All-oral longer regimens are effective for the management of multidrug-resistant tuberculosis in high-burden settings

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Shareable abstract (@ERSpublications)
Injectable agents do not offer greater effectiveness than all-oral regimens in individuals with MDR-TB receiving a bedaquiline and/or delamanid-containing regimen. Better evidence on how to effectively manage MDR-TB in people living with HIV is required. https://bit.ly/3zds5d0

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Abstract

Background Recent World Health Organization guidance on drug-resistant tuberculosis treatment de-prioritised injectable agents, in use for decades, and endorsed all-oral longer regimens. However, questions remain about the role of the injectable agent, particularly in the context of regimens using new and repurposed drugs. We compared the effectiveness of an injectable-containing regimen to that of an all-oral regimen among patients with drug-resistant tuberculosis who received bedaquiline and/or delamanid as part of their multidrug regimen.

Methods Patients with a positive baseline culture were included. 6-month culture conversion was defined as two consecutive negative cultures collected >15 days apart. We derived predicted probabilities of culture conversion and relative risk using marginal standardisation methods.

Results Culture conversion was observed in 83.8% (526 out of 628) of patients receiving an all-oral regimen and 85.5% (425 out of 497) of those receiving an injectable-containing regimen. The adjusted relative risk comparing injectable-containing regimens to all-oral regimens was 0.96 (95% CI 0.88–1.04). We found very weak evidence of effect modification by HIV status: among patients living with HIV, there was a small increase in the frequency of conversion among those receiving an injectable-containing regimen, relative to an all-oral regimen, which was not apparent in HIV-negative patients.

Conclusions Among individuals receiving bedaquiline and/or delamanid as part of a multidrug regimen for drug-resistant tuberculosis, there was no significant difference between those who received an injectable and those who did not regarding culture conversion within 6 months. The potential contribution of injectable agents in the treatment of drug-resistant tuberculosis among those who were HIV positive requires further study.

Introduction

Despite the slow decline in overall rates of tuberculosis, multidrug/rifampicin-resistant tuberculosis (MDR/RR-TB) is predicted to increase, leading to even greater morbidity and mortality [1]. Unfortunately, the direct and indirect effects of the coronavirus disease 2019 pandemic are likely to further exacerbate the situation. In addition to the human suffering, economic consequences of an unabated MDR/RR-TB epidemic are catastrophic, with the potential to consume a large portion of the annual healthcare budget in many low- and middle-income countries [2]. Without effective treatment, curtailing the epidemic spread of MDR/RR-TB will not be possible. Advances have occurred with the introduction of bedaquiline and delamanid and the repurposing of linezolid and clofazimine [3]. The ability to balance the relative drug effectiveness and duration of treatment against the risk of toxicities, cost and emergence of further resistance requires knowledge which can only be acquired through additional research studies, including randomised controlled trials (RCTs) and observational data.

Prior to August 2018, MDR/RR-TB treatment guidelines recommended that a member of the aminoglycoside (amikacin or kanamycin) or polypeptide (capreomycin) class be administered parenterally as part of treatment [4]. For the patient, this meant painful daily intramuscular injections for many months, and the risk of irreversible deafness [5] and other harms, such as renal dysfunction and electrolyte disturbance [6]. In 2019, the World Health Organization (WHO) changed the guidelines, de-prioritising the injectable-containing regimens and recommending use of both longer (18–20-month) and shorter all-oral regimens [4]. The de-prioritisation of the injectables in longer RR/MDR-TB regimens was a conditional recommendation based on a single, multicountry individualised patient meta-analysis including more than >12 000 patients from a time period when use of new and repurposed drugs was relatively uncommon [7]. The certainty in the estimate of effect was classified as "very low", leaving an open question about the role of the injectables, especially in the context of regimens containing new and repurposed drugs. In the absence of RCT data (*e.g.* endTB (NCT02754765), STREAM 2 (NCT02409290) and MDR-END (NCT02619994)), well-conducted prospective observational studies with high-quality data can inform and validate guidance in the new era of MDR/RR-TB treatment where regimens include newer drugs and are overall more effective than older regimens [8]. While prior studies examined the comparative effectiveness of replacing the injectable with bedaquiline [9–11], we sought to answer a different question related to injectable use within RR/MDR-TB treatment regimens, namely "Among individuals receiving a bedaquiline- and/or delamanid-containing regimen, do injectable-containing regimens offer greater effectiveness than all-oral regimens?". In this article, we compare the effectiveness of an injectable-containing regimen to that of an all-oral regimen by assessing sputum culture conversion by 6 months among patients with MDR/RR-TB who received bedaquiline- and/or delamanid-containing regimens under routine programme conditions.

Methods

Study design and patient population

The endTB Observational Study (NCT02754765) led by the endTB consortium partners (Partners in Health (PIH), Médecins Sans Frontières (MSF) and Interactive Research and Development (IRD)) comprises a prospective cohort of patients receiving treatment for MDR/RR-TB and has been described in detail elsewhere [12]. All patients who initiated a bedaquiline- or delamanid-containing MDR-TB regimen at an endTB study site were invited to participate in the observational study. The only exclusion criterion was refusal to consent to participate in the study. Bedaquiline and/or delamanid were prescribed to all patients who met at least one WHO indication (*i.e.* a regimen of at least four likely effective drugs could not be constructed due to toxicity or resistance, resistance to fluoroquinolones and/or injectable agents, or high risk of unfavourable treatment outcome [13]). The decision of which drugs to prescribe to form the treatment regimen was made by the responsible physicians at sites in accordance with WHO and local guidance.

