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Approval Sheet

Risk Factors for Poor Treatment Outcomes among Patients with Multi-Drug Resistant and Extensively Drug-Resistant (M/XDR) Tuberculosis in the Country of Georgia.

By

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Abstract Cover Page

Risk Factors for Poor Treatment Outcomes among Patients with Multi-Drug Resistant and Extensively Drug-Resistant (M/XDR) Tuberculosis in the Country of Georgia.

By

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An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
In partial fulfillment of the requirements for the degree of
Masters of Science
in Clinical Research
2011

Abstract

Introduction: Resistance of *M. tuberculosis* to anti-tuberculosis drugs has become a major public health problem in many countries, including Georgia. In 2008, Georgian National Tuberculosis Program introduced treatment with second line anti-tuberculosis drugs, which has allowed for treatment of multidrug or extensively drug-resistant tuberculosis (M/XDR)-TB. The study objectives were to assess treatment outcomes among the 1st cohort of patients with pulmonary M/XDR-TB and to determine risk factors for poor treatment outcomes: defined as death, failure and default.

Methods: A prospective observational cohort study was performed. All patients with M/XDR pulmonary TB who initiated treatment in 2008 were enrolled and followed until 2010. Descriptive statistics were used to determine associations between study covariates. Binary logistic regression analysis was utilized to determine independent association of prior treatment history with treatment outcome while controlling for potential confounding variables.

Results: 380 patients were included: male (71%); mean age 38 years; median age 38.4 years. 13% had XDR-TB. 1.3% had HIV co-infection. Body Mass Index (BMI) was <18.5 among 24% of the cohort, and 52% had bilateral lesions on chest X-ray. Surgery was performed in 10% (37) of cases. The treatment outcomes were as follows: 47% had a poor outcome (death among 59 patients [15%], failure among 37 [10%], and 83 [22%] - defaulted). In the final multivariable analysis, history of previous treatment (OR=2.8 95% CI 1.2 - 6.3) was significantly associated with poor treatment after controlling for risk factors. Other independent variables associated with poor treatment outcomes included absence of adjunctive surgical therapy (OR 3.7, 95%CI 1.5, 8.7), no sputum culture conversion to negative by 4 months (OR 3.0, 95%CI 1.9, 5.0), the presence of XDR-TB (OR 2.3, 95% CI 1.2, 2.4), BMI < 18.5 (OR 2.0, 95%CI 1.1, 3.4) and bilateral lesions on chest radiograph (OR 1.8, 95%CI 1.2, 2.9).

Conclusions: Overall, 47% of patients with M/XDR-TB had poor treatment outcome. In multivariable analysis, independent risk factors for a poor treatment outcome included prior TB treatment history, lack of adjunctive surgical intervention, no culture conversion by month 4, XDR-TB, low BMI (<18.5) and bilateral lesions on chest X-ray.

Cover Page

Risk Factors for Poor Treatment Outcomes among Patients with Multi-Drug Resistant and Extensively Drug-Resistant (M/XDR) Tuberculosis in Georgia.

By
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A thesis submitted to the Faculty of the
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ACKNOWLEDGMENTS:

I would like to express my deepest gratitude to my mentor Dr. Henry Blumberg for his support which made the thesis possible. I owe me deepest gratitude to Drs. John Boring and Mitchel Klein for their insightful comments. This thesis would not have been possible without the greatest support from Dr. Iagor Kalandadze. Special thanks to Matt Magee and Amanda Brzozowski for reviewing the study; It is a pleasure to thank those who made this thesis possible: Dr. Jennifer Furin for assistance thought this study; Mr. Paata Macharashvili for assistance in merging the data from laboratory register; Drs. Nino Bablishvili, Nona Tadumadze and Maka Akhalaia for assistance in laboratory aspects; Drs. Russel Kempker and Nino Lomtadze for their help; Dr. Leila Goginashvili for assistance in collecting the data; Dr. Tsira Chakhaia for assistance in literature searches; Ms. Marina Avanashvili for entering the data. Also, I am grateful to all of my patients for participating in this study.

TABLE OF CONTENTS

INTRODUCTION

Drug resistant tuberculosis (TB) has emerged as a major public health problem in many countries and is a major obstacle to effective global TB control. Multidrug-resistant (MDR)-TB is defined as resistance to isoniazid and rifampicin which are the best anti-tuberculosis drugs (1). In 2008, an estimated 440,000 cases of MDR-TB occurred yet only a small fraction were diagnosed and treated. The WHO estimates that MDR-TB accounts for > 10 percent of all new TB cases in Eastern Europe, the region most affected by drug resistant TB. In some former Soviet republics, up to 28 percent of all patients with TB have MDR strains (2).

In September, 2006, the World Health Organization (WHO) expressed concern over the emergence of extensively drug-resistant TB (XDR-TB) which is defined as resistance to any fluoroquinolone antibiotic plus resistance to at least one of three injectable second-line drugs (capreomycin, kanamycin or amikacin), in addition to multidrug-resistance. Findings from a survey conducted by WHO and the U.S. Centers for Disease Control and Prevention (CDC) found that XDR-TB has been identified in all regions of the world but is most frequent in the countries of the former Soviet Union and in Asia (2).

