JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

EECA Regional SORT IT

9-12 months short treatment for patients with MDR-TB increases treatment success in Kyrgyzstan

Elena Zhdanova[1,2], Olga Goncharova[1,2], Hayk Davtyan[3], Sevak Alaverdyan[3], Aelita Sargsyan[3], Anthony D Harries[4,5], Bolot Maykanaev[1]

[1] *National Center of Phthisiology, Ministry of Health, Bishkek, Kyrgyz Republic*
[2] *I.K. Akhunbaev Kyrgyz State Medical Academy, Bishkek, Kyrgyz Republic*
[3] *Tuberculosis Research and Prevention Center, Yerevan, Armenia*
[4] *International Union against Tuberculosis and Lung Disease, Paris, France*
[5] *London School of Hygiene and Tropical Medicine, London, United Kingdom*

Abstract

Introduction: MDR/RR-TB is a growing problem in Kyrgyzstan. In 2005, the country introduced standard or individualized treatment for 20-24 months. Because of poor treatment outcomes, in 2017 a short treatment with strict eligibility criteria was introduced. The aim of this study was to compare characteristics and treatment outcomes of MDR/RR-TB patients receiving short (9-12 months) treatment in 2017 with those receiving standard or individualized (20-24 months) treatment in 2016/2017.

Methodology: A comparative cohort study using routine programmatic data. Characteristics, sputum culture conversion and treatment outcomes were compared between those on short treatment with those on standard/individualized treatment using the chi-square test, crude and adjusted risk ratios (RR and aRR).

Results: The study included 274, 82 and 132 patients on standard, individualized and short treatment, respectively. There were more females, fewer migrants/homeless and unemployed and more new TB patients on short treatment compared with the other two groups. A favorable outcome (cure and treatment completed) was significantly higher in short treatment patients (83%) compared with those on standard (50%) or individualized (59%) treatment ($p < 0.001$). There was higher 1-month sputum culture conversion with short treatment (35%) compared with the other two groups (19% and 24%, $p < 0.05$). Short treatment (aRR 1.6, 1.4-1.8), female gender (aRR 1.2, 1.1-1.4), not being homeless (aRR 12.9, 4.5-17.3) and having new TB (aRR 1.3, 1.0-1.5) were independently associated with a favorable outcome.

Conclusions: The treatment success was higher in selected MDR-TB patients given short treatment in Kyrgyzstan: this regimen should be scaled-up to all MDR-TB patients.

Key words: SORT IT; MDR/RR-TB; short treatment; standard or individualized treatment; treatment outcomes; sputum culture conversion.

J Infect Dev Ctries 2021; 15(9.1):66S-74S. doi:10.3855/jidc.13757

(Received 24 August 2020 – Accepted 18 March 2021)

Introduction

Drug-resistant tuberculosis has become a major public health concern in many countries. Multidrug-resistant TB (MDR-TB – resistance to at least isoniazid and rifampicin) is one of the most concerning types of drug-resistant TB because of its prevalence and associated difficulties with diagnosis and effective treatment.

The prevalence of MDR-TB has been gradually increasing in the last 10-15 years, especially in the countries of the former Soviet Union including Kyrgyzstan [1]. The diagnosis of MDR-TB has improved with the advent and scale-up of the automated molecular diagnostic assay, Xpert MTB/RIF, which enables a rapid diagnosis of both TB and rifampicin resistance within 2 hours [2,3]. Because most rifampicin-mono-resistant TB is also resistant to isoniazid, rifampicin-mono-resistant TB (RR-TB) is routinely regarded and treated as MDR-TB.

In 2018, it was estimated that 484,000 persons globally had MDR/RR-TB, with 78% having resistance to both rifampicin and isoniazid and the remainder resistance to rifampicin alone [1]. Traditionally, MDR/RR-TB has required a standardized "conventional" treatment for up to 24 months with second line anti-TB drugs which are less effective, more costly and associated with more adverse events compared with first-line drugs. Under programmatic conditions, successful treatment outcomes with these

conventional regimens have been poor and have been achieved in just over half of all patients [1].

The development and use of shorter MDR-TB treatment regimens, however, has given grounds for optimism. Under operational research conditions in Bangladesh, Vietnam and various African countries, short course regimens of between 9-12 months have shown successful treatment outcomes >75% with low or even zero relapse rates [4-8]. These findings from observational studies were confirmed in 2019 in a multicenter randomized controlled trial showing successful treatment outcomes >75% and non-inferiority between short 9-12 months treatment course and standard 24-months treatment [9]. Based on operational research evidence, in 2016 the World Health Organization (WHO) recommended a short treatment regimen of 9-12 months for MDR-TB, provided patients had not been treated with second-line drugs and/or had resistance to fluoroquinolones and second-line injectable agents excluded [10]. Based on accumulating evidence of the frequency, severity and often permanency of ototoxicity from second-line injectable agents [11], the WHO has further recommended that fully oral short treatment regimens be considered [12, 13].