A shared study protocol guided data collection, but not treatment, across participating sites. Treatment comprised longer individualised treatment regimens composed according to National Tuberculosis Programme guidelines and informed by the endTB clinical guide [14]. We included patients with a positive baseline sputum culture and who had received a first treatment regimen for confirmed MDR/RR-TB between 1 April 2015 and 31 March 2018. There were only five patients who received streptomycin in the cohort and these five were excluded from this analysis.

Definitions: outcome and exposures

The outcome of interest was sputum culture conversion within the first 6 months of treatment, as this correlates with end-of-treatment outcomes and is used as a standard interim end-point in studies of MDR-TB treatment [7, 9, 12]. Positive baseline sputum culture was defined as a positive culture from the sputum sample collected closest (and <90 days prior) to the initiation of a bedaquiline- and/or

delamanid-containing regimen. Culture conversion was defined as two consecutive negative cultures collected ⩾15 days apart, the first occurring before 180 days of treatment and the second before 210 days. Local laboratory capacity and norms determined whether cultures were grown in liquid (*i.e.* Mycobacterial Growth Indicator Tube (MGIT)) or solid media. 65% of patients were enrolled in countries where sputum samples were predominantly cultured using a MGIT (Armenia, Bangladesh, Ethiopia, Haiti, Indonesia, Kenya, Lesotho, Pakistan, South Africa, Vietnam), and 35% were enrolled in countries where sputum samples were mostly cultured on solid media (Belarus, Georgia, Kazakhstan, Kyrgyzstan, Myanmar, Peru). Patients with a positive baseline sputum culture and without any follow-up culture results were defined as not having experienced culture conversion.

The exposure of interest was the use of an injectable agent at baseline. The term injectable agent refers to those agents that are used in second-line treatment. Therefore, amikacin, capreomycin and kanamycin are defined as injectable agents, while streptomycin is not. The patient had to have commenced an injectable agent within 2 days of the start of the regimen and for a minimum of 2 days to be defined as exposed.

Baseline drug-resistance category was determined based on all prior available drug susceptibility testing (DST) results. If conflicting results were reported for a single drug, a resistant result prevailed. Baseline resistance to injectables was defined as evidence of resistance to any injectable agent on all prior available DST results.

HIV status at baseline was determined by laboratory testing at enrolment. In patients missing laboratory HIV-testing data, clinical documentation of a HIV-positive status or a negative HIV test in the 6 months prior to enrolment was used. A covariate to capture the clinical phenotype of extensive disease [15] was defined by a baseline sputum smear grade (⩾3) and presence of cavitation on chest radiography.

A drug was considered likely to be effective if all reported testing confirmed susceptibility or no resistance was reported to that drug and the patient had not previously received the drug for ⩾1 month. Other covariates included previous history of TB treatment (no previous history, previous first-line and second-line treatment), baseline anaemia (haemoglobin <10 $g \cdot dL^{-1}$) and low body mass index (BMI) (<18.5 $kg \cdot m^{-2}$).

Sample size estimation

With a sample size of 1125 patients, of whom 497 received an injectable agent at baseline, we have ⩾90% power to detect a relative risk of ⩽0.9 or ⩾1.1 of 6-month sputum culture conversion in those on an injectable-containing compared to those on an all-oral regimen, assuming a Type 1 error rate of 0.05, frequency of culture conversion by 6 months of 78.8% and no site-level correlation [16].

Statistical approach

Data on baseline characteristics were summarised with standard descriptive statistics. We used a mixed-effects logistic regression model to analyse the association between exposure status to any injectable-containing regimen at baseline and culture conversion by 6 months, with a random intercept to account for clustering at the country level (primary analysis). A mixed-effects model was used to account for two sources of random variability in the data analysed: the random variability across the sites where patients are enrolled, in addition to the random variability within patient population.

A priori potential confounders were identified based on their known or hypothesised effects on culture conversion and/or injectable prescription [17, 18]. Potential confounders included age, sex, year of enrolment, previous history of TB treatment, clinical characteristics at baseline including drug resistance profile, presence of extensive disease, anaemia, low BMI, HIV status, baseline drug regimen characteristics such as inclusion of at least five probable effective drugs, and inclusion of group A drugs (bedaquiline, linezolid and fluoroquinolone) and delamanid. We conducted a secondary analysis in which we repeated these procedures to assess the relative effectiveness of each individual injectable drug (kanamycin, amikacin, capreomycin) to an all-oral regimen. We tested for effect modification by baseline resistance to any injectable agent and by HIV status. To examine whether effect modification by HIV status was primarily driven by early death or loss in HIV-positive patients, we repeated the analysis excluding deaths and losses occurring prior to conversion in the first 6 months. All p-values of the mixed-effects logistic regression models were generated by likelihood ratio tests.

For ease of interpretation, results of mixed-effects logistic regression models were presented as predicted probabilities of culture conversion with 95% confidence intervals and relative risk using marginal standardisation methods. In brief, the predicted probability of culture conversion is adjusted to a weighted average reflecting the confounder distribution in the total population [19].

