Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug resistant tuberculosis: a retrospective cohort study

By

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DECLARATION

I, Dr Ying Zhao, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

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Background

Bedaquiline is used as a substitute for second-line injectable (SLI) intolerance in the treatment of multidrug-resistant tuberculosis (MDR-TB), but the efficacy and safety of this strategy is unknown.

Methods

We performed a retrospective cohort study to evaluate treatment outcomes for MDR-TB patients who substituted bedaquiline for SLIs. Adults receiving bedaquiline substitution for MDR-TB therapy, plus a matched control group who did not receive bedaquiline, were identified from the electronic TB register in the Western Cape Province, South Africa. The primary outcome measure was the proportion of patients with death, loss to follow up, or failure to achieve sustained culture conversion at 12 months of treatment.

Results

Data from 162 patients who received bedaquiline substitution and 168 controls were analyzed; 70.6% were HIV-infected. Unfavorable outcomes occurred in 35/146 (23.9%) patients in the bedaquiline group versus 51/141 (36.2%) in the control group (relative risk, 0.66; 95% confidence interval [CI], 0.46 to 0.95). The number of patients with culture reversion was lower in those receiving bedaquiline (1 patient, 0.8%) compared to controls (12 patients, 10.3%; P = 0.001). Delayed initiation of bedaquiline was independently associated with failure to achieve sustained culture conversion (adjusted odds ratio, 1.5; 95% CI, 1.1 – 1.9, for every 30-day delay). Mortality was similar at 12 months (11 deaths in each group; P = 0.973).

Conclusions

Substituting bedaquiline for SLIs in MDR-TB treatment resulted in improved outcomes at 12 months compared with patients who remained on SLIs, supporting the use of bedaquiline for MDR-TB treatment in programmatic settings.

DEDICATION

I would like to dedicate this dissertation to my husband, Jinyong Kim who supported me through this project, and our daughters, Seohee and Amy.

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ABBREVIATIONS

MDR-TB	Multidrug resistant tuberculosis
SLI	Second-line injectable
BDQ	Bedaquiline
Pre-XDR-TB	Tuberculosis resistant to aminoglycosides or fluoroquinolones
XDR-TB	Tuberculosis resistant to aminoglycosides and fluoroquinolones
HIV	Human immunodeficiency virus
ART	Antiretroviral therapy
ECG	Electrocardiography
EDRWeb	Electronic Drug-Resistant Tuberculosis Register
BCAP	Bedaquiline Clinical Access Program
WHO	World Health Organization
IQR	Interquartile range
RR	Relative risk
OR	Odds ratio
CI	Confidence interval

ARTICLE IN PUBLICATION READY FORMAT

Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug resistant tuberculosis: a retrospective cohort study

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Keywords

Bedaquiline, drug-resistant tuberculosis, HIV-associated tuberculosis

Running title

Bedaquiline substitution for second line injectables in multidrug resistant tuberculosis

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Key point

In this population with a high rate of HIV co-infection, bedaquiline substitution for second-line injectable agents was associated with a lower proportion of unfavorable treatment outcomes at 12 months compared with a matched control group receiving standard treatment for MDR-TB.

ABSTRACT

Background

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Conclusions

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INTRODUCTION

Multidrug resistant tuberculosis (MDR-TB), defined as resistance to rifampicin and isoniazid, is associated with increased mortality and worse treatment outcomes as compared with drug-susceptible TB.[1] Second-line injectable drugs (SLIs), core agents used in the treatment of MDR-TB,[2] cause substantial toxicity and intolerance which leads to treatment discontinuation and contributes to the low success rates with conventional MDR-TB treatment.[3,4]

There is a stepwise decline in the success of TB treatment as drug resistance patterns advance,[5] and the presence of resistance to SLIs is a significant predictor of poor long-term survival in some studies.[5,6] Therefore, discontinuing SLIs from MDR-TB regimens without replacement by an effective drug may put patients at risk of worse outcomes and ongoing transmission of drug-resistant TB.

The novel diarylquinoline, bedaquiline, improves culture conversion rates when added to conventional MDR-TB treatment in clinical trials,[7-9] and has also been shown to improve treatment outcomes in observational studies.[10] However, there are safety concerns related to its effect on QT interval prolongation and the increased mortality associated with the bedaquiline arms in pooled data from phase 2 clinical trials.[11] WHO has made a conditional recommendation for the use of bedaquiline in adult MDR-TB patients who have limited treatment options,[12] which may occur in up to two thirds of cases.[13] Bedaquiline is now being widely used as a substitute in MDR-TB regimens for patients unable to tolerate SLIs,[14] but the efficacy and safety of this strategy is unknown. We conducted a retrospective cohort study to determine outcomes for South African patients who received bedaquiline as a substitution for SLIs in conventional MDR-TB therapy, with the hypothesis that this would not result in inferior outcomes at 12 months compared with patients who did not discontinue SLIs.