In 2018, Kyrgyzstan in Central Asia notified 7,585 cases of TB [1]. It has a growing problem with DR-TB, with a prevalence of MDR-TB of 29% in new patients and 68% in previously treated patients (overall, the region has the highest resistance rates among previously treated patients which are above 50%) [1]. The proportion of MDR-TB cases with resistance to a fluoroquinolone and a second-line injectable agent among all MDR-TB cases in 2012 was 8% [1]. Conventional standardized MDR-TB treatment for 20-24 months was first started in 2005. Individualized treatment regimens of the same duration could also be given based on culture and drug susceptibility status. Short MDR-TB treatment of 9-12 months was introduced in 2017 for patients meeting eligibility criteria as outlined by the WHO [10]. The proportion of successful treatment outcomes using the conventional standard regimen in a recent cohort was reported to be 53% [1], which makes the 90% treatment success rate target of WHO practically unachievable.

There is no published data from Kyrgyzstan on how treatment outcomes of short treatment compare with those obtained with standard treatment or individualized treatment. This information is of importance to the National TB Program which is also engaged in discussions with WHO about the possibility of piloting and scaling-up fully oral short MDR-TB treatment from 2020 onwards. The aim of the current study therefore was to assess and compare characteristics, sputum culture conversion and treatment outcomes of MDR/RR-TB patients who received short (9-12 months) treatment in 2017 with those who received standard (20-24 months) treatment in 2016 or individualized (20-24 months) treatment in 2016 / 2017 in Kyrgyzstan.

Methodology

Study design

This was a comparative cohort study using routine programmatic data.

Study Setting

General setting

The Republic of Kyrgyzstan is a landlocked country in Central Asia bordering Kazakhstan, Tajikistan, Uzbekistan and China. The population of the country is about 6.3 million with 36% living in urban areas. According to the World Bank, Kyrgyzstan is a lower-middle income country with GDP of USD$1281 per capita [14].

MDR/RR-TB care in Kyrgyzstan

The Directly Observed Treatment Short Course (DOTS) strategy recommended by WHO has been implemented in Kyrgyzstan since 1998. MDR-TB treatment under routine conditions in accordance with WHO guidelines was initiated in 2005.

Inpatient treatment of TB is organized in seven regional and two city TB centers while outpatient treatment is managed in facilities called “TB cabinets”. There are 61 TB cabinets located in primary health care (PHC) units across the country. The laboratory network is composed of a single National Reference Laboratory (NRL) which performs drug sensitivity testing (DST) and 6 regional laboratories which perform sputum smear microscopy, of which 24 have installed GeneXpert machines (Cepheid, Sunnyvale, CA, USA) for rapid bacteriological diagnosis of TB along with information about RR-TB. Sputum collected at regional sites (or in some cases a traditional culture of *Mycobacterium tuberculosis*) is transported to the NRL for further processing and DST utilizing various methodologies including line probe assays.

Diagnosis of DR-TB is made through Xpert MTB/RIF and Genotype MTBDRplus (Hain Lifesciences GmbH, Nehren, Germany). Specimen transportation is carried out every other week to the nearest Xpert MTB/RIF laboratory with large numbers of samples arriving at the same time. The reports of the

Xpert MTB/RIF results are transported back to the centers using the same car that transports the specimens, all of which results in delayed deliveries by up to two weeks. Treatment is initiated and managed by "Medical Conciliums" (MCs) composed of experienced medical professionals located at regional TB centers. The MCs discuss treatment options on a case-by-case basis and prescribe appropriate treatment regimens (standard, individualized or short treatment) to the patients. The three different treatment regimens and their durations of treatment are shown in Table 1**.** Patients are followed up during treatment at the nearest TB center or cabinet by clinical assessment and by monitoring sputum culture conversion for the first six months and at the end of treatment. There is a patient support programme to ensure proper adherence to treatment. This includes transportation cost coverage and monthly provision of food and hygiene product packages for patients. Final treatment outcomes are reported in line with WHO guidelines [15].

Pilot project for short course treatment

Starting from 2017, short treatment for MDR/RR-TB was prescribed to patients meeting eligibility criteria in accordance with WHO recommendations [10]. Exclusion criteria included: i) MDR/RR-TB cases with resistance to second-line drugs (presented in Table 1) used in the short treatment regimen; ii) contact with patients who had documented resistance to second-line drugs; iii) cases who received treatment with second-line drugs for more than one month; iv) a history of allergy or intolerance to the medications used in the regimen; v) disseminated types of pulmonary TB; vi) a combination of pulmonary and extra-pulmonary types of TB; vii) TB of the nervous system, spondylitis or any form of extra-pulmonary TB with HIV co-infection; viii) pregnancy; and ix) absence of antiretroviral therapy (ART) for HIV co-infected cases.