Treatment of patients with MDR- and XDR-TB is challenging and associated with high morbidity and mortality, especially among patients with HIV infection. In one cohort from Kwazulu-Natal, South Africa, 98% of XDR TB patients co-infected with HIV died, with a median time of death of only 16 days from the time of specimen collection (3,4). A case-control study, conducted in Estonia in 2003, showed that among patients with MDR-TB, the proportion of overall successful treatment outcome was 60.4%, rising to 72.8% among adherent patients. While in XDR-TB patients, these proportions were 42.6% and 50.0%, respectively (5). Risk factors for poor treatment outcome in MDR-TB were HIV

infection, previous TB treatment, resistance to ofloxacin and positive acid-fast bacilli (AFB) smear at the start of treatment. Predictors of poor treatment outcome in XDR-TB were urban residence and positive AFB smear. A retrospective cohort study, conducted in Latvia in 2004, revealed that 66% of MDR-TB patients had successful treatment outcomes. The independent risk factors significantly associated with poor outcome included previous MDR-TB treatment history (hazard ratio 5.7, 95% 1.9-16.6.) resistance to ofloxacin and body mass index less than 18.5 at start of treatment (6, 7).

A meta-analysis published in Lancet in 2009, has evaluated 33 cohort studies comprising over 8000 cases of MDR-TB. They have found an overall treatment success rate of MDR –TB was 62% (95% CI 58-67%) (8). The aim of this study was to access the clinical outcomes of the first cohort of M/XDR-TB patients in the country of Georgia and to determine risk factors and predictors for poor treatment outcome. For this purpose, all pulmonary M/XDR TB patients started treatment in 2008 were enrolled and followed until 2010.

In contrast to the studies conducted in Latvia, Tomsk and Estonia, new and previously treated pulmonary M/XDR TB cases were compared for identifying the risk factors of poor treatment outcome .As the issue is poorly studied worldwide, this study was concentrated on analysis of the factors associated with poor treatment outcome in patients with pulmonary M/XDR-TB. The results of this study will serve the basis for further programmatic interventions for TB control in Georgia.

BACKGROUND

Epidemiology of Tuberculosis in Georgia

Tuberculosis (TB) has emerged as major public health problem in the country of Georgia following the breakup of the Soviet Union. Reasons for the resurgence of TB included a marked and sudden decline in the socioeconomic status in Georgia following the dissolution of the Soviet Union, increased poverty, a civil war which occurred in 1991-1993 following Georgia's independence from the Soviet Union which resulted in hundreds of thousands of internally displaced persons, and failure of TB control and other health services due to the collapse of the public health infrastructure. According to the World Health Organization (WHO) Reports on Global TB Control, the annual incidence of TB in Georgia rose from 29.5/100 000 to 165/100 000 between 1989 and 1996. In 1996, the National Tuberculosis Program (NTP) was established and implemented a country-wide surveillance system for TB. The NTP embraced the WHO-recommended Directly Observed Therapy, Short Course (DOTS) strategy and by the year 2004 reached 100% countrywide DOTS coverage due to aggressive implementation measures. Despite significant but modest declines, TB case rates remain high in Georgia. In 2009, the annual new TB case notification rate (incidence) in Georgia was reported to be 100 cases per 100 000 population and the total TB case notification rate (new and re-treatment cases) was 134 cases per 100 000 population. In 2004, the Georgian NTP succeeded in reaching WHO targets for TB case finding (70%) and in 2008 the new smear-positive case detection rate in Georgia was 113% (indicating the number of cases detected by the NTP exceeded the WHO estimated number of cases of TB.

A WHO recommended population-based first line anti-TB drug resistance survey (DRS), conducted between July 2005 and May 2006, found high prevalence of Multidrug

Resistant TB (MDR-TB) in Georgia: 6.8% among newly diagnosed sputum smear positive TB cases and 27.4% among re-treatment TB cases (9). With the support of Global Fund to Fight AIDS, Tuberculosis and Malaria ("Global Fund") Round 4 and 6 projects, the NTP implemented a program for universal access to diagnosis to tuberculosis. This included expansion of laboratory capacity to perform cultures on all respiratory specimens and perform drug susceptibility testing on every culture positive case. Thus a population-based drug resistance surveillance system for both first and second line anti-TB drugs was established. According to data from the NTP, in 2009, MDR-TB was found among 10.3% of the newly diagnosed pulmonary TB cases and in 31.1% of the previously treated pulmonary TB cases. Overall, 15.5% of all registered TB cases in Georgia had MDR-TB. Approximately 550 MDR-TB cases were enrolled into category IV treatment countrywide per year. Among those patients with MDR-TB, 11% have XDR-TB (i.e., resistance to at least isoniazid, rifampin, a fluoroquinolone and an injectable antibiotic) based on the NTP surveillance data.

