Outcomes with a shorter multidrug-resistant tuberculosis regimen from Karakalpakstan, Uzbekistan

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ABSTRACT

Background: In 2016, World Health Organization guidelines conditionally recommended standardised shorter 9–12-month regimens for multidrug-resistant (MDR) tuberculosis (TB) treatment. We conducted a prospective study of a shorter standardised MDR-TB regimen in Karakalpakstan, Uzbekistan.

Methods: Consecutive adults and children with confirmed rifampicin-resistant pulmonary TB were enrolled between September 1, 2013 and March 31, 2015; exclusions included prior treatment with second-line anti-TB drugs, and documented resistance to ofloxacin or to two second-line injectable agents. The primary outcome was recurrence-free cure at 1 year following treatment completion.

Results: Of 146 enrolled patients, 128 were included: 67 female (52.3%), median age 30.1 (interquartile range 23.8–44.4) years. At the end of treatment, 71.9% (92 out of 128) of patients achieved treatment success, with 68% (87 out of 128) achieving recurrence-free cure at 1 year following completion. Unsuccessful outcomes during treatment included 22 (17.2%) treatment failures with fluoroquinolone-resistance amplification in 8 patients (8 out of 22, 36.4%); 12 (9.4%) lost to follow-up; and 2 (1.5%) deaths. Recurrence occurred in one patient. Fourteen patients (10.9%) experienced serious adverse events. Baseline resistance to both pyrazinamide and ethambutol (adjusted OR 6.13, 95% CI 2.01; 18.63) and adherence <95% (adjusted OR 5.33, 95% CI 1.73; 16.36) were associated with unsuccessful outcome in multivariable logistic regression.

Conclusions: Overall success with a standardised shorter MDR-TB regimen was moderate with considerable treatment failure and amplification of fluoroquinolone resistance. When introducing standardised shorter regimens, baseline drug susceptibility testing and minimising missed doses are critical. High rates globally of pyrazinamide, ethambutol and ethionamide resistance raise questions of continued inclusion of these drugs in shorter regimens in the absence of drug susceptibility testing-confirmed susceptibility.

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Introduction

Rifampicin-resistant (RR) and multidrug-resistant (MDR) tuberculosis (TB) remain a public health emergency, with an estimated 484 000 cases occurring worldwide in 2018 [1]. Diagnosis and management are expensive and resource-intensive, with only 32% of the estimated globally incident MDR-TB cases able to access treatment to international standards [1]. Standard treatment is characterised by high rates of adverse events, prolonged duration, and success rates that can be as low as 60% [2]. In 2010, a single-arm cohort study in Bangladesh assessed treatment using an initial 4–6-month intensive phase with seven anti-TB drugs, followed by 5 months with four drugs, and reported 88% treatment success, with low relapse risk [3]. The STREAM trial, a phase III randomised study, demonstrated noninferiority of a similar standardised shorter regimen to long regimens recommended in World Health Organization (WHO) 2011 guidelines [4]. In 2016, WHO guidelines conditionally recommended a shorter 9–12-month MDR-TB regimen for patients meeting specific criteria, based on results of a systematic review and individual patient data meta-analysis [5, 6]. However, uncertainty remains about the regimen's effectiveness in the presence of resistance to constituent drugs, including fluoroquinolones, ethambutol, pyrazinamide and prothionamide [7–11].

Uzbekistan is a Central Asian country of more than 34 million people. It is estimated that 4700 people suffer with RR/MDR-TB each year in the country, with 15% of new cases estimated to display RR [1]. Amongst people suffering with TB in Central Asia, prevalence of RR and second-line drug resistance is high [1]. Médecins Sans Frontières (MSF) has been supporting the Ministry of Health to treat RR/MDR-TB in the Republic of Karakalpakstan, Uzbekistan, since 2003. High numbers of patients, moderate rates of success and high loss to follow-up, despite adherence to international standards, prompted investigation of innovative treatment approaches [12]. In 2013, we initiated a prospective cohort study investigating the effectiveness of a standardised shorter regimen (SSR) for treatment of RR/MDR-TB, in accordance with WHO's recommendations on operational research [13]. We hypothesised that a SSR is effective under routine programme conditions in settings with high prevalence of RR/MDR-TB and second-line drug resistance.

Methods

Study design, setting, participants

We carried out a prospective observational cohort study enrolling RR/MDR-TB patients between September 1, 2013 and March 31, 2015 in the Republic of Karakalpakstan, Uzbekistan [14]. Enrolment occurred in three districts of the country, namely Shumunay, Kegeily and Nukus City. The primary outcome was recurrence-free cure, 1 year following treatment completion. Secondary outcomes were the frequency of all adverse events, risk factors for unsuccessful outcomes (death, loss to follow-up (LTFU), treatment failure, recurrence), and the frequency of resistance amplification.

All consecutive patients with pulmonary TB and newly identified RR who did not have a history of prior treatment with second-line anti-TB drugs for more than 1 month, and for whom informed consent could be obtained, were eligible for inclusion. Children suspected as having MDR-TB, based on contact history with a source case with confirmed RR-TB, were also eligible. Exclusion criteria comprised: baseline contraindications to study medications, estimated creatinine clearance of <30 mL·min^{-1} using the Cockcroft–Gault equation, resistance to ofloxacin or two second-line injectables (kanamycin and capreomycin), extrapulmonary TB without lung involvement, osteoarticular or meningeal TB, critical illness and in the judgement of the treating physician unlikely to survive more than 1 week, and Fridericia-adjusted QT interval >500 ms [15–17]. Patients starting treatment based on genotypic drug susceptibility testing (DST) who subsequently met any exclusion criteria from phenotypic DST, were withdrawn and commenced on individualised treatment per WHO recommendations.

