A regimen containing bedaquiline and delamanid compared to bedaquiline in patients with drug resistant tuberculosis

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Abstract

There are limited data about combining delamanid and bedaquiline in drug-resistant tuberculosis (DR-TB) regimens. Prospective long-term outcome data, including in HIV-infected persons, are unavailable.

We prospectively followed up 122 South Africans (52.5% HIV-infected) with DR-TB and poor prognostic features between 2014 and 2018. We compared outcomes and safety in those who received a bedaquiline-based regimen (n=82) to those who received a bedaquiline-delamanid combination regimen (n=40).

There was no significant difference in 6-month culture conversion (92.5% versus 81.8%; p=0.26) and 18-month favourable outcome rate (63.4% versus 67.5%; p=0.66) in the bedaquiline versus the bedaquiline-delamanid combination group, despite the latter having more advanced drug resistance (3.7% versus 22.5% resistant > 5 drugs; p= 0.001) and higher pre-treatment failure rates (12.2% versus 52.5% with pre-treatment MDR-TB therapy failure; p <0.001). Although the proportion of QTcF prolongation was higher in the combination group [>60 ms from baseline (p=0.001) or > 450 ms during treatment (p=0.001)], there were no symptomatic cases or drug withdrawal in either group. Results were similar in HIV-infected patients.

A bedaquiline-delamanid combination regimen showed comparable long-term safety, to a bedaquiline-based regimen, in patients with DR-TB irrespective of HIV status. These data inform regimen selection in patients with DR-TB from TB endemic settings.

Introduction

Drug resistant tuberculosis (DR-TB) constitutes a threat to TB control globally. In 2017, and despite high rates of underreporting and underdiagnosis, there was a 5% increase in the absolute number of DR-TB cases detected compared to 2016[1, 2]. Treatment outcomes of MDR-TB have also remained poor with a treatment success rate of 55% reported in 2017 [3, 4]. However, this is expected to improve given that newer and repurposed drugs have now been recommended by the world health organisation (WHO) for the treatment of multidrug resistant TB (MDR-TB)[5]. Indeed, studies and regimens containing bedaquiline and linezolid have shown impressive efficacy in clinical trials and real-life programmatic use[6-10].

Nevertheless, even with the use of these newer drugs, successful outcomes and treatment options are limited in patients with fluoroquinolone-resistant and XDR-TB [7]. Thus, there is frequently a difficulty in constituting an effective treatment regimen [11-15]. Patients who have had previous exposure to second line TB medication, developed resistance to multiple drugs, developed intolerability due to adverse events [16], and those who have failed therapy on bedaquiline-based regimens, are all predisposed to having a poor prognosis. In this group of patients, it is challenging to constitute a treatment regimen containing at least 4 to 5 likely effective drugs (drugs to which the isolate was susceptible and/ or to which patients had less than one month or no previous exposure) without simultaneously including bedaquiline and delamanid. The latter, a group C drug, remains widely used in clinical practice although there is currently limited evidence about the efficacy of delamanid for the treatment of MDR-TB [17-19].

Thus, in appropriate patients with high level resistance and/ or poor prognosis there is an increasing need to use a bedaquiline-delamanid combination. However, the potential for synergistic QTc prolongation from both drugs, predisposing patients to cardiac arrythmias and

sudden death, has created unease over their inclusion in the same treatment regimen [4, 20-22]. Despite this concern and more widespread use, few studies have reported on the concurrent use of delamanid and bedaquiline and have mostly described early safety and efficacy of the combination in retrospective cohorts [23, 24]. There are, however, no prospective and long-term data addressing safety, and none addressing efficacy of the combination regimen in patients with poor prognosis from a TB endemic setting. Furthermore, there are limited data about use of the bedaquiline-delamanid combination in HIV co-infected patients, and those with high level resistance e.g. patients with XDR-TB. Another major limitation has been the lack of comparative data from a bedaquiline only control group, so that the net effect of delamanid safety (and QT prolongation) over that of bedaquiline, could be ascertained. We therefore compared the treatment outcomes and adverse event profiles of DR-TB patients with poor prognostic features on a bedaquiline-based regimen to those who had received the bedaquiline-delamanid combination.

Methods

Study design and participants

We prospectively recruited, through an ongoing clinical registry, microbiologically-confirmed MDR-TB patients who were admitted to Brooklyn Chest Hospital, the designated treatment centre for drug resistant TB in the Western Cape province in South Africa. However, a per protocol analysis plan was only formulated retrospectively. All patients were admitted between January 2014 and April 2018. Patients were included in the study if their drug susceptibility and testing done prior to recruitment showed resistance to at least rifampicin and isoniazid. Sputum drug susceptibility and testing was repeated on a monthly basis following treatment initiation, to monitor treatment progress. Each patient received either a bedaquiline-based or a bedaquiline-delamanid combination regimen. Medications were administered by trained health

care workers while patients were on admission and on outpatient basis after discharged from the hospital.

Adverse events were reported by a medically qualified health care worker, using a pharmacovigilance report form provided for each patient. Each patient had an electrocardiogram (ECG) done before treatment initiation and at least on a monthly basis afterwards. QT interval was corrected using Friderica's formula (QTcF), and values greater than 450ms qualifies a patient for closer review by attending physician. Patients' demographic and clinical data were captured by a trained researcher, laboratory reports were regularly updated on a dedicated database using a standard case report form. A written consent was obtained from every participant, and ethical clearance was obtained from the University of Cape Town Human Research Ethics Committee.

Treatment groups

All patients were assigned a treatment group based on the drugs that constitute the backbone of their regimen. Bedaquiline was the backbone in the bedaquiline-based regimen group while the second group received a regimen whose backbone was a combination of bedaquiline and delamanid (bedaquiline-delamanid), administered concurrently. Indications for receiving the combination therapy were inability to construct an effective regimen (at least 4 likely effective drugs) due to extensive drug resistance patterns or adverse events, strengthening of a regimen due to late conversion, or extensive lung disease and patients who have previously failed on a bedaquiline-based regimen. Medications were individualised for patients based on their phenotypic drug susceptibility testing results.

