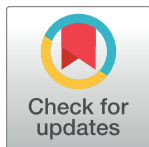


## RESEARCH ARTICLE

# The socio-demographic, clinical characteristics and outcomes of tuberculosis among HIV infected adults in Lithuania: A thirteen-year analysis

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## OPEN ACCESS

**Citation:** Matulyte E, Davidaviciene E, Kancauskiene Z, Diktanas S, Kausas A, Velyvyte D, et al. (2023) The socio-demographic, clinical characteristics and outcomes of tuberculosis among HIV infected adults in Lithuania: A thirteen-year analysis. PLoS ONE 18(3): e0282046. <https://doi.org/10.1371/journal.pone.0282046>

**Editor:** Yuan-Ti Lee, Chung Shan Medical University, TAIWAN

**Received:** May 21, 2022

**Accepted:** February 6, 2023

**Published:** March 23, 2023

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**Data Availability Statement:** All relevant data are within the paper and its [Supporting Information](#) files.

**Funding:** EM, ZK, AK and RM received grants in the frame of the project "Run-up to programmatic management of latent tuberculosis infection in HIV-infected people in Lithuania", Project ID 482020, funded by the Western-Eastern European Partnership Initiative on HIV, Viral Hepatitis and TB (WEEPI, [www.weepi.org](http://www.weepi.org)). The funders had no role

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## Abstract

### Background

Tuberculosis (TB) is a public health problem in Lithuania, among the 18 high-priority TB countries in the European region, and the most common AIDS-indicative disease with the highest proportion in the EU/EEA since 2015. The study aimed to identify socio-demographic, clinical characteristics and their relationship with TB outcomes in TB-HIV co-infected patients in Lithuania.

### Methods

A retrospective chart review analysed the characteristics of TB-HIV co-infected adults registered in State Information System of Tuberculosis over 2008–2020. The factors associated with drug-resistant TB and unsuccessful treatment outcome were identified by multivariable logistic regression.

### Results

The study included 345 cases in 311 patients (239 new, 106 previously treated cases), median age 40 years (IQR 35–45), 80.7% male. 67.8% patients knew their HIV-positive

in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** The authors have declared that no competing interests exist.

status before TB diagnosis, median time to TB diagnosis was 8 years (IQR 4–12). 83.6% were unemployed, 50.5%—anytime intravenous drug users (IDU), 34.9% abused alcohol. Drug-resistant TB rates in new and previously treated TB cases were 38.1% and 61.3%, respectively. In multivariable analysis, higher risk of drug-resistant TB was associated with imprisonment in new (aOR 3.35; 95%CI 1.17–9.57) and previously treated (aOR 6.63; 95%CI 1.09–40.35) cases. In 52.3% of new TB cases and in 42.5% previously treated TB cases the treatment outcomes were unsuccessful. In multivariable analysis of new TB cases, current imprisonment (aOR 2.77; 95%CI 1.29–5.91) and drug-resistant TB (aOR 2.18; 95%CI 1.11–4.28) were associated with unsuccessful treatment outcome. In multivariable analysis of previously treated TB cases, female gender (aOR 11.93; 95%CI 1.86–76.69), alcohol abuse (aOR 3.17; 95%CI 1.05–9.58), drug-resistant TB (aOR 4.83; 95%CI 1.53–15.28) were associated with unsuccessful treatment outcome.

## Conclusions

In the TB-HIV-infected adult cohort in Lithuania, unemployment, imprisonment, IDU, alcohol abuse, known to be risk factors for TB, were very frequent. Drug resistance was an undeniable risk factor for unsuccessful treatment outcome and imprisonment was associated with drug resistant TB.

## Introduction

Tuberculosis (TB) remains a public health issue and the leading cause of death among people living with HIV (PLHIV) in the world. In 2019, there were 10 million new cases of TB and 1.2 million TB deaths globally. Among them, 8.2% of new TB cases and 208,000 deaths were in PLHIV [1]. Besides, for the first time over a decade, TB death rate has increased in 2020 because of decreased access to prevention and care due to COVID-19 pandemic [2]. Drug-resistant TB persists as a serious public health threat accounting for nearly half million cases in 2019 worldwide and 78% of these cases were multidrug-resistant TB (MDR-TB). Treatment of MDR-TB is a challenge and requires the attention to the complexity of pill burden, drug-drug interactions and cost [1, 3, 4]. In 2019, 3.3% of new cases and 17.7% of recurrent TB cases were MDR-TB, and the highest proportions (>50% in recurrent TB cases) were in the countries of the former Soviet Union [1].

The global TB treatment success rate for new TB and drug-resistant TB cases in 2018 was 85% and 57%, respectively [1]. Among PLHIV the overall reported TB treatment success rates were generally low and for MDR-TB rarely exceeded 50% [4, 5].

Lithuania belongs to the 18 high-priority TB countries in the European region and has one of the highest rates of TB. The rate of TB notification in 2019 was 37.7 per 100,000, four-times higher than the rate of TB notification in the EU/EEA. Treatment outcomes in Lithuania were worse than expected, with treatment success rate of 87.1% in all TB patients and 70.4% in MDR-TB patients in 2019 [6]. TB is the most common AIDS-indicative disease in Lithuania, with the highest proportion in the EU/EEA since 2015 and was still >60% in 2019 [7]. It is important to know the differences of TB among PLHIV and the factors associated with the infection by multidrug-resistant *Mycobacterium tuberculosis* and unsuccessful treatment in this population as it will help TB program coordinators and scientists involved in this field to focus on strategic issues and the improvement of TB control program. Therefore, the aim of

our study was to identify socio-demographic, clinical characteristics and their relationship with TB outcomes in TB-HIV co-infected patients in Lithuania.

