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Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study

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SUMMARY

BACKGROUND: The World Health Organization recommends adding bedaquiline or delamanid to multidrug-resistant tuberculosis (MDR-TB) regimens for which four effective drugs are not available, and delamanid for patients at high risk of poor outcome.

OBJECTIVE: To identify patients at risk of unfavourable outcomes who may benefit from the new drugs.

METHODS: Retrospective cohort study of treatment outcomes involving four to five effective drugs for 15–24 months in programmes in Uzbekistan, Georgia, Armenia, Swaziland and Kenya between 2001 and 2011.

RESULTS: Of 1433 patients, 48.5% had body mass index (BMI) <18.5 kg/m^2, 72.9% had a high bacillary load, 16.7% were resistant to two injectables, 2.9% were resistant to ofloxacin (OFX) and 3.0% had extensively drug-resistant TB (XDR-TB). Treatment success ranged from 59.7% (no second-line resistance) to 27.0% (XDR-TB). XDR-TB (aOR 8.16, 95%CI 3.22–20.64), resistance to two injectables (aOR 1.90, 95%CI 1.00–3.62) or OFX (aOR 5.56, 95%CI 2.15–14.37), past incarceration (aOR 1.88, 95%CI 1.11–3.2), history of second-line treatment (aOR 3.24, 95%CI 1.53–6.85), low BMI (aOR 2.22, 95%CI 1.56–3.12) and high bacillary load (aOR 2.32, 95%CI 1.15–4.67) were associated with unfavourable outcomes. Patients started on capreomycin rather than kanamycin were more likely to have an unfavourable outcome (aOR 1.54, 95%CI 1.04–2.28).

CONCLUSION: In our cohort, patients who may benefit from bedaquiline and delamanid represented up to two thirds of all MDR-TB patients.

KEY WORDS: treatment; regimens; resource-limited; drug resistance; tuberculosis; outcomes

IN 2013, AN ESTIMATED 480 000 patients developed multidrug-resistant tuberculosis (MDR-TB, defined as TB resistant to at least isoniazid and rifampicin); of these, on average 9.0% had extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to at least one injectable).[1] Although MDR-TB is especially prevalent in Eastern Europe and Central Asia, where up to a third of new TB cases are MDR-TB, it is also increasing in Africa.[1,2]

Treatment regimens recommended by the World Health Organization (WHO) include an injectable agent during the intensive phase (kanamycin [KM], amikacin [AMK] or capreomycin [CPM]), a fluoroquinolone (FQ) throughout treatment, and other WHO Group 4 drugs (para-aminosalicylic acid, ethionamide [ETH]/prothionamide [PTH], cycloserine) or Group 5 drugs (linezolid, clofazimine, imipenem/meropenem, amoxicillin-clavulanate acid, thiacetazone, clarithromycin, high-dose INH), for a total duration of approximately 2 years. Ethambutol (EMB) and pyrazinamide (PZA) can be added, but are not considered effective due to their poor reliability or difficulties with drug susceptibility testing (DST).[3] These recommendations are mainly based on expert opinion and cohort analysis, including a meta-analysis of individual patient data. Only 40–70% of patients achieve treatment success due to poor efficacy and poor adherence.[1,4–7]

Two drugs, bedaquiline (BDQ) and delamanid (DLM), have been conditionally approved by the US Food and Drug Administration and/or the European Medicines Agency for treatment of MDR-TB. Due to limited data on their long-term efficacy and safety, these drugs have been added to the list of WHO Group 5 drugs. The WHO recommends considering the addition of BDQ or DLM when an MDR-TB regimen with four effective drugs, including an FQ

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and an injectable agent in addition to PZA, cannot be designed (additional resistance to FQ or an injectable agent, drug intolerance or contraindication). DLM may also be added for patients at higher risk of poor outcomes.[8–10] However, current guidelines do not detail the characteristics of patients at increased risk.

We present the results of a multisite, retrospective cohort analysis of MDR-TB patients treated in programmes supported by Médecins Sans Frontières (MSF) in five countries: Abkhazia, Georgia; Armenia, Karakalpakstan Region, Uzbekistan; Nairobi, Kenya; and Shiselweni Region, Swaziland. Four of the five programmes (Abkhazia, Armenia, Karakalpakstan and Shiselweni) are in high MDR-TB burden countries, with MDR-TB prevalence among new cases (2011) of between 7.7% in Swaziland and 23.2% in Armenia.[1,11,12] Four programmes have been approved by the WHO Green Light Committee (GLC) since 2004 for Abkhazia, 2003 for Karakalpakstan and Armenia and 2009 for Shiselweni.[11,13] The programme in Nairobi has not applied for GLC approval to date.

Our primary objective was to determine the odds of unfavourable outcomes to identify patients who could benefit from the addition of the new drugs.[9,10] Secondary objectives were to describe the treatment outcomes and the extension of drug resistance to FQs and injectable agents during treatment. Exploratory objectives assessed the effectiveness of treatment recommendations, such as the use of KM as the first-choice injectable agent, the addition of EMB or PZA to a regimen already including four effective drugs, and the prescription of a thioamide in pre-exposed patients.

METHODS

Periods covered by the study were 2001–2011 in Abkhazia, 2005–2011 in Armenia, 2003–2011 in Karakalpakstan, 2010–2011 in Nairobi and 2007–2011 in Shiselweni.

Patient management

Treatment regimens were individualised using four or five likely effective drugs for a duration of 15–24 months, administered under observation with psychosocial support and careful management of adverse events.[14] During the early years of the programmes in Abkhazia, Armenia and Karakalpakstan, patients were hospitalised during the intensive phase; in later years, patients were discharged for ambulatory treatment after smear conversion. In Nairobi and Shiselweni, treatment was ambulatory unless hospitalisation was clinically indicated. Monthly culture and DST were performed in quality-assured laboratories or in supranational laboratories.

Inclusion, outcome definitions and covariate definitions

The study included all patients aged $\geqslant 18$ years with a baseline DST result confirming MDR-TB (sample collected either before starting MDR-TB treatment or $\leqslant 1$ month after commencement). To account for the 2-year duration of the WHO regimen and delays in data entry, analysis of outcomes was limited to patients started on treatment up to 31 December 2009. The administrative censoring date of the database was 31 December 2011.

Clinicians used the 2008 WHO definitions of treatment outcomes requiring at least five consecutive negative culture results during the final 12 months of treatment to be classified as cured, and either $\geqslant 2$ positive results among the five cultures recorded in the final 12 months, one positive in any one of the final three cultures, or a clinical decision to discontinue treatment early due to failure.[3] Favourable outcome was defined as a combination of cured and treatment completed, and unfavourable outcome as a combination of death and failure. Drug resistance extension was defined as resistance to drugs (OFX, KM, CPM) that had not been detected at baseline.

The following patient characteristics were recorded at treatment initiation: age; sex; history of incarceration; history of MDR-TB contact; daily alcohol consumption (none, <5 drinks and $\geqslant 5$ drinks); comorbidities (known diabetes, human immunodeficiency virus infection [HIV]); past TB treatment history, defined as new cases (<1 month of anti-tuberculosis treatment), previously treated cases (first- and second line anti-tuberculosis drugs); body mass index (BMI) (low <18.5 kg/m^2); presence of cavities on chest radiograph; sputum smear microscopy results (negative, low [scanty or 1+] and high bacillary load [2+ or 3+]); and DST results. TB strain resistance profiles were defined as MDR-TB with DST to second-line drugs not known; simple MDR-TB (no resistance to OFX and an injectable agent); pre-XDR-TB one injectable agent (resistance to either KM or CPM and OFX-susceptible); pre-XDR-TB two injectable agents (resistance to KM and CPM and OFX-susceptible); pre-XDR-TB OFX (resistance to OFX and susceptibility to both KM and CPM); and XDR-TB. Other covariates were drug prescription at treatment initiation regardless of duration, number of drugs prescribed and incidence of treatment interruption of any duration per year of treatment due to side effects or patient reasons (social, refusal, travel).

