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Long-Term Mortality and Active Tuberculosis Disease Among Patients Who Were Lost to Follow-Up During Second-Line Tuberculosis Treatment in 2011–2014: Population-Based Study in the Country of Georgia

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Background. High rates of loss to follow-up (LFU) exist among patients with multidrug and extensively drug-resistant tuberculosis (M/XDR TB). We aimed to identify long-term clinical outcomes of patients who were LFU during second-line TB treatment.

Methods. We conducted a follow-up study among adults who received second-line TB treatment in the country of Georgia during 2011–2014 with a final outcome of LFU. We attempted to interview all LFU patients, administered a structured questionnaire, and obtained sputum samples. Active TB at follow-up was defined by positive sputum Xpert-TB/RIF or culture.

Results. Follow-up information was obtained for 461 patients. Among these patients, 107 (23%) died and 177 (38%) were contacted. Of those contacted, 123 (69%) consented to participate and 92 provided sputum samples. Thirteen (14%) had active TB with an estimated infectious time period for transmitting drug-resistant TB in the community of 480 days (interquartile range = 803). In multivariable analysis, positive culture at the time of LFU was associated with active TB at the time of our study (adjusted risk ratio = 13.3; 95% confidence interval, 4.2–42.2)

Conclusions. Approximately one quarter of patients on second-line TB treatment who were LFU died. Among those LFU evaluated in our study, 1 in 7 remained in the community with positive sputum cultures. To reduce death and transmission of disease, additional strategies are needed to encourage patients to complete treatment.

Keywords. LFU; MDR; outcomes; TB; tuberculosis.

Tuberculosis (TB) is a major public health problem and remains the leading cause of death from infectious disease globally. In 2018, there were 10 million new TB cases including half a million new cases of rifampicin-resistant TB, 78% of which had multidrug-resistant TB (MDR TB) [1]. Compared with drug-susceptible disease, MDR and extensively drug-resistant (XDR) have significantly higher rates of adverse treatment outcomes including mortality [2, 3]. There are high rates of loss to follow-up (LFU) during TB treatment among patients with M/XDR TB, and managing these LFU patients presents multiple public health and clinical challenges [1].

Patients who are LFU during TB treatment contribute to subsequent individual and population-level TB risks, posing a major impediment to improving TB control. Patients with M/XDR TB who are LFU have increased risk of TB-related death and contribute to ongoing community transmission of drug-resistant TB (DR-TB) [4]. In addition, patients who are LFU have increased risk of acquiring additional resistance to TB drugs [5, 6]. Therefore, LFU patients who acquire resistance and re-enter TB treatment require additional drugs and financial resources to adequately manage their care [3, 7].

Previous studies described patient characteristics and risk factors associated with LFU during TB treatment, which included male sex, illicit drug use, tobacco and alcohol use, and history of previous anti-TB treatment [8–11]. However, the long-term TB outcomes (all-cause mortality and active TB status) of M/XDR TB patients who are LFU during treatment have not been well characterized. Two studies conducted in Peru and Estonia evaluated the survival after MDR TB treatment interruption and reported high mortality rates (53% and 29%, respectively) among individuals who were later found [4, 12].

Determining long-term TB outcomes of patients with TB who were LFU during second-line treatment is imperative to better characterize the drivers of ongoing transmission of resistant TB strains in the community. Enhanced empirical data on infectiousness, acquired resistance, and long-term TB

outcomes of patients with TB who were LFU will help guide TB prevention and control strategies. To address current critical gaps in knowledge related to long-term TB outcomes of patients LFU, we aimed to (1) trace TB patients who started second-line TB treatment and were LFU and measure their long-term treatment outcomes and (2) determine characteristics associated with having active TB after LFU.

METHODS

Study Design and Setting

The country of Georgia has a high burden of M/XDR TB and is designated by the World Health Organization (WHO) as a high priority country to end TB [13, 14]. In 2009 Georgia became one of the first low- and middle-income countries to provide universal access to both diagnosis of and treatment for MDR TB [15]. Despite continued access to universal M/XDR TB diagnosis and treatment, the burden of drug-resistant TB in Georgia remains high: based on WHO estimates, 12% of new cases and 31% of retreatment cases had MDR TB in Georgia in 2018 [1, 16]. In addition to MDR and XDR TB patients, second-line treatment is prescribed for some patients with resistance to either isoniazid or rifampicin alone. A high proportion of patients are LFU during second-line TB treatment; for example, among the 2009–2011 MDR TB cohorts in Georgia, an estimated 29% of patients were LFU [8].