The Drug Resistant Surveys (DRS) and surveillance data have demonstrated that MDR-TB has emerged as a major public health problem in Georgia, and have shown that TB control efforts should be urgently implemented in order to prevent the development of new cases of MDR-TB and to treat existing MDR-TB patients. MDR-TB treatment was introduced in Georgia as a pilot project in November 2006 in Zugdidi, Samegrelo Region jointly by Medecins Sans Frontieres (MSF-France) and the National Tuberculosis Program. It has been rapidly scaled up and in 2009, Georgia achieved universal access for diagnosis and treatment of drug resistant TB, a major accomplishment for a low or middle income country (10,11). In addition to this, in 2010 Georgia received the Green Light Committee (GLC) approvals for treatment of the expansion cohort of 1,650 patients

with drug resistant TB for the next three years. Currently, more than a thousand patients with MDR-TB are receiving treatment through the National TB Program.

METHODS

Aim and hypothesis

The study had the following aims:

- To assess the clinical outcomes of the first cohort of patients in the country of Georgia treated for M/XDR-TB;

- To determine the risk factors for poor treatment outcome among those undergoing therapy for M/XDR-TB in Georgia

Null Hypothesis: The risk of having a poor treatment outcome among newly diagnosed patients with pulmonary M/XDR-TB does not differ from that of patients have a previous history of TB treatment (retreatment cases).

According to WHO recommendation, poor treatment outcomes were defined as: “Death”, “failure” and “default”. (See chapter “definitions”)

Alternative Hypothesis: Patients with pulmonary M/XDR-TB with a prior history of treatment for TB ("retreatment case") will be at a higher risk for having a poor treatment outcome compared to newly diagnosed patients wtih pulmonary M/XDR-TB.

Study Design

All patients, diagnosed with MDR-TB who began treatment between March 2008 and December 2008 in the country of Georgia, were enrolled in a prospective cohort study to determine the predictors and risk factors for poor treatment outcome. The treatment outcomes were assessed in December 2010.

Inclusion/Exclusion criteria

Patients with laboratory confirmed diagnosis of pulmonary MDR-TB (age ≥ 16 years of age) were enrolled in the NTP MDR-TB treatment program and therefore were eligible to be included in the study. All enrolled patients had to have valid drug susceptibility test (DST) results performed by the National Reference Laboratory for 2nd line anti-TB drugs within 6 months of enrollment and treatment initiation. Those enrolled into the study had to provide written informed consent. The decision on patients' enrollment and the treatment regimen prescription was made by the Drug Resistant TB committee of the NTP. Extra pulmonary TB cases and current prisoners were excluded from this study. The study protocol was approved by the local Institutional Review Board (IRB) existing at the National Center for Tuberculosis and Lung Diseases (NCTBLD) in Georgia.

Standard WHO definitions for case definition, treatment outcome and MDR and XDR TB were used. [12] MDR-TB was defined as resistance to at least isoniazid and rifampicin. XDR-TB was defined as resistance to isoniazid and rifampicin plus resistance to any fluoroquinolone drug (e.g., ofloxacin, levofloxacin, and/or moxifloxacin) and resistance to at least one of three injectable second-line drugs (capreomycin, kanamycin, or amikacin).

The type of TB case was classified into one of the following three categories based on WHO guidelines (1):

- **New TB case**: A patient who has never received treatment or less than one month of anti-tuberculosis treatment.

- **Previously treated case**: A patient who has been treated for one month or more for TB with first-line and/or with second line anti-tuberculosis drugs.

Treatment outcomes were divided into two groups based on WHO guidelines and definitions.[1] “Cured” and “treatment completed” were considered successful treatment outcomes while “death” (during treatment), “failure”, and “default” were considered poor treatment outcomes (1,6). Each of these outcomes was defined as following:

- **Died**: A patient who died due to any cause during the course of MDR-TB treatment.

- **Failed**: Treatment failure was defined a patient who had two or more of the five cultures recorded in the final 12 months of therapy are positive for *M. tuberculosis*, or if any one of the final three (sputum) specimens is culture positive for *M. tuberculosis*. Treatment was also labeled as "failed" if a clinical decision was made to terminate treatment early because of poor clinical or radiological response or adverse events.

- **Defaulted**: A patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.

Laboratory tests

Diagnosis of TB disease was initially suspected based on clinical presentation and radiographic findings and confirmed based on laboratory findings (positive AFB culture for *M. tuberculosis*). Sputum specimens were processed according to the WHO recommendations for direct acid-fast bacilli (AFB) smear microscopy using a Ziehl-Neelsen acid-fast staining procedure. [13] A semi-quantitative scale was used to assess the number of organisms present on the smear: 4-9 AFB per 100 oil immersion field - 1+., 1-9 AFB per 10 oil immersion field - 2+., 1-9 AFB per 1 oil immersion field - 3+ and more than 9 per 1 oil immersion field of the grade - 4+. All sputum samples of patients

registered in TB program (both AFB smear-positive and smear-negative) were sent for culture and drug sensitivity testing (DST) to the first-line and second-line anti-TB drugs. Culture and DST of first line anti-TB drugs was done using conventional Lowenstein-Jensen solid media and/or broth-based culture methods using the MGIT 960 system (14).

