (93.4)
	Extra pulmonary	224 (6.6)
Previous TB treatment	New	462 (13.6)

	Previously treated	2,933 (86.4)
Previous exposure to SLDs	Yes	1,421 (41.9)
	No	1,842 (54.3)
	Unknown	132 (3.9)
Drug resistance identification method	GeneXpert MTB/RIF	1,967 (57.9)
	Culture/LPA	1,275 (37.6)
	Clinical	153 (4.5)
Diagnosis method	Bacteriological	3,242 (95.5)
	Clinical	153 (4.5)
HIV sero-status	Non-reactive	2,554 (75.2)
	Sero-reactive	767 (22.6)
	Unknown	74 (2.2)
ART status	Not applicable	2,556 (75.3)
	On ART	686 (20.2)
	HIV sero-status known but, ART status unknown	79 (2.3)
	Both ART and HIV sero- statuses unknown	74 (2.2)
MDR-TB patient contact history	Yes	204 (6.0)
	No	1,511 (44.5)
	Unknown	1,680 (49.5)
Hospitalization history at treatment initiation	Hospitalized	1,831 (53.9)
	Not hospitalized	487 (14.3)
	Unknown	1,077 (31.7)
Treatment interruption	Never interrupted/interruption status unknown	3,192 (94.0)
	At least one day interrupted	203 (6.0)

TB-tuberculosis, ART-Antiretroviral therapy, SLDs-Second line drugs, HIV-Human immunodeficiency virus, MDR-Multidrug resistant, LPA-Line probe Assay

Table 2 depicts the sociodemographic and clinical characteristics distribution of treatment outcome categories. Of 1,810 patients whose isolates were resistant to rifampin, 1,052 (58.1%) were cured, 251 (13.9%) died and the treatment of 42 (2.3) patients were failed. Of patients whose isolates were resistant to rifampin and isoniazid (MDR-TB), 793 (50.0%) cured, while 180 (11.4%) died and the treatment of 24 (1.5) patients were failed. Treatment failure was five times higher in the patients who had previous TB treatment history (21.7%), than those who never treated (2.2%). Mortality was two times higher in the patients who were HIV sero-reactive (21.3%), than those who HIV non-reactive (10.2%).

Table 2: Demographic and clinical characteristics distribution of treatment outcome

Variables		Treatment outcome n (%)					P-value
		Cured	Completed	Failed	Death	LTFU	
Sex	Male	1,006 (53.8)	376 (20.1)	40 (2.1)	245 (13.1)	203 (10.9)	0.071
	Female	839 (55.0)	344 (22.6)	26 (1.7)	186 (12.2)	130 (8.5)	
Resistance type	RR/INH status	1,052 (58.1)	274 (15.1)	42 (2.3)	251 (13.9)	191 (10.6)	

	unknown						
	MDR	793 (50.0)	446 (28.1)	24 (1.5)	180 (11.4)	142 (9.0)	< 0.001
Anatomical site	EPTB	50 (22.3)	125 (55.8)	4 (1.8)	20 (8.9)	25 (11.2)	
	PTB	1,795 (56.6)	595 (18.8)	62 (2.0)	411 (13.0)	308 (9.7)	< 0.001
Previous TB treatment	New	243 (52.6)	83 (18.0)	10 (2.2)	75 (16.2)	51 (11.0)	
	Previously treated	1,602 (54.6)	637 (21.7)	56 (21.7)	356 (12.1)	282 (9.6)	0.057
Diagnosis method	Bacteriological	1,771 (54.6)	686 (21.2)	64 (2.0)	409 (12.6)	313 (9.7)	
	Clinical	74 (48.7)	34 (22.4)	2 (1.3)	22 (14.5)	20 (13.2)	0.466
HIV-sero-status	Non-reactive	1,429 (56.0)	561 (22.0)	48 (1.9)	261 (10.2)	255 (10.0)	
	Reactive	378 (49.3)	141 (18.4)	17 (2.2)	163 (21.3)	68 (8.9)	< 0.001
Anemia	None anemic	880 (55.0)	380 (23.8)	29 (1.8)	150 (9.4)	161 (10.1)	
	Any grade of anemia present	965 (53.8)	340 (18.9)	37 (2.1)	281 (15.7)	172 (9.6)	< 0.001

Treatment outcome

Of 3,395 patients included to this study 1,845 (40.0%) were cured, 720 (35.7%) were completed the treatment, 431 (12.8%) died, 333 (9.7%) lost to follow up and the treatment of 66 (1.7%) patients were failed [Fig 3]. The overall treatment success (cured plus treatment completed) was 2,565 (75.7%), whereas the overall unsuccessful treatment outcome (the sum of lost to follow up, treatment failed and death) was 830 (24.3%).

Predictors of duration from treatment initiation to death and treatment failed

Univariate analysis

The proportions of failure events were: death 431 (12.8%), treatment failure 66 (1.7%) and treatment success 2,565 (75.7%). The proportion of censored as a result of lost to follow up was 333 (9.7%). In the Univariate competing risk survival analysis model old age (*Unadjusted hazard ratio (UHR) = 1.03; 95% CI (1.04–1.05); p < 0.001*), had rifampin resistant bacilli (*UHR = 1.3; 95% CI (1.03–1.5); p = 0.022*), HIV sero-reactive (*UHR = 2.2; 95% CI (1.8–2.7); p < 0.001*) and presence of any grade of anemia (*UHR = 1.7; 95% CI (1.4–2.1); p < 0.001*) were significantly decreased duration from treatment initiation to death [Table 3]. Having previous TB treatment history (*UHR = 0.71; 95% CI (0.56–0.92); p = 0.009*) was significantly increased duration from treatment starting to death [Table 3]. However, none of variables assessed were

shown significant association with duration from treatment initiation to treatment failure [Table 3].

Table 3: Predictors of duration from treatment initiation to death and treatment failure in patients treated for MDR-TB in Ethiopia, 2009-2019 (Unavailable model)

Variable	Death		Treatment failure		
	UHR (95%CI)	P-value	UHR(95% CI)	P-value	
Sex	Female	1.00	1.00		
	Male	1.1 (0.89–1.3)	0.436	1.3 (0.78–2.1)	0.335
Age (year)		1.03 (1.04–1.05)	< 0.001	0.98 (0.96–1.0)	0.122
Anatomical sit	Extra-pulmonary	1.00		1.00	
	Pulmonary	1.5 (0.94–2.3)	0.094	1.1 (0.40–3.0)	
Drug resistance type	MDR	1.00		1.00	
	RR/INH status unknown	1.3 (1.03–1.5)	0.022	1.6 (0.95–2.6)	0.080
Previous treatment	New	1.00		1.00	
	Previously treated	0.71 (0.56–0.92)	0.009	0.86 (0.44–1.7)	0.668
Diagnosis method	Bacteriological	1.00		1.00	
	Clinical	1.2 (0.76–1.8)	0.468	0.68 (0.17–2.8)	0.589
HIV sero-status	Non-reactive	1.00		1.00	
	Reactive	2.2 (1.8–2.7)	< 0.001	1.2 (0.68–2.1)	0.548
Anemia status	Absent	1.00		1.00	
	Any grade of anemia present	1.7 (1.4–2.1)	< 0.001	1.1 (0.70–1.9)	0.592

TB-tuberculosis, HIV-Human immunodeficiency virus, UHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Multivariable analysis

In multivariable analysis older age (*Adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); p < 0.001*), being HIV sero-reactive (*AHR = 2.0; 95% CI (1.6–2.4); p < 0.001*) and presence of any grade anemia (*AHR = 1.7; 95% CI (1.4–2.0); p < 0.001*) were able to significantly decrease duration from treatment initiation to death [Table 4]. All variables included into multivariable competing risk survival analysis model were not significantly predicted duration from treatment initiation to treatment failure [Table 4].

Table 4: Predictors of duration from treatment initiation to death and treatment failure in patients treated for MDR-TB in Ethiopia, 2009-2019 (Multivariate model)

Variable	Death		Treatment failure		
	AHR (95%CI)	P-value	AHR(95% CI)	P-value	
Sex	Female	1.00	1.00		
	Male	0.92 (0.75–1.1)	0.397	1.3 (0.82–2.2)	0.248
Age (year)		1.04 (1.03–1.05)	< 0.001	0.98 (0.96–1.0)	0.077
Anatomical sit	Extra-pulmonary TB	1.00		1.00	
	Pulmonary TB	1.4 (0.91–2.2)	0.126	1.1 (0.39–3.0)	0.878

Drug resistance type	MDR	1.00		1.00	
	RR/INH status unknown	1.2 (0.98–1.5)	0.083	1.7 (0.98–2.8)	0.060
Previous treatment	New	1.00		1.00	
	Previously treated	0.79 (0.61–1.0)	0.083	0.98 (0.49–1.9)	0.947
HIV sero-status	Non-reactive	1.00		1.00	
	Reactive	2.0 (1.6–2.4)	< 0.001	1.3 (0.72–2.2)	0.425
Anemia status	Absent	1.00		1.00	
	Anemia present	1.7 (1.4–2.0)	< 0.001	1.1 (0.66–1.8)	0.767

TB-tuberculosis, HIV-Human immunodeficiency virus, AHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Drug resistance status at treatment initiation

Drug susceptibility testing was done for four first-line drugs such as rifampin, isonized, ethambutol and streptomycin [Table 5]. Rifampin susceptibility test was performed on isolates of all patients included to this study, and 99.3% of isolates were demonstrated resistance to the therapy [Table 5].

Table 5: Anti-tuberculosis drug susceptibility test results

Anti-tuberculosis drug	Susceptibility test results	n (%)
Rifampicin	Resistant	3,371 (99.3)
	Susceptible	24 (0.7)
Isonized (n = 1,313)	Resistant	1,241 (94.5)
	Susceptible	72 (5.5)
Ethambutol (n = 427)	Resistant	299 (70.0)
	Susceptible	128 (30.0)
Streptomycin (n = 443)	Resistant	337 (76.1)
	Susceptible	106 (23.9)

Discussion

The current study aimed to determine the proportion of national treatment outcomes and predictors of duration from treatment initiation to death and treatment failure in patients treated for MDR-TB in Ethiopia in past ten years. It was indicated that 75.7% of MDR-TB patients were successfully treated, whereas 12.8% died, 9.7% lost to follow up and the treatment of 1.7% patients were failed. The proportion of the patients registered for MDR-TB treatment was shown increasing trend from 2009 and the maximum proportion (19.6%) was registered in 2015. However, the proportion of the patients registered for the treatment was decreased after 2015 and the minimum patients were registered in 2019. Old age, being HIV sero-reactive and presence of any grade of anemia were significantly predicted duration from treatment initiation to death in patients treated for MDR-TB in present study. However, none of variables included to multivariable model was significantly predicted duration from treatment initiation to treatment failure.

The present study findings indicated that the proportion of treatment enrolment after 2015 was decreased and the lowest cases were recorded in 2019. This might be due to the burden of MDR-TB is decreasing in the country or case registration related problems as the result of treatment centers decentralization to the periphery. Moreover, the decreasing trend in patients enrolment into the treatment after 2015 could be due to the patients included to this study were those who had final treatment outcome results. Thus, this analysis is missed the patients who were registered in 2018 and 2019, but still on treatment during data collection period.

In the current study, treatment success proportion in MDR-TB patients who received a standardized long regimen was higher than the treatment success rate previously reported from other settings including from Ethiopia.^{7,26,27} For instance, a study reported from Morocco

1
2
3 indicated that only 53.4% of MDR-TB patients treated successfully.⁷ In addition, a study
4 reported from Armenia shows that less than 50% of MDR-TB patients are successfully treated.²⁷
5
6 A recent review study that pooled data from different settings have also shown lower treatment
7 success than our finding.¹³ These differences most likely due to the differences in quality of TB
8 control programme, sample size, severity of the disease at diagnosis, TB/HIV co-infection
9 burden and treatment regimens. A previous study conducted in Ethiopia in two treatment
10 initiation centers¹⁶ reported similar treatment success proportion with our finding (78.6% Vs
11 75.6%).
12
13
14
15
16
17
18
19
20

21 The proportion of death in the current study was considerable and it was similar with previously
22 reported findings.^{16,26} In contrast, the proportion of patients who died in our study was more than
23 double to the mortality proportion reported from Morocco (5% vs 12.7%).⁷ This difference is
24 most probably due to difference in the study period, quality of care and case registration,
25 treatment regimens, severity of the disease during treatment initiation and nutritional status of the
26 patients.
27
28
29
30
31
32
33
34

35 It is well documented that incidence and mortality is higher in TB patients in older age group.³⁸
36 Thus, particular attention has to be given to old patients to avert mortality related to TB. Our
37 study finding confirms that older age significantly associated with the duration from treatment
38 initiation to death. This is in line with the results from previous studies^{39,40} in which older age
39 significantly associated with death in MDR-TB patients. In contrast to current study, previous
40 study shown that younger age is significantly associated with poor treatment outcome than older
41 age.⁸ This difference most probably happens due to the age variation in the included patients and
42 the difference in the severity of the disease at treatment initiation.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 In the current study, as in several previous studies^{8,15,16,26,35}, HIV sero-reactive was significantly
4 associated with time from treatment initiation to death. Despite proportion of patients who were
5 not on antiretroviral therapy (ART) were low (of HIV sero-reactive patients only 4.5 %), the
6 hazard of death was 2.0 times higher in the patients HIV sero-reactive than non-reactive.
7
8 However, previous study indicated that a combined anti-TB and anti-HIV treatment has been
9 proven to improve treatment success in co-infected patients.⁴¹ The possible explanation on the
10 significant effect of HIV sero-reactivity on mortality in patients on MDR-TB treatment could be
11 due to low CD4 count, high viral load and severity of the disease at treatment initiation. Since
12 data on CD4 count, HIV viral load level and disease severity status at enrolment were not
13 registered in our data sources, we could not assess their effects on MDR-TB treatment outcome.

14
15
16
17
18
19
20
21
22
23
24
25
26 In the present study the presence of any grade of anemia was significantly associated with the
27 duration from treatment initiation to death. The current result was similar with the previous study
28 reported from Ethiopia in which the hazard of poor treatment outcome was 4.2 times higher in
29 the patients had any grade of anemia at treatment initiation than those who were non-anemic.
30
31 The presence of anemia at the treatment initiation might be due to parasitic infection and some
32 other chronic diseases. This finding tried to attract attention to the importance of hemoglobin
33 monitoring in MDR-TB patients on treatment to increase treatment success and decrease
34 mortality.
35
36
37
38
39
40
41
42
43

44
45 In the present study none of variables included to the models were significantly associated with
46 duration from treatment initiation to treatment failure. The absence of significant association
47 between the variables and duration from the treatment initiation to treatment failure could be due
48 to the number of failure event (treatment failure) was very smaller than the competing risks
49 (death and treatment success).
50
51
52
53
54
55
56
57
58
59
60

1
2
3 The main limitation of this study was the retrospective nature of the study design. Data on
4 sociodemographic, behavioural, adverse drug reactions, key laboratory variables and treatment
5 adherence status were missing for majorities of the patients, and these variables were excluded
6 from the analysis. These limited us to explore further the predictors of duration from treatment
7 initiation to death and treatment failure. Thus, the predictors of duration from treatment initiation
8 to death may not be limited to the factors presented in this study. Moreover, lack of important
9 variables could have resulted in an underestimation/overestimation of the effects of different
10 variables in the model on the duration from treatment initiation to death and treatment failure.
11 Prospective study that could capture all potential variables is important to determine predictors
12 of duration from treatment initiation to death and treatment failure.
13
14
15
16
17
18
19
20
21
22
23
24
25

26 The findings of the present study have shown clear message for TB control programme efforts.
27 Although treatment success rate is well achieved, mortality in the current study is considerable to
28 be addressed by TB programme. Old age is one of the main predictors of death in MDR-TB
29 patients on treatment. Thus, early diagnosis and commencement of treatment in old patients
30 could increase cure rate. HIV sero-reactive is also one of strong predictors of duration from
31 treatment initiation to death in MDR-TB patients. Taking in consideration the sero-status of
32 MDR-TB patients and immediate commencement of anti-TB treatment together with ART is the
33 mechanism to improve treatment success in MDR-TB patients who co-infected with HIV.
34 Moreover, our result indicates that special attention should be paid to patients who have anemia
35 at treatment initiation in order to improve their treatment outcome. Strengthen and standardizing
36 of information registration on MDR-TB treatment is crucial to facilitate further data analysis
37 which is important to monitor the status of treatment outcome.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Conclusion

In past ten years, MDR-TB treatment success in Ethiopia is well achieved. However, the proportion of patients who died is considerable, and it could be reduced through providing special attention to old, HIV-infected and anemic patients. Further prospective cohort study is required to explore predictors of duration from treatment initiation to death and treatment failure.

Acknowledgement

We would like to acknowledge Tehran University of Medical Sciences (TUMS) and Ethiopian Public Health Institute for funding this study. We also thank Ethiopian Public Health Institute, National Tuberculosis Laboratory and all DR-TB treatment centers staff members for their cooperation during data collection process. We would also like to acknowledge all patients whose data were used in this study.

Author contributions: HHT and KH conceived and designed the study; HHT, DFG, ET and ZM collected data; HHT, MAM and MY analyzed and interpreted the data; HHT drafted the manuscript. All authors have critically reviewed and approved the manuscript for submission.

Funding: This work was supported by Tehran University of Medical Sciences and Ethiopian Public Health Institute.

Competing interests: None declared.

Ethics consideration: This study was approved by the research Ethics Review Board of Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1396.4287), Ethiopian Public Health Institute (EPHI-IRB-065-2017), St. Peter's Specialized Hospital (V81622018) and Armourer Hansen Research Institute (PO13/18). We also obtained a waiver of informed consent from each

1
2
3 review board. To maintain confidentiality sensitive information that could identify participants
4
5 was not reported in this study.
6
7

8 **Data availability statement:** Data used in this study is available in the corresponding authors
9
10 and can be accessed on reasonable request.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

References

1. WHO. Global tuberculosis report 2019. Geneva, Switzerland; 2019 p. 1–297.
2. Gunther G, Lange C, Alexandru S, Altet N. Treatment Outcomes in Multidrug-Resistant Tuberculosis. *N Engl J Med*. 2016;375(11).
3. Lange C, Abubakar I, Alffenaar JC, Bothamley G, Caminero JA, Carvalho ACC, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. *Eur Respir J*. 2014;44:23–63.
4. Pontali E, Visca D, Centis R, Ambrosio LD, Spanevello A, Battista G. Multi and extensively drug-resistant pulmonary tuberculosis : advances in diagnosis and management. *Curr Opin Pulm Med*. 2018;24:244–52.
5. Curry International Tuberculosis Center, and California Department of Public Health. Drug-resistant tuberculosis: A survival guideline for clinicians. 3rd Ed. 2016 p. 1-324.
6. Yunusbaeva M, Borodina L, Alekseev P, Davydov R, Yunusbaev U, Sharipov R, et al. Treatment efficacy of drug-resistant tuberculosis in Bashkortostan, Russia : A retrospective cohort study. *Int J Infect Dis*. 2019;81(2019):203–9.
7. Hamdouni M, Bourkadi JE, Benamor J, Hassar M, Cherrah Y. Treatment outcomes of drug resistant tuberculosis patients in Morocco: multi- centric prospective study. *BMC Infect Dis*. 2019;19:316.
8. Nair D, Velayutham B, Kannan T, Tripathy J, Harries A, Natrajan M, et al. Predictors of unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India. *Public Heal Action*. 2017;7(1):32–8.
9. Yu M, Chiang C, Lee J, Chien S, Lin C, Lee S, et al. Treatment Outcomes of Multidrug-Resistant Tuberculosis in Taiwan: Tackling Loss to Follow-up. *Clin Infect Dis*. 2018;67(2):202–2010.
10. Lever TH, Lekule I, Mollel E, Lyamuya F, Kilonzo K. Predictors of Treatment Outcomes among Multidrug Resistant Tuberculosis Patients in Tanzania. *Tuberc Reserch Treat*. 2019;2019:1–10.
11. Woldeyohannes D, Assefa T, Aman R, Tekalegn Y. Predictors of time to unfavorable treatment outcomes among patients with multidrug resistant tuberculosis in Oromia region. *PLoS One*. 2019;14(10):e0224025.

12. Javaid A, Ullah I, Masud H, Basit A, Ahmad W, Butt ZA, et al. Predictors of poor treatment outcomes in multidrug-resistant tuberculosis patients: a retrospective cohort study. *Clin Microbiol Infect.* 2017;2017.
13. Bastos ML, Lan Z, Menzies D. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis. *Eur Respir J.* 2017;49:1600803.
14. The Collaborative Group for the Meta-analysis of Individual Patient Data in MDR-TB treatment–2017, Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JW, Anderson LF, et al. Articles Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data. *Lancet.* 2018;392:821–34.
15. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. *Eur Respir J.* 2009;33:1085–94.
16. Meressa D, Hurtado RM, Andrews JR, Diro E, Abato K, Daniel T, et al. Achieving high treatment success for multidrug-resistant TB in Africa : initiation and scale-up of MDR TB care in Ethiopia—an observational cohort study. *Thorax.* 2015;70:1181–8.
17. Oliveira O, Gaio R, Villar M, Duarte R. Predictors of treatment outcome in multidrug-resistant tuberculosis in. *Eur Respir J.* 2013;42:1747–9.
18. Aibana O, Bachmaha M, Krasiuk V, Rybak N, Flanigan TP, Petrenko V, et al. Risk factors for poor multidrug-resistant tuberculosis treatment outcomes in Kyiv Oblast, Ukraine. *BMC Infect Dis.* 2017;17(2017):129.
19. Ketema DB, Muchie KF, Andargie AA. Time to poor treatment outcome and its predictors among drug-resistant tuberculosis patients on second-line anti-tuberculosis treatment in Amhara region, Ethiopia : retrospective cohort study. *BMC Public Health.* 2019;19(2019):1481.
20. Samuels JP, Sood A, Campbell JR, Khan FA, Johnston JC. Comorbidities and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis. *Sci Rep.* 2018;8(2018):4980.
21. Tola HH, Holakouie-na K, Mansournia MA. Intermittent treatment interruption and its effect on multidrug resistant tuberculosis treatment outcome in Ethiopia. *Sci Rep.* 2019: 9:20030.
22. Kang Y, Kim S, Jo K, Kim H, Park S, Kim T, et al. Impact of Diabetes on Treatment Outcomes and Long-Term Survival in Multidrug-Resistant Tuberculosis. *Respiration.* 2013;86:472–8.

23. Dooley KE, Tang T, Golub JE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. *AM J Trop Med Hyg.* 2009;80(4):634–9.
24. Samuel B, Volkmann T, Cornelius S, Mukhopadhyay S, Mitra K, Kumar AMV, et al. Relationship between Nutritional Support and Tuberculosis Treatment Outcomes in West Bengal, India. *J Tuberc Res.* 2016;4(4):213–9.
25. Milanov V, Falzon D, Zamfirova M, Varleva T, Bachiyska E, Koleva A, et al. Factors associated with treatment success and death in cases with multidrug-resistant tuberculosis in Bulgaria , 2009–2010. *Int J Mycobacteriology.* 2015;4(2):131–7.
26. Alene KA, Viney K, McBryde ES, Tsegaye AT, Clements ACA. Treatment outcomes in patients with multidrug-resistant tuberculosis in north-west Ethiopia. *Trop Med Int Heal.* 2017;22(3):351–62.
27. Bastard M, Sanchez-padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, et al. Effects of treatment interruption patterns on treatment success among patients with multidrug-resistant tuberculosis in Armenia and Abkhazia. *J Infect Dis.* 2015;211:1607–16.
28. Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. *PLoS One.* 2013;8(7):e70064.
29. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. 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.
30. Umanah T, Ncayiyana J, Padanilam X, Nyasulu PS. Treatment outcomes in multidrug resistant tuberculosis-human immunodeficiency virus Co-infected patients on anti-retroviral therapy at Sizwe Tropical Disease Hospital Johannesburg, South Africa. *BMC Infect Dis.* 2015;15:478.
31. Chen Y, Yuan Z, Shen X, Wu J, Wu Z. Time to Multidrug-Resistant Tuberculosis Treatment Initiation in Association with Treatment Outcomes in Shanghai, China. *Antimicrob Agents Chemother.* 2018;62:e02259–17.
32. Tang S, Tan S, Yao L, Li F, Li L, Guo X, et al. Risk Factors for Poor Treatment Outcomes in Patients with MDR-TB and XDR-TB in China : Retrospective Multi-Center Investigation. *PLoS One.* 2013;8(12):e82943.