The treatment regimen consisted of seven drugs in the intensive phase: pyrazinamide (Z), ethambutol (E), high-dose isoniazid (H), moxifloxacin (Mfx), capreomycin (Cm) or kanamycin (Km), prothionamide (Pto) and clofazimine (Cfz) for 4 to 6 months. This was followed by a fixed 5-month continuation phase with Z, E, Mfx, Pto and Cfz, after documentation of sputum-smear microscopy conversion and at least one negative

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culture. Dosing was weight-based (supplementary appendix) and all treatment was provided under routine programmatic conditions, cost-free to the patient. Trained nurses provided directly observed therapy (DOT) in the community, 7 days per week, either at outpatient clinics or the patient's home. All patients with severe clinical conditions were hospitalised for treatment. Support for treatment adherence was provided according to national recommendations: a nurse educator provided treatment education, nutritional support for low body mass index (BMI), and psychosocial support and counselling. Adverse event monitoring was performed systematically, with daily nurse and monthly physician assessment and attention to appropriate management of side effects including use of ECG and audiometry (detailed description of the study monitoring and management of adverse events is included in the study protocol [14]). Adverse event grading was performed according to the Division of AIDS Table for Grading the Severity of Adverse Events [18]. Laboratory diagnosis was centralised and utilised Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), Genotype MTBDRplus (Hain Lifescience, Nehren, Germany), Genotype MTBDRsl version 1 (Hain Lifescience, Nehren, Germany) and MGIT960 (Becton Dickinson Diagnostic System, Sparks, MD) to confirm eligibility, culture status and drug susceptibility. DST testing was performed using BACTEC™ MGIT960 SIRE kit and the BACTEC™ MGIT960 PZA kit (Becton Dickinson Diagnostic System, Sparks, MD, USA) and published second-line DST methods and critical concentrations [19, 20]. The study reported to an independent data safety and monitoring board.

Definitions

Baseline smear, culture status and DST were defined by the availability of results from specimens submitted from 90 days prior and up to 7 days after treatment initiation. Results for baseline smear and culture were taken from the specimen submitted closest to treatment initiation. Baseline DST was defined by the most resistant result from specimens submitted during the eligible period. Patients with molecular DST test results indicating RR and fluoroquinolone sensitivity, but without phenotypic DST results during the defined baseline period, were continued on treatment and included in the analysis.

Determination of the end of treatment outcome followed WHO definitions for MDR-TB programmes, adapted for changes relevant to the shortened duration of treatment (supplementary appendix; [21]). A the end of treatment, successful outcomes were defined as cure or treatment completion, whereas LTFU, death and treatment failure were considered as unsuccessful. Whole-genome sequencing of isolates was not available, so differentiating relapse from re-infection was not possible. Recurrence was defined as any successfully treated patient who was culture-positive for RR-TB during 12 months of post-treatment follow-up.

Data collection and analysis

Data on age, sex, BMI, employment status and treatment adherence were collected for all patients. Treatment adherence assessed by DOT was determined cumulatively, based on the number of days of complete TB treatment taken, divided by the number of days of prescribed TB treatment. For patients who were LTFU, days of prescribed treatment was calculated until the last day of observed treatment. Treatment adherence <95% was classified as poor, since treatment was directly observed. Measuring treatment adherence, diabetes mellitus screening using random and fasting blood sugar levels, and screening for HIV were all mandatory in the TB programme. Baseline chest radiographs were reviewed for the presence of cavities. We estimated that 147 patients would need to be enrolled to detect recurrence-free cure of 70% with 80% power and 5% Type 1 error, assuming 15% LTFU after treatment or per protocol withdrawal [14]. Study data were collected in standardised forms and recorded using Koch6 (MSF, Paris, France) and EpiInfo version 6 (CDC, Atlanta, GA, USA). Statistical analysis was conducted in Stata v15 (StataCorp, College Station, TX, USA). The cohort study is reported according to the STROBE statement (www.strobe-statement.org; completed STROBE checklist in supporting information).

Baseline characteristics were described using frequencies and percentages for categorical variables, and medians and interquartile ranges (IQRs) for continuous variables. Descriptive analysis was performed using Chi-squared tests for categorical variables, and Wilcoxon rank-sum tests for continuous variables. Logistic regression was used to estimate adjusted odds ratios and p-values for potential predictors of unsuccessful outcome at 1 year following treatment completion, excluding patients without confirmed rifampicin resistance and fluoroquinolone sensitivity. Model construction used a manual forward step-wise approach. Age was included *a priori* in the final model, with additional variables added sequentially based on likelihood-ratio testing of model fit.

Ethical approval

The study was approved by the Ethics Review Boards of MSF and Uzbekistan. All adults included in the study provided written informed consent; for children <16 years old, written consent was obtained from their parent or guardian and the children also provided assent.