Missing data were rare, except for covariate describing extensive disease (13%). A sensitivity analysis of the primary analysis using missing indicator method was undertaken. All analyses were undertaken using Stata Statistical Software (version 16; StataCorp, College Station, TX, USA).

Ethics

The endTB Observational Study protocol was approved by central ethics review committees for each of the three consortium partners (PIH human research committee, MSF ethical review board and IRD institutional review board). In addition, local ethical approval was obtained in all endTB countries. Participants provided written informed consent for prospective inclusion in the observational cohort. We obtained ethical approvals for the inclusion of data from patients who had been commenced on a bedaquiline- or delamanid-containing regimen, but had died or were lost from care prior to providing informed consent.

Results

Overview

2058 patients with MDR/RR-TB consented to participate and initiated bedaquiline and/or delamanid as part of an MDR-TB regimen during the study period. Of these, 933 (45.3%) patients did not have a positive baseline culture and were excluded. After excluding the five patients who received streptomycin as part of their baseline regimen, the analysis included 1120 patients with a positive baseline culture. The study flowchart is shown in figure 1.

67% of the participants were male, and the median (range) age was 36 (12–82) years. Previous treatment with second-line drugs was reported in 75% of patients. Baseline DST revealed resistance to any second-line injectable in 502 (45%) patients. 65% of patients had fluoroquinolone-resistant MDR-TB; of these, 388 (53%) patients had additional resistance to a second-line injectable agent.

Injectable use within the cohort

Of the 1120 patients included, 497 (44%) received an injectable at baseline and this was probably effective in 335 (67%) patients. In those who received an injectable at baseline, 422 (85%) patients spent 100% of their total follow-up time on an injectable. For the remaining 75 patients, this was a median (interquartile range (IQR)) 73% (39–90%) of their total follow-up time. Table 1 shows the baseline characteristics of the cohort stratified by injectable use.

The proportion of patients with HIV infection was lower (6.2% *versus* 14.2%), whereas proportion with prior treatment with second-line drugs was higher (81.1% *versus* 70.6%) in those who received an injectable-containing regimen compared to those who received an all-oral regimen.

Sputum culture conversion at 6 months

Culture conversion by 6 months occurred in 83.8% (522 out of 623) of patients who received an all-oral regimen and 85.5% (425 out of 497) of those who received an injectable-containing regimen at baseline (Chi-squared=0.63; p=0.4).

Marginal predicted probabilities and relative risk of 6-month culture conversion by injectable use at baseline

Table 2 shows the marginal predicted probabilities and relative risk of 6-month culture conversion by injectable use at baseline. After adjusting for *a priori* confounders (age, sex, calendar year, previous history of TB treatment, baseline resistance profile, HIV status, low BMI, extensive disease, inclusion of each drug of interest (linezolid, bedaquiline, a fluoroquinolone, delamanid), baseline anaemia, hepatitis C seropositivity and receipt of at least five effective drugs at baseline), patients who received an injectable-containing regimen had 3% lower risk of culture conversion compared to those who received an all-oral regimen (adjusted relative risk 0.97, 95% CI 0.90–1.04) (table 2: model 1). The effect estimate did not change when using the missing indicator method (table 2: model 2). Supplementary table S1 shows mixed-effect logistic regression models used to estimate marginal predicted probabilities.

Table 3 shows the predicted probability of conversion by 6 months and relative risk for each injectable agent compared to an all-oral regimen. After adjusting for confounders, there was no evidence of an association between kanamycin, or any of the injectables and 6-month culture conversion. Mixed-effect logistic regression models for this analysis are shown in supplementary table S2. In addition, we saw no differences in effect estimates for patients with confirmed and unknown isoniazid resistance (results not shown).

