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Early View

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

Authors

Philipp du Cros[1,2], Khamraev Atadjan[3], Tigay Zinaida[4], Tleubergen Abdrasuliev[5], Jane Greig[1,2], Graham Cooke[6], Krzysztof Herboczek[1], Tanya Pylypenko[5], Catherine Berry[1], Amrita Ronnachit[5], David Lister[5], Sebastian Dietrich[7], Cono Ariti[8], Hasan Safaev[9], Bern-Thomas Nyang'wa[1], Parpieva Nargiza[9], Tillashaikhov Mirzagalib[9], Jay Achar[1, 10]

1. Manson Unit, Médecins Sans Frontières, London, United Kingdom
2. Burnet Institute, Melbourne Australia
3. Supreme Council of Karakalpakstan, Nukus, Karakalpakstan
4. Ministry of Health, Nukus, Karakalpakstan
5. Médecins Sans Frontières, Nukus, Uzbekistan
6. Imperial College London, London, United Kingdom
7. Médecins Sans Frontières, Berlin, Germany
8. Cardiff University School of Medicine, Cardiff, United Kingdom
9. Specialized Scientific Practical Medical Center of phthisiology and Pulmonology, Tashkent, Uzbekistan
10. Karolinska Institutet, Stockholm, Sweden

Corresponding Author: Philipp du Cros philipp.ducros@burnet.edu.au

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Tweetable summary: A standardised shorter MDR-TB regimen observational study in Uzbekistan showed moderate success, but high treatment failure with significant risk of amplification of fluoroquinolone resistance.

Abstract:

Background:

In 2016, WHO guidelines conditionally recommended standardised shorter 9-12 month regimens for multidrug-resistant tuberculosis (MDR-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 1st September 2013 and 31st March 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 one year following treatment completion.

Results:

Of 146 enrolled, 128 patients were included: 67 female (52.3%), median age 30.1 (IQR 23.8-44.4) years. At the end of treatment, 71.9% (92/128) patients achieved treatment success, with 68% (87/128) achieving recurrence-free cure at one year following completion. Unsuccessful outcomes during treatment included 22 (17.2%) treatment failure with fluoroquinolone resistance amplification in 8 patients (8/22, 36.4%); 12 (9.4%) loss to follow-up; 2 (1.5%) deaths. Recurrence occurred in one patient. 14 patients (10.9%) experienced serious adverse events. Baseline resistance to both pyrazinamide and ethambutol (aOR 6.13, 95% CI 2.01;18.63) and adherence < 95% (aOR 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 DST-confirmed susceptibility.

Introduction

Rifampicin resistant (RR) and multidrug-resistant tuberculosis (MDR-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 five months with four drugs, and reported 88% treatment success, with low relapse risk.[3] The STREAM trial, a phase III randomised study, demonstrated non-inferiority of a similar standardised shorter regimen to long regimens recommended in World Health Organisation (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 1st September 2013 and 31st March 2015 in the Republic of Karakalpakstan, Uzbekistan.[14] Enrolment occurred in 3 districts of the country, namely Shumunay, Kegeily and Nukus City. The primary outcome was recurrence-free cure, one 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 one 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 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, critically ill and in the judgement of the treating physician unlikely to survive more than one week, and Fridericia-adjusted QT interval greater than 500 milliseconds.[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 four to six months. This was followed by a fixed five-month continuation phase with Z, E, Mfx, Pto and Cfz, after documentation of sputum smear microscopy conversion and at least one negative 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, seven days per week, either at outpatient clinics or the patient's home. All patients with severe clinical conditions were hospitalized 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 done 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, California, 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) 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 seven days post 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]). At the end of treatment, successful outcomes were defined as cure or treatment completion, while 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, gender, 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 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% loss to follow up post 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, USA). Statistical analysis was conducted in Stata v15 (StataCorp, College Station, TX, USA). The cohort study is reported according to the STROBE statement (https://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 (IQR) for continuous variables. Descriptive analysis was done 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 one 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 Médecins sans Frontières 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

128 patients were included for the primary outcome analysis (Figure 1). 67 patients were female (52.3%); median age was 30.1 (IQR 23.8-44.4); median BMI was 19.5 (IQR 17.8-21.5), with 35.2% (45/128) patients having a BMI ≤ 18.5 kg/m^2. Diabetes mellitus was detected in 7% (9/128) and no people living with HIV were identified on screening. Cavities on baseline chest x-ray were found in 42% (50/119; Table 1).