Data management and analysis

Data were recorded in the standardised Koch 6 database (Koch 6 software, Médecins Sans Frontières [MSF], Paris, France). In Karakalpakstan, an Epi Info database (Centers for Disease Control and Prevention, Atlanta, GA, USA) was used. The primary

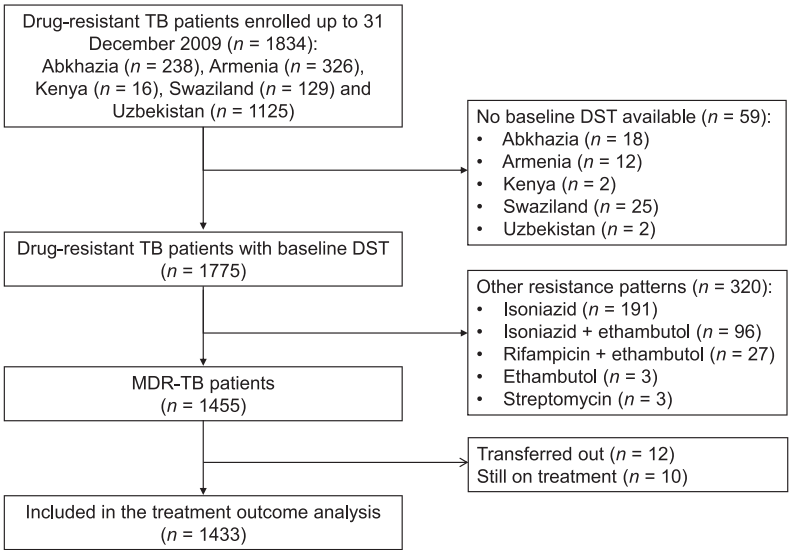

Figure Study profile. TB = tuberculosis; DST = drug susceptibility testing; MDR-TB = multidrug-resistant TB.

analysis of predictors of unfavourable outcomes was performed for all patients started on treatment, after exclusion of patients transferred out before the end of treatment or those still on treatment at analysis. Sensitivity analyses included a complete case analysis classifying patients lost to follow-up as unfavourable outcomes, a failure only analysis and a death only analysis. Secondary analyses described the treatment outcomes and the proportion of patients with drug resistance extension stratified by baseline drug resistance profiles. To describe the role of KM, CPM, EMB, PZA and ETH, exploratory analyses presented treatment outcomes stratified by individual drug resistance at baseline and previous drug exposure, and compared the success rates in patients who were not lost to follow-up.

Patient characteristics were summarised using frequencies and percentages for categorical variables, and median and interquartile ranges (IQRs) for continuous variables. The percentage of patients with drug resistance extension was calculated for those patients with a TB strain with baseline susceptibility to a drug and at least one culture result during follow-up. Univariate and multivariate random-intercept logistic regression was fitted to explore the link between patients and treatment characteristics and unfavourable outcomes. Missing values were introduced as a separate category in the model to keep the full sample size. Predictors were systematically adjusted on programme location (random-intercept) and period of inclusion (2001–2005, 2006–2007, 2008–2009). Covariates associated with $P < 0.4$ in univariate analysis were included in the initial multivariate model; a manual backward stepwise approach was used to obtain the final multivariate model. Statistical significance ($P < 0.05$) was assessed using the likelihood-ratio test. Analyses were performed using Stata 12.1 software (Stata Corporation, College Station, TX, USA).

Ethics approval

The study was approved by all the relevant health ministries. This retrospective study meets the criteria of the MSF Ethics Review Board for exemption from ethics review.

RESULTS

Patient characteristics

Of 1834 drug-resistant patients enrolled, 401 (21.9%) were excluded from the analysis. Most of the included patients (1355/1433, 94.6%) were from programmes in Eastern Europe and Central Asia, and 82.4% had been previously treated for TB, 10.8% of whom had received second-line anti-tuberculosis drugs. Resistance to EMB and PZA were reported in respectively 82.2% and 59.0% of the patients tested. Among 1243 patients with second-line DST results, respectively 817 (65.7%), 339 (31.3%) and 37 (3.0%) had simple MDR-TB (no resistance to an injectable agent and/or FQ), pre-XDR-TB and XDR-TB at baseline. Resistance to second-line anti-tuberculosis drugs was more frequent in the Eastern European and Central Asian sites than in African sites (Table 1). At treatment initiation, patients received a median of 5 (IQR 5–6) anti-tuberculosis drugs.

Predictors of unfavourable outcomes

Overall, 808/1433 (56.4%) patients achieved treatment success, 292 (20.4%) had an unfavourable outcome and 333 (23.2%) were lost to follow-up (Table 2). Past incarceration, a history of anti-tuberculosis treatment with first- or second-line anti-tuberculosis drugs, low BMI, high bacillary load, and a

