Factors associated with unfavourable treatment outcomes in people with HIV-associated tuberculosis in Armenia, 2015 to 2019

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Abstract

To evaluate factors associated with tuberculosis (TB) treatment outcomes in Human Immunodeficiency Virus-Associated (HIV) TB patients in Armenia, we conducted a nation-wide cohort study using routine programmatic data of all HIV-associated TB patients receiving TB treatment with first- or second-line drugs from 2015 to 2019. Data were obtained from the TB and HIV electronic databases. We analysed occurrence of the combined unfavourable outcome (failure, lost to follow-up, death and not evaluated) and death separately, and factors associated with both outcomes using Cox regression. There were 320 HIV-associated TB patients who contributed a total of 351 episodes of TB treatment. An unfavourable TB treatment outcome was registered in 155 (44.2%) episodes, including 85 (24.2%) due to death, 38 (10.8%) lost to follow up, 13 (3.7%) failure and 19 (5.4%) not evaluated. Multivariable analysis showed that receipt of Antiretroviral Treatment (ART) [ART start before TB treatment: adjusted hazard ratio (aHR)=0.3, 95% confidence interval (CI): 0.2-0.5, ART start within 8 weeks of TB treatment: aHR=0.2, 95% CI: 0.1-0.3; and ART start after 8 weeks:

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Key words: Tuberculosis treatment; TB/HIV co-infection; unsuccessful treatment outcome; case fatality; default; operational research.

Acknowledgements: The authors thank the National Center of Pulmonology, SNCO, and the National Center for AIDS Prevention, National Center of Pulmonology, State Non Commercial Organization (SNCO) of the Ministry of Health, for defining research questions and providing data for this study, and the secretariat of the European TB Research Initiative (ERI-TB) at the WHO Regional Office for Europe for organizing the Structured Operational Research Training (SORT-TB) for eastern European countries supported by the USAID-WHO regional partnership project to End TB in eastern Europe. SORT-TB curriculum was an adaptation of the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) SORT IT course (https://www.who.int/tdr/capacity/strengthening/sort/en/) to the eastern European context.
Our deep gratitude also goes to Ms Marine Vardanyan and Seda Andrikyan, National Center of Pulmonology, National Center of Pulmonology, State Non Commercial Organization (SNCO) of the Ministry of Health of the Republic of Armenia, Gohar Mirzoyan, the National Center for AIDS Prevention, National Center of Pulmonology, State Non Commercial Organization (SNCO) of the Ministry of Health of the Republic of Armenia, for their valuable support in data handling and Giovanni Battista, WHO Collaborating Centre for TB and Lung Diseases, Maugeri Care and Research Institute, Tradate, Italy, for his support and encouragement.

Contributions: LG, AM, RG, SH, conceived the study aims. LG, AM, RG, SH, KD, MS, VA, participated in the design, discussion of the results interpretation, read, edited, and agreed with the decision to submit the final version of the paper; KA participated in the design of the study; KD conducted the data analysis; LG, AK, EK, ad TG, led the data collection and reference literature review, read, edited, and agreed with the decision to submit the final version of the paper. LG wrote the first draft of the manuscript, and AM, SH, RG, KD, KA provided substantial revisions to the initial version of the manuscript.

Conflict of interest: The authors declare no conflict of interest.

Funding: This study was funded by the United States Agency for International Development. The funding body had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethics approval: Local ethics approval was granted by Center of Medical Genetics and Primary Health Care, Yerevan, Armenia. Exemption from an ethics review was also received from the World Health Organization Research Ethics Review Committee based in Geneva, Switzerland (ERC.0003317/11.03.2020). A waiver of informed consent was granted by ethics review bodies, as the study collected and analysed de-identified routine recording and reporting data.

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Received for publication: 10 July 2020.
Accepted for publication: 11 August 2020.

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Monaldi Archives for Chest Disease 2021; 91:1648
doi: 10.4081/monaldi.2021.1648

aHR=0.1, 95% CI: 0.07-0.3] and CD4 count >200cell/μL (aHR=0.5, 95% CI: 0.3-0.9) decreased the risk of unfavourable outcome, while TB meningitis (aHR=4.4, 95% CI: 1.6-11.9) increased the risk. The risk of death was affected by the same factors as above in addition to the low Body Mass Index (aHR=2.5, 95% CI: 1.3-4.5) and drug resistance (aHR=2.3, 95% CI: 1.0-5.4). In the subsample of episodes receiving ART, history of interruption of ART during TB treatment increased the risk of unfavourable outcome (aHR=2.1, 95% CI: 1.2-3.9), while ART start during TB treatment was associated with lower risk of both unfavourable outcome (within first 8 weeks: aHR: 0.5, 95% CI: 0.3-0.9; after 8 weeks: aHR: 0.4, 95% CI: 0.2-1.0) and death (within first 8 weeks: aHR: 0.2, 95% CI: 0.1-0.4; after 8 weeks: aHR: 0.1, 95% CI: 0.01-0.3). The rates of unfavourable TB treatment outcomes, and death in particular, among HIV-associated TB patients in Armenia are high. Our findings emphasize the protective effect of ART and the importance of proper management of cases complicated by drug resistance or meningitis.

Introduction

Tuberculosis (TB) remains a major public health problem in the world. As per 2019 World Health Organization's (WHO) Global TB Report, there were an estimated 10 million people who developed TB in 2018, of which 0.8 million were among People Living With Human Immunodeficiency Virus (PLHIV) [1]. TB is one of the top 10 causes of death worldwide, the leading cause from a single infectious agent and the most common cause of death among PLHIV [1]. There were an estimated 251,000 TB deaths among PLHIV in 2018 [1]. In HIV-associated TB, Antiretroviral Therapy (ART) is a crucial factor for successful TB treatment outcome and reduced mortality. However, only 48% of the HIV-associated TB patients received ART globally in 2018. This is much lower compared to 62% among all PLHIV [1]. Globally, the HIV burden is on the decline. The WHO European Region remains the only region with an increasing trend of both HIV and HIV-associated TB. An estimated 12% of incident TB patients in 2018 were co-infected with HIV in the Region [2]. Along with anti-TB drug resistance, HIV-associated TB and underlying health systems shortcomings remain one of the major public health challenges in the WHO European region [2].

