Impact of pyrazinamide resistance on multidrug-resistant tuberculosis in Karakalpakstan, Uzbekistan

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── S U M M A R Y

S E T T I N G : The World Health Organization (WHO) recommends the inclusion of pyrazinamide (PZA) in treatment regimens for multidrug-resistant tuberculosis (MDR-TB) unless resistance has been confirmed.

O B J E C T I V E : To investigate the association between PZA susceptibility and MDR-TB treatment outcome among patients treated with a PZA-containing regimen and whether the duration of the intensive phase of the PZA-containing regimen affected treatment outcome.

D E S I G N : We conducted a retrospective cohort study including all eligible MDR-TB patients starting treatment in 2003–2013 in the TB programme in Karakalpakstan, Uzbekistan. PZA drug susceptibility testing (DST) using liquid culture was performed, and outcomes were classified according to the WHO 2013 definitions.

R E S U L T S : Of 2446 MDR-TB patients included, 832 (34.0%) had an available baseline PZA DST result, 612 (73.6%) of whom were PZA-resistant. We found no association between treatment success and PZA susceptibility (adjusted odds ratio [aOR] 0.86, 95%CI 0.51–1.44, $P = 0.6$) in patients treated with PZA. Furthermore, among patients with no baseline PZA DST result, no evidence was seen of an association between treatment success and PZA treatment duration (aOR 0.86, 95%CI 0.49–1.51, $P = 0.6$).

C O N C L U S I O N : Treatment of MDR-TB with a standard PZA regimen does not appear to improve treatment outcomes, regardless of PZA susceptibility or duration of treatment.

K E Y W O R D S : MDR-TB; PZA; Central Asia; treatment outcome; drug resistance

A NATIONAL SURVEY IN UZBEKISTAN in 2011 identified multidrug-resistant tuberculosis (MDR-TB; defined as tuberculosis [TB] resistant to at least rifampicin [RMP] and isoniazid [INH], the two main drugs used to treat drug-susceptible TB) in 23% of new cases and 62% of retreatment cases.[1] In Karakalpakstan, a semi-autonomous republic in Uzbekistan, pyrazinamide (PZA) resistance has been reported in 63% of MDR-TB cases.[2] A recent meta-analysis estimated that 61% of patients with MDR-TB worldwide had PZA resistance, which equates to 270 000 cases annually.[3]

The World Health Organization (WHO) recommendation is to include PZA in an MDR-TB regimen unless evidence of resistance exists.[4] PZA acts predominantly as a sterilising agent on semi-dormant mycobacteria,[5] and reduces the required treatment duration in drug-susceptible TB.[6] The main therapeutic effect in drug-susceptible TB occurs during the first 2 months of treatment,[6] but whether the same is applicable for MDR-TB is not known.[4,6–8] PZA has shown synergistic effects with other anti-tuberculosis drugs,[9–11] which has resulted in its retention in the shorter WHO-recommended MDR-TB regimen, as well as in several novel regimens under evaluation.[4,12–15] Difficulties exist with PZA drug susceptibility testing (DST) using the standard phenotypic method of the BACTEC™ MGIT™ (Mycobacteria Growth Indicator Tube) 960 System, as reports have often shown uncertain reproducibility and reliability, with testing prone to false resistance results.[16–18]

A major factor influencing the WHO recommendation is a recent meta-analysis showing an association between successful outcomes and PZA susceptibility among MDR-TB patients treated with PZA-containing regimens.[19] Three small primary studies that assessed the association of PZA resistance with treatment outcomes showed conflicting results.[20–22] No larger primary study is available, and routine PZA DST was not an inclusion criterion in the meta-analysis.[19]

The primary aim of the present study was to assess

the effect of PZA susceptibility on treatment outcome among MDR-TB patients treated with an intensive-phase regimen containing PZA within the drug-resistant TB (DR-TB) programme in Karakalpakstan, Uzbekistan. We hypothesised that treatment outcomes would be better in PZA-susceptible than PZA-resistant disease. We further assessed the effect of PZA treatment duration on outcomes among patients with PZA strains of unknown resistance or PZA-resistant strains.

STUDY POPULATION AND METHODS

Drug-resistant tuberculosis programme in Karakalpakstan

Médecins Sans Frontières (MSF) and the Ministry of Health, Uzbekistan, have been collaborating since 2003 to provide treatment for DR-TB in Karakalpakstan. Three phases, beginning in 2003, 2009 and 2012, reflect changing treatment protocols.[23–25] DST for all drugs was performed initially at the Supranational Reference Laboratory in Borstel, Germany, and later in Karakalpakstan (Appendix Table A.1*). PZA was routinely included in MDR-TB regimens, but could be stopped according to the prevailing treatment protocol at any time if PZA DST showed resistance when the results became available (under the 2003 and 2009 programmes), or after the intensive phase in PZA-resistant patients (under the 2012 programme). Data were continuously collected in an electronic database (EpiInfo™; Centers for Disease Control and Prevention, Atlanta, GA, USA and Excel® 2013; MicroSoft, Redmond, WA, USA).

Study population

Patients with records in the databases from 2003 to March 2016 were screened using three inclusion criteria: anti-tuberculosis treatment initiated between October 2003 and September 2013; microbiologically confirmed diagnosis of pulmonary MDR-TB using phenotypic DST; and documented treatment outcome. Inclusion was censored in September 2013 to allow for 30 months of treatment. A diagnostic sputum sample was defined as a sample submitted before treatment started or up to 7 days later. Exclusion criteria were as follows: no outcome defined based on the WHO 2013 reporting framework;[26] outcome 'not evaluated' according to the 2013 reporting framework; never having started an MDR-TB regimen based on WHO 2016 guidelines;[4] human immunodeficiency virus (HIV) positivity; and microbiologically confirmed extensively drug-resistant TB (XDR-TB).

