Assessment of the eligibility for short course treatment regimen of multi-drug resistant tuberculosis in Armenia

Master of Public Health Integrating Experience Project

Research Grant Proposal Framework

by

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Yerevan, Armenia

2018

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LIST OF ABBREVATIONS

AM	Amikacin
BMI	Body mass index
CFZ	Clofazimine
CM	Capreomycin
CS	Cycloserine
DLM	Delamanid
DR-TB	Drug-resistant tuberculosis
DST	Drug-susceptibility testing
E	Ethambutol
ETO/PTO	Ethiot/Prothionamide
FL-LPA	First-line line probe assay
FQ	Fluorchinolones
GFX	Gatifloxacin
H	Isoniazid
HIV	Human immunodeficiency virus
KM	Kanamycin
LFX	Levofloxacin
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug-resistant Tuberculosis
MFX	Moxifloxacin
MSF	Medecins Sans Frontieres
MTB	Mycobacterium tuberculosis
NTP	National tuberculosis Program

PDR-TB	Polydrug-resistant tuberculosis
pre-XDR-TB	Pre-extensively drug-resistant tuberculosis
R	Rifampicin
RR	Rifampicine résistant
SLID	Second line injectable drug
SL-LPA	second-line like probe assay
TB	Tuberculosis
THE UNION	International Union Against Tuberculosis and Lung Disease
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

ACKNOWLEDGMENTS

I would like to express my deep gratitude to my advisors Dr. Michael E. Thompson and Dr. Haroutune Armenian for their patience and guidance. Dear Michael, special thanks for your continuous feedback and valuable comments, which had a tremendous impact on my professional writing skills.

I am very thankful to Dr. Varduhi Petrosyan for her patience, support and motivation to complete the master thesis. I would like also to express my appreciation to the whole Faculty of the Gerald & Patricia Turpanjian School of Public Health (SPH) of the American University of Armenia for the knowledge and skills gained during my study.

I am also grateful to my supervisor in Epicentre Helena Huerga and MSF TB referent Cathy Hewison for professional ideas given for the project development.

EXECUTIVE SUMMARY

Tuberculosis (TB) is a major public health issue and according to the World Health Organization (WHO) is one of the top 10 causes of death. In 2016, 10.4 million people had active TB, of which 1.7 million died. Special attention needs multidrug resistant tuberculosis. The treatment of multidrug resistant (MDR) TB is challenging. Its long duration of about 20 months is associated with high cost, greater incidence of adverse reactions, and high rate of lost-to follow up. Therefore, the finding of shorter, more effective, lower-cost treatments for MDR-TB remains a priority.

During the last years, promising results came from observational studies conducted in Bangladesh and 9 African countries, where a 12 months or less regimen for MDR-TB treatment was tested. The short course regimen showed higher success rate with a lower proportion of patients being lost to follow and reduction of cost per patient. In 2016, based on the evidence assessment of the short course treatment regimen effectiveness, WHO included the use of a 9–12 months regimen in the MDR-TB treatment policy as a conditional recommendation. The conditions included not being resistant to any component of the regimen, not having been treated for drug resistant TB in the past, and not being pregnant, etc.

Armenia is a high MDR-TB burden country, with only about half of cases finishing treatment successfully. The low success rate reflects the high proportion of lost to follow ups, which is unfortunately constantly increasing. The introduction of a shorter treatment regimen in Armenia could have positive impact on reduction of proportion of defaulters and as a result the increase of success rates.

However, before implementation of the new treatment regimen, an evaluation of its applicability in certain geographical areas and the impact of the new approach on the national tuberculosis program is needed. According to the WHO recommendations, the MDR-TB short course treatment should be started as soon as possible based on the genotypic drug susceptibility testing results, which allows identifying the resistance only to isoniazid, fluoroquinolones and injectable drugs. The empiric use of the short course regimen in a population with the high resistance rate to other components of the treatment regimen such as clofazimine, ethio/prothionamide, pyrazinamide and ethambutol will substantially reduce its success rate and will increase drugs resistance. Therefore, assessing the resistance pattern of MDR-TB in Armenia is needed to understand the appropriateness of the new recommendation to this region.

In Armenia, the majority of patients with MDR-TB was already being treated for TB, which is an exclusion criterion for short course regimen. Therefore, an estimation of the eligible patients based on the retrospective data can help to understand the impact of the new approach on the programmatic level of the National Tuberculosis program. The evaluation of the poor and successful outcome rates of the patients who could have been eligible for the short course regimen will help to estimate the added value of the new approach. In addition, to predict the

course of treatment after implementation of the new regimen, an assessment of factors which are likewise associated with the poor outcome should be performed.

INTRODUCTION/LITERATURE REVIEW

1.1 Tuberculosis overview

Tuberculosis (TB) is an airborne infection and in 2016 was one of the top 10 causes of mortality. According to the World Health Organization (WHO) Global Tuberculosis report in 2016, 10.4 million people had active TB, of which 1.7 million died[1]. TB is a main killer of people living with HIV: in 2016, TB accounts for 40% deaths among people with HIV. Multidrug resistant tuberculosis (MDR-TB) is a global public health issue needing special attention. According to the WHO report in 2014 "an estimated 3.3% of new TB cases and 20% of previously treated cases have MDR-TB". The number of new MDR-TB cases detected globally were 480 000, of which 190.000 died[2]. The level of incidence and mortality has changed little in recent years[1,3].