At baseline, 48.0% (60/125) of patients were sputum smear positive. Amongst those with baseline DST results, 72.3% (60/83) exhibited pyrazinamide resistance, 67.0% (57/85) ethambutol resistance and 26.5% (27/102) kanamycin resistance. Isoniazid resistance mutations within *katG* were detected in 98.1% (52/53) and *inh*A in 9.4% (5/53). 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 (20/128, 15.6%), with only molecular DST results recorded for 5 additional patients (5/128, 3.9%).

Outcomes

At the end of treatment, 71.9% (92/128) patients achieved a successful outcome, with 68% (87/128) achieving one-year recurrence-free cure. Unsuccessful outcomes one-year post treatment were:

treatment failure 17.2% (22/128), LTFU 12.5% (16/128), death 1.5% (2/128), recurrence 0.8% (1/128) (Table 2).

Adverse events and amplification of resistance

Adverse events were common, with 78.1% (100/128) patients reporting at least one adverse event, and a total of 826 adverse events in the cohort (Table 3). Half of all patients (64/128) had five or more adverse events. The majority (94.4%, 780/826) 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 completed treatment, no replacement outside the same drug class occurred, and only 1 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 one 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: five fluoroquinolone resistant, ten dual-injectable resistant, and three rifampicin sensitive (Table 5) detected on phenotypic DST. These patients were switched to individualised treatment according to programme guidelines. 13 (72.2%) patients achieved a successful outcome following treatment with a median duration of 20 months (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 400mg 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 *inh*A 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 XDR-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 in 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, WHO has announced changes to the treatment of drug resistant tuberculosis recommending shorter, all oral, bedaquiline-containing regimens in place of the injectable-containing standardised shorter regimen.[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 standardised shorter regimen.[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 non-core drugs would still leave sufficient likely effective drugs to achieve 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 one 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 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 generalizable 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 three 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 5 patients (5/146, 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][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 whilst 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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Table 1: Baseline characteristics and outcomes one-year post treatment completion for a standardised shorter MDR-TB regimen

Characteristic	Total N (%)	Unsuccessful N (%)	Successful N (%)
Total	128 (100)	41 (32.0)	87 (68.0)
Age 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)
Gender			
Male	61 (47.7)	19 (46.3)	42 (48.3)
Female	67 (52.3)	22 (53.7)	45 (51.7)
BMI			
> 18.5	83 (64.8)	27 (65.9)	56 (64.4)
≤ 18.5	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)
Xray Findings*			
Non-cavitary	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 ***kat***G	48 (90.6)	15 (93.8)	33 (89.2)
Resistant ***inh***A	1 (1.9)	0 (0)	1 (2.7)

Resistant ***kat***G+***Inh***A	4 (7.5)	1 (6.3)	3 (8.1)
Missing	75	25	50
Haemoglobin			
≥ 9.0 g/dl	57 (44.5)	18 (43.9)	39 (44.8)
< 9.0 g/dl	71 (55.5)	23 (56.1)	48 (55.2)
Glomerular filtration rate (GFR)			
GFR≥90 ml/min	108 (84.4)	33 (80.5)	75 (86.2)
GFR<90 ml/min	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)
Adherence			
≥95% adherence	92 (71.9)	20 (48.8)	72 (82.8)
<95% adherence	36 (28.1)	21 (51.2)	15 (17.2)

* 5 patients without employment status recorded; 3 patients without baseline smear; 2 patients without baseline culture; 9 patients without baseline chest X-ray results recorded.

[#] Percentages calculated for those with results and excluding missing from the denominator

Table 2: Treatment outcomes at end of treatment and after one year follow-up among patients treated with a standardised shorter MDR-TB regimen

	Outcome evaluated at end of treatment (n=128)	Outcome evaluated one year post 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 post treatment		4 (3.1%)*
Recurrence		1 (0.8%)[#]

*4.3% (4/92) patients who successfully completed treatment were LTFU post treatment completion.
#Overall, 1 (0.8%) patient had recurrence, for a one-year recurrence rate of 1.1 events per 100 patient-years

Table 3: Adverse events grading for patients treated with a standardised shorter MDR-TB regimen

	Grade 1 N (%)*	Grade 2 N (%)*	Grade 3 N (%)*	Grade 4 N (%)*	Total N (%of all AE)
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)

*% by grade for each AE

†one event of this adverse event grade was classified as a Serious Adverse Event (SAE)