Table 1 Patients' characteristics at initiation of MDR-TB treatment by site

	Overall ($n = 1433$) *n* (%)	Abkhazia ($n = 161$) *n* (%)	Armenia ($n = 232$) *n* (%)	Kenya ($n = 12$) *n* (%)	Swaziland ($n = 66$) *n* (%)	Karakalpakstan ($n = 962$) *n* (%)
Female	620 (43.3)	21 (13.0)	44 (19.0)	4 (33.3)	46 (69.7)	505 (52.5)
Age, years, median [IQR]	32 [24–43]	37 [30–47]	39 [29–49]	24 [20–29]	31 [28–42]	30 [23–41]
Alcohol consumption, daily						
None	1077 (75.2)	76 (47.2)	112 (48.3)	12 (100)	66 (100)	811 (84.3)
<5 drinks	330 (23.0)	72 (44.7)	111 (47.8)	0	0	147 (15.3)
⩾5 drinks	26 (1.8)	13 (8.1)	9 (3.9)	0	0	4 (0.4)
Incarceration	209 (14.6)	78 (48.4)	80 (34.5)	0	0	51 (5.3)
Tuberculosis treatment history						
None	245 (17.6)	51 (31.9)	20 (8.6)	0	3 (4.7)	171 (18.4)
Only first-line drugs	1000 (71.6)	61 (38.1)	133 (57.3)	12 (100)	54 (84.4)	740 (79.7)
With second-line drugs	151 (10.8)	48 (30.0)	79 (34.1)	0	7 (10.9)	17 (1.8)
Diabetes	79/509 (15.5)	11/161 (6.8)	31/232 (13.4)	0/12	0/66	37/38 (97.4)
HIV						
Known status	88	2	11	12	63	0
Positive	31 (35.3)	0	6 (54.5)	10 (83.3)	15 (23.8)	—
MDR-TB contact	120 (8.4)	11 (6.8)	35 (15.1)	0	0	74 (7.7)
BMI, kg/m^2, median [IQR]	18.6 [16.6–21.0]	19.7 [18.2–21.9]	20.0 [18.0–23.1]	17.6 [16.5–20.2]	18.7 [16.8–22.8]	18.0 [16.0–20.1]
<18.5	686 (48.5)	43 (28.5)	67 (28.9)	7 (58.3)	25 (43.1)	544 (56.6)
Cavity	1112 (77.6)	79 (49.0)	212 (91.4)	9 (75.0)	10 (15.2)	802 (83.4)
Sputum smear						
Negative	117 (9.5)	6 (6.4)	48 (21.6)	0	12 (21.4)	51 (6.0)
Scanty or 1+	217 (17.6)	15 (16.0)	57 (25.7)	5 (55.6)	8 (14.3)	132 (15.5)
2+ or 3+	898 (72.9)	73 (77.7)	117 (52.7)	4 (44.4)	36 (64.3)	668 (78.5)
Resistance pattern*						
Simple MDR-TB†	817 (65.7)	82 (55.4)	80 (64.5)	7 (87.5)	6 (66.7)	642 (67.3)
Pre-XDR-TB 1 injectable	146 (11.7)	39 (26.3)	3 (2.4)	1 (12.5)	2 (22.2)	101 (10.6)
Pre-XDR-TB 2 injectables	207 (16.7)	14 (9.5)	24 (19.4)	0	0	169 (17.7)
Pre-XDR-TB OFX	36 (2.9)	4 (2.7)	11 (8.9)	0	1(11.1)	20 (2.1)
XDR-TB	37 (3.0)	9 (6.1)	6 (4.8)	0	0	22 (2.3)
Unknown second-line DST	190	13	108	4	57	8
Individual drug resistance						
EMB	1170/1423 (82.2)	136/160 (85.0)	141/230 (61.3)	10/12 (83.3)	39/59 (66.1)	844/962 (87.7)
PZA	284/481 (59.0)	40/82 (48.8)	91/168 (54.2)	7/9 (77.8)	9/14 (64.3)	137/208 (65.9)
AMK/KM	387/1251 (30.9)	61/148 (41.2)	36/132 (27.3)	1/8 (12.5)	0/9	289/954 (30.3)
CPM	236/1245 (19.0)	17/148 (11.5)	31/124 (25.0)	0/8	2/9 (22.2)	186/956 (19.5)
OFX	73/1253 (5.8)	13/148 (8.8)	17/131 (13.0)	0/9	1/9 (11.1)	42/956 (4.4)
ETH/PTH	304/948 (32.1)	43/148 (29.1)	30/107 (28.0)	0/8	2/3 (66.7)	229/682 (33.6)
Number of drugs prescribed						
1–4 drugs	246 (17.2)	60 (37.3)	40 (17.2)	9 (75.0)	32 (48.5)	105 (10.9)
5–6 drugs	888 (62.0)	73 (45.3)	146 (62.9)	1 (8.3)	22 (33.3)	646 (67.2)
⩾6 drugs	288 (20.1)	25 (15.5)	46 (19.8)	0	6 (9.1)	211 (21.9)
Unknown	11 (0.8)	3 (1.9)	0	2 (16.7)	6 (9.1)	0
EMB prescription	1083 (75.6)	39 (24.2)	73 (31.5)	0	13 (19.7)	958 (99.6)
PZA prescription	1319 (92.0)	136 (84.5)	184 (79.3)	0	51 (77.3)	948 (98.5)
Fluoroquinolone prescription						
OFX/CFX	765 (53.4)	93 (57.8)	20 (8.6)	0	40 (60.6)	612 (63.6)
LFX/MFX	630 (44.0)	64 (39.7)	210 (90.5)	10 (83.3)	7 (10.6)	339 (35.2)
None	38 (2.6)	4 (2.5)	2 (0.9)	2 (16.7)	19 (28.8)	11 (1.1)
Injectable prescription						
AMK/KM	482 (33.6)	13 (8.1)	52 (22.4)	5 (41.7)	53 (80.3)	359 (37.3)
CPM	926 (64.6)	144 (89.4)	180 (77.6)	5 (41.7)	4 (6.0)	593 (61.6)
None	25 (1.7)	4 (2.5)	0	2 (16.6)	9 (13.6)	10 (1.1)
Thioamide prescription	96 (6.7)	23 (14.3)	21 (9.1)	2 (16.7)	12 (18.2)	38 (4.0)
Interruption due to side effects‡						
None	1298 (90.6)	134 (83.2)	128 (55.2)	12 (100)	66 (100)	58 (99.6)
⩾1 interruption	135 (9.4)	27 (16.8)	104 (44.8)	0	0	4 (0.4)
Period						
2001–2005	260 (18.1)	75 (46.6)	15 (6.5)	0	0	170 (17.7)
2006–2007	474 (33.1)	43 (26.7)	71 (30.6)	0	5 (7.6)	355 (36.9)
2008–2009	699 (48.8)	43 (26.7)	146 (62.9)	12 (100)	61 (92.4)	437 (45.4)

* Comparison of drug resistance patterns across the sites: $P \leqslant 0.001$.
† MDR-TB without resistance to fluoroquinolone and injectables.
‡ Characteristic at treatment follow-up and not at treatment initiation.
MDR-TB = multidrug-resistant tuberculosis; IQR = interquartile range; HIV = human immunodeficiency virus; BMI = body mass index; XDR-TB = extensively drug-resistant TB; OFX = ofloxacin; DST = drug susceptibility testing; EMB = ethambutol; PZA = pyrazinamide; AMK = amikacin; KM = kanamycin; CPM = capreomycin; ETH = ethionamide; PTH = prothionamide; CFX = ciprofloxacin; LFX = levofloxacin; MFX = moxifloxacin.

Table 2 Treatment outcomes by resistance pattern at treatment initiation

	n	Success *n* (%)	Death *n* (%)	Failure *n* (%)	Lost to follow-up *n* (%)
Simple MDR-TB	817	488 (59.7)	53 (6.5)	74 (9)	202 (24.7)
Pre-XDR-TB	389	207 (53.2)	39 (10)	59 (15.2)	84 (21.6)
Resistance to 1 injectable	146	80 (54.8)	11 (7.5)	16 (11)	39 (26.7)
Resistance to 2 injectables	207	115 (55.5)	23 (11.1)	30 (14.5)	39 (18.8)
Ofloxacin resistance	36	12 (33.3)	5 (13.9)	13 (36.1)	6 (16.7)
XDR-TB	37	10 (27.0)	9 (24.3)	8 (21.6)	10 (27)
No second-line DST	190	103 (54.2)	26 (13.7)	24 (12.6)	37 (19.5)
Overall	1433	808 (56.4)	127 (8.9)	165 (11.3)	333 (23.2)

MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant TB; DST = drug susceptibility testing.

TB strain with pre-XDR-TB specifically resistant to two injectable agents, pre-XDR-TB OFX, or XDR-TB compared with simple MDR-TB were independently associated with an unfavourable outcome (Table 3).

In the complete case sensitivity analysis, HIV infection (adjusted odds ratio [aOR] 4.68, 95% confidence interval [CI] 1.34–16.32) was also associated with an unfavourable outcome (Appendix).* Treatment history with second-line anti-tuberculosis drugs (aOR 5.34, 95%CI 2.27–13.53), low BMI (aOR 2.17, 95%CI 1.39–3.33), high sputum bacillary load (aOR 4.69, 95%CI 1.55–14.14), and XDR-TB vs. simple MDR-TB (aOR 3.59, 95%CI 1.37–9.45) were associated with death. In the failure only analysis, past incarceration, history of anti-tuberculosis treatment and high bacillary load were no longer associated (Appendix). Variance due to sites represented 1.3% of the total variance, suggesting low heterogeneity between the sites.

Treatment outcomes and resistance extension by baseline drug resistance profile

Treatment success ranged between 59.7% in patients without second-line resistance to 27.0% in XDR-TB patients (Table 2). Among simple MDR-TB patients with at least one follow-up DST result ($n = 744$), DST later revealed drug resistance extension to KM (15.2%), CPM (9.1%) and OFX (12.1%) and to XDR-TB in 5.6% (Table 4). Among pre-XDR-TB patients, 18.8% (73/350) became XDR-TB. Drug resistance extension to an injectable agent or OFX was associated with an unfavourable outcome (Table 3), while drug resistance extension to OFX (aOR 3.13, 95%CI 1.70–5.77) was associated with death (Appendix).