## Methods

### Study design and population

A retrospective chart review was conducted of all TB-HIV co-infected adults aged 18 years or older from January 1, 2008, through December 31, 2020, registered in the State Information System of Tuberculosis. The State Information System of Tuberculosis was established in 2002 to register all TB cases in Lithuania, including new and re-treatment cases, monitor and control management of TB, to evaluate the epidemiological indicators and to forecast the epidemiological situation of TB in Lithuania. The State Information System of Tuberculosis is a unified, centralized and standardized tuberculosis cases notification and registration database. The database contains the following information about a TB patient: socio-demographic, diagnostic data, drug susceptibility data of *M. tuberculosis*, treatment and outcomes.

### Ethical statement

The study was approved by the Regional Biomedical Research Ethics Committee of Vilnius University (2020-06-22, Nr.2020/61240723). The Regional Biomedical Research Ethics Committee of Vilnius University waived the requirement for the informed consent on the basis of the right granted of the Law on Ethics of Biomedical Research of Lithuania. The information obtained was made anonymous and deidentified prior to analysis to ensure confidentiality.

### Operational definitions

TB cases, drug resistance and treatment outcomes were defined according to the WHO Definitions and reporting framework for tuberculosis [8].

The following definitions were used for a standard clinical case:

- bacteriologically confirmed TB case—a case with a positive smear microscopy, culture or WHO approved rapid diagnostics (i.e. Xpert MTB/RIF);
- clinically diagnosed TB case—a case diagnosed on the basis of radiological, suggestive histological findings without laboratory confirmation.
- These standard clinical cases were classified according to:
  - anatomical site of disease
    - a. pulmonary TB—any bacteriologically or clinically confirmed TB case in which the lung parenchyma or the tracheobronchial tree is involved; *miliary TB*—a form of TB resulting of *M. tuberculosis* hematogenous dissemination from the lungs to other organs and it was assigned to pulmonary TB;
    - b. extrapulmonary TB—any bacteriologically or clinically confirmed TB case in which other organs than the lungs are involved;
- history of previous treatment
  - a. new patients—have never been treated for TB or have taken TB treatment for less than 1 month;
  - b. previously treated patients—have been treated for TB for 1 month or more in the past; they are classified as follows:

- relapse patients—have been treated for TB previously and were declared as cured or treatment completed and now are diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection);
- treatment after failure patients—have been treated for TB and their treatment failed at the end of the most recent treatment course;
- treatment after loss to follow-up—have been treated for TB and were defined as loss to follow-up at the end of the most recent treatment course;
- other previously treated patients—have been treated for TB although their treatment outcome is unknown or undocumented;
- patients with unknown previous TB treatment history—do not fill the criteria of above-mentioned categories.

According to the drug resistance, cases were classified:

- drug-susceptible TB—no evidence of *M. tuberculosis* resistance to rifampicin (not drug-resistant or multidrug-resistant TB) and no need for the treatment with a second-line drug regimen;
- drug-resistant TB—*M. tuberculosis* resistant at least to rifampicin;
- multidrug-resistant TB (MDR-TB)—*M. tuberculosis* resistant to not less than both isoniazid and rifampicin;
- extensively drug-resistant TB (XDR-TB)—*M. tuberculosis* resistant to any fluoroquinolone and to at the minimum one of three second-line injectable drugs.

According to the current WHO guidelines [9], management of MDR-TB should be the same as rifampicin resistant TB. Therefore, factors associated with MDR-TB were evaluated putting rifampicin resistant TB and MDR-TB in one category.

Treatment outcomes were categorized into the following:

- cured: negative smear microscopy or negative culture at the end of treatment and on at least one previous follow-up test;
- treatment completed: TB treatment completed without evidence of failure;
- treatment failed: positive smear microscopy or positive culture after 5 months or later during treatment;
- lost to follow-up: patient did not start treatment or interrupted their treatment for two consecutive months or more;
- died: patient died from any cause before starting or during the course of TB treatment;
- not evaluated: patient for whom no treatment outcome is ascribed; this includes patients who left the country before treatment completion;
- successful treatment outcome: the patients who were cured or completed treatment; the cases of completed treatment were evaluated as treatment success even if the results of negative smear microscopy or negative culture at the end of treatment were not received;
- unsuccessful treatment outcome: the patients with treatment failure, lost to follow-up, died or not evaluated.

Treatment outcomes were evaluated separately for new and previously treated cases.

## Data collection

A structured data collection questionnaire was prepared to extract the data from patients' medical records. It contained sociodemographic characteristics, type of tuberculosis infection, TB registration group (new patients, previously treated patients and patients with unknown previous TB treatment history), TB clinical signs, history of exposure to anti-tuberculosis treatment, TB treatment outcome, the status of HIV infection, information of antiretroviral therapy (ART), CD4 count and HIV viral load at the time of TB diagnosis, blood sample test results at the time of TB diagnosis, co-infection with hepatitis C virus (HCV) defined by positive HCV IgG antibody (anti-HCV), and hepatitis B virus (HBV) defined by positive hepatitis B surface antigen (HBsAg). Sputum-smear microscopy, *M. tuberculosis* cultures, and drug susceptibility testing were performed in local laboratories. All laboratories were quality assured by the WHO Supranational Reference Laboratory Network.

