Long-term bedaquiline-related treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa

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ABSTRACT Optimal treatment regimens for patients with extensively drug-resistant tuberculosis (XDR-TB) remain unclear. Long-term prospective outcome data comparing XDR-TB regimens with and without bedaquiline from an endemic setting are lacking.

We prospectively followed-up 272 South African patients (49.3% HIV-infected; median CD4 count 169 cells·μL^{-1}) with newly diagnosed XDR-TB between 2008 and 2017. Outcomes were compared between those who had not received bedaquiline (pre-2013; n=204) and those who had (post-2013; n=68; 80.9% received linezolid in addition).

The 24-month favourable outcome rate was substantially better in the bedaquiline *versus* the non-bedaquiline group (66.2% (45 out of 68) *versus* 13.2% (27 out of 204); p<0.001). In addition, the bedaquiline group exhibited reduced 24-month rates of treatment failure (5.9% *versus* 26.0%; p<0.001) and default (1.5% *versus* 15.2%; p<0.001). However, linezolid was withdrawn in 32.7% (18 out of 55) of patients in the bedaquiline group because of adverse events. Admission weight >50 kg, an increasing number of anti-TB drugs and bedaquiline were independent predictors of survival (the bedaquiline survival effect remained significant in HIV-infected persons, irrespective of CD4 count).

XDR-TB patients receiving a backbone of bedaquiline and linezolid had substantially better favourable outcomes compared to those not using these drugs. These data inform the selection of XDR-TB treatment regimens and roll-out of newer drugs in TB-endemic countries.

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Introduction

The persistence of the multidrug-resistant tuberculosis (MDR-TB) epidemic threatens to destabilise TB control [1, 2]. MDR-TB is defined as a TB strain with resistance to at least isoniazid and rifampicin. In 2016 ~600 000 new cases of MDR- or rifampicin-resistant TB were estimated to have occurred globally. Detection rates have more than doubled in several countries such as China, India and Russia in the last several years, and almost 20% of *Mycobacterium tuberculosis* isolates globally are now resistant to at least one first- or second-line anti-TB drug [3]. Approximately 10% of global MDR-TB strains are thought to be extensively drug-resistant TB (XDR-TB), which is MDR-TB with additional resistance to a fluoroquinolone and a second-line injectable drug. These strains may subvert TB control globally, because they are associated with high mortality and morbidity, are a major threat to healthcare workers [2, 4] and are unsustainably costly to treat in countries with high TB incidence [5]. For example, in 2016 in South Africa ~7.1% of patient samples screened were rifampicin-resistant or MDR-TB, of which ~8% were XDR-TB [6]. It was estimated that MDR-/XDR-TB will consume >80% of TB treatment costs in South African in 2017/2018, despite MDR-TB making up <10% of the total caseload [7].

Lack of an effective treatment regimen facilitates the person-to-person transmission of XDR-TB even after treatment initiation, and explains the poor outcomes associated with XDR-TB. The culture conversion rate in patients with XDR-TB between 2002 and 2008 in South Africa was only ~19% by the end of the follow-up period [8] and a prospective follow-up study indicated that only 16% of XDR-TB patients had a favourable outcome [9]. Outcomes were not any better in HIV co-infected XDR-TB patients from the KwaZulu-Natal and Eastern Cape provinces, with a reported favourable outcome rate of 12.2% in patients receiving antiretroviral drugs [10].

The advent of new and repurposed bactericidal drugs such as linezolid and bedaquiline have offered new hope for patients with XDR-TB [11–14]. However, linezolid was associated with significant myelo- and neurotoxicity mandating the withdrawal of the drug in almost 30% of patients [15, 16]. A phase II(b) study found that bedaquiline was associated with increased mortality, significant adverse events including QT prolongation and hepatitis, raising concerns about efficacy and outcome [17]. A unified analysis of bedaquiline in industry-funded clinical trials showed that bedaquiline was associated with a 24-month failure rate of almost 40% in XDR-TB patients [17]. Moreover, observational datasets from both TB-endemic and low-burden settings showed encouraging 6-month culture conversion outcomes; however, there are no long-term data [11, 18]. In addition, there were concerns that clofazimine, currently widely used to treat MDR-TB, could potentially induce cross-resistance to bedaquiline, thereby mitigating its potentially favourable impact [19, 20]. Thus, the clear-cut benefit of bedaquiline in a programmatic setting remains unclear. While there are limited but encouraging short-term outcome data from endemic settings [21, 22], the lack of long-term (24-month) comparative outcomes means that there remains controversy and equipoise regarding the immediate and widespread roll-out of bedaquiline to treat XDR-TB *versus* awaiting results from controlled clinical trials. To address this issue, we compared long-term outcomes using a bedaquiline- (and often linezolid)-containing XDR-TB regimen, to those not containing bedaquiline or linezolid, in a high TB-incidence setting.