- 1
2
3 33. Patel SV, Nimavat KB, Alpesh PB, Shukla LK, Shringarpure KS, Mehta KG, et al.
4 Treatment outcome among cases of multidrug-resistant tuberculosis (MDR TB) in Western
5 India: A prospective study. *J Infect Public Health*. 2016;9(4):478–84.
6
7
8 34. Yin J, Yuan J, Hu Y, Wei X. Association between Directly Observed Therapy and Treatment
9 Outcomes in Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis.
10 *PLoS One*. 2016;11(3):e0150511.
11
12 35. Girum T, Muktar E, Lentiro K, Wondiye H, Shewangizaw M. Epidemiology of multidrug-
13 resistant tuberculosis (MDR-TB) in Ethiopia: a systematic review and meta-analysis of the
14 prevalence, determinants and treatment outcome. *Trop Dis Travel Med Vaccines*.
15 2018;4(2018):5.
16
17 36. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis
18 treatment. Geneva, Switzerland; 2019.
19
20 37. Federal Democratic Republic of Ethiopia Ministry of Health. Guidelines for Management of
21 TB, DR-TB and Leprosy in Ethiopia: Sixth Ed. Addis Ababa, Ethiopia; 2018.
22
23 38. Li J, Li T, Bs X Du, Fhkccm PC, Zhang H. The age-structured incidence and mortality of
24 pulmonary tuberculosis reported in China, in 2005 –15: a longitudinal analysis of national
25 surveillance data. *Lancet*. 2017;390:S12.
26
27 39. Chingonzoh R, Manesen MR, Madlavu MJ, Kuonza R. Risk factors for mortality among
28 adults registered on the routine drug resistant tuberculosis reporting database in the Eastern
29 Cape Province, South Africa, 2011 to 2013. *PLoS One*. 2018;13(8):e0202469.
30
31 40. Gayoso R, Dalcolmo M, Ueleres J, Barreira D. Predictors of mortality in multidrug-resistant
32 patients from Brazilian refence centers, 2005 to 2012. *Brazilian J Infect Dis*.
33 2018;22(4):305–10.
34
35 41. Yuengling KA, Padayatchi N, Wolf A, Mathema B, Brown T, Horsburgh CR, et al. Effect of
36 antiretroviral therapy on treatment outcomes in a prospective study of extensively drug
37 resistant tuberculosis (XDR-TB) HIV co-infection treatment in KwaZulu-Natal, South
38 Africa. *Acquir Immune Defic Syndr*. 2019;79(4):474–80.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure legend

Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

For peer review only

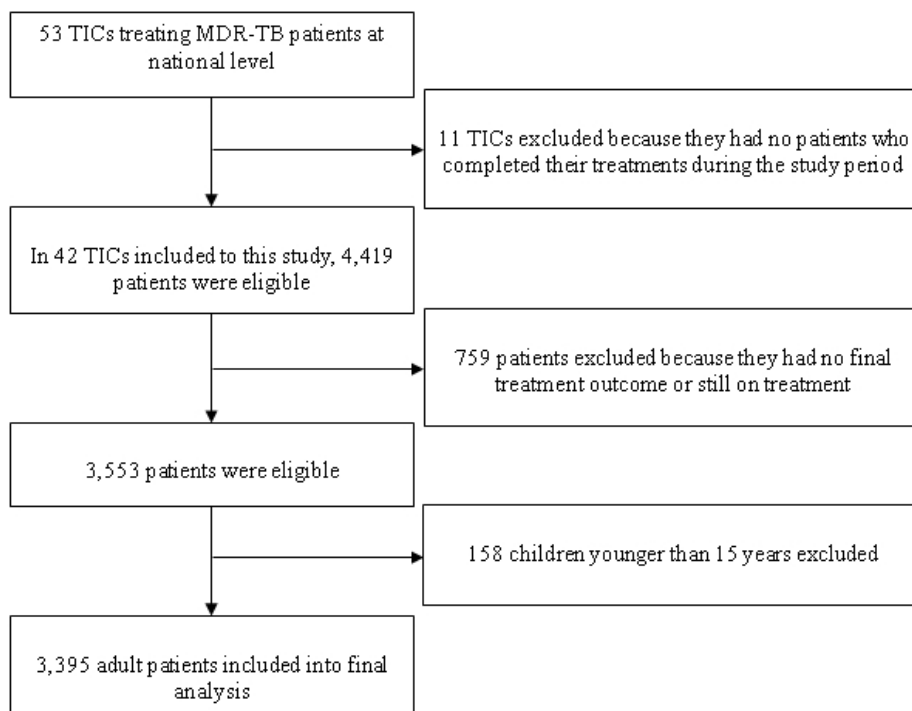


Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

171x132mm (96 x 96 DPI)

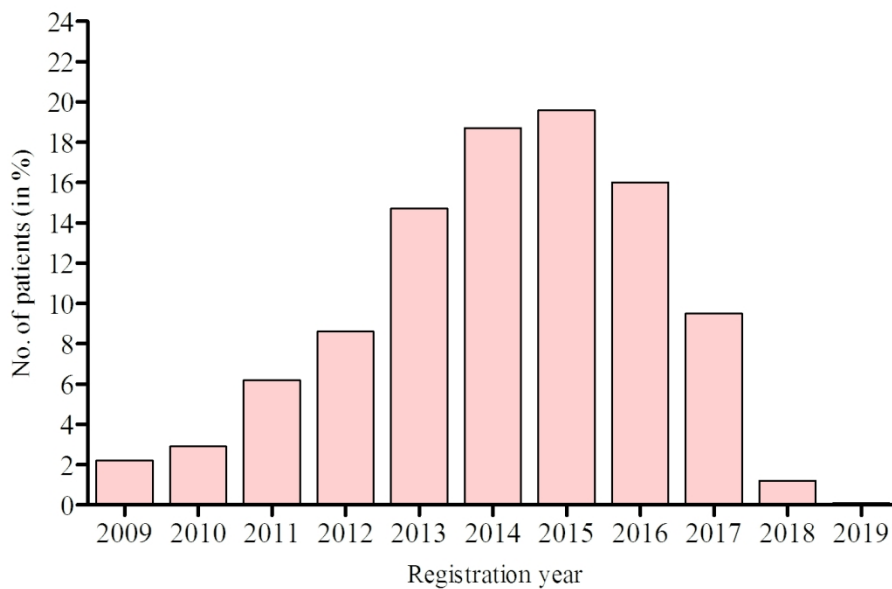


Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

137x88mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

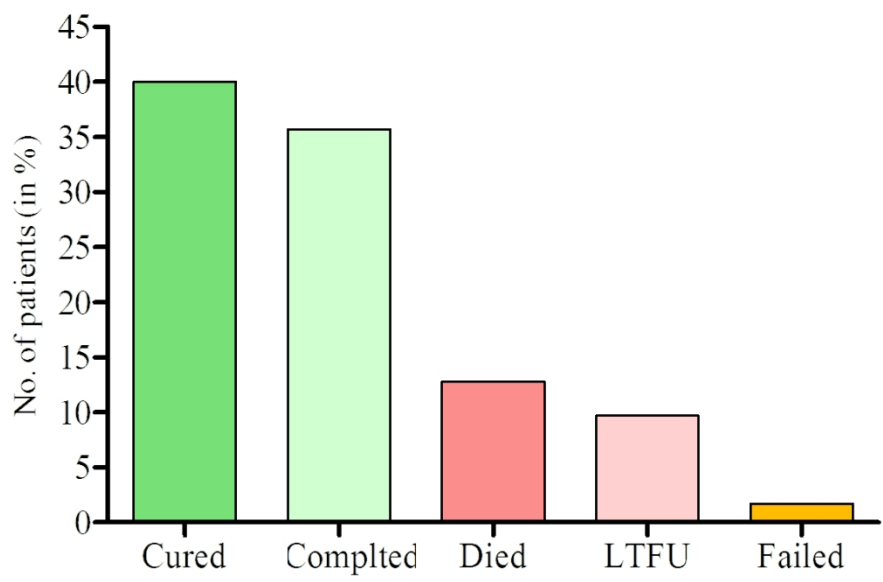


Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

110x71mm (300 x 300 DPI)

BMJ Open

National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years retrospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040862.R1
Article Type:	Original research
Date Submitted by the Author:	28-Nov-2020
Complete List of Authors:	Tola, Habteyes; Tehran University of Medical Sciences, Epidemiology and Biostatistics; Ethiopian Public Health Institute, TB/HIV Research Directorate Holakouie-Naieni, K; Tehran University of Medical Sciences, Epidemiology and Biostatistics Mansournia, Mohammad; Tehran University of Medical Sciences, Epidemiology and Biostatistics Yaseri , Mehdi ; Tehran University of Medical Sciences, Epidemiology and Biostatistics Gamtesa, Dinka; Ethiopian Public Health Institute Tsfaye , Ephrem ; Ethiopian Public Health Institute Mahamed , Zemedu ; Ethiopian Public Health Institute Sisay, Million ; Ethiopian Public Health Institute
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Global health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 National treatment outcome and predictors of death and treatment 2 failure in multidrug resistant tuberculosis in Ethiopia: A ten years 3 retrospective cohort study

4 Habteyes Hailu Tola^{1, 2}, Kourosh Holakouie-Naieni^{1*}, Mohammad Ali Mansournia¹, Mehdi
5 Yaseri¹, Dinka Fikadu Gamtesa², Ephrem Tesfaye², Zemedu Mahamed², Million Molla Sisay³

6 ¹Tehran University of Medical Sciences, School of Public Health, Department of Epidemiology
7 and Biostatistics, Tehran, Iran

8 ²Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
9 Ethiopia

10 ³Saint Peter's Specialized Hospital, Research and Evidence Generation Directorate, Addis
11 Ababa, Ethiopia

12 **Habteyes H. Tola** (MSc, PhD)

13 -Tehran University of Medical Sciences, School of Public Health
14 Department of Epidemiology and Biostatistics, Tehran, Iran

15 -Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
16 Ethiopia

17 Email: habetola@gmail.com

18 P.O. Box 1242

19 * **Corresponding author:**

20 **Kourosh Holakouie-Naieni*** (DVM, MSc, PhD)

21 Tehran University of Medical Sciences, School of Public Health
22 Department of Epidemiology and Biostatistics, Tehran, Iran

23 Phone: +98 21-88950185

24 Fax: +98 21-88950185

25 P.O. Box 1416753955

26 Email: holakoik@hotmail.com

27 **Mohammad Ali Mansournia** (MD, PhD)

28 Tehran University of Medical Sciences, School of Public Health
29 Department of Epidemiology and Biostatistics, Tehran, Iran

30 Email: mansournia_ma@yahoo.com

1
2
3 1 P. O. Box 1416753955
4

5 2 **Mehdi Yaseri** (MSc, PhD)
6

7 3 Tehran University of Medical Sciences School of Public Health
8

9 4 Department of Epidemiology and Biostatistics, Tehran, Iran
10

11 5 Email: myaseri@gmail.com
12

13 6 P. O. Box 1416753955
14

15 7 **Dinka Fikadu Gemtesa** (BSc, MPH)
16

17 8 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
18

19 9 Ethiopia
20

21 10 Email: ejeta430@gmail.com
22

23 11 P. O. Box 1242
24

25 12 **Ephrem Tesfaye** (BSc, MSc)
26

27 13 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
28

29 14 Ethiopia
30

31 15 Email: ephremt13@gmail.com
32

33 16 P. O. Box 1242
34

35 17 **Zemedu Mahamed** (BSc, MSc)
36

37 18 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
38

39 19 Ethiopia
40

41 20 Email: zemedu2003@gmail.com
42

43 21 P. O. Box 1242
44

45 22 **Million Molla Sisay** (MD, MSc)
46

47 23 Saint Peter's Specialized Hospital, Research and Evidence Generation Directorate, Addis Ababa,
48

49 24 Ethiopia
50

51 25 Email: milishagr8@gmail.com
52

53 26 P. O. Box 1242
54

1 Abstract

2 **Objectives:** Treatment success rate in patients treated for multidrug-resistant tuberculosis
3 (MDR-TB) is low, but predictors of treatment failure and death have been underreported. Thus,
4 we aimed to determine the national proportion of treatment success in the past 10 years and
5 factors that predict treatment failure and death in MDR-TB patients in Ethiopia.

6 **Setting:** A retrospective cohort study with 10 years follow up period was conducted in 42 MDR-
7 TB treatment initiating centers in Ethiopia.

8 **Participants:** A total of 3,395 adult MDR-TB patients who had final treatment outcome and
9 who were treated under national TB programme were included. Data was collected from clinical
10 charts, registration books and laboratory reports. Competing risk survival analysis model with
11 robust standard error was used to determine predictors of treatment failure and death.

12 **Primary and secondary outcomes:** Treatment outcome was a primary outcome whereas
13 predictors of treatment failure and death were a secondary outcome.

14 **Results:** The proportion of treatment success was 75.7%, death was 12.8%, treatment failure
15 was 1.7% and lost to follow up 9.7%. The significant predictors of death were older age
16 (adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); $p < 0.001$), HIV sero-reactive (AHR =
17 2.0; 95% CI (1.6–2.4); $p < 0.001$) and presence of any grade of anemia (AHR = 1.7; 95% CI
18 (1.4–2.0); $p < 0.001$). Unlike the predictors of death, all variables included into multivariable
19 model were not significantly associated with treatment failure.

20 **Conclusion:** In the past ten years, although MDR-TB treatment success in Ethiopia is well
21 achieved, the proportion of patients who died is still considerable. Death could be reduced by
22 providing special attention to old age, HIV-infected and anemic patients. Further prospective
23 cohort study is necessary to explore the predictors of treatment failure.

24 **Keywords:** Tuberculosis, Multidrug resistance, Refampin resistance, Treatment outcome

25

1 **Strengths and Limitations of this study**

- 2 ❖ National multidrug resistance tuberculosis (MDR-TB) treatment success rate in the past ten
3 years was determined using MDR-TB treatment programme data.
- 4 ❖ Although MDR-TB mortality is high, predictors of death and treatment failure are
5 underreported.
- 6 ❖ This study determined the predictors of treatment failure and death using competing risk
7 survival analysis model with robust standard error.
- 8 ❖ Retrospective nature of the study design leads to key variables such as sociodemographic,
9 behavioural, adverse drug reactions, key laboratory variables and treatment adherence status
10 missing.
- 11 ❖ Short MDR-TB treatment regimen is recently introduced in Ethiopia, therefore patients
12 treated by long regimen only were enrolled in this study.

1 Background

2 The emergence of drug resistance tuberculosis (TB) has been undermining the efforts to control
3 TB and continues to cause severe morbidity and mortality among millions across the world. The
4 World Health Organization (WHO) estimated that nearly half a million rifampin-resistant new
5 TB cases occurred in 2018 across the world.¹ Multidrug resistance (MDR) TB is defined as a
6 *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin, whereas extensively drug
7 resistance (XDR) TB refers to a *M. tuberculosis* resistance to at least rifampin and isoniazid as
8 well as resistance to any fluoroquinolone and at least one of the three injectable anti-TB drugs
9 (capreomycin, kanamycin or amikacin)². The treatment of MDR and XDR TB has been largely
10 unsuccessful due to the difficulty of the diagnosis, long duration of the treatment, the less
11 effective and toxic drugs used for the treatment, and unavailability of drug options.²⁻⁴

12 The current MDR-TB treatment success rate (the sum of cured and treatment completed) is
13 considerably low.^{1,3,6} The WHO's recent global estimation indicates that only 56% of MDR-TB
14 patients were successfully treated in 2018.¹ This indicates that nearly half of MDR-TB patients
15 who were diagnosed and treated have succumbed to unsuccessful treatment outcome which is the
16 main obstacle in achieving the WHO End TB treatment success target of $\geq 90\%$ by 2035.¹
17 Countries with low treatment success rate of MDR-TB include Russia (54%)⁶, Morocco
18 (53.4%)⁷ and India (60%)⁸. In contrast, recent studies indicated relatively higher treatment
19 success rates in certain settings.⁹⁻¹² For example, 82.4% of MDR-TB patients were treated
20 successfully in Taiwan⁹, 75.8% in Pakistan¹² and 75.7% in Tanzania.¹⁰ In Ethiopia, 78.8% of
21 MDR-TB patients were treated successfully.¹¹

22 Heterogeneous and interrelated factors are associated with poor MDR-TB treatment outcome.
23 Infection with Human Immunodeficiency Virus (HIV)¹³⁻¹⁶, diabetes mellitus^{14,17,18}, malnutrition

1 19,20, and anemia^{14,16,21} are co-morbidities that are associated with poor treatment outcome in
2 patients treated for MDR-TB. Moreover, treatment interruption^{16,22,23}, medication regimens²⁴,
3 antiretroviral therapy (ART) timing²⁵, time to MDR-TB treatment initiation after diagnosis²⁶ and
4 previous TB treatment history^{20,27} are treatment related factors that are associated with poor
5 treatment outcome in MDR-TB patients.

6 Ethiopia is among the 30 high TB and MDR-TB prevalent countries with an estimated TB
7 incidence of 165 per 100,000 population in 2018.¹ Despite an improving TB control programme
8 and relative treatment success rate, the prevalence of MDR-TB in Ethiopia remains high with
9 2.2% in new and 21.1% in previously treated TB cases²⁸. However, WHO's recent estimate in
10 Ethiopia indicated a lower prevalence of 0.71% of MDR-TB in new cases and 16% in
11 previously treated cases in 2018.¹ Although there is no national level report on MDR-TB
12 treatment outcome, studies reported from local data indicated variable treatment success ranging
13 between 63% – 78.8% in Ethiopia.^{11,21,29}

14 Although evidence indicates a low treatment success rate among MDR-TB patients, there is less
15 information on the factors that are associated with treatment failure and death in different setups.
16 Beside evidence limitation, available studies are focused in the determination of predictors of
17 unsuccessful treatment outcome by merging death, treatment failure and lost to follow up in one
18 category. However, merging of death, treatment failure and lost to follow up in one category
19 could conceal the actual predictors of death and treatment failure. To that extent, there is no
20 study that reported the predictors of death and treatment failure separately using robust standard
21 competing risk survival analysis model. Ethiopia is among the countries which lack such
22 evidence at national level to plan effective intervention that could decrease treatment failure and
23 reduce death in MDR-TB patients. Thus, we aimed to determine the national level treatment

1 success rate in the past 10 years and factors that could predict treatment failure and death in
2 MDR-TB patients in Ethiopia.

3 **Materials and methods**

4 **Study setting, population and design**

5 We conducted a retrospective cohort study on adult patients aged ≥ 15 years old, diagnosed
6 either biologically or clinically for both pulmonary and extra-pulmonary TB, and enrolled to
7 MDR-TB treatment at 42 treatment initiating centers (TICs) in Ethiopia from February 2009–
8 February 2019. MDR-TB treatment was started in February 2009 in one hospital in Addis
9 Ababa, Ethiopia.²⁹ During this study period there were a total of 53 TICs and several treatment
10 follow up centers (TFCs) in the country. The majority of MDR-TB patients initiate their
11 treatments in TICs while stable patients follow the treatment under directly observed therapy
12 (DOT) programme in nearby TICs or TFCs as ambulatory outpatients. However, all information
13 on the patients registered for MDR-TB treatment has been documented at TICs where the patient
14 started the treatment. We included a total of 42 TICs to this study, due to the remaining 11 TICs
15 had no patients who completed their treatment during the study period.

16 **Inclusion and exclusion criteria**

17 We included all adult patients who were aged 15 years and older, diagnosed either
18 bacteriologically or clinically for MDR-TB and enrolled to the treatment from February 2009.
19 Children less than 15 years old were excluded from this study, because their treatment guideline
20 is different from the adults. However, we excluded patients who had no final treatment outcome
21 (transferred out or still on treatment or treatment outcome missed from data sources).

22

1 **Laboratory test**

2 All laboratory tests were performed according to WHO recommendation and national TB
3 laboratory algorithm in quality assured TB laboratories^{30,31}. Culture tests were carried out with
4 solid (Löwenstein-Jensen (LJ)) and a fluorometric BACTEC MGIT960 at one national TB
5 reference laboratory and nine regional laboratories. In addition, Xpert MTB/RIF assay is a rapid,
6 sensitive and specific technique that has been widely using to detect *M. tuberculosis* and
7 rifampin resistant at each level in the national health system. Drug susceptibility test (DST) for
8 first-line drugs was performed by BACTEC MGIT960 system based on WHO recommended
9 critical concentrations, for rifampin (1.0 µg/ml), isoniazid (0.1 µg/ml), streptomycin (1.0 µg/ml),
10 ethambutol (5µg/ml) and pyrazinamide (100 µg/ml). DST for second-line has been recently
11 started in the country and rarely performed. Data on second-line DST was not included to this
12 study because very few DST results for SLDs obtained in the records. Quality assurance for
13 DST was regularly performed by Milan supranational reference laboratory in Italy and
14 demonstrated constant proficiency.

15 **Treatment**

16 Previously, all MDR-TB patients were treated as inpatient model of care for the first few months
17 at treatment centers until the patient become clinically stable and *M. tuberculosis* culture
18 conversion. However, according to the recent edition of national TB treatment guideline, all
19 patients with MDR-TB need to be treated under clinic-based ambulatory model of care since
20 2018, unless the patient unstable or developed severe adverse drug reaction during the course of
21 treatment. Patients either with serious medical or social conditions could be admitted with the
22 decision of the treatment panel. Standardized long treatment regimens were used to treat MDR-
23 TB patients in Ethiopia. The long treatment regimen contained at least four oral drugs which

1 used daily during full course of treatment and one injectable drug until *M. tuberculosis* culture
2 conversion. Treatment with injectable drugs continues at least for eight months based on clinical,
3 microbiological and radiographic examination results. The minimum treatment duration was 20
4 months for long regimen which is at least 18 months after bacteriological conversion, whereas
5 nine to 11 months for short treatment regimen.³¹ The second line drugs used to treat MDR-TB in
6 Ethiopia are levofloxacin, ethionamide, cycloserine, para-aminosalicylic acid (PAS),
7 pyrazinamide, prothionamide, linezolid, clofazimine and injectable drugs such as amikacin,
8 kanamycin and capreomycin.³¹ All the patients enrolled into this study were treated by a
9 standardized long term regimen consists capreomycin, levofloxacin, prothionamide, cycloserine
10 and high dose isoniazid during the intensive phase.³¹ During the continuation phase,
11 levofloxacin, prothionamide, cycloserine and high dose isoniazid were used.³¹ Laboratory tests,
12 chest X-ray and clinical investigations are used to monitor response to the treatment and to
13 identify treatment related complications in patients on MDR-TB treatment in Ethiopia. Clinical
14 investigations only are used to monitor response to the treatment, while laboratory tests are used
15 to identify treatment related complications for extra-pulmonary TB patients. MDR-TB treatment
16 is free of any cost in Ethiopia and there is full access to all categories of drugs to treat MDR-TB
17 patients.