Study population

All MDR/RR-TB patients who were enrolled in the pilot program for short treatment in 2017 as well as those given standard treatment or individualized treatment in 2016/2017 in Kyrgyzstan were included in the study.

Data sources and variables

Routine programmatic data from the National TB Programme registers and from the pilot project registers for short treatment were used for data collection which took place between February and May 2020.

Data variables included: treatment regimen; registration date; gender (male, female); age in years; TB type (pulmonary or extra-pulmonary); TB category (new or previously treated); sputum smear result (smear-positive, smear-negative, smear not done); *Mycobacterium tuberculosis* culture result (positive, negative, not done); drug susceptibility testing (DST) results if available; treatment start date; sputum culture conversion (Yes, No); date of sputum culture conversion; final treatment outcome (cured, treatment completed, treatment failed, died, lost to follow up and not evaluated) as defined by WHO [15]; and date of final treatment outcome. A favorable outcome was defined as cured and treatment completed and an unfavorable outcome as death, failure and lost to follow-up.

Statistical analysis

Data were analyzed and presented using descriptive statistics with frequencies and proportions. Baseline demographic, social and clinical characteristics, sputum culture conversion and final treatment outcomes between those on the short treatment regimen were compared with those on standard treatment and those on individualized treatment with the use of Pearson's χ^2 test (Chi square). Baseline characteristics and the different treatment regimens were assessed and compared with respect to a favorable outcome (cured and treatment completed) and results presented as risk ratios (RR) with 95% confidence intervals (95% CI). All these factors were included in an adjusted binomial regression model and presented as adjusted RR with 95% CI. Levels of significance were set at $p < 0.05$.

Ethics

The study was approved by the national ethics committee ("Preventive Medicine" ethical board at Ministry of Health, Kyrgyzstan) as well as the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease, Paris, France. As this study was a retrospective analysis of anonymized program data with no patient identifiers, informed patient consent was not required.

Results

Altogether, 274 patients were treated with standard treatment, 82 with individualized treatment and 132 with short treatment. Demographic and social characteristics of patients on the three different treatment regimens are shown in Table 2.

Table 1. Treatment regimens for MDR/RR-TB patients in Kyrgyzstan, 2016-2017.

Regimens	Standard treatment	Individualized treatment	Short treatment
Duration	20-24 months	20-24 months	9-12 months
Duration of intensive (injectable) phase	8 months	8 months (if injectable agents are used)	4-6 months (based on culture conversion)
Medications in intensive phase	Capreomycin or Kanamycin; Levofloxacin or Moxifloxacin; Prothionamide; Cycloserine; Pyrazinamide; Para-aminosalicylic acid	Medications are selected individually for each case based on drug-resistance patterns and tolerance	Isoniazid high dose (600mg); Capreomycin or Kanamycin; Moxifloxacin or Levofloxacin; Prothionamide; Pyrazinamide; Ethambutol; Clofazimine
Medications removed in continuation phase	Capreomycin or Kanamycin (injectable)	Injectable agent (if used)	Isoniazid high dose (600mg); Capreomycin or Kanamycin

MDR-TB: multidrug resistant tuberculosis (resistant to at least rifampicin and isoniazid); RR-TB: rifampicin-resistant tuberculosis.

Table 2. Demographic and social characteristics of patients treated for MDR-TB according to standard treatment, individualized treatment and short treatment in Kyrgyzstan, 2016-2017.

Characteristics	Standard treatment		Individualized treatment		Short treatment	
	n	%	n	%	n	%
Gender						
Male	173	63.1[a]	42	51.2	68	51.5
Female	101	36.9[a]	40	48.8	64	48.5
Age group in years						
0-14	0		2	2.4	2	1.5
5-14	0		3	3.7	7	5.3
15 and above	274	100[a]	77	93.9	123	93.2
Migrant						
Yes	148	54.0[a]	42	51.2	56	42.4
No	126	46.0[a]	40	48.8	76	57.6
Homeless						
Yes	36	13.1[a]	0	0	4	3.0
No	238	86.9[a]	82	100	128	97.0
Employed						
Yes	84	30.7[a]	36	43.9	72	54.5
No	190	69.3[a]	46	56.1	60	45.5
Total	**274**	**100**	**82**	**100**	**132**	**100**

MDR-TB: multidrug resistant tuberculosis (resistant to at least rifampicin and isoniazid); [a]: $P<0.05$ standard treatment compared with short treatment.