Methods

Participants

We prospectively followed-up 272 patients with laboratory-confirmed XDR-TB who started drug therapy between January 2008 and June 2017 in a programmatic setting (enrolment and follow-up censor dates were April 2016 and June 2017, respectively). 204 patients received a non-bedaquiline-based anti-TB regimen while 68 received a bedaquiline-based regimen. All patients were admitted to Brooklyn Chest Hospital (Cape Town, South Africa), which is the designated XDR-TB treatment centre in the Western Cape province of South Africa, and treatment was directly observed by trained health workers. Adverse events were graded and actively reported by medically qualified and experienced attending healthcare workers using a report form that was attached to every patient's folder (grading of adverse events is described in online supplementary table S1). Hearing impairment was measured by trained audiologists who conducted testing on all patients as part of the programmatic routine. Demographic and clinical information was obtained by a trained healthcare worker from patient records and associated healthcare and laboratory systems. The demographic variables we collected were age, sex and body weight, while the clinical variables were HIV status, drugs used in the regimen, adverse events, CD4 count, number of admission days and ECG results. QTc was corrected using Fridericia's formula and patients with values >450 ms were considered high risk and closely monitored. Upon discharge, treatment was directly observed by trained health workers in local healthcare facilities closer to patients' homes. Ethical approval was obtained from University of Cape Town human research ethics committee.

Diagnostic criteria

Of all culture-confirmed XDR-TB patients in the Western Cape between 2008 and 2017, only those who initiated treatment were included in the study. Thus, all the included patients had isolates resistant to rifampicin, isoniazid, ofloxacin and amikacin, and fulfilled the criteria for XDR-TB diagnosis. All patients underwent monthly smear microscopy and culture during hospitalisation, and sometimes less frequently following hospital discharge.

Treatment regimens

The background 24-month treatment regimen was prescribed by the attending physician following the results of individual patients' drug susceptibility testing to isoniazid, rifampicin, ofloxacin and amikacin. XDR-TB patients in the non-bedaquiline group were treated with a backbone of para-aminosalicylic acid (PAS)/clofazimine/capreomycin and second-/fourth-generation fluoroquinolones. Capreomycin was used in the hope that high serum levels would have a therapeutic effect and overcome intrinsic resistance; fluoroquinolones were used since there is differential susceptibility among them and most isolates were only tested for resistance to ofloxacin. The other components included pyrazinamide, terizidone, ethionamide, *etc*. The patients who received the bedaquiline-based treatment regimen often received clofazimine, linezolid and levofloxacin (ofloxacin susceptibility testing was performed) concurrently as major components of their regimen. HIV-infected patients received antiretroviral drugs, which included lamivudine, nevirapine, efavirenz, tenofovir and abacavir.

Outcomes

Treatment outcomes were assigned according to the adapted 2013 World Health Organization definitions and reporting frameworks for TB, and the proposed core definitions for drug-resistant TB clinical trials recommended by Furin *et al.* [23, 24] (online supplementary table S2). Patients were said to have achieved culture conversion if they had two consecutive negative sputum culture results, taken at least ~30 days apart (one missing or contaminated culture was allowed between negative cultures, and inability to produce sputum was considered to be a negative result). The treatment outcomes evaluated were cure/treatment completion, deceased, treatment failure, treatment default and lost to follow-up. Patients who achieved cure/completion were said to have had a favourable outcome while the deceased, defaulted and those who failed treatment were said to have had unfavourable outcomes.

Statistical analysis

The effect of bedaquiline treatment was determined by comparative analysis of the demographics, clinical records, survival and treatment outcomes. Quantitative and qualitative variables were reported in percentages and median (interquartile range (IQR)). Quantitative and qualitative variables were compared using Mann–Whitney U-test and Chi-squared or Fisher's exact tests, respectively. Kaplan–Meier curves were estimated for the probability of survival from date of diagnosis, and end of follow-up was date of death, date of loss to follow-up or censor date. Comparisons between strata (*e.g.* HIV-infected *versus* HIV-uninfected individuals) were made by the log-rank test. Univariate Cox proportional hazards models were used to estimate the relationship between explanatory variables and time-to-event outcomes. Multivariate Cox proportional hazards models included variables that were significantly associated with outcome ($p<0.1$) with clinical relevance and the preselected variable, sex. A p-value of <0.05 was taken as statistically significant. The sensitivity and specificity of sputum cultures to predict outcomes were computed. Statistical analyses were performed in R (v3.4.0) using the packages usdm (v1.1.18), corrplot (v0.77), survival (v2.41.3) and survminer (v0.4.0).

Results

Demographic and clinical characteristics

The non-bedaquiline group comprised 204 culture-confirmed XDR-TB patients admitted between January 2008 and September 2014. Demographic and clinical characteristics are shown in table 1. Patients were admitted for a median 199 (IQR 77–329) days and received a PAS/clofazimine/capreomycin and fluoroquinolone-based non-bedaquiline regimen containing a median of 9 (IQR 8–10) drugs (frequencies of drugs are outlined in table 2). 99 (48.5%) out of 204 patients in this group were HIV-infected with a median CD4 count of 198 (IQR 71–302) cells·μL^{-1} at admission and 90 (90.9%) out of 99 had been commenced on antiretroviral therapy prior to, or within 3 months of diagnosis of XDR-TB.