Outcomes

Culture conversion was defined as 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). Culture conversion status was compared between the two groups at two months, six months and twelve months following treatment initiation. In the first six months of therapy, changes in the QTcF interval from baseline values were also compared between the two groups to establish how it is impacted by the treatment regimens. At follow-up censor date which was a minimum of 18 months, patients were assigned to have had a favourable outcome if they completed treatment or were cured, those who died during treatment, failed to achieve culture conversion or lost to follow-up were said to have had an unfavourable outcome.

Statistical Analysis

The impact of delamanid was determined by comparative analysis of demographics, clinical characteristics, and treatment outcomes. Qualitative and quantitative 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. A univariate Cox proportional hazard model was used to estimate the relationship between independent variables (demographic and clinical characteristics) and the development of unfavourable outcome and, having at least one QTc value of greater than 450 ms; variables with a p-value less than 0.3 were included in the multivariate model. A p-value of <0.05 was taken as statistically significant. Kaplan-Meier curves for the probability of achieving an unfavourable outcome and the proportion of patients with culture positivity were estimated considering the duration between the day of treatment initiation and follow-up censor date. Comparison between strata (bedaquiline-based therapy and bedaquiline-delamanid combination therapy) were undertaken using a log-rank test. Statistical analysis was done using IBM SPSS Statistics Version 25.0(IBM Corp., Armonk, NY, USA).

Results

Demographic and clinical characteristics

In this study, a total of 122 culture-confirmed multidrug-resistant TB patients were enrolled into either a bedaquiline-based regimen group or a bedaquiline-delamanid combination regimen group. Median age at admission was 34 (IQR 27-42) years, they were on admission for a median 161 (IQR 102-230) days and 74 (60.7%) were male. The median weight at admission was 51.8 (IQR 43.8-59.0) kg, 64 (52.5%) patients were HIV-infected with median CD4 count of 154 (IQR 57- 332) cells/µl and they were all on antiretroviral therapy. Isolates from 11 (9%) patients were outrightly multidrug resistant (MDR-TB), 25 (20.5%) patients had further resistance to either a fluoroquinolone or a second line injectable (Pre-XDR TB), while 86 (70.5%) patients were resistant to both (XDR-TB).

There were 82 (67.2%) patients in the group who received bedaquiline-based regimen, they were hospitalised for a median 155 (IQR93-210) days. Patients demographic and clinical characteristics are outlined in Table 1. They received a median 8 (IQR 7-9) medications in the regimen which essentially comprised of bedaquiline, clofazimine, levofloxacin and linezolid as the major components. Other drugs and the proportion of patients who received them are outlined in Table 2. All patients received clofazimine or a fluoroquinolone which are known QTc prolonging drugs. 23 patients (28.1%) received both drugs, 55 patients (67.1%) received only clofazimine while 3 (3.7%) patients received only moxifloxacin in their regimen.

In the bedaquiline-delamanid combination regimen group, 40 (32.8%) patients were enrolled and they were hospitalized for a median 204 (IQR 124-295) days. 29 (72.5%) patients have been previously treated for TB, 9 (22.5%) were resistant to at least five drugs; other markers of disease severity are highlighted in Table 1. They received a median 10 (IQR 8-11) medications in the regimen which was significantly more than medications received in the

bedaquiline-based regimen. The major medications in this regimen are delamanid, bedaquiline, clofazimine, levofloxacin and linezolid. 37 (92.5%) patients in this group received at least one of clofazimine and moxifloxacin. 14 patients (35.0%) received both drugs, 21 patients (52.5%) received only clofazimine while 2 (5.0%) patients received only moxifloxacin in their regimen.

Markers of disease severity

There were significantly more patients (72.5%) in the bedaquiline-delamanid combination regimen group with previous exposure to TB treatment compared to those in the bedaquiline-based regimen (48.8%; p=0.01). More patients in the combination therapy group have previously failed TB treatment compared to those in the bedaquiline group (52.5% vs 12.2%; p<0001). The bedaquiline-delamanid combination regimen group also had significantly more patients with resistance to more than five drugs (22.5% vs 3.7%; p=0001). Other markers of disease severity including HIV-infection, microbial burden and weight less than 50 kg at admission were mostly higher in the bedaquiline-delamanid combination regimen group (Table 1).

Culture conversion

In the bedaquiline-based regimen group, 52 patients (63.4%) were culture positive at recruitment, 92.5% of those with laboratory results had achieved culture conversion by six months of treatment. Of the 42 HIV-infected patients in this group, 23 (54.8) were culture positive at recruitment, and 93.8% of those with laboratory results have achieved culture conversion by six months of treatment.

In the bedaquiline-delamanid combination regimen, 26 patients (65%) were culture positive at recruitment, 81.8% of those with laboratory results had achieved culture conversion by six months of treatment. Of the 22 HIV-infected patients in this group, 13 (59.1%) were culture positive at recruitment, 83.3% of those with laboratory results had achieved culture conversion

by six months of treatment. Comparison of culture conversion rates in both groups are outlined in Table S1 (Online supplement). In time to event analysis, there were more patients in the bedaquiline-delamanid combination group with culture positivity compared to those in the bedaquiline group by the end of the fifteenth month (p=0.04; Figure 1).

