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ABSTRACT

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

We prospectively followed up 272 South African patients (49.3% HIV-infected; median CD4 169 cells/µl) with newly diagnosed XDR-TB between 2008 and 2017. Outcomes were compared between those who had not received Bdq (pre-2013; n=204) to those who had (post-2013; n=68; 80.9% also received linezolid).

The 24-month favourable outcome rate was substantially better in the Bdq versus the non-Bdq group [66.2% (45/68) versus 13.2% (27/204); p<0.001]. The Bdq group also 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 However, linezolid was withdrawn in 32.7% (18/55) of patients in the Bdq group because of adverse events. Admission weight >50kg, an increasing number of anti-TB drugs, and Bdq were independent predictors of survival (the Bdq survival effect remained significant in HIV-infected persons, irrespective of CD4 count).

XDR-TB patients receiving a backbone of Bdq 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.

Key words: tuberculosis, MDR-TB, XDR-TB, bedaquiline, outcomes, human.

Introduction

The persistence of the multi-drug-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]. In 2016 in South Africa, for example, ~7.1% of patient samples screened were rifampicin resistant or MDR-TB, of which ~8% were XDR-TB [6]. It was estimated that M/XDR-TB will consume over 80% of TB treatment costs in South African in 2017/18 despite MDR-TB making up less than 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 also 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 ARVs [10].

The advent of new and repurposed bactericidal drugs such as linezolid (Lzd) and bedaquiline (Bdq) have offered new hope for patients with XDR-TB [11-14]. However, Lzd 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 Bdq was associated with increased mortality, significant adverse events including QT prolongation and hepatitis, raising concerns about efficacy and outcome [17]. A unified analysis of Bdq in industry-funded clinical trials showed that Bdq was associated with a 24-month failure rate of almost 40% in XDR-TB patients [18]. 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 [19, 20]. There were also concerns that clofazimine, currently widely used to treat MDR-TB, could potentially induce cross-resistance to Bdq thereby mitigating its potentially favourable impact [21, 22]. Thus, the clear-cut benefit of Bdq in a programmatic setting, remains unclear. Whilst there are limited but encouraging short-term outcome data from endemic settings [18, 23], the lack of long-term (24-month) comparative outcomes means that there remains controversy and equipoise regarding the immediate and widespread roll-out of Bdq to treat XDR-TB versus awaiting results from controlled clinical trials. To address this issue, we compared long-term outcomes using a Bdq- (and often Lzd)-containing XDR-TB regimen, to those not containing Bdq or Lzd, in a high TB incidence setting.

Methods

Participants

We prospectively followed up 272 patients with laboratory-confirmed XDR-TB who initiated drug therapy, between January 2008 to June 2017 in a programmatic setting (enrolment and follow-up censor dates were April 2016 and June 2017, respectively). 204 patients received a non-Bdq-based anti-TB regimen while 68 received a Bdq-based regimen. All patients were admitted to Brooklyn Chest Hospital, Cape Town, 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 health care workers using a report form that was attached to every patient's folder (see online supplement table S1 for adverse events grading. 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 health care worker from patient records and associated healthcare and laboratory systems. The demographic variables we collected were age, gender, 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 > 450ms were considered high risk and closely monitored. Upon discharge, treatment was directly observed by trained health workers in

local health care 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 had monthly smear microscopy and culture done during hospitalisation, and sometimes less frequently following hospital discharge.

Treatment regimens

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

Outcomes

Treatment outcomes were assigned according to the adapted 2013 WHO definitions and reporting frameworks for TB, and the proposed core definitions for drug-resistant TB clinical trials recommended by Furin *et al*. (online supplement Table S2) [24, 25]. 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 Bdq 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 and chi-square 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 (eg, HIV-infected vs HIV-uninfected individuals) were made by the log-rank test. Univariate Cox proportional hazards models were used to estimate the relation 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, gender. 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 done 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-Bdq 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 FQ-based non-Bdq regimen containing a median of 9 (IQR 8-10) drugs (frequencies of drugs are outlined in Table 2). 99/204 (48.5%) patients in this group were HIV-infected with a median CD4 count of 198 (IQR 71-302) cells/µl at

admission, and 90/99 (90.9%) had been commenced on anti-retroviral therapy prior to, or within 3 months of diagnosis of XDR-TB.

The Bdq 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 Bdq-based regimen which contained a median of 8 (IQR 7-8) drugs (Table 2). Patients received Bdq for a median of 178 (IQR 54-272) days. 35/68 (51.5%) were HIV-infected with a median CD4 count of 146 (IQR 57-271) cells/µl at admission, and they all received anti-retroviral therapy following diagnosis.

Culture conversion

In the non-Bdq group, 67/204 (32.8%) patients achieved culture conversion by the end of 24 months, but only 27/67 (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. The specificity of positive sputum culture to predict mortality was also high, reaching 83.6% at 6 months (Table 4).

In the Bdq group, 46/68 (67.6%) patients achieved culture conversion by the end of 24 months and 45/46 (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 4).

Treatment outcomes

A favourable outcome was achieved in only 27/204 (13.2%) patients in the non-Bdq group while the remaining patients had an unfavourable outcome after 24-month follow-up period (Table 5). Only18/99 (18.2%) of HIV-infected patients in this group had a favourable outcome.

A favourable outcome was achieved in 45/68 (66.2%) patients in the Bdq group while the remaining patients had an unfavourable outcome after 24-month follow-up period (Table 5). 24/35 (68.6%) of HIV-infected patients in this group had favourable outcome.