The bedaquiline group comprised 68 culture-confirmed XDR-TB patients admitted between November 2013 and April 2016. Patients were admitted for a median 158 (102–221) days; they received a bedaquiline-based regimen which contained a median of 8 (IQR 7–8) drugs (table 2). Patients received bedaquiline for a median 178 (IQR 54–272) days. 35 (51.5%) out of 68 patients were HIV infected, with a

TABLE 1 Comparison of demographic data, clinical characteristics and treatment outcomes between the bedaquiline and non-bedaquiline groups

	Bedaquiline	Non-bedaquiline	p-value
Patients n	68	204	
Age years	34.5 (26–55)	33.5 (18–73)	0.42
Male	41 (60.3)	120 (58.8)	0.89
Body weight at admission kg	51.8 (33.3–78.1)	51.9 (21.0–89.9)	0.76
Patients weighing >50 kg	39 (57.4)	115 (56.4)	0.89
Previous TB treatment	33 (48.5)	171 (83.8)	<0.001
HIV-infected	35 (51.5)	99 (48.5)	0.81
HIV-infected on ARV therapy	35 (100)	90 (90.9)	0.11
Median CD4 count at admission μL·mL^{-1}	146 (57–271)	198 (71–302)	0.51
Anti-TB drugs received[#] n	8 (7–8)	9 (8–10)	<0.001
Patients in whom at least one drug was withdrawn due to adverse events	40 (58.8)	78 (38.2)	0.005
Days of admission n	158 (102–221)	199 (77–329)	0.05
Outcomes			
Favourable (cured/completed treatment)	45 (66.2)	27 (13.2)	<0.001
Unfavourable outcome	23 (33.8)	175 (85.8)	
Deceased	10 (14.7)	69 (33.8)	0.004
Failed	4 (5.9)	53 (26)	<0.001
LTFU	8 (11.8)	22 (10.8)	1
Defaulted	1 (1.5)	31 (15.2)	<0.001
On treatment	0 (0)	2 (1)	
Patients with favourable outcome despite drug withdrawal due to adverse events[¶]	23 (57.5)	10 (12.8)	<0.001
HIV-infected patients with a favourable outcome	24 (68.6)	18 (18.2)	<0.001

Data are presented as median (interquartile range) or n (%), unless otherwise stated. TB: tuberculosis; ARV: antiretroviral; LTFU: lost to follow-up. [#]: bedaquiline was included in the total number of anti-TB drugs used in the bedaquiline group; [¶]: this was to identify the proportion of patients who had a favourable outcome (regardless of adverse events that necessitated the withdrawal of at least one drug in the treatment regimen).

median CD4 count of 146 (IQR 57–271) cells·μL^{-1} at admission, and they all received antiretroviral therapy following diagnosis.

Culture conversion

In the non-bedaquiline group, 67 (32.8%) out of 204 patients achieved culture conversion by the end of 24 months, but only 27 (40.3%) of these patients achieved a favourable outcome. The sensitivity of a negative sputum culture to predict survival was 81.0% at 6 months. In addition, the specificity of positive sputum culture to predict mortality was high, reaching 83.6% at 6 months (table 3).

In the bedaquiline group, 46 (67.6%) out of 68 patients achieved culture conversion by the end of 24 months and 45 (97.8%) of them achieved a favourable outcome. The sensitivity of a negative sputum culture to predict survival was 97.2% at 6 months. The specificity of positive sputum culture to predict mortality at 6 months was 33.3% (table 3).

Treatment outcomes

A favourable outcome was achieved in only 27 (13.2%) out of 204 patients in the non-bedaquiline group, while the remaining patients had an unfavourable outcome after the 24-month follow-up period (table 4). Only 18 (18.2%) out of 99 HIV-infected patients in this group had favourable outcomes.

A favourable outcome was achieved in 45 (66.2%) out of 68 patients in the bedaquiline group, while the remaining patients had an unfavourable outcome after the 24-month follow-up period (table 4). 24 (68.6%) out of 35 HIV-infected patients in this group had favourable outcomes.