18 **Data collection**

19 We collected data on socio-demographic variables such as sex, age and regional state. We also
20 collected TB related data such as anatomical site of TB (pulmonary vs extra pulmonary), drug
21 resistance type (RR vs MDR), previous treatment (new vs previously treated), diagnosis method
22 (bacteriologically vs clinically), HIV sero-status (reactive vs non-reactive) and antiretroviral
23 therapy (ART) status (on ART vs not applicable vs not on ART). In addition, we collected

1 information on bacteriological status (smear, Xpert MTB/RIF, culture or first-line drugs DST
2 results) at treatment initiation. All data were extracted from patients' clinical charts, registration
3 books and laboratory reports. Data were collected by health professionals familiar with MDR-TB
4 treatment after two days practical training on data collection tool.

5 **Definitions**

6 In this study, we used standard WHO and national treatment guidelines definitions for laboratory
7 confirmations, patient categories and treatment outcomes.^{30,31} Clinically diagnosed MDR-TB
8 refers to those cases with no documented drug susceptibility test (DST) results but treated
9 empirically with a course of treatment including SLDs based on clinical criteria and contact
10 history.³¹ However, bacteriologically confirmed MDR-TB refers to those cases with documented
11 DST results. All patients were categorized into new patients (never treated for TB or has treated
12 for less than one month) and patients previously treated for tuberculosis. The final treatment
13 outcomes of MDR-TB were cured, treatment completed, death, treatment failed and lost to
14 follow up. Cured is refers to a patient initially bacteriologically confirmed and completed the
15 treatment without the evidence of treatment failure and three or more consecutive cultures taken
16 at least 30 days apart are negative after the intensive phase. Treatment completed is defined as a
17 patient who completed the treatment without the evidence of treatment failure but there is no
18 record that indicates three or more consecutive cultures taken at least 30 days apart are negative
19 after the intensive phase. A patient whose treatment is terminated or need for permanent regimen
20 change of at least two anti-TB drugs is categorized as treatment failure. Lost to follow up is also
21 refers to a patient whose treatment is interrupted for two consecutive months or more. Successful
22 treatment outcome was the sum of cured and treatment completed, whereas unsuccessful was the
23 combination of death, treatment failed and lost to follow up.

1 **Data analysis**

2 We entered data into CPro software version 6.1 and analyzed by STATA version 14
3 (StataCorp, College Station, TX, USA). The data were confirmed from each data source and
4 cleaned for errors before main analysis. We described participants' demographic and clinical
5 characteristics using descriptive statistics. The proportions of MDR-TB treatment outcomes were
6 frequency weighed by the total number of patients registered from February 30, 2009–February
7 30, 2019 in each TIC.

8 We used a competing risk survival analysis model with robust standard error to assess the effects
9 of different variables on the treatment failure and death. Effect levels were reported by Hazard
10 Ratio (HR) with 95% Confidence Intervals (CIs). We included variables scored p-values less
11 than or equal to 0.2 during bivariate analysis and clinically or epidemiologically relevant. We
12 considered death as failure event to estimate the effects of different variables on death, while
13 treatment failure and success considered as competing risks. Similarly, we considered treatment
14 failure as failure event to estimate the effects of different variables on the duration from
15 treatment enrolment to treatment failure, whereas death and treatment success considered as
16 competing risks. Lost to follow up was considered as a censored across the fitted models. Level
17 of significance was set at 5% for all analysis.

18 **Patient and public involvement:** Both patient and public were not involved in this study.

19 **Results**

20 **Participants' characteristics**

21 A total of 4,419 patients were enrolled to MDR-TB treatment in 42 of 53 (79.2%) treatment
22 initiating centers (TICs) in Ethiopia from February, 2009 to February, 2019 [Fig 1]. Of the 4,419
23 patients, 3,395 (76.8%) fulfilled our inclusion criteria and enrolled to this study [Fig 1].

1 The highest number of patients enrolled into the treatment were in 2015 (667 patients), while the
2 lowest number of patients were registered in 2019 (only 4 patients) [Fig 2].

3 Of the 3,395 patients included into this study, 1,870 (55.1%) were male, and the mean age was
4 31.6 (SD \pm 11.7) years with the age range of 15 to 85 years. Seventy two percent of the patients
5 were in the age category of 15 to 35 years [Table 1]. Ninety three percent of the participants
6 were pulmonary TB patients [Table 1]. Eighty six percent of patients had previous TB treatment
7 history. Drug resistance status of 3,242 (95.5%) isolates were bacteriologically confirmed at the
8 initiation of treatment [Table 1]. The main drug resistance diagnosis method was GeneXpert
9 MTB/RIF (57.9%). Of the 3,395 patients, 1,421 (41.9%) had previous exposure to second line
10 drugs and 767 (22.6%) were HIV infected [Table 1] of which 686 (89.4%) were on ART. Only
11 6.0% of the patients had previous MDR-TB patient contact history and 1,831 (53.9%) of patients
12 were hospitalized at the treatment initiation [Table 1] with mean duration of hospitalization 81.7
13 (\pm 47.4) days.

14 **Table 1: Demographic and clinical characteristics of the patients (n = 3,395)**

Variable		n (%)
Sex	Male	1,870 (55.1)
	Female	1,525 (44.9)
Age (in year)	15–25	1,268 (37.3)
	26–35	1,186 (34.9)
	36–45	529 (15.6)
	\geq 46	412 (12.1)
Drug resistance type	RR/INH status unknown	1,810 (53.3)
	MDR-TB	1,585 (46.7)
Anatomical site of TB	Pulmonary	3,171 (93.4)
	Extra pulmonary	224 (6.6)
Previous TB treatment	New	462 (13.6)
	Previously treated	2,933 (86.4)
Previous exposure to SLDs	Yes	1,421 (41.9)
	No	1,842 (54.3)
	Unknown	132 (3.9)
Drug resistance identification method	GeneXpert MTB/RIF	1,967 (57.9)
	Culture/LPA	1,275 (37.6)
	Clinical	153 (4.5)
Diagnosis method	Bacteriological	3,242 (95.5)
	Clinical	153 (4.5)
HIV sero-status	Non-reactive	2,554 (75.2)

	Sero-reactive	767 (22.6)
	Unknown	74 (2.2)
ART status	Not applicable	2,556 (75.3)
	On ART	686 (20.2)
	HIV sero-status known but, ART status unknown	79 (2.3)
	Both ART and HIV sero- statuses unknown	74 (2.2)
MDR-TB patient contact history	Yes	204 (6.0)
	No	1,511 (44.5)
	Unknown	1,680 (49.5)
Hospitalization history at treatment initiation	Hospitalized	1,831 (53.9)
	Not hospitalized	487 (14.3)
	Unknown	1,077 (31.7)
Treatment interruption	Never interrupted/interruption status unknown	3,192 (94.0)
	At least one day interrupted	203 (6.0)

1 *TB-tuberculosis, ART-Antiretroviral therapy, SLDs-Second line drugs, HIV-Human immunodeficiency virus, MDR-*
 2 *Multidrug resistant, LPA-Line probe Assay*

3 **Drug resistance status at treatment initiation**

4 Drug susceptibility testing was performed for four first-line drugs which are rifampin, isoniazid,
 5 ethambutol and streptomycin [Table 2]. Rifampin susceptibility test was performed on isolates of
 6 all patients included into this study and 99.3% of isolates demonstrated resistance to the therapy
 7 [Table 2].

8 **Table 2: Anti-tuberculosis drug susceptibility test results**

Anti-tuberculosis drug	Susceptibility test results	n (%)
Rifampin (n=3,395)	Resistant	3,371 (99.3)
	Susceptible	24 (0.7)
Isoniazid (n = 1,313)	Resistant	1,241 (94.5)
	Susceptible	72 (5.5)
Ethambutol (n = 427)	Resistant	299 (70.0)
	Susceptible	128 (30.0)
Streptomycin (n = 443)	Resistant	337 (76.1)
	Susceptible	106 (23.9)

9
 10 Table 3 depicts the distribution of treatment outcome categories by sociodemographic and
 11 clinical characteristics. Of 1,585 patients whose isolates were resistant to rifampin and isoniazid
 12 (MDR-TB), 793 (50.0%) cured, while 180 (11.4%) died and the treatment of 24 (1.5%) patients

1 were failed. Treatment failure was almost ten times higher in patients who had previous TB
 2 treatment history (21.7%), than those who were never treated (2.2%). Moreover, mortality was
 3 two times higher in patients who were HIV sero-reactive (21.3%), than those who were HIV
 4 non-reactive (10.2%).

6 Table 3: Demographic and clinical characteristics distribution of treatment outcome

Variables	Treatment outcome n (%)						P-value	
	Cured	Completed	Treatment success	Failed	Death	LTFU		
Sex	Male	1,006 (53.8)	376 (20.1)	1,382 (73.9)	40 (2.1)	245 (13.1)	203 (10.9)	0.071
	Female	839 (55.0)	344 (22.6)	1,183 (77.6)	26 (1.7)	186 (12.2)	130 (8.5)	
Resistance type	RR/INH status unknown	1,052 (58.1)	274 (15.1)	1,326 (73.2)	42 (2.3)	251 (13.9)	191 (10.6)	< 0.001
	MDR	793 (50.0)	446 (28.1)	1,239 (78.1)	24 (1.5)	180 (11.4)	142 (9.0)	
Anatomical site	EPTB	50 (22.3)	125 (55.8)	173 (78.1)	4 (1.8)	20 (8.9)	25 (11.2)	< 0.001
	PTB	1,795 (56.6)	595 (18.8)	2,390 (75.4)	62 (2.0)	411 (13.0)	308 (9.7)	
Previous TB treatment	New	243 (52.6)	83 (18.0)	326 (70.6)	10 (2.2)	75 (16.2)	51 (11.0)	0.057
	Previously treated	1,602 (54.6)	637 (21.7)	2,239 (76.3)	56 (21.7)	356 (12.1)	282 (9.6)	
Diagnosis method	Bacteriological	1,771 (54.6)	686 (21.2)	5,457 (75.8)	64 (2.0)	409 (12.6)	313 (9.7)	0.466
	Clinical	74 (48.7)	34 (22.4)	108 (71.1)	2 (1.3)	22 (14.5)	20 (13.2)	
HIV-sero-status	Non-reactive	1,429 (56.0)	561 (22.0)	1,990 (78.0)	48 (1.9)	261 (10.2)	255 (10.0)	< 0.001
	Reactive	378 (49.3)	141 (18.4)	519 (67.7)	17 (2.2)	163 (21.3)	68 (8.9)	
Anemia	None anemic	880 (55.0)	380 (23.8)	1,260 (78.8)	29 (1.8)	150 (9.4)	161 (10.1)	< 0.001
	Any grade of anemia present	965 (53.8)	340 (18.9)	1,305 (72.7)	37 (2.1)	281 (15.7)	172 (9.6)	

7 Treatment outcome

8 Of the 3,395 patients enrolled into this study, 1,845 (40.0%) were cured, 720 (35.7%) completed
 9 the treatment, 431 (12.8%) have died, 333 (9.7%) were lost to follow up and the treatment of 66
 10 (1.7%) patients failed [Fig 3]. The overall treatment success (cured plus treatment completed)
 11 was 2,565 (75.7%), whereas the overall unsuccessful treatment outcome (the sum of lost to
 12 follow up, treatment failed and death) was 830 (24.3%).

1 Predictors of treatment failure and death

2 Bivariate analysis

3 In the current competing risk survival analysis model, failure events were treatment success
 4 (2,565), treatment failure (66) and death 431 (431). To the contrary, 333 (9.7%) lost to follow up
 5 were considered as censored. In the bivariate competing risk survival analysis model, old age
 6 (unadjusted hazard ratio (UHR) = 1.03; 95% CI (1.04–1.05); $p < 0.001$), HIV sero-reactive
 7 (UHR = 2.2; 95% CI (1.8–2.7); $p < 0.001$) and presence of any grade of anemia (UHR = 1.7;
 8 95% CI (1.4–2.1); $p < 0.001$) were significantly associated with death [Table 4]. Moreover,
 9 having previous TB treatment history (UHR = 0.71; 95% CI (0.56–0.92); $p = 0.009$) and
 10 presence of rifampin resistant bacilli (UHR = 1.3; 95% CI (1.03–1.5); $p = 0.022$) were
 11 significantly associated with death [Table 4]. However, none of the variables assessed had shown
 12 significant association with treatment failure [Table 4].

13 **Table 4:** Predictors of duration from treatment initiation to death and treatment failure in patients
 14 treated for MDR-TB in Ethiopia, 2009-2019 (Unavailable model)

Variable	Death		Treatment failure	
	UHR (95%CI)	P-value	UHR(95% CI)	P-value
Sex	Female	1.00	1.00	
	Male	1.1 (0.89–1.3)	0.436	1.3 (0.78–2.1)
Age (year)	1.03 (1.04–1.05)	< 0.001	0.98 (0.96–1.0)	0.122
Anatomical sit	Extra-pulmonary	1.00	1.00	
	Pulmonary	1.5 (0.94–2.3)	0.094	1.1 (0.40–3.0)
Drug resistance type	MDR	1.00	1.00	
	RR/INH status unknown	1.3 (1.03–1.5)	0.022	1.6 (0.95–2.6)
Previous treatment	New	1.00	1.00	
	Previously treated	0.71 (0.56–0.92)	0.009	0.86 (0.44–1.7)
Diagnosis method	Bacteriological	1.00	1.00	
	Clinical	1.2 (0.76–1.8)	0.468	0.68 (0.17–2.8)
HIV sero-status	Non-reactive	1.00	1.00	
	Reactive	2.2 (1.8–2.7)	< 0.001	1.2 (0.68–2.1)
Anemia status	Absent	1.00	1.00	
	Any grade of anemia present	1.7 (1.4–2.1)	< 0.001	1.1 (0.70–1.9)

15 *TB-tuberculosis, HIV-Human immunodeficiency virus, UHR- Unadjusted hazard ratio, CI-Confidence interval,*
 16 *MDR-Multidrug resistant*

1 Multivariable analysis

2 In multivariable analysis, older age (Adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); p
3 < 0.001), HIV sero-reactive (AHR = 2.0; 95% CI (1.6–2.4); p < 0.001) and presence of any grade
4 anemia (AHR = 1.7; 95% CI (1.4–2.0); p < 0.001) were significantly associated with death
5 [Table 5]. All variables included into multivariable competing risk survival analysis model were
6 not significantly associated with treatment failure [Table 5]. Although presence of rifampin
7 resistant bacilli and having previous TB treatment history were significantly associated with
8 death in the unadjusted analysis, they failed to significantly associate in the adjusted analysis.

9 **Table 5:** Predictors of duration from treatment initiation to death and treatment failure in patients
10 treated for MDR-TB in Ethiopia, 2009-2019 (Multivariate model)

Variable	Death		Treatment failure	
	AHR (95%CI)	P-value	AHR(95% CI)	P-value
Sex				
	Female	1.00	1.00	
	Male	0.92 (0.75–1.1)	1.3 (0.82–2.2)	0.248
Age (year)		1.04 (1.03–1.05)	0.98 (0.96–1.0)	0.077
Anatomical sit				
	Extra-pulmonary TB	1.00	1.00	
	Pulmonary TB	1.4 (0.91–2.2)	1.1 (0.39–3.0)	0.878
Drug resistance type				
	MDR	1.00	1.00	
	RR/INH status unknown	1.2 (0.98–1.5)	1.7 (0.98–2.8)	0.060
Previous treatment				
	New	1.00	1.00	
	Previously treated	0.79 (0.61–1.0)	0.98 (0.49–1.9)	0.947
HIV sero-status				
	Non-reactive	1.00	1.00	
	Reactive	2.0 (1.6–2.4)	1.3 (0.72–2.2)	0.425
Anemia status				
	Absent	1.00	1.00	
	Anemia present	1.7 (1.4–2.0)	1.1 (0.66–1.8)	0.767

11 *TB-tuberculosis, HIV-Human immunodeficiency virus, AHR- Unadjusted hazard ratio, CI-Confidence interval,*
12 *MDR-Multidrug resistant*

14 Discussion

15 The current study aimed to determine the proportion of national treatment success rate and
16 predictors of treatment failure and death in patients treated for MDR-TB in Ethiopia in the past
17 ten years. We have found that 75.7% of MDR-TB patients were successfully treated, whereas
18 12.8% died, 9.7% lost to follow up and the treatment of 1.7% patients failed. The proportion of
19 the patients registered for MDR-TB treatment has shown increasing trend from 2009 and the

1 maximum proportion (19.6%) was registered in 2015. However, the proportion of the patients
2 registered for the treatment has decreased after 2015 and the minimum patients were registered
3 in 2019. Old age, being HIV sero-reactive and presence of any grade of anemia had significantly
4 predicted death in patients treated for MDR-TB in the present study. However, none of the
5 variables included into the multivariable model were able to significantly predict treatment
6 failure.

7 The present study indicates that the proportion of treatment enrolment after 2015 has decreased
8 and the lowest cases were recorded in 2019. This might be due to the burden of MDR-TB
9 decreasing in the country or case registration related problems as the result of treatment centers
10 were decentralized to the periphery. As patients included into this study were those who had final
11 treatment outcome results, enrolment of patients in 2018 and 2019 is expectedly low as they
12 were still on treatment.

13 In the current study, treatment success proportion in MDR-TB patients who received a
14 standardized long regimen was higher than the treatment success rate previously reported from
15 other settings including from Ethiopia.^{8,21,22} For instance, a study reported from Morocco
16 indicated that only 53.4% of MDR-TB patients were treated successfully.⁸ In addition, a study
17 reported from Armenia shows that less than 50% of MDR-TB patients were successfully
18 treated.²² A recent review study that pooled data from different settings have also shown lower
19 treatment success rate than our findings.³² These differences originate most likely due to the
20 differences in the quality of TB control programme, sample size, severity of the disease at
21 diagnosis, TB/HIV co-infection burden and treatment regimens. A previous study conducted in
22 Ethiopia in two treatment initiation centers²⁹ reported very similar treatment success proportion
23 with our finding (78.6% Vs 75.7%).

1
2
3 1 The proportion of death in the current study was considerably higher and it was similar with
4
5 2 previously reported findings.^{21,29} Case in point, the proportion of patients who died in our study
6
7 3 was more than double compared to the mortality proportion reported from Morocco (5% vs
8
9 4 12.7%).⁸ This difference is most probably due to difference in the study period, quality of care,
10
11 5 treatment regimens, and severity of the disease during treatment initiation.

12
13
14 6 Our study finding shows that older age is significantly associated with death from MDR-TB. In
15
16 7 agreement with this findings, it is well documented that MDR-TB mortality is higher in older age
17
18 8 group.³³⁻³⁵ Thus, particular attention has to be given to older patients to avert mortality related to
19
20 9 TB. A previous study has shown that younger age is significantly associated with poor treatment
21
22 10 outcome than older age.⁷ This difference could probably be due to the age variation in the
23
24 11 included patients and the difference in the severity of the disease at treatment initiation.

25
26
27
28 12 In the current study, as in several previous studies^{7,21,27-29}, HIV sero-reactive was significantly
29
30 13 associated with death. Despite the proportion of patients who were not on antiretroviral therapy
31
32 14 (ART) were low (of HIV sero-reactive patients only 4.5 %), the hazard of death was 2.0 times
33
34 15 higher in sero-reactive HIV patients. The possible explanation for the significant effect of HIV
35
36 16 sero-reactivity on mortality in patients on MDR-TB treatment could be due to low CD4 count,
37
38 17 high viral load and severity of the disease at treatment initiation. However, since data on CD4
39
40 18 count, HIV viral load level and disease severity status at enrolment were not registered in our
41
42 19 data sources, we were not able to verify their effects on MDR-TB treatment outcome.
43
44 20 Furthermore, a previous study indicated that a combined anti-TB and anti-HIV treatment has
45
46 21 been proven to improve treatment success in co-infected patients.³⁶

47
48
49 22 In the present study, the presence of any grade of anemia was significantly associated with death
50
51 23 due to MDR-TB. This finding is similar with a previous study reported from Ethiopia in which
52
53
54
55
56
57
58
59
60

1 the hazard of poor treatment outcome was 4.2 times higher in the patients who had any grade of
2 anemia at treatment initiation than those who were non-anemic.²¹ The presence of anemia at the
3 treatment initiation might be due to parasitic infections and some other chronic diseases. This
4 finding highlights the importance of hemoglobin monitoring in MDR-TB patients on treatment to
5 increase treatment success and decrease mortality.

6 In the present study, none of the variables included into the multivariable model were
7 significantly associated with treatment failure. The absence of significant association between
8 the variables and treatment failure could be due to the number of treatment failure events were
9 very smaller than the competing risks i.e. death and treatment success.

10 The main limitation of this study is the retrospective nature of the study design. Data on
11 sociodemographic, behavioural, adverse drug reactions, key laboratory variables and treatment
12 adherence status were missing for the majority of the patients, hence these variables were
13 excluded from the analysis. This limited us to further explore the predictors of treatment failure
14 and death.. Thus, the predictors of death may not be limited to the factors presented in this study.
15 Moreover, lack of important variables could have resulted in an underestimation/overestimation
16 of the effects of the investigated variables in the model such as age, HIV status, previous TB
17 treatment history etc on treatment failure and death.. A prospective study that could capture all
18 these uninvestigated variables is important to determine predictors of treatment failure and
19 death..

20 The findings of the present study have clearly indicated the message for TB control programme
21 efforts. Although treatment success rate is well achieved, mortality in the current study is
22 considerably high and hence should be addressed by the TB programme. Old age is one of the
23 main predictors of death in MDR-TB patients on treatment. Thus, early diagnosis and

1 commencement of treatment in old patients could increase the cure rate. HIV sero-reactive is
2 also one of strong predictors of death in MDR-TB patients. Taking in consideration the sero-
3 status of MDR-TB patients and immediate commencement of anti-TB treatment together with
4 ART is the mechanism to improve treatment success in MDR-TB patients with HIV co-
5 infection.. Moreover, our result indicates that special attention should be paid to patients who
6 have anemia at treatment initiation in order to improve their treatment outcome. Strengthen and
7 standardizing information registration on MDR-TB treatment is crucial to facilitate further data
8 analysis which is important to monitor the status of treatment outcome.

9 **Conclusion**

10 In past ten years, MDR-TB treatment success in Ethiopia is well achieved. However, the
11 proportion of patients who died is considerably high, and it could be reduced through providing
12 special attention to old, HIV-infected and anemic patients. Further prospective cohort study is
13 required to explore other predictors of treatment failure and death.

14 **Acknowledgement**

15 We would like to acknowledge the Tehran University of Medical Sciences (TUMS) and the
16 Ethiopian Public Health Institute (EPHI) for funding this study. We also thank EPHI, National
17 Tuberculosis Laboratory and all DR-TB treatment centers staff members for their cooperation
18 during the data collection process. We would also like to acknowledge all patients whose data
19 were used in this study.

20 **Author contributions:** HHT and KH conceived and designed the study; HHT, DFG, ET, ZM
21 and MMS collected the data; HHT, MAM and MY analyzed and interpreted the data; HHT

1 drafted the manuscript. All authors have critically reviewed and approved the manuscript for
2 submission.

3 **Funding:** This work was supported by Tehran University of Medical Sciences and Ethiopian
4 Public Health Institute. The grand number of the funded institute is not applicable.

5 **Competing interests:** None declared.

6 **Ethics consideration:** This study was approved by the research Ethics Review Board of Tehran
7 University of Medical Sciences (IR.TUMS.SPH.REC.1396.4287), Ethiopian Public Health
8 Institute (EPHI-IRB-065-2017), St. Peter's Specialized Hospital (V81622018) and Armauer
9 Hansen Research Institute (PO13/18). We also obtained a waiver of informed consent from each
10 review board. To maintain confidentiality, sensitive information that could identify participants
11 was not reported in this study.