Identification of Mycobacterium species was done using the p-nitrobenzoic acid (PBN) and thiophene carboxylic acid hydrazine (TCH) resistance test (15).

DST to first and second line drugs method: Drug susceptibility testing to the first line drugs including streptomycin (SM), rifampicin (RIF), isoniazid (INH), ethambutol (EMB) and to second line anti-TB drugs including ethionamide (ETH), ofloxacin (OFL), para-aminosalicylic acid (PAS), capreomycin (CM) and kanamycin (KM) was performed using the standard culture-based method on Löwenstein–Jensen medium. The susceptibility testing to the first line anti-TB drugs on Löwenstein–Jensen medium was performed using the absolute concentration method.[15] The critical concentrations used in the standard test were: SM - 4 µg /ml; INH - 0.2 µg /ml; RIF - 40 µg /ml and EMB - 2 µg /ml. The DST plates were examined for interpretation after 28 days of incubation. Pyrazinamide susceptibility testing was performed using the MGIT 960 system (100mg/l) (16).

Susceptibility testing to second line anti-TB drugs: Second line DST was performed on Löwenstein–Jensen medium using the proportion concentration method (16). The critical concentrations used in the standard test were: ETH - 40,0 µg /ml; OFL - 2,0 µg /ml; PAS - 0,5 µg /ml, CM - 40,0 µg /ml and KM - 30,0 µg /ml. External quality control of the National Reference Laboratory was performed by the Supranational Reference Laboratory of Antwerp, Belgium (15,16).

Treatment

Patients with MDR-TB were treated with an individualized treatment regimen based upon the specific drug susceptibility pattern of the *M. tuberculosis* isolate recovered from that particular patient. [17] The individualized treatment regimen always contained at least 4 drugs to which susceptibility was documented (and included the remaining first line drugs ethambutol and pyrazinamide if susceptible) as well as an injectable agent (e.g., capreomycin, kanamycin, or amikacin) and a flouroquinolone antibiotic if the organism was susceptible to these agents. In general, at least 2 additional second line drugs were required including prothionamide, cycloserine, or para-amino salicylic acid. In general, the injectable drug was given for a minimum of 6 months (18, 19). In the post-injectable phase at least 3 and ideally 4 drugs added to which the patient's *M. tuberculosis* isolate had documented sensitivity. For the treatment of XDR TB cases, the following “third line drugs” were added: to the treatment regimen including amoxicillin-clavulanic acid, clofazimine, and clarithromycin (20, 21).

For treatment monitoring purposes, during in the injectable phase (i.e., first 6 months of treatment of MDR-TB), AFB smear microscopy and culture were performed monthly, and DST at month 2 and 6 of treatment. During the post-injectable phase, smear microscopy and culture were performed every 2-3 months (DST if culture was positive) or more frequently if clinically indicated. Treatment for all patients with MDR-TB was continued for at least 18 month past the point of culture conversion (change from a positive culture to a negative culture) (22, 23). Patients had both in-patient and out-patient treatment. Generally, patients received the initial treatment as an inpatient at a TB hospital in Georgia and continued treatment in outpatient settings after assuring treatment adherence, low risk of infection transmission, and patient support and direct observation

of treatment. All treatment (both as an inpatient and outpatient) was delivered by directly observed therapy.

Data collection

Demographic information (patient age, gender, marital and employment status including whether the patient was an internally displaced person or migrant worker) as well as information about substance abuse (smoking, alcohol abuse, and injection drug use), contact with known M/XDR TB case, previous treatment history, chest radiograph results, information about co-morbidities, treatment regimen and dosage, and body mass index (BMI) at the beginning of therapy was collected using the "treatment enrollment" form . This information was recorded on each patient by the physician providing care for the patient and was sent to the national registry at the Georgian National Center for Tuberculosis and Lung Disease (part of the NTP) in Tbilisi, Georgia at the initiation of therapy. Treatment outcomes were collected as part of ongoing surveillance at the NTP using a standardized "treatment outcomes" form. This form was completed at the end of the treatment course and entered into a database at the National Center for Tuberculosis and Lung Disease.

Laboratory results: Sputum AFB smear microscopy, culture and DST results for first and second line drugs were entered in the national laboratory register at NRL.

Data entry

Clinical and laboratory data obtained through data abstraction and surveillance activities were entered into a software program called "SAFE" at the National Center for Tuberculosis and Lung Diseases (NCTBLD). Data from a web-application, called SAFE (Satellites For Epidemiology) was created and then exported to SAS (SAS software, version 9.1, Cary, NC, USA) which was used to carry out all data analyses.

Variables

The data base contained information 34 variables that are listed in Table 1. The main exposure or predictor variable is **previous exposure to anti-TB treatment (TRT) for more than one month**. It is coded as neworrw 0=new 1= previously treated cases.