We performed a nationwide follow-up study among adult patients with pulmonary TB who initiated second-line anti-TB treatment within the Georgian National TB Program during 2011–2014 and were subsequently defined as LFU. Diagnostic work up and treatment were provided at no charge to patients through the Georgian National TB Program. Inpatient and outpatient clinical care was provided by the National Center for Tuberculosis and Lung Disease (NCTLD) in Tbilisi and specialized TB centers throughout the country [8]. Most patients who started second-line treatment were hospitalized during the intensive phase of treatment and were transitioned to outpatient care after conversion of sputum smears to negative and clinical improvement. Various patient adherence support activities were in place during 2011–2014, including home-based treatment for eligible patients and food vouchers for good adherence to ambulatory treatment. Treatment adherence consultants worked with noncompliant patients during TB treatment; however, no additional programmatic efforts were used after an LFU outcome was assigned to a patient.

Participants

Eligible study participants included adults (age ≥18 years) with sputum culture-confirmed pulmonary TB who initiated second-line treatment during 2011–2014 at NCTLD and were subsequently categorized as LFU (LFU was defined by WHO as treatment interruption >2 months) [17] for their final treatment outcome. Those TB patients who returned to TB treatment during the follow-up period (date of LFU through December 2016) and had treatment outcome other than LFU were excluded from the study.

Data Collection and Study Measures

From May to December 2016, LFU patients were contacted. Verbal consent after reading an information sheet about the study written in the patient's native language was required for study participation. Those who consented were enrolled in the study. Contact information (phone number and address) was obtained through TB treatment records. Study investigators throughout the country attempted to contact each LFU person via phone several times throughout the study period to schedule an in-person meeting. If investigators were unable to reach patients via phone, the study team visited the patients' listed residence. If patients were not located during a residential visit, we attempted to contact patients' family members or neighbors to obtain information about the patients' location and vital status. If patients were found, we scheduled a study visit with them either at their residence or at a local healthcare facility, based on patients' preference. During the study visit, we conducted an interview using a standardized questionnaire (see Supplement A). In addition, participants were informed that they were eligible for free sputum testing as part of the National TB Program (NTP). If they provided verbal consent, sputum samples were collected by the trained nurses from NTP, and sputum test results were later obtained by the study team from NTP.

Variables collected during the study visit questionnaire included the following: location of the patient (region, district, address); demographic information (sex, date of birth, employment status, education, marital status, income); TB symptoms at the time of the study visit; and history of the patient's treatment (including self-reported data about treatment adherence during the last TB treatment episode before LFU). Patients who were LFU but resumed treatment ≥1 time(s) before a final LFU treatment outcome was assigned were classified as having a history of re-entering TB treatment. A 3-category combined treatment adherence variable was created using 2 self-reported variables: drug intake regularity and receiving all prescribed drugs while on treatment. Full adherence was defined as receiving all prescribed drugs regularly, partial adherence was defined as either 1 of the 2 self-reported measures, and nonadherence was defined as none of the self-reported adherence measures. In addition, from prior TB treatment records, we obtained sputum culture results and drug-susceptibility testing (DST) results at the start of TB treatment and before LFU.

Laboratory Procedures

Two sputum samples were collected in sterile plastic containers by NTP nurses. Sputum containers were sealed with a cold pack and transferred to the nearest state TB laboratory for testing.

Smear microscopy, culture, and DST (on first- and second-line drugs) were performed by state TB laboratories using methods previously described [18, 19]. Active TB at study follow-up was defined by either a positive Xpert TB/RIF test or positive culture result. The DST for first- and second-line anti-TB drugs was performed in patients with a positive sputum culture. The DST profiles were compared at 3 time points: (1) time of TB treatment start; (2) most recent DST available before LFU; and (3) at current study enrollment.