12 **Data availability statement:** Data used in this study is available from the corresponding authors
13 and accessible upon reasonable request.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1

2

For peer review only

1 References

1. WHO. Global tuberculosis report 2019. Geneva, Switzerland; 2019 p. 1–297.
2. Curry International Tuberculosis Center, and California Department of Public Health. Drug-resistant tuberculosis: A survival guideline for clinicians. 3rd Ed. 2016 p. 1-324.
3. Gunther G, Lange C, Alexandru S, Altet N. Treatment Outcomes in Multidrug-Resistant Tuberculosis. *N Engl J Med*. 2016;375(11).
4. Lange C, Abubakar I, Alffenaar JC, Bothamley G, Caminero JA, Carvalho ACC, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. *Eur Respir J*. 2014;44:23–63.
5. Pontali E, Visca D, Centis R, Ambrosio LD, Spanevello A, Battista G. Multi and extensively drug-resistant pulmonary tuberculosis : advances in diagnosis and management. *Curr Opin Pulm Med*. 2018;24:244–52.
6. Yunusbaeva M, Borodina L, Alekseev P, Davydov R, Yunusbaev U, Sharipov R, et al. International Journal of Infectious Diseases Treatment ef fi cacy of drug-resistant tuberculosis in Bashkortostan, Russia : A retrospective cohort study. *Int J Infect Dis*. 2019;81(2019):203–9.
7. Nair D, Velayutham B, Kannan T, Tripathy J, Harries A, Natrajan M, et al. Predictors of unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India. *Public Heal Action*. 2017;7(1):32–8.
8. Hamdouni M El, Bourkadi JE, Benamor J, Hassar M, Cherrah Y. Treatment outcomes of drug resistant tuberculosis patients in Morocco: multi- centric prospective study. *BMC Infect Dis*. 2019;19:316.
9. Yu M, Chiang C, Lee J, Chien S, Lin C, Lee S, et al. Treatment Outcomes of Multidrug-Resistant Tuberculosis in Taiwan : Tackling Loss to Follow-up. *Clin Infect Dis*. 2018;67(2):202–2010.
10. Leverl TH, Lekule I, Mollel E, Lyamuya F, Kilonzo K. Predictors of Treatment Outcomes among Multidrug Resistant Tuberculosis Patients in Tanzania. *Tuberc Reserch Treat*. 2019;2019:1–10.
11. Woldeyohannes D, Assefa T, Aman R, Tekalegn Y. Predictors of time to unfavorable treatment outcomes among patients with multidrug resistant tuberculosis in Oromia region. *PLoS One*. 2019;14(10):e0224025.
12. Javaid A, Ullah I, Masud H, Basit A, Ahmad W, Butt ZA, et al. Predictors of poor treatment outcomes in multidrug-resistant tuberculosis patients: a retrospective cohort study. *Clin Microbiol Infect*. 2017;2017.
13. Aibana O, Bachmaha M, Kراسiuk V, Rybak N, Flanigan TP, Petrenko V, et al. Risk factors for poor multidrug-resistant tuberculosis treatment outcomes in Kyiv Oblast, Ukraine. *BMC Infect Dis*. 2017;17(2017):129.
14. Ketema DB, Muchie KF, Andargie AA. Time to poor treatment outcome and its predictors among drug-resistant tuberculosis patients on second-line anti- tuberculosis treatment in Amhara region , Ethiopia : retrospective cohort study. *BMC Public Health*. 2019;19(2019):1481.
15. Samuels JP, Sood A, Campbell JR, Khan FA, Johnston JC. Comorbidities and treatment outcomes in multidrug resistant tuberculosis : a systematic review and meta-analysis. *Sci Rep*. 2018;8(2018):4980.

16. Tola HH, Holakouie-na K, Mansournia MA. Intermittent treatment interruption and its effect on multidrug resistant tuberculosis treatment outcome in. *Sci Rep*. 2019;9:20030.
17. Kang Ya, Kim S, Jo K, Kim H, Park S, Kim T, et al. Impact of Diabetes on Treatment Outcomes and Long-Term Survival in Multidrug-Resistant Tuberculosis. *Respiration*. 2013;86:472–8.
18. Dooley KE, Tang T, Golub JE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. *AM J Trop Med Hyg*. 2009;80(4):634–9.
19. Samuel B, Volkmann T, Cornelius S, Mukhopadhyay S, Mitra K, Kumar AM V, et al. Relationship between Nutritional Support and Tuberculosis Treatment Outcomes in West Bengal, India. *J Tuberc Res*. 2016;4(4):213–9.
20. Milanov V, Falzon D, Zamfirova M, Varleva T, Bachiyska E, Koleva A, et al. Factors associated with treatment success and death in cases with multidrug-resistant tuberculosis in Bulgaria, 2009 – 2010. *Int J Mycobacteriology*. 2015;4(2):131–7.
21. Alene KA, Viney K, McBryde ES, Tsegaye AT, Clements ACA. Treatment outcomes in patients with multidrug-resistant tuberculosis in north-west Ethiopia. *Trop Med Int Heal*. 2017;22(3):351–62.
22. Bastard M, Sanchez-padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, et al. Effects of treatment interruption patterns on treatment success among patients with multidrug-resistant tuberculosis in Armenia and Abkhazia. *J Infect Dis*. 2015;211:1607–16.
23. Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. *PLoS One*. 2013;8(7):e70064.
24. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. 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.
25. Umanah T, Ncayiyana J, Padanilam X, Nyasulu PS. Treatment outcomes in multidrug resistant tuberculosis-human immunodeficiency virus Co-infected patients on anti-retroviral therapy at Sizwe Tropical Disease Hospital Johannesburg, South Africa. *BMC Infect Dis*. 2015;15:478.
26. Chen Y, Yuan Z, Shen X, Wu J, Wu Z. Time to Multidrug-Resistant Tuberculosis Treatment Initiation in Association with Treatment Outcomes in Shanghai, China. *Antimicrob Agents Chemother*. 2018;62:e02259–17.
27. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. *Eur Respir J*. 2009;33:1085–94.
28. Girum T, Muktar E, Lentiro K, Wondiye H, Shewangizaw M. Epidemiology of multidrug-resistant tuberculosis (MDR-TB) in Ethiopia: a systematic review and meta-analysis of the prevalence, determinants and treatment outcome. *Trop Dis Travel Med Vaccines*. 2018;4(2018):5.
29. Meressa D, Hurtado RM, Andrews JR, Diro E, Abato K, Daniel T, et al. Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia — an observational cohort study. *Thorax*. 2015;70:1181–8.
30. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva, Switzerland; 2019.
31. Federal Democratic Republic of Ethiopia Ministry of Health. Guidelines for Management of TB, DR-TB and Leprosy in Ethiopia: Sixth Ed. Addis Ababa, Ethiopia; 2018.

- 1
2
3
4 1 32. Bastos ML, Lan Z, Menzies D. An updated systematic review and meta-analysis for
5 2 treatment of multidrug-resistant tuberculosis. *Eur Respir J.* 2017;49:1600803.
6 3 33. Li J, Li T, Bs X Du, Fhkccm PC, Zhang H. The age-structured incidence and mortality of
7 4 pulmonary tuberculosis reported in China , in 2005 – 15 : a longitudinal analysis of national
8 5 surveillance data. *Lancet.* 2017;390:S12
9 6 34. Chingonzoh R, Manesen MR, Madlavu MJ, Kuonza R. Risk factors for mortality among
10 7 adults registered on the routine drug resistant tuberculosis reporting database in the Eastern
11 8 Cape Province, South Africa, 2011 to 2013. *PLoS One.* 2018;13(8):e0202469.
12 9 35. Gayoso R, Dalcolmo M, Ueleres J, Barreira D. Predictors of mortality in multidrug-resistant
13 10 patients from Brazilian refence centers, 2005 to 2012. *Brazilian J Infect Dis.* 2018;22(4):305–
14 11 10.
15 12 36. Yuengling KA, Padayatchi N, Wolf A, Mathema B, Brown T, Horsburgh CR, et al. Effect of
16 13 antiretroviral therapy on treatment outcomes in a prospective study of extensively drug
17 14 resistant tuberculosis (XDR-TB) HIV co-infection treatment in KwaZulu-Natal, South
18 15 Africa. *Acquir Immune Defic Syndr.* 2019;79(4):474–80.
19 16
20 17
21 18
22 19

23 18 **Figure legend**

24 19 **Figure 1:** Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment
25 20 initiating centers)
26 21

27 21 **Figure 2:** Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–
28 22 2019)
29 23

30 23 **Figure 3:** MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)
31 24
32 25
33 26
34 27
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

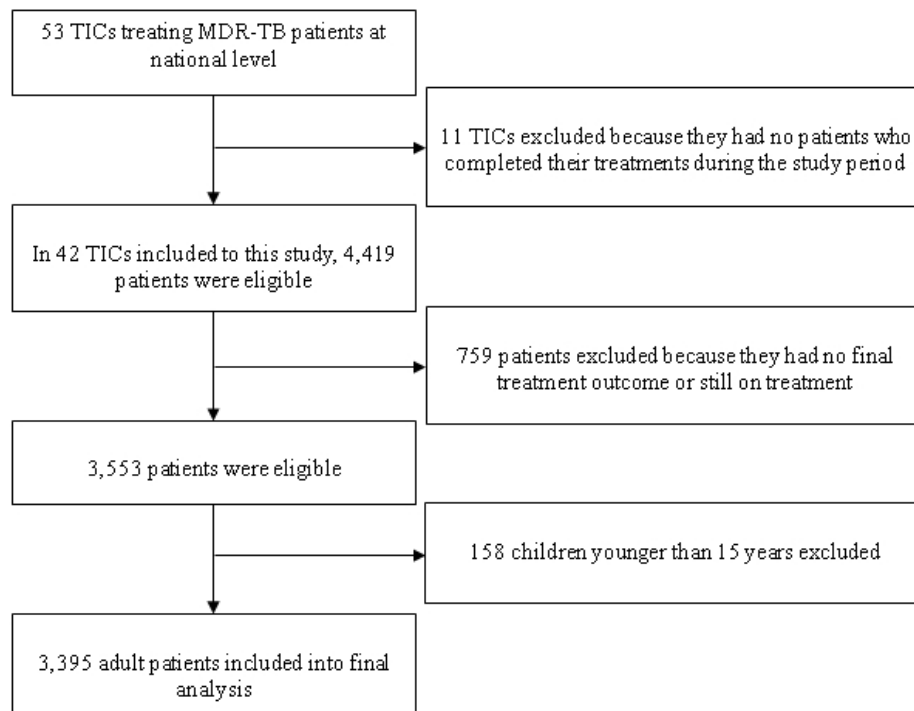


Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

171x132mm (96 x 96 DPI)

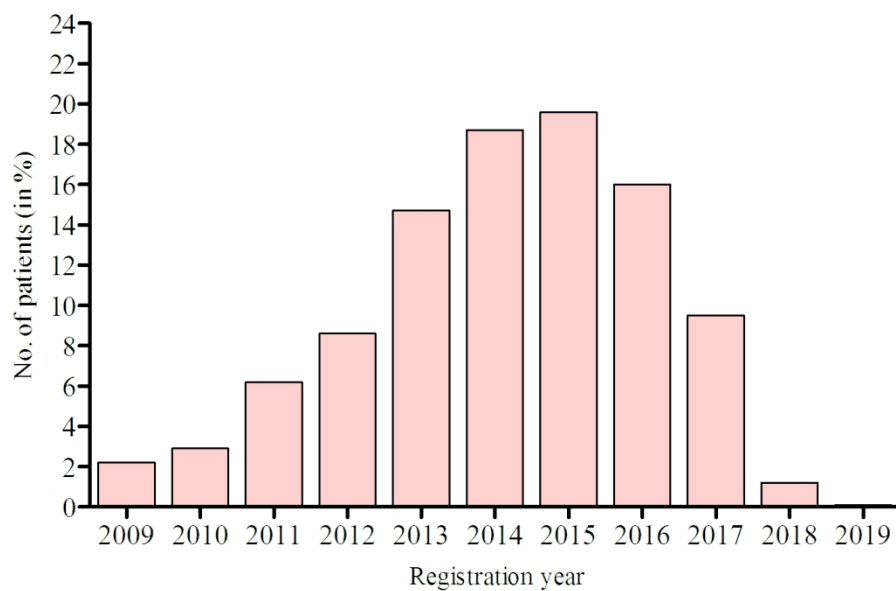


Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

137x88mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

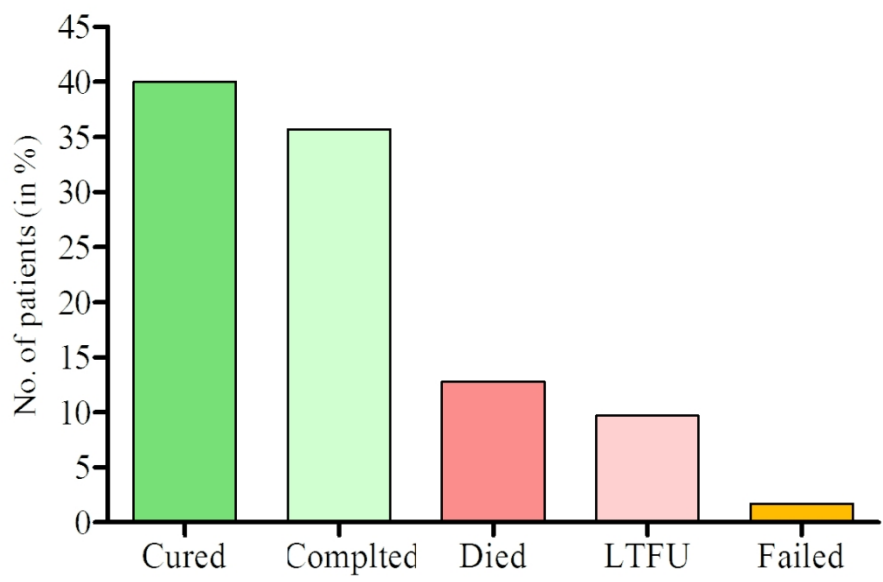


Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

110x71mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 - 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	NA NA Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11-13 Fig 1 11
Outcome data	15*	Report numbers of outcome events or summary measures over time	15

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
2		(b) Report category boundaries when continuous variables were categorized		
3		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	16-17
7	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	20
10	Other information			
11	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years retrospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040862.R2
Article Type:	Original research
Date Submitted by the Author:	10-Jan-2021
Complete List of Authors:	Tola, Habteyes; Tehran University of Medical Sciences, Epidemiology and Biostatistics; Ethiopian Public Health Institute, TB/HIV Research Directorate Holakouie-Naieni, K; Tehran University of Medical Sciences, Epidemiology and Biostatistics Mansournia, Mohammad; Tehran University of Medical Sciences, Epidemiology and Biostatistics Yaseri , Mehdi ; Tehran University of Medical Sciences, Epidemiology and Biostatistics Gamtesa, Dinka; Ethiopian Public Health Institute Tesfaye , Ephrem ; Ethiopian Public Health Institute Mahamed , Zemedu ; Ethiopian Public Health Institute Sisay, Million ; Ethiopian Public Health Institute
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Global health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 National treatment outcome and predictors of death and treatment 2 failure in multidrug resistant tuberculosis in Ethiopia: A ten years 3 retrospective cohort study

4 Habteyes Hailu Tola^{1, 2}, Kourosh Holakouie-Naieni^{1*}, Mohammad Ali Mansournia¹, Mehdi
5 Yaseri¹, Dinka Fikadu Gamtesa², Ephrem Tesfaye², Zemedu Mahamed², Million Molla Sisay³

6 ¹Tehran University of Medical Sciences, School of Public Health, Department of Epidemiology
7 and Biostatistics, Tehran, Iran

8 ²Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
9 Ethiopia

10 ³Saint Peter's Specialized Hospital, Research and Evidence Generation Directorate, Addis
11 Ababa, Ethiopia

12 **Habteyes H. Tola** (MSc, PhD)

13 -Tehran University of Medical Sciences, School of Public Health
14 Department of Epidemiology and Biostatistics, Tehran, Iran

15 -Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
16 Ethiopia

17 Email: habetola@gmail.com

18 P.O. Box 1242

19 * **Corresponding author:**

20 **Kourosh Holakouie-Naieni*** (DVM, MSc, PhD)

21 Tehran University of Medical Sciences, School of Public Health
22 Department of Epidemiology and Biostatistics, Tehran, Iran

23 Phone: +98 21-88950185

24 Fax: +98 21-88950185

25 P.O. Box 1416753955

26 Email: holakoik@hotmail.com

27 **Mohammad Ali Mansournia** (MD, PhD)

28 Tehran University of Medical Sciences, School of Public Health
29 Department of Epidemiology and Biostatistics, Tehran, Iran

30 Email: mansournia_ma@yahoo.com

1
2
3 1 P. O. Box 1416753955

4
5 2 **Mehdi Yaseri** (MSc, PhD)

6
7 3 Tehran University of Medical Sciences School of Public Health

8
9 4 Department of Epidemiology and Biostatistics, Tehran, Iran

10
11 5 Email: myaseri@gmail.com

12
13 6 P. O. Box 1416753955

14
15 7 **Dinka Fikadu Gemtesa** (BSc, MPH)

16
17 8 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,

18
19 9 Ethiopia

20
21 10 Email: ejeta430@gmail.com

22
23 11 P. O. Box 1242

24
25 12 **Ephrem Tesfaye** (BSc, MSc)

26
27 13 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,

28
29 14 Ethiopia

30
31 15 Email: ephremt13@gmail.com

32
33 16 P. O. Box 1242

34
35 17 **Zemedu Mahamed** (BSc, MSc)

36
37 18 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,

38
39 19 Ethiopia

40
41 20 Email: zemedu2003@gmail.com

42
43 21 P. O. Box 1242

44
45 22 **Million Molla Sisay** (MD, MSc)

46
47 23 Saint Peter's Specialized Hospital, Research and Evidence Generation Directorate, Addis Ababa,

48
49 24 Ethiopia

50
51 25 Email: milishagr8@gmail.com

52
53 26 P. O. Box 1242

1 Abstract

2 **Objectives:** Treatment success rate in patients treated for multidrug-resistant tuberculosis
3 (MDR-TB) is low, but predictors of treatment failure and death have been underreported. Thus,
4 we aimed to determine the national proportion of treatment success rate in the past 10 years and
5 factors that predict treatment failure and death in MDR-TB patients in Ethiopia.

6 **Setting:** A retrospective cohort study with 10 years follow up period was conducted in 42 MDR-
7 TB treatment initiating centers in Ethiopia.

8 **Participants:** A total of 3,395 adult MDR-TB patients who had final treatment outcome and
9 who were treated under national TB programme were included. Data was collected from clinical
10 charts, registration books and laboratory reports. Competing risk survival analysis model with
11 robust standard error was used to determine predictors of treatment failure and death.

12 **Primary and secondary outcomes:** Treatment outcome was a primary outcome whereas
13 predictors of treatment failure and death were a secondary outcome.

14 **Results:** The proportion of treatment success was 75.7%, death rate was 12.8%, treatment
15 failure was 1.7% and lost-to-follow up 9.7%. The significant predictors of death were older age
16 (adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); $p < 0.001$), HIV infection (AHR =
17 2.0; 95% CI (1.6–2.4); $p < 0.001$) and presence of any grade of anemia (AHR = 1.7; 95% CI
18 (1.4–2.0); $p < 0.001$). Unlike the predictors of death, all variables included into multivariable
19 model were not significantly associated with treatment failure.

20 **Conclusion:** In the past ten years, although MDR-TB treatment success in Ethiopia has been
21 consistently favorable, the proportion of patients who died is still considerable. Death could be
22 attributed to advanced age, HIV-infection and anemia. Prospective cohort studies are necessary
23 to further explore the potential modifiable predictors of treatment failure.

24 **Keywords:** Tuberculosis, Multidrug resistance, Rifampin resistance, Treatment outcome

25

1 **Strengths and Limitations of this study**

- 2 ❖ National multidrug resistance tuberculosis (MDR-TB) treatment success rate in the past ten
3 years was determined using MDR-TB treatment programme data.
- 4 ❖ Although MDR-TB mortality is high, predictors of death and treatment failure are
5 underreported.
- 6 ❖ This study determined the predictors of treatment failure and death using competing risk
7 survival analysis model with robust standard error.
- 8 ❖ Retrospective nature of the study design leads to key variables such as sociodemographic,
9 behavioural, adverse drug reactions, key laboratory variables and treatment adherence status
10 missing.
- 11 ❖ A short MDR-TB treatment regimen is recently introduced in Ethiopia, therefore patients
12 treated by long regimen only were enrolled into this study.

1 Background

2 The emergence of drug resistance tuberculosis (TB) has been undermining the efforts to control
3 TB and continues to cause severe morbidity and mortality among millions across the world. The
4 World Health Organization (WHO) estimated that nearly half a million rifampin-resistant new
5 TB cases occurred in 2019 across the world.¹ Multidrug resistance (MDR) TB is defined as a
6 *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin, whereas extensively drug
7 resistance (XDR) TB refers to a *M. tuberculosis* resistance to at least rifampin and isoniazid as
8 well as resistance to any fluoroquinolone and at least one of the three injectable anti-TB drugs
9 (capreomycin, kanamycin or amikacin)². The treatment of MDR and XDR TB has been largely
10 unsuccessful due to the difficulty of the diagnosis, long duration of the treatment, the less
11 effective and toxic drugs used for the treatment, and unavailability of drug options.³⁻⁵

12 The current MDR-TB treatment success rate (the sum of cured and treatment completed) is
13 considerably low.^{1,3,6} The WHO's recent global estimation indicates that only 57% of MDR-TB
14 patients were successfully treated in 2017.¹ Moreover, a recently published -individual patient
15 data meta-analysis study indicated that 61% of MDR-TB patients treated successfully.⁶
16 However, recent studies indicated relatively higher treatment success rates in certain settings.⁷⁻¹⁰
17 For example, 82.4% of MDR-TB patients were treated successfully in Taiwan⁷, 75.8% in
18 Pakistan¹⁰ and 75.7% in Tanzania.⁸

19 Heterogeneous and interrelated factors are associated with poor MDR-TB treatment outcome.
20 Infection with Human Immunodeficiency Virus (HIV)¹¹⁻¹⁴, diabetes mellitus^{12,15,16}, malnutrition
21 ^{17,18}, and anemia^{12,14,19} are co-morbidities that are associated with poor treatment outcome in
22 patients treated for MDR-TB. Moreover, treatment interruption^{14,20,21}, medication regimens²²,
23 antiretroviral therapy (ART) timing²³, time to MDR-TB treatment initiation after diagnosis²⁴ and

1 previous TB treatment history^{18,25} are treatment related factors that are associated with poor
2 treatment outcome in MDR-TB patients.

3 Ethiopia is among the 30 high TB and MDR-TB prevalent countries with an estimated TB
4 incidence of 140 per 100,000 population in 2019.¹ Despite an improving TB control programme
5 and relative treatment success rate, the prevalence of MDR-TB in Ethiopia remains high with
6 2.2% in new and 21.1% in previously treated TB cases.²⁶ However, WHO's recent estimate in
7 Ethiopia indicated a lower prevalence of 0.71% of MDR-TB in new cases and 12% in
8 previously treated cases in 2019.¹ Although there is no national level report on MDR-TB
9 treatment outcome in Ethiopia, studies reported from local data indicated variable treatment
10 success that ranges between 63%–78.8%.^{9,19,27}

11 The global treatment success rate of MDR-TB is low and there is evidence limitation on the
12 factors that associated with poor treatment outcome. Furthermore, available studies are focused
13 in the determination of predictors of unsuccessful treatment outcome by merging death,
14 treatment failure and lost to follow up in one category. However, this could conceal the actual
15 predictors of death and treatment failure. To that extent, there is no study that reported the
16 predictors of death and treatment failure separately using competing risk survival analysis model
17 with robust standard error. Ethiopia is among the countries which lack such evidence at national
18 level to plan effective intervention that could decrease treatment failure and reduce death in
19 MDR-TB patients. Thus, we aimed to determine the national level treatment success rate in the
20 past 10 years and factors that could predict treatment failure and death in MDR-TB patients in
21 Ethiopia.