Role of kanamycin, capreomycin, ethambutol, pyrazinamide and ethionamide

The risk of an unfavourable outcome was increased by 54% with prescription of CPM rather than KM (Table 3). Among patients with a TB strain susceptible to both injectable agents, success was higher in those initiated on KM rather than CPM (82.6% vs. 74.2%, $P = 0.013$). Among those patients susceptible to both drugs, 229/360 (63.6%) started on CPM were switched to KM when KM susceptibility was confirmed. The proportion who switched was similar between patients with an unfavourable outcome and those with favourable outcomes (63/99, 63.6% vs. 166/271, 61.2%, $P = 0.676$). Among patients susceptible to EMB at baseline, treatment success rates did not differ between those who were prescribed EMB and those who were not. Similar results were found with PZA; however, only 33.6% of patients underwent DST against PZA (Table 5). Among patients who were ETH-susceptible at baseline, those previously exposed to ETH had lower treatment success rates than those who were never exposed (43.7% vs. 77.3%). Patients who did not receive ETH/PTH in their initial prescription (aOR 2.07, 95%CI 1.08–3.99) were more likely to die (Appendix).

DISCUSSION

This is one of the largest reported multisite cohorts of MDR-TB patients using data from GLC-approved programmes. Our analysis confirms the poor effectiveness of treatment regimens for MDR-TB and drug resistance extension.[13,15,16] In addition to programmatic challenges, the use of long, poorly effective and badly tolerated regimens increases the risk of loss to follow-up.[17] Unsurprisingly, resistance to an injectable agent and/or FQ was a risk factor for poor outcome.[7,13,18,19] Previous exposure to anti-tuberculosis drugs, low BMI and high bacillary load ($\geqslant 2+$) were also risk factors for unfavourable outcomes in our study, as previously reported.[5,19] Our findings confirm those from meta-analyses showing no benefit, and only an unnecessary increase in pill burden, in the systematic addition of EMB to MDR-TB treatment, even in patients with an EMB-susceptible strain.[6,21,22] They also suggest no additional benefit of systematically adding PZA to the

* The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2016/00000020/00000002/art00010

Table 3 Odds of unfavourable outcomes (defined as death and failure) on MDR-TB treatment in multisite cohort by baseline and treatment characteristics, $n = 1100$

	Univariate		Multivariate	
Risk factor for unfavourable outcomes	OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Sex				
Female	1			
Male	1.02 (0.76–1.36)	0.914		
Age, years				
<35	1			
⩾35	1.44 (1.09–1.90)	0.011		
Incarceration				
No	1		1	
Yes	1.64 (1.07–2.52)	0.023	1.88 (1.11–3.20)	0.019
Alcohol consumption, daily				
None	1			
<5 drinks	0.86 (0.59–1.24)	0.414		
⩾5 drinks	1.14 (0.35–3.65)	0.839		
Contact with an MDR-TB patient				
No	1			
Yes	0.82 (0.49–1.37)	0.451		
Anti-tuberculosis treatment history				
None	1		1	
Only first-line drugs	2.55 (1.58–4.11)	<0.001	1.97 (1.14–3.42)	0.015
With second-line drugs	6.69 (3.53–12.66)	<0.001	3.24 (1.53–6.85)	0.002
Unknown	3.52 (1.41–8.80)	0.007	3.67 (1.26–10.67)	0.017
Diabetes				
No	1			
Yes	1.54 (0.88–2.69	0.127		
Unknown	0.54 (0.41–0.73)	<0.001		
HIV				
Negative	1			
Positive	3.95 (1.15–13.51)	0.029		
Unknown	3.03 (0.96–9.57)	0.058		
Cavity				
No	1			
Yes	1.65 (1.12–2.43)	0.011		
BMI, kg/m^2				
>18.5	1		1	
<18.5	2.08 (1.56–2.70)	<0.001	2.22 (1.56–3.12)	<0.001
Unknown	0.50 (0.13–1.92)	0.310	0.28 (0.06–1.32)	0.106
Smear at initiation				
Negative	1		1	
Scanty/1+	1.26 (0.63–2.53)	0.518	1.11 (0.49–2.54)	0.800
2+/3+	2.71 (1.48–4.98)	0.001	2.32 (1.15–4.67)	0.018
Unknown	1.66 (0.81–3.43)	0.167	1.78 (0.74–4.25)	0.197
DST at admission				
First-line resistance only	1		1	
Pre-XDR-TB 1 injectable agent	1.26 (0.78–2.05)	0.345	0.84 (0.45–1.56)	0.578
Pre-XDR-TB 2 injectable agents	1.83 (1.25–2.69)	0.002	1.90 (1.00–3.62)	0.050
Pre-XDR-TB OFX	5.42 (2.52–11.65)	<0.001	5.56 (2.15–14.37)	<0.001
XDR-TB	6.39 (2.84–14.40)	<0.001	8.16 (3.22–20.64)	<0.001
Second-line DST not performed	1.40 (0.85–2.29)	0.181	3.20 (1.73–5.91)	<0.001
Extension of resistance to injectable				
No	1		1	
Yes	3.12 (2.02–4.81)	<0.001	2.13 (1.22–3.71)	0.007
Unknown	0.90 (0.64–1.27)	0.569	0.60 (0.27–1.32)	0.203
Extension of resistance to OFX				
No	1		1	
Yes	15.40 (9.52–24.89)	<0.001	15.75 (9.39–26.44)	<0.001
Unknown	1.39 (0.97–2.00)	0.074	1.80 (0.86–3.74)	0.117
Number of drugs taken at initiation				
1–4	1			
5–6	0.96 (0.66–1.41)	0.940		
>6	1.09 (0.70–1.71)	0.701		
Unknown	1.29 (0.21–7.74)	0.780		
Incidence of interruptions due to side effects				
Number/year	1.66 (1.26–2.17)	<0.001	1.79 (1.30–2.45)	<0.001

Table 3 (continued)

Risk factor for unfavourable outcomes	Univariate		Multivariate	
	OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Prescription of FQs				
Received OFX/CFX	1			
Received LFX/MFX	0.98 (0.72–1.33)			
Did not receive FQs	1.31 (0.57–3.01)			
Prescription of injectable drugs				
Received AMK/KM	1		1	
Received CPM	1.74 (1.27–2.38)	0.001	1.54 (1.04–2.28)	0.031
Did not receive injectables	1.02 (0.32–3.26)	0.973	1.08 (0.28–4.20)	0.909
Prescription of thioamides				
Received thioamides	1			
Did not receive thioamides	1.64 (0.99–2.7)	0.053		
Period of inclusion				
2001–2005	1		1	
2006–2007	0.74 (0.51–1.09)	0.131	1.04 (0.64–1.70)	0.876
2008–2009	0.59 (0.40–0.85)	0.005	0.99 (0.60–1.62)	0.955
Resistance to ETH				
Susceptible	1			
Resistant	1.78 (1.26–2.53)	0.001		
Missing	0.97 (0.70–1.36)	0.874		
Resistance to PZA				
Susceptible	1			
Resistance	1.38 (0.88–2.16)	0.161		
Missing	0.78 (0.51–1.18)	0.233		
Resistance to EMB				
Susceptible	1			
Resistance	1.53 (1.04–2.25)	0.032		
Missing	2.32 (0.58–9.34)	0.237		

MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; HIV = human immunodeficiency virus; BMI = body mass index; DST = drug susceptibility testing; XDR-TB = extensively drug-resistant TB; OFX = ofloxacin; FQ = fluoroquinolone; CFX = ciprofloxacin; LFX = levofloxacin; MFX = moxifloxacin; AMK = amikacin; KM = kanamycin; CPM = capreomycin; ETH = ethionamide; PZA = pyrazinamide; EMB = ethambutol.