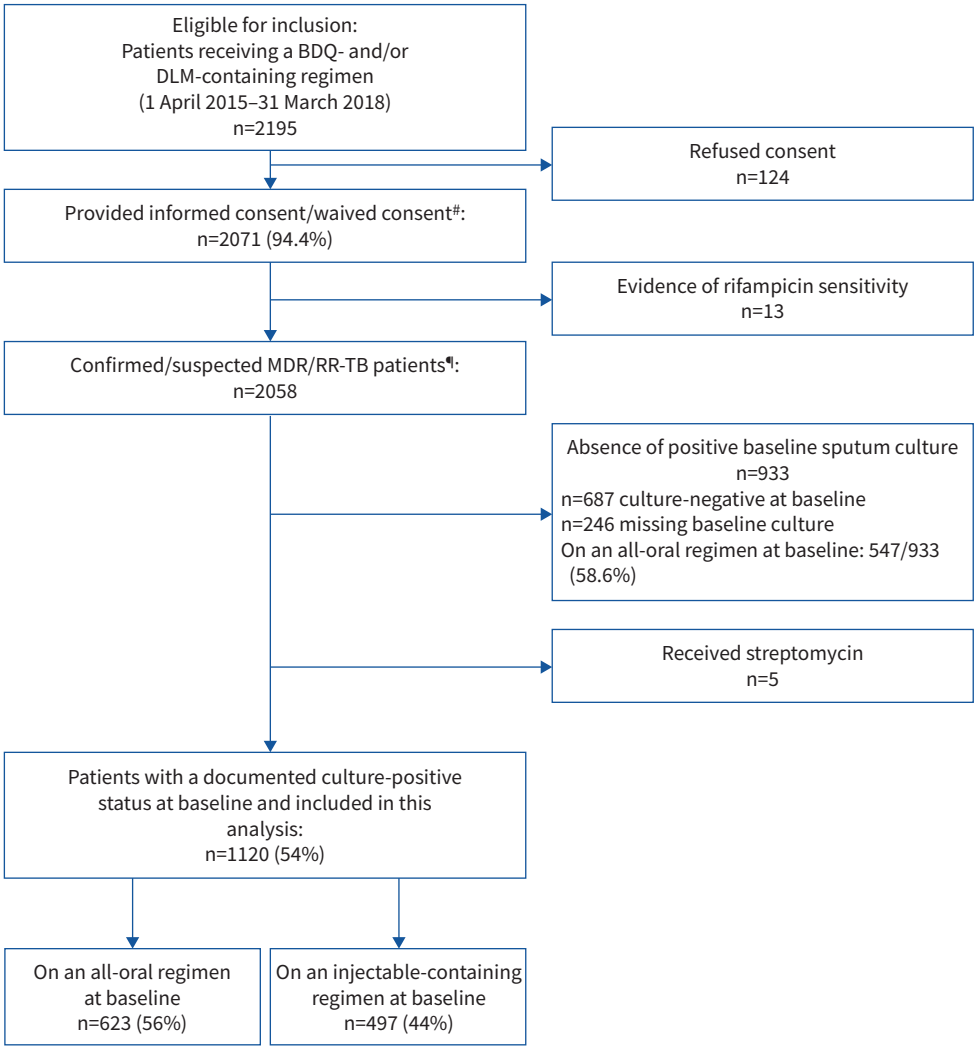

FIGURE 1 Study flowchart. BDQ: bedaquiline; DLM: delamanid; MDR/RR-TB multidrug/rifampicin-resistant tuberculosis. #: n=47 (2.3%) study-eligible patients whose treatment ended for any reason (*e.g.* death, loss to follow-up, *etc.*) before informed consent could be solicited were included retrospectively; ¶: n=52 (2.5%) patients with missing data on rifampicin resistance were included.

Effect modification of the association of injectable use and culture conversion at 6 months by baseline resistance to any injectable agent and HIV status

We found no evidence that the relationship between injectable use and culture conversion within 6 months was modified by baseline resistance to injectables (supplementary table S3). However, there was very weak evidence for effect modification of the primary exposure–outcome relationship by HIV status after adjusting for confounding (table 4) (p=0.17 for the adjusted model 2 including missing indicator variables). Very weak evidence for effect modification was still present after excluding nonconversions due to death and loss to follow-up (table 4) (p=0.18 for adjusted model 3). Figure 2 illustrates the predicted probabilities of culture conversion by injectable use and HIV status estimated from these models. Probability of conversion at 6 months was 10% higher in HIV-positive patients who received an injectable-containing regimen compared to HIV-positive on an all-oral regimen, but confidence intervals were wide (figure 2a). After exclusion of nonconversions due to death and losses, the predicted probabilities of culture conversion were higher in all groups, but the trend for a higher probability of 6-month culture conversion in HIV-positive patients who received an injectable-containing regimen remained (figure 2b). Supplementary table S5 shows the characteristics of patients stratified by HIV status and injectable use. Among patients living with HIV, those on an all-oral regimen were more likely to have anaemia at baseline (35% *versus* 23%) and less likely to have fluoroquinolone-resistance or extensively

TABLE 1 Baseline characteristics of the cohort stratified by injectable use

	All-oral regimen	Injectable-containing regimen
Patients	623	497
Demographic		
Age at treatment initiation median (range)	37 (14–82)	35 (12–70)
Female	199 (32.0)	168 (33.8)
Country		
Armenia	36 (5.8)	38 (7.7)
Bangladesh	143 (23.0)	16 (3.2)
Belarus	34 (5.4)	19 (3.8)
Ethiopia	3 (0.5)	13 (2.6)
Georgia	67 (10.7)	113 (22.7)
Haiti	2 (0.3)	0 (0)
Indonesia	17 (2.7)	3 (0.6)
Kazakhstan	137 (22.0)	83 (16.7)
Kenya	1 (0.2)	2 (0.4)
Kyrgyzstan	4 (0.6)	4 (0.8)
Lesotho	71 (11.4)	12 (2.4)
Myanmar	13 (2.1)	1 (0.2)
North Korea	1 (0.2)	15 (3.0)
Pakistan	56 (9.0)	108 (21.7)
Peru	26 (4.2)	66 (13.3)
South Africa	12 (1.9)	0 (0)
Vietnam	0 (0)	4 (0.8)
Calendar year of study recruitment		
2015	44 (7.0)	51 (10.3)
2016	167 (26.8)	238 (47.9)
2017	290 (46.6)	158 (31.8)
2018	122 (19.6)	50 (10.1)
Comorbidities at baseline		
Diabetes mellitus (n=1056)[#]	91 (15.7)	47 (9.9)
HIV infection (n=1104)	88 (14.2)	30 (6.2)
Hepatitis B serology positive (n=1113)	37 (6.0)	9 (1.8)
Hepatitis C serology positive (n=1113)	82 (13.3)	73 (14.7)
At least one other comorbidity[¶]	73 (11.7)	43 (8.5)
TB-related		
Prior TB treatment		
No prior treatment	64 (10.3)	59 (11.9)
Prior treatment only with first-line drugs	119 (19.0)	35 (7.0)
Prior treatment with second-line drugs	440 (70.6)	403 (81.1)
Cavitary disease and smear status (n=977)[+]		
No cavitary disease, smear status <3+	159 (29.1)	132(30.6)
Cavitary disease, smear status <3+	285 (52.2)	234(54.3)
No cavitary disease, smear status 3+	22 (4.0)	18(4.2)
Cavitary disease, smear status 3+	80 (14.7)	47(10.9)
Resistance profile at baseline[§]		
MDR/RR-TB without any injectable or fluoroquinolone resistance	160 (25.7)	63 (12.7)
MDR/RR-TB without testing for injectable or fluoroquinolone resistance	44 (7.1)	6 (1.2)
MDR/RR-TB with injectable resistance, without fluoroquinolone resistance	73(11.7)	35 (7.0)
MDR/RR-TB with fluoroquinolone resistance, without injectable resistance	94 (15.1)	238 (47.9)
XDR-TB	242 (38.8)	146 (29.4)
Missing rifampicin resistance status	10 (1.6)	9 (1.8)
Anaemia (haemoglobin <10.0 g·dL^{-1}) (n=1069)	91 (15.3)	44 (9.3)
Body mass index <18.5 kg·m^{-2} (n=1110)	286 (46.3)	208 (42.3)
Baseline regimen characteristics		
Drugs comprising the baseline regimen		
Bedaquiline	324 (52.0)	383 (53.8)
Delamanid	202 (32.4)	101 (20.3)
Bedaquiline and delamanid	97 (15.6)	13 (2.6)
Moxifloxacin or levofloxacin	392 (62.9)	253 (50.9)