1 **Materials and methods**

2 **Study setting, population and design**

3 We conducted a retrospective cohort study on adult patients aged ≥ 15 years old, diagnosed
4 either biologically or clinically for both pulmonary and extra-pulmonary TB, and enrolled to
5 MDR-TB treatment at 42 treatment initiating centers (TICs) in Ethiopia from February 2009 to
6 February 2019. MDR-TB treatment was started in February 2009 in one hospital in Addis
7 Ababa, Ethiopia.²⁷ During this study period, there were a total of 53 TICs and several treatment
8 follow up centers (TFCs) in the country. The majority of MDR-TB patients initiate their
9 treatments in TICs while stable patients follow the treatment under directly observed therapy
10 (DOT) programme in nearby TICs or TFCs as ambulatory outpatients. However, all information
11 on the patients registered for MDR-TB treatment has been documented at TICs where the patient
12 started the treatment. We included a total of 42 TICs into this study; the remaining 11 TICs had
13 no patients who completed their treatment during the study period.

14 **Inclusion and exclusion criteria**

15 We included all adult patients who were aged 15 years and older, diagnosed either
16 bacteriologically or clinically for MDR-TB and enrolled to the treatment from February 2009.
17 Children less than 15 years old were excluded from this study, because their treatment guideline
18 is different from the adults. Moreover, we excluded patients who had no final treatment outcome
19 (transferred out or still on treatment or treatment outcome missed from data sources).

20 **Laboratory test**

21 All laboratory tests were performed according to WHO recommendation and national TB
22 laboratory algorithm in quality assured TB laboratories.^{28,29} To detect drug resistant TB, culture
23 tests were carried out with solid media (Löwenstein-Jensen (LJ)) and a fluorometric BACTEC

1 MGIT960 at one national TB reference laboratory and nine regional laboratories. In addition,
2 GeneXpert MTB/RIF assay was used to detect rifampin resistant TB. This assay is a rapid,
3 sensitive and specific technique that is widely used to detect *M. tuberculosis* and rifampin
4 resistance at each level in the national health system. Drug susceptibility test (DST) for first-line
5 drugs was performed by BACTEC MGIT960 system based on WHO recommended critical
6 concentrations for rifampin (1.0 µg/ml), isoniazid (0.1 µg/ml), streptomycin (1.0 µg/ml),
7 ethambutol (5µg/ml) and pyrazinamide (100 µg/ml). DST for second-line drugs has been
8 recently started in the country and rarely performed. Data on second-line DST was not included
9 to this study because very few DST results for SLDs were obtained in the records. Quality
10 assurance for DST was regularly performed by Milan supranational reference laboratory in Italy
11 and demonstrated constant proficiency.

12 **Treatment**

13 Previously, all MDR-TB patients were treated as inpatient model of care for the first few months
14 at treatment centers until the patient were clinically stable with culture conversion. However,
15 according to the recent edition of national TB treatment guideline (2018), all patients with MDR-
16 TB need to be treated under clinic-based ambulatory model of care²⁹, unless the patients are
17 clinically unstable, or developed severe adverse drug reaction. Patients either with serious
18 medical or social conditions could be admitted with the decision of the treatment panel.
19 Standardized long treatment regimens were used to treat MDR-TB patients in Ethiopia. The long
20 treatment regimen contained at least four oral drugs used daily during full course of treatment
21 and one injectable drug until *M. tuberculosis* culture conversion. Treatment with injectable drugs
22 continues at least for eight months based on clinical, microbiological and radiographic
23 examination results. The minimum treatment duration was 20 months -at least 18 months after

1 bacteriological conversion. The 9–11 months (short treatment regimen) was not used.²⁹ The
2 second line drugs used to treat MDR-TB in Ethiopia are levofloxacin, ethionamide, cycloserine,
3 para-aminosalicylic acid (PAS), pyrazinamide, prothionamide, linezolid, clofazimine and
4 injectable drugs such as amikacin, kanamycin and capreomycin.²⁹ All the patients enrolled into
5 this study were treated by a standardized long term regimen consisting of capreomycin,
6 levofloxacin, prothionamide, cycloserine and high dose isoniazid during the intensive phase.²⁹
7 During the continuation phase, levofloxacin, prothionamide, cycloserine and high dose isoniazid
8 were used.²⁹ Laboratory tests, chest X-ray and clinical investigations are used to monitor
9 response to the treatment and to identify treatment related complications in patients on MDR-TB
10 treatment in Ethiopia. Clinical investigations only are used to monitor response to the treatment,
11 while laboratory tests are used to identify treatment related complications for extra-pulmonary
12 TB patients. MDR-TB treatment is free of any cost in Ethiopia and there is full access to all
13 categories of drugs to treat MDR-TB patients.

14 **Data collection**

15 We collected data on socio-demographic variables such as sex, age and regional state. We also
16 collected TB related data such as anatomical site of TB (pulmonary vs extra pulmonary), drug
17 resistance type (RR vs MDR), previous treatment (new vs previously treated), diagnosis method
18 (bacteriologically vs clinically), HIV status (HIV-infected vs not infected) and antiretroviral
19 therapy (ART) status (on ART vs not on ART vs not applicable). In addition, we collected
20 information on bacteriological status (smear, GeneXpert MTB/RIF, culture or first-line drugs
21 DST results) at treatment initiation. All data were extracted from patients' clinical charts,
22 registration books and laboratory reports. Data were collected by health professionals familiar
23 with MDR-TB treatment after two days practical training on data management.

1 **Definitions**

2 In this study, we used standard WHO and national treatment guidelines definitions for laboratory
3 confirmations, patient categories and treatment outcomes.^{28,29} Clinically diagnosed MDR-TB
4 refers to those cases with no documented drug susceptibility test (DST) results but treated
5 empirically with a course of treatment including SLDs based on clinical criteria and contact
6 history.²⁹ However, bacteriologically confirmed MDR-TB refers to those cases with documented
7 DST results. All patients were categorized into new patients (never treated for TB or for less than
8 one month) and patients previously treated for TB. The final treatment outcomes of MDR-TB
9 were cured, treatment completed, death, treatment failed and lost to follow up. Cured is refers to
10 a patient initially bacteriologically confirmed and completed the treatment without the evidence
11 of treatment failure and three or more consecutive cultures taken at least 30 days apart being
12 negative after the intensive phase. Treatment completed is defined as a patient who completed
13 the treatment without the evidence of treatment failure but there is no record that indicates three
14 or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. A
15 patient whose treatment is terminated or need for permanent regimen change of at least two anti-
16 TB drugs is categorized as treatment failure. Lost to follow up also refers to a patient whose
17 treatment is interrupted for two consecutive months or more. Successful treatment outcome was
18 the sum of cured and treatment completed, whereas unsuccessful was the combination of death,
19 treatment failed and lost to follow up.

20 **Data analysis**

21 We entered data into CSPro software version 6.1 and analyzed by STATA version 14
22 (StataCorp, College Station, TX, USA). The data were confirmed from each data source and
23 cleaned for errors before main analysis. We described participants' demographic and clinical

1 characteristics using descriptive statistics. The proportions of MDR-TB treatment outcomes were
2 frequency weighed by the total number of patients registered from February, 2009 to February,
3 2019 in each TIC.

4 We used a competing risk survival analysis model with robust standard error to assess the effects
5 of different variables on the treatment failure and death. Effect levels were reported by Hazard
6 Ratio (HR) with 95% Confidence Intervals (CIs). We included variables scored p-values less
7 than or equal to 0.2 during bivariate analysis and clinically or epidemiologically relevant. We
8 considered death as failure event to estimate the effects of different variables on death, while
9 treatment failure and success were considered as competing risks. Similarly, we considered
10 treatment failure as failure event to estimate the effects of different variables on the duration
11 from treatment enrolment to treatment failure, whereas death and treatment success were
12 considered as competing risks. Lost to follow up was considered as a censored across the fitted
13 models. Level of significance was set at 5% for all analysis.

14 **Patient and public involvement:** Both patient and public were not involved in this study.

15 Results

16 Participants' characteristics

17 A total of 4,419 patients were enrolled to MDR-TB treatment in 42 of 53 (79.2%) treatment
18 initiating centers (TICs) in Ethiopia from February, 2009 to February, 2019 [Fig 1]. Of the 4,419
19 patients, 3,395 (76.8%) fulfilled our inclusion criteria and enrolled to this study [Fig 1].

20 The highest number of patients enrolled into the treatment was in 2015 (667 patients), while in
21 2019 the smallest number of patients were registered (only 4 patients) [Fig 2].

22 Of the 3,395 patients included into this study, 1,870 (55.1%) were male, and the mean age was
23 31.6 (SD \pm 11.7) years with the age range of 15 to 85 years. Seventy two percent of the patients

1 were in the age category of 15 to 35 years [Table 1]. Ninety three percent of the participants
 2 were pulmonary TB patients [Table 1]. Eighty six percent of patients had previous TB treatment
 3 history. Drug resistance status of 3,242 (95.5%) isolates were bacteriologically confirmed at the
 4 initiation of treatment [Table 1]. The main drug resistance diagnosis method was GeneXpert
 5 MTB/RIF (57.9%). Of the 3,395 patients, 1,421 (41.9%) had previous exposure to second line
 6 drugs and 767 (22.6%) were HIV infected [Table 1] of which 686 (89.4%) were on ART. Only
 7 6.0% of the patients had previous MDR-TB patient contact history and 1,831 (53.9%) of patients
 8 were hospitalized at the treatment initiation [Table 1] with mean duration of hospitalization 81.7
 9 (± 47.4) days.

10 **Table 1: Demographic and clinical characteristics of the patients (n = 3,395)**

Variable		n (%)
Sex	Male	1,870 (55.1)
	Female	1,525 (44.9)
Age (in year)	15–25	1,268 (37.3)
	26–35	1,186 (34.9)
	36–45	529 (15.6)
	≥ 46	412 (12.1)
Drug resistance type	RR/INH status unknown	1,810 (53.3)
	MDR-TB	1,585 (46.7)
Anatomical site of TB	Pulmonary	3,171 (93.4)
	Extra pulmonary	224 (6.6)
Previous TB treatment	New	462 (13.6)
	Previously treated	2,933 (86.4)
Previous exposure to SLDs	Yes	1,421 (41.9)
	No	1,842 (54.3)
	Unknown	132 (3.9)
Drug resistance identification method	GeneXpert MTB/RIF	1,967 (57.9)
	Culture/LPA	1,275 (37.6)
	Clinical	153 (4.5)
Diagnosis method	Bacteriological	3,242 (95.5)
	Clinical	153 (4.5)
HIV infection	Not infected	2,554 (75.2)
	Infected	767 (22.6)
	Unknown	74 (2.2)
ART status	Not applicable	2,556 (75.3)
	On ART	686 (20.2)
	HIV status known but, ART status	79 (2.3)
	unknown	
	Both ART and HIV statuses unknown	74 (2.2)
MDR-TB patient contact history	Yes	204 (6.0)
	No	1,511 (44.5)
	Unknown	1,680 (49.5)

Hospitalization history at treatment initiation	Hospitalized	1,831 (53.9)
	Not hospitalized	487 (14.3)
	Unknown	1,077 (31.7)
Treatment interruption	Never interrupted/interruption status unknown	3,192 (94.0)
	At least one day interrupted	203 (6.0)

1 *TB-tuberculosis, ART-Antiretroviral therapy, SLDs-Second line drugs, HIV-Human immunodeficiency virus, MDR-*
 2 *Multidrug resistant, LPA-Line probe Assay*

3 **Drug resistance status at treatment initiation**

4 Drug susceptibility testing was performed for four first-line drugs which are rifampin, isoniazid,
 5 ethambutol and streptomycin [Table 2]. Rifampin susceptibility test was performed on isolates of
 6 all patients included into this study and 99.3% of isolates demonstrated resistance to the therapy
 7 [Table 2].

8 **Table 2: Anti-tuberculosis drug susceptibility test results**

Anti-tuberculosis drug	Susceptibility test results	n (%)
Rifampin (n=3,395)	Resistant	3,371 (99.3)
	Susceptible	24 (0.7)
Isoniazid (n = 1,313)	Resistant	1,241 (94.5)
	Susceptible	72 (5.5)
Ethambutol (n = 427)	Resistant	299 (70.0)
	Susceptible	128 (30.0)
Streptomycin (n = 443)	Resistant	337 (76.1)
	Susceptible	106 (23.9)

9 Table 3 depicts the distribution of treatment outcome categories by sociodemographic and
 10 clinical characteristics. Of 1,585 patients whose isolates were resistant to rifampin and isoniazid
 11 (MDR-TB), 793 (50.0%) cured, while 180 (11.4%) died and the treatment of 24 (1.5%) patients
 12 were failed. Treatment failure was almost ten times higher in patients who had previous TB
 13 treatment history (21.7%), than those who were never treated (2.2%). Moreover, mortality was
 14 two times higher in patients who were HIV infected (21.3%), than those who were HIV non-
 15 reactive (10.2%).

1 Table 3: Demographic and clinical characteristics distribution of treatment outcome

Variables	Treatment outcome n (%)							P-value
	Cured	Completed	Treatment success	Failed	Death	LTFU		
Sex	Male	1,006 (53.8)	376 (20.1)	1,382 (73.9)	40 (2.1)	245 (13.1)	203 (10.9)	0.071
	Female	839 (55.0)	344 (22.6)	1,183 (77.6)	26 (1.7)	186 (12.2)	130 (8.5)	
Resistance type	RR/INH status	1,052 (58.1)	274 (15.1)	1,326 (73.2)	42 (2.3)	251 (13.9)	191 (10.6)	< 0.001
	unknown							
Anatomical site	MDR	793 (50.0)	446 (28.1)	1,239 (78.1)	24 (1.5)	180 (11.4)	142 (9.0)	< 0.001
	EPTB	50 (22.3)	125 (55.8)	173 (78.1)	4 (1.8)	20 (8.9)	25 (11.2)	
Previous TB treatment	PTB	1,795 (56.6)	595 (18.8)	2,390 (75.4)	62 (2.0)	411 (13.0)	308 (9.7)	< 0.001
	New	243 (52.6)	83 (18.0)	326 (70.6)	10 (2.2)	75 (16.2)	51 (11.0)	
Diagnosis method	Previously treated	1,602 (54.6)	637 (21.7)	2,239 (76.3)	56 (21.7)	356 (12.1)	282 (9.6)	0.057
	Bacteriological	1,771 (54.6)	686 (21.2)	5,457 (75.8)	64 (2.0)	409 (12.6)	313 (9.7)	
HIV status	Clinical	74 (48.7)	34 (22.4)	108 (71.1)	2 (1.3)	22 (14.5)	20 (13.2)	0.466
	Non-reactive	1,429 (56.0)	561 (22.0)	1,990 (78.0)	48 (1.9)	261 (10.2)	255 (10.0)	
Anemia	Reactive	378 (49.3)	141 (18.4)	519 (67.7)	17 (2.2)	163 (21.3)	68 (8.9)	< 0.001
	None anemic	880 (55.0)	380 (23.8)	1,260 (78.8)	29 (1.8)	150 (9.4)	161 (10.1)	
	Any grade of anemia present	965 (53.8)	340 (18.9)	1,305 (72.7)	37 (2.1)	281 (15.7)	172 (9.6)	< 0.001

2 Treatment outcome

3 Of the 3,395 patients enrolled into this study, 1,845 (40.0%) were cured, 720 (35.7%) completed
 4 the treatment, 431 (12.8%) died, 333 (9.7%) were lost to follow up and the treatment of 66
 5 (1.7%) patients failed [Fig 3]. The overall treatment success (cured plus treatment completed)
 6 was 2,565 (75.7%), whereas the overall unsuccessful treatment outcome (the sum of lost to
 7 follow up, treatment failed and death) was 830 (24.3%).

8 Predictors of treatment failure and death

9 Bivariate analysis

10 In the current competing risk survival analysis model, failure events were treatment success
 11 (2,565), treatment failure (66) and death 431 (431). To the contrary, 333 (9.7%) lost to follow up
 12 were considered as censored. In the bivariate competing risk survival analysis model, old age
 13 (unadjusted hazard ratio (UHR) = 1.03; 95% CI (1.04–1.05); $p < 0.001$), HIV infection (UHR =
 14 2.2; 95% CI (1.8–2.7); $p < 0.001$) and presence of any grade of anemia (UHR = 1.7; 95% CI

(1.4–2.1); $p < 0.001$) were significantly associated with death [Table 4]. Moreover, having previous TB treatment history (UHR = 0.71; 95% CI (0.56–0.92); $p = 0.009$) and presence of rifampin resistant bacilli (UHR = 1.3; 95% CI (1.03–1.5); $p = 0.022$) were significantly associated with death [Table 4]. However, none of the variables assessed had shown significant association with treatment failure [Table 4].

Table 4: Predictors of duration from treatment initiation to death and treatment failure in patients treated for MDR-TB in Ethiopia, 2009-2019 (Unavailable model)

Variable	Death		Treatment failure	
	UHR (95%CI)	P-value	UHR(95% CI)	P-value
Sex	Female	1.00	1.00	
	Male	1.1 (0.89–1.3)	0.436	1.3 (0.78–2.1)
Age (year)	1.03 (1.04–1.05)	< 0.001	0.98 (0.96–1.0)	0.122
Anatomical sit	Extra-pulmonary	1.00	1.00	
	Pulmonary	1.5 (0.94–2.3)	0.094	1.1 (0.40–3.0)
Drug resistance type	MDR	1.00	1.00	
	RR/INH status unknown	1.3 (1.03–1.5)	0.022	1.6 (0.95–2.6)
Previous treatment	New	1.00	1.00	
	Previously treated	0.71 (0.56–0.92)	0.009	0.86 (0.44–1.7)
Diagnosis method	Bacteriological	1.00	1.00	
	Clinical	1.2 (0.76–1.8)	0.468	0.68 (0.17–2.8)
HIV status	Non-reactive	1.00	1.00	
	Reactive	2.2 (1.8–2.7)	< 0.001	1.2 (0.68–2.1)
Anemia status	Absent	1.00	1.00	
	Any grade of anemia present	1.7 (1.4–2.1)	< 0.001	1.1 (0.70–1.9)

8 *TB-tuberculosis, HIV-Human immunodeficiency virus, UHR- Unadjusted hazard ratio, CI-Confidence interval,*
9 *MDR-Multidrug resistant*

10 Multivariable analysis

11 In multivariable analysis, older age (Adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); p
12 < 0.001), HIV infection (AHR = 2.0; 95% CI (1.6–2.4); $p < 0.001$) and presence of any grade
13 anemia (AHR = 1.7; 95% CI (1.4–2.0); $p < 0.001$) were significantly associated with death
14 [Table 5]. All variables included into multivariable competing risk survival analysis model were
15 not significantly associated with treatment failure [Table 5]. Although presence of rifampin
16 resistant bacilli and having previous TB treatment history were significantly associated with
17 death in the unadjusted analysis, they failed to significantly associate in the adjusted analysis.

Table 5: Predictors of duration from treatment initiation to death and treatment failure in patients treated for MDR-TB in Ethiopia, 2009-2019 (Multivariate model)

Variable		Death		Treatment failure	
		AHR (95%CI)	P-value	AHR(95% CI)	P-value
Sex	Female	1.00		1.00	
	Male	0.92 (0.75–1.1)	0.397	1.3 (0.82–2.2)	0.248
Age (year)		1.04 (1.03–1.05)	< 0.001	0.98 (0.96–1.0)	0.077
Anatomical sit	Extra-pulmonary TB	1.00		1.00	
	Pulmonary TB	1.4 (0.91–2.2)	0.126	1.1 (0.39–3.0)	0.878
Drug resistance type	MDR	1.00		1.00	
	RR/INH status unknown	1.2 (0.98–1.5)	0.083	1.7 (0.98–2.8)	0.060
Previous treatment	New	1.00		1.00	
	Previously treated	0.79 (0.61–1.0)	0.083	0.98 (0.49–1.9)	0.947
HIV status	Non-reactive	1.00		1.00	
	Reactive	2.0 (1.6–2.4)	< 0.001	1.3 (0.72–2.2)	0.425
Anemia status	Absent	1.00		1.00	
	Anemia present	1.7 (1.4–2.0)	< 0.001	1.1 (0.66–1.8)	0.767

TB-tuberculosis, HIV-Human immunodeficiency virus, AHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Discussion

The current study aimed to determine the proportion of national treatment success rate and predictors of treatment failure and death in patients treated for MDR-TB in Ethiopia in the past ten years. We have found that 75.7% of MDR-TB patients were successfully treated, whereas 12.8% died, 9.7% lost to follow up and the treatment of 1.7% patients failed. The proportion of the patients registered for MDR-TB treatment has shown increasing trend from 2009 and the maximum proportion (19.6%) was registered in 2015. However, the proportion of patients registered for the treatment has decreased after 2015 and the minimum patients were registered in 2019. Old age, HIV infection and any grade of anemia were significant predictors of death in patients treated for MDR-TB in the present study. However, none of the variables included into the multivariable model were able to significantly predict treatment failure.

The present study indicates that the proportion of treatment enrolment after 2015 has decreased and the lowest number of cases were recorded in 2019. We do not think that the MDR-TB incidence decreased importantly, and we therefore think that there might have been registration-related problems as the result of decentralization of TB care to the communities. As patients

1 included into this study were those who had final treatment outcome results, enrolment of
2 patients in 2018 and 2019 is expectedly low as they were still on treatment.

3 In the current study, treatment success proportion in MDR-TB patients who received a
4 standardized long regimen was higher than the treatment success rate previously reported from
5 other settings including from Ethiopia.^{19,20,30} For instance, a recent study reported from Morocco
6 indicated that only 53.4% of MDR-TB patients were treated successfully.³⁰ In addition, a study
7 reported from Armenia shows that less than 50% of MDR-TB patients were successfully
8 treated.²⁰ A recent review study that pooled data from different settings have also shown lower
9 treatment success rate than our findings.³¹ These differences originate most likely from the
10 differences in the quality of TB control programme, sample size, severity of the disease at
11 diagnosis, TB/HIV co-infection burden, treatment regimens and study period. A previous study
12 conducted in Ethiopia in two treatment initiation centers²⁷ reported very similar treatment
13 success rate with our finding (78.6% vs 75.7%).

14 The proportion of death in the current study was considerably higher and it was similar with
15 previously reported findings.^{19,27} Case in point, the proportion of patients who died in our study
16 was more than double compared to the mortality proportion reported from Morocco (5% vs
17 12.7%).³⁰ This difference is most probably due to difference in the study period, quality of care,
18 treatment regimens, and severity of the disease during treatment initiation.