STUDY POPULATION AND METHODS

Study population and eligibility criteria

In September 2015, the Western Cape Provincial Department of Health expanded and decentralized bedaquiline access for adults who had confirmed MDR-TB without additional

second-line drug resistance who were unable to tolerate SLIs. Under this expanded program, which is ongoing, local clinicians made requests for bedaquiline access for individual patients to a Provincial Clinical Advisory Committee using a standardized application form. If approved, bedaquiline was provided for a minimum of 24 weeks (with a loading dose of 400 mg once daily for the initial two weeks followed by 200 mg three times per week for 22 weeks). Other drugs in the MDR-TB regimen included moxifloxacin (which was replaced by levofloxacin at bedaquiline initiation, due to the greater QT-prolonging effect of moxifloxacin), pyrazinamide, ethionamide, high dose isoniazid, ethambutol and terizidone. Until late 2017, this standardized MDR-TB regimen was generally administered for a total of 18 to 24 months, including the use of an SLI for 6 to 8 months, according to South African National Treatment Program guidelines (the World Health Organization shorter MDR-TB regimen was introduced in the Western Cape Province in late 2017, after the enrolment window for this study). As bedaquiline exposure is reduced by efavirenz co-administration, HIV-infected patients on efavirenz were switched to either nevirapine or lopinavir/ritonavir at bedaquiline initiation.

We screened all applications to the Provincial Clinical Advisory Committee and included consecutive cases that received bedaquiline as a substitution for SLIs between October 2014 and October 2016. We also included a group of control patients with MDR-TB who did not receive bedaquiline, matched 1:1 for clinic location and time of treatment initiation within a +/- 6-month window. These patients were identified from the South African Electronic Drug-Resistant Tuberculosis Register (EDRWeb), a web-based network used in the surveillance and management of drug-resistant TB in South Africa. Patients younger than 18 years, and those with *M. tuberculosis* strains known to be resistant to aminoglycosides and/or fluoroquinolones (extensively drug-resistant tuberculosis (XDR-TB) or pre-XDR-TB) were excluded.

Outcome measures

The primary outcome measure was the proportion of patients with unfavorable outcomes at 12 months, defined as a composite of death, loss to follow up, or treatment failure (failure to achieve sustained culture conversion). Sustained culture conversion was defined as at least two consecutive negative cultures with the last culture performed 12 months (+/-

2 months) after starting antituberculosis treatment, including from patients with negative or absent baseline sputum cultures. To account for missing data in the primary outcome measure, we created a secondary composite outcome of death, loss to follow up, and a modified definition of treatment failure where any positive sputum culture result between 6 and 12 months after initiation of MDR-TB treatment was regarded as treatment failure. Outcomes were censored at 12 months due to limited availability of sputum culture data beyond that time.

Time to initial sputum culture conversion was defined as two consecutive negative cultures taken at least 30 days apart, in a patient with a positive baseline sputum culture, with the collection date of the first negative culture specimen reported as the conversion date. Culture reversion was defined as two positive cultures, taken at least 30 days apart, after initial sputum culture conversion at any time after starting MDR-TB treatment, as per WHO criteria. Patients were considered lost to follow up when there was a gap of more than 1 month in clinic visits or dispensing of ART or antituberculosis treatment after the last recorded health care contact and no further contact by 12 months. Outcomes data at 18 months were collected for those patients with sufficient follow-up time.

Sample size estimation

The sample size estimation was calculated using death as an outcome. This was chosen because of the signal of excess mortality in the bedaquiline arm in a clinical trial,[9] and because our composite primary endpoint of unfavorable outcomes at 12 months has not been previously assessed for bedaquiline. Mortality assumptions were based on a comparative mortality analysis from South Africa, published in the 2016 WHO Bedaquiline Guideline Development Group report.[10] With a sample size of 330 patients, we estimated that we would have sufficient power (> 80%), at a one-sided a significance level of 2.5%, for a non-inferiority margin of 10% in proportion of deaths at 12 months between the bedaquiline group and the standard treatment group (estimated at 20%).