Continued

TABLE 1 Continued

	All-oral regimen	Injectable-containing regimen
Linezolid	479 (76.9)	443 (89.1)
Clofazimine	458 (73.5)	357 (71.8)
Cycloserine	392 (62.9)	341 (68.6)
Imipenem/cilastatin or meropenem/cilastatin	188 (30.2)	52 (10.5)
Prothionamide or ethionamide	289 (46.4)	173 (37.4)
P-aminosalicylic acid	151 (24.2)	161 (51.4)
Pyrazinamide	341 (54.7)	299 (46.5)
Amikacin		138 (27.8)
Capreomycin		290 (58.4)
Kanamycin		69 (13.9)
Number of drugs included in baseline regimen	6 (5–6)	6 (6–7)
Number of probable effective drugs included in baseline regimen[f]	4 (4–5)	4 (4–5)
⩾5 effective drugs included in the baseline regimen	297 (47.7)	272 (54.7)

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. n=1120. TB: tuberculosis; MDR: multidrug-resistant; RR: rifampicin-resistant; XDR: extensively drug-resistant. [#]: diabetes determined based on laboratory results (*i.e.* random blood sugar >200 mg·dL^{-1} or 11.1 mmol·L^{-1}; fasting blood sugar ⩾126 mg·dL^{-1} and glycated haemoglobin (HbA1c) ⩾6.5%; or two HbA1c results ⩾6.5%) or clinician report. [¶]: comorbidity other than HIV, hepatitis B, hepatitis C or diabetes mellitus. [+]: clinical phenotype of extensive disease defined by a baseline sputum smear grade ⩾3+ and presence of cavitation on chest radiography. [§]: resistance profile categories are mutually exclusive. [f]: a drug was considered probably effective if all reported testing to that drug confirmed susceptibility or no resistance to the drug was reported and the patient had not previously received the drug for ⩾1 month. Otherwise, the drug was not considered probably effective.

drug-resistant TB (30% *versus* 73%) than those on an injectable-containing regimen. 16 (18%) out of 88 of HIV-positive patients on an all-oral regimen had died or were lost to follow-up in the first 6 months of treatment, as compared to three (10.0%) out of 30 on an injectable-containing regimen.

Discussion

We present generalisable findings from 1120 MDR/RR-TB patients treated in 16 countries supporting the use of all-oral regimens, which have a comparable efficacy to injectable-containing regimens in the treatment of MDR/RR-TB. In our analysis, there was no evidence of an association between injectable use

TABLE 2 Marginal predicted probabilities and relative risk of 6-month conversion by injectable use at baseline

	Unadjusted analysis			Adjusted analyses					
				Model 1: complete case			Model 2: missing indicator method		
	Marginal predicted probability of conversion (95% CI)[#]	Crude relative risk (95% CI)[#] n=1120	p-value	Marginal predicted probability of conversion (95% CI)[¶]	Adjusted relative risk (95% CI)[¶] n=938	p-value	Marginal predicted probability of conversion (95% CI)[+]	Adjusted relative risk (95% CI)[+] n=1110[§]	p-value
All-oral regimen	0.79 (0.71–0.87)	Reference		0.84 (0.77–0.91)	Reference		0.83 (0.78–0.89)	Reference	
Injectable-containing regimen	0.82 (0.75–0.89)	1.04 (0.97–1.11)	0.25	0.82 (0.74–0.90)	0.97 (0.90–1.04)	0.40	0.80 (0.73–0.87)	0.96 (0.90–1.03)	0.26