Table 3. Clinical characteristics of patients treated for MDR-TB according to standard treatment, individualized treatment and short treatment in Kyrgyzstan, 2016-2017.

Characteristics	Standard treatment		Individualized treatment		Short treatment	
	n	%	n	%	n	%
Type of TB						
Smear-positive	154	56.2	56	68.3	84	63.6
Smear-negative	98	35.8	20	24.4	36	27.3
EPTB	22	8.0	6	7.3	12	9.1
***MTB* Culture**						
Positive	201	73.4	68	82.9	100	75.8
Negative	0	0	0	0	0	0
Not determined	73	26.6	14	17.1	32	24.2
Category of TB						
Previously treated	130	47.4[a]	36	43.9[b]	16	12.1
New	144	52.6[a]	46	56.1[b]	116	87.9
Type of Resistance						
RR-TB	50	18.2	6	7.3	16	12.1
MDR-TB	224	81.8	72	87.8	116	87.9
Not determined	0	0	4	4.9	0	0
HIV status						
Negative	244	89.1	76	92.7	118	89.4
Positive	20	7.3	6	7.3	0	0
Not determined	10	3.6	0	0	14	10.6
Total	**274**	**100**	**82**	**100**	**132**	**100**

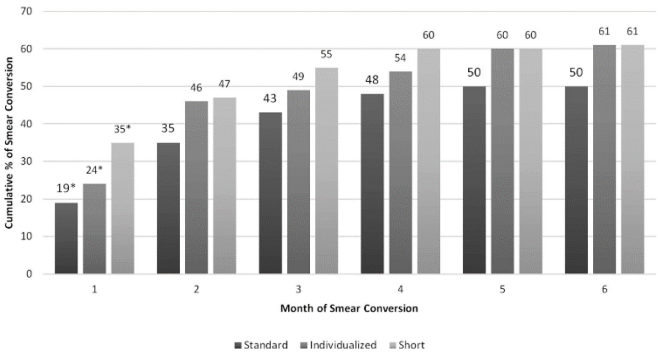
[a] $P<0.05$ standard treatment compared with short treatment; [b] $P<0.05$ individualized treatment compared with short treatment; EPTB: extrapulmonary tuberculosis; MDR-TB: multidrug resistant tuberculosis (resistant to at least rifampicin and isoniazid); RR-TB: rifampicin-resistant tuberculosis; TB: tuberculosis.

For those on short treatment, there were significantly more females, fewer adults, fewer migrants, fewer homeless persons and more employed persons compared with those on standard treatment. There were no significant differences in characteristics between those on short and individualized treatment.

Clinical characteristics of patients on the three different treatment regimens are shown in Table 3. Altogether, between the three cohorts, there were more patients with smear-positive TB, with new TB, with confirmed MDR-TB and with negative HIV status. New TB was significantly more common in those on short treatment compared with those on the longer treatments, but other characteristics were similar between the treatment groups.

Cumulative monthly rates of sputum culture conversion over the first six months of treatment for the three different treatment regimens are shown in Figure 1. In the first month, significantly more patients on short treatment had sputum culture conversion compared with the two longer regimens, but thereafter cumulative sputum conversion rates were similar. Final treatment outcomes are shown in Table 4. Significantly more patients on short treatment had a favorable outcome compared with the other two treatment groups. Characteristics associated with a favorable outcome are shown in Table 5. After adjusting for confounders, the key characteristics associated with a favorable outcome were short treatment, being female, not being homeless and having new TB.

Figure 1. Cumulative sputum conversion rate during the first 6-months of treatment in patients with MDR-TB according to standard treatment, individualized treatment and short treatment in Kyrgyzstan, 2016-2017.



* Statistically significant differences between short treatment and the other two longer treatments ($p<0.05$).

Discussion

This is the first study in Kyrgyzstan to assess outcomes of patients with MDR/RR-TB treated with 9-12 months short treatment compared with 20-24 months standard or individualized treatment. The findings were encouraging.

Over 80% of patients treated with a short regimen had a favorable outcome which was significantly better than patients treated with a standard or individualized regimen in whom favorable outcomes were observed in less than 60%. After adjusting for baseline characteristics, short treatment was still independently associated with a more favorable outcome. Mortality and treatment failure rates, as well as losses to follow-up were all lower in patients on short treatment. Sputum culture conversion was higher in those on short treatment at the end of the first month but thereafter rates of culture conversion were similar between the three groups for up to six months of follow-up. We speculate that this might be due to the high-dose isoniazid in the short treatment regimen: isoniazid is an effective rapidly acting bactericidal drug which can retain activity in patients with isoniazid resistance due to *inhA* or *katG* 315 Thr resistance mutations [16].