Efficacy of the treatment regimens

In the bedaquiline-based regimen group, 52 patients (63.4%) achieved a favourable outcome while the remaining patients had unfavourable outcome by the end of follow-up period. 29 (69.1%) out of 42 HIV-infected patients in this group also, achieved a favourable outcome. In the bedaquiline-delamanid combination regimen group, 27 patients (67.5%) achieved a favourable outcome while the remaining patients had unfavourable outcome by the end of follow-up period. 15 (68.2%) out of 22 HIV-infected patients in this group also, achieved a favourable outcome. There was no significant difference in the favourable outcome rate between the two groups even when they were stratified by resistance patterns (Table 1; online supplement Table S2). In time to event analysis, there was no difference in the probability of achieving an unfavourable outcome between the two groups (p=0.54; Figure 1). Regression analysis showed that moxifloxacin (HR 1.023; p=0.89) and clofazimine (HR 0.711; p=0.35) which were the other QTcF prolonging drugs used in both regimens did not predispose to having unfavourable outcome (Table 3). It also suggested that days to sputum culture positivity less than seven days (H.R.= 2.712; p=0.006) and resistance to more than five drugs (H.R.= 2.173; p=0.08) are independent predictors of an unfavourable outcome (Table 3).

Adverse events

In the bedaquiline-based regimen group, 73 patients (89.0%) reported a total of 250 adverse events, each patient reporting a median 2 (IQR 1-4) adverse events in the course of treatment. The most commonly reported adverse events were hearing loss (50.0%), most likely from

previous second line injectable treatment, elevated liver enzymes (28%) with median ALT of 112 U/L (IQR 81-173) in affected patients, anaemia (34.1%), peripheral neuropathy (22.0%) and vomiting (24.4%). ALT elevation in the HIV-infected patients in this group was by a median 107 U/L (IQR 71-154).

In the bedaquiline-delamanid combination regimen group, 37 patients (92.5%) reported a total of 125 adverse events, each patient reporting a median 3 (IQR 2-4) adverse events in the course of treatment. The most commonly reported adverse events in this group were hearing loss (45%), elevated liver enzymes (32.5%) with median ALT of 111U/L (IQR 85-155), anaemia (37.5%) and peripheral neuropathy (30.0%). ALT elevation in the HIV-infected patients in this group was by a median 133 U/L (IQR 91-155), this was essentially similar to those in the bedaquiline regimen (p=0.34). There were no significant differences in the occurrence of adverse events reported in the two groups except for psychosis which was likely associated with higher rate of simultaneous use of terizidone and high dose isoniazid in the bedaquiline-delamanid combination regimen group. Other adverse events and the proportion of patients who had them are reported in Table 4.

QTcF interval changes

The median baseline QTcF value for the bedaquiline-based regimen group was 408 ms (IQR 388-425). In the first six months of treatment, there was a maximum QTcF prolongation of median 27 ms (IQR 13-42) from the baseline values, and only 6 patients (7.3%) had a QTcF prolongation greater than 60 ms from baseline values. 16 patients (19.5%) in this group also had at least one QTcF value greater than 450 ms in the course of treatment, but none reached

the threshold limit of 500 ms, and none of them had bedaquiline discontinued due to changes in QTcF values (Table 5).

The median baseline QTcF value for the bedaquiline-delamanid regimen group was 419 ms (389-436). In the first six months of treatment, there was a maximum QTcF prolongation of median 23 ms (8-54) from the baseline values, and only 7 patients (20.6%) had a QTcF prolongation greater than 60 ms from baseline values. 15 patients (44.1%) in this group also had at least one QTcF value greater than 450 ms in the course of treatment, none of them reached the threshold limit of 500 ms, and neither bedaquiline nor delamanid was discontinued in any of the patients due to changes in QTcF values (Table 5).

There was no definitive pattern to the changes (increase or decrease) in QTcF values observe over a period of 6 months (online supplement Figure S1, but there were more patients in the bedaquiline-delamanid regimen group who reported a QTcF prolongation of more than 60 ms from baseline values ($p<0.001$) and at least one QTcF value greater than 450 ms ($p<0.001$) in the course of treatment. Increasing age (H.R.=1.039; p= 0.04) and the use of delamanid (H.R.= 3.504; p= 003) were independent predictors of having at least one QTcF value greater than 450 ms (Table 6). There were however no cardiac symptoms necessitating the withdrawal of delamanid from the treatment regimen from any of the affected patients.

Discussion

This is the first prospective study comparing long-term treatment outcomes and safety data in drug-resistant TB patients who received bedaquiline versus bedaquiline-delamanid

combination therapy. The main findings of the study were that (i) combination therapy was associated with significant QTcF prolongation from baseline values but there were no patients who became symptomatic from a cardiovascular point of view (syncope, collapse, arrythmia, hypotension etc.) or reached the threshold limit of 500ms that would have necessitated recommended withdrawal of either bedaquiline or delamanid (and despite the concomitant use of other QT-prolonging drugs), (ii) bedaquiline-delamanid combination therapy was associated with modestly good culture conversion and favourable outcome rates (and comparable to a bedaquiline-based regimen) despite being used in patients from a poorer prognostic category i.e. high proportion of patients who had previously been declared therapeutically destitute, and/ or whose isolates were resistant to > 5 drugs, and (iii) these findings were broadly similar in HIV-infected patients.

Thus, our data support the use of the combination in patients in whom there is a difficulty in constituting a regimen with at least four effective drugs. Our data are concordant with 2 recent publications, which also confirmed the safety profile of the bedaquiline/delamanid combination[24, 25]. However, there are several important strengths and incremental contributions of our study findings. Here, we are able to confirm the long-term safety, safety in HIV-infected persons (which has always remained the concern given their higher frequency of adverse events to drugs in general), and importantly we were able to discern the incremental QT prolongation effect of delamanid within the combination, when compared to a bedaquiline only group. This should allay anxiety amongst clinicians who often need to include delamanid in treatment regimens but are concerned by the WHO Guidelines which express reservation about the safety of simultaneous use of these drugs[26]. Other QT-prolonging drugs like clofazimine and moxifloxacin were used substantially, and to a similar extent, in both groups and thus we could account for their effect when comparisons were made. Nevertheless, ECG

monitoring is still required when the combination is used, especially together with other QT-prolonging drugs, given that discontinuation of drugs have been documented in a few patients[26]. However, our findings support the notion that this is not a major issue and is uncommon.