Results

Descriptive data

Overall, 128 patients were included for the primary outcome analysis (figure 1); 67 patients were female (52.3%); median age was 30.1 years (IQR 23.8–44.4); median BMI was 19.5 kg·m^{-2} (IQR 17.8–21.5), with 35.2% (45 out of 128) patients having a BMI⩽18.5 kg·m^{-2}. Diabetes mellitus was detected in 7% (9 out of 128) and no people living with HIV were identified on screening. Cavities on baseline chest radiography were found in 42% of patients (50 out of 119; table 1).
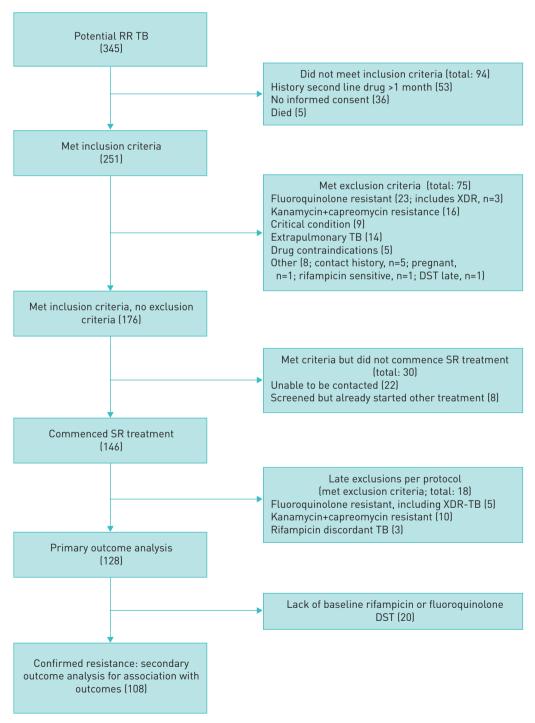
FIGURE 1 Patient enrolment flow diagram. RR: rifampicin-resistant; TB: tuberculosis; XDR: extensively drug-resistant; DST: drug susceptibility testing; SR: study regimen.

Characteristic	Total	Unsuccessful	Successful
Total	128 (100%)	41 (32.0%)	87 (68.0%)
Age years median (IQR)	30.1 (23.8–44.4)	30.0 (24.1–52.6)	30.1 (23.7–40.3)
Age			
<15 years	2 (1.6%)	0 (0.0%)	2 (2.3%)
15–44 years	95 (74.2%)	26 (63.4%)	69 (79.3%)
⩾45 years	31 (24.2%)	15 (36.6%)	16 (18.4%)
Sex			
Male	61 (47.7%)	19 (46.3%)	42 (48.3%)
Female	67 (52.3%)	22 (53.7%)	45 (51.7%)
BMI			
>18.5 kg·m^{-2}	83 (64.8%)	27 (65.9%)	56 (64.4%)
⩽18.5 kg·m^{-2}	45 (35.2%)	14 (34.1%)	31 (35.6%)
Employment[#]			
Not employed	110 (89.4%)	33 (84.6%)	77 (91.7%)
Employed	13 (10.6%)	6 (15.4%)	7 (8.3%)
Diabetes mellitus			
No	119 (93.0%)	36 (87.8%)	83 (95.4%)
Yes	9 (7.0%)	5 (12.2%)	4 (4.6%)
HIV status			
Negative	107 (83.6%)	32 (78.0%)	75 (86.2%)
Positive	0	0	0
HIV status unknown	21 (16.4%)	9 (22.0%)	12 (13.8%)
Previous TB treatment			
New	88 (68.8%)	29 (70.7%)	59 (67.8%)
Previously treated	30 (23.4%)	11 (26.8%)	19 (21.8%)
Radiography findings[#]			
Noncavitary	69 (58.0%)	20 (52.6%)	49 (60.5%)
Cavitary	50 (42.0%)	18 (47.4%)	32 (39.5%)
Baseline smear status[#]			
Negative	65 (52.0%)	17 (42.5%)	48 (56.5%)
Positive	60 (48.0%)	23 (57.5%)	37 (43.5%)
Baseline culture status[#]			
Negative	30 (23.4%)	8 (19.5%)	22 (25.3%)
Positive	96 (75.0%)	32 (78.0%)	64 (73.6%)
Baseline pyrazinamide resistance[¶]			
Sensitive	23 (27.7%)	3 (9.7%)	20 (38.5%)
Resistant	60 (72.3%)	28 (90.3%)	32 (61.5%)
Missing	45	10	35
Baseline ethambutol resistance[¶]			
Sensitive	28 (32.9%)	5 (16.7%)	23 (41.8%)
Resistant	57 (67.1%)	25 (83.3%)	32 (58.2%)
Missing	43	11	32
Baseline kanamycin resistance[¶]			
Sensitive	75 (73.5%)	25 (73.5%)	50 (73.5%)
Resistant	27 (26.5%)	9 (26.5%)	18 (26.5%)
Missing	26	7	19
Baseline isoniazid-resistance mutations[¶]			
Resistant *katG*	48 (90.6%)	15 (93.8%)	33 (89.2%)
Resistant *inhA*	1 (1.9%)	0 (0%)	1 (2.7%)
Resistant *katG+inhA*	4 (7.5%)	1 (6.3%)	3 (8.1%)
Missing	75	25	50
Haemoglobin			
⩾9.0 g·dL^{-1}	57 (44.5%)	18 (43.9%)	39 (44.8%)
<9.0 g·dL^{-1}	71 (55.5%)	23 (56.1%)	48 (55.2%)
Glomerular filtration rate			
⩾90 mL·min^{-1}	108 (84.4%)	33 (80.5%)	75 (86.2%)
<90 mL·min^{-1}	20 (15.6%)	8 (19.5%)	12 (13.8%)
Initial injectable agent			
Capreomycin	110 (85.9%)	34 (82.9%)	76 (87.4%)
Kanamycin	18 (14.1%)	7 (17.1%)	11 (12.6%)