## Outcome

We focused on three outcomes: infection with drug-resistant TB and unsuccessful TB treatment outcomes in new and previously treated cases.

## Statistical analysis

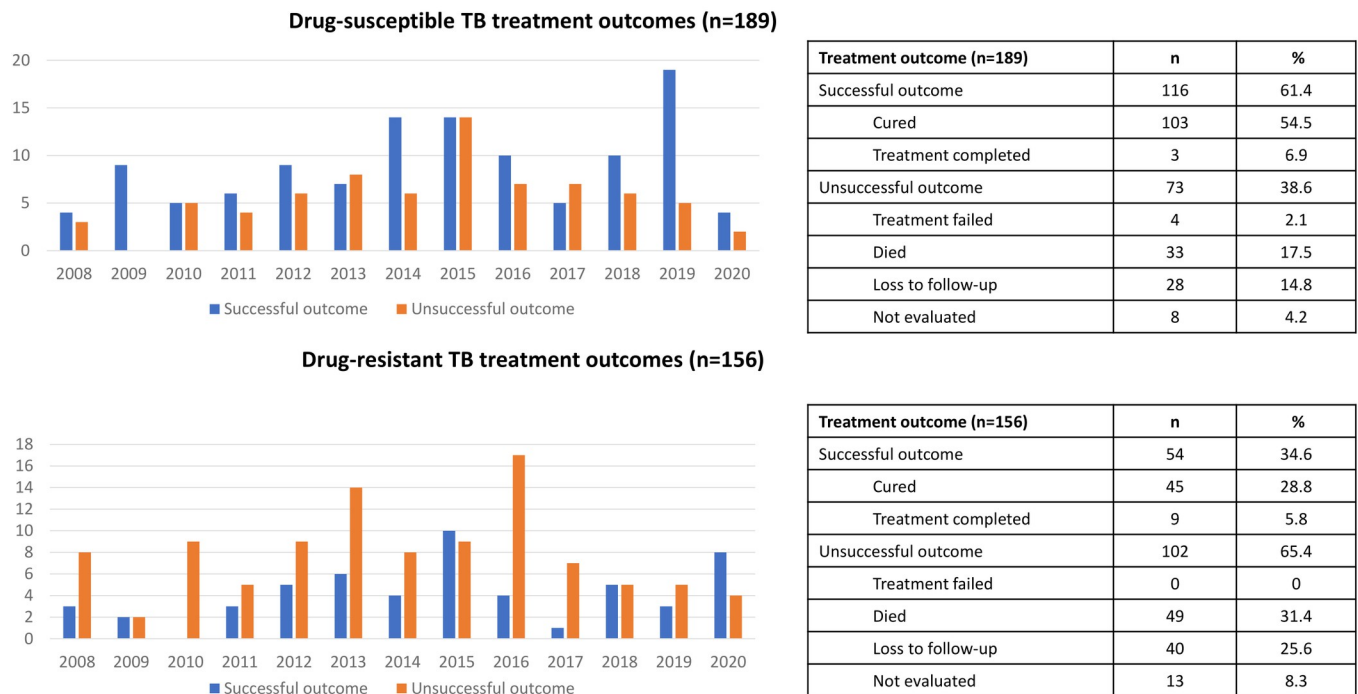
The collected data were coded and entered into computer using Epidata version 3.1. Analysis was done using IBM SPSS version 20.0. Frequencies, proportions and summary statistics were used to describe the study population in relation to socio-demographic and clinical characteristics. Categorical variables were analyzed using Pearson chi-square and Fisher exact tests when appropriate. Continuous variables were expressed as median and interquartile range (IQR). Nonparametric Mann-Whitney U test was used to identify differences between groups in continuous outcomes. Univariable logistic analysis was used to explore unadjusted association between variables (socio-demographic characteristics, imprisonment, smoking, any-time intravenous drug use, alcohol abuse, HIV acquisition way, time of HIV diagnosis, hepatitis status, sputum-smear microscopy, TB clinical signs, CD4 count and HIV viral load at the time of TB diagnosis, blood sample test results at the time of TB diagnosis) and outcome. Variables with a *p* value less than 0.05 in univariable analysis were included in multivariable analysis restricted to individuals with complete data.

## Results

### Socio-demographic and clinical characteristics of study participants

Out of the cumulative number of 3,431 PLHIV in Lithuania at the end of 2020 [10], 345 cases with active TB in 311 patients (9,1%) were registered in the State Information System of Tuberculosis over the period 2008 to 2020. All the cases were included in the study (Fig 1). All patients were white, 251 (80.7%) were male and the median age was 40 years (IQR 35–45). The socio-demographic and clinical characteristics of study participants are shown in Tables 1 and 2.