Statistical Analysis

We compared patient characteristics by active TB status at the time of study enrollment using χ^2 tests for categorical variables and the Wilcoxon signed-rank test for continuous variables. We also used χ^2 tests to compare the basic demographic characteristics (age, sex, and region of residence) between the study participants who provided sputum and those who refused to participate or were unable to provide sputum for testing. Multivariable analyses were conducted using modified Poisson regression with a robust error variance [20]. Three main exposures of interest explored in multivariable models were history of re-entering treatment, treatment duration, and *Mtb* culture status before LFU. Primary outcome of interest was presence of active TB at the time of study. Multivariable model specification was based on purposeful selection of variables and directed acyclic graph (DAG) theory [21, 22]. The unadjusted associations of covariates with the outcome (active TB) and the primary exposures of interest contributed to DAG formation in combination with literature-based approach. Collinearity of predictors in the final multivariable models was assessed using tetrachoric correlations (correlation >0.7 was defined as collinear). Goodness of fit was assessed using deviance statistic. A 2-sided $P < .05$ was considered statistically significant, and statistical analyses were performed using SAS, version 9.4.

Ethical Review

The study was approved by the Institutional Review Boards of the National Center for Disease Control and Public Health (NCDC) in Tbilisi, Georgia, and Georgia State University, Atlanta, Georgia. All study methods were performed in accordance with the relevant guidelines and regulations.

Patient Consent Statement

Because biological samples were collected and tested as part of the National TB Program, this component of the study was deemed to be a nonresearch public health activity and written informed consent was waived by NCDC Institutional Review Board (IRB00002150).

RESULTS

Description of Study Population

During 2011–2014, 2432 patients initiated second-line TB treatment in Georgia, 605 (25%) of whom were categorized as LFU (Figure 1). Among these 605 patients LFU, we obtained follow-up information for 461 (76%) patients. Among these patients, 64 (14%) emigrated, 107 (23%) died, 35 (8%) were incarcerated, and 78 (17%) resumed TB treatment. Among the remaining 177 (38%) patients, 54 (31%) refused to participate, 123 (70%) enrolled, and 92 (52%) produced sputum samples and were included in the final analysis. Comparing patients who provided sputum and were tested in our study (n = 92) versus those who were not tested (n = 85), we found no significant difference by sex; however, older patients and those from Tbilisi were less likely to have sputum tested (Supplement B Table 1). Of the 92 patients who provided sputum samples, the majority were male (89%) and 28% were from Tbilisi (Table 1). Median age of patients at study enrollment was 42.5 years (interquartile range [IQR] = 15.9); 23% were employed at the time of enrollment; and the mean annual household income was 4824 Georgian Lari (US ~$1800), approximately 3 times less than the average household income in Georgia [23]. The median time from LFU to study enrollment was 1095 (IQR = 715) days, and 20% (n = 18) of patients self-reported cough between LFU and study enrollment.

Second-Line Tuberculosis Treatment Before Loss to Follow-up

The median duration of TB treatment during the prior TB treatment episode before LFU was 341 (IQR = 290) days (Table 1). Overall, 14 patients (15%) had a positive *Mtb* sputum culture at their last culture measured before LFU. Regular intake of second-line drugs during the latest treatment episode was reported by 82%, whereas only 67% of patients reported intake of all prescribed drugs. Among those patients who did not ingest all prescribed drugs, 19 (21%) indicated that they did not ingest para-aminosalicylic acid (PAS), and 8% reported resuming treatment with self-prescribed medication. Full adherence to treatment was reported by 60% of patients.

Active Tuberculosis at Study Enrollment

At the time of enrollment, a total of 13 (14%) patients had active TB (8 culture and Xpert-TB/RIF positive, 3 culture positive only, and 2 Xpert-TB/RIF positive only). Overall, 5 patients had a positive smear microscopy, 4 of which had positive results on both Xpert TB/RIF and culture, and 1 had negative result on both. Among n = 13 with active TB, the estimated infectious time period for transmitting drug-resistant TB in community was 480 days (IQR = 803) (the median time from LFU to study enrollment). However, among 13 patients with active TB, only 3 (23%) reported cough (Table 1).