Patients who received Bdq had a higher probability of survival (p<0.001; Figure 1A) in time to event analysis. Bdq had a similar effect in HIV-infected patients (p<0.001; Figure 1B). Patients in the Bdq group who received anti-retroviral therapy (p<0.001) had a significantly higher probability of survival than their counterparts in the non-Bdq group (Figure 1C). Bdq also provided the survival advantage to HIV-infected patients regardless of their CD4 count at admission (Figures 1D and 1E).

Adverse events

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

226 adverse events were reported by 65/68 (95.6%) patients in the Bdq group. More patients in this group, 40/68 (58.8%), had at least one drug withdrawn (p=0.005), and 23/40 (57.5%) of them achieved a favourable outcome. None of the patients had Bdq withdrawn from the treatment regimen, although 7/68 (10.3%) had a prolonged QT interval within 450-470ms. 5 (71.4%) of these 7 patients achieved a favourable outcome, 1 (14.3%) was lost to follow-up and 1 (14.3%) died. The deceased patient achieved culture conversion after 41 days of Bdq treatment but reverted 61 days later and never achieved another conversion till death; this patient has been on Bdq for 170 days.

Multivariate analysis

Multivariate analysis of patients in both groups suggested that, receiving Bdq (p=0.05; HR=0.24) and number of anti-TB drugs received (p=0.01; HR=0.83) were independent predictors of survival. It also suggested that patients who were HIV-infected (p=0.02; HR=1.51) and those who weighted less than 50kg at admission (p<0.001; HR=1.96), were more likely to die (Table 6I). In HIV-infected patients, receiving Bdq (p=0.01; HR=0.01) and any aminoglycoside (p=0.02, HR=0.06) were independent predictors of survival, and those weighting ≤50kg at admission (p=0.004; HR=2.06) were more likely to die (Table 6II).

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 Bdq, 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 that: (i) favourable outcomes using Bdq (and Lzd) were more than 5-fold better compared to regimens not containing Bdq; (ii) mortality in the Bdq group was more than halved; (iii) treatment failure rates were reduced by more than 4-fold and there was a more than 10-fold reduction in default rates; (iv) Bdq remained an independent predictor of survival (despite the use of Lzd), and other independent outcome predictors included admission weight of more than 50kg (probably reflecting the immune and nutritional status of the patient) and an increasing number of anti-TB drugs used; (v) the Bdq survival and favourable outcome effect remained significant in HIV-infected persons and even at low CD4 counts; (vi) a 6-month negative culture was ~95% predictive of patient survival in the Bdq group, and 81% predictive of a favourable outcome (by contrast, a positive culture at 6 months was highly predictive of death or unfavourable outcome); and (vi) Bdq-related prolonged QT interval occurred in about 10% of the cohort but none had Bdq withdrawn and most still achieved a favourable outcome. By contrast, 33% of patients experienced Lzd withdrawal due to adverse events.

The dominant finding was that Bdq is an independent predictor of survival and favourable outcome, and the backbone of Bdq and Lzd was associated with remarkably better treatment outcomes compared to regimens not containing these drugs. There was also a higher frequency of death in the Bdq group within the first 2 months of treatment initiation (likely due to a survival bias related a higher rate of pre-diagnostic death in the non-Bdq group), however, exclusion of deaths in this early period did not change the study conclusions (see data supplement; Table S10). Concerns regarding QT prolongation and the potential toxicity of Bdq (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 SLI and FQ-based regimen [3], and this raises the question of whether Bdq and Lzd 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

Bdq within the context of a prospective study. By contrast, studies on patients with XDR-TB have, hitherto, reported short-term outcomes only, or those from non-endemic settings. A retrospective study from South Africa [18], an Indian study [23], and a study from KwaZulu-Natal in South Africa [20] reported 6-month culture conversion rates of 76% (n=63), 65% (n=20) and 68% (n=123), respectively, in Bdq-treated patients with XDR-TB. Importantly, the Bdq 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 [26]. In our study, more than a third of patients still had unfavourable outcomes and mortality was almost 15% despite Bdq treatment. Firstly, this highlights the poor outcomes associated with XDR-TB (despite Bdq), 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) [27]. Indeed, in South Africa we are now facing the problem of patients who have failed Bdq and Lzd-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, practice strict antibiotic stewardship, and underscores the need to develop alternative treatment dosing and delivery strategies that minimise amplification of resistance within TB cavities [28]. Introduction of new and active drugs like carbapenem and delamanid may also be considered to construct effective treatment regimens and protect new drugs, thus limiting the amplification of resistance.

When using a Bdq and Lzd-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 Bdq-based regimens (if confirmed in prospective studies), or as an early signal to switch to a salvage regimen. These data mirror the findings of Gunther *et al* 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 [29].

Several studies have highlighted high toxicity profiles of regimens used to treat drug-resistant TB [30], and concern has been raised about the potential toxicity of Bdq [31]. Ten percent 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 Bdq due to adverse events, and only 0.6% discontinued Bdq because of prolonged QTc interval [32]. There is accumulating experience that Bdq is safe, though published studies have not been powered to detect a small potential mortality increase [14, 33]. Other substantial toxicities were likely related to Lzd. The rate of peripheral neuropathy was almost 4-fold higher than in the non-Bdq group and anaemia was almost 20-fold higher. Indeed, Lzd needed to be stopped in 33% of patients in the Bdq group; nevertheless, patients in this group still had better outcomes notwithstanding the higher rate of drug withdrawal. It is believed that regimens tailored to individual's metabolism will not only reduce Lzd-related toxicity, but also enhance its role in managing XDR-TB [34].The significantly higher portion of patients with hearing impairment in the Bdq 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 set up 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 (x-rays 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 health care 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 [35]. Default and loss to follow-up may have impacted the robustness of our data as this was almost 27% in the non-Bdq group. This is likely 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. By contrast, we think that the Bdq 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 mortems 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 Bdq and Lzd-based regimen result 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.