The underlying mixed effects logistic regression models are presented in supplementary table S1. [#]: adjusted for clustering by country; [¶]: adjusted for clustering by country and *a priori* covariates (age, sex, year of enrolment, HIV status, previous history of tuberculosis (TB) treatment, baseline resistance profile, body mass index (BMI) <18.5 kg·m^{-2}, presence of extensive disease at baseline (cavitation and ⩾3+ smear grade), inclusion of group A drugs in the baseline regimen as binary variables (*e.g.* linezolid 0/1; bedaquiline 0/1; fluoroquinolone 0/1), delamanid (0/1), at least five effective drugs in the baseline regimen, anaemia, hepatitis C seropositivity) (complete case analysis: n=938); [+]: adjusted for clustering by country and *a priori* covariates (age, sex, year of enrolment, HIV status, previous history of TB treatment, baseline resistance profile, BMI <18.5 kg·m^{-2}, presence of extensive disease at baseline (cavitation and ⩾3+ smear grade), inclusion of group A drugs in the baseline regimen as binary variables (*e.g.* linezolid 0/1; bedaquiline 0/1; fluoroquinolone 0/1), delamanid (0/1), at least five effective drugs in the baseline regimen, anaemia, hepatitis C seropositivity) (including missing indicator variables: n=1110); [§]: model dropped missing indicator variable for low BMI (n=10), as predicted outcome perfectly.

TABLE 3 Marginal predicted probabilities and relative risk of 6-month culture conversion by injectable agent in baseline regimen

	Unadjusted analysis			Adjusted analyses					
				Model 1: complete case			Model 2: missing indicator method		
	Marginal predicted probability of conversion (95% CI)[#]	Crude relative risk (95% CI)[#] n=1120	p-value	Marginal predicted probability of conversion (95% CI)[¶]	Adjusted relative risk (95% CI)[¶] n=938	p-value	Marginal predicted probability of conversion (95% CI)[+]	Adjusted relative risk (95% CI)[+] n=1110[§]	p-value
No injectable use	0.78 (0.71–0.86)	Reference		0.83 (0.76–0.91)	Reference		0.83 (0.77–0.89)	Reference	
Amikacin	0.79 (0.69–0.90)	1.01 (0.90–1.13)	0.84	0.79 (0.67–0.92)	0.95 (0.83–1.07)	0.44	0.77 (0.67–0.88)	0.93 (0.82–1.05)	0.24
Kanamycin	0.90 (0.82–0.98)	1.15 (1.03–1.27)	0.014	0.88 (0.78–0.98)	1.06 (0.93–1.19)	0.39	0.88 (0.78–0.97)	1.06 (0.94– 1.17)	0.35
Capreomycin	0.80 (0.72–0.89)	1.02 (0.94–1.10)	0.65	0.80 (0.70–0.90)	0.96 (0.87–1.04)	0.33	0.79 (0.71–0.87)	0.95 (0.87–1.03)	0.22

[#]: adjusted for clustering by site; [¶]: adjusted for clustering by country and *a priori* covariates (age, sex, year of enrolment, HIV status, previous history of tuberculosis (TB) treatment, baseline resistance profile, body mass index (BMI) <18.5 kg·m^{-2}, presence of extensive disease at baseline (cavitation and ⩾3+ smear grade), inclusion of group A drugs in the baseline regimen as binary variables (*e.g.* linezolid 0/1; bedaquiline 0/1, *etc.*), delamanid, at least five effective drugs in the baseline regimen, anaemia, hepatitis C seropositivity) (complete case analysis: n=938); [+]: mixed-effects logistic regression model adjusted for clustering by country and *a priori* covariates (age, sex, year of enrolment, HIV status, previous history of TB treatment, baseline resistance profile, BMI <18.5 kg·m^{-2}, presence of extensive disease at baseline (cavitation and ⩾3+ smear grade), inclusion of group A drugs in the baseline regimen as binary variables (*e.g.* linezolid 0/1; bedaquiline 0/1, *etc.*), delamanid, at least five effective drugs in the baseline regimen, anaemia, hepatitis C seropositivity) (including missing indicator variables: n=1110); [§]: model dropped missing indicator for low BMI (n=10), as predicted outcome perfectly.

at baseline and culture conversion by 6 months in individuals with MDR/RR-TB receiving a bedaquiline- and/or delamanid-containing regimen.

In June 2018, almost 18 months prior to the updated WHO recommendations [4], South Africa became the first country to replace the injectable agent with bedaquiline in the routine treatment of MDR/RR-TB patients (aged ⩾12 years) [20]. Motivation for the change ahead of WHO guidance was a national retrospective cohort analysis of medical records of drug-resistant TB patients which found that patients receiving MDR-TB treatment inclusive of bedaquiline had a marked reduction in all-cause mortality compared with standard regimens including an injectable [21]. Evidence from a subsequent observational study in the Western Cape showed improved treatment outcomes when bedaquiline was substituted for injectable agents [10], in keeping with accumulating data on the efficacy of bedaquiline in clinical practice [9, 22]. In the propensity-matched individual patient data meta-analysis [7] informing the latest United States [11] and WHO [4] guidelines, the use of amikacin and streptomycin in susceptible disease was associated with an increase in treatment success when compared to not receiving these agents. However, because of their toxicity and modest efficacy compared with other less toxic drugs, their conclusions were that these specific drugs should be reserved for scenarios when more-effective or less-toxic therapies cannot be assembled to achieve a total of five effective drugs [11].