The majority (83.6%) of participants were unemployed and 62.5% had a history of imprisonment. Smoking, any-time intravenous drug usage (IDU) and abuse of alcohol were identified in 83.6%, 50.5% and 34.9% patients, respectively. Sixty-eight percent of patients knew their HIV-positive status before TB diagnosis, the median time to TB diagnosis was 8 years (IQR 4–12). Regarding the gender related characteristics, imprisonment in history (71.5% vs. 20.6%,  $p < 0.001$ ), IDU (54.0% vs. 35.6%,  $p = 0.01$ ), HIV acquisition by IDU (56.8% vs. 40.7%,  $p = 0.03$ ) and HCV co-infection (68.5% vs. 53.7%,  $p = 0.04$ ) were more common among men (S1 Table).



TB: Tuberculosis; HIV: Human immunodeficiency virus

**Fig 1. Dynamics of TB treatment outcomes in TB/HIV cases (n = 345) in Lithuania.**

<https://doi.org/10.1371/journal.pone.0282046.g001>

According to the history of previous TB treatment, 239 (69.3%) were new cases and 106 (30.7%) were previously treated cases: 64 (61%) were relapsed, 10 (9.5%) were failed and 32 (30.2%) were returnees after loss to follow-up. Regarding clinical characteristics, drug-susceptible TB (61.9% vs. 38.7%,  $p < 0.001$ ) and hemoglobin (Hb)  $< 100$  g/l at the time of TB diagnosis (26.9% vs. 3.8%,  $p = 0.01$ ) were more common in new TB cases, and positive culture (83.3% vs. 99.1%,  $p < 0.001$ ) and GeneXpert (29.5% vs. 61.5%,  $p = 0.03$ )—in previously treated TB cases (Table 2).

Regarding the HIV related characteristics of new TB cases, median CD4 count at TB diagnosis was 136 (IQR 53–289) cells/mm<sup>3</sup>, median HIV-RNA— 94,700 (IQR 1,845–230,000) copies/ml and 15.3% of patients had undetectable ( $< 200$  copies/ml) viral load. Thirty-two percent of new cases had started antiretroviral therapy (ART) before TB treatment, median time of ART to TB diagnosis was 201 days (IQR 47–677). In previously treated TB cases, median CD4 count at TB diagnosis was 197 (IQR 105–344) cells/mm<sup>3</sup>, median HIV-RNA— 155,000 (IQR 16,925–254,000) copies/ml and 33.3% of patients had undetectable viral load. Thirty-nine percent of previously treated TB cases received ART before TB diagnosis, median time of ART to TB diagnosis was 770 days (IQR 161–1,814).

Out of 239 patients with new TB, 28 developed a recurrent TB episode. Among 72 previously treated patients, 6 patients had one more recurrence during the study. Overall, the number of recurrence per patient was 0.34. In all study population, the median time to the first TB recurrence (n = 100) was 54 months (IQR 35–95) and to the second recurrence (n = 6)— 74 months (31.5–166). The unadjusted odds ratio for TB recurrence (n = 311) were significantly higher for unemployed (OR 4.2; 95% CI 1.46–12.12;  $p = 0.008$ ), smokers (OR (4.18; 95% CI 1.45–12.05;  $p = 0.008$ ) and patients with drug-resistant TB (OR 2.28; 95% CI 1.33–3.89;  $p = 0.003$ ). Multivariable analysis (n = 298) confirmed the same risk factors: unemployment

**Table 1. Socio-demographic characteristics of TB-HIV co-infected patients in Lithuania, 2008–2020 (n = 311).**

Characteristics	n	N	%
<b>Sex</b>			
Male	251	311	80.7
Female	60	311	19.3
<b>Age (years)</b>			
18–24	5	311	1.6
25–34	71	311	22.8
35–49	187	311	60.1
≥50	48	311	15.4
<b>Place of residence</b>			
Urban	260	309	84.1
Rural	49	309	15.9
<b>Predisposing factors</b>			
Homelessness	26	300	8.7
Unemployment	254	304	83.6
Imprisonment in history	120	192	62.5
Current	52	120	43.3
Previous	68	120	56.7
Smoking	255	305	83.6
Any-time intravenous drug use	155	307	50.5
Alcohol abuse	107	307	34.9
Exposure to active TB any time	66	270	24.4
<b>HIV transmission route</b>			
Intravenous drug use	161	300	53.7
Heterosexual	117	300	39.0
Men who have sex with men	1	300	0.3
Unknown	21	300	7.0
<b>Time of HIV diagnosis</b>			
Before TB diagnosis *	181	267	67.8
On TB diagnosis	86	267	32.2
<b>HCV co-infection</b>	179	273	65.6
<b>HBV co-infection</b>	5	222	2.3
<b>TB registration status</b>			
New	239	311	76.8
Previously treated	72	311	23.2
Relapse	41	72	56.9
Treatment failure	8	72	11.1
Treatment after loss to follow-up	23	72	31.9

TB: Tuberculosis; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; HBV: Hepatitis B virus;

\* The median time to TB diagnosis was 8 years (IQR 4–12).

<https://doi.org/10.1371/journal.pone.0282046.t001>

(aOR 4.11; 95% CI 1.40–12.03;  $p = 0.01$ ), smoking (aOR 3.69; 95% CI 1.26–10.83;  $p = 0.02$ ) and drug-resistant TB (aOR 2.13; 95% CI 1.22–3.73;  $p = 0.01$ ).