Table 1: Comparison of demographic data, clinical characteristics, and treatment outcomes between the bedaquiline and non-bedaquiline groups. Data is n (%) unless otherwise stated.

VARIABLES	Bdq (n = 68)	Non-Bdq (n=204)	p-values
Median age (years)	34.5 (IQR 26-55)	33.5 (IQR 18-73)	0.42
Gender (male)	41 (60.3)	120 (58.8)	0.89
Median body weight at admission (kg)	51.8 (IQR 33.3-78.1)	51.9 (IQR 21.0-89.9)	0.76
Proportion >50kg	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	35 (100)	90 (90.9)	0.11
Median CD4 count at admission (µl/ml)	146 (IQR 57-271)	198 (IQR 71-302)	0.51
[#]Median number of anti-TB drugs received	8 (IQR 7-8)	9 (IQR 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
Median number of days of admission	158 (IQR 102-221)	199 (IQR 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 persons with a favourable outcome	24 (68.6)	18 (18.2)	<0.001

*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); LTFU = Lost to follow-up, [#]Bdq was included in the total number of anti-TB drugs used in the Bdq group.

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. Data is n (%) unless otherwise stated.

Drugs	Bdq (n=68)		Non-Bdq (n=204)		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)	
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	<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
##3rd or 4th 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
Amoxycillin	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

#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.

Table 3: List of all adverse events reported in the bedaquiline and the non-bedaquiline group. Data is n (%) unless otherwise stated.

Adverse Event	Bdq group (N=68)	Non-Bdq group (N=204)	p-value
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
Haematogical 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

N/A= not applicable

Table 4: Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of culture negativity at specific time points to predict A) survival and B) favourable treatment outcome in each group. See supplementary Table S9 for a combined analysis.

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

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).

Table 5: Treatment outcomes at specific time-points as measured from treatment initiation. Outcomes were assigned as described in Table S2 (online supplement) for the Bdq (n=68) and non-Bdq (n=204) groups. Data is number of patients (%).

Treatment outcome	12 months		18 months		24 months	
	Bdq	Non-Bdq	Bdq	Non-Bdq	Bdq	Non-Bdq
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)

N/A= Not applicable, p-values were less than *0.05 or [#]0.005 when comparing time specific treatment outcomes between patients in the Bedaquiline and non-bedaquiline groups. LTFU= Lost to follow-up

Table 6: Multivariate Cox proportional hazard model for risk of death in both groups; A) all the XDR-TB patients (n=271), B) HIV-infected patients (n=132). Univariate analyses are shown in supplementary Tables S3 and S4 for the whole cohort and the HIV-infected subgroups, respectively.

Variables	Hazard ratio (95% C.I.)	p-value
I) All the XDR-TB patients ([A]n=271)		
Weight <50kg at admission	1.96 (1.38,2.78)	<0.001
Gender (male)	1.08 (0.76,1.52)	0.67
[A]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
[B]Bedaquiline	0.24 (0.06,0.98)	0.05
[B]Linezolid	0.43 (0.11,1.61)	0.21
Clofazamine	0.80 (0.47,1.37)	0.42
[C]Third and fourth generation fluoroquinolones	1.10 (0.68,1.76)	0.70
[D]Any aminoglycoside	0.95 (0.24,3.69)	0.94
II) HIV-infected patients ([E]n=132)		
Weight <50kg at admission	2.06 (1.26,3.36)	0.004
Gender (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 cell/µl X	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
Clofazamine	0.62 (0.3,1.31)	0.21
Previous TB treatment	1.29 (0.65,2.54)	0.47

A) One patient refused testing; B) 55 of the 68 (80.9%) patients who received bedaquiline also received linezolid. We performed sub-analyses to investigate the effect of linezolid treatment, and to investigate collinear variables (supplementary Table S5). C) 3rd and 4th generation fluoroquinolones = moxifloxacin and levofloxacin; D) Any aminoglycoside = amikacin, capreomycin and kanamycin; E) 2 patients did not have CD4 count done at admission (n=132). X - 31 of the 35 (88.6%) patients who received bedaquiline also received linezolid.