In Armenia there were an estimated 3500 PLHIV in 2018 [3]. The prevalence of HIV infection among all TB patients increased from 3.4% in 2008 to 10.3% in 2018 [2]. This proportion is similar to the 13.1% of HIV positive patients among new and relapse TB cases in the WHO European Region for the same year [2]. In Armenia the coverage of HIV testing among TB patients is higher than the European average – 95.2% compared to 91.5% in 2018 [2]. According to the WHO and the National TB and HIV guidelines ART treatment should be initiated for all ART naïve HIV-associated TB patients, regardless of their CD4 cell counts [4]. TB treatment should be started first, followed by ART as soon as possible within the first eight weeks of TB treatment. Those with profound immunosuppression (e.g., CD4 counts less than 50 cells/mm^3) should receive ART within the first two weeks of TB treatment [4,5]. In Armenia the coverage of ART among registered HIV-associated TB patients was 98.6% in 2018, which is above the European average of 73.1% [2]. However, TB treatment success rate in HIV-associated TB patients in Armenia was only 54% in 2017 [2].

Globally the risk factors associated with unfavourable TB treatment outcomes [death, Lost To Follow Up (LTFU), failure, not evaluated] among HIV-associated TB patients include age, poor nutrition, alcohol abuse, diabetes, previous treatment of TB, late diagnosis of HIV and low CD4 cell count [6-8]. Since these factors are closely related to socio-demographic and medical characteristics, country-specific data are needed to inform policies and practices. The studies on this topic in Armenia are limited. To address this issue, we evaluated the associations of a number of factors with treatment outcomes in a cohort of HIV-associated TB patients receiving anti-TB treatment with first- or second-line drugs.

Materials and Methods

Study design and period

This was a cohort study using routine programmatic data from all HIV-associated TB patients registered in the National TB Program (NTP) from 2015 to 2019.

Setting

Armenia is one of the 18 TB high priority countries in the WHO European Region [2]. In 2006, it adopted significant reforms implemented by the NTP, with technical support from the WHO Regional Office for Europe. All patients diagnosed with TB receive care free of charge within the NTP and in accordance with the WHO and the National TB guidelines [5,9]. The National Center of Pulmonology (NCP) implements the NTP and inpatient diagnosis and treatment of all forms of TB. In accordance with the WHO consolidated guidelines on drug-resistant tuberculosis treatment Armenia started to use fully oral regimens for a duration of 18-20 months from September 2019 [5]. In the period of 2015-2019 injectable drugs were included in the national drug-resistant TB treatment regimens. Bedaquiline and delamanid were available during the study period and were included in the treatment regimens for patients with rifampicin-resistant/multidrug-resistant/extensively drug-resistant (RR/MDR/XDR) TB.

TB diagnosis is provided by the National Reference Laboratory located in Abovyan city and a network of 25 smear microscopy laboratories and 14 GeneXpert sites. The National Reference Laboratory is the only national site that performs culture, molecular diagnosis of drug resistance (line probe assay) and phenotypic drug susceptibility testing (DST). The samples are transported from the capital Yerevan and the provincial smear microscopy laboratories to the National Reference Laboratory.

Armenia has centralized model of ART services [10]. Confirmation of HIV and the HIV related follow-up services (treatment and care) are available only at the National Center for AIDS Prevention (NCAP) free of charge. The results of HIV tests are registered by local laboratories and reported to the NCAP. The ART regimens for HIV-associated TB patients are defined by the National ART guidelines and are in line with the WHO recommendations [11].

Collaborative TB/HIV activities are included in the National TB and HIV strategies and implemented by the NCP and the NCAP. However, a clear mechanism of collaboration and integrated TB and HIV service delivery model is not established. HIV counselling and testing is limited only to confirmed TB cases, although according to the National HIV guidelines, it should be offered to people with presumptive TB as well. HIV specialists perform regular visits to NCP to manage confirmed HIV diagnosis of TB patients and to provide further HIV treatment and care. There is no link between electronic databases of TB and HIV programs.

Study population

All pulmonary and extrapulmonary HIV-associated TB patients (both adults and children) receiving TB treatment with first- or second-line drugs from 1 January 2015 to 31 July 2019 in Armenia were included in the study.

Data variables and analysis

The data for this study were obtained from three sources: National TB database, National HIV database, and patients' medical records.

We extracted core demographic characteristics, TB treatment history, laboratory assessment results, TB localization, chest radiography features from the National TB database. Treatment outcome definitions follow the WHO 2013 *Definitions and Reporting Framework for Tuberculosis* [12,13]. Since the National TB database contains data on multiple treatment episodes, we chose treatment episode as a unit of analysis and each patient could contribute to more than one episode to the study. Data on HIV diagnosis, CD4 count at baseline and ART were retrieved from the National HIV database. Records with matching patient identifiers were extracted and merged with the main dataset.

Socio-demographic and clinical characteristics of the study sample were described using proportions for categorical variables and measures of central tendency (median, interquartile range) for continuous variables. Labour migration history was extracted from the patients' medical records and was defined as the movement of person from Armenia to another country for the purpose of seasonal work and living there for at least three months, regardless of whether they found work or not. Body Mass Index (BMI) was calculated using the standard formula and standard categories were assigned [14]. The outcomes of interest were the combined unfavourable treatment outcome (death, LTFU, treatment failure or not evaluated) and death separately. Survival methods were used to describe occurrence of the outcomes of interest. Person-time was calculated from the date of diagnosis to the end of treatment of the episode or an outcome event. Unadjusted analysis was done using univariable Cox regression for each potential predictor. Variables significant at $p<0.1$ level in the univariable analysis, as well as key demographic and clinical variables (sex, age, BMI) were included into the multivariable Cox regression model. We constructed additional models for a subsample of patients who received ART. These included all variables from the main models with the addition of ART interruption (defined as not receiving ART for ≥1 month) during TB treatment and time between HIV diagnosis and first ART initiation. The proportional hazard assumption was verified for each variable included in the models. Data were analysed using SPSS (v23 for Windows, IBM Corporation, USA).