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

	Total N (% of column)	Unsuccessful N (% of row)	Successful N (% of row)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	p-value
Total						
Age: median (IQR)	108	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
Gender						
Male	50 (46.3)	17 (47.2)	33 (45.8)	Reference		
Female	58 (53.7)	19 (52.8)	39 (54.2)	0.95 (0.42; 2.11)		
BMI						
> 18.5	70 (64.8)	25 (69.4)	45 (62.5)	Reference		
≤ 18.5	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)	Reference		
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)	Reference		
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)	Reference		
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)	Reference		
Previously treated	28 (27.7)	10 (28.6)	18 (27.3)	1.07 (0.43; 2.65)		
X-ray Findings*						
Non-cavitary	57 (57.0)	17 (50.0)	40 (60.6)	Reference		
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)	Reference		
Positive	56 (52.3)	21 (58.3)	35 (49.3)	1.44 (0.64; 3.24)		
Baseline Pyrazinamide resistance						
Sensitive	23 (21.3)	3 (9.7)	20 (39.2)	Reference		
Resistant	59 (54.6)	28 (90.3)	31 (60.8)	6.02 (1.61; 22.47)		
Missing	26 (24.1)	5	21			
Baseline ethambutol resistance						
Sensitive	27 (25.0)	5 (16.7)	22 (40.7)	Reference		
Resistant	57 (52.8)	25 (83.3)	32 (59.3)	3.44 (1.14; 10.36)		
Missing	24 (22.2)	6	18			

Baseline ethambutol and pyrazinamide resistance						
No known resistance[+]	38 (35.2)	7 (19.4)	31 (43.1)	Reference	Reference	
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)	Reference		
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 ***kat***G	52 (48.2)	17 (94.4)	35 (89.7)	#		
Resistant ***inh***A	1 (0.9)	0	1 (2.6)			
Resistant ***kat***G+***Inh***A	4 (3.7)	1 (5.6)	3 (7.7)			
Missing	51 (47.2)	18 (50.0)	33 (45.8)			
Haemoglobin						
≥ 9.0 g/dl	49 (45.4)	15 (41.7)	34 (47.2)	Reference		
< 9.0 g/dl	59 (54.6)	21 (58.3)	38 (52.8)	1.25 (0.56; 2.81)		
Glomerular filtration rate (GFR)						
GFR ≥90 ml/min	90 (83.3)	28 (77.8)	62 (86.1)	Reference		
GFR <90 ml/min	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)	Reference		
Kanamycin	13 (12.0)	4 (11.1)	9 (12.5)	0.88 (0.25; 3.06)		
Adherence						
≥95% adherence	79 (73.2)	19 (52.8)	60 (83.3)	Reference	Reference	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)	

Note: 20 patients from original 128 excluded from univariable and multivariable analysis due to lack of rifampicin and ofloxacin DST within 90 days prior to 7 days after commencement of SSR. Of the 108 included patients, 103 were ofloxacin sensitive by baseline ofloxacin culture and 5 were sensitive by baseline Hain SL.

*Missing values excluded from table as less than 10% of values: employment (5); previous TB treatment (7); X-ray findings (8).

#Not included in logistic regression as high proportion missing values and overwhelming majority *kat*G mutation.

[+]No known resistance includes sensitive or missing results to ethambutol and pyrazinamide

Table 5: Characteristics, management and outcomes of late exclusions from the standardised shorter MDR-TB regimen

Reason for exclusion	Months on study regimen	Months follow up	Regimen*	Final Outcome
XDR	1	26	(H) (E) Z, (Cm), Mfx, Pto, Cs, PAS, Amox-cl, Cfz	**Cured**
MDR (Cm/Km R)	1.5	30	(Z), (Cm), Mfx, Pto, Cs, PAS, Amox-cl, Cfz	**Cured**
MDR (Cm/Km R)	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 R)	4.5	24	(H), (E), Z, (Cm), Mfx, Pto, Cs, PAS, Amox-cl, (Cfz)	**Treatment Complete**
MDR (Cm/Km R)	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 R)	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 done.
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 R)	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 R)	0.5	19	Z, Cm, Cs, PAS, Pto, Mfx, (Lfx) Amox-cl, Cfz	**Failure** on long regimen amplified to XDR
MDR (Cm/Km R)	2.5	26	Z, Km, Mfx, Pto, Cs, PAS, Amox-cl, Cfz	**Failure** on long regimen Amplified to XDR
MDR (Cm/Km R)	2	30	Z, Cm, Mfx, Pto, Cs, (PAS), Amox-cl, Cfz	**LTFU** (clinical evidence of treatment failure)
MDR (Cm/Km R)	3.5	24	(H), (E), Z, Cm, Mfx, Cs, PAS, Amox-cl, Cfz, (Pto)	**LTFU** (clinical evidence of treatment failure)
MDR (Ofl R)	4.5	23	(H), E, Z, (Cm), Mfx, Pto, Cfz	**LTFU**