19 Our study finding shows that older age is significantly associated with death from MDR-TB. In
20 agreement with this findings, it is well documented that MDR-TB mortality is higher in older age
21 group.³²⁻³⁴ Thus, particular attention has to be given to older patients to reduce mortality related
22 to TB. A previous study has shown that younger age is significantly associated with poor

1 treatment outcome than older age.³⁵ This difference could probably be due to the age variation in
2 the included patients and the difference in the severity of the disease at treatment initiation.
3 In the current study, as in several previous studies^{19,25–27,35}, HIV infection was significantly
4 associated with death. Despite the proportion of patients who were not on antiretroviral therapy
5 (ART) were low (of HIV infected patients only 4.5 %), the hazard of death was 2.0 times higher
6 in HIV infected patients. The possible explanation for the significant effect of HIV status on
7 mortality in patients on MDR-TB treatment could be due to low CD4 count, high viral load and
8 severity of the disease at treatment initiation. However, since data on CD4 count, HIV viral load
9 level and disease severity status at enrolment were not registered in our data sources, we were
10 not able to verify their effects on MDR-TB treatment outcome. Furthermore, a previous study
11 indicated that a combined anti-TB and anti-HIV treatment has been proven to improve treatment
12 success in co-infected patients.³⁶
13 In the present study, the presence of any grade of anemia was significantly associated with death
14 due to MDR-TB. This finding is similar with a previous study reported from Ethiopia in which
15 the hazard of poor treatment outcome was 4.2 times higher in the patients who had any grade of
16 anemia at treatment initiation than those who were non-anemic.¹⁹ The presence of anemia at the
17 treatment initiation might be due to parasitic infections and some other chronic diseases. This
18 finding highlights the importance of hemoglobin monitoring in MDR-TB patients on treatment to
19 increase treatment success and decrease mortality.
20 In the current study, none of the variables included into the multivariable model were
21 significantly associated with treatment failure. The absence of significant association between
22 the variables and treatment failure could be due to the number of treatment failure events that
23 was much smaller than the competing risks i.e. death and treatment success.

1 The main limitation of this study is the retrospective nature of the study design. Data on
2 sociodemographic, behavioural, adverse drug reactions, key laboratory variables and treatment
3 adherence status were missing for the majority of the patients; hence these variables were
4 excluded from the analysis. This limited us to further explore the predictors of treatment failure
5 and death. Thus, the predictors of death may not be limited to the factors presented in this study.
6 Moreover, lack of important variables could have resulted in an underestimation/overestimation
7 of the effects of the investigated variables in the model such as age, HIV status, previous TB
8 treatment history etc on treatment failure and death. A prospective study that could capture all
9 these uninvestigated variables is important to determine predictors of treatment failure and death.

10 The findings of the present study have clearly indicated the message for TB control programme
11 efforts. Although treatment success rate is well achieved, mortality in the current study is
12 considerable and hence should be addressed by the TB programme. HIV infection is one of
13 strong predictors of death in MDR-TB patients. Taking in consideration of HIV infected MDR-
14 TB patients and immediate commencement of anti-TB treatment together with ART is the
15 mechanism to improve treatment success in MDR-TB patients. Moreover, our result indicates
16 that special attention should be given to patients who have anemia at treatment initiation in order
17 to improve their treatment outcome. Strengthening and standardizing information registration on
18 MDR-TB treatment is crucial to facilitate further data analysis which is important to monitor the
19 status of treatment outcome.

20 **Conclusion**

21 In the past ten years, MDR-TB treatment in Ethiopia has been successful. However, the
22 proportion of patients who died is considerable, and it could be reduced through providing

1 special attention to HIV-infected and anemic patients. Further prospective cohort study is
2 required to explore other predictors of treatment failure and death.

3 **Acknowledgement**

4 We would like to acknowledge the Tehran University of Medical Sciences (TUMS) and the
5 Ethiopian Public Health Institute (EPHI) for funding this study. We also thank EPHI, National
6 Tuberculosis Laboratory and all DR-TB treatment centers staff members for their cooperation
7 during the data collection process. We would also like to acknowledge all patients whose data
8 were used in this study.

9 **Author contributions:** HHT and KH conceived and designed the study; HHT, DFG, ET, ZM
10 and MMS collected the data; HHT, MAM and MY analyzed and interpreted the data; HHT
11 drafted the manuscript. All authors have critically reviewed and approved the manuscript for
12 submission.

13 **Funding:** This work was supported by Tehran University of Medical Sciences and Ethiopian
14 Public Health Institute. The grand number of the funded institute is not applicable.

15 **Competing interests:** None declared.

16 **Ethics consideration:** This study was approved by the research Ethics Review Board of Tehran
17 University of Medical Sciences (IR.TUMS.SPH.REC.1396.4287), Ethiopian Public Health
18 Institute (EPHI-IRB-065-2017), St. Peter's Specialized Hospital (V81622018) and Armauer
19 Hansen Research Institute (PO13/18). We also obtained a waiver of informed consent from each
20 review board. To maintain confidentiality, sensitive information that could identify participants
21 was not reported in this study.

1 **Data availability statement:** Data used in this study is available from the corresponding authors
2 and accessible upon reasonable request.

3 **References**

- 4 1. World Health Organization. Global tuberculosis report 2020. 2020 p. 1–232.
- 5 2. Curry International Tuberculosis Center, and California Department of Public Health Drug-resistant tuberculosis: A survival guideline for clinicians. 2016.
- 6 3. Gunther G, Lange C, Alexandru S, Altet N. Treatment Outcomes in Multidrug-Resistant Tuberculosis. *N Engl J Med*. 2016;375(11).
- 7 4. Lange C, Abubakar I, Alffenaar JC, Bothamley G, Caminero JA, C.Carvalho AC, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. *Eur Respir J*. 2014;44:23–63.
- 8 5. Pontali E, Visca D, Centis R, Ambrosio LD, Spanevello A, Battista G. Multi and extensively drug-resistant pulmonary tuberculosis: advances in diagnosis and management. *Curr Opin Pulm Med*. 2018;24:244–52.
- 9 6. Ahmad N, Ahuja S, Akkerman O, Alffenaar J, Anderson L, Baghaei P, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data metaanalysis. *Lancet*. 2018;392(10150):821–34.
- 10 7. Yu M, Chiang C, Lee J, Chien S, Lin C, Lee S, et al. Treatment Outcomes of Multidrug-Resistant Tuberculosis in Taiwan: Tackling Loss to Follow-up. *Clin Infect Dis*. 2018;67(2):202–210.
- 11 8. Leveru TH, Lekule I, Mollel E, Lyamuya F, Kilonzo K. Predictors of Treatment Outcomes among Multidrug Resistant Tuberculosis Patients in Tanzania. *Tuberc Reserch Treat*. 2019;2019:1–10.
- 12 9. Woldeyohannes D, Assefa T, Aman R, Tekalegn Y. Predictors of time to unfavorable treatment outcomes among patients with multidrug resistant tuberculosis in Oromia region. *PLoS One*. 2019;14(10):e0224025.
- 13 10. Javaid A, Ullah I, Masud H, Basit A, Ahmad W, Butt ZA, et al. Predictors of poor treatment outcomes in multidrug-resistant tuberculosis patients: a retrospective cohort study. *Clin Microbiol Infect*. 2017;2017.
- 14 11. Aibana O, Bachmaha M, Krasiuk V, Rybak N, Flanigan TP, Petrenko V, et al. Risk factors for poor multidrug-resistant tuberculosis treatment outcomes in Kyiv Oblast, Ukraine. *BMC Infect Dis*. 2017;17(2017):129.
- 15 12. Ketema DB, Muchie KF, Andargie AA. Time to poor treatment outcome and its predictors among drug-resistant tuberculosis patients on second-line anti-tuberculosis treatment in Amhara region, Ethiopia: retrospective cohort study. *BMC Public Health*; 2019;19(2019):1481.
- 16 13. Samuels JP, Sood A, Campbell JR, Khan FA, Johnston JC. Comorbidities and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis. *Sci Rep*; 2018;8(2018):4980.
- 17 14. Tola HH, Holakouie-na K, Mansournia MA, Yaseri M, Tesfaye E, Mahamed et al. Intermittent treatment interruption and its effect on multidrug resistant tuberculosis treatment outcome in Ethiopia. *Sci Rep*. 2019;9:20030.

- 1 15. Kang Ya, Kim S, Jo K, Kim H, Park S, Kim T, et al. Impact of Diabetes on Treatment
2 Outcomes and Long-Term Survival in Multidrug-Resistant Tuberculosis. *Respiration*.
3 2013;86:472–8.
- 4 16. Dooley KE, Tang T, Golub JE, Cronin W. Impact of diabetes mellitus on treatment outcomes
5 of patients with active tuberculosis. *AM J Trop Med Hyg*. 2009;80(4):634–9.
- 6 17. Samuel B, Volkmann T, Cornelius S, Mukhopadhyay S, Mitra K, Kumar AM V, et al.
7 Relationship between Nutritional Support and Tuberculosis Treatment Outcomes in West
8 Bengal, India. *J Tuberc Res*. 2016;4(4):213–9.
- 9 18. Milanov V, Falzon D, Zamfirova M, Varleva T, Bachiyska E, Koleva A, et al. Factors
10 associated with treatment success and death in cases with multidrug-resistant tuberculosis
11 in Bulgaria , 2009 – 2010. *Int J Mycobacteriology*. 2015;4(2):131–7.
- 12 19. Alene KA, Viney K, Mcbryde ES, Tsegaye AT, Clements ACA. Treatment outcomes in
13 patients with multidrug-resistant tuberculosis in north-west Ethiopia. *Trop Med Int Heal*.
14 2017;22(3):351–62.
- 15 20. Bastard M, Sanchez-padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, et al.
16 Effects of treatment interruption patterns on treatment success among patients with
17 multidrug-resistant tuberculosis in Armenia and Abkhazia. *J Infect Dis*. 2015;211:1607–
18 16.
- 19 21. Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of treatment interruption among
20 patients with multidrug-resistant TB (MDR TB) and association with interim and final
21 treatment outcomes. *PLoS One*. 2013;8(7):e70064.
- 22 22. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug
23 resistant pulmonary tuberculosis treatment regimens and patient outcomes: An individual
24 patient data meta-analysis of 9,153 Patients. *PLoS Med*. 2012;9(8):e1001300.
- 25 23. Umanah T, Ncayiyana J, Padanilam X, Nyasulu PS. Treatment outcomes in multidrug
26 resistant tuberculosis-human immunodeficiency virus Co-infected patients on anti-
27 retroviral therapy at Sizwe Tropical Disease Hospital Johannesburg, South Africa. *BMC*
28 *Infect Dis*. 2015;15:478.
- 29 24. Chen Y, Yuan Z, Shen X, Wu J, Wu Z. Time to Multidrug-Resistant Tuberculosis Treatment
30 Initiation in Association with Treatment Outcomes in Shanghai, China. *Antimicrob Agents*
31 *Chemother*. 2018;62:e02259–17.
- 32 25. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-
33 resistant pulmonary TB. *Eur Respir J*. 2009;33:1085–94.
- 34 26. Girum T, Muktar E, Lentiro K, Wondiye H, Shewangizaw M. Epidemiology of multidrug-
35 resistant tuberculosis (MDR-TB) in Ethiopia: a systematic review and meta-analysis of
36 the prevalence, determinants and treatment outcome. *Trop Dis Travel Med Vaccines*.
37 *Tropical Diseases, Travel Medicine and Vaccines*; 2018;4(2018):5.
- 38 27. Meressa D, Hurtado RM, Andrews JR, Diro E, Abato K, Daniel T, et al. Achieving high
39 treatment success for multidrug- resistant TB in Africa : initiation and scale-up of MDR
40 TB care in Ethiopia — an observational cohort study. *Thorax*. 2015;70:1181–8.
- 41 28. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis
42 treatment. Geneva, Switzeland; 2019.
- 43 29. Federal Democratic Republic of Ethiopia Ministry of Health. Guidelines for Management of
44 TB, DR-TB and Leprosy in Ethiopia: Sixth Ed. Addis Ababa, Ethiopia; 2018.

- 1
2
3 1 30. Hamdouni M El, Bourkadi JE, Benamor J, Hassar M, Cherrah Y. Treatment outcomes of
4 2 drug resistant tuberculosis patients in Morocco: multi- centric prospective study. *BMC*
5 3 *Infect Dis*; 2019;19:316.
6 4
7 4 31. Bastos ML, Lan Z, Menzies D. An updated systematic review and meta-analysis for
8 5 treatment of multidrug-resistant tuberculosis. *Eur Respir J* ; 2017;49:1600803.
9 6
10 6 32. Li J, Li T, Bs X Du, Fhkccm PC, Zhang H. The age-structured incidence and mortality of
11 7 pulmonary tuberculosis reported in China , in 2005 – 15 : a longitudinal analysis of
12 8 national surveillance data. *Lancet*; 2017;390:S12.
13 9
14 10 33. Chingonzoh R, Manesen MR, Madlavu MJ, Kuonza R. Risk factors for mortality among
15 11 adults registered on the routine drug resistant tuberculosis reporting database in the
16 12 Eastern Cape Province, South Africa, 2011 to 2013. *PLoS One*. 2018;13(8):e0202469.
17 13
18 12 34. Gayoso R, Dalcolmo M, Ueleres J, Barreira D. Predictors of mortality in multidrug-resistant
19 13 patients from Brazilian refence centers, 2005 to 2012. *Brazilian J Infect Dis*;
20 14 2018;22(4):305–10.
21 15
22 15 35. Nair D, Velayutham B, Kannan T, Tripathy J, Harries A, Natrajan M, et al. Predictors of
23 16 unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India.
24 17 *Public Heal Action*. 2017;7(1):32–8.
25 18
26 18 36. Yuengling KA, Padayatchi N, Wolf A, Mathema B, Brown T, Horsburgh CR, et al. Effect of
27 19 antiretroviral therapy on treatment outcomes in a prospective study of extensively drug
28 20 resistant tuberculosis (XDR-TB) HIV co-infection treatment in KwaZulu-Natal, South
29 21 Africa. *Acquir Immune Defic Syndr*. 2019;79(4):474–80.
30 22
31 23

30 24 **Figure legend**

31 25 **Figure 1:** Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment
32 26 initiating centers)

33 27 **Figure 2:** Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–
34 28 2019)

35 29 **Figure 3:** MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

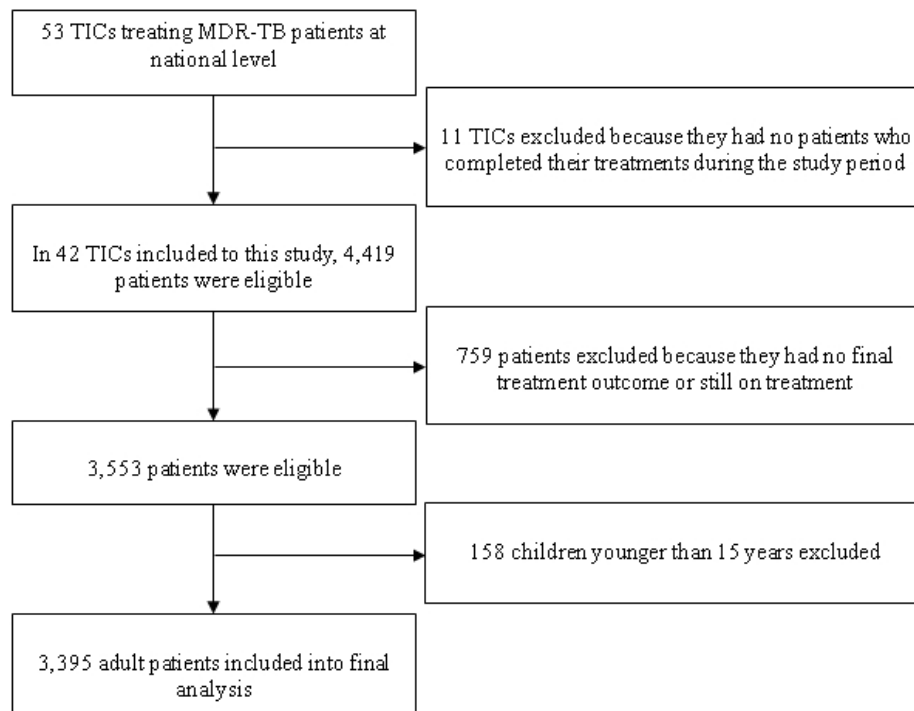


Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

171x132mm (96 x 96 DPI)

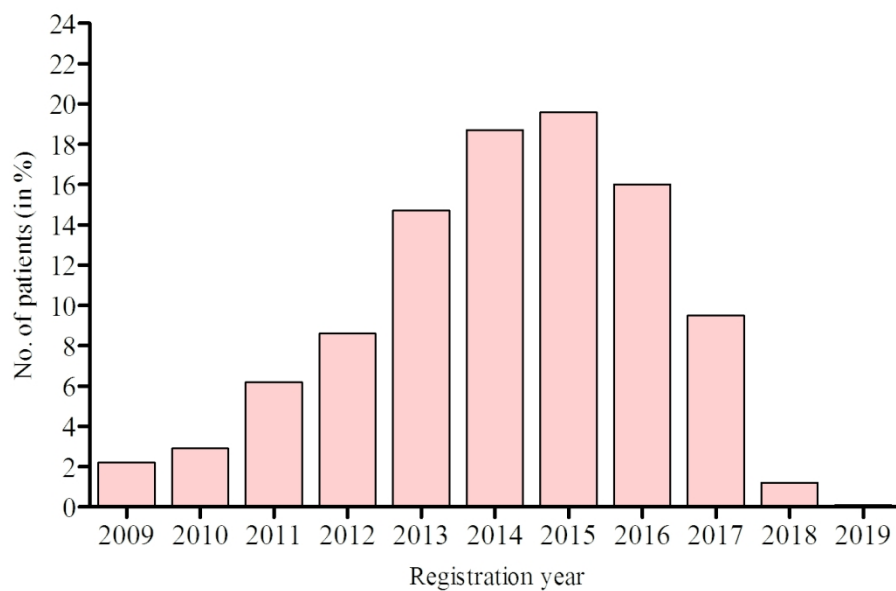


Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

137x88mm (300 x 300 DPI)

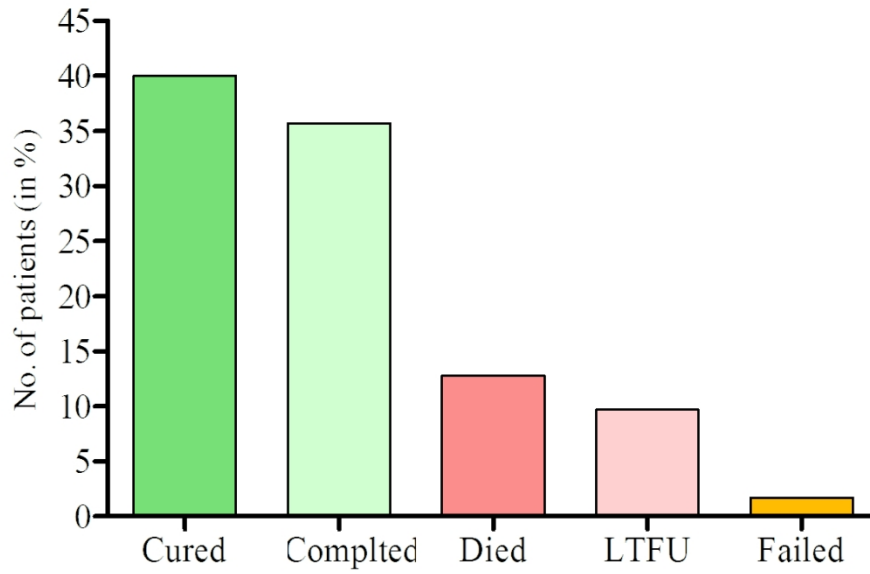


Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

110x71mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 - 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	NA NA Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11-13 Fig 1 11
Outcome data	15*	Report numbers of outcome events or summary measures over time	15

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
2		(b) Report category boundaries when continuous variables were categorized		
3		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	16-17
7	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	20
10	Other information			
11	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years retrospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040862.R3
Article Type:	Original research
Date Submitted by the Author:	04-May-2021
Complete List of Authors:	Tola, Habteyes; Tehran University of Medical Sciences, Epidemiology and Biostatistics; Ethiopian Public Health Institute, TB/HIV Research Directorate Holakouie-Naieni, K; Tehran University of Medical Sciences, Epidemiology and Biostatistics Mansournia, Mohammad; Tehran University of Medical Sciences, Epidemiology and Biostatistics Yaseri, Mehdi; Tehran University of Medical Sciences, Epidemiology and Biostatistics Gamtesa, Dinka; Ethiopian Public Health Institute Tesfaye, Ephrem; Ethiopian Public Health Institute Mahamed, Zemedu; Ethiopian Public Health Institute Sisay, Million; Ethiopian Public Health Institute
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Global health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Tropical medicine < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 National treatment outcome and predictors of death and treatment failure 2 in multidrug resistant tuberculosis in Ethiopia: A ten years retrospective 3 cohort study

4 Habteyes Hailu Tola^{1, 2}, Kourosh Holakouie-Naieni^{1*}, Mohammad Ali Mansournia¹, Mehdi
5 Yaseri¹, Dinka Fikadu Gamtesa², Ephrem Tesfaye², Zemedu Mahamed², Million Molla Sisay³

6 ¹Tehran University of Medical Sciences, School of Public Health, Department of Epidemiology
7 and Biostatistics, Tehran, Iran

8 ²Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa,
9 Ethiopia

10 ³Saint Peter's Specialized Hospital, Research and Evidence Generation Directorate, Addis
11 Ababa, Ethiopia

12 **Habteyes H. Tola** (MSc, PhD)

13 -Tehran University of Medical Sciences, School of Public Health
14 Department of Epidemiology and Biostatistics, Tehran, Iran

15 -Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa, Ethiopia
16 Email: habtetola@gmail.com

17 P.O. Box 1242

18 * **Corresponding author:**

19 **Kourosh Holakouie-Naieni***(DVM, MSc, PhD)

20 Tehran University of Medical Sciences, School of Public Health

21 Department of Epidemiology and Biostatistics, Tehran, Iran

22 Phone: +98 21-88950185

23 Fax: +98 21-88950185

24 P.O. Box 1416753955

25 Email: holakoik@hotmail.com

26 **Mohammad Ali Mansournia** (MD, PhD)

27 Tehran University of Medical Sciences, School of Public Health

28 Department of Epidemiology and Biostatistics, Tehran, Iran

29 Email: mansournia_ma@yahoo.com

30 P. O. Box 1416753955

1
2
3 1 **Mehdi Yaseri** (MSc, PhD)

4
5 2 Tehran University of Medical Sciences School of Public Health

6
7 3 Department of Epidemiology and Biostatistics, Tehran, Iran

8
9 4 Email: myaseri@gmail.com

10
11 5 P. O. Box 1416753955

12
13 6 **Dinka Fikadu Gemtesa** (BSc, MPH)

14
15 7 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa, Ethiopia

16
17 8 Email: ejeta430@gmail.com

18
19 9 P. O. Box 1242

20
21
22 10 **Ephrem Tesfaye** (BSc, MSc)

23
24 11 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa, Ethiopia

25
26 12 Email: ephremt13@gmail.com

27
28 13 P. O. Box 1242

29
30
31 14 **Zemedu Mahamed** (BSc, MSc)

32
33 15 Ethiopian Public Health Institute, Tuberculosis/HIV Research Directorate, Addis Ababa, Ethiopia

34
35 16 Email: zemedu2003@gmail.com

36
37 17 P. O. Box 1242

38
39
40 18 **Million Molla Sisay** (MD, MSc)

41
42 19 Saint Peter's Specialized Hospital, Research and Evidence Generation Directorate, Addis Ababa,
43 20 Ethiopia

44
45 21 Email: milishagr8@gmail.com

46
47 22 P. O. Box 1242

48
49 23

1 Abstract

2 **Objectives:** Treatment success rate in patients treated for multidrug-resistant tuberculosis (MDR-
3 TB) is low, but predictors of treatment failure and death have been underreported. Thus, we aimed
4 to determine the national proportion of treatment success rate in the past 10 years and factors that
5 predict treatment failure and death in MDR-TB patients in Ethiopia.

6 **Setting:** A retrospective cohort study with 10 years follow up period was conducted in 42 MDR-
7 TB treatment initiating centers in Ethiopia.

8 **Participants:** A total of 3,395 adult MDR-TB patients who had final treatment outcome and who
9 were treated under national TB programme were included. Data was collected from clinical charts,
10 registration books and laboratory reports. Competing risk survival analysis model with robust
11 standard error was used to determine predictors of treatment failure and death.