regimen, as recently shown by Franke et al., but their interpretation is limited by the small number of patients with DST results for PZA.[23] The significant reduction in numbers of deaths among patients started on ETH/PTH was unexpected, but consistent with previous cohorts.[18,19] The higher proportion of unfavourable outcomes in patients with ETH-susceptible strains who were previously exposed to ETH/PTH than non-exposed patients may just reflect the poor reliability of DST for these drugs.[24]

Almost a quarter of the MDR-TB patients in our cohort were resistant to OFX or two injectable agents, and would be eligible for BDQ or DLM.[9,10] However, patients at high risk of poor outcome and who could also benefit from the prescription of DLM represented a much higher proportion.[9] Considering only BMI <18.5 kg/m^2 and high bacillary load at treatment initiation—both factors associated with poor outcomes in our study and in previous studies—respectively 48.5% and 72.9% of patients presented these characteristics.[5,19] These figures go far beyond the 20% estimated target of MDR-TB patients with DLM by 2020 announced by Otsuka et al. at the 2015 WHO GLI/GDI (Global Laboratory Initiative/Global Drug-Resistant TB Initiative) Partners Forum.[25]

We also identified potential differences in treatment effectiveness between KM and CPM, which has

Table 4 Extension of drug resistance to injectable drugs and OFX during treatment

	Total	⩾1 follow-up DST	KM	CPM	KM and CPM	OFX
	n	*n*	*n* (%)	*n* (%)	*n*	*n* (%)
Simple MDR-TB	817	744	113 (15.2)	68 (9.1)	63	90 (12.1)
Pre-XDR-TB KM	139	127	NA	37 (29.1)	NA	19 (15.0)
Pre-XDR-TB CPM	7	7	4	NA	NA	2
Pre-XDR-TB both injectables	207	187	NA	NA	NA	47 (25.1)
Pre-XDR-TB OFX	36	29	4 (13.8)	4 (13.8)	3	NA
XDR-TB KM*	37	31	NA	6 (19.3)	NA	NA
XDR-TB KM	22	19	0	NA	NA	NA

* All 37 XDR-TB patients were KM-resistant at baseline; 22 were also resistant to CPM.
OFX = ofloxacin; DST = drug susceptibility test; KM = kanamycin; CPM = capreomycin; MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant TB; NA = not applicable.

Table 5 Treatment outcomes according to drug prescription

	Outcomes					Exclusion of LTFU		
		Success	Death	Failure	LTFU		Success	
	n	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n*	%	*P* value*
KM vs. CPM								
KM vs. CPM in patients susceptible to both at treatment initiation								0.013
KM in initial treatment regimen	352	218 (61.9)	15 (4.3)	31 (8.8)	88 (25.0)	264	82.6	
CPM in initial treatment regimen	472	267 (56.6)	42 (8.9)	51 (10.8)	112 (23.7)	360	74.2	
KM vs. CPM in patients resistant to KM at treatment initiation								0.386
KM in initial treatment regimen	56	34 (60.7)	5 (8.9)	7 (12.5)	10 (17.9)	46	73.9	
CPM in initial treatment regimen	330	170 (51.5)	36 (10.9)	46 (13.9)	78 (23.6)	252	67.5	
EMB								
Past history of EMB intake in EMB-susceptible patients at treatment initiation								0.718
History of EMB	205	119 (58)	13 (6.3)	23 (11.2)	50 (24.4)	155	76.8	
No history of EMB	48	31 (64.6)	4 (8.3)	4 (8.3)	9 (18.7)	39	79.5	
EMB prescription in EMB-susceptible patients at treatment initiation								0.484
EMB in initial treatment regimen	157	94 (59.9)	7 (4.4)	18 (11.5)	38 (24.2)	119	79.0	
EMB not in initial treatment regimen	96	56 (58.3)	10 (10.4)	9 (9.4)	21 (21.9)	75	74.7	
EMB prescription in EMB-resistant patients at treatment initiation								0.767
EMB in initial treatment regimen	108	60 (55.5)	11 (10.2)	13 (12.0)	24 (22.2)	84	71.4	
EMB not in initial treatment regimen	1062	593 (55.8)	95 (8.9)	125 (11.8)	249 (23.4)	813	72.9	
PZA								
Past history of PZA intake in PZA-susceptible patients at treatment initiation								0.083
History of PZA	187	98 (52.4)	15 (8)	24 (12.8)	50 (26.7)	137	71.5	
No history of PZA	10	4 (40)	6 (60)	0	0	10	40.0	
PZA prescription in PZA-susceptible patients at treatment initiation								0.357
PZA in initial treatment regimen	174	93 (53.4)	17 (9.8)	21 (12.1)	43 (24.7)	131	71.0	
PZA not in initial treatment regimen	23	9 (39.1)	4 (17.4)	3 (13)	7 (30.4)	16	56.2	
PZA prescription in PZA-resistant patients at treatment initiation								0.157
PZA in initial treatment regimen	191	89 (46.6)	24 (12.6)	35 (18.3)	43 (22.5)	148	60.1	
PZA not in initial treatment regimen	93	55 (59.1)	9 (9.7)	15 (16.1)	14 (15)	79	69.6	
Thioamides								
Past history of ETH/PTH intake in ETH-susceptible patients at treatment initiation								0.002
History of ETH/PTH intake	24	7 (29.2)	4 (16.7)	5 (20.8)	8 (33.3)	16	43.7	
No history of ETH/PTH intake	620	364 (58.7)	43 (6.9)	64 (10.3)	149 (24)	471	77.3	
ETH/PTH prescription in ETH-susceptible patients at treatment initiation								0.557
ETH/PTH in initial treatment regimen	337	206 (61.1)	26 (7.7)	42 (12.5)	63 (18.7)	274	75.2	
ETH/PTH not in initial treatment regimen	307	165 (53.7)	21 (6.8)	27 (8.8)	94 (30.6)	213	77.5	

* All *P* values correspond to the comparison of treatment success between different groups after exclusion of LTFU patients.
LTFU = lost to follow-up; KM = kanamycin; CPM = capreomycin; EMB = ethambutol; PZA = pyrazinamide; ETH = ethionamide; PTB = prothionamide.

not been previously reported. KM seemed more effective than CPM in patients whose isolates were susceptible to both drugs, and the effect remained after adjustment for patient comorbidities, treatment history, baseline drug resistance profiles and prescription of FQ. These findings support the selection of KM as the injectable agent of choice. They also indicate that it may be beneficial to switch patients already on CPM to KM if DST shows KM susceptibility. If the superiority of KM is confirmed, this would be especially important for countries with limited resources, given the lower cost of KM (USD2.58/g) compared with CPM (USD4/g) and the poor availability of CPM.[21,26]

Compared to the meta-analysis of individualised patient data, our study results were obtained from programmes using the same treatment strategies and the same data recording system, which reduced the variability between sites and gave us the possibility to adjust for more covariates, such as comorbidities, disease severity and treatment tolerability.[6,7,18,27] As the overlap with the recent meta-analysis was limited to 77 patients from Karakalpakstan, the present study describes a new, large population.[6,7,18,27]

The study has several limitations. First, due to its complexity, DST against PZA was only performed in 33.6% of patients based on clinician's request in supranational laboratories. Missing PZA DST results were not equally distributed among risk factors of unfavourable outcomes (data not shown), and might have biased the effect of resistance to PZA on treatment outcome.