TABLE 1 Baseline characteristics and outcomes 1-year after treatment completion for a standardised shorter multidrug-resistant tuberculosis (TB) regimen

TABLE 1 Continued			
Characteristic	**Total**	**Unsuccessful**	**Successful**
Adherence			
⩾95% adherence	92 (71.9%)	20 (48.8%)	72 (82.8%)
<95% adherence	36 (28.1%)	21 (51.2%)	15 (17.2%)

IQR: interquartile range; BMI: body mass index. [#]: five patients without employment status, three patients without baseline smear, two patients without baseline culture and nine patients without baseline chest radiography results. [¶]: percentages calculated for those with results and excluding missing from the denominator.

At baseline, 48.0% (60 out of 125) of patients were sputum-smear positive. Amongst those with baseline DST results, 72.3% (60 out of 83) exhibited pyrazinamide resistance, 67.0% (57 out of 85) had ethambutol resistance and 26.5% (27 out of 102) had kanamycin resistance. Isoniazid-resistance mutations within *katG* were detected in 98.1% (52 out of 53) and *inhA* in 9.4% (5 out of 53) of patients. A high proportion of baseline DST results had not been performed, were contaminated or not recorded during the specified period (table 1). Molecular and phenotypic fluoroquinolone DST results were unavailable for 20 patients (20 out of 128, 15.6%), with only molecular DST results recorded for 5 additional patients (5 out of 128, 3.9%).

Outcomes

At the end of treatment, 71.9% (92 out of 128) patients achieved a successful outcome, with 68% (87 out of 128) achieving 1-year recurrence-free cure. Unsuccessful outcomes 1-year after treatment were: treatment failure 17.2% (22 out of 128), LTFU 12.5% (16 out of 128), death 1.5% (2 out of 128), recurrence 0.8% (1 out of 128) (table 2).

Adverse events and amplification of resistance

Adverse events were common, with 78.1% (100 out of 128) patients reporting at least one adverse event, and a total of 826 adverse events in the cohort (table 3). Half of all patients (64 out of 128) had five or more adverse events. The majority (94.4%, 780 out of 826) of adverse events were grade 1 and 2. A total of 46 grade 3 or higher adverse events were experienced by 28 (21.9%) patients. There were 15 serious adverse events (SAEs) reported from 14 (10.9%) patients (table 3). Eight SAEs were assessed as being possibly related to the drug regimen, with seven SAEs assessed as unlikely related. Amongst patients who

TABLE 2 Treatment outcomes at end of treatment and after 1-year follow-up among patients treated with a standardised shorter multidrug-resistant tuberculosis regimen		
	Outcome evaluated at end of treatment (n=128)	**Outcome evaluated 1 year after treatment completion (n=128)**
Successful outcomes		
Cure	55 (43.0%)	
Complete	37 (28.9%)	
Recurrence-free cure		87 (68.0%)
Unsuccessful outcomes		
Died	2 (1.5%)	2 (1.5%)
Treatment regimen failure, microbiological	16 (12.5%)	16 (12.5%)
Treatment regimen failure, adverse event	6 (4.7%)	6 (4.7%)
LTFU during treatment	12 (9.4%)	12 (9.4%)
LTFU after treatment		4 (3.1%)[#]
Recurrence		1 (0.8%)[¶]

LTFU: lost to follow-up. [#]: 4.3% (four out of 92) patients who successfully completed treatment were LTFU after treatment completion; [¶]: overall, one (0.8%) patient had recurrence, for a 1-year recurrence rate of 1.1 events per 100 patient-years.

TABLE 3 Adverse event (AE) grading for patients treated with a standardised shorter multidrug-resistant tuberculosis regimen