12 **Primary and secondary outcomes:** Treatment outcome was a primary outcome whereas
13 predictors of treatment failure and death were a secondary outcome.

14 **Results:** The proportion of treatment success was 75.7%, death rate was 12.8%, treatment failure
15 was 1.7% and lost-to-follow up 9.7%. The significant predictors of death were older age (adjusted
16 hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); $p < 0.001$), HIV infection (AHR = 2.0; 95% CI
17 (1.6–2.4); $p < 0.001$) and presence of any grade of anemia (AHR = 1.7; 95% CI (1.4–2.0); $p <$
18 0.001). Unlike the predictors of death, all variables included into multivariable model were not
19 significantly associated with treatment failure.

20 **Conclusion:** In the past ten years, although MDR-TB treatment success in Ethiopia has been
21 consistently favorable, the proportion of patients who died is still considerable. Death could be
22 attributed to advanced age, HIV-infection and anemia. Prospective cohort studies are necessary to
23 further explore the potentially modifiable predictors of treatment failure.

24 **Keywords:** Tuberculosis, Multidrug resistance, Rifampin resistance, Treatment outcome

25

1 **Strengths and Limitations of this study**

- 2 ❖ National multidrug resistance tuberculosis (MDR-TB) treatment success rate in the past ten
3 years was determined using MDR-TB treatment programme data.
- 4 ❖ Although MDR-TB mortality is high, predictors of death and treatment failure are
5 underreported.
- 6 ❖ This study determined the predictors of treatment failure and death using competing risk
7 survival analysis model with robust standard error.
- 8 ❖ Retrospective nature of the study design leads to key variables such as sociodemographic,
9 behavioural, adverse drug reactions, key laboratory variables and treatment adherence status
10 missing.
- 11 ❖ A short MDR-TB treatment regimen is recently introduced in Ethiopia, therefore patients
12 treated by long regimen only were enrolled into this study.

1 Background

2 The emergence of drug resistance tuberculosis (TB) has been undermining the efforts to control
3 TB and continues to cause severe morbidity and mortality among millions across the world. The
4 World Health Organization (WHO) estimated that nearly half a million rifampin-resistant new TB
5 cases occurred in 2019 across the world.¹ Multidrug resistance (MDR) TB is defined as a
6 *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin, whereas extensively drug
7 resistance (XDR) TB refers to a *M. tuberculosis* resistance to at least rifampin and isoniazid as
8 well as resistance to any fluoroquinolone and at least one of the three injectable anti-TB drugs
9 (capreomycin, kanamycin or amikacin)². The treatment of MDR and XDR TB has been largely
10 unsuccessful due to the difficulty of the diagnosis, long duration of the treatment, the less effective
11 and toxic drugs used for the treatment, and unavailability of drug options.³⁻⁵

12 The current MDR-TB treatment success rate (the sum of cured and treatment completed) is
13 considerably low.^{1,3,6} The WHO's recent global estimation indicates that only 57% of MDR-TB
14 patients were successfully treated in 2017.¹ Moreover, a recently published -individual patient data
15 meta-analysis study indicated that 61% of MDR-TB patients were treated successfully.⁶ However,
16 recent studies indicated relatively higher treatment success rates in certain settings.⁷⁻¹⁰ For
17 example, 82.4% of MDR-TB patients were treated successfully in Taiwan⁷, 75.8% in Pakistan¹⁰
18 and 75.7% in Tanzania.⁸

19 Heterogeneous and interrelated factors are associated with poor MDR-TB treatment outcome.
20 Infection with Human Immunodeficiency Virus (HIV)¹¹⁻¹⁴, diabetes mellitus^{12,15,16}, malnutrition
21 ^{17,18}, and anemia^{12,14,19} are co-morbidities that are associated with poor treatment outcome in
22 patients treated for MDR-TB. Moreover, treatment interruption^{14,20,21}, medication regimens²²,
23 antiretroviral therapy (ART) timing²³, time to MDR-TB treatment initiation after diagnosis²⁴ and

1 previous TB treatment history^{18,25} are treatment related factors that are associated with poor
2 treatment outcome in MDR-TB patients.

3 Ethiopia is among the 30 high TB and MDR-TB prevalent countries with an estimated TB
4 incidence of 140 per 100,000 population in 2019.¹ Despite an improving TB control programme
5 and relative treatment success rate, the prevalence of MDR-TB in Ethiopia remains high with 2.2%
6 in new and 21.1% in previously treated TB cases.²⁶ However, WHO's recent estimate in Ethiopia
7 indicated a lower prevalence of 0.71% of MDR-TB in new cases and 12% in previously treated
8 cases in 2019.¹ Although there is no national level report on MDR-TB treatment outcome in
9 Ethiopia, studies reported from local data indicated variable treatment success that ranges between
10 63%–78.8%.^{9,19,27}

11 The global treatment success rate of MDR-TB is low and there is evidence limitation on the factors
12 that associated with poor treatment outcome. Furthermore, available studies are focused in the
13 determination of predictors of unsuccessful treatment outcome by merging death, treatment failure
14 and lost to follow up in one category. However, this could conceal the actual predictors of death
15 and treatment failure. To that extent, there is no study that reported the predictors of death and
16 treatment failure separately using competing risk survival analysis model with robust standard
17 error. Ethiopia is among the countries which lack such evidence at national level to plan effective
18 intervention that could decrease treatment failure and reduce death in MDR-TB patients. Thus, we
19 aimed to determine the national level treatment success rate in the past 10 years and factors that
20 could predict treatment failure and death in MDR-TB patients in Ethiopia.

21

22

23 **Materials and methods**

1 Study setting, population and design

2 We conducted a retrospective cohort study on adult patients aged ≥ 15 years old, diagnosed either
3 biologically or clinically for both pulmonary and extra-pulmonary TB, and enrolled to MDR-TB
4 treatment at 42 treatment initiating centers (TICs) in Ethiopia from February 2009 to February
5 2019. MDR-TB treatment was started in February 2009 in one hospital in Addis Ababa, Ethiopia.²⁷
6 During this study period, there were a total of 53 TICs and several treatment follow up centers
7 (TFCs) in the country. The majority of MDR-TB patients initiate their treatments in TICs while
8 stable patients follow the treatment under directly observed therapy (DOT) programme in nearby
9 TICs or TFCs as ambulatory outpatients. However, all information on the patients registered for
10 MDR-TB treatment has been documented at TICs where the patient started the treatment. We
11 included a total of 42 TICs into this study; the remaining 11 TICs had no patients who completed
12 their treatment during the study period.

13 Inclusion and exclusion criteria

14 We included all adult patients who were aged 15 years and older, diagnosed either
15 bacteriologically or clinically for MDR-TB and enrolled to the treatment from February 2009.
16 Children less than 15 years old were excluded from this study, because their treatment guideline
17 is different from the adults. Moreover, we excluded patients who had no final treatment outcome
18 (transferred out or still on treatment or treatment outcome missed from data sources).

19 Laboratory test

20 All laboratory tests were performed according to WHO recommendation and national TB
21 laboratory algorithm in quality assured TB laboratories.^{28,29} To detect drug resistant TB, culture
22 tests were carried out with solid media (Löwenstein-Jensen (LJ)) and a fluorometric BACTEC
23 MGIT960 at one national TB reference laboratory and nine regional laboratories. In addition,

1 GeneXpert MTB/RIF assay was used to detect rifampin resistant TB. This assay is a rapid,
2 sensitive and specific technique that is widely used to detect *M. tuberculosis* and rifampin
3 resistance at each level in the national health system. Drug susceptibility test (DST) for first-line
4 drugs was performed by BACTEC MGIT960 system based on WHO recommended critical
5 concentrations for rifampin (1.0 µg/ml), isoniazid (0.1 µg/ml), streptomycin (1.0 µg/ml),
6 ethambutol (5µg/ml) and pyrazinamide (100 µg/ml). DST for second-line drugs has been recently
7 started in the country and rarely performed. Data on second-line DST was not included to this
8 study because very few DST results for SLDs were obtained in the records. Quality assurance for
9 DST was regularly performed by Milan supranational reference laboratory in Italy and
10 demonstrated constant proficiency.

11 **Treatment**

12 Previously, all MDR-TB patients were treated as inpatient model of care for the first few months
13 at treatment centers until the patient were clinically stable with culture conversion. However,
14 according to the recent edition of national TB treatment guideline (2018), all patients with MDR-
15 TB need to be treated under clinic-based ambulatory model of care²⁹, unless the patients are
16 clinically unstable, or developed severe adverse drug reaction. Patients either with serious medical
17 or social conditions could be admitted with the decision of the treatment panel. Standardized long
18 treatment regimens were used to treat MDR-TB patients in Ethiopia. The long treatment regimen
19 contained at least four oral drugs used daily during full course of treatment and one injectable drug
20 until *M. tuberculosis* culture conversion. Treatment with injectable drugs continues at least for
21 eight months based on clinical, microbiological and radiographic examination results. The
22 minimum treatment duration was 20 months -at least 18 months after bacteriological conversion.
23 The 9–11 months (short treatment regimen) was not used.²⁹ The second line drugs used to treat

1 MDR-TB in Ethiopia are levofloxacin, ethionamide, cycloserine, para-aminosalicylic acid (PAS),
2 pyrazinamide, prothionamide, linezolid, clofazimine and injectable drugs such as amikacin,
3 kanamycin and capreomycin.²⁹ All the patients enrolled into this study were treated by a
4 standardized long term regimen consisting of capreomycin, levofloxacin, prothionamide,
5 cycloserine and high dose isoniazid during the intensive phase.²⁹ During the continuation phase,
6 levofloxacin, prothionamide, cycloserine and high dose isoniazid were used.²⁹ Laboratory tests,
7 chest X-ray and clinical investigations are used to monitor response to the treatment and to identify
8 treatment related complications in patients on MDR-TB treatment in Ethiopia. Clinical
9 investigations only are used to monitor response to the treatment, while laboratory tests are used
10 to identify treatment related complications for extra-pulmonary TB patients. MDR-TB treatment
11 is free of any cost in Ethiopia and there is full access to all categories of drugs to treat MDR-TB
12 patients.

13 **Data collection**

14 We collected data on socio-demographic variables such as sex, age and regional state. We also
15 collected TB related data such as anatomical site of TB (pulmonary vs extra pulmonary), drug
16 resistance type (RR vs MDR), previous treatment (new vs previously treated), diagnosis method
17 (bacteriologically vs clinically), HIV status (HIV-infected vs not infected) and antiretroviral
18 therapy (ART) status (on ART vs not on ART vs not applicable). In addition, we collected
19 information on bacteriological status (smear, GeneXpert MTB/RIF, culture or first-line drugs DST
20 results) at treatment initiation. All data were extracted from patients' clinical charts, registration
21 books and laboratory reports. Data were collected by health professionals familiar with MDR-TB
22 treatment after two days practical training on data management.

23 **Definitions**

1 In this study, we used standard WHO and national treatment guidelines definitions for laboratory
2 confirmations, patient categories and treatment outcomes.^{28,29} Clinically diagnosed MDR-TB
3 refers to those cases with no documented drug susceptibility test (DST) results but treated
4 empirically with a course of treatment including SLDs based on clinical criteria and contact
5 history.²⁹ However, bacteriologically confirmed MDR-TB refers to those cases with documented
6 DST results. All patients were categorized into new patients (never treated for TB or for less than
7 one month) and patients previously treated for TB. The final treatment outcomes of MDR-TB were
8 cured, treatment completed, death, treatment failed and lost to follow up. Cured is refers to a patient
9 initially bacteriologically confirmed and completed the treatment without the evidence of
10 treatment failure and three or more consecutive cultures taken at least 30 days apart being negative
11 after the intensive phase. Treatment completed is defined as a patient who completed the treatment
12 without the evidence of treatment failure but there is no record that indicates three or more
13 consecutive cultures taken at least 30 days apart are negative after the intensive phase. A patient
14 whose treatment is terminated or need for permanent regimen change of at least two anti-TB drugs
15 is categorized as treatment failure. Lost to follow up also refers to a patient whose treatment is
16 interrupted for two consecutive months or more. Successful treatment outcome was the sum of
17 cured and treatment completed, whereas unsuccessful was the combination of death, treatment
18 failed and lost to follow up.

19 **Data analysis**

20 We entered data into CSPro software version 6.1 and analyzed by STATA version 14 (StataCorp,
21 College Station, TX, USA). The data were confirmed from each data source and cleaned for errors
22 before main analysis. We described participants' demographic and clinical characteristics using

1 descriptive statistics. The proportions of MDR-TB treatment outcomes were frequency weighed
2 by the total number of patients registered from February, 2009 to February, 2019 in each TIC.

3 We used a competing risk survival analysis model with robust standard error to assess the effects
4 of different variables on the treatment failure and death. Effect levels were reported by Hazard
5 Ratio (HR) with 95% Confidence Intervals (CIs). We included variables scored p-values less than
6 or equal to 0.2 during bivariate analysis and clinically or epidemiologically relevant. We
7 considered death as failure event to estimate the effects of different variables on death, while
8 treatment failure and success were considered as competing risks. Similarly, we considered
9 treatment failure as failure event to estimate the effects of different variables on the duration from
10 treatment enrolment to treatment failure, whereas death and treatment success were considered as
11 competing risks. Lost to follow up was considered as a censored across the fitted models. Level of
12 significance was set at 5% for all analysis.

13 **Patient and public involvement:** Both patient and public were not involved in this study.

14 Results

15 Participants' characteristics

16 A total of 4,419 patients were enrolled to MDR-TB treatment in 42 of 53 (79.2%) treatment
17 initiating centers (TICs) in Ethiopia from February, 2009 to February, 2019 [Fig 1]. Of the 4,419
18 patients, 3,395 (76.8%) fulfilled our inclusion criteria and enrolled to this study [Fig 1].

19 The highest number of patients enrolled into the treatment was in 2015 (667 patients), while in
20 2019 the smallest number of patients were registered (only 4 patients) [Fig 2].

21 Of the 3,395 patients included into this study, 1,870 (55.1%) were male, and the mean age was
22 31.6 (SD \pm 11.7) years with the age range of 15 to 85 years. Seventy two percent of the patients
23 were in the age category of 15 to 35 years [Table 1]. Ninety three percent of the participants were

1 pulmonary TB patients [Table 1]. Eighty six percent of patients had previous TB treatment history.
 2 Drug resistance status of 3,242 (95.5%) isolates were bacteriologically confirmed at the initiation
 3 of treatment [Table 1]. The main drug resistance diagnosis method was GeneXpert MTB/RIF
 4 (57.9%). Of the 3,395 patients, 1,421 (41.9%) had previous exposure to second line drugs and 767
 5 (22.6%) were HIV infected [Table 1] of which 686 (89.4%) were on ART. Only 6.0% of the
 6 patients had previous MDR-TB patient contact history and 1,831 (53.9%) of patients were
 7 hospitalized at the treatment initiation [Table 1] with mean duration of hospitalization 81.7 (\pm 47.4)
 8 days.

9 **Table 1: Demographic and clinical characteristics of the patients (n = 3,395)**

Variable		n (%)
Sex	Male	1,870 (55.1)
	Female	1,525 (44.9)
Age (in year)	15–25	1,268 (37.3)
	26–35	1,186 (34.9)
	36–45	529 (15.6)
	\geq 46	412 (12.1)
Drug resistance type	RR/INH status unknown	1,810 (53.3)
	MDR-TB	1,585 (46.7)
Anatomical site of TB	Pulmonary	3,171 (93.4)
	Extra pulmonary	224 (6.6)
Previous TB treatment	New	462 (13.6)
	Previously treated	2,933 (86.4)
Previous exposure to SLDs	Yes	1,421 (41.9)
	No	1,842 (54.3)
	Unknown	132 (3.9)
Drug resistance identification method	GeneXpert MTB/RIF	1,967 (57.9)
	Culture/LPA	1,275 (37.6)
	Clinical	153 (4.5)
Diagnosis method	Bacteriological	3,242 (95.5)
	Clinical	153 (4.5)
HIV infection	Not infected	2,554 (75.2)
	Infected	767 (22.6)
	Unknown	74 (2.2)
ART status	Not applicable	2,556 (75.3)
	On ART	686 (20.2)
	HIV status known but, ART status unknown	79 (2.3)
	Both ART and HIV statuses unknown	74 (2.2)
MDR-TB patient contact history	Yes	204 (6.0)
	No	1,511 (44.5)
	Unknown	1,680 (49.5)
Hospitalization history at treatment initiation	Hospitalized	1,831 (53.9)
	Not hospitalized	487 (14.3)

	Unknown	1,077 (31.7)
Treatment interruption	Never interrupted/interruption status unknown	3,192 (94.0)
	At least one day interrupted	203 (6.0)

1 *TB-tuberculosis, ART-Antiretroviral therapy, SLDs-Second line drugs, HIV-Human immunodeficiency virus, MDR-*
 2 *Multidrug resistant, LPA-Line probe Assay*

3 Drug resistance status at treatment initiation

4 Drug susceptibility testing was performed for four first-line drugs which are rifampin, isoniazid,
 5 ethambutol and streptomycin [Table 2]. Rifampin susceptibility test was performed on isolates of
 6 all patients included into this study and 99.3% of isolates demonstrated resistance to the therapy
 7 [Table 2].

8 Table 2: Anti-tuberculosis drug susceptibility test results

Anti-tuberculosis drug	Susceptibility test results	n (%)
Rifampin (n=3,395)	Resistant	3,371 (99.3)
	Susceptible	24 (0.7)
Isoniazid (n = 1,313)	Resistant	1,241 (94.5)
	Susceptible	72 (5.5)
Ethambutol (n = 427)	Resistant	299 (70.0)
	Susceptible	128 (30.0)
Streptomycin (n = 443)	Resistant	337 (76.1)
	Susceptible	106 (23.9)

9 Table 3 depicts the distribution of treatment outcome categories by sociodemographic and clinical
 10 characteristics. Of 1,585 patients whose isolates were resistant to rifampin and isoniazid (MDR-
 11 TB), 793 (50.0%) cured, while 180 (11.4%) died and the treatment of 24 (1.5%) patients were
 12 failed. Treatment failure was almost ten times higher in patients who had previous TB treatment
 13 history (21.7%), than those who were never treated (2.2%). Moreover, mortality was two times
 14 higher in patients who were HIV infected (21.3%), than those who were HIV non-reactive
 15 (10.2%).

17 Table 3: Demographic and clinical characteristics distribution of treatment outcome

Treatment outcome n (%)

Variables		Cured	Completed	Treatment success	Failed	Death	LTFU	P-value
Sex	Male	1,006 (53.8)	376 (20.1)	1,382 (73.9)	40 (2.1)	245 (13.1)	203 (10.9)	0.071
	Female	839 (55.0)	344 (22.6)	1,183 (77.6)	26 (1.7)	186 (12.2)	130 (8.5)	
Resistance type	RR/INH status unknown	1,052 (58.1)	274 (15.1)	1,326 (73.2)	42 (2.3)	251 (13.9)	191 (10.6)	< 0.001
	MDR	793 (50.0)	446 (28.1)	1,239 (78.1)	24 (1.5)	180 (11.4)	142 (9.0)	
Anatomical site	EPTB	50 (22.3)	125 (55.8)	173 (78.1)	4 (1.8)	20 (8.9)	25 (11.2)	< 0.001
	PTB	1,795 (56.6)	595 (18.8)	2,390 (75.4)	62 (2.0)	411 (13.0)	308 (9.7)	
Previous TB treatment	New	243 (52.6)	83 (18.0)	326 (70.6)	10 (2.2)	75 (16.2)	51 (11.0)	0.057
	Previously treated	1,602 (54.6)	637 (21.7)	2,239 (76.3)	56 (21.7)	356 (12.1)	282 (9.6)	
Diagnosis method	Bacteriological	1,771 (54.6)	686 (21.2)	5,457 (75.8)	64 (2.0)	409 (12.6)	313 (9.7)	0.466
	Clinical	74 (48.7)	34 (22.4)	108 (71.1)	2 (1.3)	22 (14.5)	20 (13.2)	
HIV status	Non-reactive	1,429 (56.0)	561 (22.0)	1,990 (78.0)	48 (1.9)	261 (10.2)	255 (10.0)	< 0.001
	Reactive	378 (49.3)	141 (18.4)	519 (67.7)	17 (2.2)	163 (21.3)	68 (8.9)	
Anemia	None anemic	880 (55.0)	380 (23.8)	1,260 (78.8)	29 (1.8)	150 (9.4)	161 (10.1)	< 0.001
	Any grade of anemia present	965 (53.8)	340 (18.9)	1,305 (72.7)	37 (2.1)	281 (15.7)	172 (9.6)	

1 Treatment outcome

2 Of the 3,395 patients enrolled into this study, 1,845 (40.0%) were cured, 720 (35.7%) completed
 3 the treatment, 431 (12.8%) died, 333 (9.7%) were lost to follow up and the treatment of 66 (1.7%)
 4 patients failed [Fig 3]. The overall treatment success (cured plus treatment completed) was 2,565
 5 (75.7%), whereas the overall unsuccessful treatment outcome (the sum of lost to follow up,
 6 treatment failed and death) was 830 (24.3%).

7 Predictors of treatment failure and death

8 Bivariate analysis

9 In the current competing risk survival analysis model, failure events were treatment success
 10 (2,565), treatment failure (66) and death 431 (431). To the contrary, 333 (9.7%) lost to follow up
 11 were considered as censored. In the bivariate competing risk survival analysis model, old age
 12 (unadjusted hazard ratio (UHR) = 1.03; 95% CI (1.04–1.05); $p < 0.001$), HIV infection (UHR =
 13 2.2; 95% CI (1.8–2.7); $p < 0.001$) and presence of any grade of anemia (UHR = 1.7; 95% CI (1.4–
 14 2.1); $p < 0.001$) were significantly associated with death [Table 4]. Moreover, having previous TB

1 treatment history (UHR = 0.71; 95% CI (0.56–0.92); p = 0.009) and presence of rifampin resistant
 2 bacilli (UHR = 1.3; 95% CI (1.03–1.5); p = 0.022) were significantly associated with death [Table
 3 4]. However, none of the variables assessed had shown significant association with treatment
 4 failure [Table 4].

5 **Table 4:** Predictors of duration from treatment initiation to death and treatment failure in patients
 6 treated for MDR-TB in Ethiopia, 2009-2019 (Unavailable model)

Variable	Death		Treatment failure		
	UHR (95%CI)	P-value	UHR(95% CI)	P-value	
Sex	Female	1.00	1.00		
	Male	1.1 (0.89–1.3)	0.436	1.3 (0.78–2.1)	0.335
Age (year)		1.03 (1.04–1.05)	< 0.001	0.98 (0.96–1.0)	0.122
Anatomical sit	Extra-pulmonary	1.00		1.00	
	Pulmonary	1.5 (0.94–2.3)	0.094	1.1 (0.40–3.0)	
Drug resistance type	MDR	1.00		1.00	
	RR/INH status unknown	1.3 (1.03–1.5)	0.022	1.6 (0.95–2.6)	0.080
Previous treatment	New	1.00		1.00	
	Previously treated	0.71 (0.56–0.92)	0.009	0.86 (0.44–1.7)	0.668
Diagnosis method	Bacteriological	1.00		1.00	
	Clinical	1.2 (0.76–1.8)	0.468	0.68 (0.17–2.8)	0.589
HIV status	Non-reactive	1.00		1.00	
	Reactive	2.2 (1.8–2.7)	< 0.001	1.2 (0.68–2.1)	0.548
Anemia status	Absent	1.00		1.00	
	Any grade of anemia present	1.7 (1.4–2.1)	< 0.001	1.1 (0.70–1.9)	0.592

7 *TB-tuberculosis, HIV-Human immunodeficiency virus, UHR- Unadjusted hazard ratio, CI-Confidence interval,*
 8 *MDR-Multidrug resistant*

9 **Multivariable analysis**

10 In multivariable analysis, older age (Adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); p
 11 < 0.001), HIV infection (AHR = 2.0; 95% CI (1.6–2.4); p < 0.001) and presence of any grade
 12 anemia (AHR = 1.7; 95% CI (1.4–2.0); p < 0.001) were significantly associated with death [Table
 13 5]. All variables included into multivariable competing risk survival analysis model were not
 14 significantly associated with treatment failure [Table 5]. Although presence of rifampin resistant
 15 bacilli and having previous TB treatment history were significantly associated with death in the
 16 unadjusted analysis, they failed to significantly associate in the adjusted analysis.