Analysis and reporting

We calculated the proportions of cases versus controls with the composite primary and secondary endpoints of unfavorable outcome at 12 months and compared these outcomes

with the χ^2 test. We also analyzed individual components of the composite outcome as binary variables, as well as the proportions with culture reversion, and 18-month outcomes where data were available. Logistic regression analysis was performed to adjust for potential confounders in the primary outcome, and to evaluate predictors for failure to achieve sustained culture conversion in the bedaquiline group. Time to initial sputum culture conversion and death was displayed with Kaplan-Meier plots and compared with the log rank test; patients lost to follow up or died were censored at 12 months for the time to culture conversion analysis. We used a Cox proportional-hazards model with adjustment for baseline smear positivity and HIV status to compare the time to culture conversion in the two study groups. Statistical analysis was performed using Stata, version 14.2.

Ethics approval

This study was approved by the Human Research Ethics Committee at the University of Cape Town (Ref: 446/2016).

RESULTS

Patient characteristics

Data from 330 patients with laboratory-confirmed pulmonary MDR-TB (70.6% HIV-infected) were analyzed: 162 cases with bedaquiline substitution and 168 controls who did not receive bedaquiline. Demographic and clinical characteristics at the time of initiation of MDR-TB therapy are summarized in Table 1. The groups were well-matched besides for age which was higher in the bedaquiline group, and CD4 cell count which was lower amongst HIV-infected patients in the bedaquiline group.

Management in the bedaquiline group

Twenty-nine (18.6%) patients did not receive any SLI treatment and initiated bedaquiline at a median of 29 days (interquartile range (IQR) 18 – 49, range 0 – 161) after the start of MDR-TB treatment. In the other 127 patients for whom this was documented, SLIs were stopped at a median of 54 days (IQR) 25 – 82) after TB treatment initiation. There was a 44-day (IQR 29 – 70, range 11-161) delay from SLI withdrawal to starting bedaquiline. Hearing loss was the most common reason for SLI discontinuation, present in 115 (74%) of those who switched. SLIs were also discontinued because of renal impairment in 28 (18%) and

hypokalemia in 13 (8%) patients.

Outcomes

The number of patients assessed for the primary outcome is shown in Figure 1. Unfavorable outcome according to the primary composite measure was assessed in 287 (87%) patients (146 in the bedaquiline group and 141 controls). This outcome occurred in 35 (23.9%) patients in the bedaquiline group versus 51 (36.2%) patients in the control group (relative risk (RR), 0.66; 95% confidence interval [CI], 0.46 to 0.95; P = 0.024). The odds of unfavorable outcomes remained significantly lower in the bedaquiline group after adjusting for age, CD4 count, HIV status, and baseline smear positivity in a multivariate logistic regression model (adjusted odds ratio [aOR] 0.38; 95% CI, 0.18 to 0.81). Bedaquiline use was associated with a protective effect of similar magnitude when almost the full cohort (n = 310) was assessed for the secondary composite outcome, where 44 (27.9%) patients in the bedaquiline group versus 58 (38.2%) in the control group had unfavorable outcomes at 12 months (RR, 0.73; 95% CI 0.53 to 1.0; P = 0.053).

As shown in Table 2, the proportion of deaths in the bedaquiline group (11 deaths, 7.6%) was non-inferior to the control group (11 deaths, 7.5%) at 12 months (risk difference 0.1%; 95% CI, -5.9 to 6.1; within the pre-specified non-inferiority limit of 10%). The reduction in unfavorable outcomes with bedaquiline use was mainly influenced by differences in sustained culture conversion rates: only 7 (5.9%) patients switched to bedaquiline failed to achieve sustained culture conversion at 12 months compared with 19 (17.4%) in the control group, P = 0.006. The effect of bedaquiline on sustained culture conversion persisted at 18 months (Table 2). A total of 13 (5.4%, n = 241) patients with a positive baseline culture reverted to culture-positive after initial culture conversion (i.e. two consecutive negative sputum cultures), at a median time of 263 days (IQR 217 – 296) from the start of treatment. The number of patients with culture reversion was significantly lower in the bedaquiline group (1 patient, 0.8% vs. 12 patients, 10.3% in the control group; P = 0.001). The proportion of cases with missing culture reversion outcome data was not different between the groups (P = 0.097).

In the bedaquiline group, the proportion of HIV-infected patients with unfavorable

outcomes at 12 months (20 (20.0%), n = 100) was not significantly different to HIV-uninfected patients (15 (32.6%), n = 46; P = 0.143). This included mortality, with 5 (5.1%) deaths amongst HIV-infected and 6 (12.8%) deaths amongst HIV-uninfected patients (P = 0.176). On univariate analysis, shown in Table 3, timing of initiation of bedaquiline from the start of MDR-TB treatment was the only factor associated with failure to achieve sustained sputum culture conversion at 12 months (unadjusted OR, 1.4; 95% CI, 1.1 – 1.9 for every 30-day delay). This remained an independent predictor after adjustment for comorbidities and HIV status (aOR, 1.5; 95% CI, 1.1 – 1.9).