Results

The study included 320 HIV-associated TB patients. Thirty-one (9.7%) of them had more than one episode of TB treatment during 2015-2019: as a result, a total of 351 episodes of HIV-associated TB were analysed. The median duration of treatment was as following: cured – 6.8 months, Interquartile Range (IQR): 6.2-10.0, treatment completed – 6.9 months, IQR: 6.1-9.0, LTFU – 5.7 months, IQR: 4.3-7.4, died – 0.5 months, IQR: 0.3-5.0, failure – 5.4, IQR: 4.0-7.0 for drug sensitive/mono/poly-resistant TB, cured – 22.7 months, IQR: 20.1-25.1, treatment completed – 24.0 months, IQR: 20.6-24.2, LTFU – 9.3 months, IQR: 7.5-14.6, died – 2.3 months, IQR: 0.4-6.7, failure – 6.5, IQR: 3.7-7.7 for RR/MDR/XDR TB.

Socio-demographic and clinical characteristics of the cohort are presented in Table 1. The vast majority of episodes occurred in males (288/82.1%) and in people of 31-50 years of age category (230/65.5%). Three participants were children aged one, two and five years. Patients were mostly from urban areas, particularly from the capital Yerevan (23.4%) and Shirak region (15.4%). Tavush region (0.9%) and Artsakh (0.9%) had the lowest representation and 0.9% of the cohort were foreigners.

The vast majority of episodes (82.6%) consisted of pulmonary TB. Of all episodes, 86 (24.5%) were smear-positive and 132 (37.6%) were culture-positive at the beginning of TB treatment. Ninety-four (26.8%) episodes had positive Xpert MTB/RIF result. Laboratory confirmation was available only for 170 (48.4%) and drug susceptibility testing was conducted for 150 (42.7%) episodes, of which 68 (45.3%) had drug-susceptible, 22 (14.7%) mono-resistant, 4 (2.7%) poly-resistant, 6 (4%) RR, 44 (29.3%) MDR and 6 (4%) XDR forms of TB. A multivariable analysis showed a high (27.9%) mortality in HIV-associated TB episodes for those who did not have DST results.

ART was prescribed during TB treatment in 291 (82.9%) of all episodes. In 83 of them (28.5%) ART had been started before TB treatment initiation, and in 208 (71.5%) after TB treatment initiation. ART was never given in 45 (12.8%) TB episodes, and for 15 (4.3%) there was no ID matching between TB and HIV databases, and they were assumed as not being on ART. Out of 58 episodes of patients who started ART during TB treatment and had CD4 50 cells/μL or less at the time of ART initiation (baseline), only 6 (10.3%) started ART within the first 2 weeks of TB treatment. Of 79 who started ART during TB treatment and had more than 50 CD4 cells/μL at baseline, 64 (81%) started ART within 8 weeks of TB treatment. Out of 291 (82.9%) episodes of patients who were receiving ART during TB treatment, in 22 episodes (7.6%) ART was interrupted and not resumed at the time of data collection, in 5 (1.7%) ART was interrupted (for less than a month in 2 and more than a month in 3 instances) and then resumed.

A favourable TB treatment outcome (cure or treatment completion) was achieved in 196 (55.8%) episodes. An unfavourable TB treatment outcome was registered in 155 (44.2%) episodes, with 85 (24.2%) deaths, 38 (10.8%) LTFU, 13 (3.7%) failures and 19 (5.4%) not evaluated. Out of 86 episodes of patients who were smear-positive at TB diagnosis, smear conversion was achieved in 62 (72.1%). The median time to smear conversion was 1.9 months, IQR: 1.1-2.8. Culture conversion was achieved in 102 (77.3%) out of 132 episodes, who were culture-positive at TB diagnosis. The median time to culture conversion was 2.3 months, IQR: 1.2-3.2.

The multivariable analysis of the combined unfavourable outcome (Table 2) showed that receiving ART regardless of time of initiation [before TB treatment initiation: adjusted hazard ratio (aHR): 0.3, 95% confidence interval (CI): 0.2-0.5; within the first 8 weeks: aHR: 0.2, 95% CI: 0.1-0.3; after 8 weeks: aHR: 0.2, 95% CI: 0.1-0.3], as well as baseline CD4 count of more than 200 cells/μl (aHR: 0.5, 95% CI:0.3-0.9 compared to ≤50 cells/μl) have a protective effect. TB meningitis was the only factor associated with increased risk of unfavourable outcome (aHR: 4.4, 95% CI: 1.6-11.9).

In the subsample of episodes receiving ART (Table 2), ART start during TB treatment (at any time) was associated with lower risk of unfavourable outcome compared to those who started ART before TB treatment (within first 8 weeks: aHR: 0.5, 95% CI: 0.3-0.9; after 8 weeks: aHR: 0.4, 95% CI: 0.2-1.0) and the history of ART interruption was associated with increased risk of unfavourable outcome (aHR: 2.1, 95% CI: 1.2-3.9), while baseline CD4 cell count was not significantly associated with TB treatment outcome in this subsample.

Table 1. Socio-demographic and clinical characteristics of HIV-associated TB patients (adult and children) who were enrolled on first-line and second-line TB treatment from 2015 to 2019 in Armenia (N=351) by treatment outcomes.