Patients who were culture-positive for TB at the time of LFU were more likely to have active TB at study follow up compared with those who were culture-negative at the time of LFU (8 of 14 [57%] vs 3 of 74 [4.1%], $P < 0.01$). Patients with history of re-entering TB treatment after initial LFU from second-line TB treatment were more likely to have active TB (odds ratio = 3.9;
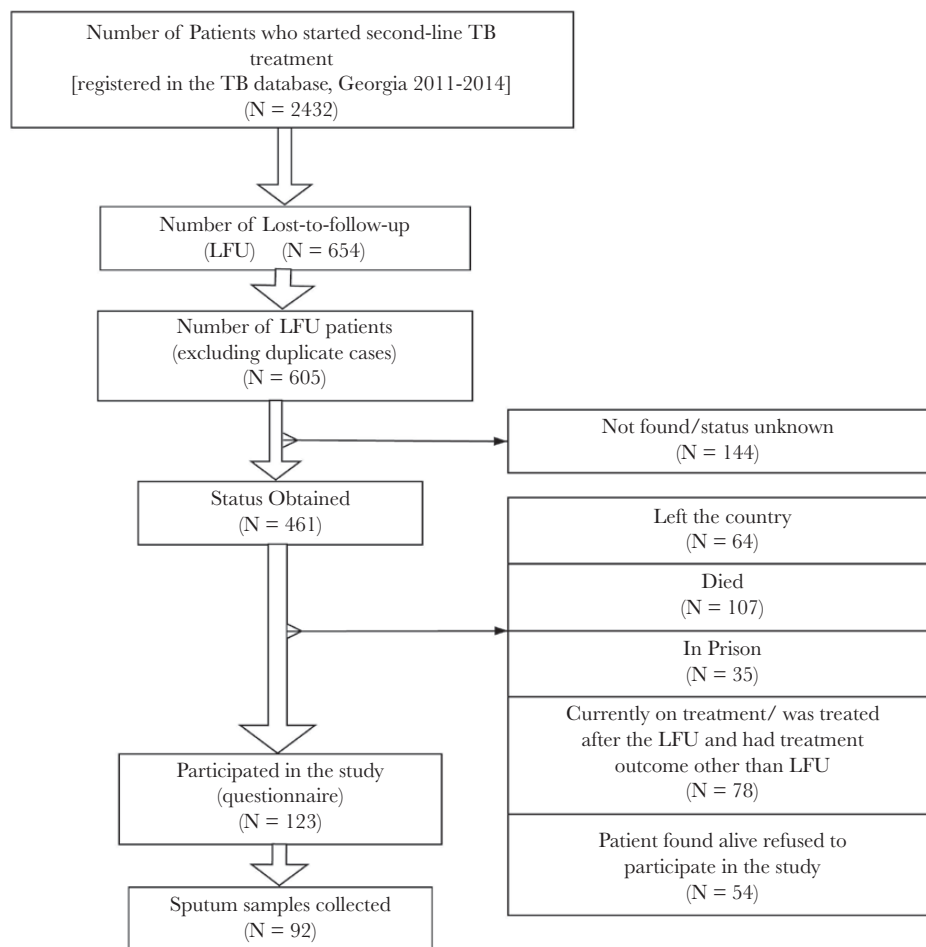
Figure 1. Flow diagram of patients who initiated second-line tuberculosis (TB) treatment in Georgia, 2011–2014.

95% confidence interval [CI], 1.1–13.7) at study enrollment. The median number of days on TB treatment during the latest treatment episode was 171 days (IQR = 391) in those with active TB versus 342 days (IQR = 258, $P = 0.15$) in those who had no evidence of active TB at the time of our study. In multivariable model adjusted for age and sex, history of re-entering TB treatment (adjusted risk ratio [aRR] = 3.7; 95% CI, 1.1–12.7) and positive culture at the time of LFU (aRR = 18.7; 95% CI, 4.5–77.8) were associated with active TB at the time of our study. In the fully adjusted model, positive culture at the time of LFU remained statistically significantly associated with the active TB (aRR = 13.3; 95% CI, 4.2–42.2) (Table 2, Supplement B Table 2, Supplement B Figure 1).