Patients who received bedaquiline had a higher probability of survival ($p<0.001$; figure 1a) in time-to-event analysis. Bedaquiline had a similar effect in HIV-infected patients ($p<0.001$; figure 1b). Patients in the bedaquiline group who received antiretroviral therapy ($p<0.001$) had a significantly higher probability of survival than their counterparts in the non-bedaquiline group (figure 1c). In addition,

TABLE 2 List of drugs used in the bedaquiline and the non-bedaquiline treatment regimens, the proportion of patients who used them and the frequency of drug withdrawal due to adverse events

Drugs	Bedaquiline		Non-bedaquiline		p-values (comparing proportions of patients who received drug)
	Patients who received drug	Patients in whom drug was withdrawn due to adverse events (grade ⩾3)	Patients who received drug	Patients in whom drug was withdrawn due to adverse events (grade ⩾3)	
Patients n		68		204	
Capreomycin	7 (10.3)	6 (85.7)	196 (95.6)	43 (21.9)[+]	<0.001
Kanamycin	1 (1.5)	1 (100)	110 (53.9)	12 (10.9)	<0.001
Amikacin	0	0	2 (1.0)	0	N/A
Any aminoglycoside[#]	8 (11.8)	0	202 (99.0)	47 (23.0)	<0.001
Para-amino salicylic acid	64 (94.1)	10 (15.6)	194 (95.1)	13 (6.7)	0.75
Pyrazinamide	66 (97.1)	3 (4.5)	201 (98.5)	10 (5.0)	0.60
Terizidone	61 (89.7)	8 (13.1)	201 (98.5)	10 (5.0)	0.003
Moxifloxacin	13 (19.1)	1 (7.7)	101 (49.5)	3 (3.0)	<0.001
Ofloxacin	0	0	127 (62.3)	3 (2.4)	N/A
Levofloxacin	67 (98.5)	0	0	0	N/A
Ciprofloxacin	0	0	1 (0.5)	0	N/A
Third- or fourth-generation fluoroquinolone[¶]	68 (98.5)	0	101 (49.5)	0	<0.001
Clofazimine	67 (98.5)	1 (1.5)	65 (31.9)	2 (3.1)	<0.001
Linezolid	55 (80.9)	18 (32.7)	0	0	N/A
Ethambutol	26 (38.2)	5 (19.2)	189 (92.7)	15 (7.9)	<0.001
Ethionamide	15 (22.1)	6 (40)	198 (97.1)	12 (6.1)	<0.001
High-dose isoniazid	22 (32.4)	3 (13.6)	133 (65.2)	13 (9.8)	<0.001
Dapsone	0	0	34 (16.7)	0	N/A
Co-amoxiclavulanate	2 (2.9)	0	79 (38.7)	0	<0.001
Clarithromycin	0	0	43 (21.1)	0	N/A
Amoxicillin	0	0	13 (6.4)	0	N/A
Azithromycin	0	0	1 (0.5)	0	N/A
Meropenem	1 (1.5)	0	0 (0.0)	0	N/A
Bedaquiline	68 (100)	0	0 (0.0)	0	N/A

Data are presented as n (%), unless otherwise stated. N/A: not applicable. [#]: combination of amikacin, kanamycin and capreomycin; kanamycin was replaced by capreomycin in the course of the treatment; [¶]: treatment with either moxifloxacin or levofloxacin; [+]: significant difference between number of patients from whom drugs were withdrawn.

bedaquiline provided the survival advantage to HIV-infected patients regardless of their CD4 count at admission (figure 1d and e).

Adverse events

486 adverse events were reported by 143 (70.1%) out of 204 patients in the non-bedaquiline group. Frequencies of adverse events are reported in table 5. 78 (38.2%) out of 204 patients had at least one drug withdrawn due to adverse events (grade ⩾3) during treatment. Only 10 (12.8%) out of 78 patients from whom drugs were withdrawn achieved a favourable outcome.

226 adverse events were reported by 65 (95.6%) out of 68 patients in the bedaquiline group. More patients in this group, 40 (58.8%) out of 68, had at least one drug withdrawn (p=0.005), and 23 (57.5%) of them achieved a favourable outcome. None of the patients had bedaquiline withdrawn from the treatment regimen, although seven (10.3%) out of 68 had a prolonged QT interval within 450–470 ms. Five (71.4%) of these seven patients achieved a favourable outcome, one (14.3%) was lost to follow-up and one (14.3%) died. The deceased patient achieved culture conversion after 41 days of bedaquiline treatment, but reverted 61 days later and did not achieve another conversion before death; this patient has been on bedaquiline for 170 days.

Multivariate analysis

Multivariate analysis of patients in both groups suggested that receiving bedaquiline (hazard ratio (HR) 0.24; p=0.05) and number of anti-TB drugs received (HR 0.83; p=0.01) were independent predictors of survival. In addition, it is suggested that patients who were HIV-infected (HR 1.51; p=0.02) and those who

TABLE 3 Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of culture negativity at specific time points to predict survival and favourable treatment outcome in each group