Characteristics		Total N (col.%)	Unfavourable outcome N (row %)	Favourable outcome N (row %)	HR	95% CI for HR	Alive N (row %)	Deceased N (row %)	HR	95% CI for HR
	Total	351 (100.0)	196 (55.8)	155 (44.2)			266 (75.8)	85 (24.2)		
Sex	Female	63 (17.9)	32 (50.8)	31 (49.2)	1.33	(0.87-2.02)	42 (66.7)	21 (33.3)	1.71	(1.04-2.8)
	Male	288 (82.1)	164 (56.9)	124 (43.1)			224 (77.8)	64 (22.2)		
Age	≤30	29 (8.3)	18 (62.1)	11 (37.9)			21 (72.4)	8 (27.6)		
	31-40	115 (32.8)	64 (55.7)	51 (44.3)	0.87	(0.44-1.69)	92 (80.0)	23 (20.0)	0.72	(0.32-1.6)
	41-50	115 (32.8)	64 (55.7)	51 (44.3)	0.81	(0.42-1.58)	90 (78.3)	25 (21.7)	0.72	(0.32-1.61)
	>50	92 (26.2)	50 (54.3)	42 (45.7)	1.08	(0.55-2.11)	63 (68.5)	29 (31.5)	1.16	(0.53-2.53)
BMI°	Underweight	96 (27.4)	52 (54.2)	44 (45.8)	1.44	(0.94-2.21)	72 (75.0)	24 (25.0)	1.93	(1.09-3.43)
	Normal	160 (45.6)	102 (63.8)	58 (36.3)			137 (85.6)	23 (14.4)		
	Overweight or Obese	28 (8.0)	16 (57.1)	12 (42.9)	1.02	(0.48-2.16)	24 (85.7)	4 (14.3)	1.10	(0.38-3.19)
CD4 cell count at baseline	Unknown	67 (19.1)	26 (38.8)	41 (61.2)	2.98	(1.96-4.53)	33 (49.3)	34 (50.7)	4.59	(2.7-7.82)
	≤50	97 (27.6)	51 (52.6)	46 (47.4)			65 (67.0)	32 (33.0)		
	51-200	65 (18.5)	40 (61.5)	25 (38.5)	0.66	(0.39-1.12)	52 (80.0)	13 (20.0)	0.61	(0.32-1.16)
	>201	62 (17.7)	42 (67.7)	20 (32.3)	0.56	(0.32-0.97)	57 (91.9)	5 (8.1)	0.22	(0.08-0.56)
	Unknown	127 (36.2)	63 (49.6)	64 (50.4)	0.92	(0.61-1.37)	92 (72.4)	35 (27.6)	0.84	(0.52-1.36)
Time from TB diagnosis to treatment start in days	Up to 2	298 (85.6)	173 (58.1)	125 (41.9)			227 (76.2)	71 (23.8)		
	3-14	34 (9.8)	16 (47.1)	18 (52.9)	1.25	(0.74-2.11)	25 (73.5)	9 (26.5)	1.15	(0.57-2.3)
	>14	16 (4.6)	5 (31.3)	11 (68.8)	1.17	(0.51-2.66)	12 (75.0)	4 (25.0)	1.33	(0.49-3.66)
Time from HIV diagnosis to ART	Up to 1 month	109 (31.1)	64 (58.7)	45 (41.3)			90 (82.6)	19 (17.4)		
	2-3 months	77 (21.9)	51 (66.2)	26 (33.8)	0.68	(0.4-1.15)	63 (81.8)	14 (18.2)	0.95	(0.47-1.89)
	>3 months	102 (29.1)	71 (69.6)	31 (30.4)	0.65	(0.4-1.06)	93 (91.2)	9 (8.8)	0.45	(0.2-0.99)
	Unknown	63 (17.9)	10 (15.9)	53 (84.1)	4.14	(2.7-6.33)	20 (31.7)	43 (68.3)	6.47	(3.75-11.14)
Time from TB treatment to ART	Did not start ART or unknown	60 (17.1)	9 (15.0)	51 (85.0)			18 (30.0)	42 (70.0)		
	ART before TB treatment	83 (23.6)	41 (49.4)	42 (50.6)	0.26	(0.16-0.4)	59 (71.1)	24 (28.9)	0.25	(0.15-0.41)
	ART within 8 weeks of TB treatment	163 (46.4)	113 (69.3)	50 (30.7)	0.15	(0.1-0.23)	146 (89.6)	17 (10.4)	0.08	(0.04-0.14)
	ART after 8 weeks of TB treatment	45 (12.8)	33 (73.3)	12 (26.7)	0.15	(0.08-0.28)	43 (95.6)	2 (4.4)	0.03	(0.01-0.14)
Time from HIV to TB diagnosis	HIV before TB	222 (63.2)	131 (59.0)	91 (41.0)			171 (77.0)	51 (23.0)		
	HIV on the same day or after TB	111 (31.6)	59 (53.2)	52 (46.8)	1.29	(0.9-1.86)	82 (73.9)	29 (26.1)	1.26	(0.8-1.98)
	Unknown date of HIV diagnosis	18 (5.1)	6 (33.3)	12 (66.7)	1.43	(0.73-2.78)	13 (72.2)	5 (27.8)	1.31	(0.52-3.28)
Type of drug resistance (DST)	Not tested	201 (57.3)	122 (60.7)	79 (39.3)	1.33	(0.87-2.04)	145 (72.1)	56 (27.9)	3.16	(1.56-6.39)
	Sensitive/Mono/Poly	94 (26.8)	57 (60.6)	37 (39.4)			85 (90.4)	9 (9.6)		
	RR/MDR/XDR	56 (16.0)	17 (30.4)	39 (69.6)	1.46	(0.88-2.43)	36 (64.3)	20 (35.7)	3.43	(1.55-7.63)
Diabetes	Yes	4 (1.1)	1 (25.0)	3 (75.0)			3 (75.0)	1 (25.0)		
	No	347 (98.9)	195 (56.2)	152 (43.8)	0.96	(0.24-3.89)	263 (75.8)	84 (24.2)	0.97	(0.13-6.99)
HCV	Yes	63 (17.9)	31 (49.2)	32 (50.8)			48 (76.2)	15 (23.8)		
	No	288 (82.1)	165 (57.3)	123 (42.7)	1.08	(0.71-1.64)	218 (75.7)	70 (24.3)	1.18	(0.67-2.06)
HBV	Yes	4 (1.1)	2 (50.0)	2 (50.0)			2 (50.0)	2 (50.0)		
	No	347 (98.9)	194 (55.9)	153 (44.1)	0.53	(0.13-2.16)	264 (76.1)	83 (23.9)	0.43	(0.11-1.75)
Mental disorders	Yes	3 (0.9)	2 (66.7)	1 (33.3)			3 (100.0)	0 (0.0)		
	No	348 (99.1)	194 (55.7)	154 (44.3)	20.36	(0-)	263 (75.6)	85 (24.4)	20.31	
Cardio-vascular diseases	Yes	13 (3.7)	4 (30.8)	9 (69.2)	1.86	(0.94-3.66)	7 (53.8)	6 (46.2)	1.98	(0.86-4.55)
	No	338 (96.3)	192 (56.8)	146 (43.2)			259 (76.6)	79 (23.4)		
ART interruption/termination history	Yes	26 (7.4)	9 (34.6)	17 (65.4)	2.03	(1.19-3.48)	21 (80.8)	5 (19.2)	1.21	(0.47-3.1)
	No	229 (65.2)	164 (71.6)	65 (28.4)			195 (85.2)	34 (14.8)		
	Did not start ART	45 (12.8)	4 (8.9)	41 (91.1)	11.88	(7.81-18.07)	7 (15.6)	38 (84.4)	14.82	(9.11-24.12)
	Unknown	51 (14.5)	19 (37.3)	32 (62.7)	1.50	(0.85-2.65)	43 (84.3)	8 (15.7)	1.69	(0.78-3.65)