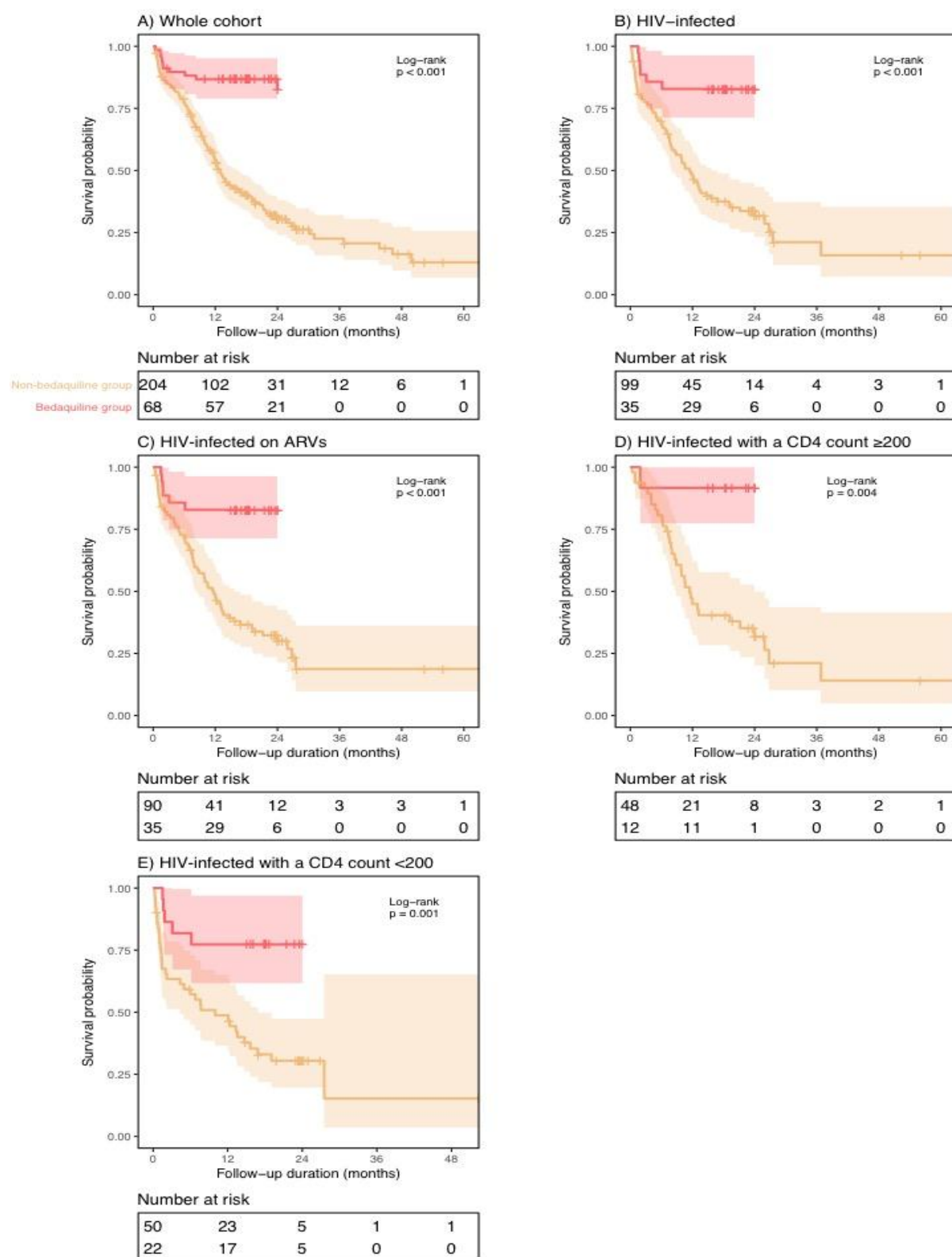Figure 1: Kaplan-Meier survival estimate for patients in the bedaquiline (Bdq) and the non-bedaquiline (non-Bdq) groups. Shading indicates the 95% confidence interval and plus signs represent patients censoring events. A) Whole cohort. B) HIV-infected patients. C) HIV-infected patients who received ARV. HIV-infected patients whose CD4 count were D) greater than or equal to 200 cells/µl, and E). CD4 count were less than 200 cells/µl.

References

1. Dheda K, Barry CE, Maartens G: **Tuberculosis**. *The Lancet* 2016, **387**(10024):1211-1226.
2. O'Donnell MR, Jarand J, Loveday M, Padayatchi N, Zelnick J, Werner L, Naidoo K, Master I, Osburn G, Kvasnovsky C: **High incidence of hospital admissions with multidrug-resistant and extensively drug-resistant tuberculosis among South African health care workers**. *Annals of internal medicine* 2010, **153**(8):516-522.
3. WHO: **Global Tuberculosis Report 2016- World Health Organisation**. 2016.
4. Migliori GB, Sotgiu G, Gandhi NR, Falzon D, DeRiemer K, Centis R, Hollm-Delgado M-G, Palmero D, Pérez-Guzmán C, Vargas MH: **Drug resistance beyond XDR-TB: results from a large individual patient data meta-analysis**. *European Respiratory Journal* 2012:erj01363-02012.
5. Pooran A, Pieterson E, Davids M, Theron G, Dheda K: **What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa?** *PLoS One* 2013, **8**(1):e54587.
6. WHO: **Global tuberculosis report 2017**. 2017:1-3.
7. Council: DoHaSANA: **South African HIV and TB Investment Case - Summary Report Phase 1.** March 2016.:274-275.
8. Dheda K, Shean K, Zumla A, Badri M, Streicher EM, Page-Shipp L, Willcox P, John M-A, Reubenson G, Govindasamy D: **Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study**. *The Lancet* 2010, **375**(9728):1798-1807.
9. Pietersen E, Ignatius E, Streicher EM, Mastrapa B, Padanilam X, Pooran A, Badri M, Lesosky M, van Helden P, Sirgel FA *et al*: **Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study**. *The Lancet* 2014, **383**(9924):1230-1239.
10. Charlotte L. Kvasnovsky JPC, Martie L. van der Walt: **Treatment Outcomes for Patients with Extensively Drug-Resistant Tuberculosis, KwaZulu-Natal and Eastern Cape Provinces, South Africa**. *Emerging Infectious Diseases* 2016, **22**(9):1529-1536.
11. Alexander S. Pym AHD S-JT, Francesca Conradie,, Manfred Danilovits CC, Irina Vasilyeva, Koen Andries,, Nyasha Bakare TDM, Myriam Haxaire-Theeuwes, Nacer Lounis,, Paul Meyvisch BVB, Rolf P.G. van Heeswijk and, Dannemann B.: **Bedaquiline in the treatment ofmultidrug- and extensively drugresistanttuberculosis**. *Eur Respir J* 2016, **47**:564–574.
12. Guglielmetti L, Le Dû D, Jachym M, Henry B, Martin D, Caumes E, Veziris N, Métivier N, Robert J: **Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort**. *Clinical Infectious Diseases* 2014, **60**(2):188-194.
13. Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, Via LE, Goldfeder LC, Kang E, Jin B: **Linezolid for treatment of chronic extensively drug-resistant tuberculosis**. *New England Journal of Medicine* 2012, **367**(16):1508-1518.
14. Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB: **Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence**. *Eur Respir J* 2016, **47**(2):394-402.
15. Zhang X, Falagas ME, Vardakas KZ, Wang R, Qin R, Wang J, Liu Y: **Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis**. *Journal of thoracic disease* 2015, **7**(4):603.
16. Sotgiu G, Centis R, D'Ambrosio L, Alffenaar J-WC, Anger HA, Caminero JA, Castiglia P, De Lorenzo S, Ferrara G, Koh W-J: **Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis**. *European Respiratory Journal* 2012, **40**(6):1430-1442.