	Grade 1[#]	Grade 2[#]	Grade 3[#]	Grade 4[#]	Total[¶]
Nausea and vomiting	158 (81.0%)	34 (17.4%)	3 (1.5%)	0	195 (23.6%)
Weakness, fatigue	59 (67.8%)	22 (25.3%)	6 (6.9%)	0	87 (10.5%)
Abdominal pain	75 (86.2%)	9 (10.3%)	2 (2.2%)[+]	1 (1.1%)[+]	87 (10.5%)
Headache	56 (83.6%)	10 (14.9%)	1 (1.5%)	0	67 (8.1%)
Arthralgia	51 (85.0%)	7 (11.7%)	2 (3.3%)[+]	0	60 (7.3%)
Renal failure	36 (64.3%)	14 (25.0%)	6 (10.7%)	0	56 (6.8%)
Anorexia/constipation	36 (67.9%)	16 (30.2%)	1 (1.9%)	0	53 (6.4%)
Ototoxicity	30 (75%)	7 (17.5%)	3 (7.5%)[+]	0	40 (4.8%)
Diarrhoea	22 (78.6%)	6 (21.4%)	0	0	28 (3.4%)
Flushing/itching	20 (83.3%)	4 (16.7%)	0	0	24 (2.9%)
Hepatitis	17 (81.0%)	3 (14.3%)[+]	1 (4.8%)	0	21 (2.5%)
Rash	15 (75.0%)	3 (15.0%)	2 (10.0%)	0	20 (2.4%)
QTc prolongation	6 (40.0%)	4 (26.7%)	4 (26.7%)	1 (6.7%)	15 (1.8%)
Anaemia	6 (50.0%)	3 (25.0%)	3 (25.0%)	0	12 (1.5%)
Depression/anxiety	7 (63.6%)	1 (9.1%)	2 (19.2%)	1 (9.1%)	11 (1.3%)
Electrolyte loss	9 (100.0%)	0	0	0	9 (1.1%)
Neuromuscular weakness	5 (83.3%)	0	1 (16.7%)[+]	0	6 (0.7%)
Visual loss	3 (75.0%)	1 (25.0%)	0	0	4 (0.5%)
Cramps	2 (50.0%)	2 (50.0%)	0	0	4 (0.5%)
Gastritis	3 (75.0%)	1 (25.0%)	0	0	4 (0.5%)
Altered mental status	2 (50.0%)	0	1 (25.0%)[+]	1 (25.0%)[+]	4 (0.5%)
Skin colour change	2 (66.7%)	1 (33.3%)	0	0	3 (0.4%)
Hypothyroidism	0	3 (2.0%)	0	0	3 (0.4%)
Psychosis	3 (100.0%)	0	0	0	3 (0.4%)
Allergic reaction	1 (50.0%)	1 (50.0%)[+]	0	0	2 (0.2%)
Haemorrhage	1 (50.0%)[+]	0	0	1 (50.0%)[+]	2 (0.2%)
Infection	1 (50.0%)	0	1 (50.0%)[+]	0	2 (0.2%)
Seizure	1 (100.0%)	0	0	0	1 (0.1%)
Syncope	0	1 (100.0%)[+]	0	0	1 (0.1%)
Hypoglycaemia	0	0	1 (100.0%)[+]	0	1 (0.1%)
Diabetes mellitus	0	0	0	1 (100.0%)[+]	1 (0.1%)
Total	627 (75.9%)	153 (18.5%)	40 (4.8%)	6 (0.7%)	826 (100%)

[#]: percentage by grade for each AE; [¶]: percentage of all AEs; [+] one event of this adverse event grade was classified as a serious AE.

completed treatment, no replacement outside the same drug class occurred, and only one patient permanently ceased a drug (prothionamide) during the continuation phase.

Amongst 22 patients who suffered treatment failure, 16 (72.7%) had confirmed microbiological failure. Resistance amplification to injectables or fluoroquinolones was confirmed in eight (36.4%) patients: seven acquired resistance to ofloxacin, and one acquired resistance to both ofloxacin and capreomycin. The single patient with recurrence had confirmed MDR-TB, but not confirmed amplification of fluoroquinolone resistance.

Predictors of unsuccessful outcome
Factors associated with unsuccessful outcome at 1 year following treatment completion in univariable analysis included pyrazinamide resistance (OR 6.02; 95% CI 1.61; 22.47), ethambutol resistance (OR 3.44; 95% CI 1.14; 10.36), resistance to both pyrazinamide and ethambutol (OR 4.83; 95% CI 1.77; 13.18) and adherence less than 95% (OR 3.96; 95% CI 1.57; 9.97). Strong evidence of an association between baseline resistance to both pyrazinamide and ethambutol, and adherence <95% remained following adjustment for age (table 4).

Outcomes of late exclusions
18 patients met exclusion criteria after having commenced the SSR: 5 were fluoroquinolone-resistant, 10 were dual-injectable-resistant, and 3 were rifampicin-sensitive (table 5) detected on phenotypic DST. These patients were switched to individualised treatment according to programme guidelines. Thirteen (72.2%) patients achieved a successful outcome following treatment with a median duration of 20 months

TABLE 4 Comparison of patient characteristics with 1-year post-completion treatment response amongst all patients with confirmed baseline ofloxacin drug-susceptibility testing (108 patients)