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Table 1. Continued from previous page.

Characteristics		Total N (col.%)	Unfavourable outcome N (row %)	Favourable outcome N (row %)	HR	95% CI for HR	Alive N (row %)	Deceased N (row %)	HR	95% CI for HR
Patient residence	Urban	212 (60.4)	125 (59.0)	87 (41.0)			164 (77.4)	48 (22.6)		
	Rural	113 (32.2)	61 (54.0)	52 (46.0)	1.15	(0.8-1.66)	87 (77.0)	26 (23.0)	1.00	(0.62-1.62)
	Unknown	26 (7.4)	10 (38.5)	16 (61.5)	2.30	(1.29-4.08)	15 (57.7)	11 (42.3)	2.38	(1.23-4.6)
Labour migration	Yes	55 (15.7)	25 (45.5)	30 (54.5)	0.99	(0.64-1.53)	47 (85.5)	8 (14.5)	0.51	(0.24-1.05)
	No	296 (84.3)	171 (57.8)	125 (42.2)			219 (74.0)	77 (26.0)		
Incarceration history	Yes	27 (7.7)	13 (48.1)	14 (51.9)			21 (77.8)	6 (22.2)		
	No	324 (92.3)	183 (56.5)	141 (43.5)	1.13	(0.63-2.01)	245 (75.6)	79 (24.4)	1.35	(0.58-3.11)
Previous TB treatment	No	270 (76.9)	153 (56.7)	117 (43.3)			203 (75.2)	67 (24.8)		
	Yes	81 (23.1)	43 (53.1)	38 (46.9)	0.78	(0.53-1.16)	63 (77.8)	18 (22.2)	0.75	(0.45-1.27)
TB treatment	First line drugs	264 (75.2)	162 (61.4)	102 (38.6)			200 (75.8)	64 (24.2)		
	Second line drugs	87 (24.8)	34 (39.1)	53 (60.9)	0.86	(0.57-1.28)	66 (75.9)	21 (24.1)	0.88	(0.52-1.48)
Type of TB site	Pulmonary	290 (82.6)	159 (54.8)	131 (45.2)			216 (74.5)	74 (25.5)		
	Extrapulmonary	36 (10.3)	25 (69.4)	11 (30.6)	0.48	(0.24-0.99)	32 (88.9)	4 (11.1)	0.41	(0.15-1.13)
	Combined	25 (7.1)	12 (48.0)	13 (52.0)	0.97	(0.49-1.91)	18 (72.0)	7 (28.0)	1.29	(0.59-2.8)
Laboratory confirmed TB	Yes	170 (48.4)	83 (48.8)	87 (51.2)	0.93	(0.66-1.31)	136 (80.0)	34 (20.0)	0.64	(0.41-0.99)
	No	181 (51.6)	113 (62.4)	68 (37.6)			130 (71.8)	51 (28.2)		
Baseline smear microscopy	Positive	86 (24.5)	39 (45.3)	47 (54.7)			65 (75.6)	21 (24.4)		
	Negative	242 (68.9)	143 (59.1)	99 (40.9)	0.94	(0.65-1.37)	181 (74.8)	61 (25.2)	1.13	(0.68-1.85)
	Unknown	23 (6.6)	14 (60.9)	9 (39.1)	0.52	(0.22-1.22)	20 (87.0)	3 (13.0)	0.53	(0.16-1.77)
Smear conversion*	Yes[#]	62 (72.1)	38 (61.3)	24 (38.7)			54 (87.1)	8 (12.9)		
	No[#]	12 (13.9)	0 (0.0)	12 (100.0)	5.97	(2.82-12.66)	7 (58.3)	5 (41.7)	4.88	(1.59-14.99)
	No point for conversion/ initially negative/unknown	277 (78.9)	158 (57.0)	119 (43.0)	1.88	(1.14-3.08)	205 (74.0)	72 (26.0)	2.47	(1.19-5.13)
Baseline culture	Positive	132 (37.6)	68 (51.5)	64 (48.5)			105 (79.5)	27 (20.5)		
	Negative	191 (54.4)	111 (58.1)	80 (41.9)	1.15	(0.81-1.64)	137 (71.7)	54 (28.3)	1.63	(1.02-2.6)
	Unknown	28 (8.0)	17 (60.7)	11 (39.3)	0.68	(0.32-1.42)	24 (85.7)	4 (14.3)	0.73	(0.26-2.09)
Culture conversion*	Yes[#]	102 (77.3)	61 (59.8)	41 (40.2)			91 (89.2)	11 (10.8)		
	No[#]	13 (9.8)	1 (7.7)	12 (92.3)	6.52	(3.32-12.81)	6 (46.2)	7 (53.8)	8.20	(3.14-21.41)
	No point for conversion/ initially negative/unknown	236 (67.2)	134 (56.8)	102 (43.2)	1.82	(1.22-2.73)	169 (71.6)	67 (28.4)	3.47	(1.82-6.63)
Result of GeneXpert	MTB Positive	94 (26.8)	53 (56.4)	41 (43.6)			79 (84.0)	15 (16.0)		
	MTB Negative	193 (55.0)	109 (56.5)	84 (43.5)	1.49	(0.99-2.24)	136 (70.5)	57 (29.5)	2.26	(1.27-4.02)
	Unknown	64 (18.2)	34 (53.1)	30 (46.9)	1.28	(0.77-2.13)	51 (79.7)	13 (20.3)	1.44	(0.69-3.05)
GeneXpert Rifampicin resistance[§]	Detected	30 (31.9)	15 (50.0)	15 (50.0)			19 (63.3)	11 (36.7)		
	Not detected	64 (68.1)	38 (59.4)	26 (40.6)	1.27	(0.62-2.61)	60 (93.8)	4 (6.3)	0.18	(0.06-0.59)
Chest radiography assessment	Cavity	145 (41.3)	77 (53.1)	68 (46.9)	1.77	(0.84-3.72)	114 (78.6)	31 (21.4)	2.00	(0.7-5.66)
	No cavity with other abnormalities	144 (41.0)	86 (59.7)	58 (40.3)			108 (75.0)	36 (25.0)	2.41	(0.86-6.78)
	No abnormalities	36 (10.3)	25 (69.4)	11 (30.6)	2.01	(0.96-4.23)	32 (88.9)	4 (11.1)		
	Unknown	26 (7.4)	8 (30.8)	18 (69.2)	5.21	(2.25-12.03)	12 (46.2)	14 (53.8)	6.37	(2.09-19.4)
Chest radiography assessment of disease spread	Unilateral	128 (36.5)	76 (59.4)	52 (40.6)	1.57	(0.74-3.33)	109 (85.2)	19 (14.8)	1.32	(0.45-3.87)
	Bilateral	160 (45.6)	86 (53.8)	74 (46.3)	2.20	(1.06-4.59)	112 (70.0)	48 (30.0)	3.03	(1.09-8.4)
	No abnormalities	36 (10.3)	25 (69.4)	11 (30.6)			32 (88.9)	4 (11.1)		
	Unknown	27 (7.7)	9 (33.3)	18 (66.7)	4.83	(2.09-11.14)	13 (48.1)	14 (51.9)	6.02	(1.98-18.32)
TB meningitis	Yes	7 (2.0)	1 (14.3)	6 (85.7)	4.84	(1.97-11.88)	2 (28.6)	5 (71.4)	6.79	(2.74-16.85)
	No	344 (98.0)	195 (56.7)	149 (43.3)			264 (76.7)	80 (23.3)		