Table 5: Predictors of duration from treatment initiation to death and treatment failure in patients treated for MDR-TB in Ethiopia, 2009-2019 (Multivariate model)

Variable		Death		Treatment failure	
		AHR (95%CI)	P-value	AHR(95% CI)	P-value
Sex	Female	1.00		1.00	
	Male	0.92 (0.75–1.1)	0.397	1.3 (0.82–2.2)	0.248
Age (year)		1.04 (1.03–1.05)	< 0.001	0.98 (0.96–1.0)	0.077
Anatomical sit	Extra-pulmonary TB	1.00		1.00	
	Pulmonary TB	1.4 (0.91–2.2)	0.126	1.1 (0.39–3.0)	0.878
Drug resistance type	MDR	1.00		1.00	
	RR/INH status unknown	1.2 (0.98–1.5)	0.083	1.7 (0.98–2.8)	0.060
Previous treatment	New	1.00		1.00	
	Previously treated	0.79 (0.61–1.0)	0.083	0.98 (0.49–1.9)	0.947
HIV status	Non-reactive	1.00		1.00	
	Reactive	2.0 (1.6–2.4)	< 0.001	1.3 (0.72–2.2)	0.425
Anemia status	Absent	1.00		1.00	
	Anemia present	1.7 (1.4–2.0)	< 0.001	1.1 (0.66–1.8)	0.767

TB-tuberculosis, HIV-Human immunodeficiency virus, AHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Discussion

The current study aimed to determine the proportion of national treatment success rate and predictors of treatment failure and death in patients treated for MDR-TB in Ethiopia in the past ten years. We have found that 75.7% of MDR-TB patients were successfully treated, whereas 12.8% died, 9.7% lost to follow up and the treatment of 1.7% patients failed. The proportion of the patients registered for MDR-TB treatment has shown increasing trend from 2009 and the maximum proportion (19.6%) was registered in 2015. However, the proportion of patients registered for the treatment has decreased after 2015 and the minimum patients were registered in 2019. Old age, HIV infection and any grade of anemia were significant predictors of death in patients treated for MDR-TB in the present study. However, none of the variables included into the multivariable model were able to significantly predict treatment failure.

The present study indicates that the proportion of treatment enrolment after 2015 has decreased and the lowest number of cases were recorded in 2019. We do not think that the MDR-TB incidence decreased importantly, and we therefore think that there might have been registration-related problems as the result of decentralization of TB care to the communities. As patients

1 included into this study were those who had final treatment outcome results, enrolment of patients
2 in 2018 and 2019 is expectedly low as they were still on treatment.

3 In the current study, treatment success proportion in MDR-TB patients who received a
4 standardized long regimen was higher than the treatment success rate previously reported from
5 other settings including from Ethiopia.^{19,20,30} For instance, a recent study reported from Morocco
6 indicated that only 53.4% of MDR-TB patients were treated successfully.³⁰ In addition, a study
7 reported from Armenia shows that less than 50% of MDR-TB patients were successfully treated.²⁰
8 A recent review study that pooled data from different settings have also shown lower treatment
9 success rate than our findings.³¹ These differences originate most likely from the differences in the
10 quality of TB control programme, sample size, severity of the disease at diagnosis, TB/HIV co-
11 infection burden, treatment regimens and study period. A previous study conducted in Ethiopia in
12 two treatment initiation centers²⁷ reported very similar treatment success rate with our finding
13 (78.6% vs 75.7%).

14 The proportion of death in the current study was considerably higher and it was similar with
15 previously reported findings.^{19,27} Case in point, the proportion of patients who died in our study
16 was more than double compared to the mortality proportion reported from Morocco (5% vs
17 12.7%).³⁰ This difference is most probably due to difference in the study period, quality of care,
18 treatment regimens, and severity of the disease during treatment initiation.

19 Our study finding shows that older age is significantly associated with death from MDR-TB. In
20 agreement with this findings, it is well documented that MDR-TB mortality is higher in older age
21 group.³²⁻³⁴ Thus, particular attention has to be given to older patients to reduce mortality related
22 to TB. A previous study has shown that younger age is significantly associated with poor treatment

1 outcome than older age.³⁵ This difference could probably be due to the age variation in the included
2 patients and the difference in the severity of the disease at treatment initiation.

3 In the current study, as in several previous studies^{19,25–27,35}, HIV infection was significantly
4 associated with death. Despite the proportion of patients who were not on antiretroviral therapy
5 (ART) were low (of HIV infected patients only 4.5 %), the hazard of death was 2.0 times higher
6 in HIV infected patients. The possible explanation for the significant effect of HIV status on
7 mortality in patients on MDR-TB treatment could be due to low CD4 count, high viral load and
8 severity of the disease at treatment initiation. However, since data on CD4 count, HIV viral load
9 level and disease severity status at enrolment were not registered in our data sources, we were not
10 able to verify their effects on MDR-TB treatment outcome. Furthermore, a previous study
11 indicated that a combined anti-TB and anti-HIV treatment has been proven to improve treatment
12 success in co-infected patients.³⁶

13 In the present study, the presence of any grade of anemia was significantly associated with death
14 due to MDR-TB. This finding is similar with a previous study reported from Ethiopia in which the
15 hazard of poor treatment outcome was 4.2 times higher in the patients who had any grade of anemia
16 at treatment initiation than those who were non-anemic.¹⁹ The presence of anemia at the treatment
17 initiation might be due to parasitic infections and some other chronic diseases. This finding
18 highlights the importance of hemoglobin monitoring in MDR-TB patients on treatment to increase
19 treatment success and decrease mortality.

20 In the current study, none of the variables included into the multivariable model were significantly
21 associated with treatment failure. The absence of significant association between the variables and
22 treatment failure could be due to the number of treatment failure events that was much smaller
23 than the competing risks i.e. death and treatment success.

1 The main limitation of this study is the retrospective nature of the study design. Data on
2 sociodemographic, behavioural, adverse drug reactions, key laboratory variables and treatment
3 adherence status were missing for the majority of the patients; hence these variables were excluded
4 from the analysis. This limited us to further explore the predictors of treatment failure and death.
5 Thus, the predictors of death may not be limited to the factors presented in this study. Moreover,
6 lack of important variables could have resulted in an underestimation/overestimation of the effects
7 of the investigated variables in the model such as age, HIV status, previous TB treatment history
8 etc on treatment failure and death. The final treatment outcome of 759 patients was also not
9 obtained and the patients were excluded from the analysis. This might be overestimated the
10 treatment success rate in the current study. A prospective study that could capture all these
11 uninvestigated variables is important to determine predictors of treatment failure and death.

12 The findings of the present study have clearly indicated the message for TB control programme
13 efforts. Although treatment success rate is well achieved, mortality in the current study is
14 considerable and hence should be addressed by the TB programme. HIV infection is one of strong
15 predictors of death in MDR-TB patients. Taking in consideration of HIV infected MDR-TB
16 patients and immediate commencement of anti-TB treatment together with ART is the mechanism
17 to improve treatment success in MDR-TB patients. Moreover, our result indicates that special
18 attention should be given to patients who have anemia at treatment initiation in order to improve
19 their treatment outcome. Strengthening and standardizing information registration on MDR-TB
20 treatment is crucial to facilitate further data analysis which is important to monitor the status of
21 treatment outcome.

22 **Conclusion**

1 In the past ten years, MDR-TB treatment in Ethiopia has been successful. However, the proportion
2 of patients who died is considerable, and it could be reduced through providing special attention
3 to HIV-infected and anemic patients. Further prospective cohort study is required to explore other
4 predictors of treatment failure and death.

5 **Acknowledgement**

6 We would like to acknowledge the Tehran University of Medical Sciences (TUMS) and the
7 Ethiopian Public Health Institute (EPHI) for funding this study. We also thank EPHI, National
8 Tuberculosis Laboratory and all DR-TB treatment centers staff members for their cooperation
9 during the data collection process. We would also like to acknowledge all patients whose data were
10 used in this study.

11 **Author contributions:** HHT and KH conceived and designed the study; HHT, DFG, ET, ZM and
12 MMS collected the data; HHT, MAM and MY analyzed and interpreted the data; HHT drafted the
13 manuscript. All authors have critically reviewed and approved the manuscript for submission.

14 **Funding:** This work was supported by Tehran University of Medical Sciences and Ethiopian
15 Public Health Institute. The grand number of the funded institute is not applicable.

16 **Competing interests:** None declared.

17 **Ethics consideration:** This study was approved by the research Ethics Review Board of Tehran
18 University of Medical Sciences (IR.TUMS.SPH.REC.1396.4287), Ethiopian Public Health
19 Institute (EPHI-IRB-065-2017), St. Peter's Specialized Hospital (V81622018) and Armauer
20 Hansen Research Institute (PO13/18). We also obtained a waiver of informed consent from each
21 review board. To maintain confidentiality, sensitive information that could identify participants
22 was not reported in this study.

1 **Data availability statement:** Data used in this study is available from the corresponding authors
 2 and accessible upon reasonable request.

3 **References**

- 4 1. World Health Organization. Global tuberculosis report 2020. 2020 p. 1–232.
- 5 2. Curry International Tuberculosis Center, and California Department of Public Health Drug-resistant tuberculosis: A survival guideline for clinicians. 2016.
- 6 3. Gunther G, Lange C, Alexandru S, Altet N. Treatment Outcomes in Multidrug-Resistant Tuberculosis. *N Engl J Med*. 2016;375(11).
- 7 4. Lange C, Abubakar I, Alffenaar JC, Bothamley G, Caminero JA, C.Carvalho AC, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. *Eur Respir J*. 2014;44:23–63.
- 8 5. Pontali E, Visca D, Centis R, Ambrosio LD, Spanevello A, Battista G. Multi and extensively drug-resistant pulmonary tuberculosis : advances in diagnosis and management. *Curr Opin Pulm Med*. 2018;24:244–52.
- 9 6. Ahmad N, Ahuja S, Akkerman O, Alffenaar J, Anderson L, Baghaei P, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data metaanalysis. *Lancet*. 2018;392(10150):821–34.
- 10 7. Yu M, Chiang C, Lee J, Chien S, Lin C, Lee S, et al. Treatment Outcomes of Multidrug-Resistant Tuberculosis in Taiwan : Tackling Loss to Follow-up. *Clin Infect Dis*. 2018;67(2):202–2010.
- 11 8. Leveru TH, Lekule I, Mollel E, Lyamuya F, Kilonzo K. Predictors of Treatment Outcomes among Multidrug Resistant Tuberculosis Patients in Tanzania. *Tuberc Reserch Treat*. 2019;2019:1–10.
- 12 9. Woldeyohannes D, Assefa T, Aman R, Tekalegn Y. Predictors of time to unfavorable treatment outcomes among patients with multidrug resistant tuberculosis in Oromia region. *PLoS One*. 2019;14(10):e0224025.
- 13 10. Javaid A, Ullah I, Masud H, Basit A, Ahmad W, Butt ZA, et al. Predictors of poor treatment outcomes in multidrug-resistant tuberculosis patients : a retrospective cohort study. *Clin Microbiol Infect*. 2017;2017.
- 14 11. Aibana O, Bachmaha M, Krasiuk V, Rybak N, Flanigan TP, Petrenko V, et al. Risk factors for poor multidrug-resistant tuberculosis treatment outcomes in Kyiv Oblast, Ukraine. *BMC Infect Dis*, 2017;17(2017):129.
- 15 12. Ketema DB, Muchie KF, Andargie AA. Time to poor treatment outcome and its predictors among drug-resistant tuberculosis patients on second-line anti- tuberculosis treatment in Amhara region , Ethiopia : retrospective cohort study. *BMC Public Health*; 2019;19(2019):1481.
- 16 13. Samuels JP, Sood A, Campbell JR, Khan FA, Johnston JC. Comorbidities and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis. *Sci Rep*; 2018;8(2018):4980.
- 17 14. Tola HH, Holakouie-na K, Mansournia MA, Yaseri M, Tesfaye E, Mahamed et al. Intermittent treatment interruption and its effect on multidrug resistant tuberculosis treatment outcome in Ethiopia. *Sci Rep*. 2019;9:20030.

15. Kang Ya, Kim S, Jo K, Kim H, Park S, Kim T, et al. Impact of Diabetes on Treatment Outcomes and Long-Term Survival in Multidrug-Resistant Tuberculosis. *Respiration*. 2013;86:472–8.
16. Dooley KE, Tang T, Golub JE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. *AM J Trop Med Hyg*. 2009;80(4):634–9.
17. Samuel B, Volkmann T, Cornelius S, Mukhopadhyay S, Mitra K, Kumar AM V, et al. Relationship between Nutritional Support and Tuberculosis Treatment Outcomes in West Bengal, India. *J Tuberc Res*. 2016;4(4):213–9.
18. Milanov V, Falzon D, Zamfirova M, Varleva T, Bachiyska E, Koleva A, et al. Factors associated with treatment success and death in cases with multidrug-resistant tuberculosis in Bulgaria , 2009 – 2010. *Int J Mycobacteriology*. 2015;4(2):131–7.
19. Alene KA, Viney K, Mcbryde ES, Tsegaye AT, Clements ACA. Treatment outcomes in patients with multidrug-resistant tuberculosis in north-west Ethiopia. *Trop Med Int Heal*. 2017;22(3):351–62.
20. Bastard M, Sanchez-padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, et al. Effects of treatment interruption patterns on treatment success among patients with multidrug-resistant tuberculosis in Armenia and Abkhazia. *J Infect Dis*. 2015;211:1607–16.
21. Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. *PLoS One*. 2013;8(7):e70064.
22. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. 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.
23. Umanah T, Ncayiyana J, Padanilam X, Nyasulu PS. Treatment outcomes in multidrug resistant tuberculosis-human immunodeficiency virus Co-infected patients on anti-retroviral therapy at Sizwe Tropical Disease Hospital Johannesburg, South Africa. *BMC Infect Dis*. 2015;15:478.
24. Chen Y, Yuan Z, Shen X, Wu J, Wu Z. Time to Multidrug-Resistant Tuberculosis Treatment Initiation in Association with Treatment Outcomes in Shanghai, China. *Antimicrob Agents Chemother*. 2018;62:e02259–17.
25. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. *Eur Respir J*. 2009;33:1085–94.
26. Girum T, Muktar E, Lentiro K, Wondiye H, Shewangizaw M. Epidemiology of multidrug-resistant tuberculosis (MDR-TB) in Ethiopia: a systematic review and meta-analysis of the prevalence, determinants and treatment outcome. *Trop Dis Travel Med Vaccines. Tropical Diseases, Travel Medicine and Vaccines*; 2018;4(2018):5.
27. Meressa D, Hurtado RM, Andrews JR, Diro E, Abato K, Daniel T, et al. Achieving high treatment success for multidrug-resistant TB in Africa : initiation and scale-up of MDR TB care in Ethiopia — an observational cohort study. *Thorax*. 2015;70:1181–8.
28. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva, Switzerland; 2019.
29. Federal Democratic Republic of Ethiopia Ministry of Health. Guidelines for Management of TB, DR-TB and Leprosy in Ethiopia: Sixth Ed. Addis Ababa, Ethiopia; 2018.
30. Hamdouni M El, Bourkadi JE, Benamor J, Hassar M, Cherrah Y. Treatment outcomes of drug resistant tuberculosis patients in Morocco: multi- centric prospective study. *BMC Infect Dis*; 2019;19:316.

- 1
2
3 1 31. Bastos ML, Lan Z, Menzies D. An updated systematic review and meta-analysis for treatment
4 2 of multidrug-resistant tuberculosis. *Eur Respir J* ; 2017;49:1600803.
5 3 32. Li J, Li T, Bs X Du, Fhkccm PC, Zhang H. The age-structured incidence and mortality of
6 4 pulmonary tuberculosis reported in China , in 2005 – 15 : a longitudinal analysis of national
7 5 surveillance data. *Lancet*; 2017;390:S12.
8 6 33. Chingonzoh R, Manesen MR, Madlavu MJ, Kuonza R. Risk factors for mortality among adults
9 7 registered on the routine drug resistant tuberculosis reporting database in the Eastern Cape
10 8 Province, South Africa, 2011 to 2013. *PLoS One*. 2018;13(8):e0202469.
11 9 34. Gayoso R, Dalcolmo M, Ueleres J, Barreira D. Predictors of mortality in multidrug-resistant
12 10 patients from Brazilian refence centers, 2005 to 2012. *Brazilian J Infect Dis*;
13 11 2018;22(4):305–10.
14 12 35. Nair D, Velayutham B, Kannan T, Tripathy J, Harries A, Natrajan M, et al. Predictors of
15 13 unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India.
16 14 *Public Heal Action*. 2017;7(1):32–8.
17 15 36. Yuengling KA, Padayatchi N, Wolf A, Mathema B, Brown T, Horsburgh CR, et al. Effect of
18 16 antiretroviral therapy on treatment outcomes in a prospective study of extensively drug
19 17 resistant tuberculosis (XDR-TB) HIV co-infection treatment in KwaZulu-Natal, South
20 18 Africa. *Acquir Immune Defic Syndr*. 2019;79(4):474–80.
21 19
22 20
23 21
24 22
25 23
26 24
27 25
28 26
29 27
30 28
31 29
32 30
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure legend

Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

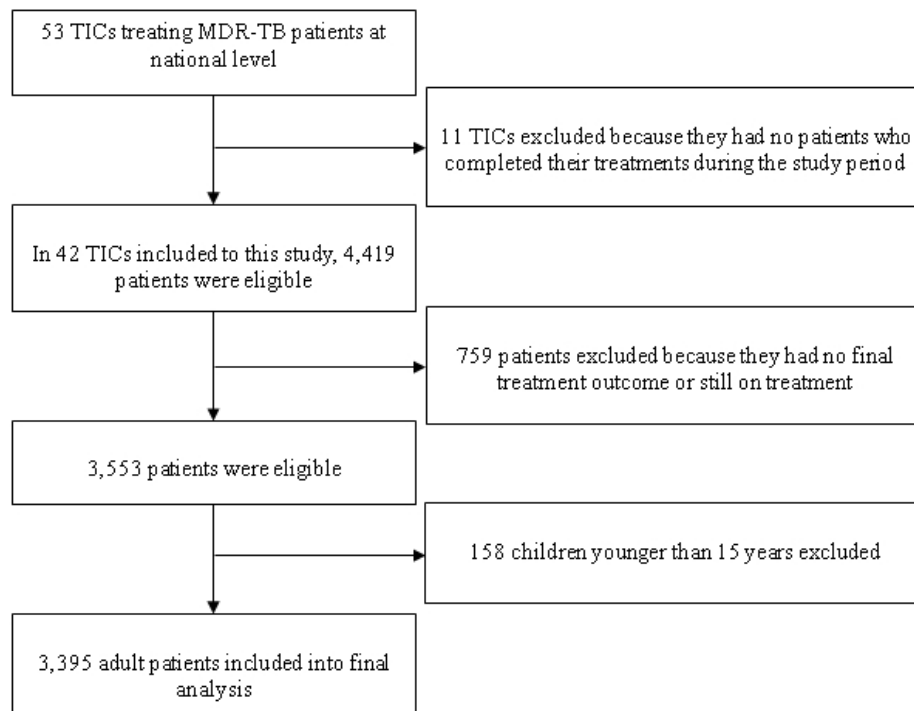


Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

171x132mm (96 x 96 DPI)

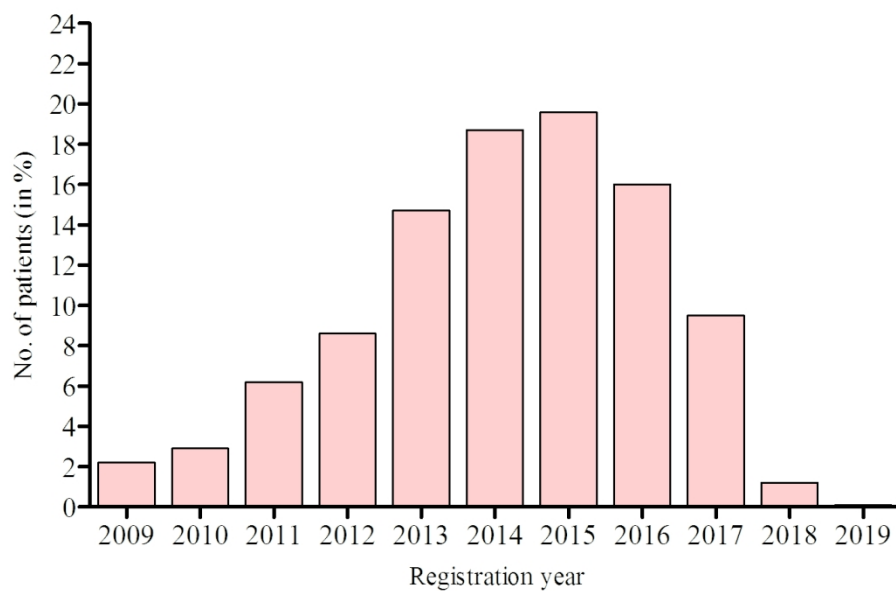


Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

137x88mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

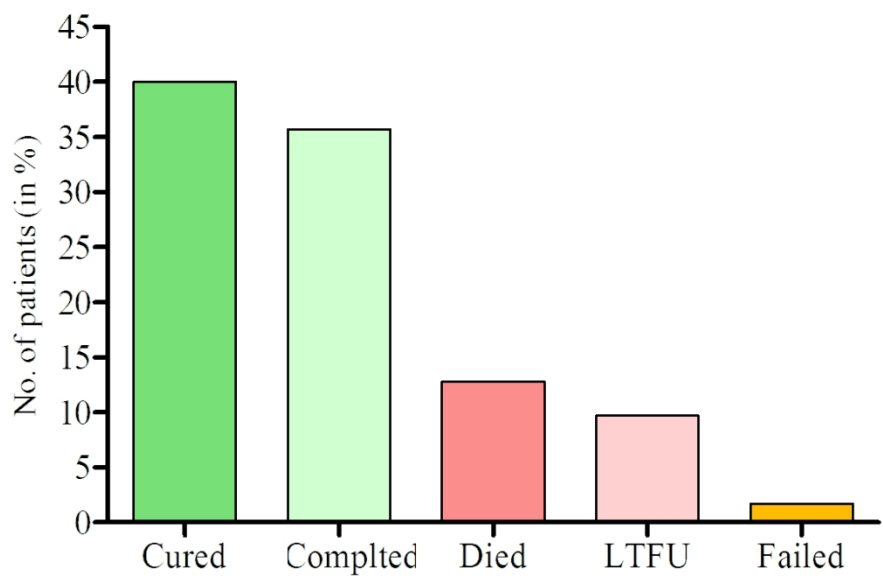


Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

110x71mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 - 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	NA NA Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11-13 Fig 1 11
Outcome data	15*	Report numbers of outcome events or summary measures over time	15

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
2				
3			(b) Report category boundaries when continuous variables were categorized	
4			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
5	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
6				
7				
8				
9				
10				
11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	16-17
13	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
14				
15	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20
16				
17	Generalisability	21	Discuss the generalisability (external validity) of the study results	20
18				
19				
20				
21	Other information			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21
23				
24				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.