* The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2018/00000022/00000005/art00014

Definitions

We calculated the number of (non-PZA) drugs to which the strain was resistant at diagnosis as the sum of resistance to INH, RMP, ethambutol (EMB), streptomycin (SM), ofloxacin (OFX), kanamycin (KM) and capreomycin (CPM). If DST results against a drug were unavailable, the strain was assumed to have unknown resistance to the drug in question. Patients with MDR-TB strains were either known to be susceptible or had unknown DST results against the second-line drugs (SLDs) OFX, KM and CPM. Pre-XDR-TB strains had confirmed resistance to either OFX or both KM and CPM. XDR-TB strains had confirmed resistance to OFX and at least one of KM and CPM.

Potentially effective drugs, excluding PZA, were each counted as 1 if DST showed susceptibility or was not performed (see Appendix). Acquired resistance from follow-up DST was taken into account in the monthly calculations; the median in the intensive phase was also estimated. DST for RMP, INH, EMB, OFX, KM, CPM, and SM was included. DST for ethionamide, para-aminosalicylic acid and cycloserine was not considered due to reports of unreliable results;[27] universal susceptibility to these agents was an inherent assumption. OFX-resistant specimens were also considered resistant to levofloxacin and moxifloxacin (MFX), as neither of these were tested. KM-resistant specimens were considered CPM-susceptible if CPM DST showed susceptibility or was unknown, and vice versa. We calculated PZA treatment through days of prescribed PZA.

We defined PZA treatment as a full PZA-containing intensive phase as PZA treatment on ⩾80% of days during the intensive phase, a partial PZA regimen as <80% of days in the intensive phase, an incomplete PZA regimen as ⩾16% but <80% of days in the intensive phase, and no PZA treatment as <16% of days in the intensive phase (equivalent to <30 days in a 6-month intensive phase). All outcomes were based on the WHO 2013 definitions.[26] A 6-month cut-off was used until the outcome 'failure due to culture conversion and culture reversion' could be declared, as this was the defined intensive phase; 'failure due to acquired resistance' could be declared at any time.[26] 'Death' and 'loss to follow-up (LTFU)' were defined according to programme decisions, unless a patient had been defined as 'failure' earlier during treatment.

Data management and analysis

We used a retrospective cohort study design and multivariable logistic regression. The primary analysis in patients receiving a full PZA-containing intensive phase with known PZA DST results was used to calculate the odds ratio (OR) of a successful outcome (cure or treatment completed) for PZA

susceptibility compared with resistance. A successful outcome was compared with unsuccessful outcomes (failure or death). We decided a priori to include the variables sex, age, previous use of first-line drugs (FLDs) RMP, INH, EMB, PZA and SM, and presence of cavities on chest X-ray, which are commonly associated with treatment outcome and are adjusted for in other studies.[19,22,28] We also included year of treatment initiation to account for unmeasured time-dependent effects. The secondary analysis assessed the association between successful outcome and duration of PZA treatment, first among patients without diagnostic PZA DST results and then among patients with PZA resistance. We restricted the analysis to patients with no PZA DST results to reduce bias,[29] as a PZA DST result could guide clinical decisions. The same analyses could not be performed in patients with PZA susceptibility at diagnosis due to low numbers.

In the descriptive analysis, we used the χ^2 test for statistical testing for categorical variables and the Wilcoxon rank-sum test for continuous variables. We used the Wald test in the crude and multivariable models, and the likelihood ratio test to assess interaction in the final multivariable logistic models. Missing values were included as unknown if >10% were missing, but were otherwise coded as missing. Data cleaning and analysis were performed using STATA v14.1 (Stata Corporation, College Station, TX, USA).

Power calculations for the main analysis using the available patient cohort ($n = 508$, outcomes ratio 3.5 [successful 396; death/failure 112], baseline proportion of success 78%) used an OR of 1.6 for successful outcome in PZA-susceptible compared with PZA-resistant MDR-TB based on a meta-analysis,[19] with a two-sided likelihood ratio test and $\alpha = 0.05$, yielding a power of 40%.

Sensitivity analyses were undertaken for the primary analysis in patients with only bacteriologically confirmed TB, receiving ⩾6 months of treatment, and only under the 2012 programme. An additional model compared treatment success with death/failure/LTFU.

The study fulfilled the exemption criteria of the MSF Ethics Review Board (ERB) for a posteriori analyses of routinely collected clinical data, and did not require MSF ERB review.[30] The study was conducted with permission from Dr S Wong (Medical Director, MSF, Operational Centre Amsterdam, The Netherlands). The study protocol was also approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee, London, UK.

RESULTS

Patient characteristics
Of a total of 2593 patients, 2446 (94.3%) were included, 832 (34.0%) of whom had a diagnostic

PZA DST result available (Appendix Figure). Table 1 shows the characteristics of the 2446 patients included. The median treatment duration was 20 months (range 0–38), and the median duration of PZA treatment was 12 months (range 0–34). Isolates were resistant to a median of four drugs at diagnosis (interquartile range 4–4); 87.2% ($n = 2132$) of the intensive phase regimens contained at least five effective drugs. A successful outcome was recorded in 59.4% of patients, 5.8% died, 11.9% failed treatment and 22.9% were lost to follow-up. A full PZA regimen was prescribed in 90.1% (1450/1610) of patients with no available PZA DST result, 90.8% (197/217) of those with PZA-susceptible strains and 76.6% (469/612) of those with PZA-resistant strains (seven patients were excluded as they had received PZA treatment only in the continuation phase). Of patients with available PZA DST results at diagnosis, 73.6% (612/832) had PZA-resistant strains.

Main results
In the primary unadjusted analysis (Table 2), we found no evidence of an association between a successful outcome and PZA susceptibility among patients receiving a full PZA-containing intensive phase (odds ratio [OR] 1.04, 95% confidence interval [CI] 0.65–1.65, $P = 0.9$). Patients with previous use of FLDs (OR 0.54, 95%CI 0.31–0.93, $P = 0.03$) and SLDs (OR 0.55, 95%CI 0.32–0.95, $P = 0.03$) had approximately 45% lower odds of success. The odds of a successful outcome decreased with increasing numbers of drugs to which the strain was resistant at diagnosis (OR 0.64, 95%CI 0.51–0.81 per resistant drug, $P < 0.001$).