Drug Resistance Profile

Drug-susceptibility testing on first- and second-line anti-TB drugs were performed in the 11 patients who were culture positive at study enrollment. We observed phenotypic differences in DST results for at least 1 drug in 7 of 11 (64%) patients (Table 3). Three patients were sensitive to kanamycin, pyrazinamide, and ethambutol at TB treatment start and had resistance to those

drugs at enrollment into our study. Four patients were resistant to kanamycin, capreomycin, PAS, and ethambutol on the DST at TB treatment start, and they were susceptible to the same drugs at time of study enrollment; among these 4 who became susceptible, 2 had susceptible results at the most recent DST before LFU.

DISCUSSION

Among patients LFU from second-line TB treatment, our study documented high mortality proportion, laboratory-confirmed active TB, and a strong potential for transmitting DR-TB in the community. We determined the post-LFU status for 76% of all patients (n = 605) who were treated during 2011–2014 and subsequently LFU. Approximately one quarter of LFU patients died, and 1 in every 6 resumed treatment. High mortality rates among patients previously treated for TB, even with favorable treatment outcomes, is a serious clinical concern [24, 25]. Among LFU patients who were alive and contacted by our study team, 14% had laboratory-confirmed active TB disease. Factors associated with active TB after LFU included culture

Table 1. Active TB Disease Status at Study Enrollment Among Adult Patients With Pulmonary TB Who Initiated Second-Line Anti-TB Treatment Within the Georgian National TB Program During 2011–2014 and Were Subsequently Defined as LFU (N = 92 Study Participants Who Were Tested)

Characteristics	Total N[a] (%) = 92 (100)	TB+ n (%) = 13 (14)	TB– n (%) = 79 (86)	OR (95% CI)	P Value
Demographics					
Gender					.69
Male	82 (89.1)	12 (14.6)	70 (85.4)	1.5 (0.2–13.3)	
Female	10 (10.9)	1 (10.0)	9 (90.0)	1[b]	
Age*					
Median (IQR)	42.5 (15.9)	40.5 (13)	43 (16.4)		.62[c]
Age Categories					.82[c]
0–40	38 (41.3)	5 (13.2)	33 (86.8)	1	
41+	54 (58.7)	8 (14.8)	46 (85.2)	1.2 (0.3–3.8)	
Region					.38
Tbilisi	26 (28.3)	5 (19.2)	21 (80.8)	1.7 (0.5–5.9)	
Other	66 (71.7)	8 (12.1)	58 (87.9)	1	
Employment Status					.48
Employed	21 (23.1)	2 (9.5)	19 (90.5)	1	
Unemployed	70 (76.9)	11 (15.7)	59 (84.3)	1.8 (0.4–8.7)	
Income*					
Median (IQR)	3600 (3600)	3600 (1800)	3840 (3600)		.73[c]
Education					.38
High School or low	68 (74.7)	11 (16.2)	57 (83.8)	2.0 (0.4–9.9)	
Above High School	23 (25.3)	2 (8.7)	21 (91.3)	1	
Marital Status					.28
Currently married	55 (61.1)	6 (10.9)	49 (89.1)	1	
Never married	21 (23.3)	6 (28.6)	15 (71.4)	3.3 (0.9–11.6)	
Widow	0 (0)	0 (0)	0 (0)	-	
Divorced	12 (13.3)	1 (8.3)	11 (91.7)	0.7 (0.1–6.8)	
Missing/Refusal	2 (2.2)	2 (100)	0 (0)	-	
Number of household members (in addition to patient)					
Median (IQR)	3 (2)	3 (4)	3 (2)		.75[c]
Drug intake regularity during the latest episode of treatment					.22
Regular	75 (81.5)	9 (12)	66 (88)	1	
Irregular	17 (18.5)	4 (23.5)	13 (76.5)	2.3 (0.6–8.4)	
Medicine Intake During the Latest Episode of Treatment					.63
All prescribed drugs	62 (67.4)	8 (12.9)	54 (87.1)	1	
Not all prescribed drugs	30 (32.6)	5 (16.7)	25 (83.3)	1.4 (0.4–4.6)	
Treatment Adherence (Combined Variable)					.33
Full adherence	55 (59.8)	7 (12.7)	48 (87.3)	1	
Partial adherence	27 (29.3)	3 (11.1)	24 (88.9)	0.9 (0.2–3.6)	
No adherence	10 (10.9)	3 (30.0)	7 (70.0)	2.9 (0.6–14.1)	
Culture Status Before LFU					<.01
Negative	74 (84.1)	3 (4.1)	71 (95.9)	1	
Positive	14 (15.9)	8 (57.1)	6 (42.9)	31.6 (6.6–151.2)	
Re-Enter Treatment After Initial LFU					.03
Yes	38 (41.3)	9 (23.7)	29 (76.3)	3.9 (1.1–13.7)	
No	54 (58.7)	4 (7.4)	50 (92.6)	1	
Days on Treatment During Last Episode*					
Median (IQR)	341 (290)	171 (391)	342 (258)		.15[c]
Days From LFU to Study Enrollment*					
Median (IQR)	1095 (715)	480 (803)	1119 (627)		<.01[c]
Current Signs and Symptoms					
Cough					.73
Yes	18 (19.6)	3 (16.7)	15 (83.3)	1.3 (0.3–5.2)	
No	74 (80.4)	10 (13.5)	64 (86.5)	1	
Cough With Blood or Vomiting Blood During the Last 3 Months					
Yes	2 (2.2)	0 (0)	2 (100)		
No	90 (97.8)	13 (14.4)	77 (85.6)		