Overall, the treatment success was 116 (61.4%) for drug-susceptible TB and 54 (34.6%) for drug-resistant TB cases (Fig 1).

Table 2. Clinical characteristics of TB-HIV cases in Lithuania, 2008–2020 (n = 345).

Characteristics	New TB cases		Previously treated TB cases		p-value
	N	%	N	%	
<b>Type of TB</b>					
Pulmonary TB	205/239	85.8	95/106	89.6	0.15
Smear-positive	116/205	56.6	64/95	67.4	0.08
Smear-negative	89/205	43.4	31/95	32.6	0.08
Miliary TB	30/239	12.6	7/106	6.6	0.11
Extrapulmonary TB	34/239	14.2	11/106	10.4	0.36
<b>Diagnosis supported by</b>					
Culture positive*	199/239	83.3	105/106	99.1	<0.001
Smear positive	121/239	50.6	64/106	60.4	0.09
GeneXpert positive**	43/146	29.5	8/13	61.5	0.03
<b>Drug resistance</b>					
Drug-susceptible TB	148/239	61.9	41/106	38.7	<0.001
Drug-resistant TB	91/239	38.1	65/106	61.3	<0.001
MDR-TB	62/239	25.9	38/106	35.8	0.05
XDR-TB	5/239	2.1	15/106	14.2	<0.001
<b>Clinical signs</b>					
Cough	160/207	77.3	31/39	79.5	0.76
Fever	148/207	71.5	25/39	64.1	0.35
Weight loss	140/207	67.6	24/39	61.5	0.46
Night sweats	106/207	51.2	20/39	51.3	0.99
<b>BMI, kg/m<sup>2</sup></b>					
<18.5	22/106	20.8	0/19	0.0	0.09
18.5–24.9	73/106	68.9	17/19	89.5	
≥25.0	11/106	10.4	2/19	10.5	
<b>CD4 count at the time of TB diagnosis, cells/mm<sup>3</sup></b>					
<50	28/119	23.5	1/31	3.2	0.08
50–99	19/119	16.0	5/31	16.1	
100–349	51/119	42.9	17/31	54.8	
≥350	21/119	17.6	8/31	25.8	
<b>HIV-RNA at the time of TB diagnosis, copies/mL</b>					
<200	13/85	15.3	5/17	29.4	0.09
200–999	5/85	5.9	1/17	5.9	
1,000–9,999	9/85	10.6	5/17	29.4	
10,000–99,999	16/85	18.8	1/17	5.9	
≥100,000	42/85	49.4	5/17	29.4	
<b>Baseline Hb, g/l</b>					
<100	36/134	26.9	1/26	3.8	0.01
≥100	98/134	73.1	25/26	96.2	0.01
<b>Baseline PLT, x10e9/l</b>					
<150	33/131	25.2	5/26	19.2	0.52
≥150	98/131	74.8	21/26	80.8	0.52
<b>Baseline CRP count, mg/l</b>					
<50	46/100	46.0	9/15	60.0	0.31
≥50	54/100	54.0	6/15	40.0	0.31

(Continued)



Table 2. (Continued)

Characteristics	New TB cases		Previously treated TB cases		p-value
	N	%	N	%	
Type of TB					
On ART	55/171	32.1	16/41	39.0	0.41

TB: Tuberculosis; HIV: Human immunodeficiency virus; MDR-TB: Multidrug-resistant tuberculosis; XDR-TB: Extensively drug-resistant tuberculosis; CD4: Cluster differentiation-4; Hb: Hemoglobin; PLT: Platelet; CRP: C-reactive protein; BMI: body mass index; ART: antiretroviral therapy

\*Drug resistance found in 90/239 (37.7%) new and in 64/106 (60.4%) previously treated cases;

\*\*Drug resistance found in 16/146 (10.9%) new and in 4/13 (30.8%) previously treated cases.

<https://doi.org/10.1371/journal.pone.0282046.t002>

### Factors associated with drug-resistant TB

Both univariable and multivariable analysis were done to identify the association between drug-resistant TB and the socio-demographic and clinical characteristics of new and previously treated TB cases.

In univariable analysis of new cases ( $n = 237$ ), imprisonment (OR 3.28; 95% CI 1.44–7.46;  $p = 0.01$ ), IDU (OR 1.89; 95% CI 1.07–3.36;  $p = 0.03$ ) and HIV acquisition by IDU (OR 2.31; 95% CI 1.27–4.18;  $p = 0.01$ ) were associated with drug-resistant TB.

Univariable analysis of previously treated cases ( $n = 104$ ) revealed imprisonment (OR 3.50; 95% CI 1.09–11.29;  $p = 0.04$ ), IDU (OR 2.99; 95% CI 1.35–6.65;  $p = 0.01$ ) and loss to follow-up (OR 3.67; 95% CI 1.39–9.64;  $p = 0.008$ ) association with drug-resistant TB.

Figs 2 and 3 show the final multivariable model: imprisonment was the only factor associated with drug resistant TB in new and previously treated TB cases.