	Total[#]	Unsuccessful[¶]	Successful[¶]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Total	108					
Age years median (IQR)		31.3 (23.9–53.5)	28.4 (23.2–39.5)	1.02 (0.99–1.05)	1.01 (0.98–1.04)	0.645
Sex						
Male	50 (46.3%)	17 (47.2%)	33 (45.8%)	Ref.		
Female	58 (53.7%)	19 (52.8%)	39 (54.2%)	0.95 (0.42–2.11)		
BMI						
>18.5 kg·m^{-2}	70 (64.8%)	25 (69.4%)	45 (62.5%)	Ref.		
⩽18.5 kg·m^{-2}	38 (35.2%)	11 (30.6%)	27 (37.5%)	0.73 (0.31–1.72)		
Employment[+]						
Not employed	93 (90.3%)	28 (82.4%)	65 (94.2%)	Ref.		
Employed	10 (9.7%)	6 (17.6%)	4 (5.8%)	3.48 (0.91–13.3)		
Diabetes mellitus						
No	99 (91.7%)	31 (86.1%)	68 (94.4%)	Ref.		
Yes	9 (8.3%)	5 (13.9%)	4 (5.6%)	2.74 (0.69–10.92)		
HIV status						
Negative	91 (84.3%)	29 (80.6%)	62 (86.1%)	Ref.		
Positive	0	0	0			
Missing	17 (15.7%)	7 (19.4%)	10 (13.9%)	1.50 (0.52–4.33)		
Previous TB treatment[+]						
New	73 (72.3%)	25 (71.4%)	48 (72.7%)	Ref.		
Previously treated	28 (27.7%)	10 (28.6%)	18 (27.3%)	1.07 (0.43–2.65)		
Radiography findings[+]						
Noncavitary	57 (57.0%)	17 (50.0%)	40 (60.6%)	Ref.		
Cavitary	43 (43.0%)	17 (50.0%)	26 (39.4%)	1.54 (0.67–3.54)		
Baseline smear status						
Negative	51 (47.7%)	15 (41.7%)	36 (50.7%)	Ref.		
Positive	56 (52.3%)	21 (58.3%)	35 (49.3%)	1.44 (0.64–3.24)		
Baseline Z resistance						
Sensitive	23 (21.3%)	3 (9.7%)	20 (39.2%)	Ref.		
Resistant	59 (54.6%)	28 (90.3%)	31 (60.8%)	6.02 (1.61–22.47)		
Missing	26 (24.1%)	5	21			
Baseline E resistance						
Sensitive	27 (25.0%)	5 (16.7%)	22 (40.7%)	Ref.		
Resistant	57 (52.8%)	25 (83.3%)	32 (59.3%)	3.44 (1.14–10.36)		
Missing	24 (22.2%)	6	18			
Baseline E and Z resistance						
No known resistance^f	38 (35.2%)	7 (19.4%)	31 (43.1%)	Ref.	Ref.	
Resistance to either E or Z detected	24 (22.2%)	5 (13.9%)	19 (26.4%)	1.17 (0.32–4.20)	1.05 (0.27–4.11)	0.950
Resistance to both Z and E	46 (42.6%)	24 (66.7%)	22 (30.6%)	4.83 (1.77–13.18)	6.13 (2.01–18.63)	0.001
Baseline kanamycin resistance						
Sensitive	75 (69.4%)	25 (73.5%)	50 (73.5%)	Ref.		
Resistant	27 (25%)	9 (26.5%)	18 (26.5%)	1.00 (0.39–2.54)		
Missing	6 (5.5%)	2	4			
Baseline isoniazid-resistance mutations						
Resistant *katG*	52 (48.2%)	17 (94.4%)	35 (89.7%)	§		
Resistant *inhA*	1 (0.9%)	0	1 (2.6%)			
Resistant *katG+inhA*	4 (3.7%)	1 (5.6%)	3 (7.7%)			
Missing	51 (47.2%)	18 (50.0%)	33 (45.8%)			
Haemoglobin						
⩾9.0 g·dL^{-1}	49 (45.4%)	15 (41.7%)	34 (47.2%)	Ref.		
<9.0 g·dL^{-1}	59 (54.6%)	21 (58.3%)	38 (52.8%)	1.25 (0.56–2.81)		
Glomerular filtration rate						
⩾90 mL·min^{-1}	90 (83.3%)	28 (77.8%)	62 (86.1%)	Ref.		
<90 mL·min^{-1}	18 (16.7%)	8 (22.2%)	10 (13.9%)	1.77 (0.63–4.97)		
Initial injectable agent						
Capreomycin	95 (88.0%)	32 (88.9%)	63 (87.5%)	Ref.		
Kanamycin	13 (12.0%)	4 (11.1%)	9 (12.5%)	0.88 (0.25–3.06)		

Continued

TABLE 4 Continued

	Total#	Unsuccessful¶	Successful¶	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Adherence						
⩾95% adherence	79 (73.2%)	19 (52.8%)	60 (83.3%)	Ref.	Ref.	0.003
<95% adherence	29 (26.8%)	17 (47.2%)	12 (16.7%)	3.96 (1.57–9.97)	5.33 (1.73–16.36)	

20 patients from the original 128 were excluded from univariable and multivariable analysis due to a lack of rifampicin and ofloxacin drug-susceptibility testing within 90 days prior to 7 days after commencement of standardised shorter regimen. Of the 108 included patients, 103 were ofloxacin-sensitive by baseline ofloxacin culture and five were sensitive by baseline Hain SL. IQR: interquartile range; BMI: body mass index; TB: tuberculosis; Z: pyrazinamide; E: ethambutol. #: column percentage; ¶: row percentage; +: missing values excluded from table as <10% of values (employment, n=5; previous TB treatment, n=7; radiography findings, n=8); §: not included in logistic regression as high proportion missing values and overwhelming majority *kat*G mutation; *f*: includes sensitive or missing results to E and Z.

(IQR 7.5–21.5). Four patients were continued on SSR, due to patient and clinician choice in discussion with the principal investigator, and achieved a successful outcome.

Discussion

In this cohort study we found that a SSR with standard-dose moxifloxacin achieved moderate success with a low recurrence rate. We showed lower successful outcomes than have been reported from other settings, with high treatment failure due to both microbiological failure with amplification of fluoroquinolone resistance, and regimen toxicity [3, 4, 22]. Diminished adherence and resistance to both pyrazinamide and ethambutol were associated with unsuccessful outcome.