	Sensitivity		Specificity		PPV		NPV		Patients considered n	
	Bedaquiline	Non-bedaquiline	Bedaquiline	Non-bedaquiline	Bedaquiline	Non-bedaquiline	Bedaquiline	Non-bedaquiline	Bedaquiline	Non-bedaquiline
A) Survival as dependent variable										
2 months	82.5	50.0	0	79.0	86.8	54.1	0	76.2	45	121
3 months	91.5	66.7	33.3	79.5	95.6	66.7	20.0	79.5	50	134
6 months	97.2	81.0	33.3	83.6	94.6	75.6	50.0	87.5	39	109
12 months	90.3	75.0		84.2		75.0		84.2	31	62
18 months	96.2	78.3		71.4		81.8		66.7	26	37
B) Favourable treatment outcome as dependent variable										
2 months	88.2	60	27.3	75.2	78.9	32.4	42.9	90.5	45	121
3 months	94.6	72.7	23.1	68.8	77.8	31.4	60.0	92.8	50	134
6 months	100	94.7	22.2	70.0	81.1	40.0	100	98.4	39	109
12 months	96.2	100	40.0	74.5	89.3	45.8	66.7	100	31	62
18 months	100	93.3	50.0	63.6	96	63.6	100	93.3	26	37

Data are presented as %, unless otherwise stated. Sensitivity: probability that a negative sputum culture will result in patient survival (or in the case of section B, a favourable treatment outcome); specificity: probability that a positive sputum culture will result in patient mortality (or in the case of section B, a favourable treatment outcome); PPV: probability that a patient with a negative sputum culture survived (or in the case of section B, a favourable treatment outcome); NPV: probability a patient with a positive sputum culture died (or in the case of section B, a favourable treatment outcome). A combined analysis is shown in online supplementary table S9.

TABLE 4 Treatment outcomes at specific time points as measured from treatment initiation

Treatment outcome	12 months		18 months		24 months	
	Bedaquiline	Non-bedaquiline	Bedaquiline	Non-bedaquiline	Bedaquiline	Non-bedaquiline
Favourable	N/A	N/A	N/A	N/A	45 (66.2)	27 (13.2)#
Unfavourable	21 (30.9)	160 (78.4)	23 (33.8)	173 (84.8)	23 (33.8)	175 (85.8)#
Deceased	8 (11.8)	55 (27)*	9 (13.2)	60 (29.4)*	10 (14.7)	69 (33.8)*
Default	2 (2.9)	21 (10.3)	2 (2.9)	26 (12.7)*	1 (1.5)	31 (15.2)#
Treatment failed	5 (7.4)	70 (34.3)#	4 (5.9)	69 (33.8)#	4 (5.9)	53 (26.0)#
LTFU	6 (8.8)	14 (6.9)	8 (11.8)	18 (8.8)	8 (11.8)	22 (10.8)
On treatment	47 (69.1)	44 (21.6)	45 (66.2)	31 (15.2)	0 (0)	2 (1.0)

Data are presented as n (%). Outcomes were assigned as described in online supplementary table S2 for the bedaquiline (n=68) and non-bedaquiline (n=204) groups. LTFU: lost to follow-up; N/A: not applicable. p-values were *: <0.05 or #: <0.005 when comparing time-specific treatment outcomes between patients in the bedaquiline and non-bedaquiline groups.

weighed <50 kg at admission (HR 1.96; p<0.001) were more likely to die (table 6). In HIV-infected patients, receiving bedaquiline (HR 0.01; p=0.01) and any aminoglycoside (HR 0.06; p=0.02) were independent predictors of survival, and those who weighed ⩽50 kg at admission (HR 2.06; p=0.004) were more likely to die (table 6).

Discussion

To our knowledge, this is the first prospective comparative study reporting long-term (24-month) treatment-related outcomes in patients with XDR-TB, treated with and without bedaquiline, in a TB-endemic setting. These data represent pragmatic and "real-world" outcomes as they are derived from a programmatic setting. The key findings of the study were as follows. 1) Favourable outcomes using bedaquiline (and linezolid) were more than five-fold better compared to regimens not containing bedaquiline; 2) mortality in the bedaquiline group was more than halved; 3) treatment failure rates were reduced by more than four-fold and there was a >10-fold reduction in default rates; 4) bedaquiline remained an independent predictor of survival (despite the use of linezolid), and other independent outcome predictors included admission weight of >50 kg (probably reflecting the immune and nutritional status of the patient) and an increasing number of anti-TB drugs used; 5) the bedaquiline survival and favourable outcome effect remained significant in HIV-infected persons and even at low CD4 counts; 6) a 6-month negative culture was ∼95% predictive of patient survival in the bedaquiline group, and 81% predictive of a favourable outcome (in contrast, a positive culture at 6 months was highly predictive of death or unfavourable outcome); and 6) bedaquiline-related prolonged QT interval occurred in ∼10% of the cohort, but none had bedaquiline withdrawn and most still achieved a favourable outcome. In contrast, 33% of patients experienced linezolid withdrawal due to adverse events.