17.	Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, Leimane V, Andries K, Bakare N, De Marez T *et al*: **Multidrug-resistant tuberculosis and culture conversion with bedaquiline**. *N Engl J Med* 2014, **371**(8):723-732.

18.	Ndjeka N, Conradie F, Schnippel K, Hughes J, Bantubani N, Ferreira H, Maartens G, Mametja D, Meintjes G, Padanilam X: **Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis**. *The International Journal of Tuberculosis and Lung Disease* 2015, **19**(8):979-985.

19.	Pym AS, Diacon AH, Tang S-J, Conradie F, Danilovits M, Chuchottaworn C, Vasilyeva I, Andries K, Bakare N, De Marez T: **Bedaquiline in the treatment of multidrug-and extensively drug-resistant tuberculosis**. *European Respiratory Journal* 2015:ERJ-00724-02015.

20.	N. Bionghi NP, I. Master , K. Naidoo , M. R. O'Donnell **Bedaquiline And Linezolid For The Operational Treatment Of Multidrug-Resistant And Extensively Drug-Resistant Tuberculosis In A High Burden Hiv Setting**. *American journal of respiratory and critical care medicine 2017* 2017, **195**(A3090).

21.	Andries K, Villellas C, Coeck N, Thys K, Gevers T, Vranckx L, Lounis N, de Jong BC, Koul A: **Acquired resistance of Mycobacterium tuberculosis to bedaquiline**. *PLoS One* 2014, **9**(7):e102135.

22.	Hartkoorn RC, Uplekar S, Cole ST: **Cross-resistance between clofazimine and bedaquiline through upregulation of MmpL5 in Mycobacterium tuberculosis**. *Antimicrob Agents Chemother* 2014, **58**(5):2979-2981.

23.	Udwadia ZF, Ganatra S, Mullerpattan JB: **Compassionate use of bedaquiline in highly drug-resistant tuberculosis patients in Mumbai, India**. *Eur Respir J* 2017, **49**(3).

24.	WHO: **Definitions and reporting framework for tuberculosis,– 2013 revision (updated December 2014)**. 2013.

25.	Furin J, Alirol E, Allen E, Fielding K, Merle C, Abubakar I, Andersen J, Davies G, Dheda K, Diacon A *et al*: **Drug-resistant tuberculosis clinical trials: proposed core research definitions in adults**. *Int J Tuberc Lung Dis* 2016, **20**(3):290-294.

26.	Guglielmetti L, Jaspard M, Le Du D, Lachatre M, Marigot-Outtandy D, Bernard C, Veziris N, Robert J, Yazdanpanah Y, Caumes E *et al*: **Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis**. *Eur Respir J* 2017, **49**(3).

27.	Dheda K, Limberis JD, Pietersen E, Phelan J, Esmail A, Lesosky M, Fennelly KP, te Riele J, Mastrapa B, Streicher EM *et al*: **Outcomes, infectiousness, and transmission dynamics of patients with extensively drug-resistant tuberculosis and home-discharged patients with programmatically incurable tuberculosis: a prospective cohort study**. *The Lancet Respiratory Medicine* 2017, **5**(4):269-281.

28.	Dheda K, Gumbo T, Maartens G, Dooley KE, McNerney R, Murray M, Furin J, Nardell EA, London L, Lessem E *et al*: **The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis**. *Lancet Respir Med* 2017.

29.	Gunther G, Lange C, Alexandru S, Altet N, Avsar K, Bang D, Barbuta R, Bothamley G, Ciobanu A, Crudu V *et al*: **Treatment Outcomes in Multidrug-Resistant Tuberculosis**. *N Engl J Med* 2016, **375**(11):1103-1105.

30.	D'Ambrosio L, Centis R, Sotgiu G, Pontali E, Spanevello A, Migliori GB: **New anti-tuberculosis drugs and regimens: 2015 update**. *ERJ Open Res* 2015, **1**(1).

31.	Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, Sotgiu G, Tiberi S, Alffenaar JW, Maryandyshev A *et al*: **Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study**. *Eur Respir J* 2017, **49**(5).

32.	Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB: **Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence**. *In.*: Eur Respiratory Soc; 2017.

33.   Diacon AH, Pym A, Grobusch MP, de Los Rios JM, Gotuzzo E, Vasilyeva I, Leimane V, Andries K, Bakare N, De Marez T: **Multidrug-resistant tuberculosis and culture conversion with bedaquiline**. *New England Journal of Medicine* 2014, **371**(8):723-732.
34.   Sotgiu G, Pontali E, Migliori GB: **Linezolid to treat MDR-/XDR-tuberculosis: available evidence and future scenarios**. *Eur Respir J* 2015, **45**(1):25-29.
35.   Berhanu R, Schnippel K, Mohr E, Hirasen K, Evans D, Rosen S, Sanne I: **Early Outcomes Of Decentralized Care for Rifampicin-Resistant Tuberculosis in Johannesburg, South Africa: An Observational Cohort Study**. *PLoS One* 2016, **11**(11):e0164974.