In addition to the low success rate, the treatment of MDR-TB is challenging by reason of its long duration, which is associated with high cost, greater incidence of adverse reactions, and high rate of lost-to follow up [3–6]. On average 23% patients default from the treatment[4]. The cost per patient treated for MDR-TB varies on average from US$ 6 826 in low-income countries to US$ 21 265 in upper middle-income countries[3]. Therefore, finding shorter, more effective and low-cost treatment for MDR-TB remain a priority.

1.2 Tuberculosis Treatment Approaches

To treat MDR-TB, the WHO recommends use of four second-line anti-TB drugs (second line injectable drugs (SLID) such as Amikacin (Am), Kanamycin (Km) and Capreomycin (Cm), fluorquinolones such as ofloxacin (Ofx), lebofloxacin (Lfx), moxifloxacin (Mfx) and gatifloxacin (Gfx), clofazemine (Cfz), cycloserine (Cs), linezolid (Lzd), ethio/prothionamide

(Eto/Pto), para-aminosalicylic acid (PAS), imipenem (Imp), amoxicillin/clavulonate (Amx/Clv)) likely to be effective, as well as pyrazinamide (Z) in the intensive phase with a total treatment duration of 20 months[7]. Despite the long duration, treatment success rate (proportion of patients who was declared as cured or completed at the end of 20th months) for MDR-TB is still low, which ranges from 50% to 60% [4,8,9]. In 2017 the failure rate was around 10%, with highest in Europe, and death rate around 20 %, with highest in the African region [1].

During the last years, promising results for shorter protocols came from observational studies conducted in Bangladesh, Cameroon and Niger, where 12 months or less regimen for MDR-TB treatment were applied [10–13]. These studies showed that the short course treatment regimen would be adequate to achieve high rates of success among MDR-TB patients who meet certain set of criteria. In the prospective observational study conducted in Bangladesh patients with proven or highly likely MDR-TB received 9-12 months of treatment with Gfx, Cfz, ethambutol (E), and Z throughout the treatment period, added by Pto, Km, and high-dose isoniazid (H) during an intensive phase. The exclusion criteria for the study were a history of previous treatment with second-line drugs, overt liver disease, having extra-pulmonary TB or being pregnant. Out of 515 enrolled patients, 435 (84.5%) had a treatment outcome cured or completed. On success rate negative impact had high-level fluoroquionolone (FQ) resistance, especially when accompanied by initial Z resistance. The incidence of adverse events and its severity was not assessed, since adverse drug events were not systematically recorded [11].

The same treatment regimen/duration and inclusion/exclusion criteria were applied in observational study of short-course treatment regimen of MDR-TB in Cameroon and Niger, where 150 and 58 patients were enrolled. In Cameroon 89% (134/150) and in Niger 89.2% (51/58) patients successfully finished the treatment. The most important adverse event in both

studies were hearing impairment, which occurred in 43% patients in Cameron and in 11 (20%) in Niger [12,13].

Similarly encouraging results were obtained in a collaborative study of MDR-TB short course treatment regimen conducted by the International Union Against Tuberculosis and Lung Disease (The Union) in West and Central African countries. An observational study was conducted in several African countries with participants who have MDR-TB and received standardized 9-month regimen. The study team applied addition exclusion criteria such as known resistance to FQ and SLID and QT interval showing 500 msec in pre-treatment ECG. In the drug regimen the high dose Gfx was replaced by normal dose Mfx. Trebucq *at el.* presented the results from1006 patients, where successful outcome was observed among 81.6% of patients (72.4% cured and 9.2% treatment completed). The important point for this study was that about 20% (200/106) of patients were infected with HIV which was associated with the lower probability of a successful treatment (71.7% vs. 83.4%; p=0.0001). The reason for lower success rate was the high proportion of deaths among patients living with HIV (19.0% vs. 5.0%, p=0.001). The common adverse drug event was again hearing impairment (11.4%) [14].

In 2016, a panel of experts of WHO found that patients who received the shorter MDR-TB treatment regimen had higher treatment success rate than those who received the longer conventional MDR-TB regimens: 90% versus 78% when comparing success with treatment failure/relapse/death and 84% versus 62% when comparing success with treatment failure/relapse/death/loss to follow-up. WHO therefore included in the MDR-TB treatment policy the use of a 9–12 month shorter MDR-TB regimen in MDR-TB patients as under the conditional recommendations [15]. According to the WHO MDR-TB treatment policy published in 2016 “the short-course regimen consists of a 4-6 month intensive phase including Km, Mfx, Eto,

Cfz, Z, high-dose H and E and a 5-month continuation phase that includes Mfx, Cfz, Z and E". According to the same policy the exclusion criteria for the short course regimen are:

- "Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- Exposure to >1 second-line medicines in the shorter MDR-TB regimen for >1 month
- Intolerance to >1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- Pregnancy
- Extra-pulmonary disease
- At least one medicine in the shorter MDR-TB regimen not available in the programme." [16]