### Factors associated with unsuccessful TB treatment outcome

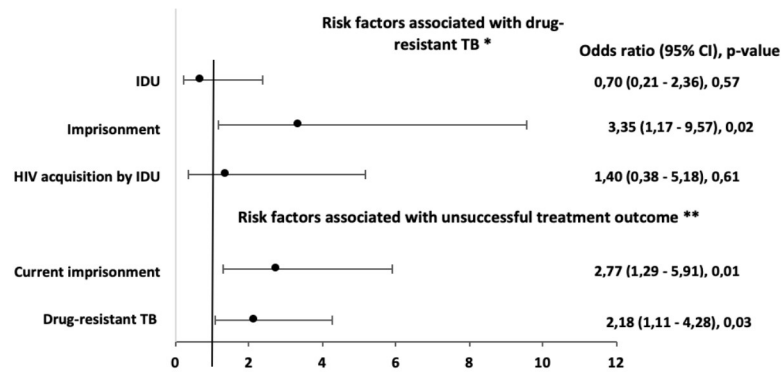
In 125/239 (52.3%) of new TB cases and in 45/106 (42.5%) of previously treated TB cases, the treatment outcomes were unsuccessful.

In univariable analysis of new TB cases, imprisonment in history (OR 2.59; 95% CI 1.3–5.19;  $p = 0.01$ ) and drug-resistant TB were associated with unsuccessful treatment (OR 2.49; 95% CI 1.45–4.24;  $p = 0.001$ ). Current imprisonment was a risk factor to unsuccessful treatment outcome (OR 2.65; 95% CI 1.26–5.57;  $p = 0.01$ ), while previous imprisonment was not found to be associated with unsuccessful treatment outcome (OR 1.38; 95% CI 1.08–1.73;  $p = 0.21$ ). Multivariable analysis revealed that current imprisonment (aOR 2.77; 95% CI 1.29–5.91,  $p = 0.01$ ) and drug-resistant TB (aOR 2.18, 95% CI 1.11–4.28;  $p = 0.03$ ) were risk factors to unsuccessful treatment outcome (Fig 2).

In univariable analysis of previously treated TB cases, female gender (OR 5.27; 95% CI 1.12–24.86;  $p = 0.04$ ), homelessness (OR 8.41; 95% CI 1.02–69.21;  $p = 0.048$ ), alcohol abuse (OR 2.57; 95% CI 1.12–5.91;  $p = 0.03$ ), drug-resistant TB (OR 4.2; 95% CI 1.83–9.63;  $p = 0.001$ ) and loss to follow-up (OR 6.20; 95% CI 2.07–18.54;  $p = 0.001$ ) were associated with a higher risk of unsuccessful treatment; and in multivariable analysis—female gender (aOR 11.93; 95% CI 1.86–76.69;  $p = 0.01$ ), alcohol abuse (aOR 3.17; 95% CI 1.05–9.58;  $p = 0.04$ ) and drug-resistant TB (aOR 4.83; 95% CI 1.53–15.28;  $p = 0.01$ ) (Fig 3).

### Mortality rates and associated risk factors

During the study period, 79 (25.4%) out of 311 patients died: 62/239 (25.9%) new patients and 17/72 (23.6%) previously treated patients.



TB: Tuberculosis; HIV: Human immunodeficiency virus; IDU: any-time intravenous drug use; CI: Confidence interval

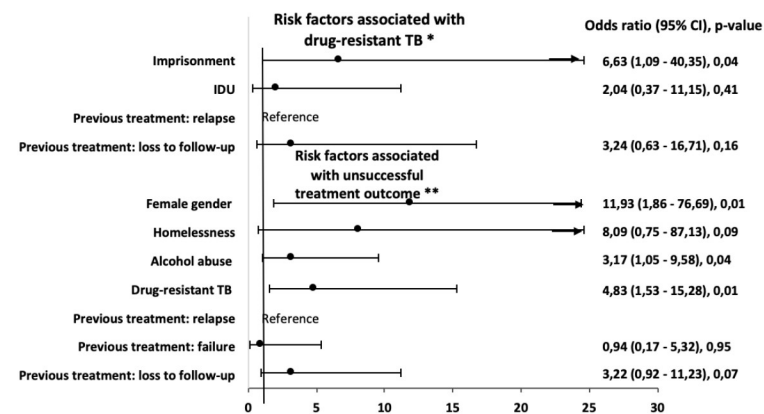
\* 148 cases included, 91 cases excluded due to missing data. A description of multivariable model: N=148, LR  $\chi^2$  =9.76, df=3, p=0.021, Hosmer-Lemeshow  $\chi^2$  =0.98, df=3, p=0.806, Nagelkerke R<sup>2</sup> =0.09

\*\* 154 cases included, 85 cases excluded. A description of multivariable model: N=154, LR  $\chi^2$  =11.99, df=2, p=0.002, Hosmer-Lemeshow  $\chi^2$  =0, df=2, p=1, Nagelkerke R<sup>2</sup> =0.1

**Fig 2. Multivariable analysis of factors associated with drug-resistant TB and unsuccessful treatment outcomes in new TB-HIV cases in Lithuania, 2008–2020 (n = 239).**

<https://doi.org/10.1371/journal.pone.0282046.g002>

Socio-demographic and clinical characteristics, including the number of TB episodes, and their association with death assessed through univariable and multivariable analysis. The unadjusted OR of death (n = 311) were significantly higher for alcohol abusers (OR 2.11; 95% CI 1.25–3.58; p = 0.005), patients with Hb < 100 g/l at the time of TB diagnosis (OR 2.73; 95%