The question we aimed to assess with this analysis will not be addressed by any ongoing RCTs, although an RCT comparing injectable-containing with all-oral (STREAM 2) shorter regimen will contribute some information regarding management of fluoroquinolone-susceptible MDR-TB disease. The endTB and TB-PRACTECAL trials which use evolving standard of care (injectable-containing through 2018) will also afford a look at short, all-oral, compared to long-injectable containing regimens. However, we know that not all patients with pulmonary TB will be treated successfully with shorter regimens [15]; therefore, it is important to optimise the longer regimen for patients vulnerable to poor outcomes on shorter regimens. People living with HIV are potentially one such group, although there is currently no evidence to support a different composition or duration of MDR-TB treatment for people living with HIV, especially if started on antiretroviral therapy (ART) in a timely fashion.

HIV infection was inversely associated with conversion in this cohort, a finding that was not driven solely by the higher frequency of death in this group [23]. Interestingly, in this analysis we found weak evidence that the effect of the injectable agent on 6-month culture conversion varied by HIV status. Specifically, patients living with HIV experienced a slightly higher frequency of conversion by 6 months if they

TABLE 4 Assessing for effect modification by HIV status: marginal predicted probabilities and relative risk of 6-month culture conversion associated with injectable use stratified by HIV status in baseline regimen (n=1104)[#]

	Unadjusted analysis			Adjusted analyses					
	Marginal predicted probability of conversion (95% CI)[¶]	Crude relative risk (95% CI)[¶] n=1104	p-value	Model 1: complete case: adjusted relative risk (95% CI)[+] n=938	p-value	Model 2: missing indicator: adjusted relative risk (95% CI)[§] n=1094	p-value	Model 3: deaths and losses excluded adjusted relative risk (95% CI)[f] n=1025	p-value
HIV negative n=986			0.39[##]		0.23[##]		0.17[##]		0.18[##]
All-oral regimen	82.3 (75.3–89.3)	Reference		Reference		Reference		Reference	
Injectable-containing regimen	84.3 (77.7–91.0)	1.03 (0.96–1.09)		0.96 (0.89–1.03)		0.95 (0.88–1.01)		0.94 (0.88–1.00)	
HIV positive n=118									
All-oral regimen	66.6 (52.5–80.7)	Reference		Reference		Reference		Reference	
Injectable-containing regimen	79.4 (63.8–95.0)	1.17 (0.89–1.45)		1.12 (0.83–1.41)		1.10 (0.85–1.34)		1.06 (0.86–1.26)	

[#]: n=16 were missing data on baseline HIV status; [¶]: adjusted for clustering by site; [+]: adjusted for clustering by country and *a priori* covariates (age, sex, year of enrolment, previous history of tuberculosis (TB) treatment, baseline resistance profile, body mass index (BMI) <18.5 kg·m^{-2}, presence of extensive disease at baseline (cavitation and ⩾3+ smear grade), inclusion of group A drugs in the baseline regimen as binary variables (*e.g.* linezolid 0/1; bedaquiline 0/1, *etc.*), delamanid, at least five effective drugs in the baseline regimen, anaemia, hepatitis C seropositivity) (complete case analysis: n=941); [§]: mixed-effects logistic regression model adjusted for clustering by country and *a priori* covariates (age, sex, year of enrolment, previous history of TB treatment, baseline resistance profile, BMI <18.5 kg·m^{-2}, presence of extensive disease at baseline (cavitation and ⩾3+ smear grade), inclusion of group A drugs in the baseline regimen as binary variables (*e.g.* linezolid 0/1; bedaquiline 0/1, *etc.*), delamanid, at least five effective drugs in the baseline regimen, anaemia, hepatitis C seropositivity) (including missing indicator variables: n=1099; model dropped missing indicator for low BMI (n=10) as predicted outcome perfectly); [f]: mixed effects logistic regression model adjusted for clustering by country and *a priori* covariates (age, sex, year of enrolment, previous history of TB treatment, baseline resistance profile, BMI <18.5 kg·m^{-2}, presence of extensive disease at baseline (cavitation and ⩾3+ smear grade), inclusion of group A drugs in the baseline regimen as binary variables (*e.g.* linezolid 0/1; bedaquiline 0/1, *etc.*), delamanid, at least five effective drugs in the baseline regimen, anaemia, hepatitis C seropositivity) (including missing indicator variables and having dropped n=69 deaths and losses: n=1030; model dropped missing indicator for low BMI (n=10) as predicted outcome perfectly); [##]: likelihood ratio test for effect modification of underlying mixed-effect logistic regression model (model shown in supplementary table S4).