Table 1. Continued

Characteristics	Total Nᵃ (%) = 92 (100)	TB+ n (%) = 13 (14)	TB− n (%) = 79 (86)	OR (95% CI)	P Value
Fever					.99
Yes	7 (7.6)	1 (14.3)	6 (85.7)	1.0	
No	85 (92.4)	12 (14.1)	73 (85.9)	1	
Significant Weight Loss (≥3 kg in 1 Month)					.68
Yes	10 (11)	1 (10)	9 (90)	0.6 (0.1–5.5)	
No	81 (89)	12 (14.8)	69 (85.2)	1	
Night Sweats					.91
Yes	15 (16.5)	2 (13.3)	13 (86.7)	0.9 (0.2–4.6)	
No	76 (83.5)	11 (14.5)	65 (85.5)	1	
Chest Pain					.83
Yes	19 (20.9)	3 (15.8)	16 (84.2)	1.2 (0.3–4.7)	
No	72 (79.1)	10 (13.9)	62 (86.1)	1	

Abbreviations: CI, confidence interval; IQR, interquartile range; LFU, loss to follow-up; OR, odds ratio; TB, tuberculosis.

NOTE: Continuous variables (*) are presented as median (IQR), and categorical variables are summarized as frequencies (valid percentage).

ᵃIndividual variable totals might not sum up to 92 due to missing values.

ᵇ1 = reference value.

ᶜP value from Wilcoxon signed-rank test.

positivity at the time of LFU and history of re-entering TB treatment after LFU.

Few previous studies have examined the long-term TB outcomes and mortality proportions after LFU among patients with TB. One retrospective cohort study of 671 Peruvian patients who initiated MDR TB treatment during 1999–2002 reported that 67 patients were LFU after treatment. The Peruvian study determined outcomes for 47 of those LFU during MDR TB treatment, and among those 53% died [4]. In another retrospective study of culture-confirmed pulmonary TB patients from Estonia, 9% (104 of 1107) of patients were LFU during TB treatment [12]. Among the 102 who were LFU and traced in the Estonian study, 30% died. The study from Estonia included both drug-susceptible and drug-resistant TB. Unlike the relatively smaller Peruvian and Estonian analyses, our study obtained the status n = 461 patients who were LFU after second-line TB treatment. The mortality proportion after LFU in our study was

similar to that from Estonia (23% vs 30%), likely due to similar demographic and regional similarities in TB epidemics.

Our study also highlights the epidemiologic importance of LFU patients as a contributing source to ongoing transmission of DR-TB in the community. Among the 13 LFU patients with laboratory-confirmed TB at the time of our follow-up study, the majority had been residing in the community for more than 1 year post-LFU. Given the social, economic, and health resources required to treat DR-TB, tracing patients early after LFU may be a valuable approach to prevent additional community transmission. Additional study designs would benefit from using phylogenetic methods to link LFU patients to future case of DR-TB to estimate the number of new cases attributable to LFU patients.