TB: Tuberculosis; HIV: Human immunodeficiency virus; IDU: any-time intravenous drug use; CI: Confidence interval

\* 49 cases included, 57 cases excluded due to missing data. A description of multivariable model: N=49, LR  $\chi^2$  =18.82, df=3, p<0.001, Hosmer-Lemeshow  $\chi^2$  =0.33, df=3, p=0.427, Nagelkerke R<sup>2</sup> =0.43

\*\* 90 cases included, 16 cases excluded. A description of multivariable model: N=90, LR  $\chi^2$  =32.54, df=6, p<0.001, Hosmer-Lemeshow  $\chi^2$  =8.05, df=8, p=0.429, Nagelkerke R<sup>2</sup> =0.41

**Fig 3. Multivariable analysis of factors associated with drug-resistant TB and unsuccessful treatment outcomes in previously treated TB-HIV cases in Lithuania, 2008–2020 (n = 106).**

<https://doi.org/10.1371/journal.pone.0282046.g003>

CI 1.23–6.07;  $p = 0.014$ ) and drug-resistant TB (OR 2.02; 95% CI 1.2–3.39;  $p = 0.008$ ). Multi-variable analysis ( $n = 149$ ) confirmed the same risk factors: drug-resistant TB (aOR 2.70; 95% CI 1.19–6.10;  $p = 0.02$ ), alcohol abuse (aOR 2.36; 95% CI 1.06–5.23;  $p = 0.04$ ) and Hb  $< 100$  g/l (aOR 2.81; 95% CI 1.17–6.75;  $p = 0.02$ ).

## Discussion

This study aimed to determine socio-demographic, clinical characteristics and their relationship with TB outcomes in TB-HIV co-infected patients in Lithuania. We found that the treatment success rate among cases with drug-susceptible and drug-resistant TB (61.4% and 34.6%, respectively) was low. Thirty-eight percent of new cases and 61% of previously treated cases were drug-resistant TB, which is consistent with other studies conducted in Eastern European region [11–15] but higher compared with other European regions [16]. The rate of previously treated cases for TB was high (30.7%) and the prevalence of relapse after treatment completion among them was also high. According to WHO 2020 Global Tuberculosis report, the global TB treatment success rate for PLHIV was 76% and in the WHO Europe region it was 51% [1]. In the End TB Strategy, WHO aims TB treatment success rate to be  $\geq 90\%$  of all notified cases by 2025 [17]. Therefore, our findings emphasize the importance of improving TB treatment and control programs in Lithuania in order to achieve WHO the End TB Strategy goals.

Unemployment, imprisonment, alcohol abuse and intravenous drug use, known social risk factors for TB, were frequent in our study population [1, 18–23]. Several studies found that unemployment rate increased more than twice during the TB episode [24, 25]. Imprisonment is commonly the primary risk factor for TB or an additional factor for TB evolution in the population with other high-risk factors, i.e., substance abuse and HIV infection. A recent study carried out in Brazil showed that imprisonment was the primary risk factor, as TB risk increased markedly during imprisonment period and among ex-prisoners, and declined in the years after the release [26]. Furthermore, the review of factors defining transmission of HIV, HCV and TB in Eastern Europe and Central Asia found that 75% of incident TB cases among intravenous drug users were associated with imprisonment [27–29]. We found that new patients with TB and having a history of imprisonment had 2.59 times higher odds of having unsuccessful TB treatment outcome and current imprisonment was associated with 2.77 higher odds of unsuccessful treatment outcome. Additionally, the adjusted odds of having drug-resistant TB were 3.35 and 6.63 higher for new and previously treated TB patients with a history of imprisonment, respectively. During the study period, imprisoned patients in Lithuania were treated using centralized purchase funded by the Ministry of Justice and not the Ministry of Health, which possibly resulted in the delay in TB treatment. In addition, the adherence of these patients and the continuation of TB treatment after imprisonment remain a challenge in Lithuania due to social (unstable place of residence, lack of relatives and social workers who ensure the care for the patient), as well as financial issues (cost of travel to the clinic) and a lack of awareness of the importance of TB treatment. Also, drug-resistant TB, anemia and alcohol abuse were risk factors of death. Therefore, our study findings emphasize the need of increased focus on optimizing social conditions among un-employers, providing support to overcome alcohol and intravenous drug use and focus on involving family or other support persons in TB treatment. It also highlights the necessity to improve treatment strategies in imprisonment and the importance of social help during and after imprisonment period.

At the time of first TB episode, our study patients were with marked immunodeficiency and high HIV-RNA viral load: CD4 count  $< 350$  cells/mm<sup>3</sup> was in 42.9% and  $< 50$  cells/mm<sup>3</sup> – in 23.5% of patients and only 15.3% had viral load  $< 200$  copies/mL. These findings are characteristic of eastern Europe, which were clearly distinguished in a large prospective cohort

study of TB co-infected PLHIV across eastern and western Europe, and Latin America and a low CD4 cell count was found as a factor related to the increased TB-related mortality: the adjusted odds of TB-related death in the cases with CD4 count  $\leq 50$  cells/ $\mu$ l were 2.45 and 3.46 in all study participants and patients from Eastern Europe region, respectively [16, 27]. More than half (67.8%) of patients knew their HIV diagnosis prior to TB diagnosis and only 32.2% were on ART at the time of TB diagnosis. These findings are largely in agreement with the studies published from the Eastern European region [18, 30, 31]. The low uptake of ART could be associated with the governmental regulations of ART initiation in Lithuania as the “treat all” approach was only adopted in February 2018 [32]. The screening for latent TB with interferon-gamma release assay (IGRA) has not been included into Lithuanian HIV management guidelines until mid-2018. Also, no further steps after IGRA positivity detection and treatment of latent TB among PLHIV have been foreseen. Therefore, the high percentage of patients who knew their HIV status before TB diagnosis emphasizes the need to increase awareness of TB in this population and the need of policy for programmatic management of latent TB in PLHIV.