Amongst those with positive sputum cultures at baseline (n = 290), 87.4% (95% CI, 81.1 to 92.4) in the bedaquiline group had achieved sputum culture conversion by 6 months versus 78.3% (95% CI, 71.0 to 85.0) in the control group; crude hazard ratio (HR) for culture conversion in the bedaquiline group 1.32; 95% CI, 1.02 to 1.71; P = 0.032, Fig. 2). This effect persisted after adjusting for HIV status and baseline sputum smear positivity (adjusted HR, 1.32; 95% CI 1.00 to 1.76; P = 0.048). The median time to death within 12 months of initiation of TB treatment was not different between bedaquiline-exposed and -unexposed patients (P = 0.962, Fig. 3).

DISCUSSION

In this population with MDR-TB and a high burden of HIV co-infection, substituting bedaquiline for SLIs resulted in fewer unfavorable outcomes after 12 months of treatment compared with regimens containing an SLI for its full course. To our knowledge this is the first study to specifically evaluate a strategy of bedaquiline substitution for SLIs in conventional MDR-TB therapy.

Our results are consistent with those from other observational studies assessing the efficacy of bedaquiline in clinical practice.[15,16] A WHO meta-analysis evaluating the use of bedaquiline amongst 391 patients with drug-resistant TB, including XDR-TB, showed that almost 80% had culture converted at 6 months and that treatment success was achieved in 69%.[10] Importantly, in our study the number of patients with culture reversion was significantly lower in those switched to bedaquiline, suggesting a persistent effect after stopping the 6-month course, in keeping with its long terminal elimination half-life.[17] These

findings lend support to the use of bedaquiline in shorter MDR-TB regimens, although this needs to be evaluated in prospective studies with longer term follow-up to assess true relapse.

The 12-month outcomes observed in the control arm of our study were better than the expected treatment success rates with conventional MDR-TB therapy of ~54% in programmatic settings.[1,18] However, the standard definition of treatment success involves a longer follow up duration to treatment completion, which was not assessed in our cohort, and could account for this discrepancy[19]. The external validity of our findings is supported by a recent systematic review which found similar 6-month culture conversion rates (75%; 95% CI, 60–90) with the use of standardized treatment regimens for MDR-TB.[18]

The mortality associated with MDR-TB is consistently around 15%,[1,20] similar to the proportion of deaths observed in our cohort at 18 months. The meta-analysis conducted by WHO found a 10.6% overall mortality with the use of bedaquiline,[10] but with a large degree of heterogeneity between populations, ranging from ~6.8% in a French cohort[15] to ~20% in the South African Bedaquiline Clinical Access Program (BCAP).[10] Unlike in our study, which included only patients with MDR-TB, most patients in those cohorts had MDR-TB with additional resistance to second line agents, limiting conclusions that can be drawn from direct comparison.

It is reassuring that there were no differences in the 12- and 18-month mortality rates between bedaquiline-exposed and -unexposed patients in our study. In a phase 2b trial, which found a significantly higher mortality with bedaquiline use compared to placebo, almost all deaths occurred after 6 months, at a median time of 49 weeks after stopping bedaquiline.[9] Bedaquiline undergoes extensive tissue distribution with intracellular accumulation resulting in an extremely long elimination half-life.[17,21] The impact of these pharmacokinetic characteristics on QT prolongation and other toxic effects is unknown, and this is an important area for future research and pharmacovigilance.

Only 138 HIV-infected patients were included in the WHO meta-analysis, and of concern, these patients appeared to have a higher mortality compared to HIV-uninfected patients on

bedaquiline (13% vs. 9%, respectively).[10] In our study, which included 110 HIV-infected patients on bedaquiline, we found no difference in 12-month mortality compared with those who were HIV-uninfected. This may be related to the relatively high proportion of patients on ART (85%), and is consistent with a previous report from the South African BCAP that bedaquiline can be used successfully in HIV-infected patients receiving ART.[16]

In our cohort, later initiation of bedaquiline after the start of MDR-TB treatment was independently associated with failure to achieve sustained culture conversion at 12 months. Maintaining effective systems for decentralized bedaquiline implementation is challenging and will require continuous monitoring and review.