Baseline characteristics between the three treatment groups were slightly different with more females, fewer migrants, fewer homeless and unemployed persons and more patients with new TB on the short treatment regimen. Being female and not being homeless were

Table 4. Treatment outcomes of patients with MDR-TB according to standard treatment, individualized treatment and short treatment in Kyrgyzstan, 2016-2017.

Characteristics	Standard treatment		Individualized treatment		Short treatment	
	n	%	n	%	n	%
Favorable outcome	137	50[a]	48	58.5[b]	110	83.3
Cured	89	32.5[a]	29	35.4[b]	74	56.1
Treatment completed	48	17.5[a]	19	23.2	36	27.3
Unfavorable outcome	137	50[a]	34	41.5[b]	22	16.7
Died	36	13.1[a]	4	4.9	0	0
Failed treatment	8	2.9	12	14.6[a]	4	3.0
Lost to follow-up	93	33.9[a]	18	22.0	18	13.6
Total patients treated	**274**	**100**	**82**	**100**	**132**	**100**

MDR-TB: multidrug resistant tuberculosis (resistant to at least rifampicin and isoniazid); [a] $P<0.05$ standard treatment compared with short treatment; [b] $P<0.05$ individualized treatment compared with short treatment.

also independent factors associated with better treatment outcomes. Previous studies have found better outcomes in females compared with males [17,18], the latter frequently showing socio-economic or behavioral characteristics that lead to poor access to health services and unreliable follow-up while on treatment. The association between homelessness and TB, and particularly poor treatment success, has long been recognized with homelessness often associated with older age, injecting drug use and HIV infection [19,20].

New TB was an independent factor for having a favorable outcome, so this might have biased the short treatment patients towards better outcomes. Previous studies in Eastern Europe have shown similar findings with better treatment outcomes in those with new compared with previously treated TB [17,21,22]. This is not surprising as those with previous TB may have residual restrictive or obstructive lung disease consequent upon their initial TB or more severe acquired drug resistance [23], and this may adversely affect their prognosis if they get a further episode of TB.

Finally, the criteria that excluded patients from the short regimen, but not the longer regimens, may also have biased the short treatment group towards a better

Table 5. Characteristics associated with a favorable treatment outcome in patients with MDR-TB according to standard treatment, individualized treatment and short treatment in Kyrgyzstan, 2016-2017.

Characteristics	Total	Favorable outcome		RR	95% CI	*P* value	aRR	95% CI	*P* value
		n	%						
Treatment regimen									
Standard	274	137	50	Ref	-	-	-	-	-
Individualized	82	48	59	1.17	0.92-1.40	0.176	1.08	0.81-1.35	0.552
Short	132	110	83	1.67	1.50-1.79	<0.001	1.60	1.38-1.77	<0.001
Gender									
Male	283	149	53	Ref	-	-	-	-	-
Female	205	146	71	1.35	1.19-1.49	<0.001	1.24	1.05-1.42	0.015
Age group in years									
0-4	4	2	50	Ref	-	-	-	-	-
5-14	10	8	80	1.60	0.48-1.97	0.277	1.38	0.01-2.00	1.000
15 and above	474	285	60	1.20	0.30-1.85	0.683	0.68	0.00-2.00	0.993
Migrant									
Yes	246	153	62	Ref	-	-	-	-	-
No	242	142	59	0.94	0.80-1.08	0.427	1.13	0.61-1.47	0.601
Homeless									
Yes	40	2	5	Ref	-	-	-	-	-
No	448	293	65	13.1	7.25-18.4	<0.001	12.94	4.53-17.30	<0.001
Employed									
Yes	192	134	70	Ref	-	-	-	-	-
No	296	161	54	0.78	0.64-0.91	<0.001	1.01	0.54-1.31	0.972
Type of TB									
Smear-positive	294	177	60	Ref	-	-	-	-	-
Smear-negative	154	90	58	0.97	0.81-1.12	0.718	1.10	0.91-1.20	0.316
EPTB	40	28	70	1.16	0.89-1.38	0.235	1.22	0.88-1.47	0.205
***MTB* Culture**									
Positive	369	224	61	Ref	-	-	-	-	-
Negative	0	0	0	NA	NA	NA	NA	NA	NA
Not determined	119	71	60	0.98	0.81-1.14	0.840	1.04	0.79-1.26	0.742
Category of TB									
Previously treated	182	84	46	Ref	-	-	-	-	-
New	306	211	69	1.49	1.31-1.66	<0.001	1.28	1.04-1.50	0.024
Type of Resistance									
RR-TB	72	42	58	Ref	-	-	-	-	-
MDR-TB	412	253	61	1.05	0.84-1.24	0.622	0.85	0.54-1.15	0.36
Not determined	4	0	0	NA	NA	NA	NA	NA	NA
HIV status									
Negative	438	271	62	Ref	-	-	-	-	-
Positive	26	14	54	0.87	0.56-1.17	0.416	1.15	0.79-1.41	0.389
Not determined	24	10	42	0.67	0.37-1.00	0.054	0.52	0.22-0.94	0.024
Total treated	**488**	**295**	**60**	**-**	**-**	**-**	**-**	**-**	**-**