Second, most patients not tested for HIV were from the Eastern European or Central Asian regions. This could explain the association between unknown HIV test result and unfavourable outcomes in the univariate analysis, as patients from these regions were more likely to be infected with XDR-TB or a pre-XDR-TB strain. The association disappeared after adjustment for these factors. The loss of association between HIV

infection and unfavourable outcomes after multivariate analysis could be explained by the very low number of patients with HIV results.

Third, treatment interruptions for patient reasons were used as a proxy for adherence to compensate for the absence of adherence data (not collected) from the site in Swaziland. This did not allow appropriate adjustment for treatment adherence.

Fourth, the prescription of drugs was only considered at treatment initiation. This did not reflect the real effect of the drug on treatment outcomes, as the initial prescription might be changed during treatment due to poor tolerability or based on DST results. Specifically, the effect of switching patients between CPM and KM after receiving the DST results could not be assessed.

Fifth, drug resistance amplification could not be described due to lack of genotyping evidence. Results of drug resistance extension and its effect on treatment outcomes should be interpreted with caution, keeping in mind that reasons other than amplification could explain the increase in resistance.

Sixth, most patients were from the Eastern European or Central Asian regions, which may limit the generalisability of these results to other regions. However, the predictor analysis was systematically adjusted for programme location.

Seventh, the *P* value was not corrected or adjusted despite the risk of increased type I error resulting from multiple comparisons in the multivariate logistic model. The interpretation of the findings should be based more on the ORs and their CIs rather than on the *P* values.

Finally, due to the retrospective study design based on routinely collected data, we did not have sufficiently repeated measurements of time-dependent variables to perform a marginal structural model to account for the time-dependent nature of confounders (drug resistance extension, treatment change). Time-dependent confounders might therefore lead to biased estimates of exposure effects. However, when removing time-dependent confounders (drug resistance extension, incidence of interruption due to side effects) from the multivariate model, we found similar estimates for baseline variables on outcome (data not shown).

CONCLUSION

We identified some patient characteristics that were associated with higher risk of poor outcome and which could guide the prescription of new drugs when designing an MDR-TB regimen. In our study settings, up to two thirds of MDR-TB patients are likely to benefit from the new drugs, especially DLM. Other risk factors for poor outcome may exist in other settings and more studies are needed. Our study results also support the prescription of KM as the injectable agent of choice.

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APPENDIX

Table A.1 Odds of unfavourable outcomes (defined as death, failure and default) on MDR-TB treatment in multisite cohort by baseline and treatment characteristics ($n = 1433$)

	Univariate		Multivariate	
Risk factor for unfavourable outcomes	OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Sex				
Female	1			
Male	1.27 (1.02–1.60)	0.036		
Age, years		0.044		
<35	1			
⩾35	1.32 (1.06–1.65)	0.012		
History of incarceration				
No	1		1	
Yes	1.76 (1.25–2.48)	0.001	1.68 (1.15–2.45)	0.007
Alcohol consumption, daily		0.148		
None	1			
Moderate	1.20 (0.91–1.57)	0.187		
Excessive	2.04 (0.85–4.88)	0.108		
Contact with an MDR-TB patient				
No	1			
Yes	0.88 (0.60–1.30)	0.526		
Anti-tuberculosis treatment history		<0.001		
New case	1		1	
First-line drugs	1.45 (1.07–1.96)	0.015	1.35 (0.96–1.89)	0.085
Second-line drugs	2.97 (1.87–4.71)	<0.001	2.05 (1.21–3.47)	0.007
Unknown	2.04 (1.01–4.13)	0.047	1.62 (0.72–3.63)	0.244
Diabetes status		0.126		
No	1			
Yes	1.22 (0.65–2.28)	0.532		
Unknown	0.65 (0.28–1.49)	0.306		
HIV status		0.013		
Negative	1		1	
Positive	5.22 (1.55–17.57)	0.008	4.68 (1.34–16.32)	0.016
Unknown	5.71 (1.70–19.12)	0.005	3.62 (1.12–11.65)	0.031
Cavitation				
No	1			
Yes	1.32 (0.99–1.75)	0.060		
BMI, kg/m^2		0.001		
<18.5	1		1	
⩾18.5	0.72 (0.58–0.90)	0.004	0.73 (0.57–0.93)	0.013
Unknown	3.54 (1.04–12.01)	0.042	4.24 (1.28–14.11)	0.018
Smear at initiation		0.106		
Negative	1		1	
Scanty/1+	1.04 (0.65–1.67)	0.862	1.15 (0.67–1.96)	0.617
2+/3+	1.44 (0.95–2.17)	0.084	1.58 (0.99–2.53)	0.059
Unknown	1.40 (0.85–2.29)	0.182	1.65 (0.95–2.90)	0.078
DST at admission		0.003		
First-line resistance only	1		1	
Pre-XDR-TB 1 injectable	1.09 (0.75–1.57)	0.653	1.09 (0.73–1.64)	0.664
Pre-XDR-TB 2 injectables	1.21 (0.88–1.65)	0.234	1.00 (0.71–1.43)	0.974
Pre-XDR-TB OFX	2.71 (1.32–5.57)	0.006	2.38 (1.10–5.17)	0.028
XDR-TB	3.52 (1.66–7.44)	0.001	4.13 (1.85–9.21)	0.001
Second-line DST not performed	1.09 (0.70–1.67)	0.707	1.06 (0.65–1.72)	0.809
Extension of resistance to injectables		0.006		
No	1			
Yes	1.83 (1.26–2.66)	0.002		
Unknown	1.14 (0.88–1.48)	0.302		
Extension of resistance to OFX				
No	1	<0.001	1	
Yes	6.75 (4.43–10.29)	<0.001	7.63 (4.93–11.82)	<0.001
Unknown	1.56 (1.22–2.01)	<0.001	1.51 (1.13–1.80)	0.005

Table A.1 (continued)

	Univariate		Multivariate	
Risk factor for unfavourable outcomes	OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Number of drugs taken at initiation		0.361		
1–4	1			
5–6	0.97 (0.71–1.32)	0.844		
>6	1.00 (0.70–1.45)	0.980		
Unknown	3.74 (0.85–16.43)	0.080		
Prescription of injectable drugs		0.136		
Received AMK/KM	1			
Received CPM	1.27 (1.00–1.61)	0.052		
Did not receive injectables	1.37 (0.58–3.21)	0.473		
Prescription of FQ drugs		0.427		
Received OFX/CFX	1			
Received LFX/MFX/GFX	1.08 (0.85–1.37)	0.539		
Did not receive FQ	1.57 (0.76–3.26)	0.225		
Prescription of thioamides				
Received	1			
Did not receive	1.34 (0.87–2.07)	0.180		
Incidence of interruptions due to side effects				
Number/year	1.47 (1.16–1.85)	0.001	1.43 (1.13–1.80)	0.003
Incidence of interruptions due to patient				
Number/year	1.07 (1.04–1.06)	<0.001	1.08 (1.05–1.10)	<0.001
Period of inclusion				
2001–2005	1			
2006–2007	1.03 (0.75–1.41)	0.858		
2008–2009	0.97 (0.71–1.32)	0.837		
Resistance to ETH				
Susceptible	1			
Resistant	1.48 (1.12–1.96)	0.006		
Missing	0.97 (0.75–1.26)	0.847		
Resistance to PZA				
Susceptible	1			
Resistant	1.18 (0.81–1.72)	0.382		
Missing	0.98 (0.70–1.38)	0.917		
Resistance to EMB				
Susceptible	1			
Resistant	1.30 (0.97–1.74)	0.078		
Missing	1.78 (0.46–6.80)	0.401		

MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; HIV = human immunodeficiency virus; BMI = body mass index; DST = drug susceptibility testing; XDR-TB = extensively drug-resistant TB; OFX = ofloxacin; AMK = amikacin; KM = kanamycin; CPM = capreomycin; FQ = fluoroquinolone; CFX = ciprofloxacin; LFX = levofloxacin; MFX = moxifloxacin; GFX = gatifloxacin; ETH = ethionamide; PZA = pyrazinamide; EMB = ethambutol.