Establishing resistance raises some concerns. The second line LPA is a genotypic methods of the anti-tuberculosis drug resistance identification in Mycobacterium tuberculosis isolates based on the identification of the genetic mutations responsible for resistance. It detects resistance to the two major classes of second-line drugs such as FQ and second line injectable (SLID) with shorter turnaround time (2 hours to 2 weeks) in comparison to the phenotypic drug-susceptibility testing (4-8 weeks)[17]. Therefore, WHO endorses its use for quick identification of eligible patients and start of short course regimen,[15] however, molecular methods have less sensitivity then phenotypic DST, which show resistance irrespective of the genetic mutations. In the last guideline on the use of second-line line probe assay (SL-LPA), WHO reviewed the sensitivity and specificity of the molecular method and for FQ pooled sensitivity was 85.6% and pooled specificity 98.5%. Pooled sensitivity for SLID was about 76.5% and pooled specificity was

99.1% [18]. This finding means that SL-LPA will rarely give positive result for non-resistant strains, however some resistant cases which will be missed.

Although genotypic DST allows to detect resistance to two core drugs in the regimen (FQ and SLID), the question regarding the identification of the resistance to other agents in the regimen (Z, Cfz, E, Eto/Pto) remains open. The use of first-line line probe assay (FL-LPA) can be useful tool for identification of the second-line drugs resistance, since it detects the mutation of inhA genes associated with low-level isoniazid resistance, which is cross- resistant with the component of the short regimen Eto/Pto [19,20]. This is explained by the fact that H is Eto are the structural analogs and both of them are pro-drugs [21,22]. A systematic review performed by Seifert *et al.* showed that in European region about 14% phenotypic isoniazid resistance was linked to the inhA mutation, which means that at those patients we will likely observe also Eto resistance [23].

Another question for discussion is the applicability of the recommendation in different geographical settings according to the pattern of the resistance. The data from Pakistan and Brazil showed high eligibility rates of 50% or higher, which are very optimistic in regards of applicability [24,25]. However, the data coming from Europe are less optimistic. Marieke J. van der Werf *et al.* assessed proportion of RR/MDR-TB cases who could be eligible for the shorter treatment course among all DR-TB cases who started treatment between 2010 and 2014 in the 26 EU/EEA countries including 3 post-soviet union countries such as Latvia, Lithuania and Estonia. Among 1774 new cases with pulmonary TB who were tested for FQ and SLID resistance 524 (29.5%) were eligible for shorter MDR TB regimen[26]. The proportion of eligible patients would be reduced in case of accounting other excluding criteria, such as intolerance to second-line drugs, pregnancy and extra-pulmonary TB.

For more precise applicability assessment, it is important to account the resistance to all drugs in the regimen. A study in Singapore which receives migrant workers from South-East Asia were less promising and showed that (71.2%) (190/267) percent of patients were resistant to one or more drugs of the six components of the WHO shorter regimen, which means that only about 30% were eligible. However, authors express "caution in the use of this regimen in patients from the South-east Asian countries, due to absence of the full DST and accuracy of the patients provided information pertaining to new or previously treated TB" [27].

Lange *et al.* estimated the proportion of patients who could be eligible for the short MDR-TB treatment regimen in Europe by analyzing data for resistance to all components in short course regimen in 1140 patients with DR-TB. Only 612 (53.7%) had a comprehensive DST for the components used in the short course regimen, from which only 48 (7.8%) patients were infected with strains with full susceptibility to the drugs proposed in the short-course MDR-TB regimen. A total of 36.8% of patients had strains with resistance to SLIDs and 33% to FQ. They also noticed a high rate of resistance to ethambutol (59.5%), pyrazinamide (66.8%), and prothionamide/ethionamide (64.4%). Authors mentioned the number will be reduced after application of the other excluding criteria, such as previous exposure to second-line drugs, intolerance to second-line drugs, pregnancy, extra-pulmonary TB [28].

A meta-analysis of data from 26 countries, including three former soviet countries (Uzbekistan, Estonia, and Latvia), showed a high rate of resistance to the MDR-TB treatments pyrazinamide (50%) and ethionamithe (61%). [29] This can be an explanation for considerably lower success rate observed in Uzbekistan (64%), where a short course MDR-TB treatment regimen was implemented by Medicins Sans Frontieres (MSF) [30].

High prevalence of resistance to additional components of the short regimen can preclude the implementation of the short course treatment approach, since it can lead to the acquisition of extensive drug resistance rather than cure MDR-TB.

The use of short course regimen among non-susceptible patients will lead to an acquisition of resistance to other drugs in the short course regimen.

Thus, only for MDR-TB patients whose resistance type is amenable, is a short regimen more effective and less costly, benefitting both the individual and society. The introduction of a shorter treatment regimen in Armenia could have positive impact by reducing the proportion of defaulters and increasing the success rate. Not less important point is the minimization of the costs of MDR-TB treatment, which will be approximately 6 times lower in comparison to the cost of the standard MDR-TB treatment regimen and will amount to US$ 1000 per person[1].