°Normal: BMI 18.5-24.9, underweight: BMI less than 18.5, overweight: BMI 25.0-29.9, obese: BMI more than 30; *conversion from positive to negative; [#]calculated out of those who were initially positive; [§]calculated out of those who were Xpert MTB/RIF positive; HIV, human immunodeficiency virus; TB, tuberculosis; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ART, antiretroviral therapy; DST, drug susceptibility testing: RR, rifampicin resistance; MDR, multidrug-resistant TB; XDR, extensively drug-resistant TB; HCV, hepatitis C virus; HBV, hepatitis B virus; MTB, mycobacterium tuberculosis.

The multivariable analysis of factors associated with death (Table 3) similarly showed that ART receipt at any point and higher CD4 cell count were protective and TB meningitis was a risk factor. In addition, the presence of drug resistance (aHR: 2.3, 95% CI: 1.0-5.4) and low BMI (underweight) (aHR: 2.5, 95% CI: 1.3-4.5) were associated with increased risk of death.

In the subsample of episodes receiving ART (Table 3), ART start during TB treatment was associated with lower risk of death compared to those who start ART before TB treatment (within first 8 weeks: aHR: 0.2, 95% CI: 0.1-0.4; after 8 weeks: aHR: 0.1, 95% CI: 0.01-0.3), whereas CD4 count and history of ART interruption was not associated with the outcome of death.

Discussion

We found a high rate of unfavourable TB treatment outcome among HIV-associated TB patients in Armenia. The fatality rate was particularly high (24.2%). The percentage of favourable TB treatment outcome was 55.8%, which is much lower than the global target of 90% [15]. Predictors of unfavourable TB treatment outcomes included not receiving ART, CD4 cell count 50 or less, and TB meningitis. Specific predictors of death included not receiving ART, CD4 cell count 50 or less, having RR/MDR/XDR-TB, TB meningitis and being underweight. Death mostly occurred in the early phase of the TB treatment.

Table 2. Factors associated with combined unfavourable outcome (death, loss to follow-up or treatment failure) in all HIV-associated TB patients (N=330) and for a sub-sample of patients with history of ART (N=269) who were enrolled in first-line and second-line TB treatment from 2015 to 2019 in Armenia.