Table A.2 Odds of MDR-TB treatment failure in multisite cohort by baseline and treatment characteristics ($n = 973$)

	Univariate		Multivariate	
Risk factor of failure	OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Sex				
Female	1			
Male	0.93 (0.62–1.34)	0.715		
Age, years				
<35	1			
⩾35	1.31 (0.93–1.84)	0.125		
History of incarceration				
No	1			
Yes	1.26 (0.75–2.11)	0.383		
Alcohol consumption, daily				
None	1			
Moderate	0.95 (0.61–1.47)	0.806		
Excessive	1.34 (0.35–5.13)	0.672		
Contact with an MDR-TB patient				
No	1			
Yes	0.76 (0.40–1.44)	0.397		
Anti-tuberculosis treatment history				
New case	1			
First-line drugs	2.29 (1.25–4.17)	0.007		
Second-line drugs	3.16 (1.46–6.81)	0.003		
Unknown	4.63 (1.65–13.00)	0.004		
Diabetes status				
No	1			
Yes	1.50 (0.74–3.03)	0.257		
Unknown	0.84 (0.41–1.74)	0.641		
HIV status				
Negative	1			
Positive	3.49 (0.38–32.09)	0.270		
Unknown	6.84 (0.88–52.81)	0.065		
Cavitation				
No	1			
Yes	1.56 (0.97–2.50)	0.068		
BMI, kg/m^2				
<18.5	1		1	
⩾18.5	0.65 (0.46–0.93)	0.018	0.66 (0.44–0.98)	0.042
Unknown	2.45 (0.56–10.64)	0.232	2.66 (0.55–12.8)	0.221
Smear at initiation				
Negative	1			
Scanty/1+	1.35 (0.62–2.95)	0.453		
2+/3+	1.62 (0.81–3.25)	0.172		
Unknown	1.35 (0.58–3.16)	0.484		
DST at admission				
First-line resistance only	1		1	
Pre-XDR-TB 1 injectable	1.34 (0.74–2.42)	0.330	1.88 (0.42–1.84)	0.735
Pre-XDR-TB 2 injectables	1.60 (1.00–2.55)	0.049	2.67 (1.16–6.14)	0.02
Pre-XDR-TB OFX	5.03 (2.32–10.93)	<0.001	11.12 (4.15–29.78)	<0.001
XDR-TB	2.91 (1.22–6.95)	0.016	7.85 (2.75–22.46)	<0.001
Second-line DST not performed	1.05 (0.58–1.91)	0.863	4.40 (2.07–9.19)	<0.001
Extension of resistance to injectable		<0.001		
No	1		1	
Yes	4.3 (2.65–7.06)		3.0 (1.71–5.39)	<0.001
Unknown	0.73 (0.47–1.13)		0.51 (0.21–1.23)	0.135
Extension of resistance to OFX		<0.001		
No	1		1	
Yes	12 (7.23–19.91)		10.62 (6.27–18.0)	<0.001
Unknown	1.1 (0.68–1.78)		1.14 (0.48–2.72)	0.77
Number of drugs taken at initiation				
1–4	1			
5–6	1.09 (0.68–1.74)	0.714		
>6	0.67 (0.37–1.22)	0.187		
Unknown	—			
Incidence of interruptions due to side effects				
Number/year	1.57 (1.24–1.98)	<0.001	1.50 (1.16–1.93)	0.002
Incidence of interruptions due to patient				
Number/year	1.03 (0.99–1.06)	0.095	1.03 (1.0–1.07)	0.024

Table A.2 (continued)

	Univariate		Multivariate	
Risk factor of failure	OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Prescription of injectable drugs				
Received AMK/KM	1			
Received CPM	1.50 (1.02–2.21)	0.041		
Did not receive injectables	1.05 (0.23–4.80)	0.954		
Prescription of FQs				
Received OFX/CFX	1			
Received LFX/MFX	0.92 (0.62–1.36)	0.674		
Did not receive FQs	2.01 (0.71–5.73)	0.191		
Prescription of thioamides				
Received thioamides	1			
Did not receive thioamides	0.93 (0.47–1.82)	0.824		
Resistance to ETH				
Susceptible	1			
Resistant	1.62 (1.07–2.45)	0.022		
Missing	0.81 (0.54–1.23)	0.320		
Resistance to PZA				
Susceptible	1			
Resistance	1.53 (0.88–2.63)	0.129		
Missing	0.87 (0.51–1.48)	0.609		
Resistance to EMB				
Susceptible	1			
Resistance	1.35 (0.85–2.17)	0.206		
Period of inclusion				
2001–2005	1			
2006–2007	0.86 (0.55–1.36)	0.522		
2008–2009	0.50 (0.32–0.80)	<0.001		

MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; HIV = human immunodeficiency virus; BMI = body mass index; DST = drug susceptibility testing; XDR-TB = extensively drug-resistant TB; OFX = ofloxacin; AMK = amikacin; KM = kanamycin; CPM = capreomycin; FQ = fluoroquinolone; CFX = ciprofloxacin; LFX = levofloxacin; MFX = moxifloxacin; ETH = ethionamide; PZA = pyrazinamide; EMB = ethambutol.

Table A.3 Odds of death of patients on MDR-TB treatment in multisite cohort, by baseline and on-treatment characteristics ($n = 935$)

	Univariate		Multivariate	
Risk factor of death	OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Sex				
Female	1			
Male	1.13 (0.76–1.69)	0.543		
Age, years				
<35	1			
⩾35	1.41 (0.96–2.08)	0.077		
History of incarceration				
No	1			
Yes	1.77 (1.03–3.03)	0.039		
Alcohol consumption, daily				
None	1			
Moderate	0.82 (0.50–1.36)	0.443		
Excessive	0.89 (0.18–4.31)	0.887		
Contact with an MDR-TB patient				
No	1			
Yes	0.98 (0.49–1.97)	0.964		
Anti-tuberculosis treatment history				
New case	1		1	
First-line drugs	2.41 (1.18–4.92)	0.016	1.98 (0.95–4.13)	0.070
Second-line drugs	6.96 (3.00–16.14)	<0.001	5.54 (2.27–13.53)	<0.001
Unknown	1.47 (0.30–7.25)	0.636	1.24 (0.24–6.57)	0.794
Diabetes status				
No	1			
Yes	1.38 (0.63–3.02)	0.418		
Unknown	0.50 (0.24–1.03)	0.061		
HIV status				
Negative	1			
Positive	3.24 (0.81–12.91)	0.096		
Unknown	1.30(0.34–4.92)	0.697		
Cavitation				
No	1			
Yes	1.61 (0.93–2.79)	0.086		
BMI, kg/m^2				
<18.5	1		1	
⩾18.5	0.42 (0.28–0.64)	<0.001	0.46 (0.30–0.72)	<0.001
Unknown	1.00 (0.23–4.24)	1.000	1.25 (0.26–6.07)	0.782
Smear at initiation				
Negative	1		1	
Scanty/1+	0.89 (0.24–3.27)	0.857	1.04 (0.27–4.03)	0.950
2+/3+	4.19 (1.47–11.97)	0.007	4.69 (1.55–14.14)	0.006
Unknown	2.13 (0.65–6.99)	0.212	2.36 (0.66–8.43)	0.186
DST at admission				
First-line resistance only	1		1	
Pre-XDR-TB 1 injectable	1.09 (0.54–2.19)	0.807	0.94 (0.45–1.95)	0.872
Pre-XDR-TB 2 injectables	1.78 (1.05–3.02)	0.032	1.43 (0.82–2.51)	0.209
Pre-XDR-TB OFX	2.16 (0.78–5.97)	0.138	1.48 (0.48–4.57)	0.493
XDR-TB	5.41 (2.28–12.79)	<0.001	3.59 (1.37–9.45)	0.010
Second-line DST not performed	1.76 (0.90–3.44)	0.096	1.74 (0.82–3.72)	0.149
Extension of resistance to injectable				
No	1			
Yes	0.94 (0.48–1.84)	0.848		
Unknown	1.17 (0.74–1.86)	0.505		
Extension of resistance to OFX				
No	1		1	
Yes	3.53 (1.96–6.35)	<0.001	3.13 (1.70–5.77)	<0.001
Unknown	1.71 (1.04–2.79)	0.034	1.72 (0.98–3.01)	0.058
Number of drugs taken at initiation				
1–4	1			
5–6	0.82 (0.48–1.40)	0.479		
>6	1.74 (0.97–3.13)	0.063		
Unknown	2.60 (0.42–16.24)	0.307		
Incidence of interruptions due to side effects				
Number/year	1.11 (0.93–1.33)	0.248		
Incidence of interruptions due to patient				
Number/year	0.97 (0.93–1.02)	0.231		