This study has important limitations. The retrospective design introduces sources of bias, particularly in the selection of cases. For example, the process used by the Provincial Clinical Advisory Committee to evaluate applications may have systematically allocated patients with different disease characteristics to the bedaquiline group; this is possibly reflected by the older age and lower CD4 cell counts in those patients. But this would tend to bias toward worse outcomes in the bedaquiline group, raising the possibility that bedaquiline could have an even larger effect on treatment efficacy in an unselected population. Adjustment for potential confounders did not change the effect of bedaquiline on reduction of unfavorable outcomes. We minimized selection bias by including consecutive applications for bedaquiline substitution, and by matching cases with control patients for time of starting MDR-TB treatment and for clinic location, which would tend to reduce confounding related to variations in quality of care between clinics. Although baseline characteristics were similar, our inability to perform adjustment for variables known to have prognostic significance (such as radiographic abnormalities and weight) is an additional limitation.

This study involves one of the largest published cohorts to describe the programmatic use of bedaquiline, but difficulties in ascertaining outcomes data retrospectively limited the power and accuracy of our primary endpoint. Data on the composite primary endpoint was missing for 43 (13%) patients, mainly because of restricted access to the national death registry and incomplete follow up culture results. However, the proportion of cases with missing outcomes data was similar between the groups, and we were able to verify the internal

validity of the primary outcome by showing similar results with the use of a secondary outcome measure, which included a more conservative definition of treatment failure (any positive sputum culture result after month 6 of treatment) that evaluated almost the entire cohort (n = 310).

Another limitation is the possibility of immortal time bias conferring an early survival advantage on the bedaquiline group.[22] This is due to the initial period of observation time before SLI substitution when the primary outcome cannot occur in the bedaquiline group, as opposed to controls who entered the study from start of MDR-TB treatment. However, early mortality (as shown in Figure 3) was relatively low and not significantly different between the groups, suggesting limited bias towards survival in the bedaquiline group.

We were not able to obtain specific safety data related to bedaquiline use. Although pharmacovigilance is in place, the decentralization of bedaquiline use across many sites made obtaining ECG recordings unfeasible with the available resources for this study. Reassuringly, accumulating safety data from prospective observational studies suggest that the association with QT prolongation has not translated into adverse clinical outcomes.[10,23]

CONCLUSIONS

Substituting bedaquiline for SLIs in the programmatic treatment of MDR-TB is not associated with increased mortality, and results in fewer unfavorable outcomes at 12 months compared with patients who remain on SLIs. The improved outcomes with bedaquiline use were driven by differences in sustained culture conversion, and reflected by the significantly lower rates of culture reversion amongst those patients. Notwithstanding the limitations of the study design, these findings provide additional evidence to support the routine inclusion of bedaquiline in MDR-TB regimens.[24]

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TABLES

Table 1. Baseline Demographic and Clinical Characteristics

Variable	**Bedaquiline (N = 162)**	**Control (N = 168)**	**P-value**
Age, years	42 (35-49)	35 (28-42)	< 0.001
Male sex	93 (57.4)	97 (58.1)[a]	0.901
Weight, kg	54 (45-62)	ND	NA
Any co-morbidity	44 (27.2)	ND	NA
HIV-infection	110 (67.9)	94 (74.0)[b]	0.258
CD4 count, cells/mm^3	97 (45-201)	205 (59-362)	0.007
Viral load lower than detectable limit	46 (63.0)[c]	50 (72.5)[d]	0.229
On ART	94 (85.5)[e]	ND	NA
Previous TB (any)	88 (63.3)[f]	95 (56.6)	0.229
Extra-pulmonary TB	18 (11.4)[g]	13 (7.8)[a]	0.268
Sputum culture positive	142 (87.7)	148 (88.1)	0.902
Sputum Xpert MTB/RIF positive	111 (68.5)	112 (66.7)	0.719
Sputum smear positive	98 (60.5)	112 (66.7)	0.244
INH mutation[h]			
• inhA	33 (55.9)	ND	NA
• katG	16 (27.1)	ND	NA
• Both	2 (3.4)	ND	NA
ND = no data; NA = not applicable Data are n (%) or median (interquartile range); the data for ART, CD4, and viral load apply only to HIV-infected patients (n 204), and were recorded the at start of MDR-TB or bedaquiline treatment. P-values calculated using Wilcoxon rank-sum test for continuous variables and χ^2 test for binary variables. a. n = 167; b. n = 127; c. n = 73; d. n = 69; e. n = 110; f. n = 139; g. n = 158; h. n = 59.			