		All sample		Patients with history of ART	
		p-value	aHR (95% CI)	p-value	aHR (95% CI)
Sex	Female		ref		ref
	Male	0.833	0.95 (0.6-1.5)	0.957	0.98 (0.5-1.92)
Age	≤30		ref		ref
	31-40	0.970	1.01 (0.49-2.1)	0.778	1.17 (0.39-3.54)
	41-50	0.868	0.94 (0.46-1.93)	0.784	0.85 (0.28-2.63)
	51+	0.569	1.23 (0.61-2.48)	0.924	1.06 (0.33-3.34)
BMI°	Normal		ref		ref
	Underweight	0.190	1.36 (0.86-2.16)	0.675	1.13 (0.64-2.01)
	Overweight or obese	0.812	1.1 (0.5-2.42)	0.478	0.7 (0.26-1.87)
	Unknown	**0.000**	**2.4 (1.48-3.9)**	**0.003**	**2.56 (1.37-4.78)**
Time between TB diagnosis and treatment in days	Up to 2		ref		ref
	3-14	0.582	1.17 (0.67-2.03)	0.966	1.02 (0.45-2.32)
	>14	0.745	1.16 (0.47-2.89)	0.727	0.78 (0.2-3.08)
Type of drug resistance	Sensitive/mono/poly		ref		ref
	not tested	0.991	1 (0.44-2.3)	0.727	0.82 (0.27-2.48)
	RR/MDR/XDR	0.173	1.64 (0.8-3.37)	0.630	1.24 (0.51-3.02)
CD4 cell count at baseline	≤50		ref		ref
	51-200	0.543	0.84 (0.48-1.48)	0.755	0.89 (0.44-1.81)
	>201	**0.019**	**0.48 (0.26-0.89)**	0.581	0.8 (0.36-1.76)
	Unknown	0.604	0.89 (0.56-1.4)	0.355	1.33 (0.72-2.45)
Time between TB treatment and ART	Did not start ART or unknown		ref		
	ART before TB treatment	**0.000**	**0.3 (0.18-0.51)**		ref
	ART within 8 weeks of treatment	**0.000**	**0.18 (0.11-0.29)**	**0.020**	**0.53 (0.31-0.91)**
	ART after 8 weeks of treatment	**0.000**	**0.15 (0.07-0.31)**	**0.046**	**0.44 (0.2-0.99)**
Cardio-vascular diseases	No		ref		ref
	Yes	0.251	1.58 (0.72-3.44)	0.280	1.87 (0.6-5.85)
Labour migration	No		ref		ref
	Yes	0.519	1.19 (0.7-2.01)	0.212	1.48 (0.8-2.73)
TB treatment type	First line		ref		ref
	Second line	0.087	0.52 (0.25-1.1)	0.284	0.63 (0.27-1.47)
Laboratory confirmed TB	No		ref		ref
	Yes	0.583	1.24 (0.57-2.71)	0.758	0.85 (0.29-2.46)
TB meningitis	No		ref		ref
	Yes	**0.003**	**4.4 (1.63-11.86)**	0.142	3.31 (0.67-16.38)
Time from HIV diagnosis to ART	Up to 1 month				ref
	2-3 months			0.194	0.67 (0.37-1.22)
	>3 months			0.297	0.72 (0.39-1.34)
ART interruption/ termination history	No				ref
	Yes			**0.012**	**2.15 (1.18-3.9)**
	Unknown			0.630	1.27 (0.48-3.32)

°Normal: BMI 18.5-24.9, underweight: BMI less than 18.5, overweight: BMI 25.0-29.9, obese: BMI more than 30; HIV, human immunodeficiency virus; TB, tuberculosis; ART, antiretroviral therapy; aHR, adjusted hazard ratio; CI, confidence interval; BMI, body mass index RR, rifampicin resistance; DR, multidrug-resistant TB; XDR, extensively drug-resistant TB.

In a subsample receiving ART a specific predictor of unfavourable TB treatment outcome was ART interruption during TB treatment. In addition, ART start during TB treatment was associated with lower risk of both unfavourable TB treatment outcome and death compared to ART start before TB treatment.

Globally there are many studies showing that the early start of ART has a protective effect against death among HIV-associated TB patients [7,16,17]. Multivariable analysis in our study confirmed the strong protective effect of ART regardless the time of initiation against death as well as combined TB treatment unfavourable outcome. Although a high proportion of HIV-associated TB patients in our cohort received timely ART, the fatality rate was still extremely high. One of the explanations, supported also by the literature, is that the proportion of PLHIV who were on ART and developed active TB could in fact have been receiving ineffective treatment, due to the development of HIV drug resistance or poor treatment adherence [18,19]. This hypothesis could not be tested in our study as the HIV viral resistance pattern was not determined at the time of TB diagnosis.

In our subsample of episodes with ART, higher rate of death and combined TB treatment unfavorable outcome in those who started ART before TB treatment compared to those who started ART during TB treatment, could be explained by ART-caused immune reconstitution. This could lead to activation of TB infection and result in severe disease [20]. However, it was impossible to assess ART-caused immune reconstitution because the data on this was not recorded in any of the sources.

There is a strong evidence in the literature that patients with low baseline CD4 cell count have high rates of unfavourable TB treatment outcome including death and this was also confirmed by

Table 3. Factors associated with death outcome in all HIV-associated TB patients (N=333) and for a sub-sample of patients receiving ART (N=272) who were enrolled in first line and second line TB treatment from 2015 to 2019 in Armenia.