The emerging of recurrent TB posed a huge challenge for TB elimination programs worldwide. In our study, the number of TB recurrence per patient was 0.34 and it was similar to recurrent TB rates reported in other studies performed in different geographical regions [33–36]. We found smoking, unemployment and drug-resistant TB as risk factors for recurrent TB. A recent large multicenter prospective study in China showed that patients who continued smoking during TB treatment were at higher risk for TB recurrence and this risk remained significant even in those who stopped smoking [37]. Also, the WHO/Union Monograph on TB and Tobacco highlights smoking as one of the most important risk factors that increases the probability of TB recurrence [38]. Previous studies have also established that socio-economic determinants—low income, unemployment—were factors increasing the risk of TB recurrence [39, 40]. In accordance with other studies [33–36], drug-resistant TB was associated with TB recurrence and it emphasizes the importance of search for more effective TB management strategies. Also, the long period of time to TB recurrence (54 months to the first recurrence) in our study highlights the need of longer follow-up observation after the treatment completion. On contrary to other studies [41–43], the recurrent TB was not associated with death.

In our study, female gender, drug-resistant TB and alcohol abuse were associated with unsuccessful treatment outcome in previously treated TB cases. In other studies [5, 28, 44–53], women were more likely to develop severe forms of TB and recurrent TB, and the duration of TB treatment was longer. However, factors related to unsuccessful treatment, such as imprisonment and IDU, except alcohol abuse, were more common among men in our study. These differences can possibly be explained by behavioral (men tend to have a higher number of social contacts and engage in high-risk behaviors) and biological hypotheses (immune responses modulated by sex hormones and increased genetic susceptibility to TB among men) [54, 55]. Our study findings suggest the importance of search for new strategies of TB management in the settings with high TB prevalence, which would cover access to care facilitation, the new TB drug regimens, abuse treatment options and integrated services. It highlights the necessity of screening for active TB. Also, integrated services of substance abuse treatment for TB-HIV co-infected patients should be considered.

In our study the prevalence of extrapulmonary TB was similar (14.2% in new TB cases and 10.4% in previously treated TB cases) compared to the global notification rate of WHO Europe region—16% [1]. The rate of miliary TB was 12.6% in new TB cases and 6.6% in previously treated TB cases and this form of TB was not associated with the poorer treatment outcome. In other large multicenter prospective studies [16, 56], the rate of miliary TB was higher and the association with the increased risk of death was found. These differences could be explained by a larger number of participants and different stratifications used for analysis.

The strength of this study is that it largely describes the characteristics of all nationally registered TB cases of HIV co-infected patients in the context of the high prevalence of TB and drug-resistant TB over the period of more than ten years. In addition, the study highlights the important factors and features that have to be improved in the management of TB cases while strengthening the TB control program. Furthermore, TB treatment outcomes and associated risk factors were evaluated separately for new and previously treated TB cases.

Our study has also several limitations. First, the retrospective nature of the study limited the data on detailed medical information on the participants. A number of participants had missing CD4 cell counts, HIV-RNA, blood sample test and biochemistry measurements hindering a more accurate evaluation of laboratory results association with the infection by multidrug-resistant *M. tuberculosis* and unsuccessful treatment outcome. Second, due to retrospective type of our study and different treatment environments of included prisons, our study was not designed to assess antituberculosis treatment related factors, such as treatment regimen, duration and adherence, which undoubtedly had an impact on outcomes. Third, we did not analyze the trends in drug susceptibility testing because of limited availability of such data in the database. Finally, the information about the prescription of opioid substitution therapy was not available and we could not evaluate the impact of opioid substitution therapy to TB outcome.

## Conclusions

In the TB-HIV-infected adult cohort in Lithuania, unemployment, imprisonment, IDU, alcohol abuse, known to be risk factors for TB, were very frequent. Drug resistance was an undeniable risk factor for unsuccessful treatment outcome and imprisonment was associated with drug resistant TB. Further interventions to address these challenges should focus on improving TB management, especially in socially marginalised groups including prison, and providing integrated person-centred rather than disease-centred care.

The assessment of TB treatment outcomes, analysis and prevention of factors associated with unsuccessful treatment results is of crucial importance in reaching the success in TB control programme. In the frame of WHO End TB Strategy [56], this study identified risk groups requiring integrated programmatic case management.

## Supporting information

**S1 Table. Socio-demographic and clinical characteristics of TB-HIV co-infected patients according to gender in Lithuania, 2008–2020 (n = 311).**

(DOCX)

**S1 Dataset.**

(XLS)

## Acknowledgments

We acknowledge professor Kęstutis Žagminas for support with statistical data analysis and the WEEPI collaboration group for their support in the preparation of this manuscript.

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