We were also able to evaluate the long-term efficacy, in terms of outcomes, in the bedaquiline only and combination groups, respectively. It is reassuring that we found similar long-term outcomes in the bedaquiline-delamanid combination group despite this group having a higher frequency of poor prognostic features (at least half the group were MDR treatment failures compared to ~10% in the bedaquiline group, and almost a quarter of isolates in the combination group were resistant to 5 or more drugs compared to about ~5% in the bedaquiline only group). Furthermore, usage of WHO group A and group B drugs, i.e. (linezolid, any fluoroquinolone, clofazimine, and terizidone) were similar in both groups. Despite recent findings suggesting limited efficacy of this drug (and when using 6-month culture conversion as an outcome)[17], our data suggest that delamanid may be a useful addition in patients where an appropriate regimen of 4 to 5 likely effective drugs cannot be constituted because of toxicity or high-level resistance. Indeed, despite the combination group having an ~50% prior treatment failure rate, the 6-month culture conversion rate in this group was over 80%, and the overall long-term favourable outcome rate was almost 70%. This far exceeds the dismal outcomes seen with XDR-TB prior to the advent of newer drugs[27, 28]. Nevertheless, ~10% of patients in each group failed treatment. Thus, programmatically incurable TB is an emerging problem in TB endemic countries and public health efforts are needed to manage such patients on a long-term basis. Besides establishing palliative care and long-term community-based residential facilities[29], preventative measures such as optimal antibiotic stewardship, active case finding, and wider roll-out of new diagnostics and drugs are urgently required[15].

In HIV-infected patients the adverse event profile and treatment outcomes showed similar patterns compared to HIV-uninfected patients. These findings are highly relevant to high TB and HIV-endemic settings. Besides QT-prolongation, other important adverse events, such as elevation of liver enzymes, were found to be similar in the HIV-infected patients in both groups, further confirming safety and compatibility with antiretrovirals in this group.

There are several limitations of our findings. Our study was of limited sample size and a larger study may have shown different results given that cardiovascular events related to QT prolongation is rare. A larger sample size may have also allowed some clear-cut outcome effect to be discerned. However, this study has reported the largest number of patients on bedaquiline-delamanid combination therapy (n = 40), the largest number of patients with XDR-TB (n = 86), and the multivariable analysis, even when taking into account the poorer prognostic features in the combination group, failed to identify the combination as an independent predictor of outcome. Rather, bacterial load remained the only significant and independent predictor of outcome. This highlights another limitation, which is the failure to evaluate radiographic disease extent at the time of diagnosis, which would better enable us to account for initial disease severity. However, logistical and technical issues prevented us from accessing the pre-treatment chest radiographs. Nevertheless, we were able to get a fairly good comparative estimation of disease severity in both groups through evaluation of other prognostic features such as admission weight, HIV status, CD4 count, previous treatment history, resistance to 5 or more drugs, and mycobacterial load, which are all proxies of disease severity. Selection bias could have also impacted our findings including the cases and controls study design. However, all the patients were prospectively recruited in the same region and over a similar timeframe. It is possible that some patients with events could have been missed as the programme in the Western Cape became more decentralised. However, our recruitment

network spanned the entire region and also utilised a region-wide electronic capture and surveillance system.

In summary, our findings suggest that a bedaquiline-delamanid combination has a comparable long-term safety profile to a bedaquiline-based regimen in patients with drug-resistant TB irrespective of HIV status. Delamanid appeared to be a useful adjunct in the treatment of patients with poor prognostic features or high-level resistance where constituting an appropriate regimen would be otherwise challenging. These data inform regimen selection in patients with drug-resistant TB from TB endemic settings.

Table 1: Comparison of demographic and clinical characteristics between patients in the bedaquiline and the combination regimen groups. Data are reflected as number of persons (%) or median (interquartile range) unless otherwise stated.

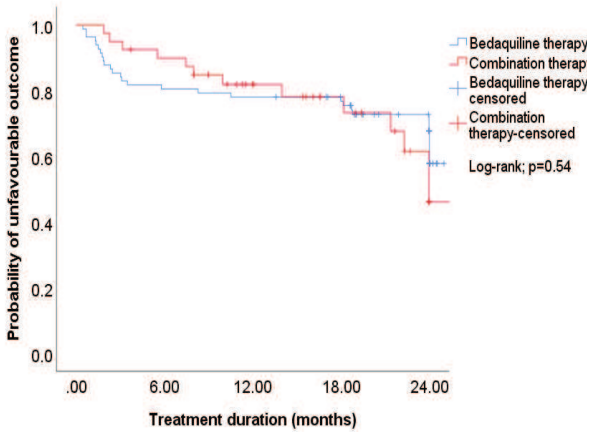
Variables	Patients who received bedaquiline-based regimen (n=82)	Patients who received bedaquiline-delamanid combination regimen (n=40)	p-value
Age (years)	33 (IQR 28-42)	34 (IQR 27-42)	0.04
Gender (male)	50 (61.0)	24 (60.0)	0.92
Weight at admission (kg)	51.8 (IQR 45.6- 58.3)	51.8 (IQR 43.3- 60.8)	0.36
Days hospitalized	155 (IQR 93-210)	204 (IQR 124- 295)	0.38
Number of medications	8 (IQR 7-9)	10 (IQR 8-11)	0.001
5 likely effective medications	59 (72%)	26 (65%)	0.43
Number of adverse events	2 (IQR 1-4)	3 (IQR 2-4)	0.51
Time to culture positivity (days)	14 (IQR 10-17)	10 (IQR 8-14)	0.46
Diagnosis: XDR-TB	67 (81.7)	19 (47.5)	<0.001
PRE-XDR TB	10 (12.2)	15 (37.5)	<0.001
MDR-TB	5 (6.1)	6 (15)	<0.001
Markers of disease severity			
Patients with weight <50kg	34 (41.5)	19 (47.5)	0.53
Patients with previous MDR-TB treatment failure	10 (12.2)	21 (52.5)	<0.001
Patients with previous TB treatment	40 (48.8)	29 (72.5)	0.01
HIV-infected	42 (51.2)	22 (55.0)	0.69
CD4 Count (cells/µl)	135 (60-279)	234 (52- 367)	0.41
Patients with CD4<200 cells/µl	26 (31.7)	10 (29.4)	0.19
Diabetic patient	2 (2.4)	1 (2.5)	0.98
Patients resistant to ≥5 drugs	3 (3.7)	9 (22.5)	0.001
Patients with either resistant to ≥ 5 drugs or previous treatment failure	13 (15.9)	23(57.5)	<0.001
Smear grade>2 plusses	14 (17.1)	8 (20.0)	0.69
Time to culture positivity≤ 7 days	9 (10.9)	7 (17.5)	0.32
Treatment outcome			
Favourable outcome	52 (63.4)	27 (67.5)	0.66
Unfavourable Outcome	30 (36.6)	13 (32.5)	