Table 2. Treatment Outcomes

Variable	Bedaquiline n = 162	Control n = 168	P-Value
At 12 months			
Composite unfavorable outcome (primary)*	35/146 (23.9)	51/141 (36.2)	0.024
Composite unfavorable outcome (secondary)#	44/158 (27.9)	58/152 (38.2)	0.053
Died	11/145 (7.6)	11/147 (7.5)	0.973
Loss to follow up	17/162 (10.5)	21/168 (12.5)	0.568
Treatment failure^	7/119 (5.9)	19/109 (17.4)	0.006
Modified treatment failure$^{\Delta}$	16/138 (11.6)	29/131 (22.1)	0.021
At 18 months			
Died	13/79 (16.5)	15/100 (15.0)	0.790
Failed to achieve sustained culture conversion	3/93 (3.2)	16/81 (19.8)	< 0.001

Data are no./total no. (%)

* Defined as: death, loss to follow up, or treatment failure. Outcomes were recorded as missing in cases where there was no failure event and ≥ 1 of the components of the composite endpoint was absent.

Defined as: death, loss to follow up, or modified definition of treatment failure. Outcomes were recorded as missing in cases where there was no data for all of the

components of the composite endpoint. The difference in the proportion of missing culture results between groups was not significant (P = 0.092).

Note that the components of the secondary composite outcome do not sum in the bedaquiline group due to overlap in outcomes in 2 patients (modified treatment failure plus death in one and modified treatment failure plus loss to follow up in the other)

^ Defined as failure to achieve sustained culture conversion (at least two consecutive negative cultures with the last culture performed 12 months (+/- 2 months) after starting antituberculosis treatment). Outcomes were recorded as missing in cases where sustained culture conversion, as per the prespecified definition, could not be assessed due to missing sputum culture results. Proportions with missing sputum results were similar between the groups (P = 0.092).

$^{\Delta}$ Defined as any positive sputum culture result between 6 and 12 months after initiation of MDR-TB treatment. Outcomes were recorded as missing in cases where there were no sputum culture results available after 6 months of therapy. Proportions with missing sputum results were similar between the groups (P = 0.092).

Table 3. Predictors of Failure to Achieve Sustained Culture Conversion At 12 Months in the Bedaquiline Group

Variable	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Sputum smear positive at baseline	1.4 (0.3 – 7.8)	0.669		
Comorbid illness	2.1 (0.5 – 10.2)	0.336	1.6 (0.3 – 9.5)	0.606
HIV infection	0.3 (0.06 – 1.4)	0.115	0.3 (0.5 – 1.7)	0.173
Per 30-day delay from start of treatment	1.4 (1.1 – 1.9)	0.007	1.5 (1.1 – 1.9)	0.010
Goodness-of-fit test P = 0.108 for final multivariate model (baseline smear status did not influence the effect size of the estimates in the multivariate model and was dropped to improve fit)				