		All sample		Patients with history of ART	
		p-value	aHR (95% CI)	p-value	aHR (95% CI)
Sex	Female	ref		ref	
	Male	0.618	1.15 (0.67-1.96)	0.895	0.94 (0.39-2.3)
Age	≤30	ref		ref	
	31-40	0.772	0.88 (0.37-2.09)	0.941	1.07 (0.19-5.91)
	41-50	0.931	0.96 (0.41-2.26)	0.634	0.65 (0.11-3.74)
	51+	0.242	1.64 (0.72-3.76)	0.621	1.54 (0.28-8.64)
BMI°	Normal	ref		ref	
	Underweight	**0.004**	**2.47 (1.34-4.54)**	0.073	2.17 (0.93-5.08)
	Overweight or obese	0.373	1.68 (0.54-5.23)	0.293	0.32 (0.04-2.65)
	Unknown	**0.000**	**3.36 (1.76-6.42)**	**0.000**	**8.56 (3.32-22.1)**
Time between TB diagnosis and treatment in days	up to 2	ref		ref	
	3-14	0.790	0.93 (0.55-1.57)	0.951	0.97 (0.43-2.22)
	>14	**0.002**	**3.15 (1.51-6.56)**	**0.000**	**6.7 (2.5-17.93)**
Type of drug resistance	Sensitive/Mono/Poly	ref		ref	
	Not tested	0.243	2 (0.62-6.43)	0.437	1.96 (0.36-10.66)
	RR/MDR/XDR	**0.046**	**2.33 (1.01-5.38)**	0.114	2.54 (0.8-8.05)
CD4 cell count at baseline	≤50	ref		ref	
	51-200	0.769	1.11 (0.55-2.23)	0.746	1.18 (0.44-3.19)
	>201	**0.004**	**0.21 (0.07-0.61)**	0.616	0.71 (0.18-2.74)
	Unknown	0.602	1.16 (0.67-1.99)	0.111	2.13 (0.84-5.4)
Time between TB treatment and ART	Did not start ART or unknown	ref			
	ART before TB treatment	0.001	0.36 (0.2-0.66)	ref	
	ART within 8 weeks of TB treatment	**0.000**	**0.1 (0.05-0.19)**	**0.000**	**0.19 (0.09-0.41)**
	ART after 8 weeks of TB treatment	**0.000**	**0.04 (0.01-0.18)**	**0.001**	**0.07 (0.01-0.32)**
Cardio-vascular diseases	No	ref			
	Yes	0.126	2.11 (0.81-5.47)	**0.029**	**6.25 (1.2-32.5)**
Labour migration	No	ref		ref	
	Yes	0.579	0.78 (0.33-1.85)	0.647	1.3 (0.42-4.04)
Laboratory confirmed TB	No	ref		ref	
	Yes	0.863	1.09 (0.4-2.95)	0.714	0.75 (0.16-3.48)
TB meningitis	No	ref		ref	
	Yes	**0.001**	**5.9 (2.02-17.24)**	**0.022**	**7.85 (1.34-46.04)**
Time from HIV diagnosis to ART	Up to 1 month			ref	
	2-3 months			0.163	1.83 (0.78-4.27)
	>3 months			0.377	0.64 (0.24-1.71)
ART interruption/termination history	No			ref	
	Yes			0.484	1.47 (0.5-4.34)
	Unknown			0.673	1.31 (0.37-4.65)

°Normal: BMI 18.5-24.9, underweight: BMI less than 18.5, overweight: BMI 25.0-29.9, obese: BMI more than 30; HIV, human immunodeficiency virus; TB, tuberculosis; ART, antiretroviral therapy; aHR, adjusted hazard ratio; CI, confidence interval; BMI, body mass index RR, rifampicin resistance; : MDR, multidrug-resistant TB; XDR, extensively drug-resistant TB.

our study [7,18,21]. We also found that ART interruption during TB treatment increased the risk of unfavourable TB treatment outcome. Literature shows that ART interruptions are associated with a decrease in CD4 cell count, increase in viral load and development of opportunistic infections [22,23].

Even though TB meningitis was a rare event in our cohort, it was significantly associated with an increased risk of unfavourable TB treatment outcome and death. Studies showed that the diagnosis of TB meningitis is often difficult and delayed, due to the atypical clinical and laboratory presentation in PLHIV, thus leading to poor treatment outcomes [24,25]. The effect of HIV infection on the outcome of MDR-TB is shown in many studies globally, [18,26,27]. We confirmed that RR/MDR/XDR TB patients had higher risk of death compared to patients with drug susceptible/mono/poly-resistant TB forms. We also found a high mortality in HIV-associated TB episodes for those who did not have DST results. Although a multivariable analysis did not demonstrate a difference between untested and susceptible TB cases, the high percentage of deaths can be either due to undiagnosed resistance treated with inappropriate anti-TB treatment regimens or to an overdiagnosis of TB disease [28-30]. Another independent risk factor associated with death was low BMI. The association between being underweight and the increased risk of death in both TB and HIV patients has been also demonstrated by many studies [31-33]. Among HIV-associated TB patients, underweight patients have slow restoration of immunity, which may increase the risk of death [34].

Our study has several limitations. Data on baseline and follow-up CD4 cell count, as well as viral load and ART was incomplete. Treatment adverse events and development of immune reconstitution inflammatory syndrome had not been recorded in any of the three sources and hence we were unable to include these factors in our multivariable analysis.

Strengths of our study were the following: first, the study included a nationally representative cohort, thus, study findings are generalizable to the entire country. Second, we included multiple sources for the data collection and we were able to validate clinical and laboratory information. In addition, we were able to include in the study both drug-susceptible and drug-resistant TB patients of all ages, which allowed exploration of these variables in the adjusted model.

In conclusion, we provide the first detailed analysis of treatment outcomes and their risk factors among HIV-associated TB patients in Armenia. Our findings highlight a persistently high fatality rate despite adequate access to ART. This requires further steps to improve management of patients, including a precise diagnosis of TB, an appropriate TB treatment regimen, and a timely and uninterrupted ART. In a large proportion of cases a microbiological diagnosis of TB could not be made, thus limiting information on drug susceptibility and increasing the risk of mismatch between sensitivity pattern and treatment regimen adopted. Similarly, the efficacy of ART should be systematically ascertained, particularly in patients on treatment who develop opportunistic infection including TB. HIV patients should be properly tested for TB and other infections to minimize immune reconstitution inflammatory syndrome after ART initiation.

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