1.3 Situation in Armenia

Armenia is an ex-soviet union country with overall 1080 TB cases notified in 2016 and with estimated incidence rate of 44 per 100.000 population. Although the incidence rate of tuberculosis has steadily declined during the last years, drug resistant tuberculosis remains a public health issue as in other post-soviet union countries. In 2016 about 11% of new cases and 47% of retreated cases had MDR-TB [31].

Patients with MDR-TB receive individualized treatment regimen based on the results of drug susceptibility testing which contains at least four effective drugs in compliance with the WHO recommendation with a total duration of the treatment 20 months or 18 months after culture conversion [32,33]. Only about half of cases in Armenia finished treatment successfully, with outcome cured or completed (58% success rate among cohort 2014 and 43% among cohort of

2015)[31,32]. The low success rate reflects the high proportion of lost to follow ups which is unfortunately constantly increasing. In 2013, 19.5 % did not complete the treatment and was declared as lost to follow up, whereas in 2017 the proportion of defaulters reached 31% [32]. A study conducted by Epicentre reviewed data for 381 Patients who started DR-TB treatment from 2005 to 2011 in Armenia and showed that the median duration of treatment for patients who defaulted was 6.5 months (interquartile range [IQR] 4.3–12.0) [34].

The introduction of a shorter treatment regimen in Armenia could have positive impact on reduction of proportion of defaulters and as a result the increase of success rates. Not less important point is the minimization of the costs of MDR-TB treatment, which will be approximately 6 times lower in comparison to the cost of the standard MDR-TB treatment regimen. However, before implementation, a preliminary evaluation of the applicability of the new approach is needed taking in to consideration the doubts expressed by different authors in terms of diagnostic methods mentioned in WHO policy and recommendation of the same approach in different geographical areas irrespective of the resistance pattern [35–37].

An estimation of specificity and sensitivity of molecular methods in Armenia will help to evaluate the proportion of patients who will be missed as being resistant to FQ and SLID, and potentially will develop Therefore the analysis of the retrospective FL-LPA results can be useful in understanding the proportion of patients with resistance to Eto/Pto in Armenia. Based on the results the recommendations can be made if the FL LPA should be part of the diagnostic algorithm of MDR-TB before start of the short course regimen as a tool for reducing the possibility of enrollment the potentially resistant to the sort course regimen component drug patients.

Therefore, before implementing the new approach in Armenia, an analysis of the genotypic and phenotypic DST are essential to understand the resistance pattern of MDR-TB strains in order to assess the applicability of the WHO recommendation in Armenia.

The assessment of the short course treatment impact on programmatic level requires the estimation of the proportion of patients in the whole MDR-TB cohort who could benefit from the new treatment approach. In Armenia the majority of patients with MDR-TB was already being treated for TB, which is an exclusion criteria for short course regimen [16]. In addition to the identification of the resistance pattern, a retrospective analysis of the past TB treatment history as well as disease site (pulmonary vs extra-pulmonary) would be helpful for more precise calculation of the eligible patients.

The rate of failures among DR-TB in 2017 in Armenia was 15.5% and rate of died 7.7%[32]. The National statistic does not represent separately the rate of successful (cured and completed) and poor (died, failed and defaulted) outcomes for MDR-TB. Before implementation of the program the preliminary estimation of the poor and successful outcome rates of those MDR TB patients who could have been eligible for the short course regimen are needed to understand the potential of the short treatment approach. In addition, evaluation of the factors which are likewise associated with the poor outcome should be performed to predict the course of treatment after implementation of the new regimen. According to the several publication, the factors which are associated with the poor outcome are human immunodeficiency virus (HIV), cavitary disease, body mass index (BMI) less than 18.5 kg/m2, diabetes, previous TB treatment, being male and substance abuse, resistance pattern and number of effective drugs used in the regimen [38–41].

In Armenia, Medecins Sans Frontieres (MSF) in collaboration with National Tuberculosis Program (NTP) has provided care for patients with DR-TB since 2005. The DR-TB program catchment area includes Yerevan and 5 regions (Ararat, Armavir, Shirak, Lori and Kotayk) where about 77.5 % of the country's population residing. MSF maintains a robust clinical and socio-demographic dataset on its DR-TB patients.

In order to understand the applicability and potential for the use of shorter MDR-TB treatment regimen within the Armenia, we propose to perform an eligibility assessment based on the retrospective data collected by NTP/MSF. The preliminary analysis of the poor outcome rates and factors associated with them is also needed to understand the potential of the short course treatment regimen. The results of the project is essential for stakeholders on making decision about implementation of the new MDR-TB treatment approach in Armenia.

1.4 Aims and Research Questions of the Study

The aim of the study will be to assess the eligibility of patients for the short course MDR TB treatment regimen in Armenia.

The primary objective of the study will be:

- To estimate the proportion of patients who are eligible for the short course MDR-TB treatment regimen.

The secondary objectives of the study will be:

- To estimate the proportion of RR patients who are susceptible to FQ and SLID
- To estimate the proportion of RR patients having additional to FQ and SLID resistance
- To estimate the proportion of the patients with inhA mutation

- To estimate the agreement for detection of FQ and SLID resistance between phenotypic and genotypic DST methods
- To estimate the poor outcome rate of the patients who could be eligible for short course regimen and started conventional MDR-TB treatment
- To estimate the factors associated with the poor outcomes

2 METHODS

2.1 Study design

We propose conducting a secondary analysis of the existing MSF Koch6 database. The retrospective cohort study design was chosen the most appropriate for this investigation, since all the Koch6 database includes all the needed data elements and spans from 2005- 2015.