In the multivariable analysis (Table 2), there was also no evidence of an association between a successful outcome and PZA susceptibility (OR 0.86, 95%CI 0.51–1.44, $P = 0.6$), after adjustment for sex, age, previous FLD use, cavities on chest X-ray at diagnosis, programme year and number of drugs to which the diagnostic strain was resistant. We found no clinically important interaction variables in the final model. Sputum smear and previous use of SLDs did not change the OR by more than 10% in the multivariable model, and were not included in the final analysis. The model comparing success with death/failure/LTFU had comparable results (Appendix Table A.2). Similar results were seen in the three sensitivity analyses (Appendix Tables A.3–A.5).

The secondary adjusted multivariable analyses showed no evidence of an association between successful outcome and a full PZA-containing intensive phase, either in patients with no available baseline PZA DST results at diagnosis (OR 0.86, 95%CI 0.49–1.51, $P = 0.6$; Appendix Table A.6) or in patients with PZA-resistant MDR-TB strains (OR 1.38, 95%CI 0.71–2.68, $P = 0.3$; Appendix Table

Table 1 Demographic and clinical characteristics of MDR-TB patients with and without a PZA DST result available and PZA-resistant and PZA-susceptible patients

	All included patients (n = 2446, 100%) n (%)	PZA DST result not available (1614/2446, 66.0) n (%)	PZA DST result available (832/2446, 34.0) n (%)	P value*	PZA-resistant (612/832, 73.6) n (%)	PZA-susceptible (220/832, 26.4) n (%)	P value*
Sex							
Female	1257 (51.4)	834 (51.7)	423 (50.8)		318 (52.0)	105 (47.7)	
Male	1189 (48.6)	780 (48.3)	409 (49.2)	0.7	294 (48.0)	115 (52.3)	0.3
Age, years, median [IQR]	30.5 [24–42]	30 [24–41]	31 [24–42]	0.2	31 [24–42]	32 [25–41.5]	0.3
Marital status							
Not married	1046 (42.8)	694 (43.0)	352 (42.3)		260 (42.5)	92 (41.8)	
Married	1400 (57.2)	920 (57.0)	480 (57.7)	0.7	352 (57.5)	128 (58.2)	0.9
Employment status							
Other†	1099 (44.9)	714 (44.2)	385 (46.3)		284 (46.4)	101 (45.9)	
Unemployed	1347 (55.1)	900 (55.8)	447 (53.7)	0.3	328 (53.6)	119 (54.1)	0.9
Body mass index, kg/m²							
Normal (⩾18.5)	1156 (47.3)	764 (47.3)	392 (47.1)		297 (48.5)	95 (43.2)	
Underweight (<18.5)	1290 (52.4)	850 (52.7)	440 (52.9)	0.9	315 (51.5)	125 (56.8)	0.2
TB programme							
2003	852 (34.8)	673 (41.7)	179 (21.5)		115 (18.8)	64 (29.1)	
2009	844 (34.5)	601 (37.2)	243 (29.2)		199 (32.5)	44 (20.0)	
2012	750 (30.7)	340 (21.1)	410 (49.3)	<0.001	298 (48.7)	112 (50.9)	<0.001
Alcohol use‡							
No	2182 (89.2)	1437 (89.0)	745 (89.5)		551 (90.0)	194 (88.2)	
Yes	264 (10.8)	177 (11.0)	87 (10.5)	0.7	61 (10.0)	26 (11.8)	0.4
Diabetes							
No	1130 (46.2)	527 (32.7)	603 (72.5)		455 (74.3)	148 (67.3)	
Yes	105 (4.3)	63 (3.9)	42 (5.0)		35 (5.7)	7 (3.2)	
Unknown	1211 (49.5)	1024 (63.4)	187 (22.5)	<0.001	122 (19.9)	65 (29.5)	0.007
Previous first-line drugs							
No	309 (12.6)	132 (8.2)	177 (21.3)		123 (20.1)	54 (24.5)	
Yes	2137 (87.4)	1482 (91.8)	655 (78.7)	<0.001	489 (79.9)	166 (75.5)	0.2
Previous second-line drugs							
No	1931 (79.1)	1270 (78.7)	661 (79.4)		489 (79.9)	172 (78.2)	
Yes	515 (21.1)	344 (21.3)	171 (20.6)	0.7	123 (20.1)	48 (21.8)	0.6
Cavities on X-ray§							
No	419 (18.6)	223 (15.6)	196 (23.6)		142 (23.4)	54 (24.8)	
Yes	1835 (81.4)	1206 (84.4)	629 (75.6)	<0.001	465 (76.6)	164 (75.2)	0.7
Sputum smear¶							
Negative	491 (21.0)	284 (18.8)	207 (25.1)		153 (25.3)	54 (24.7)	
Scanty/1+	691 (29.6)	450 (29.7)	241 (29.2)		180 (29.8)	61 (27.9)	
2+/3+	1155 (49.4)	779 (51.5)	376 (45.6)	0.001	272 (45.0)	104 (47.5)	0.8
Resistance pattern							
MDR-TB	2054 (84.0)	1368 (84.8)	780 (93.8)		500 (81.7)	186 (84.5)	
Pre-XDR-TB	392 (16.0)	246 (15.2)	146 (17.5)	0.1	112 (18.3)	34 (15.5)	0.3
Number of drugs to which diagnostic strain is resistant, median [IQR]	4 [4–4]	4 [4–4]	4 [4–5]	0.003	4 [4–5]	4 [3–4]	<0.001
Median potentially effective drugs in the intensive phase#							
2–4	314 (12.8)	151 (9.4)	163 (19.6)		112 (18.3)	51 (23.2)	
5–6	2029 (83.0)	1388 (86.0)	641 (77.0)		479 (78.3)	162 (73.6)	
7–8	103 (4.2)	75 (4.6)	28 (3.4)	<0.001	21 (3.4)	7 (3.2)	0.3
Outcome							
Success	1453 (59.4)	958 (59.4)	495 (59.5)		362 (59.2)	133 (60.5)	
Death	141 (5.8)	80 (5.0)	61 (7.3)		47 (7.7)	14 (6.4)	
Failure	291 (11.9)	196 (12.1)	95 (11.4)		73 (11.9)	22 (10.0)	
Loss to follow-up	561 (22.9)	380 (23.5)	181 (21.8)	0.09	130 (21.2)	51 (23.2)	0.8

* χ^2 test for categorical and Wilcoxon rank sum test for continuous variables.
† Including the following categories: employed, retired, student, housework, disabled.
‡ Self-reported.
§ Missing values, n = 192.
¶ Missing values, n = 109.
# Median of monthly number of potentially effective drugs, except PZA, in the intensive phase, with all drugs counted as 1.
MDR-TB = multidrug-resistant TB; PZA = pyrazinamide; DST = drug susceptibility testing; IQR = interquartile range; TB = tuberculosis; XDR = extensively drug-resistant TB.