To our knowledge, our study is the first to compare DST results across 3 different time points (start of TB treatment, most recent DST before LFU, and at post-LFU). Although only n = 11 patients had DST results at all 3 time points, we found 36% had

Table 2. Multivariable Analysis for Association Between History to TB Retreatment, Treatment Duration, and *Mtb* Culture Status Before LFU With Risk of Active TB Disease Among Adult Patients With Pulmonary TB Who Initiated Second-Line Anti-TB Treatment Within the Georgian National TB Program During 2011–2014 and Were Subsequently Defined as LFU (N = 92 Study Participants Who Were Tested)

Characteristics	RR (95% CI)	aRR (95% CI)ᵃ	aRR (95% CI)ᵇ
Exposure 1: History of re-entering TB treatment	3.2 (1.1–9.6)	3.7 (1.1–12.7)	1.5 (0.4–5.3)ᶜ
Exposure 2: Treatment duration (per 30 day increase)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.0)ᵈ
Exposure 3: Positive *Mtb* culture before LFU	14.1 (4.3–46.7)	18.7 (4.5–77.8)	13.3 (4.2–42.2)ᵉ

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; LFU, loss to follow-up; RR, risk ratio; TB, tuberculosis.

ᵃAdjusted for age and sex. All aRRs were estimated using robust Poisson regression models.

ᵇSee Supplemental Figure 1 for corresponding directed acyclic graphs. In assessment of goodness of fit, none of the adjusted models suggested evidence of poor fit (all devicance P > .05).

ᶜAdjusted for age, *Mtb* culture before LFU, and combined treatment adherence variable. Sex was not included in the model due to collinearity with *Mtb* culture before LFU and re-entering TB treatment.

ᵈAdjusted for age, sex, and combined treatment adherence variable.

ᵉAdjusted for age and combined treatment adherence variable. Sex was not included in the model due to collinearity with *Mtb* culture before LFU.

Table 3. Change in Susceptibility to Second-Line Tuberculosis Drugs Among Patients Who Started TB Treatment and Were Lost to Follow Up

Patient	DST Time	INH	RIF	E	Pza	Km	Ofx	Cm	Eto	Pas
Patient 1	TB treatment start	R	R	R	M	S	R	S	M	S
	Before LFU	M	M	M	M	M	M	M	M	M
	Study enrollment	R	R	R	R	R	R	S	M	S
Patient 2	TB treatment start	R	R	R	M	R	R	R	R	S
	Before LFU	M	M	M	R	S	R	S	M	S
	Study enrollment	R	R	R	R	S	R	S	M	S
Patient 3	TB treatment start	R	R	R	M	S	R	S	M	R
	Before LFU	M	M	M	M	M	M	M	M	M
	Study enrollment	R	R	R	R	S	R	S	M	S
Patient 4	TB treatment start	R	R	R	M	R	S	R	M	S
	Before LFU	R	R	R	S	R	S	R	M	S
	Study enrollment	R	R	R	R	R	S	R	M	S
Patient 5	TB treatment start	R	R	M	M	M	M	M	M	M
	Before LFU	M	M	M	M	S	R	S	M	S
	Study enrollment	R	R	S	R	S	R	S	M	S
Patient 6	TB treatment start	R	S	R	S	S	S	S	M	S
	Before LFU	M	M	M	M	M	M	M	M	M
	Study enrollment	R	S	R	S	S	S	S	M	S
Patient 7	TB treatment start	R	R	S	M	S	R	S	M	S
	Before LFU	M	M	M	M	M	M	M	M	M
	Study enrollment	R	R	R	R	S	R	S	M	S
Patient 8	TB treatment start	R	R	R	M	R	S	S	R	S
	Before LFU	M	M	M	M	S	R	S	M	S
	Study enrollment	R	R	R	R	S	R	S	M	S
Patient 9	TB treatment start	R	R	R	M	S	R	S	M	S
	Before LFU	M	M	M	M	M	M	M	M	M
	Study enrollment	R	R	R	R	S	R	S	M	S
Patient 10	TB treatment start	R	R	R	M	S	S	S	R	S
	Before LFU	M	M	M	M	M	M	M	M	M
	Study enrollment	R	R	S	S	M	M	M	M	M
Patient 11	TB treatment start	R	R	R	M	R	S	S	R	S
	Before LFU	R	R	R	M	R	S	S	M	S
	Study enrollment	R	R	R	R	R	S	S	M	S