FIGURES

Figure 1

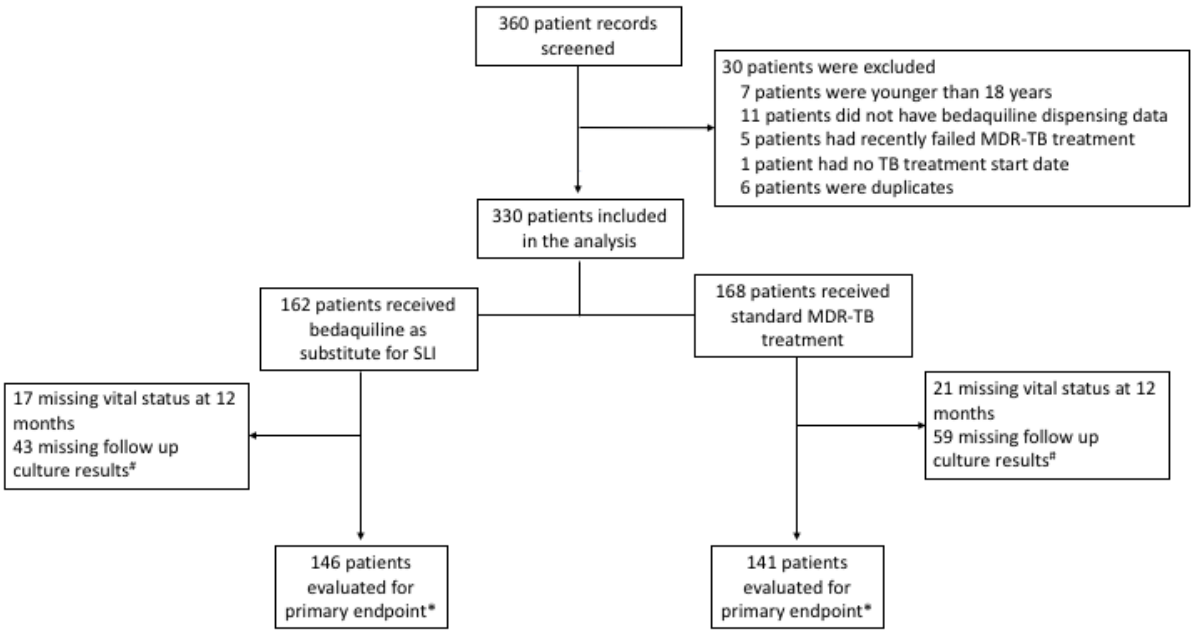

Figure 1. Flow diagram showing screening and inclusion of study population.

MDR-TB = multidrug-resistant tuberculosis; SLI = second-line injectable drugs.

At least two consecutive negative cultures with the last culture performed 12 months (+/- 2 months) after starting antituberculosis treatment, as per the definition of sustained culture conversion for this study. Outcomes were recorded as missing in cases where there were insufficient culture results to evaluate sustained culture conversion, as per the prespecified definition. The proportion of cases with missing data was not different between groups (P = 0.092)

* The missing data do not sum to this value due to overlap in outcomes (i.e. any failure event contributes to the composite outcome, even if another component has a missing outcome)

Figure 2

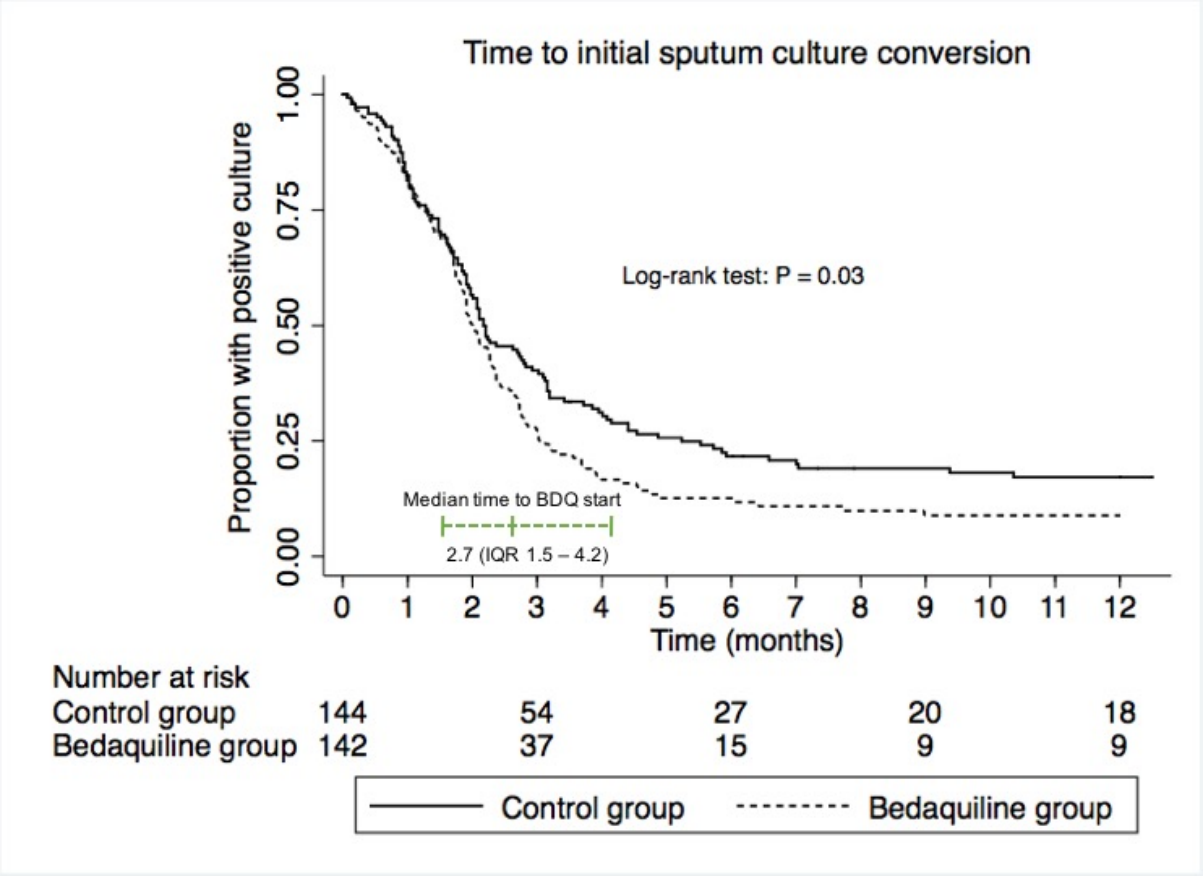

Figure 2. Kaplan-Meier graph of time to initial sputum culture conversion in each study group during the first 12 months of therapy. Superimposed on the graph is a plot of the median (IQR) time to initiation of bedaquiline after the start of MDR-TB therapy.