Table 2 Crude and adjusted analyses of the effect of PZA susceptibility and other exposure variables on treatment outcome among patients treated with a full PZA-containing intensive phase

	Death/failure (112/508, 22.0)* n (%)	Success (396/508, 78.0)* n (%)	OR (95%CI)	P value[†]	aOR (95%CI)[‡]	P value[†]
Pyrazinamide						
Resistant	80 (22.2)	280 (77.8)	1.00			
Susceptible	32 (21.6)	116 (78.4)	1.04 (0.65–1.65)	0.9	0.86 (0.51–1.44)	0.6
Sex						
Female	63 (22.6)	216 (77.4)	1.00			
Male	49 (21.4)	180 (78.6)	1.07 (0.70–1.63)	0.7	1.04 (0.67–1.61)	0.9
Age, years, median [IQR]	32 [26.0–43.5]	30 [23.5–41.5]	0.99 (0.97–1.00)	0.06	0.99 (0.97–1.00)	0.07
Previous outcome						
Other	83 (20.4)	324 (79.6)	1.00			
Loss to follow-up	6 (46.2)	7 (53.8)	0.30 (0.10–0.91)	0.03		
Failure	23 (26.1)	65 (73.9)	0.72 (0.42–1.23)	0.2		
TB programme						
2003	12 (20.3)	47 (79.7)	1.00			
2009	42 (27.1)	113 (72.9)	0.69 (0.33–1.42)	0.3	0.58 (0.26–1.29)	0.2
2012	58 (19.7)	236 (80.3)	1.04 (0.52–2.08)	0.9	0.91 (0.41–1.99)	0.8
Diabetes						
No	90 (21.5)	328 (78.5)	1.00			
Yes	9 (37.5)	15 (62.5)	0.46 (0.19–1.08)	0.07		
Unknown	13 (19.7)	53 (80.3)	1.12 (0.58–2.14)	0.7		
Previous first-line drugs						
No	18 (14.8)	104 (85.2)	1.00			
Yes	94 (24.4)	292 (75.6)	0.54 (0.31—0.93)	0.03	0.55 (0.31–0.99)	0.05
Previous second-line drugs						
No	88 (20.4)	344 (79.6)	1.00			
Yes	24 (31.6)	52 (68.4)	0.55 (0.32–0.95)	0.03		
Cavities on X-ray						
No	26 (18.6)	114 (81.4)	1.00			
Yes	86 (23.4)	282 (76.6)	0.75 (0.46–1.22)	0.3	0.83 (0.49–1.39)	0.5
Sputum smear[§]						
Negative	18 (12.9)	121 (87.1)	1.00			
Scanty/1+	40 (23.5)	130 (76.5)	0.48 (0.26–0.89)	0.02		
2+/3+	53 (26.9)	144 (73.1)	0.40 (0.22–0.73)	0.002		
Resistance pattern						
MDR-TB	84 (19.6)	344 (80.4)	1.00			
Pre-XDR-TB	28 (35.0)	52 (65.0)	0.45 (0.27–0.76)	0.003		
Number of drugs to which diagnostic strain is resistant, median [IQR]	4 [4–5]	4 [4–4]	0.64 (0.51–0.81)	<0.001	0.64 (0.50–0.81)	<0.001
Median potentially effective drugs in the intensive phase[¶]						
2–4	24 (21.4)	88 (78.6)	1.00			
5–6	77 (20.5)	298 (79.5)	1.06 (0.63–1.77)	0.8		
7-8	11 (52.4)	10 (47.6)	0.25 (0.09–0.65)	0.005		
Ofloxacin treatment						
No	100 (22.3)	349 (77.7)	1.00			
Yes	12 (20.3)	47 (79.7)	1.12 (0.57–2.20)	0.7		

* Of 651 patients with outcome death/failure/cure/treatment completed, 142 excluded due to no PZA treatment in the full intensive phase, one patient excluded due to unknown X-ray result.
[†] Wald test.
[‡] Adjusted for age, sex, previous first-line drugs, cavities on X-ray, programme year and number of drugs to which strain was resistant at diagnosis.
[§] Two missing values due to unknown smear result.
[¶] Median monthly number of potentially effective drugs, except PZA, in intensive phase, with all drugs counted as 1.
PZA = pyrazinamide; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; IQR = interquartile range; TB = tuberculosis; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB.

A.6). Results were similar for patients who were treated with an incomplete PZA regimen or a full PZA-containing intensive phase compared with no PZA treatment among those with no PZA DST result and those with PZA-resistant MDR-TB strains. The same analyses using the death/failure/LTFU model had comparable results (Appendix Table A.7).

DISCUSSION

This is the largest single-site study to assess the impact of PZA resistance and treatment duration on treatment outcome in patients with MDR-TB. We found no evidence of an association between a successful outcome and PZA susceptibility among MDR-TB

patients treated with a standard full PZA-containing intensive phase of a WHO-recommended regimen in a high MDR-TB burden setting. There was no evidence of an association between a successful outcome and PZA treatment duration in the intensive phase.

The main result was unexpected, and did not support our hypothesis that a treatment regimen with a full PZA-containing intensive phase would improve treatment outcomes in patients with PZA-susceptible strains compared with PZA-resistant strains. Our results are therefore consistent with two smaller previous primary studies,[20,21] but not with the meta-analysis and another small primary study from Peru.[19,31]

Several explanations could be postulated. Even with the inclusion of all eligible patients for more than one decade, the sample size had low power for the main analysis. The retrospective and observational nature of the study contributed to an increased risk of bias. Prescription of a full PZA-containing intensive phase could also have been influenced by PZA DST results or other associated baseline characteristics, resulting in selection bias, although clear protocols were in use to routinely include PZA in MDR-TB regimens.