Poor treatment outcome represents the primary outcome variable, it is dichotomous variable coded as outcomegroups where 1=yes and 0=No. (Appendix 1)

Statistical Analysis

The statistical analyses were performed with SAS version 9.1 software (SAS Inc., Cary, N.C. USA). Descriptive statistics were used to determine associations between study covariates with the primary outcome (Treatment Outcome) and also with the main exposure variable (Prior Treatment History). The Pearson Chi-Square test was used to assess statistical differences in proportions between categorical covariates (including demographic, potential risk factors, clinical characteristics, and laboratory results) and the primary treatment and exposure variables. For the continuous variable of age, a two sample t-test was used to evaluate for any difference in mean age between the two groups. Statistical tests with a p-value ≤ 0.05 were considered significant.

Binary logistic regression analysis was utilized to determine the independent association of Prior Treatment History with Treatment Outcome while controlling for other risk factors and potential confounding variables. Conceptual and data based approaches were used to build the logistic regression model. Directed acyclic graphs (DAGS) were used to estimate causal associations and potential confounding variables. For the data-based approach model building and selection was based on the purposeful selection of covariates strategy proposed by Hosmer, Lemeshow, and May. The first step was to perform a univariable analysis for each variable under consideration. This was done

utilizing a logistic regression model using the PROC LOGISTIC statement in SAS. An odds ratio (OR), 95 % confidence interval (CI), and Wald Chi-square p-value were recorded for each variable in the model. Any variable that had a significant univariate test with a p-value <0.20 (with the Prior Treatment History variable also in the model) was retained for multivariable analysis. The initial model included the following variables: Logit P(Y=1, poor treatment outcome) = β_0 + $\beta_1$neworre + $\beta_2$age + β_3 gender+ β_4 mstatus+ β_5 estatus +β_6 IDU + β_7 Alcohol use +β_8XDR +$\beta_9$surgery + β_{10}BMI + β_{11}Xray + β_{12} cultureconversion4month.

A logistic regression model was then used to perform a multivariable model with all variables significant in univariate analysis and now a p value <.10 was considered significant. As with previous models ORs, 95% CIs, and p-values were generated. As each non significant variable was removed from the multivariable model, a change of 20% in any of the remaining parameter estimates was considered confounding. Any variable found to be a confounder was kept in the model. The next step was to add back the variables that were not included in the initial multivariable model one at a time to evaluate significant variables (p-value <0.10) or confounders (change in parameter estimates > 20%). This step was used to identify variables that, by themselves, were not significantly related to the outcome (univariable analysis) but made an important contribution to the association between the primary exposure and outcome variables in the multivariable analysis. At the end of this step the preliminary main effects model was generated. Additionally, based on the DAG and previous literature the age and gender variables were kept in the model even though they did not meet the data base approach criteria.

To assess interaction likelihood ratio test was performed. Likelihood ratio tests were performed by comparing the -2log likelihood from the full model (with interaction terms)

and comparing it to the -2 log likelihood of the reduced model (without interaction terms). Interaction term variables were created for each covariate with the main exposure variable (Previous Treatment History). Next, PROC LOGISTIC was used to run the final multivariable model including all interaction terms. All variables with $P \leq 0.05$ were excluded. In addition, the likelihood ratio test was used to compare the final multivariable with and without all simultaneous interaction terms. No interaction terms were found to be significant by either method.

Once the final model was obtained, a logistic regression model using the PROG LOGISTIC statement in SAS was used to generate ORs, 95%, and p-values for each variable in the multivariable analysis.

RESULTS

During 2008, 380 patients with laboratory confirmed pulmonary M/XDR-TB, were enrolled in drug-resistant TB treatment. This was the first cohort of patients in the country of Georgia to receive treatment for MDR-TB. The mean and median age of persons in the cohort was 38 years. Among the 380 patients, 271 (71%) were male and 109 (29%) were female, 68% were married and 86% were unemployed; HIV seroprevalence was 1.3% and 9% had Diabetes mellitus (Table 1). Forty percent of the cohort indicated they currently smoked cigarettes, 4% were injection drug users (IDU) and 25% had a history of alcohol use. Among the cohort of M/XDR TB patients, 24% (92) had a BMI <18.5 and 52% (199) had bilateral lesions on chest X-ray. Adjunct surgical therapy such as pneumonectomy or lobectomy was performed on 37 (10%) of M/XDR TB cases. General sample characteristics are shown in the table 1.

Treatment Outcomes

Among the 380 patients with M/XDR TB who made up the first cohort of patients in Georgia to receive treatment, 201 (53%) had a successful outcome (cured or completed treatment) and 179 (47%) had a poor treatment outcome including 59 (15%) who died, 37 (10%) who had treatment failure and 83 (22%) who defaulted from treatment. Among those who had a good treatment outcome group, 37 (18%) were new cases and 164 (82%) previously treated, as compared to 9 (5%) and 170 (95%) in the poor treatment outcome group and this difference was statistically significant. Mean age was 36.6 and median 35 in the good treatment outcome and 40.4 and 41 in the poor treatment outcome group (ttest 0.0056). Sample characteristics by outcome variable are described in the table 2.