The dominant finding was that bedaquiline is an independent predictor of survival and favourable outcome, and the backbone of bedaquiline and linezolid was associated with remarkably better treatment outcomes compared to regimens not containing these drugs. In addition, there was a higher frequency of death in the bedaquiline group within the first 2 months of treatment initiation (probably due to a survival bias related a higher rate of pre-diagnostic death in the non-bedaquiline group); however, exclusion of deaths in this early period did not change the study conclusions (online supplementary table S10). Concerns regarding QT prolongation and the potential toxicity of bedaquiline (reassuringly low in this study) must be compared against the dramatic and exceptional survival improvement in a disease where mortality is ∼70% when using a second-line injectable and fluoroquinolone-based regimen [3], and this raises the question of whether bedaquiline and linezolid should now be included in all regimens for the treatment of XDR-TB in programmatic settings. Our outcome data are compelling because they allow direct comparison between individuals from the same region who had long-term survival outcomes before and after the introduction of bedaquiline within the context of a prospective study. In contrast, hitherto, studies on patients with XDR-TB have reported short-term outcomes only, or those from non-endemic settings. A retrospective study from South Africa [21], an Indian study [22], and a study from KwaZulu-Natal in South Africa [18] reported 6-month culture conversion rates of 76% (n=63), 65% (n=20) and 68% (n=123), respectively, in bedaquiline-treated patients with XDR-TB. Importantly, the bedaquiline effect dominated and remained significant, even in HIV-infected individuals and those with low CD4 counts. Nevertheless, our results were inferior to the 24-month 80% favourable outcome rate reported from France in 45 patients where 53% of the cohort had XDR-TB [25]. In our study, more than a

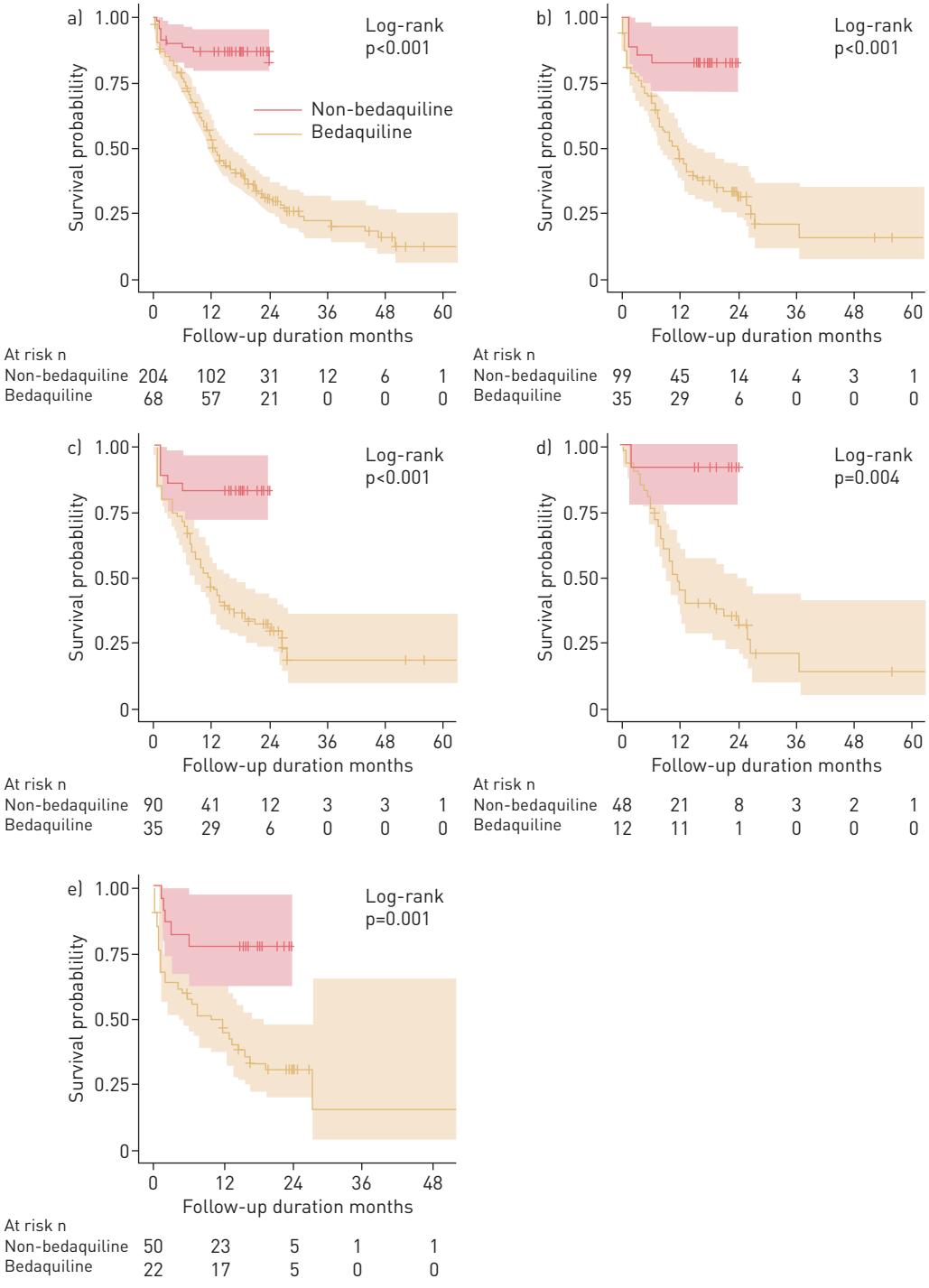

FIGURE 1 Kaplan–Meier survival estimate for patients in the bedaquiline and the non-bedaquiline groups. Shading indicates the 95% confidence interval and plus signs represent patients censoring events. a) Whole cohort; b) HIV-infected patients; c) HIV-infected patients who received antiretroviral therapy; d, e) HIV-infected patients whose CD4 counts were d) ⩾200 cells·μL^{-1} and e) <200 cells·μL^{-1}.