ONLINE SUPPLEMENT

Table S1: Grading of adverse events severity[1]

Grade 0	No Adverse events
Grade 1	Mild adverse event, requiring no intervention
Grade 2	Moderate adverse event requiring either changing the dose or frequency of the offending drug, or prescribing another drug to manage the adverse event
Grade 3	Severe adverse event, enough to stop the offending drug
Grade 4	Life threatening or disabling adverse event
Grade 5	Death resulting from the adverse event

[1]Grading was done according to the modified American National Institute of Health common terminology of criteria for adverse events

Table S2: Treatment-related outcome definitions applied, as adapted from the 2013 WHO revised definitions and reporting framework for TB guidelines, and the core research definitions for drug-resistant TB clinical trials recommended by Furin *et al* [1, 2].

Treatment outcome		Definition
Favourable outcome	Cured	Treatment completed, as recommended by the National TB programme, without evidence of failure or an unfavourable outcome as defined below. Three or more consecutive negative sputum cultures, taken at least 30 days apart, after the intensive phase (up to 12 months from the initiation of treatment), or a participant's last two culture results at the end of treatment are negative.
	Completed treatment	Treatment completed, as recommended by the National TB programme, without evidence of failure or an unfavourable outcome, however no record of three or more consecutive negative sputum cultures, taken at least 30 days apart, after the intensive phase (up to 12 months from the initiation of treatment), or a participant's last two culture results at the end of treatment are not recorded as negative.
Unfavourable outcome	Treatment failure	Treatment terminated (stopping of two or more drugs), or the need for permanent regimen change of at least two anti-TB drugs (stoppage of or the change one drug in the case of linezolid or bedaquiline) because of one or more of the following: i) lack of sputum culture conversion, or culture reversion after initial conversion, or culture positivity after month 6 [1], (ii) drug-related adverse events (AEs), (iii) evidence of additional acquired drug resistance precluding the composition of a regimen of at least 4 likely effective drugs. (In the case culture positivity during or after month 6, only 1 positive culture is deemed to be sufficient when considered in the context of other biomarkers including weight, radiological disease extent, symptoms etc, based on the core research definitions for drug-resistant TB clinical trials recommended by Furin *et al* [1].)
	Died while on treatment	A patient who died for any reason while on any TB treatment, or within 7 days of termination of treatment. For post treatment time-specific outcome all-cause mortality will be used. Death superseded any treatment outcome at a specific time point.
	Recurrence (relapse or re-infection)	Two or more consecutive positive sputum cultures, at least 7 to 30 days apart, subsequent to the outcome of 'Cure' or 'Treatment Complete'. Genotyping is required to distinguish relapse from re-infection.
	Defaulted	A patient who interrupted treatment for 2, or more, consecutive months and who did not restart treatment but remained hospitalised or traceable in the community.
	Loss to follow up	A patient who interrupted treatment for 2, or more, consecutive months and who did not restart treatment but remains untraceable despite intensive and best efforts to find or track down the patient.
Indeterminate	Ongoing treatment	A patient for whom no treatment outcome can be assigned due to ongoing treatment in accordance with the National TB programme.

Table S3: Univariate Cox proportional hazard model for risk of death for all the XDR-TB patients (n=272).

Variable	Hazard ratio (95% C.I.)	p-value
Age at XDR-TB diagnosis (years)	1.00 (0.99,1.02)	0.51
Weight <50	1.68 (1.22,2.32)	0.002
Duration of TB treatment (days)	0.98 (0.98,0.98)	<0.001
Gender (male)	0.93 (0.67,1.29)	0.66
Median number of days of admission	1.00 (1.00,1.00)	0.03
Median number of anti-TB drugs received	0.92 (0.83,1.03)	0.14
*HIV Infected	1.17 (0.85,1.61)	0.35
Previous TB treatment	1.60 (1.04,2.44)	0.03
Amikacin	2.37 (0.58,9.59)	0.23
Capreomycin	3.51 (2.09,5.91)	<0.001
Kanamycin	1.80 (1.30,2.50)	<0.001
[a]Any aminoglycosides	4.96 (2.60,9.44)	<0.001
PAS	0.35 (0.19,0.68)	0.002
Moxifloxacin	0.91 (0.66,1.26)	0.57
Levofloxacin	0.17 (0.09,0.33)	<0.001
[b]Third generation quinolones	0.46 (0.33,0.64)	<0.001
Clofazimine	0.36 (0.25,0.51)	<0.001
Linezolid	0.15 (0.07,0.34)	<0.001
Bedaquiline	0.17 (0.09,0.32)	<0.001
Ethionamide	4.33 (2.34,8.03)	<0.001
Amoxycillin	0.94 (0.46,1.92)	0.86
Age at XDR-TB diagnosis (years)	1.00 (0.99,1.02)	0.51

*One patient refused HIV testing, n=271; [a]amikacin, capreomycin and/or kanamycin; [b]moxifloxacin or levofloxacin.

Table S4: Univariate Cox proportional hazard model for risk of death for HIV-infected patients in both groups (n=134).