Previously published studies of similar SSR regimens have reported end-of-treatment success between 81.6–89.2% [3, 22–25]. There are several potential reasons for the discrepancy between these rates and our outcomes. In our study, patients were started on capreomycin until injectable sensitivity results were known. Recently, inclusion of capreomycin in RR/MDR-TB regimens has been negatively associated with treatment response [26]. The regimen included moxifloxacin at a standard dosing of 400 mg daily, while fluoroquinolones were used at up to twice this dosage in other studies [3, 4]. It is unclear whether switching to amikacin and higher-dose moxifloxacin would improve outcomes in this region given uncertainty about circulating *eis*, *gyrA* and *gyrB* mutations. In addition, the SSR included prothionamide throughout the treatment period. We did not have phenotypic prothionamide DST available; however, only a minority of those tested had *inhA* mutations.

Treatment failure was 17.1%, which is higher than internationally reported pooled rates of 11% (10–12%) for the longer MDR-TB regimen excluding extensively drug-resistant TB [2]. The majority of treatment failure was microbiologically confirmed, while more than a quarter was due to toxicity or intolerance. LTFU with the long MDR-TB regimen has been reported to be 20% within the Karakalpakstan MDR-TB program, higher than the 9.4% LTFU rate in our study cohort [12]. LTFU may have been reduced further if prothionamide was not used for the full duration as in other cohorts [3, 22]. Our results support the STREAM trial outcomes, suggesting that while a SSR may considerably reduce LTFU, these regimens also have a higher rate of treatment failure [4]. It is concerning that more than one-third of patients with treatment failure had confirmed amplification of resistance mutations to ofloxacin.

Recently, the WHO has announced changes to the treatment of drug-resistant TB, recommending shorter, all-oral, bedaquiline-containing regimens in place of the injectable-containing SSR [27]. In the primary analysis on which the WHO guidelines decision was based, treatment success rates for the all-oral bedaquiline-containing regimen was 73% *versus* 60% in the SSR [28]. Uncertainty exists over whether those with isolates resistant to ethambutol, pyrazinamide or ethionamide should be excluded from SSR treatment, particularly in the absence of an accurate rapid diagnostic test for these drugs, or treated with alternative medications [9, 11]. The design of the seven-drug "Bangladesh" SSR regimen was such that resistance to one or two noncore drugs would still leave sufficient likely effective drugs to achieve a cure [29]. In a large meta-analysis, fluoroquinolone and pyrazinamide resistance was associated with lower treatment success [23]. In a large study in nine countries in Africa, there was no association found between pyrazinamide and ethambutol resistance and unsuccessful outcomes, likely due to the very small number of patients that failed [22]. Our study looked at combined resistance of pyrazinamide and ethambutol, which was strongly associated with unsuccessful outcomes at 1 year following treatment completion, even when accounting for other measured confounders. Number of effective drugs within a regimen has been associated with RR/MDR-TB treatment outcomes, with inclusion of drugs with

TABLE 5 Characteristics, management and outcomes of late exclusions from the standardised shorter multidrug-resistant (MDR) tuberculosis regimen

Reason for exclusion	Time on study regimen months	Follow-up time months	Regimen	Final outcome
XDR	1	26	(H) (E) Z, (Cm), Mfx, Pto, Cs, PAS, Amox-cl, Cfz	Cured
MDR (Cm/Km resistant)	1.5	30	(Z), (Cm), Mfx, Pto, Cs, PAS, Amox-cl, Cfz	Cured
MDR (Cm/Km resistant)	2	29	(Z), (Cm), Mfx, Pto, Cs, PAS, Amox-cl, Cfz	Cured
XDR	2	31	(Z), (Cm), Mfx, Pto, Cs, PAS, Amox-cl, Cfz	Cured
Drug sensitive	3	28	(H), E, Z, (Cm), Mfx, Pto, Cfz (9–11-month standardised shorter regimen)	Cured
PDR	3.5	27	R, Z, E, Lfx	Cured
XDR	5	21	(H), E, Z, (Cm), Mfx, Pto, Cfz	Cured
MDR (Cm/Km resistant)	4.5	24	(H), (E), Z, (Cm), Mfx, Pto, Cs, PAS, Amox-cl, (Cfz)	Treatment complete
MDR (Cm/Km resistant)	0.5	36	(Z), (Cm), Mfx, Pto, Cs, PAS, Amox-cl, Cfz	Treatment complete
PDR	1	36	R, Z, E, (Cm), Lfx	Treatment complete
MDR (Cm/Km resistant)	7	12	(H), (Cm), Z, E, Mfx, Pto, Cfz (9–11-month standardised shorter regimen)	Treatment complete No recurrence at 12 months; well at 6-month follow-up, smear negative, culture not performed
XDR	8	23	(H), E, Z, (Cm), Mfx, Pto, Cfz (9–11-month standardised shorter regimen)	Treatment complete No recurrence at 12 months post-treatment (sputum culture negative)
MDR (Cm/Km resistant)	8	18	(H), E, Z, (Cm), Mfx, Pto, Cfz (9–11-month standardised shorter regimen)	Treatment complete No recurrence at 12 months post-treatment (sputum culture negative)
MDR (Cm/Km resistant)	0.5	19	Z, Cm, Cs, PAS, Pto, Mfx, (Lfx) Amox-cl, Cfz	Failure on long regimen Amplified to XDR
MDR (Cm/Km resistant)	2.5	26	Z, Km, Mfx, Pto, Cs, PAS, Amox-cl, Cfz	Failure on long regimen Amplified to XDR
MDR (Cm/Km resistant)	2	30	Z, Cm, Mfx, Pto, Cs, (PAS), Amox-cl, Cfz	LTFU Clinical evidence of treatment failure
MDR (Cm/Km resistant)	3.5	24	(H), (E), Z, Cm, Mfx, Cs, PAS, Amox-cl, Cfz, (Pto)	LTFU Clinical evidence of treatment failure
MDR (Ofl resistant)	4.5	23	(H), E, Z, (Cm), Mfx, Pto, Cfz	LTFU