third of patients still had unfavourable outcomes and mortality was almost 15% despite bedaquiline treatment. Firstly, this highlights the poor outcomes associated with XDR-TB (despite bedaquiline), which is worse than that seen in several common cancers. Secondly, treatment failure still remains a problem. We have previously highlighted the problem of programmatically incurable TB and the substantial longevity of these patients following discharge into the community (given the lack of facilities and bed space, this is the only option available in many TB-endemic countries including India, China and Russia) [26]. Indeed, in

TABLE 5 List of all adverse events reported in the bedaquiline and the non-bedaquiline groups

	Bedaquiline group	Non-bedaquiline group	p-value
Subjects n	68	204	
Peripheral neuropathy	15 (22.1)	13 (6.4)	<0.001
Dizziness/disorientation	11 (16.2)	35 (17.2)	0.85
Depression	2 (2.9)	27 (13.2)	0.02
Headache	2 (2.9)	12 (5.9)	0.53
Psychosis	3 (4.4)	17 (8.3)	0.42
Blurred vision	5 (7.4)	5 (2.5)	0.14
Hearing impairment	29 (42.7)	31 (15.2)	<0.001
Tinnitus	1 (1.5)	4 (2.0)	1
Abdominal pain	15 (22.1)	34 (16.7)	0.41
Vomiting	16 (23.5)	58 (28.4)	0.71
Nausea	16 (23.5)	59 (28.9)	0.65
Diarrhoea	6 (8.8)	21 (10.3)	0.91
Acute liver failure	1 (1.5)	6 (2.9)	0.68
Dyspepsia	3 (4.4)	5 (2.5)	0.42
Skin reaction	20 (29.4)	40 (19.6)	0.13
Arthralgia	13 (19.1)	15 (7.4)	0.011
Body pains	19 (27.9)	32 (15.7)	0.04
Anaemia	14 (20.6)	2 (1.0)	<0.001
Deranged renal function	14 (20.6)	41 (20.1)	0.93
Pruritus	3 (4.4)	12 (5.9)	0.77
Hypothyroidism	6 (8.8)	10 (4.9)	0.37
Haematological disorders	2 (2.9)	2 (1.0)	0.26
Oedema	1 (1.4)	1 (0.5)	0.44
Anxiety	1 (1.5)	N/A	N/A
Sore throat	1 (1.5)	N/A	N/A
Insomnia	0 (0)	4 (2.0)	N/A
Prolonged QT interval	7 (10.3)	N/A	N/A

Data are presented as n (%), unless otherwise stated. N/A: not applicable.

South Africa we are now facing the problem of patients who have failed bedaquiline- and linezolid-based regimens. Only a minority of these patients have access to, or qualify for, surgical lung resection, and it is difficult, if not impossible, to construct a salvage regimen for such patients. This highlights the need to protect existing drugs and practise strict antibiotic stewardship, and underscores the need to develop alternative treatment dosing and delivery strategies that minimise amplification of resistance within TB cavities [27]. Introduction of new and active drugs such as carbapenem and delamanid may be considered to construct effective treatment regimens and protect new drugs, thus limiting the amplification of resistance.

When using a bedaquiline- and linezolid-based regimen for XDR-TB we found that culture negativity at 6 months had an almost 95% predictive value for survival, and an 81% predictive value for a favourable outcome. By contrast, culture positivity at the same time point was associated with a 100% unfavourable outcome and 50% mortality rate. We believe that this could serve as an important biomarker when evaluating new bedaquiline-based regimens (if confirmed in prospective studies), or as an early signal to switch to a salvage regimen. These data mirror the findings of Günther *et al.* [28] in MDR-TB, where culture negativity at 6 months had a high predictive value for a favourable outcome in MDR-TB using a capreomycin- and ofloxacin-based regimen.