2.2 Study population

The target population for the study will be adults (18+ years old) with drug resistant TB residing in Yerevan and 5 regions covered by MSF (Armavir, Ararat, Shirak, Lori, Kotayk), who were enrolled in the NTP/MSF DR-TB program from January 2005 till end of December of 2015.

2.3 Data sources

Data source will be Koch6 (Koch 6 software, Medecins Sans Frontieres [MSF], Paris, France) de-identified electronic database designed by MSF for programmatic management of the DR-TB patients, and contains information about MDR TB patients who started treatment in the MSF catchment area in Armenia from 2005-to 2015. A unique number is assigned to a patent who was enrolled in the DR-TB program therefore database includes only de-identified information. The database contains information regarding socio-demographic characteristics, history of substance

abuse, TB treatment history, clinical and radiographic findings, bacteriological results, resistance pattern, comorbidities, treatment regimen, treatment changes and interruptions, drug side effects, vital signs, adherence and treatment outcome.

2.4 Statistical analysis

Descriptive statistic will be used to estimate the distribution of the major variables among RR cohort (see Table 1). Continuous variables will summarized as median and inter-quartile range (IQR). Categorical variables will be summarized as counts and percentages.

In order to estimate the proportion of eligible patients for short course MDR-TB treatment regimen the number of patients with pulmonary, newly diagnosed RR tuberculosis who are susceptible to FQ, SLID, Z, E and Eto/Pto (N4) will be divided by the number of patients with RR TB diagnosed from 2005 till 2015 (N1) (Figure 1). To evaluate the proportion of RR patients who are resistant to FQ, SLID or have additional to FQ and SLID resistance among eligible cases, the number of patients with resistance to certain drug will be divided by the number of patients having new pulmonary TB (Table 2). The prevalence of inhA mutation among newly diagnosed pulmonary RR TB patients will be calculated according to the Figure 2.

The successful (cured and completed) and poor (died, failed and lost to follow up) outcome rates will be assessed for the patients who were eligible for the short course treatment regimen and outcomes died, lost to follow up, failures will be compared with patients who were cured or completed. Patients with outcome not evaluated will be excluded from the comparison. Factors associated with treatment outcomes will be assessed using univariate logistic regression (Table 3, 4 and 5). All statistically significant variables in univariate analysis or epidemiologically or clinically relevant will be included in a multivariate analysis. Missing data will be not replaced

or imputed. Data will be analyzed using Stata v.14 for Windows (Stata Corp, College Station, TX, USA). A p-value 0.05 will be considered as statistically significant.

ETHICAL CONSIDERATION

The proposal will be presented to the Institutional Review Board (IRB) of the American University of Armenia for approval. No informed consent are needed since all data entered in to the database are de-identified. The National Tuberculosis Center and MSF in Armenia should give their permission to access the electronic database of DR-TB patients.

BUDGET

The budget of this project is calculated based on operational research costs. Staff will include one project manager and one statistician, since data already collected and entered. The project manager will be responsible for communication with NTP and MSF, retrieving datasets from Koch6, writing report and dissemination of the results. The statistician will be responsible for merging datasets and performing data analysis. The whole project will last 2 months and the total budget will sum up to 987.000 AMD (see Table 6).

REFERNCE LIST

1. WHO. *Global Tuberculosis Report 2017. Geneva*.; 2017. http://apps.who.int/iris/bitstream/handle/10665/259366/9789241565516-eng.pdf;jsessionid=D6FF7085B39539EB4D479137BD31B270?sequence=1. Accessed April 7, 2018.

2. WHO | Tuberculosis: Fact sheet. WHO. http://www.who.int/mediacentre/factsheets/fs104/en/. Published 2018. Accessed April 7, 2018.

3. WHO. *Global Tuberculosis Report 2015, Geneva*.; 2015. http://apps.who.int/iris/bitstream/handle/10665/191102/9789241565059_eng.pdf?sequence=1. Accessed April 7, 2018.

4. Ahuja SD, Ashkin D, Avendano M, et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients. *PLoS Med*. 2012;9(8). doi:10.1371/journal.pmed.1001300

5. Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. *Int J Tuberc Lung Dis*. 2004;8(11):1382-1384. http://www.ncbi.nlm.nih.gov/pubmed/15581210. Accessed April 7, 2018.

6. Sahakyan S, Petrosyan V, Abrahamyan L. Retrospective cohort study of lost to follow up predictors among TB patients in Yerevan, Armenia. *Eur J Public Health*. 2017;27(suppl_3). doi:10.1093/eurpub/ckx187.692

7. WHO. *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis - 2011 Update*.; 2011. http://apps.who.int/iris/bitstream/handle/10665/44597/9789241501583_eng.pdf?sequence=1. Accessed April 7, 2018.