Drug in brackets means that drug was given during regimen but discontinued. Drugs not in brackets were given for the entire duration. XDR: extensively drug-resistant; H: isoniazid; E: ethambutol; Z: pyrazinamide; Cm: capreomycin; Mfx: moxifloxacin; Pto: prothionamide; Cs: cycloserine; PAS: para-aminosalicylic acid; Amox-cl: amoxicillin-clavulanic acid; Cfz: clofazimine; Km: kanamycin; PDR: polydrug resistant; R: rifampicin; Lfx: levofloxacin; LTFU: lost to follow-up; Ofl: ofloxacin.

resistance or without DST potentially adding cost and toxicity [30]. Given the high rates globally of pyrazinamide, ethambutol and ethionamide resistance, this raises questions of continued inclusion of these drugs in standardised shorter regimens in the absence of DST-confirmed susceptibility.

Patients who missed more than 5% of prescribed doses had greater odds of unsuccessful outcomes. The programme in Uzbekistan provided counselling and psychosocial support to patients within a decentralised system. Even with DOT, patients can still miss doses due to medication adverse events, social marginalisation, stigma, and economic consequences [31, 32]. DOT can ignore the patient's perspective, and fail to provide required support for adherence [33]. Empowerment of patients through provision of knowledge and greater control over treatment are factors that have been shown to positively influence adherence in Uzbekistan [34]. The high proportion of patients experiencing adverse events in our study may also have impacted on treatment adherence and interruptions. Programmatic implementation of shorter regimens requires close attention to the management of side effects, and infrastructure to support patient adherence. Including adherence data is important for future short-regimen studies, given our findings.

There are a number of strengths of this study. Firstly, this study was performed under programmatic conditions and therefore reflects a realistic scenario; results are likely to be generalisable to programs in similar settings. Secondly, there was careful attention to monitoring with the majority of patients having baseline DST results, attention to standardised reporting of adverse events, and follow-up for potential relapse for 1 year after treatment completion. Finally, the study has been able to provide important new data on the importance of ethambutol and pyrazinamide resistance and the impact of treatment adherence on risk of failure.

There were a number of limitations in this single-arm study. A proportion of patients did not have baseline rifampicin and pyrazinamide resistance results within 3 months of treatment beginning. Inclusion of patients with a long delay between baseline test performance and the start of treatment may have introduced survival bias, resulting in overestimation of treatment effectiveness. Additionally, partial treatment and development of undetected resistance may have resulted in over- or under-estimation of regimen performance. Missing baseline DST results may have underestimated the influence of pyrazinamide and ethambutol resistance status on treatment response. Due to missing DST results, patients with unidentified fluoroquinolone resistance may still have been included in the study. The MTBDRsl version 1 has a moderate sensitivity of 83–85%, with five patients (5 out of 146, 3.4%) enrolled subsequently shown to have fluoroquinolone resistance [35]. We therefore only included patients with DST-confirmed fluoroquinolone susceptibility in the univariable and multivariable analysis. Phenotypic DST for ethambutol, pyrazinamide and capreomycin is recognised as unreliable and, therefore, may have resulted in misclassification bias. Similarly, use of ofloxacin for fluoroquinolone DST may not have accurately assessed moxifloxacin susceptibility. Next-generation sequencing would have reduced this bias but was unavailable. Finally, the limited cohort size yields imprecision during multivariable analysis.

Updated WHO guidelines for RR/MDR-TB conditionally recommend a shorter bedaquiline-containing regimen for patients without previous exposure to second-line treatment and without fluoroquinolone resistance [25, 28]. Outcomes of substituting bedaquiline for the injectable agent when toxicity occurred are promising [36]. Further operational research using SSRs incorporating more efficacious drugs, including bedaquiline and linezolid, and removing drugs with high rates of resistance globally, including ethionamide, pyrazinamide and ethambutol, would yield important real-world results, while waiting for ongoing randomised trials to finish [37].

Conclusions

Overall treatment success of the studied SSR was moderate, with high rates of microbiological failure and amplification of fluoroquinolone resistance, as compared with other studies; the reasons for these differences are unclear. Baseline drug resistance and small reductions in adherence were associated with unsuccessful outcomes, highlighting the importance of availability of DST for drugs used within a SSR and reinforcing the importance of supporting adherence. Our results argue for the urgent need for improved SSRs in order to effectively respond to RR/MDR-TB in settings with high levels of first and second-line drug resistance.

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