The main effect of PZA may be its contribution to shortening the duration of treatment,[32,33] rather than improving the outcome of an already lengthy regimen. This would also support the improved result of the shortened treatment regimen now recommended by the WHO that includes PZA.[4] Patients might also have had sufficient likely effective drugs in their regimen (87.2% had five or more likely effective drugs in the intensive phase; Table 1), rendering additional PZA redundant.[22]

The secondary analysis also showed insufficient evidence of an association between a successful outcome and a full PZA-containing intensive phase among patients with unknown PZA DST results and those with PZA-resistant MDR-TB strains. A possible explanation in the former could be the high background PZA resistance in MDR-TB patients in Karakalpakstan (73.6%; Table 1). Optimal PZA treatment duration in MDR-TB may be longer than the 2 months used for drug-susceptible TB[6] due to the lower efficacy of SLDs. This effect could be limited to patients with PZA-susceptible MDR-TB strains, but PZA-resistant strains might also benefit, due to a synergistic effect with other drugs.[34] We did not find that a different duration of PZA treatment in the intensive phase was associated with greater odds of a successful outcome, although some numbers were small (Appendix Table A.6).

The generalisability of this study would be limited to settings with low HIV prevalence and high background prevalence of SLD resistance, as in other former Soviet Union countries. Caution is needed when extrapolating the results to other settings, as background resistance patterns might be expected to change the impact of PZA treatment. Furthermore, these results refer to a background standard MDR-TB regimen, but might not be applicable to newer regimens.

The main limitation of our study was the low power for the main analysis and the risk of bias due to the observational study design. Although we used both restriction and stratification, bias cannot be accounted for in the analysis. Patients were included over a long time, and unmeasured factors could lead to residual confounding, although we adjusted for programme year. Another limitation was the determination of PZA susceptibility using MGIT, with possible false resistance, which could have affected the results. Furthermore, adjustment was made for initial PZA DST results, but not for acquired PZA resistance during treatment. Another limitation was the way in which potentially effective drugs were all counted as 1; we were unable to justify the assignment of differential weights.

Nevertheless, because this was the first large primary study with these findings, with all the associated limitations of a retrospective observational cohort, cautious consideration should be made before changing treatment protocols. A clinical trial assessing the effect of PZA inclusion and treatment duration could address this question, but might not be regarded as a priority in the current arena. An updated meta-analysis including this full cohort would be worthwhile.

CONCLUSIONS

The present study provided provocative but insufficient evidence to warrant changing PZA treatment protocols, although the evidence relating to PZA for the WHO 2016 guidelines was weak. Until further evidence supporting these findings emerges, it seems prudent to continue including PZA in standard MDR-TB regimens unless resistance is certain.

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APPENDIX

Drug groups for the treatment of multidrug-resistant tuberculosis according to World Health Organization 2016 guidelines.[26]

Group A: Levofloxacin, moxifloxacin, gatifloxacin
Group B: Amikacin, kanamycin, capreomycin (streptomycin)
Group C: Ethionamide/prothionamide, cycloserine/terizidone, linezolid, clofazimine
Group D:
  D1: Pyrazinamide, ethambutol, high-dose isoniazid
  D2: Bedaquiline, delamanid
  D3: Para-aminosalicylic acid, imipenem-cilastin, meropenem, amoxicillin-clavulanate, thioacetazone.
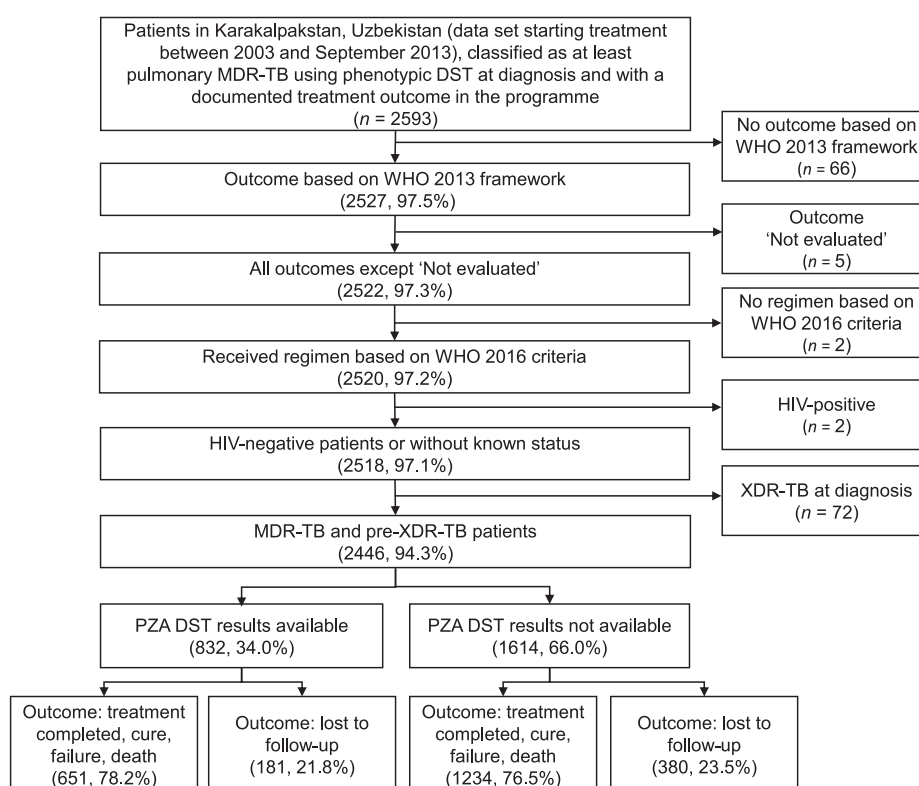

Figure Flow diagram of the inclusion and exclusion criteria of patients from the DR-TB treatment programme in Karakalpakstan, Uzbekistan. MDR-TB = multidrug-resistant tuberculosis; DST = drug susceptibility testing; WHO = World Health Organization; HIV = human immunodeficiency virus; XDR-TB = extensively drug-resistant tuberculosis; PZA = pyrazinamide.