Several studies have highlighted high toxicity profiles of regimens used to treat drug-resistant TB [29], and concern has been raised about the potential toxicity of bedaquiline [30]. 10% of individuals in our study had a prolonged QT interval but none had to stop the drug. In a systematic review involving 1266 patients, 3.5% discontinued bedaquiline due to adverse events, and only 0.6% discontinued bedaquiline because of prolonged QTc interval [31]. There is accumulating experience that bedaquiline is safe, although published studies have not been powered to detect a small potential mortality increase [14, 17]. Other substantial toxicities were probably related to linezolid. The rate of peripheral neuropathy was almost four-fold higher than in the non-bedaquiline group and anaemia was almost 20-fold higher. Indeed, linezolid needed to be stopped in 33% of patients in the bedaquiline group; nevertheless, patients in this group still had better outcomes, notwithstanding the higher rate of drug withdrawal. It is believed

TABLE 6 Multivariate Cox proportional hazard model for risk of death in the bedaquiline and the non-bedaquiline groups

	Hazard ratio (95% CI)	p-value
All XDR-TB patients (n=271)[#]		
Weight <50 kg at admission	1.96 (1.38–2.78)	<0.001
Male	1.08 (0.76–1.52)	0.67
HIV-infected[#]	1.51 (1.06–2.15)	0.02
Previous TB treatment	1.08 (0.69–1.68)	0.73
Number of anti-TB drugs received	0.83 (0.72–0.96)	0.01
Bedaquiline[¶]	0.24 (0.06–0.98)	0.05
Linezolid[¶]	0.43 (0.11–1.61)	0.21
Clofazimine	0.80 (0.47–1.37)	0.42
Third- and fourth-generation fluoroquinolones[+]	1.10 (0.68–1.76)	0.70
Any aminoglycoside[§]	0.95 (0.24–3.69)	0.94
HIV-infected patients (n=132)[f]		
Weight <50 kg at admission	2.06 (1.26–3.36)	0.004
Male	0.73 (0.43–1.23)	0.24
Number of anti-TB drugs received	0.87 (0.67–1.11)	0.26
Any aminoglycoside	0.06 (0.01–0.67)	0.02
On ARV treatment	1.13 (0.44–2.91)	0.80
CD4 count <200 cells·μL^{-1}	1.4 (0.85–2.32)	0.19
Bedaquiline[##]	0.01 (0–0.33)	0.01
Linezolid	0.87 (0.1–7.82)	0.90
Clofazimine	0.62 (0.3–1.31)	0.21
Previous TB treatment	1.29 (0.65–2.54)	0.47

Univariate analyses are shown in online supplementary tables S3 and S4 for the whole cohort and the HIV-infected subgroups, respectively. XDR-TB: extensively drug-resistant tuberculosis; ARV: antiretroviral. [#]: one patient refused testing. [¶]: 55 (80.9%) out of the 68 patients who received bedaquiline also received linezolid. We performed subanalyses to investigate the effect of linezolid treatment, and to investigate collinear variables (online supplementary table S5). [+]: moxifloxacin and levofloxacin. [§]: amikacin, capreomycin and kanamycin. [f]: two patients did not have CD4 count done at admission (n=132). [##]: 31 (88.6%) out of the 35 patients who received bedaquiline also received linezolid.

that regimens tailored to individual's metabolism will not only reduce linezolid-related toxicity, but also enhance its role in managing XDR-TB [32]. The significantly higher portion of patients with hearing impairment in the bedaquiline arm reflects the high proportion of patients that were previously treated with aminoglycosides and was not directly related to the drugs used in this regimen.

There are a number of limitations of this study including inclusion bias (patients with severe disease may have died prior to laboratory diagnosis or before treatment initiation). However, our setup was able to capture all patients with a laboratory diagnosis and this bias would have impacted both arms. We did not expressly correct for radiological disease extent at diagnosis (radiographs were non-digitalised and followed patients to their local clinics); however, there were no significant intergroup differences in terms of demographic factors, weight, HIV status (and CD4 count) and microbiological disease severity (smear and time-to-positivity), which are broadly all proxies of disease extent/severity. Our study was conducted in the Western Cape province of South Africa, which arguably has better healthcare infrastructure and lower HIV co-infection rates. Thus, outcomes might be different in settings where the healthcare infrastructure was less developed and where HIV co-infection rates are higher. Almost all the patients in this study were admitted to the designated XDR-TB hospital. It is possible that results may be different in settings where there are no facilities for inpatient treatment reflecting nosocomial transmission and/or a poorer level of care. However, data from MDR-TB decentralisation programmes in South Africa suggest that outcomes are similar to an inpatient setting [33]. Default and loss to follow-up may have impacted the robustness of our data as this was almost 27% in the non-bedaquiline group. This is probably due to several factors including using an ineffective regimen and a longer total treatment duration due to the higher rates of previous TB; however, excluding defaulters from the analysis did not change the study conclusions. In contrast, we think that the bedaquiline outcomes were less likely to have been impacted to a significant extent as default/loss to follow-up rates were lower. Finally, *post mortem* studies were not performed so that the cause of death could be substantiated. However, this is not practical in a resource-constrained setting, and *post mortem* studies cannot confirm or refute that the cause of death is drug-related arrhythmia.

In summary, these prospective long-term outcome data from a TB-endemic setting indicate that a bedaquiline- and linezolid-based regimen results in substantial and remarkable improvement in outcomes in patients with XDR-TB. These data inform clinical practice in endemic settings and make a strong case for the immediate and accelerated roll-out of these drugs for the treatment of XDR-TB in endemic settings.

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