Table A.3 (continued)

	Univariate		Multivariate	
Risk factor of death	OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Prescription of injectable drugs				
Received AMK/KM	1			
Received CPM	1.91 (1.18–3.08)	0.008		
Did not receive injectables	0.91 (0.19–4.37)	0.907		
Prescription of FQs				
Received OFX/CFX	1			
Received LFX/MFX	1.06 (0.69–1.62)	0.786		
Did not receive FQs	0.75 (0.23–2.41)	0.628		
Prescription of thioamides				
Received thioamides	1		1	
Did not receive thioamides	2.28 (1.27–4.11)	0.006	2.07 (1.08–3.99)	0.029
Resistance to ETH				
Susceptible	1			
Resistant	1.61 (0.99–2.61)	0.052		
Missing	1.23 (0.77–1.97)	0.378		
Resistance to PZA				
Susceptible	1			
Resistance	1.05 (0.57–1.91)	0.884		
Missing	0.71 (0.41–1.23)	0.225		
Resistance to EMB				
Susceptible	1			
Resistance	1.54 (0.88–2.69	0.128		
Missing	5.50 (1.27–23.79)	0.022		
Period of inclusion				
2001–2005	1			
2006–2007	0.67 (0.39–1.16)	0.151		
2008–2009	0.85 (0.51–1.40)	0.521		

MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; HIV = human immunodeficiency virus; BMI = body mass index; DST = drug susceptibility testing; XDR-TB = extensively drug-resistant TB; OFX = ofloxacin; AMK = amikacin; KM = kanamycin; CPM = capreomycin; FQ = fluoroquinolone; CFX = ciprofloxacin; LFX = levofloxacin; MFX = moxifloxacin; ETH = ethionamide; PZA = pyrazinamide; EMB = ethambutol.

RESUME

CADRE : L'Organisation Mondiale de la Santé recommande l'addition de la bédaquiline ou de la délamanide lorsqu'un traitement pour la tuberculose multirésistante (TB-MDR) avec quatre antituberculeux efficaces ne peut pas être proposé. La délamanide est aussi recommandée chez les patients qui ont un risque accru d'échec thérapeutique.

OBJECTIF : Identifier les patients à risque d'échec de traitement qui pourraient bénéficier des nouveaux antituberculeux.

MÉTHODE : Etude de cohorte rétrospective sur les résultats de traitement avec 4–5 antituberculeux efficaces pour une durée de 15–24 mois entre 2001 et 2011 dans des programmes en Ouzbékistan, Géorgie, Arménie, Swaziland et Kenya.

RÉSULTATS : Sur 1433 patients, 48,5% avaient un index de masse corporelle (BMI) <18,5 kg/m^2 ; 72,9% avaient une forte charge bacillifère ; 16,7% étaient infectés avec une souche résistante à deux injectables ; 2,9% à l'ofloxacine ; et 3,0% avaient une TB ultrarésistante (TB-XDR). La proportion de succès thérapeutique variait entre 59,7% (pas de résistance aux antituberculeux de seconde ligne) et 27,0% (TB-XDR). TB-XDR (aOR 8,16 ; IC95% 3,22–20,64) ; la résistance à deux injectables (OR ajusté [ORa] 1,90 ; IC95% 1,00–3,62) ou à l'ofloxacine (ORa 5,56 ; IC95% 2,15–14,37) ; une histoire d'incarcération (ORa 1,88 ; IC95% 1,11–3,2) ou de traitement aux antituberculeux de seconde ligne (ORa 3,24 ; IC95% 1,53–6,85]) ; un faible BMI (ORa 2,22 ; IC95% 1,56–3,12) et une forte charge bacillifère (ORa 2,32 ; IC95% 1,15–4,67) étaient associés à une mauvaise réponse thérapeutique. Les patients initiés avec capreomycine au lieu de kanamycine étaient plus à risque d'avoir une mauvaise réponse au traitement (ORa 1,54 ; IC95% 1,04–2,28).

CONCLUSION : Dans notre cohorte, les patients pouvant bénéficier des nouveaux antituberculeux représentaient jusqu'à deux tiers de tous les patients TB-MDR.

RESUMEN

MARCO DE REFERENCIA: La Organización Mundial de la Salud recomienda la adición de bedaquilina o delamanida cuando no se puede planificar un régimen con cuatro medicamentos eficaces contra la tuberculosis multidrogorresistente (TB-MDR) y delamanida en pacientes con alto riesgo de presentar desenlaces clínicos desfavorables.

OBJETIVO: Reconocer a los pacientes propensos a obtener desenlaces desfavorables, en quienes podrían ser útiles los nuevos medicamentos.

MÉTODOS: Fue este un estudio retrospectivo de cohortes sobre los desenlaces terapéuticos de regímenes con 4–5 medicamentos eficaces durante 15–24 meses del 2001 al 2011 en los programas de Uzbekistán, Georgia, Armenia, Swazilandia y Kenia.

RESULTADOS: De los 1433 pacientes analizados, el 48,5% presentaba un índice de masa corporal (BMI) <18,5 kg/m^2, el 72,9% una alta carga bacilar, el 16,7% albergaba cepas resistentes a dos medicamentos inyectables, el 2,9% cepas resistentes a ofloxacino y el 3,0% presentaba TB extremadamente drogorresistente (TB-XDR). El éxito terapéutico osciló entre 59,7% (sin resistencia a medicamentos de segunda línea) y 27,0% (TB-XDR). Los factores que se asociaron con un desenlace desfavorable fueron los siguientes: la TB-XDR (OR ajustado [ORa] 8,16; IC95% 3,22–20,64); la resistencia a dos medicamentos inyectables (ORa 1,90; IC95% 1,00–3,62) u ofloxacino (ORa 5,56; IC95% 2,15–14,37); el antecedente de encarcelamiento (ORa 1,88; IC95% 1,11–3,2); el antecedente de tratamiento con medicamentos de segunda línea (ORa 3,24; IC95% 1,53 –6,85); un bajo BMI (ORa 2,22; IC95% 1,56–3,12); y una alta carga bacilar (ORa 2,32; IC95% 1,15–4,67). Los pacientes que iniciaron capreomicina tuvieron desenlaces desfavorables más frecuentes que los pacientes que iniciaron kanamicina (ORa 1,54; IC95% 1,04–2,28).

CONCLUSION: En la cohorte estudiada, los nuevos medicamentos serían útiles en cerca de dos tercios de todos los pacientes con diagnóstico de TB-MDR.