Table A.1 Methods and location of DST used by the DR-TB programme in Karakalpakstan, Uzbekistan

DST method	Supranational Reference Laboratory, Borstel, Germany	Laboratory in Karakalpakstan
Culture-based DST, except PZA		
MGIT*	2003–2007	2007 onwards
Löwenstein-Jensen†	NA	2003 onwards
PZA DST method		
MGIT*	Routinely conducted between 2003–2006	Started November 2010, routinely conducted from 2012 onwards

*BACTEC™ MGIT™ 960 system (BD Biosciences, Sparks, MD, USA).
†Proportion method.
DST = drug susceptibility testing; DR-TB = drug-resistant tuberculosis; PZA = pyrazinamide; MGIT = Mycobacteria Growth Indicator Tube.

Table A.2   Crude and adjusted analyses of the effect of PZA susceptibility and other exposure variables on treatment outcome among patients treated with a regimen with PZA throughout the intensive phase: death/failure/LTFU model

	Death/failure/LTFU n (%)	Success n (%)	OR (95%CI)	P value*	aOR (95%CI)[†]	P value*
Pyrazinamide	267/663* (40.3)	396/663* (59.7)				
Resistant	188 (40.2)	280 (59.8)	1.00			
Susceptible	79 (40.5)	116 (59.5)	0.99 (0.70–1.39)	0.9	0.80 (0.56–1.17)	0.3
Sex						
Female	121 (35.9)	216 (64.1)	1.00			
Male	146 (44.8)	180 (55.2)	0.69 (0.51–0.94)	0.02	0.67 (0.49–0.93)	0.02
Age, years, median [IQR]	32 [25–43]	30 [23.5–41.5]	0.99 (0.98–1.00)	0.05	0.99 (0.98–1.00)	0.08
Previous outcome						
Other	206 (38.9)	324 (61.1)	1.00			
LTFU	13 (65.0)	7 (35.0)	0.34 (0.13–0.87)	0.03		
Failure	48 (42.5)	65 (57.5)	0.86 (0.57–1.30)	0.5		
TB programme						
2003	21 (30.9)	47 (69.1)	1.00			
2009	99 (46.7)	113 (53.3)	0.51 (0.29–0.91)	0.02	0.42 (0.22–0.79)	0.007
2012	147 (38.4)	236 (61.6)	0.72 (0.41–1.25)	0.3	0.61 (0.33–1.13)	0.1
Diabetes						
No	223 (40.5)	328 (59.5)	1.00			
Yes	22 (59.5)	15 (40.5)	0.46 (0.24–0.91)	0.03		
Unknown	22 (29.3)	53 (70.7)	1.12 (0.58–2.14)	0.07		
Previous first-line drugs						
No	61 (37.0)	104 (63.0)	1.00			
Yes	206 (41.4)	292 (58.6)	0.83 (0.58–1.20)	0.3	0.83 (0.57–1.22)	0.3
Previous second-line drugs						
No	227 (39.8)	344 (60.2)	1.00			
Yes	40 (43.5)	52 (56.5)	0.86 (0.55–1.34)	0.5		
Cavities on X-ray						
No	65 (36.3)	114 (63.7)	1.00			
Yes	202 (41.7)	282 (58.3)	0.80 (0.56–1.13)	0.2	0.81 (0.56–1.18)	0.3
Sputum smear[‡]						
Negative	66 (35.3)	121 (64.7)	1.00			
Scanty/1+	86 (39.8)	130 (60.2)	0.82 (0.55–1.24)	0.4		
2+/3+	114 (44.2)	144 (55.8)	0.69 (0.47–1.02)	0.06		
Resistance pattern						
MDR-TB	217 (38.7)	344 (61.3)	1.00			
Pre-XDR-TB	50 (49.0)	52 (51.0)	0.66 (0.43–1.00)	0.05		
Number of drugs to which diagnostic strain is resistant, median [IQR]	4 [4–5]	4 [4–4]	0.76 (0.63–0.91)	0.002	0.74 (0.62–0.89)	0.002
Median potentially effective drugs in the intensive phase[§]						
2–4	49 (35.8)	88 (64.2)	1.00			
5–6	205 (40.8)	298 (59.2)	0.81 (0.55–1.20)	0.3		
7–8	13 (56.5)	10 (43.5)	0.43 (0.17–1.05)	0.06		
Ofloxacin treatment						
No	246 (41.3)	349 (58.7)	1.00			
Yes	21 (30.9)	47 (69.1)	1.58 (0.92–2.71)	0.1		

* Wald test.
[†] Adjusted for age, sex, previous first-line drug, cavities on X-ray, programme year and number of drugs to which strain is resistant at diagnosis.
* Of 832 patients with PZA DST available at diagnosis, 166 were excluded because they received no PZA in the intensive phase and three due to unknown X-ray results.
[‡] Two missing values due to unknown smear result.
[§] Median number of potentially effective drugs per month, except PZA, in the intensive phase, with all drugs counted as 1.
PZA = pyrazinamide; LTFU = loss to follow-up; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; IQR = interquartile range; TB = tuberculosis; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB; DST = drug susceptibility testing.

Table A.3   Crude and adjusted analyses of the effect of PZA susceptibility on treatment outcome among patients treated with a full PZA-containing intensive phase and who had bacteriologically confirmed TB:* death/failure model

	Death/failure n (%)	Success n (%)	OR (95%CI)	P value[†]	aOR (95%CI)[‡]	P value[†]
Pyrazinamide	82/368[§] (22.3)	286/368[§] (77.7)				
Resistant	60 (22.2)	210 (77.8)	1.00			
Susceptible	22 (21.4)	76 (77.6)	0.99 (0.57–1.72)	1.0	0.87 (0.48–1.59)	0.7

* Sputum submitted between 30 days before and 7 days after starting treatment.
[†] Wald test.
[‡] Adjusted for age, sex, previous first-line drugs, cavities on X-ray, programme year and number of drugs to which strain was resistant at diagnosis.
[§] Of 579 patients with PZA DST result available and bacteriologically confirmed TB, 94 were excluded as they received no PZA in the intensive phase, and 117 due to loss to follow-up.
PZA = pyrazinamide; TB = tuberculosis; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; DST = drug susceptibility testing.