Abbreviations: Cm, capreomycin; DST, drug-susceptibility testing; E, ethambutol; Eto, ethionamide; INH, isoniazid; Km, kanamycin; LFU, loss to follow-up; M, result is not available (missing); Ofx, ofloxacin; Pas, para-aminosalicylic acid; Pza, pyrazinamide; R, resistant; RIF, rifampicin; S, sensitive; TB, tuberculosis.

🟨 Possibility of getting new strains during the treatment or laboratory error.

🟥 Possibility of acquiring drug resistance or reinfection with the new strains or laboratory error.

increased resistance to at least 1 second-line drug—most likely due to acquired drug resistance or potentially infected with new *Mtb* strains. Of interest, we observed 4 patients who were initially resistant to a second-line drug who later reported susceptibility to the same drug. This "acquired susceptibility" can likely be explained by transmission of a new TB strains, misclassification of initial resistance status due to laboratory DST error, and/or the possibility that these patients had multiple concurrent strains of *Mtb*. Larger cohorts that include longitudinal genotypic tests are needed to determine reasons for the difference between DST patterns at the start of TB treatment, during follow-up, and after LFU.

Overall, our findings underline the need to strengthen strategies to improve retention-in-care and treatment adherence among DR-TB patients. A systematic review conducted by Law et al [26] found that individual counseling support and home visits by health workers, provided throughout treatment, were associated with fewer LFU than when they were provided only at the start of treatment, or not at all. Although new anti-TB drugs were not available under programmatic use during 2011–2014, a recent study examining treatment outcomes among patients receiving bedaquiline- and delamanid-containing regimens also found high rates of LFU [27]. Both long duration of treatment and adverse side effects of second-line TB drugs are established risk factors for LFU [28, 29]. The relationship between second-line regimens and LFU partially influenced recently released guidance from WHO to shift to using shorter, all-oral treatment regimens that may improve treatment adherence and overall treatment outcomes [30].

Our study was subject to limitations. First, there were n = 144 (24%) patients who were LFU for whom we could not find or determine their current vital and active TB status. It is

plausible that many of these patients with missing status were deceased; therefore, our reported mortality proportion may underestimate the true mortality proportion among LFU patients. Second, we only collected 1 sputum sample for culture/Xpert testing. Repeated collection of sputum or induced sputum (in those who could not produce it) may have increased the sensitivity of our measure of active TB at study enrollment. Thus, our reported prevalence of active TB may underestimate the true prevalence of active TB in patients LFU. Due to the small number of participants in the study who had active TB, we have observed wide CIs for some of effect estimates in our analyses.

Despite limitations, our study had key strengths. We used data from the entire national population receiving second-line TB therapy for 4 consecutive years in Georgia. Inference from this large sample is likely widely generalizable to most LFU patients in Georgia. In addition, patients in our population-based cohort had a median follow-up time of 3 years between LFU and study enrollment, providing information about the long-term TB outcomes of patients after they were LFU. Another major strength is that our study determined the prevalence of active TB among patients who were LFU using culture- and Xpert-confirmed measures. Therefore, the specificity of our estimated TB prevalence used current gold-standard criteria for active TB diagnosis.

CONCLUSIONS

In conclusion, among Georgian patients who were LFU and later recruited in this study, we found high percentage of mortality and confirmed active TB. Given the substantial number of patients who were LFU who then either emigrated, were incarcerated, or returned to TB care, our findings emphasize the need for strong coordination between and among public health institutions and other sectors. We demonstrated that intensified public health approaches to find TB patients who were LFU during second-line treatment is feasible. If programmatic and clinical care measures to prevent LFU during TB treatment are unsuccessful, TB control agencies should engage in intensified efforts to find patients and bring them back into the appropriate healthcare system. Such intensified efforts for TB patients who were LFU may prevent death and reduce transmission of disease.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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