***** Z=pyrazinamide E=ethambutol H=isoniazid Km=kanamycin Cm=capreomycin Mfx=moxifloxacin Lfx=levofloxacin Pto=prothionamide Cfz=clofazimine Cs=cycloserine PAS=paraaminosalicylic acid Amox-cl=amoxicillin-clavulanic acid. Drug in brackets means drug given during regimen but discontinued. Drugs not in brackets given for entire duration.

Supporting Information

Supporting Information File 1: completed STROBE checklist (https://strobe-statement.org)

Online Supplementary Appendix: Supplementary Tables 1 and 2

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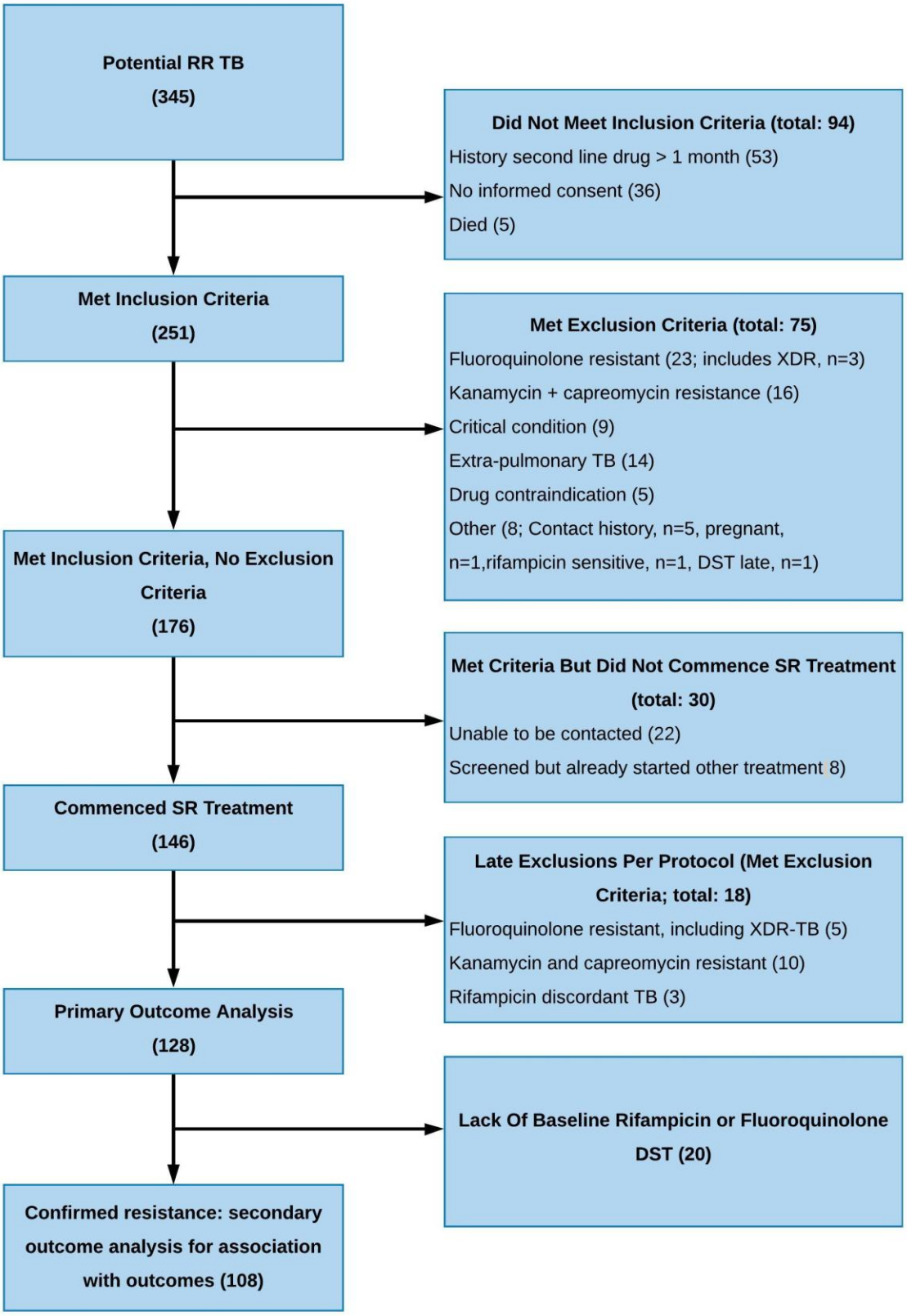
Figure 1: Patient enrolment flow diagram