Table A.4   Crude and adjusted analyses of the effect of PZA susceptibility on treatment outcome among patients treated with a full PZA-containing intensive phase who had confirmed receipt of at least 6 months of treatment: death/failure model

	Death/failure n (%)	Success n (%)	OR (95%CI)	P value*	aOR (95%CI)[†]	P value*
Pyrazinamide	81/477[‡] (17.0)	396/477[‡] (83.0)				
Resistant	58 (17.2)	280 (82.8)	1.00			
Susceptible	23 (16.5)	116 (83.5)	1.04 (0.62–1.77)	0.9	0.97 (0.54–1.74)	0.9

* Wald test.
[†] Adjusted for age, sex, previous first-line drugs, cavities on X-ray, programme year and number of drugs to which strain was resistant at diagnosis. Model with PZA-resistant strains at diagnosis: also adjusted for previous outcome.
[‡] Of 667 patients with PZA DST result available who had at least 6 months of total treatment, 135 were excluded beacause they received no PZA in the intensive phase, 1 due to unknown X-ray results and 54 due to loss to follow-up.
PZA = pyrazinamide; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; DST = drug susceptibility testing.

Table A.5   Crude and adjusted analyses of the effect of PZA susceptibility on treatment outcome among patients treated with a full PZA-containing intensive phase who started in the 2012 programme: death/failure model

	Death/failure n (%)	Success n (%)	OR (95%CI)	P value*	aOR (95%CI)[†]	P value*
Pyrazinamide	58/294[‡] (19.7)	236/294[‡] (80.3)				
Resistant	44 (20.4)	172 (79.6)	1.00			
Susceptible	14 (17.6)	64 (82.1)	1.17 (0.60–2.28)	0.6	1.03 (0.51–2.08)	0.9

* Wald test.
[†] Adjusted for age, sex, previous first-line drugs, cavities on X-ray, programme year and number of drugs to which strain was resistant at diagnosis. Model with PZA-resistant strains at diagnosis: also adjusted for previous outcome.
[‡] Of 410 patients with PZA DST results available who started in the 2012 programme, 24 were excluded because they did not receive PZA in the intensive phase and 92 because they were lost to follow-up.
PZA = pyrazinamide; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; DST = drug susceptibility testing.

Table A.6   Crude and adjusted analyses of effect of PZA regimen received on treatment outcome among patients with no available PZA DST results at diagnosis and among patients with PZA-resistant strains at diagnosis: two PZA treatment duration models

	Death/failure n (%)	Success n (%)	OR (95%CI)	P value*	aOR (95%CI)[†]	P value*
PZA DST results at diagnosis not available	247/1114[‡] (22.2)	867/1114[‡] (77.8)				
Partial and full PZA regimen						
Partial (<80% in the intensive phase)	18 (18.9)	77 (81.1)	1.00			
Full PZA regimen (≥80% in the intensive phase)	229 (22.5)	790 (77.5)	0.81 (0.47–1.38)	0.4	0.86 (0.9–1.51)	0.6
None, incomplete and full PZA regimen *in the intensive phase*						
None (<16% in the intensive phase)[§]	14 (18.4)	62 (81.6)	1.00			
Incomplete (≥16% and <80%)[¶]	4 (21.1)	15 (78.9)	0.85 (0.24–2.94)	0.8	0.80 (0.22–2.94)	0.7
Full PZA regimen (≥80% in the intensive phase)	229 (22.5)	790 (77.5)	0.78 (0.43–1.42)	0.4	0.82 (0.43–1.55)	0.5
PZA-resistant strains at diagnosis	119/480[#] (24.8)	361/480 (75.2)				
Partial and full PZA regimen						
Partial (<80% in the intensive phase)	39 (32.5)	81 (67.5)	1.00			
Full PZA regimen (≥80% in the intensive phase)	80 (22.2)	280 (77.8)	1.69 (1.07–2.66)	0.03	1.38 (0.71–2.68)	0.3
None, incomplete and full PZA regimen** *in the intensive phase*						
None (<16% in the intensive phase)[§]	12 (27.3)	32 (72.7)	1.00			
Incomplete (≥16% and <80%)[¶]	27 (35.5)	49 (64.5)	0.68 (0.30–1.53)	0.4	0.51 (0.20–1.32)	0.2
Full PZA regimen (≥80% in the intensive phase)	80 (22.2)	280 (77.8)	1.31 (0.65–2.67)	0.5	0.80 (0.29–2.23)	0.7

* Wald test.
[†] Adjusted for age, sex, previous first-line drugs, cavities on X-ray, programme year and number of drugs to which strain was resistant at diagnosis.
[‡] Of 1614 patients with no available PZA DST at diagnosis; 157 excluded as PZA DST had not been defined as diagnostic before starting treatment; four because they were given PZA treatment only in the continuation phase; and 339 due to LTFU.
[§] <16% of days in the intensive phase (equivalent to <30 days in a 6-month intensive phase).
[¶] ≥16% but <80% of days in the intensive phase.
[#] Of 612 patients with PZA-resistant MDR-TB strains at diagnosis, 127 excluded due to outcome LTFU and five patients due to unknown X-ray result out.
** Also adjusted for median potentially effective drugs in the intensive phase.
PZA = pyrazinamide; DST = drug susceptibility testing; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; MDR-TB = multidrug-resistant tuberculosis; LTFU = loss to follow-up.