Comparison of New and Previously Treated TB Cases

Among the cohort of M/XDR patients, 46 (12%) were newly diagnosed TB cases and 334 (88%) were previously treated cases ("retreatment cases"). The mean age was 33 years among new and 39 among previously treated patient groups. Overall, 37 (80%) of the 46 new TB cases and 164 (49%) of the 334 previously treated M/XDR TB cases had a good treatment outcome (Mantel-Haenzel P value <.0001). A total of 13% of the cohort had XDR-TB; this included 9% of the new and 13% of the previously treated cases. Sputum culture conversion by month 4 was detected among 15 (33%) of the new TB cases and among 192 (57%) of the previously treated TB cases. (Table 3).

Bivariate analysis

The results of the bivariate analysis are shown in Table 2. Patients who had previous treatment history, XDR TB, did not undergo surgical resection, had a BMI <18.5, bilateral lesions on chest radiograph, and no sputum culture conversion by month 4 were significantly more likely to have a poor outcome. There were no significant differences in the bivariate analysis with respect to treatment outcome based on substance abuse (smoking, alcohol or injection drug use) and gender. (Table 2)

Multivariate analysis

The final model included the following variables:

Logit P(Y=1, poor treatment outcome) = $\beta_{0} + \beta_{1}$neworre + β_{2}age + β_{3} gender +β_{4}XDR +β_{5}surgery + β_{6}BMI + β_{7}Xray + β_{8} cultureconversion4month.

In multivariate analysis, independent risk factors for having a poor treatment outcome including having previously been treated for TB (OR=2.8 95%CI 1.2-6.3), not having adjunctive surgery (OR=3.7 95%CI 1.5-8.7), lack of sputum culture conversion by month 4 of therapy (OR=3.0 95%CI 1.9-5.0), have XDR TB (OR=2.3 95%CI 1.2, 2.4), BMI

<18.5(OR=2.0 95%CI 1.1-3.4) and bilateral lesions on chest radiograph (OR=1.8 95%CI 1.2-2.9). The final multivariable model with OR and 95% CI is shown in the table 4.

DISCUSION

Georgia is one of the few low and middle income countries which has had a rapid scale up of treatment for M/XDR-TB (beginning in 2008) and in only 1½ years achieved universal access to diagnosis and treatment of M/XDR-TB. This study examined treatment outcomes among first cohort of patients with pulmonary M/XDR TB patients to undergo treatment in the country of Georgia. We found that 53 % of the cohort of patients with pulmonary M/XDR-TB had a good treatment outcome and 47% had a poor treatment outcome. Standard WHO definitions were employed to determine good treatment outcome (cured or completed treatment) or poor treatment outcome (death, failure, or default) (1, 2).

The proportion of good and poor treatment outcomes in our study was similar to some previously published studies but overall slightly lower than that reported in a meta-analysis published by Orenstein *et al,* in which successful outcome was reported among 62% (95% CI 58-67%) of patients with MDR-TB in 34 studies which were included in their report (8). Some differences that may have accounted for a slightly lower success rate are the high proportion of retreatment cases in our study, many who had very chronic disease and had received multiple treatment regimens in the past prior to the availability of diagnosis and treatment of M/XDR-TB in Georgia (10). In addition, 13% of our cohort had XDR-TB which increased the risk of a poor outcome and these types of patients may have been more prevalent in our study than in those included in the meta-analysis and in some MDR-TB treatment studies, patients with XDR-TB may have been excluded from the study. From our results as well as a recently published meta-analysis on the treatment of XDR-TB (in which 56% of patients had a poor outcome), it is clear that the success rate for those with XDR-TB is less than patients with MDR-TB (24-27). The finding that 13% of our cohort had XDR-TB in prior to the availability of second line

drugs from the Georgian NTP may be explained by the availability of second line anti-tuberculosis drugs over the counter without a prescription in local pharmacies (28). It possible that misuse of these anti-TB agents led to the development of further drug resistance including the development of XDR-TB.

Our study of the first cohort of patients treated for TB in Georgia revealed that independent risk factors associated with poor treatment outcomes were history of previous treatment, no surgery interventions, lack of culture conversion by month 4 of therapy, the presence of XDR-TB, BMI less than 18.5 and bilateral lesions on chest X-ray. Other studies, conducted in Latvia, Russia and Estonia, have reported that poor outcomes have been seen among those with HIV infection, previous TB treatment, resistance to ofloxacin, positive acid-fast bacilli (AFB) smear at the start of treatment and body mass index less than 18.5 (29-35).

In contrast to the studies by Leimane V et al, Keshavjee S et al and Kliiman K et al, our study revealed two important factors that were associated with a better treatment outcome. This included having adjunctive surgery for lung resection and having sputum culture conversion by month 4. The most common surgical intervention performed with pulmonary MDR-TB patients, was resection surgery (pneumonectomy or lobectomy). Large case-series analysis has shown resection surgery appared to be effective and safe under appropriate surgical conditions (36). Based on the results of our study, adjunctive surgery appeared to be beneficial for patients when the lesions are not bilateral and excellent postoperative care are available. Thus, surgical therapy should be considered as an important tool in the management of MDR-TB and can play a key part in producing good MDR-TB outcomes.