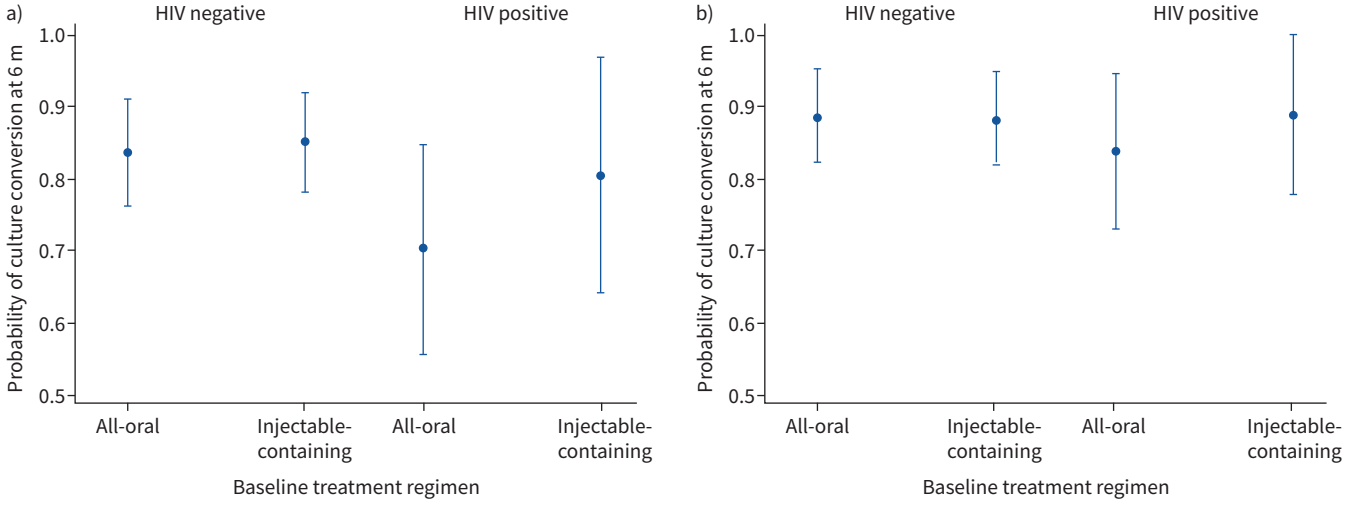

FIGURE 2 Plots of the predicted probabilities of culture conversion at 6 months by injectable use in the baseline regimen and HIV status. a) Includes all participants with known HIV status; b) excludes the deaths and losses.

received an injectable as part of a multidrug regimen; however, confidence intervals were wide and this may be a chance finding. An alternative explanation is that the injectable agent has a small differential effect on survival in the HIV-positive patient population, for reasons that may be indirectly related to MDR-TB disease (*e.g.* empirical treatment of concurrent bacterial sepsis from bacterial translocation) [24]. By reducing early death from bacterial sepsis, HIV-positive patients on an injectable are then able to convert in the subsequent months. However, after excluding deaths and losses to follow-up, the difference in marginal probability of culture conversion remained higher in the HIV-positive group that received an injectable at baseline. Although we adjusted for the inclusion of group A and B drugs in the regimen, residual confounding may still be present with drug–drug interactions with ART directing clinician choice of anti-tubercular regimens. Linezolid use was lower in the HIV-positive patients on an all-oral regimen (45% *versus* 90%), as was bedaquiline use (35% *versus* 60%) compared to HIV-positive patients on an injectable-containing regimen. Thus, another potential explanation is that, among patients living with HIV, an injectable-containing regimen confers a benefit relative to all-oral regimens that do not include bedaquiline and/or linezolid. There is accumulating evidence that optimal treatment may be different for HIV-positive and HIV-negative patients with MDR/RR-TB disease. There was weak evidence from the STREAM trial that the risk of an unfavourable outcome was higher in HIV-positive patients compared to HIV-negative patients [25], which was more pronounced in the shorter regimen arm [26]. Additionally, irreversible toxicity rates may differ by HIV status: a recent meta-analysis of data from South Africa, Namibia and Botswana found that individuals with MDR-TB and HIV co-infection had a 22% higher risk of developing aminoglycoside-induced hearing loss than non-HIV-infected individuals (pooled relative risk 1.22, 95% CI 1.10–1.36) during MDR-TB treatment [27]. Whether our finding of effect modification by HIV status is due to random chance or not, further research on how best to manage HIV-positive MDR/RR-TB patients is urgently required in specifically designed observational and interventional studies for this special population.

With regards to baseline resistance, prior evidence suggests that the use of drugs despite *in vitro* resistance leads to poor outcomes for MDR-TB patients [28–30]. In our study, we did not find that the association between an injectable-containing regimen and culture conversion by 6 months differed by documented baseline injectable resistance. It may have been that use of new and repurposed drugs compensated for the lack of effectiveness of the injectable, or that any marginal benefit of injectables, in presence of susceptibility, was not detectable in regimens containing new and repurposed drugs. It is also possible that clinicians accounted for a potential lack of effectiveness by adding additional drugs to the regimen.

Limitations of this study include restriction of the analysis to patients who were culture-positive at the start of treatment, although at present there is no standardised interim outcome in patients who are lacking a culture or culture-negative at baseline. We were unable to account for variability in local laboratory capacity, and exploration of potential differences in culture-conversion by culture-type was hampered by some patients having both MGIT and solid-culture results. In addition, we did not adjust for time-varying confounders, such as treatment changes, although injectable use did not vary markedly in the first 6 months [31]. The presence of unmeasured confounding cannot be ruled out, and residual confounding is expected when using the missing indicator method to adjust for missing data on confounders; however, the relatively small amount of missing data should limit this bias. Future research examining comparative effectiveness of RR/MDR-TB treatment with regard to end-of-treatment outcomes, acquired resistance and adverse events will contribute to a more comprehensive understanding of optimal regimens.

Our analyses of standardised programmatic data from diverse settings spanning 16 countries supports the de-prioritisation of the injectable agents in most MDR-TB patients and highlights the need for more specifically designed robust observational studies to complement ongoing RCTs to generate real-world evidence on how best to effectively manage MDR/RR-TB disease, particularly among patients living with HIV.

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