Variable	Hazard ratio (95% C.I.)	p-value
Age at XDR-TB diagnosis (Years)	1.00 (0.97,1.03)	0.87
Gender (Male)	0.89 (0.56,1.41)	0.61
Weight <50kg at admission	1.65 (1.04,2.62)	0.03
Previous TB treatment	1.44 (0.77,2.68)	0.25
On ARV treatment	0.65 (0.28,1.50)	0.31
*Median CD4 count <200 cells/µl at admission	1.14 (0.72,1.81)	0.58
Median number of anti-TB drugs received	0.94 (0.79,1.11)	0.47
Median number of days of admission	1.00 (1.00,1.00)	0.01
Median duration of TB treatment (in days)	0.98 (0.98,0.98)	<0.001
Bedaquiline	0.20 (0.08,0.45)	<0.001
Clofazimine	0.31 (0.19,0.50)	<0.001
Linezolid	0.19 (0.08,0.47)	<0.001
Capreomycin	3.42 (1.70,6.89)	<0.001
Kanamycin	2.32 (1.46,3.68)	<0.001
Amikacin	1.64 (0.23,11.85)	0.62
[a]Any aminoglycosides	4.10 (1.87,8.97)	<0.001
Levofloxacin	0.21 (0.09,0.48)	<0.001
Moxifloxacin	1.02 (0.64,1.62)	0.93
[b]3rd Generation fluoroquinolones	0.45 (0.28,0.73)	<0.001
PAS	0.34 (0.14,0.85)	0.02
Ethionamide	4.34 (1.87,10.04)	<0.001
Amoxycillin	1.43 (0.45,4.56)	0.54

*2 patients did not have CD4 count done at admission (n=132); [a]amikacin, capreomycin and/or kanamycin; [b]moxifloxacin or levofloxacin.

Table S5: Multivariate Cox proportional hazard model for risk of death in both groups excluding colinear variables; A) all the XDR-TB patients (n=271), B) HIV-infected patients (n=132). Univariate analyses are shown in supplementary Tables S3 and S4 for the whole cohort and the HIV-infected subgroups respectively.

Variables	Hazard ratio (95% C.I.)	p-value
I) All the XDR-TB patients (n=271)		
Weight <50kg at admission	1.96 (1.38,2.77)	<0.001
Gender (male)	1.06 (0.76,1.49)	0.72
[A]HIV-infected	1.49 (1.05,2.11)	0.03
Previous TB treatment	1.08 (0.69,1.67)	0.74
Number of anti-TB drugs received	0.83 (0.72,0.96)	0.01
[B]Bedaquiline	0.14 (0.06,0.30)	<0.001
Clofazamine	0.80 (0.47,1.37)	0.42
[C]Third generation fluoroquinolones	1.10 (0.68,1.76)	0.70
II) HIV-infected patients (n=132)		
Weight <50kg at admission	1.86 (1.13,3.08)	0.02
Gender (male)	0.72 (0.43,1.20)	0.21
Number of anti-TB drugs received	0.86 (0.66,1.12)	0.26
[D]Any aminoglycoside	0.05 (0.00,0.58)	0.02
On ARV treatment	1.29 (0.49,3.38)	0.6
[E]CD4 count <200 cell/µl	1.53 (0.92,2.54)	0.11
[B]Bedaquiline	0.01 (0.00,0.16)	<0.001
Clofazamine	0.63 (0.3,1.33)	0.23
Kanamycin	1.50 (0.88,2.55)	0.14
Previous TB treatment	1.21 (0.61,2.38)	0.58

A) One patient refused testing; B) 53 of the 68 (77.9%) patients who received bedaquiline also received linezolid; C) 3rd generation fluoroquinolones = moxifloxacin and levofloxacin; D) Any aminoglycoside = amikacin, capreomycin and kanamycin. E) 2 patients did not have CD4 count done at admission (n=132).

Secondary analyses using treatment outcome (rather than survival) as the dependant outcome variable, mirroring the analyses shown in the main manuscript.

<u>Definitions</u>

Favourable outcome = cured or completed treatment.

Unfavourable outcome = treatment failed, lost to follow-up, defaulted, died.

Table S6: Univariate Cox proportional hazard model for risk of unfavourable treatment outcome for all the XDR-TB patients (n=270).

Variable	Hazard ratio (95% C.I.)	p-value
Age at XDR-TB diagnosis (years)	1.00 (0.99,1.02)	0.51
Weight <50	1.47 (1.11,1.95)	0.01
Duration of TB treatment (days)	0.98 (0.98,0.98)	<0.001
Gender (male)	1.05 (0.79,1.39)	0.74
Median number of days of admission	1.00 (1.00,1.00)	0.02
Median number of anti-TB drugs received	0.94 (0.86,1.03)	0.21
*HIV Infected	1.07 (0.80,1.41)	0.66
Previous TB treatment	1.41 (0.99,2.00)	0.06
Amikacin	2.06 (0.51,8.33)	0.31
Capreomycin	2.57 (1.70,3.86)	<0.001
Kanamycin	1.59 (1.20,2.11)	<0.001
[a]Any aminoglycoside	3.15 (1.97,5.02)	<0.001
PAS	0.40 (0.22,0.73)	0.003
Moxifloxacin	0.96 (0.72,1.27)	0.76
Levofloxacin	0.32 (0.20,0.49)	<0.001
[b]Third generation quinolones	0.58 (0.44,0.77)	<0.001
Clofazimine	0.49 (0.37,0.66)	<0.001
Linezolid	0.30 (0.18,0.51)	<0.001
Bedaquiline	0.31 (0.20,0.48)	<0.001
Ethionamide	2.96 (1.87,4.66)	<0.001
Amoxycillin	1.15 (0.66,2.03)	0.62

*one patient refused HIV testing, n=269; [a]amikacin, capreomycin and/or kanamycin; [b]moxifloxacin or levofloxacin.