Table 2. List of drugs used in the bedaquiline-based regimen and bedaquiline-delamanid combination regimen and the proportion of patients who received them. Data is n (%).

Drugs	Patients who received bedaquiline-based regimen (n=82)	Patients who received bedaquiline-delamanid combination regimen (n=40)	p-value
Kanamycin	16 (19.5)	8 (20)	0.95
Terizidone	75 (91.5)	33 (82.5)	0.15
Pyrazinamde	80 (97.6)	37 (92.5)	0.19
Para-aminosalicylic acid	75 (91.5)	31 (77.5)	0.03
Meropenem	0 (0)	5 (12.5)	N/A*
Any fluoroquinilone	81 (98.8)	37 (92.5)	0.07
Moxifloxacin	26 (31.7)	16 (40)	0.37
Levofloxacin	81 (98.8)	33 (82.5)	0.001
Linezolid	67 (81.7)	36 (90)	0.24
High dose Isoniazid	34 (41.5)	20 (50)	0.37
Ethionamide	27 (32.9)	13 (32.5)	0.96
Ethambutol	38 (46.3)	14 (35)	0.23
Clofazimine	78 (95.1)	35 (87.5)	0.13
Capreomycin	7 (8.5)	3 (7.5)	0.85
Bedaquiline	82 (100)	40 (100)	N/A*
Delamanid	0 (0)	40 (100)	N/A*

N/A*: Not applicable

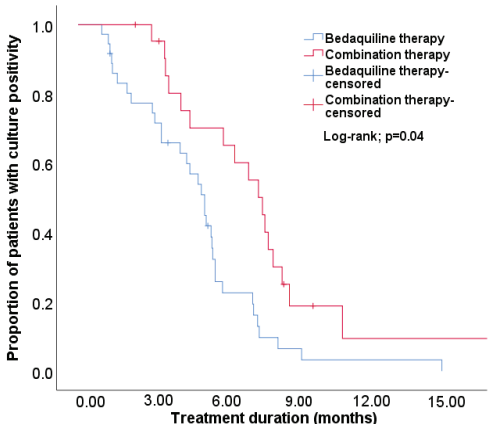
I



Number at risk

B	82	14	12	11	4
DB	40	9	6	5	0

II



Number at risk

B	52	46	42	41	40	40
DB	26	25	24	21	16	16

Figure 1: Kaplan Meier estimate for the probability of achieving an unfavourable outcome (I) and the proportion of patients with culture positivity by the fifteenth month (II) in patients who received bedaquiline-based regimen (B) versus a bedaquiline-delamanid combination regimen (DB).

Table 3: Univariate and multivariate Cox proportional hazard model for developing unfavourable outcome in the whole cohort (N=122)

Variables	Hazard ratio (95% C.I)	p-value
Univariate analysis		
Age (years)	0.997 (0.967- 1.028)	0.85
Gender (male)	1.231 (0.662-2.289)	0.51
Weight (kg)	0.986 (0.960- 1.014)	0.33
Age at admission < 50 years	1.137 (0.624- 2.070)	0.68
HIV-infection	1.181 (0.874- 1.595)	0.28
CD4 Count (cells/µl)	1.000 (0.998- 1.002)	0.84
Previous TB treatment	1.013 (0.556- 1.848)	0.97
Previous treatment failures	1.367 (0.580- 3.223)	0.48
Days of admission	1.000 (0.997- 1.002)	0.87
Clofazimine treatment	0.505 (0.122- 2.090)	0.35
Delamanid treatment	0.877 (0.627- 1.225)	0.44
Moxifloxacin treatment	1.023 (0.743- 1.408)	0.89
Levofloxacin treatment	0.968 (0.473- 1.980)	0.93
Any fluoroquinolone	0.897 (0.123- 6.555)	0.92
Linezolid treatment	0.959 (0.426- 2.157)	0.92
Bedaquiline-delamanid treatment	0.814 (0.416- 1.593)	0.55
Number of medications	1.112 (0.935- 1.322)	0.23
Number of adverse events	1.026 (0.898- 1.171)	0.71
5 likely effective drugs	0.840 (0.589- 1.196)	0.33
Resistant to >5 drugs	2.173 (0.900- 5.246)	0.08
TTP* < 7 days	2.712 (1.331- 5.522)	0.006
Smear grade	1.583 (0.779- 3.216)	0.20
Multivariate Analysis		
HIV-infection	1.940 (0.791- 2.751)	0.22
Isolate resistant to >5 drugs	1.940 (0.787- 4.779)	0.15
TTP* < 7 days	2.681 (1.196- 6.011)	0.02*
Number of medications	1.144 (0.957- 1.368)	0.14
Smear grade	1.084 (0.489-2.403)	0.84

Variables with p-value less than 0.3 were included in the multivariate model; TTP= time to culture positivity.