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

Online Supplementary Appendix

Supplementary Table 1: Standardised shorter MDR-TB regimen and weight-based dosing

	Intensive Phase (4-6 months)	Continuation Phase (5 months)
Duration	Pyrazinamide + ethambutol + isoniazid + moxifloxacin + capreomycin (kanamycin) + prothionamide + clofazimine for at least four months and smear negative. If smear positive at four months, continue until first sputum culture is negative, maximum six months (when five-month culture result becomes available.)	Pyrazinamide + ethambutol + moxifloxacin + prothionamide + clofazimine for five months, starting after four months or first negative culture, whichever is later.
Description	Seven drugs; includes injectable & high dose isoniazid	Five drugs; only oral drugs in standard dosages.

Dosing of standardised MDR-TB drugs for adults and adolescents >25 kg

Drug	**Frequency**	**Weight range in Kg**			
		<25	**25-32**	**33-50**	**>50***
Isoniazid (H)	Once daily	15-20 mg/kg	300mg	400mg	600mg*
Pyrazinamide (Z)	Once daily	30-40 mg/kg	1000mg	1600mg	2000mg
Ethambutol (E)	Once daily	15-25 mg/kg	600mg	800mg	1200mg
Moxifloxacin (Mfx)	Once daily	7.5-10 mg/kg	400mg	400mg	400mg
Prothionamide (Pto)	Once daily [#]	15/25 mg/kg	250mg	500mg	750mg*
Clofazimine (Cfz)	Once daily	2-3 mg/kg	100mg	100mg	100mg
Capreomycin (Cm)[$]	Once daily		15mg/kg		

*For Prothionamide and isoniazid highest doses are given above 55kg

[#] Prothionamide can be given in divided doses in the intensive phase if maximum doses are used and the patient has major gastrointestinal side effects not responding to anti-emetics.

$ If sensitive to kanamycin and not taken kanamycin previously then change to kanamycin at the same dose.

Supplementary Table 2: Outcome definitions for shorter MDR-TB regimen

Outcome	Definition
Cure	Cure was defined as an MDR-TB patient who completed the treatment according to protocol and has at least four negative cultures from samples collected at least 30 days apart within the final five months of treatment. If there was a positive culture then a minimum of three consecutive negative cultures taken at least 30 days apart in the final 3 months of treatment was required for cure.
Treatment complete	Defined as an MDR-TB patient who completed treatment according to the protocol, but did not meet the definition for cure because of lack of sufficient bacteriological results.
Death	Defined as a patient who died for any reason during the course of MDR-TB treatment, or during one year's follow-up, and not already classified as having treatment failure prior to death.
Treatment failure	Failure was defined if a patient met one of three criteria: 1. Failure to culture convert: did not achieve negative culture by the end of month five, had two positive cultures during the continuation phase or one positive culture during the last three months of treatment. 2. Resistance amplification: amplification of resistance to either ofloxacin or to two injectables (capreomycin and kanamycin) on a sputum sample collected 30 days or more after the start of treatment. 3. Clinical decision due to lack of clinical response, drug toxicity or intolerance.
Lost to follow-up (LTFU) during treatment	Defined as treatment interruption for two or more consecutive months, for any reason.
LTFU post treatment	An MDR-TB patient with an outcome at the end of treatment of either treatment cure, complete, treatment outcome "other", or transfer out, who is non-contactable during the twelve-month post-treatment period (as assessed at the end of 12 +/-3 months).
Recurrence-free cure	An MDR-TB patient who meets the criteria of cured, or completed short course of treatment, and remains asymptomatic at the end of the follow-up period (one year after treatment completion).
Recurrence	An MDR-TB patient who meets the criteria of cured, or completed SR, and at any time during the follow up period (first year after treatment completion) is subsequently diagnosed with at least one sample of bacteriologically positive RR-TB by culture and DST.