Data from our study has demonstrated that no culture conversion by month 4 of therapy is a predictor for poor treatment outcome. This highlights the importance of monitoring M/XDR TB patients based on culture results. In addition to this, it enables a doctor to assess the risk of poor treatment outcome at the earlier stage and gives a possibility to review the treatment regimen in relation to medical history, and all DST results, in order to avoid treatment failure at the end.

Strength of this study includes its prospective design while all above mentioned studies were retrospective. Also our study provides country wide data and includes all patients treated with pulmonary M/XDR-TB in Georgia through the National TB program: It should be emphasized that the study had some limitations. First, this study only included those M/XDR TB patients who had valid DST results (i.e., DST performed in the previous 6 months prior to initiation of treatment). Second, although it was the policy of Georgian NTP to do sputum cultures monthly they were not performed in every patient, 38 (10%) were missed more than 2 cultures. Third, some of the variables such as HIV status, alcohol and IDU were not filled missed and were considered as negative. HIV status was missed in 103 (27%) cases, IDU and alcohol use in 62 (16%) cases. Fourth, one of the most important confounders, adherence to treatment, was not collected.

The findings from this study have several implications for TB control activities in Georgia. First of all, according the study results previously treated cases are tended to have poor treatment outcomes and therefore, special attention is needed to detect M/XDR TB cases as early as possible. This issue itself highlights the importance and necessity of implementing rapid diagnostic tests to shorten patient delay and start treatment as early as possible. Second, one of the strongest risk factor for developing poor treatment outcome was presence of XDR, and thereby it is crucial to strengthen activities for effective use and control of second line drugs to prevent the further emergence of drug

resistant TB. Third, with better public health awareness and advocacy it is possible to avoid misuse of second line drugs, and at the same time improve adherence which itself lead to decrease default rate.

CONCLUSION

There was a rapid scale up of treatment of MDR-TB treatment in Georgia beginning in 2008. In the first cohort of 380 patients treatment for M/XDR-TB, 53% had a good treatment outcome and 47% had a poor treatment outcome. In multivariate analysis, after adjusting for confounding, independent risk factors for a poor treatment outcome included prior treatment history (“retreatment case”) was associated with poor treatment outcome (OR=2.8), lack of adjunctive surgery (OR=3.67), lack of culture conversion by month 4 (OR=3.02), presence of XDR-TB (OR=2.3), BMI (≤18.5) (OR=1.97) and bilateral lesions on chest radiograph (OR=1.8).

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TABLES

Table 1.

General sample characteristics

Exposure	**Total N=380 % (N)**	**Mantel-Haenzsel P value**
Gender		0.02
M	271 (71%)	
F	109 (29%)	
Age		0.01
Mean	38	
Median	38.4	
Currently Married	258 (68%)	0.10
Currently unemployed	328 (86%)	0.05
New cases	46 (12%)	<.0001
Previously treated cases	**334 (88%)**	**<.0001**
XDR	49 (13%)	0.01
Current smoker	152 (40%)	0.77
ID user	14 (4%)	0.19
Alcohol user	94 (25%)	0.11
HIV Positive	5 (1.3%)	0.75
Any history of incarceration	51 (13%)	0.23
No Surgery intervention	37	0.001
BMI < 18.5	92 (24%)	0.0004
Bilateral lesions on X-ray	199 (52%)	<.0001
Diabetes mellitus	35 (9%)	0.86
No Culture conversion by month 4	207 (55%)	<.0001

Table 2.

Sample characteristics by outcome variable

Exposure	Good outcome N=201 % (N)	Poor outcome N=179 % (N)	OR	95% CI	Mantel-Haenzsel P value
Gender F	68 (34%)	41 (23%)	0.58	0.37-0.92	**0.02**
Age Mean (SD) Median	36.6 (12.9) 35	40.4 (13.3) 41			0.01 (ttest)
Currently Married	129 (64%)	129 (72%)	1.44	0.93-2.22	0.10
Currently unemployed	167 (83%)	161 (90 %)	0.55	0.30-1.01	0.05
TB cases New Re-treatment	37 (18%) 164 (82%)	9 (5%) 170 (95%)	4.26	1.99-9.10	**<.0001**
XDR	17 (8%)	32 (18%)	2.36	1.26-4.41	0.01
Current smoker	79(39%)	73 (41%)	1.06	0.70-1.60	0.77
ID user	5 (2 %)	9 (5 %)	2.07	0.69-6.31	0.19
Alcohol user	43 (21%)	51 (28%)	1.46	0.91-2.33	0.11
HIV Positive	3 (2%)	2 (1.5%)	0.75	0.12-4.51	0.75
Any history of incarceration	23 (11%)	28 (16%)	1.43	0.79-2.60	0.23
No surgery intervention	29 (14%)	8 (4.4 %)	0.28	0.12-0.62	**0.0011**
BMI > 18.5	34 (17 %)	58 (32 %)	0.43	0.26-0.69	**0.0004**
Bilateral lesions on X-ray	86 (42%)	113 (63%)	2.24	1.51-3.46	**<.0001**
Diabetes mellitus	19 (9%)	16 (9%)	0.94	0.47-1.90	0.86
Culture conversion by month 4	81 (40%)	126 (70%)	0.28	0.18-0.43	**<.0001**

Table 3.