8. Kibret KT, Moges Y, Memiah P, Biadgilign S. Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: A systematic review and meta-analysis of published studies. *Infect Dis Poverty*. 2017;6(1):1-8. doi:10.1186/s40249-016-0214-x

9. Bastos ML, Lan Z, Menzies D. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis. *Eur Respir J*. 2017;49(3):1600803. doi:10.1183/13993003.00803-2016

10. Van Deun A, Maug AKJ, Salim MAH, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2010;182(5):684-692. doi:10.1164/rccm.201001-0077OC

11. Aung KJM, Van Deun A, Declercq E, et al. Successful "9-month Bangladesh regimen" for multidrugresistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis*. 2014;18(10):1180-1187. doi:10.5588/ijtld.14.0100

12. Kuaban C, Noeske J, Rieder HL, Aït-Khaled N, Abena Foe JL, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *Int J Tuberc*

Lung Dis. 2015;19(5):517-524. doi:10.5588/ijtld.14.0535

13. Piubello A, Harouna SH, Souleymane MB, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int J Tuberc Lung Dis*. 2014;18(10):1188-1194. doi:10.5588/ijtld.13.0075

14. Trébucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *Int J Tuberc Lung Dis*. 2018;22(1):17-25. doi:10.5588/ijtld.17.0498

15. WHO. *WHO Treatment Guidelines for Drug- Resistant Tuberculosis, 2016 Update. October 2016 Revision*.; 2016. http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1. Accessed April 7, 2018.

16. WHO. *THE SHORTER MDR-TB REGIMEN*.; 2016. http://www.who.int/tb/Short_MDR_regimen_factsheet.pdf. Accessed April 7, 2018.

17. Varaine F, Rich ML, Amy Elizabeth Barrera-Cancedda P, et al. Tuberculosis Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. http://refbooks.msf.org/msf_docs/en/tuberculosis/tuberculosis_en.pdf. Accessed April 7, 2018.

18. WHO. *The Use of Molecular Line Probe Assays for the Detection of Resistance to Second-Line Anti-Tuberculosis Drugs. Policy Guidance.*; 2016. http://apps.who.int/iris/bitstream/handle/10665/246131/9789241510561-eng.pdf?sequence=1. Accessed April 7, 2018.

19. Nathavitharana RR, Cudahy PGT, Schumacher SG, Steingart KR, Pai M, Denkinger CM. Accuracy of line probe assays for the diagnosis of pulmonary and multidrug-resistant tuberculosis: A systematic review and meta-analysis. *Eur Respir J*. 2017;49(1). doi:10.1183/13993003.01075-2016

20. World Health Organization. *WHO Guideline: The Use of Molecular Line Probe Assays for the Detection of Resistance to Isoniazid and Rifampicin*.; 2016. http://apps.who.int/iris/bitstream/handle/10665/250586/9789241511261-eng.pdf?sequence=1. Accessed April 7, 2018.

21. Morlock GP, Metchock B, Sikes D, Crawford JT, Cooksey RC. ethA, inhA, and katG loci of ethionamide-resistant clinical Mycobacterium tuberculosis isolates. *Antimicrob Agents Chemother*. 2003;47(12):3799-3805. doi:10.1128/AAC.47.12.3799-3805.2003

22. Vilchèze C, Jacobs JR. WR. Resistance to Isoniazid and Ethionamide in Mycobacterium tuberculosis: Genes, Mutations, and Causalities. *Microbiol Spectr*. 2014;2(4):1-21. doi:10.1128/microbiolspec.MGM2-0014-2013

23. Seifert M, Catanzaro D, Catanzaro A, Rodwell TC. Genetic mutations associated with isoniazid resistance in Mycobacterium tuberculosis: A systematic review. *PLoS One*. 2015;10(3):1-13. doi:10.1371/journal.pone.0119628

24. Javaid A, Ahmad N, Khan AH, Shaheen Z. Applicability of the World Health Organization recommended new shorter regimen in a multidrug-resistant tuberculosis high

burden country. *Eur Respir J*. 2017;49(1):1601967. doi:10.1183/13993003.01967-2016

25. Dalcolmo M, Gayoso R, Sotgiu G, et al. Resistance profile of drugs composing the "shorter" regimen for multidrug-resistant tuberculosis in Brazil, 2000–2015. *Eur Respir J*. 2017;49(4):1602309. doi:10.1183/13993003.02309-2016

26. Van Der Werf MJ, Hollo V, Ködmön C, Dara M, Catchpole M. Eligibility for shorter treatment of multidrug-resistant tuberculosis in the European Union. *Eur Respir J*. 2017;49(3):10-13. doi:10.1183/13993003.01992-2016

27. Chee CBE, KhinMar KW, Sng LH, et al. The shorter multidrug-resistant tuberculosis treatment regimen in Singapore: Are patients from South-East Asia eligible? *Eur Respir J*. 2017;50(2). doi:10.1183/13993003.00753-2017

28. Lange C, Duarte R, Fréchet-Jachym M, et al. Limited Benefit of the New Shorter Multidrug-Resistant Tuberculosis Regimen in Europe. *Am J Respir Crit Care Med*. 2016;194(8):1029-1031. doi:10.1164/rccm.201606-1097LE

29. Falzon D, Gandhi N, Migliori GB, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. *Eur Respir J*. 2013;42(1):156-168. doi:10.1183/09031936.00134712

30. Achar J. Potential of short-course regimens. Presented at the 5th TB Symposium – Eastern Europe and Central Asia. In: 22-23 March, 2016, Tbilisi, Georgia; 2016. http://www.tb-symposium.org/documents/en/5_IMPROVING_PATIENTS_EXPERIENCE/patient_association_groups.pdf. Accessed April 7, 2018.