aRR: adjusted relative risk; CI: confidence interval; EPTB: extrapulmonary tuberculosis; Favorable outcome: cured or treatment completed; MDR-TB: multidrug resistant tuberculosis (resistant to at least rifampicin and isoniazid); NA: not applicable; Ref: reference; RR: relative risk; RR-TB: rifampicin-resistant tuberculosis; TB: tuberculosis.

outcome as patients with disseminated TB, with HIV-positive status not on ART and with resistance to other second-line drugs are known to have poorer outcomes [24].

The strengths of this study were the large nationwide sample, the implementation of the study within the national TB programme and the conduct and reporting of the study in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [25]. There were some limitations. We had some important missing information in baseline socio-demographic and clinical characteristics such as smoking, alcohol abuse and diabetes mellitus which can directly impact on treatment outcomes [20], and we had missing information regarding drug-susceptibility testing. Given the exclusion criteria, patients receiving short treatment were a highly selective group of individuals and this limits the generalizability of the findings. We also had no data to present on adverse or serious adverse events, and this is an area needing further study in the country. Additionally, many factors such as changes in TB management guidelines and diagnostic algorithms may have influenced the treatment outcomes in the different treatment cohorts and biased the results. Hence, the before and after comparison may not adequately control for secular trends.

Limitations notwithstanding, there are three important programmatic implications from this study. First, the good treatment success from short treatment should encourage Kyrgyzstan to continue with and scale up short treatment and phase out the longer standard and individualized treatment regimens. This should lead not only to better individual treatment outcomes but also to better acceptability for patients for whom 20-24 months of treatment can be mentally and physically debilitating [26]. Modelling studies have also shown that an effective 9-month treatment regimen at the population level can double treatment access and reduce MDR-TB incidence by 23% over 8 years [27], and in neighboring Uzbekistan a 9-11 month regimen can reduce MDR-TB incidence from 15.2 to 9.7 per 100,000 population and MDR-TB mortality from 3.0 to 1.7 deaths per 100,000 per year [28]. Community benefits should therefore be expected as a result of scaling up short MDR-TB treatment.

Second, more attention in terms of further research and targeted strategies should be paid to improving the current treatment outcomes in males, the homeless and those who have been previously treated, and this may help towards meeting the 90% treatment success target set in the 2016-2020 Global Plan of the Stop TB Partnership [29].

Third, the country needs to consider switching to a fully oral short treatment regimen and eliminate the injectable component of drug-resistant treatment, which is associated with too high risk of ototoxicity and poorer treatment outcomes, including death [11, 30]. The most recent WHO guidelines recommend a short all-oral bedaquiline-containing regimen of 9-12 months in eligible patients with confirmed MRD/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month and in whom resistance to fluoroquinolones has been excluded [13]. For patients who have resistance to fluoroquinolones and additional second-line drugs, other effective oral treatment regimens are being studied, one of which (bedaquiline, pretomanid and linezolid) has been shown to be effective in South Africa [31]. This is an exciting time for the treatment of drug-resistant TB with more effective and safer drugs becoming rapidly available [32]. However, these drugs come at a financial cost, and lower middle-income countries such as Kyrgyzstan will need financial support in the future to ensure they can deliver for their affected communities.

Conclusions

In Kyrgyzstan over 80% of patients with MDR/RR-TB treated with 9-12 months short treatment in 2017 had a favorable outcome (defined as cured or completed treatment) compared with less than 60% of patients treated with 20-24 months standard or individualized regimens in 2016/2017. After adjusting for confounders, independent factors associated with a favorable outcome were short treatment, being female, not being homeless and having new TB. These encouraging findings should pave the way for the scale up of short treatment in the country as well as support a move to fully oral treatment regimens for MDR-TB.

Acknowledgements

This research was conducted through the Structured Operational Research and Training Initiative (SORT IT), a global partnership coordinated by TDR (the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases). The specific SORT IT programme that led to these publications included a partnership between TDR and the European Tuberculosis Research Initiative (ERI-TB) at the WHO Regional Office for Europe, and was implemented by: the Tuberculosis Research and Prevention Center, Armenia; The Alliance for

Public Health, Ukraine; The Centre for Operational Research, The Union, France; the Operational Research Unit (LuxOR), Médecins Sans Frontières, Brussels Operational Centre, Luxembourg; Sustainable Health Systems Sierra Leone; and TDR.