Sample characteristics by exposure variable

Exposure	New case N=46 % (N)	Re-treatment N=334 % (N)	Total N=380 % (N)	Mantel-Haenzsel P value
Gender				**0.01**
M	25 (54%)	246 (74%)	**271 (71%)**	
F	21 (46%)	88 (26%)	**109 (29%)**	
Age				0.004
Mean	33	39	38.3	
Currently Married	29 (63%)	229 (69%)	258 (68%)	0.45
Currently unemployed	36 (78%)	292 (87%)	328 (86%)	0.09
Outcome				**<.0001**
Good	37 (80%)	164 (49%)	201 (53%)	
Poor	**9 (20%)**	**170 (51%)**	**179 (47%)**	
XDR	4 (9%)	45 (13%)	49 (13%)	0.36
Current smoker	14 (30%)	138 (41%)	152 (40%)	0.16
ID user	0	14 (4%)	14 (4%)	0.16
Alcohol user	6 (13%)	88 (26%)	94 (25%)	0.05
HIV Positive	1 (2%)	4 (1%)	5 (1.3%)	0.59
Any History of incarceration	4 (9%)	47 (14%)	51 (13%)	0.32
No Surgery intervention	5 (11%)	32 (10%)	**37 (10%)**	**0.78**
BMI < 18.5	8 (17%)	84 (25%)	**92 (24%)**	**0.25**
Bilateral lesions on X-ray	17 (37%)	182 (54%)	**199 (52%)**	**0.03**
Diabetes mellitus	4 (9%)	31 (9%)	35 (9%)	0.90
No culture conversion by month 4	15 (33%)	192 (57%)	207 (55%)	0.0015

Table 4.

Final multivariable model

Variables	OR	95% CI	P value
Previously treated cases	**2.8**	**1.2 - 6.3**	**0.02**
No surgery intervention	3.7	1.5 - 8.7	0.003
No Sputum Culture Conversion by month 4	3.0	1.9 – 5.0	<0.001
Presence of XDR-TB	2.3	1.2 – 2.4	0.02
BMI <18.5	2.0	1.1 – 3.4	0.02
Bilateral lesions on X-ray	1.8	1.2 - 2.9	0.01
Age (continuous, per yr)	1.0	0.9 - 1.0	0.23
Gender (Male)	0.7	0.4 - 1.2	0.18

APPENDIX

Appendix 1.

Variable names and value

N	variable name	type	Value	Measure
	Demographic data			
1.	Gender	numeric	0=male 1=female	nominal
2.	Year of birth (Y)	numeric		scale
3.	Age	numeric		scale
4.	Mstatus	numeric	0=single 1=married	nominal
5.	Estatus	numeric	0=unemployed 1=employed	nominal
	Clinical data			
6.	IDuser	numeric	0=no 1=yes	nominal
7.	surgery	numeric	0=no 1=yes	nominal
8.	smoker	numeric	0=no 1=yes	nominal
9.	alchocoluser	numeric	0=no 1=yes	nominal
10.	Prison	numeric	0=no 1=yes	nominal
11.	SITEDIS	numeric	1=- pulmonary	nominal
12.	PATFIRST	numeric	1= new 2=previously treated with 1st line 3=previously treated with 2nd line	nominal
13.	NeworRe	numeric	1= new cases 2=retreatment cases	nominal
14.	Outcome	numeric	1=cured 2=completed 3=defaulted 4=died 5=failed	nominal
15.	Outcomegroups	numeric	0=successful 1=poor	scale
16.	x ray	numeric	0=unilateral 1=bilateral	nominal
17.	weight	numeric		scale
18.	height	numeric		scale
19.	BMI	numeric		scale
20.	BMIgroup	numeric	0=BMI < 18.5 1=BMI >18.5	nominal
21.	Diabetes	numeric	0=no disease 1=yes	nominal

	Lab results			
22.	HIV	numeric	0=negative 1=positive	nominal
23.	H	numeric	1= resistant	nominal
24.	R	numeric	1=resistant	nominal
25.	E	numeric	1=resistant 0=sensitive	nominal
26.	Z	numeric	1=resistant 0=sensitive	nominal
27.	S	numeric	1=resistant 0=sensitive	nominal
28.	Km	numeric	1=resistant 0=sensitive	nominal
29.	Cm	numeric	1=resistant 0=sensitive	nominal
30.	Ofx	numeric	1=resistant 0=sensitive	nominal
31.	Eto	numeric	1=resistant 0=sensitive	nominal
32.	PAS	numeric	1=resistant 0=sensitive	nominal
33.	Cs	numeric	1=resistant 0=sensitive	nominal
34.	Cultureconversion4month	numeric	0=no 1=yes	nominal