31. WHO. Tuberculosis country profile: Armenia. 2016. https://extranet.who.int/sree/Reports?op=Replet&name=/WHO_HQ_Reports/G2/PROD/EXT/TBCountryProfile&ISO2=AM&outtype=html. Published 2016. Accessed April 7, 2018.

32. National Tuberculosis Program A. *2017 Թվ ական ի ն Հ այ աս տան ի Հ ան ր ապե տո ւ թյ ան Տ ո ւ բ ե ր կ ո ւ լ ո զ ի Հ ամ աճ ար ակ աբ ան ակ ան Ի ր ավ ի ճ ակ ը*.; 2017. http://www.ntp.am/wp-content/uploads/2018/02/2017_S Բ_վ ի ճ ակ ագ ր ակ ան _վ ե ր լ ո ւ ծ ո ւ թյ ո ւ ն .pdf. Accessed April 7, 2018.

33. Հ Հ Առ ո ղ ջ ապահ ո ւ թյ ան Նախար ար ո ւ թյ ո ւ ն . Մե թ ո դ ակ ան Ո ւ ղ ե ց ո ւ յ ց ,,Հ այ աս տան ո ւ մ Տ ո ւ բ ե ր կ ո ւ լ ո զ ի Կառ ավ ար մ ան ,,.; 2016. http://www.ntp.am/wp-content/uploads/2017/01/TB UXECUYC.pdf. Accessed April 7, 2018.

34. Sanchez-Padilla E, Marquer C, Kalon S, et al. Reasons for defaulting from drug-resistant tuberculosis treatment in Armenia: A quantitative and qualitative study. *Int J Tuberc Lung Dis*. 2014;18(2):160-167. doi:10.5588/ijtld.13.0369

35. Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Zumla A, Migliori GB. WHO recommendations on shorter treatment of multidrug-resistant tuberculosis. *Lancet*. 2016;387(10037):2486-2487. doi:10.1016/S0140-6736(16)30729-2

36. Regimen SMT, Mtbdr TH. No Title. 2016;194(8):1028-1029.

37. Laniado-Laborín R. The WHO Shorter MDR-TB Regimen. Who Will Benefit With It? *J Respir Res*. 2016;2(4):1-10. doi:10.17554/j.issn.2412-2424.2016.02.23

38. Kurbatova E V., Taylor A, Gammino VM, et al. Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. *Tuberculosis*. 2012;92(5):397-403. doi:10.1016/j.tube.2012.06.003

39. Tang S, Tan S, Yao L, et al. Risk factors for poor treatment outcomes in patients with MDR-TB and XDR-TB in China: Retrospective multi-center investigation. *PLoS One*. 2013;8(12):1-8. doi:10.1371/journal.pone.0082943

40. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: A systematic review and meta-analysis. *PLoS One*. 2009;4(9). doi:10.1371/journal.pone.0006914

41. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. *Eur Respir J*. 2009;33(5):1085-1094. doi:10.1183/09031936.00155708

TABLES

Table 1. Study variables

Variable Name	Type	Measure
Address/region categorical	Categorical	• Yerevan • Ararat • Armavir • Kotayk • Lori • Shirak
Gender	Binary	• Female • Male
Age	Continuos	• Numbers
BMI	Continuos	• Numbers
Pregnant	Binary	• Yes • No
Diabetes	Binary	• Yes • No
HIV positive	Binary	• Yes • No
Substance abuse	Binary	• Yes • No
Previous DR TB treatment	Binary	• Yes • No
Previous DS-TB treatment	Binary	• Yes • No
Date of current MDR-TB diagnosis	Continuos	• Year
Site of disease	Binary	• Pulmonary • Extra-pulmonary
Extent of disease	Binary	• Unilateral • Bilateral
Presence of cavity	Binary	• Yes • No
Resistance to rifampicin based on the genotypic DST	Binary	• Yes • No
Resistance to rifampicin based on phenotypic DST	Binary	• Yes • No
Presence of inhA mutation on the genotypic DST	Binary	• Yes • No
Presence of katG mutation on the genotypic DST	Binary	• Yes • No

Resistance to FQ based on the genotypic DST	Binary	• Yes • No
Resistance to SLID based on the genotypic DST	Binary	• Yes • No
Resistance to FQ based the phenotypic DST	Binary	• Yes • No
Resistance to SLID based on the phenotypic DST	Binary	• Yes • No
Resistance to ethio/prothionamide based on the phenotypic DST	Binary	• Yes • No
Resistance to ethambutol based on the phenotypic DST yes no	Binary	• Yes • No
Resistance to pyrazinamide based on the phenotypic DST	Binary	• Yes • No
Drug used in the treatment regimen	Categorical	• Pyrazinamide • Ethambutol • Amikacin • Kanamycin • Capreomycin • Ofloxacin • Levofloxacin • Moxifloxacin • Ethionamide/Prothionamide • Cycloserine • Clofazemine • Para-aminosalycisil acid • Amoxicillin/clavulonate • Imipenem/Cilastatin
MDR-TB treatment outcome	Categorical	• Cured • Completed • Failed • Lost to follow up • Died • Unknown
Time to lost to follow up	Continuous	• Months
Adverse events during treatment	String	• Free text