Table S7: Univariate Cox proportional hazard model for risk of unfavourable treatment outcome in HIV-infected patients from both groups (n=133).

Variable	Hazard ratio (95% C.I.)	p-value
Age at XDR-TB diagnosis (Years)	1.00 (0.97,1.02)	0.79
Gender (Male)	1.00 (0.66,1.51)	0.99
Weight <50kg at admission	1.75 (1.15,2.66)	0.008
Previous TB treatment	1.34 (0.78,2.30)	0.30
On ARV treatment	0.94 (0.41,2.20)	0.89
*Median CD4 count <200 cells/µl at admission	1.10 (0.72,1.67)	0.66
Median number of anti-TB drugs received	0.91 (0.78,1.07)	0.24
Median number of days of admission	1.00 (1.00,1.00)	<0.001
Median duration of TB treatment (in days)	0.98 (0.97,0.98)	<0.001
Bedaquiline	0.30 (0.16,0.57)	<0.001
Clofazimine	0.38 (0.25,0.59)	<0.001
Linezolid	0.28 (0.14,0.57)	<0.001
Capreomycin	2.42 (1.36,4.31)	<0.001
Kanamycin	1.94 (1.27,2.96)	<0.001
Amikacin	1.47 (0.20,10.63)	0.70
[a]Any aminoglycoside	2.85 (1.54,5.26)	<0.001
Levofloxacin	0.32 (0.17,0.60)	<0.001
Moxifloxacin	1.02 (0.67,1.54)	0.93
[b]3rd Generation fluoroquinolones	0.54 (0.35,0.83)	0.004
PAS	0.35 (0.15,0.80)	0.01
Ethionamide	3.18 (1.64,6.17)	<0.001
Amoxycillin	1.68 (0.61,4.61)	0.31

*2 patients did not have CD4 count done at admission (n=131); [a]amikacin, capreomycin and/or kanamycin; [b]moxifloxacin or levofloxacin.

Table S8: Multivariate Cox proportional hazard model for risk of unfavourable treatment outcome in both groups A) all the XDR-TB patients (n=271), B) HIV-infected patients in the (n=132).

Variables	Hazard ratio (95% C.I.)	p-value
I) All the XDR-TB patients (n=271)		
Weight <50kg at admission	1.72 (1.27,2.33)	<0.001
Gender (male)	1.19 (0.88,1.60)	0.26
[A]HIV-infected	1.25 (0.92,1.70)	0.15
Previous TB treatment	1.05 (0.72,1.52)	0.81
Number of anti-TB drugs received	0.85 (0.76,0.96)	0.01
[B]Bedaquiline	0.24 (0.14,0.42)	<0.001
Clofazamine	0.92 (0.58,1.46)	0.74
[C]Third generation fluoroquinolones	1.13 (0.74,1.73)	0.57
II) HIV-infected patients (n=132)		
Weight <50kg at admission	2.21 (1.39,3.51)	<0.001
Gender (male)	0.83 (0.52,1.33)	0.44
Number of anti-TB drugs received	0.8 (0.63,1.01)	0.06
[D]Any aminoglycoside	0.04 (0.00,0.45)	0.008
On ARV treatment	1.59 (0.61,4.14)	0.34
[E]CD4 count <200 cell/μl	1.37 (0.87,2.17)	0.17
[B]Bedaquiline	0.01 (0.00,0.12)	<0.001
Clofazamine	0.84 (0.44,1.63)	0.61
Kanamycin	1.24 (0.75,2.05)	0.41
Previous TB treatment	1.26 (0.69,2.31)	0.46

*one patient refused testing; **2 patients did not have CD4 count done at admission (n=132).

Table S9: Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of culture negativity at specific time points to predict A) survival and B) favourable treatment outcome for all patients.

A) Survival as dependant variable					
Month	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Number of patients considered
2	77.8	70.5	56	86.8	166
3	86.4	64	53.1	90.9	184
6	98	65.7	58.5	98.5	148
12	97.3	71.4	69.2	97.6	93
18	97.4	62.5	80.9	93.8	63
24	100	71.4	76.5	100	27
B) Favourable treatment outcome as dependant variable					
2	66.3	74.4	70.7	70.3	166
3	78.6	77.9	80.2	76.1	184
6	88.5	81.4	84.1	86.4	148
12	83.6	84.2	88.5	78	93
18	87.8	71.4	91.5	62.5	63
24	78.9	75	88.2	60	27

Table S10: Comparisons of treatment outcomes (A) and survival (B) between the Bdq and non-Bdq treatment groups with patients who died within the first two months following diagnosis excluded.The results show that our conclusions remain unchanged.

A) Comparison of Bdq and non-Bdq treatment groups by outcomes			
Variable	BDQ (n=62)	nonBDQ (n=172)	p value
Favourable (cured/completed treatment)	45 (73%)	27 (15%)	<0.001
Unfavourable outcome (treatment failed, deceased)	17 (27%)	151 (85%)	
B) Comparison of Bdq and non-Bdq treatment groups by survival			
Variable	BDQ (n=62)	nonBDQ (n=180)	p value
Alive	58 (94%)	65 (36%)	<0.001
Deceased	4 (6%)	115 (63%)	

Reference

1.   Furin J, Alirol E, Allen E, Fielding K, Merle C, Abubakar I, Andersen J, Davies G, Dheda K, Diacon A *et al*: **Drug-resistant tuberculosis clinical trials: proposed core research definitions in adults**. *Int J Tuberc Lung Dis* 2016, **20**(3):290-294.

2.   WHO: **Definitions and reporting framework for tuberculosis,– 2013 revision (updated December 2014)**. 2013.