Funding

TDR and partners are able to conduct their work thanks to the commitment and support of a variety of funders. These include long-term core contributors from national governments and international institutions, as well as designated funding for specific projects within current priorities. A full list of TDR donors is available on our website at: https://www.who.int/tdr/about/funding/en/

This SORT IT programme was funded by the United States Agency for International Development (USAID) and supported by implementing partners. Funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

EZ: Conception of the study; designing the protocol; data collection, analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. OG: Designing the protocol; data collection, analysis and interpretation; critically reviewing the paper and giving approval for the final version to be published. HD: Designing the protocol; data analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. SA: Data analysis and interpretation; critically reviewing the paper and giving approval for the final version to be published. AS: Writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. ADH: Designing the protocol; data analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. BM: Designing the protocol; critically reviewing the paper and giving approval for the final version to be published.

References

1. World Health Organisation (2019) Global Tuberculosis Report 2019. WHO, Geneva, Switzerland. WHO/CDS/TB/2019.15
2. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, Allen J, Tahirli R, Blakemore R, Rustomjee R, Milovic A, Jones M, O'Brien SM, Persing DH, Ruesch-Gerdes S, Gotuzzo E, Rodrigues C, Alland D, Perkins MD (2010) Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 363: 1005-1015.
3. World Health Organisation (2013) Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. WHO, Geneva Switzerland. Available: https://apps.who.int/iris/bitstream/handle/10665/112472/9789241506335_eng.pdf?sequence=1 Accessed 15 July 2020.
4. Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, Rieder HL (2010) Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 182: 684-692.
5. Piubello A, Harouna SH, Souleymane MB, Boukary I, Morou S, Daouda M, Hanki Y, Van Deun A (2014) High cure rate with standardised shor-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis 18: 1188-1194.
6. Aung KJM, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, Rieder HL (2014) Sucessful "9-month Bangladesh regimen" for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis 19: 517-525.
7. Trebucq A, Schwoebel V, Kashongwe Z, Bakayoko A, Kuaban C, Noeske J, Hassane S, Souleymane B, Piubello A, Ciza F, Fikouma V, Gasana M, Ouedraogo M, Gninafon M, Van Deun A, Cirillo DM, Koura KG, Rieder HL (2018) Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. Int J Tuberc Lung Dis 22: 17-25.
8. Anh LTN, Kumar AMV, Ramaswamy G, Htun T, Thi TTH, Nguyen GH, Quelapio M, Gebhard A, Nguyen HB, Nguyen NV (2020) High levels of treatment success and zero relapse in multidrug-resistant tuberculosis patients receiving a levofloxacin-based shorter treatment regimen in Vietnam. Trop Med Infect Dis 5: 43.
9. Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, van Deun A, Dat PT, Lan N, Master I, Mebrahtu T, Meressa D, Moodliar R, Ngubane N, Sanders K, Squire SB, Torrea G, Tsogt B, Rusen ID; STREAM Study Collaborators (2019) A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med 380: 1201-1213.
10. World Health Organisation (2016) WHO treatment guidelines for drug-resistant tuberculosis. 2016 Update. OCTOBER 2016 REVISION. WHO, Geneva, Switzerland. Available: https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1 Accessed 15 July 2020.
11. Reuter A, Tisile P, Von Delft D, Cox H, Cox V, Ditiu L, Garcia-Prats A, Koenig S, Lessem E, Nathavitharana R, Seddon JA, Stillo J, von Delft A, Furin J (2017) The devil we know: Is the use of injectable agents for the treatment of MDR-TB justified? Int J Tuberc Lung Dis 21: 1114-1126.
12. World Health Organisation (2018) Rapid Communication: Key changes to the treatment of drug-resistant tuberculosis. WHO, Geneva, Switzerland. Available: https://www.who.int/tb/publications/2019/WHO_RapidCommunicationMDRTB2019.pdf?ua=1Accessed 15 July 2020.
13. World Heath Organization (2020) WHO Consolidated guideines on tuberculosis. Module 4. Treatment. Drug-resistant tuberclosis treatment. WHO, Geneva, Switzerland. Available: https://www.who.int/publications/i/item/9789240007048 Accessed 15 July 2020.
14. The World Bank (2019) Kyrgyz Republic: Available: http://data.worldbank.org/country/kyrgyz-republic#cp_wdi Accessed 15 July 2020.
15. World Health Organization (2014) Definitions and reporting framework for tuberculosis - 2013 revision (updated December 2014 and January 2020. WHO, Geneva, Switzerland. Available: https://apps.who.int/iris/bitstream/handle/10665/79199/9789241505345_eng.pdf?sequence=1 Accessed 15 July 2020.
16. van Deun A, Decroo T, Piubello A, de Jong BC, Lynen L, Rieder HL (2018). Principles for constructing a tuberculosis