Table 2. Resistance to the drugs in short regimen

Anti-TB drugs	**Resistance** n/N3 (%) (95%CI)
Fluoroquinolones	
Second line injectable drugs	
Pyrazinamide	
Ethambutol	
Ethio/Prothionamide	

Table 3: Univariate logistic regression analysis for predictive variables of outcome died

	OR	**95%CI**	**p-value**
Gender			
Female	Ref		
Male			
BMI			
≥18.5 kg/m^2	Ref		
<18.5 kg/m^2			
Substance abuse			
No	Ref		
Yes			
Diabetes			
No	Ref		
Yes			
Cavitary disease			
No	Ref		
Yes			
HIV			
No	Ref		
Yes			
Number of effective drugs in the regimen	Ref		
≥5			
<5			

Table 4. Univariate logistic regression analysis for predictive variables of outcome failed

	OR	**95%CI**	**p-value**
Gender Female Male	Ref		
BMI ≥18.5 kg/m^2 <18.5 kg/m^2	Ref		
Substance abuse No Yes	Ref		
Diabetes No Yes	Ref		
Cavitary disease No Yes	Ref		
HIV No Yes	Ref		
Number of effective drugs in the regimen ≥5 <5	Ref		

Table 5. Univariate logistic regression analysis for predictive variables of outcome failed

	OR	**95%CI**	**p-value**
Gender Female Male	Ref		
BMI ≥18.5 kg/m^2 <18.5 kg/m^2	Ref		
Substance abuse No Yes	Ref		
Diabetes No Yes	Ref		

Cavitary disease No Yes	Ref		
HIV No Yes	Ref		
Number of effective drugs in the regimen ≥5 <5	Ref		

Table 6. Budget

Cost Type	**Unit cost in AMD**	**Number of Units**	**Total**
Staff/Statistician	200.000	2	400.000
Staff/Project manager	250.000	2	500.000
Transport/Taxi	100	200	20.000
Office supplies	20.000	1	20.000
Unforeseen expenses (5% of the total budget)	47.000	1	47.000
Total			**987.000**

FIGURES

Figure 1. Assessment of eligibility

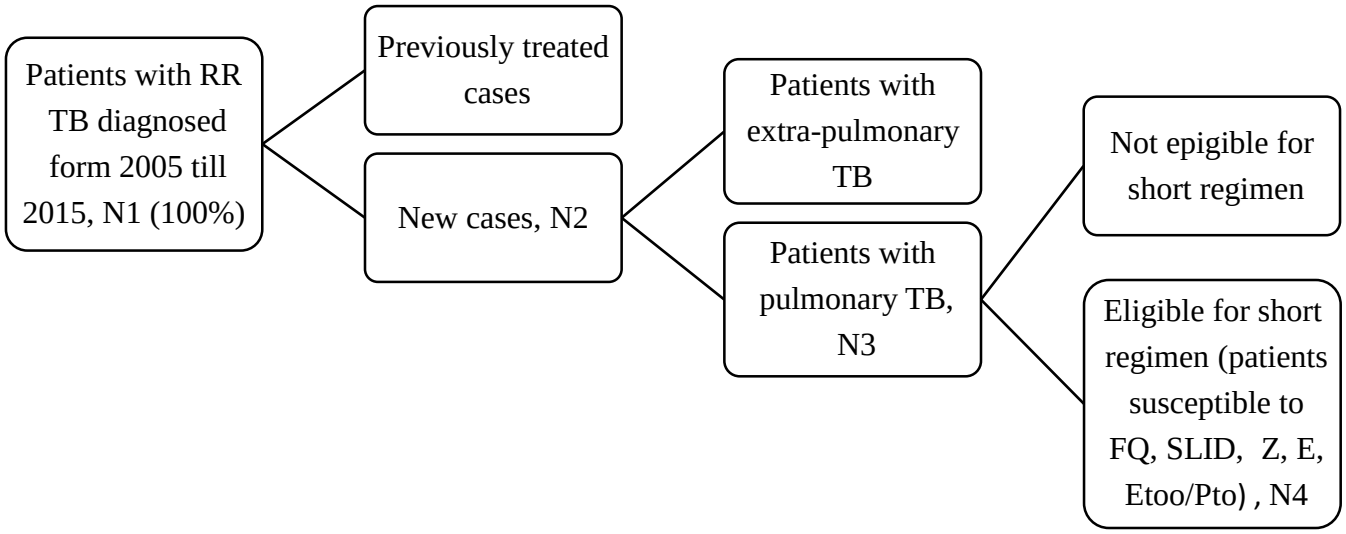

Figure 2: Prevalence of inhA mutation among new pulmonary RR TB cases