Table A.7   Crude and adjusted analyses of the effect of PZA regimen received on treatment outcome among patients with no PZA DST result available at diagnosis and among patients with PZA-resistant strains at diagnosis: two PZA treatment length models

	Death/failure/LTFU n (%)	Success n (%)	OR (95%CI)	P value*	aOR (95%CI)[†]	P value*
PZA DST result at diagnosis not available	586/1453[‡] (40.3)	867/1453[‡] (59.7)				
Partial and full PZA regimen						
Partial (<80% in the intensive phase)	48 (38.4)	77 (61.6)	1.00			
Full PZA regimen (≥80% in the intensive phase)	538 (40.5)	790 (59.5)	0.92 (0.63–1.33)	0.6	0.95 (0.63–1.41)	0.8
None, incomplete and full PZA regimen *in the intensive phase*						
None (<16% in the intensive phase)[§]	35 (36.1)	62 (63.9)	1.00			
Incomplete (≥16% and <80%)[¶]	13 (46.4)	15 (53.6)	0.65 (0.28–1.52)	0.3	0.59 (0.24–1.42)	0.2
Full PZA regimen (≥80% in the intensive phase)	538 (40.5)	790 (59.5)	0.83 (0.54–1.27)	0.4	0.84 (0.53–1.31)	0.4
PZA-resistant strains at diagnosis	246/607[#] (40.5)	361/607[#] (59.5)				
Partial and full PZA regimen						
Partial (<80% in the intensive phase)	58 (41.7)	81 (58.3)	1.00			
Full PZA regimen (≥80% in the intensive phase)	188 (40.2)	280 (59.8)	1.07 (0.73–1.57)	0.7	1.14 (0.66–1.96)	0.6
None, incomplete and full PZA regimen *in the intensive phase*						
None (<16% in the intensive phase)[§]	17 (34.7)	32 (65.3)	1.00			
Incomplete (≥16% and <80%)[¶]	41 (45.6)	49 (54.4)	0.63 (0.31–1.30)	0.2	0.61 (0.27–1.36)	0.2
Full PZA regimen (≥80% in the intensive phase)	188 (40.2)	280 (59.8)	0.79 (0.43–1.47)	0.5	0.77 (0.33–1.78)	0.5

* Wald test.
[†] Adjusted for age, sex, previous first-line drugs, cavities on X-ray, programme year and number of drugs to which strain was resistant at diagnosis. Model with PZA-resistant strains at diagnosis: also adjusted for previous outcome.
[‡] 157 excluded as PZA DST had not been defined as diagnostic before starting treatment and four because they were given PZA treatment only in the continuation phase.
[§] <16% of days in the intensive phase (equivalent to <30 days in a 6-month intensive phase period).
[¶] ≥16% but <80% of days in the intensive phase.
[#] Five patients excluded due to unknown X-ray results.
PZA = pyrazinamide; LTFU = loss to follow-up; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; DST = drug susceptibility testing.

RÉSUMÉ

CONTEXTE : L'Organisation Mondiale de la Santé (OMS) recommande l'inclusion du pyrazinamide (PZA) dans les protocoles de traitement de la tuberculose multirésistante (TB-MDR) sauf si la résistance au PZA est certaine.

OBJECTIF : Examiner l'association entre sensibilité au PZA et résultat du traitement de la TB-MDR parmi les patients traités avec un protocole PZA et voir si la durée de la phase intensive du traitement par PZA a affecté les résultats du traitement.

SCHÉMA : Nous avons réalisé une étude rétrospective de cohorte, incluant tous les patients TB-MDR éligibles ayant commencé leur traitement en 2003–2013 au sein du programme TB à Karakalpakstan, Ouzbékistan. Le test de pharmacosensibilité (DST) au PZA a recouru à la culture en milieu liquide et les résultats ont été classés en fonction des définitions 2013 de l'OMS.

RÉSULTATS : Sur 2446 patients TB-MDR inclus, 832 (34,0%) disposaient d'un DST au PZA de départ, dont 612 (73,6%) ont été résistants au PZA. Nous n'avons pas trouvé d'association entre le succès du traitement et la sensibilité au PZA (OR ajusté [ORa] 0,86 ; IC95% 0,51–1,44 ; $P = 0,6$) chez les patients traités par PZA. De plus, aucune preuve n'a mis en évidence une association entre succès du traitement et durée du traitement par PZA (ORa 0,86 ; IC95% 0,49–1,51 ; $P = 0,6$) parmi les patients sans DST au PZA de départ.

CONCLUSION : Le traitement de la TB-MDR avec un protocole standard de PZA ne semble pas améliorer les résultats du traitement, quelles que soient la sensibilité au PZA ou la durée du traitement.

RESUMEN

MARCO DE REFERENCIA: La Organización Mundial de la Salud (OMS) recomienda que se incluya la pirazinamida (PZA) en las pautas de tratamiento de la tuberculosis multirresistente (TB-MDR), a menos de que exista certeza sobre la resistencia.

OBJETIVO: Investigar la asociación entre la sensibilidad a la PZA y el desenlace del tratamiento de la TB-MDR en los pacientes que reciben una pauta con PZA y determinar si la duración de la fase intensiva del tratamiento con PZA tiene algún efecto sobre el desenlace terapéutico.

MÉTODO: Se llevó a cabo un estudio de cohortes retrospectivo de todos los pacientes con TB-MDR que cumplían los requisitos y habían iniciado tratamiento del 2003 al 2013 en el marco del programa contra la tuberculosis en Karakalpakistán, en Uzbekistán. Se practicó la prueba de sensibilidad a PZA en medio líquido y los desenlaces se clasificaron según las definiciones de la OMS del 2013.

RESULTADOS: De los 2446 pacientes con TB-MDR incluidos, 832 contaban con una prueba inicial de sensibilidad a PZA (34,0%) y de ellos, 612 eran resistentes a PZA (73,6%). No se observó ninguna asociación entre el éxito terapéutico y la sensibilidad a PZA en los pacientes que recibieron un tratamiento con PZA (OR ajustado [ORa] 0,86; IC95% 0,51–1,44; $P = 0,6$). Además, no se encontraron indicios de una asociación entre el éxito terapéutico y la duración del tratamiento con PZA en los pacientes que no contaban con una prueba inicial de resistencia a PZA (ORa 0,86; IC95% 0,49–1,51; $P = 0,6$).

CONCLUSIÓN: El tratamiento de la TB-MDR con una pauta corriente que contiene PZA no parece mejorar los desenlaces terapéuticos, sea cual fuere la situación frente a la sensibilidad a PZA o la duración de su administración.