Table 4: Adverse events reported by patients who received bedaquiline-based regimen and those who received bedaquiline-delamanid combination regimen. Data is n (%).

Adverse event	Patients who received bedaquiline-based (n=82)	Patients who received bedaquiline and delamanid (n=40)	p-values
Dizziness/disorientation	12 (14.6)	9 (22.5)	0.28
Psychosis	3 (3.7)	6 (15)	0.02*
Blurred vision	5 (6.1)	3 (7.5)	0.77
Hearing loss	41 (50.0)	18 (45.0)	0.60
Hypothyroidism	6 (7.3)	3 (7.5)	0.97
Peripheral neuropathy	18 (22.0)	12 (30.0)	0.33
Anaemia	28 (34.1)	15 (37.5)	0.72
Diarrhoea	7 (8.5)	6 (15)	0.28
Abdominal pain	16 (19.5)	5 (12.5)	0.34
Vomiting	20 (24.4)	8 (20.0)	0.59
Nausea	16 (19.5)	5 (12.5)	0.34
Elevated liver enzyme	23 (28.0)	13 (32.5)	0.61
Deranged renal function	17 (20.7)	9 (22.5)	0.82
Arthralgia	15 (18.3)	5 (12.5)	0.42

*33.3% of patients who had psychosis in the bedaquiline-delamanid group received terizidone and high dose isoniazid in their regimen compared to 11% in the bedaquiline group; both drugs are associated with increased risk of developing psychosis.

Table 5: QTcF profiles of patients who received bedaquiline-based regimen and those who received bedaquiline-delamanid combination regimen in the whole cohort and in HIV-infected patients. Data is n (%) and median (interquartile range).

Variable	Patients who received bedaquiline-based regimen	Patients who received bedaquiline-delamanid combination therapy	p-values
Whole cohort	**n=82**	**n=40**	
Baseline QTcF	408 (IQR 388-425)	419 (IQR 389-436)	0.32
Maximum QTcF change from baseline	27 (IQR 13-42)	23 (IQR 8-54)	0.11
Patients with QTcF increment from baseline greater than 60 ms	6 (7.3)	7 (20.6)	<0.001
Patients with at least one QTcF greater than 450 ms	16 (19.5)	15 (44.1)	<0.001
Patients with at least one QTcF greater than 500 ms	0 (0)	0 (0)	N/A*
HIV-infected patients	**n=42**	**n=22**	**p-values**
Baseline QTcF	407 (IQR 385-428)	417 (IQR 378- 436)	0.54
QTcF change from baseline	32 (IQR 14-44)	22 (IQR 6-56)	0.19
Patients with QTcF difference greater than 60 ms	5 (11.9)	4 (18.2)	0.49
Patients with QTcF greater than 450 ms	11 (26.2)	7 (31.8)	0.32
Patients with QTcF greater than 500 ms	0 (0)	0 (0)	N/A*
HIV uninfected patients	**n=40**	**n=18**	
Baseline QTcF	409 (IQR 394- 419)	419 (IQR 393-429)	0.21
QTcF change from baseline	22 (IQR 12- 37)	32 (IQR 13- 52)	0.48
Patients with QTcF difference greater than 60 ms	1	3	0.06
Patients with QTcF greater than 450 ms	5	8	0.02
Patients with QTcF greater than 500 ms	0	0	N/A*

N/A*: Not applicable

Table 6: Cox proportional hazard model for having at least one QTc value of greater than 450ms

Variables	Hazard ratio (95% C.I)	p-value
Univariate analysis		
Age (years)	1.031 (0.998- 1.066)	0.07
Gender (male)	1.221 (0.570- 2.614)	0.61
Weight (kg)	0.980 (0.948- 1.014)	0.24
Age at admission < 50 years	0.427 (0.146-1.248)	0.12
HIV-infection	1.043 (0.504- 2.158)	0.91
Previous TB treatment	1.195 (0.579- 2.466)	0.63
Previous treatment failures	1.304 (0.536- 3.173)	0.56
Days of admission	1.002 (1.000- 1.004)	0.06
Clofazimine treatment	0.731 (0.220- 2.426)	0.61
Delamanid treatment	3.668 (1.712- 7.859)	**0.001**
Moxifloxacin treatment	1.306 (0.619- 2.757)	0.48
Levofloxacin treatment	1.564 (0.748- 3.271)	0.24
Linezolid treatment	0.605 (0.244-1.501)	0.28
Number of medications	1.104 (0.884- 1.380)	0.38
Number of adverse events	0.976 (0.832- 1.145)	0.77
5 likely effective drugs	2.025 (0.761- 5.386)	0.16
TTP* < 7 days	0.777 (0.184- 3.282)	0.73
SMG$^{\#}$ > 2 plusses	1.504 (0.609- 3.714)	0.38
Multivariate analysis		
5 likely effective drugs	3.167 (0.995- 10.08)	0.05
Age	1.039 (1.000- 1.078)	**0.04**
Delamanid treatment	3.504 (1.544- 7.954)	**0.003**
Linezolid treatment	0.539 (0.200- 1.454)	0.22
Levofloxacin treatment	1.357 (0.494- 3.730)	0.55
Days of admission	1.001 (0.998- 1.004)	0.46
Weight	0.975 (0.937- 1.015)	0.23

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A regimen containing bedaquiline and delamanid compared to bedaquiline alone in patients with drug resistant tuberculosis with poor prognosis

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Table S1: Culture conversion status of patients who received bedaquiline-based and those who received bedaquiline-delamanid combination regimens at different time points during treatment. Data is n (%).