treatment regimen: the role and definition of core and companion drugs. Int J Tuberc Lung Dis 22: 239-245.
17. Kuksa L, Riekstina V, Leimane V, Ozere I, Skenders G, van den Bergh R, Kremer K, Acosta CD, Harries AD (2014) Multi- and extensively drug-resistant tuberculosis in Latvia: trends, characteristics and treatment outcomes. Public Health Action 4: S47-S53.
18. Kuchukhidze G, Kumar AMV, de Colombani P, Khogali M, Nanava U, Blumberg HM, Kempker RR (2014) Risk factors associated with loss to follow-up among multidrug-resistant tuberculosis patients in Georgia. Public Health Action 4: S41-S46.
19. Dias M, Gaio R, Sousa P, Abranches M, Gomes M, Oliveira O, Correia-Neves M, Ferreira E, Duarte R (2017) Tuberculosis among the homeless: should we change the strategy? Int J Tuberc lung Dis 21: 327-332.
20. Duarte M, Lonnroth K, Carvalho C, Lima F, Carvalho ACC, Munoz-Torrico M, Centis R (2018) Tuberculosis, social determinants and co-morbidities (including HIV). Pulmonol 24: 115-119.
21. Khaliaukin A, Kumar AMV, Skrahina A, Hurevich H, Rusovich V, Gadoev J, Falzon D, Khogali M, de Colombani P (2014) Poor treatment outcomes among multidrug-resistant tuberculosis patients in Gomel region, Republic of Belarus. Public Health Action 4: S24-S28.
22. Lytvynenko N, Cherenko S, Feschenko Y, Pogrebna M, Senko Y, Barbova A, Manzi M, Denisiuk O, Ramsay A, Zachariah R (2014) Managment of multi- and extensively drug-resistant tuberculosis in Ukraine: how well are we doing? Public Health Action 4: S67-S72.
23. Harries AD, Dlodlo RA, Brigden G, Mortimer K, Jensen P, Fujiwara PI, Castro JL, Chakaya JM (2019) Should we consider a "fourth 90" for tuberculosis? Int J Tuberc Lung Dis 23: 1253-1256.
24. Khan FA, Salim MAH, du Cross P, Casas EC, Khamraev A, Sikhondze W, Benedetti A, Bastos M, Lan Z, Jaramillo E, Falzon D, Menzies D (2017) Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. Eur Respir J 50: 1700061.
25. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP; STROBE initiative (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bull World Health Organ 85: 867-72.
26. Isaakidis P, Rangan S, Pradhan A, Ladomirska J, Reid T, Kielmann K (2013) "I cry every day": experiences of patients co-infected with HIV and multidrug-resistant tuberculosis. Trop Med Int Health 18: 1128-1133.
27. Kendall EA, Fojo AT, Dowdy DW (2017) Expected effects of adopting a 9 month regimen for multidrug-resistant tuberculosis: a population modelling analysis. Lancet Respir Med 5: 191-199.
28. Trauer JM, Achar J, Parpieva N, Khamraev A, Denholm JT, Falzon D, Jaramillo E, Mesic A, du Cros P, McBryde ES (2016) Modelling the effect of short-course multidrug-resistant tuberculosis treatment in Karakalpakstan, Uzbekistan. BMC Med 14: 187.
29. Stop TB Partnership. The paradigm shift. 2016-2020. Global Plan to end TB. WHO, Geneva Switzerland. Available: http://www.stoptb.org/assets/documents/global/plan/GlobalPlanToEndTB_TheParadigmShift_2016-2020_StopTBPartnership.pdf Accessed 19 July 2020.
30. Collaborative Group for the Meta-Analysis of Individual patient data in MDR-TB treatment-2017: Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JWC, Anderson LF, Baghaei P, Bang D, Barry PM, Bastosm ML, Behera D, et al (2018) Treatment correlates of succesful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data-meta-analysis. Lancet 392: 821-834.
31. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, Mendel CM, Egizi E, Moreira J, Timm J, McHugh TD, Wills GH, Bateson A, Hunt R, Van Niekerk C, Li M, Olugbosi M, Spigelman M; Nix-TB Trial Team (2020) Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 382: 893-902.
32. Farmer PE (2018) Better and safer treatment for multidrug-resistant tuberculosis. Lancet 392: 798-800.

Corresponding author

Elena Zhdanova, MD
National Center of Phthisiology, Ministry of Health, Bishkek, Kyrgyz Republic
Phone: +996 772 75 56 74
Email: elenazhdanova201@gmail.com

Conflict of interests: No conflict of interests is declared.