	Patients who received bedaquiline-based regimen (n=82)	Patients who received delamanid-bedaquiline combination regimen (n=40)	p-values
Positive at baseline	52/82 (63.4)	26/40 (65.0)	0.86
Culture Conversion at 2 months	25/38 (65.8)	13/23 (56.5)	0.47
Culture Conversion at 6 months	33/36 (92.5)	18/22 (81.8)	0.26
Culture Conversion at 12 months	27/31 (87.1)	13/15 (86.7)	0.97

Patients who were culture negative at the point of recruitment were excluded from the analysis at 2, 6 and 12 months.

Table S2: Comparison of treatment outcomes between patients who received bedaquiline-based regimen and those who received delamanid-bedaquiline combination regimen. Data is (n)%

	Patients who received bedaquiline-based regimen (n=82)	Patients who received delamanid-bedaquiline combination regimen (n=40)	p-values
XDR-TB	n=67	n=19	
Favourable outcome	44 (65.7)	14 (73.7)	0.51
Unfavourable Outcome	23 (34.3)	5 (26.3)	
PRE-XDRTB	n=10	n=15	
Favourable outcome	4 (40)	9 (60)	0.32
Unfavourable Outcome	6 (60)	6 (40)	
MDR-TB	n=5	n=6	
Favourable outcome	4 (80)	4 (66.67)	0.62
Unfavourable Outcome	1 (20)	2(33.33)	

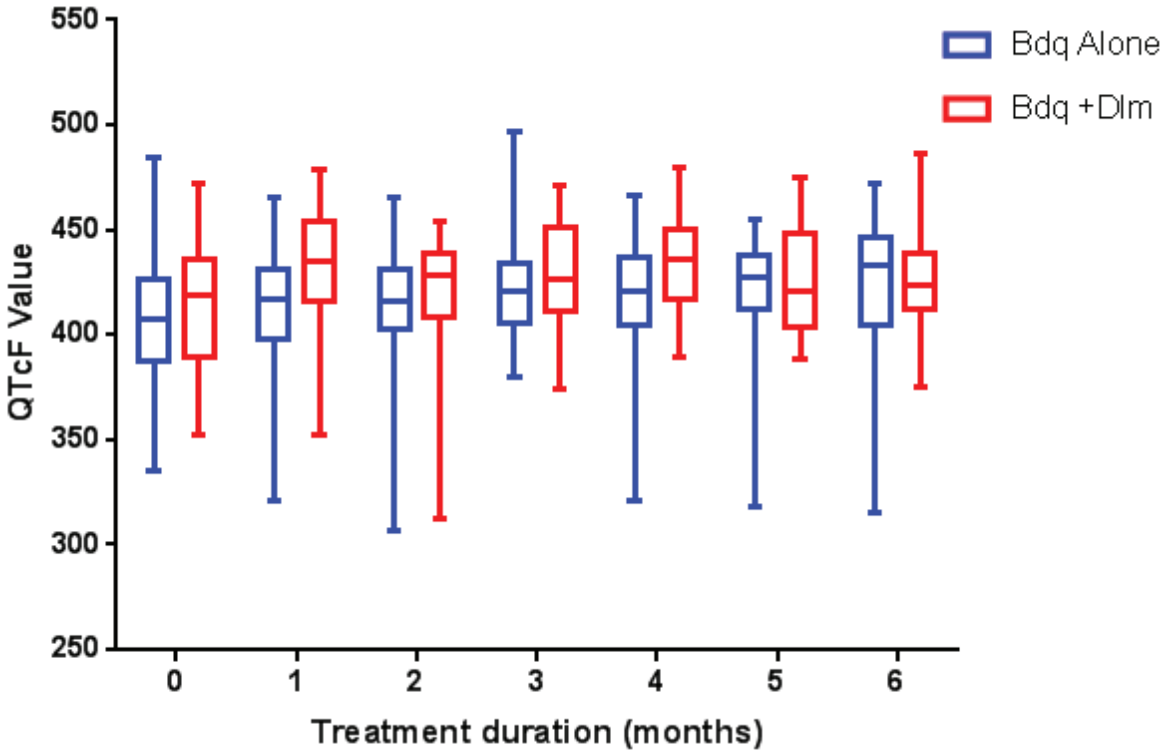


Figure S1: QTcF values at different time points during treatment with either bedaquiline-based regimen or delamanid-bedaquiline combination regimen. Boxes represent the median and IQR, while error bars represent range values

Table S3: (A) Univariate Cox proportional hazard model for developing unfavourable outcome in the HIV-infected patients

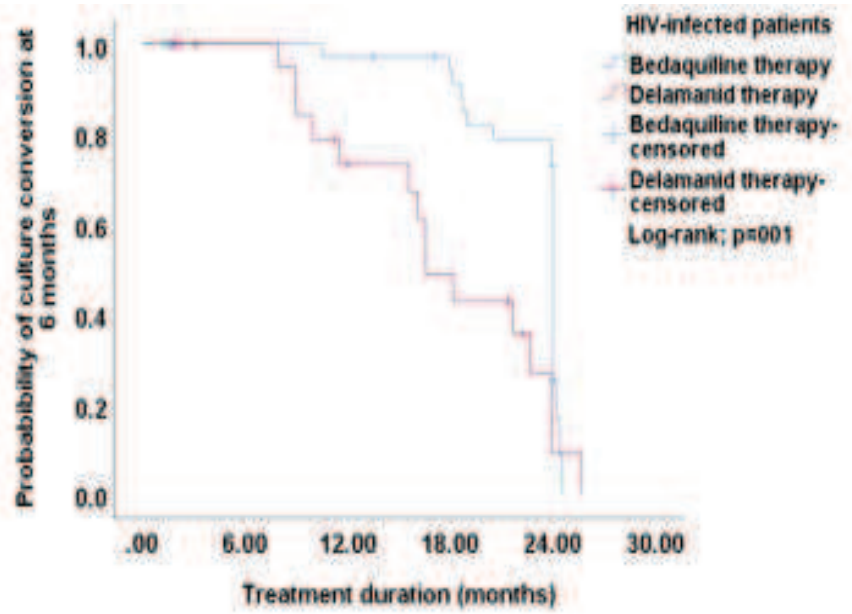
Variables	Hazard ratio (95% C.I)	p-value
Age (years)	1.013 (0.960- 1.068)	0.64
Gender (male)	1.173 (0.479- 2.871)	0.73
Weight (kg)	0,981 (0.945- 1.018)	0.31
Age at admission < 50 years	0.206 (0.058- 0.734)	0.02
Previous TB treatment	1.808 (0.748- 4.367)	0.19
Days of admission	0.993 (0.986- 0.999)	0.03
Clofazimine treatment	0.596 (0.080- 4.467)	0.62
Delamanid treatment	0.785 (0.485- 1.269)	0.32
Moxifloxacin treatment	1.262 (0.484- 3.293)	0.64
Levofloxacin treatment	0.883 (0.116- 6.717)	0.88
Any fluoroquinolone	0.047 (0.000-10560)	0.63
Linezolid treatment	0.416 (0.056- 3.109)	0.39
Delamanid-bedaquiline treatment	0.651 (0.248- 1.706)	0.38
Number of medications	1.099 (0.847- 1.426)	0.48
Number of adverse events	1.137 (0.960-1.347)	0.14
5 likely effective drugs	0.684 (0.395- 1.183)	0.17
Resistant to >5 drugs	2.688 (0.762- 9.482)	0.12
TTP* < 7 days	1.709 (0.570- 5.119)	0.34
SMG$^{\#}$ > 2 plusses	2.270 (0.752- 6.847)	0.15
(B) Multivariate Cox proportional hazard model for unfavourable outcome		
Age at admission < 50 years	0.333 (0.079-1.396)	0.13
Resistant to >5 drugs	4.725 (1.041-21.43)	0.04
Previous TB treatment	2.181 (0.810- 5.871)	0.12
Days of admission	0.990 (0.982- 0.998)	0.02
5 likely effective drugs	0.465 (0.142- 1.520)	0.21
Number of adverse events	1.173 (0.949- 1.449)	0.14
SMG$^{\#}$ > 2 plusses	2.442 (0.690- 8.640)	0.17

Table S4: Adverse events reported by HIV-infected patients who received bedaquiline-based regimen and those who received delamanid-bedaquiline combination regimen. Data is n (%).

Adverse event	Patients who received bedaquiline alone (n=42)	Patients who received bedaquiline and delamanid (n=22)	p-values
Dizziness/disorientation	5 (11.9)	4 (18.2)	0.49
Psychosis	2 (4.8)	4 (18.2)	0.08
Blurred vision	1 (2.4)	2 (9.1)	0.23
Hearing loss	20 (47.6)	8 (36.4)	0.39
Hypothyroidism	4 (9.5)	2 (9.1)	0.96
Peripheral neuropathy	6 (14.3)	7 (31.8)	0.098
Anaemia	7 (16.7)	11 (50)	0.005*
Diarrhoea	3 (7.1)	4 (18.2)	0.18
Abdominal pain	8 (19.0)	1 (4.5)	0.11
Vomiting	11 (26.2)	4 (18.2)	0.47
Nausea	9 (21.4)	3 (13.6)	0.45
Elevated liver enzyme	15 (35.7)	8 (36.4)	0.96
Deranged renal function	12 (28.6)	8 (36.4)	0.52
Arthralgia	8 (19)	3 (13.6)	0.59

*95.5% of patients in the bedaquiline-delamanid group received linezolid in their regimen compared to 88.1% in the bedaquiline group; linezolid is associated with increased risk of developing anaemia.

A



B

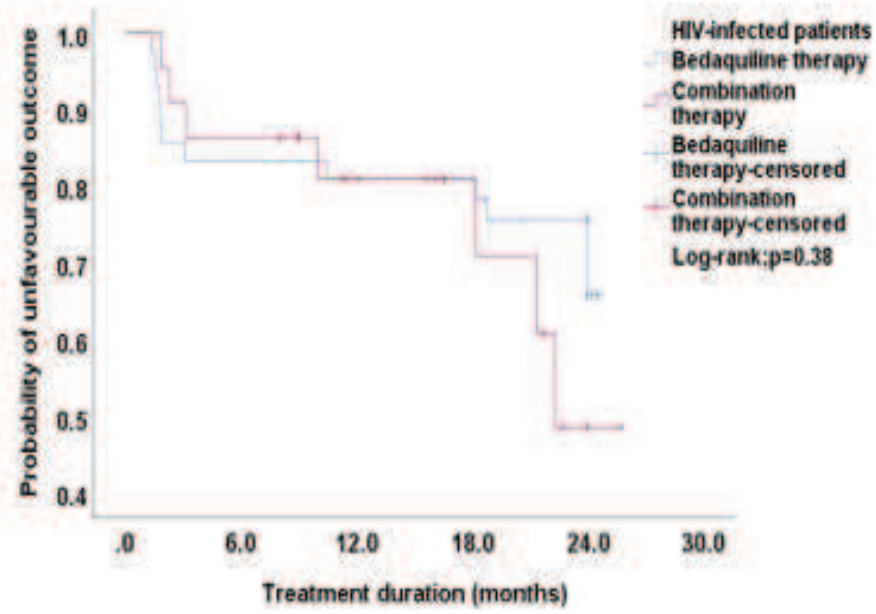


Figure S2 (A): Kaplan Meier estimate for the probability of culture conversion and (B) the probability of achieving an unfavourable outcome in HIV-infected patients who received bedaquiline-alone regimen and those who received delamanid-bedaquiline combination regimen.