This analysis only includes patients with a positive baseline culture. There was no difference between groups in the proportion of patients who were baseline culture-negative (P =0.902). Median time to bedaquiline start 2.7 months (IQR 1.5 to 4.2)

Figure 3

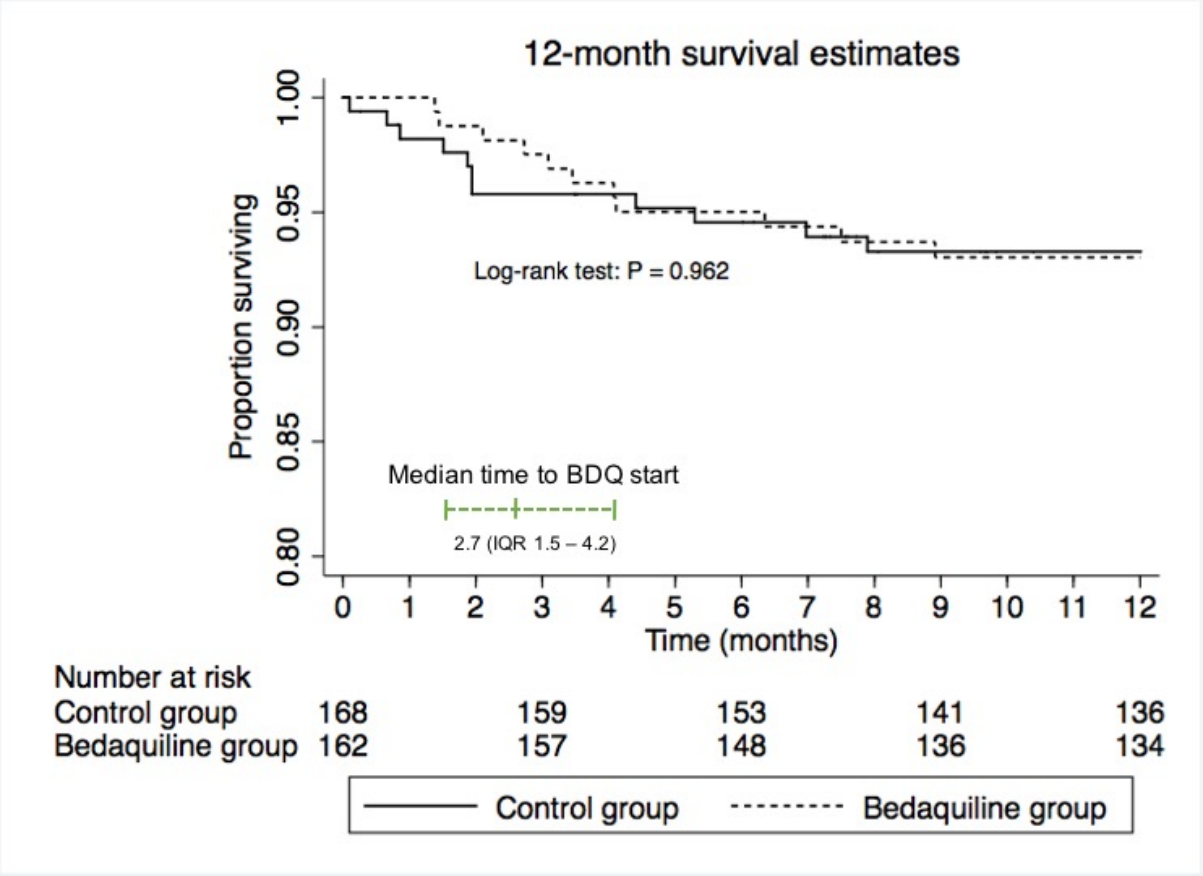

Figure 3. Kaplan-Meier graph of time to death in each study group during the first 12 months of therapy. Superimposed on the graph is a plot of the median (IQR) time to initiation of bedaquiline after the start of MDR-TB therapy.

Note the truncated scale on the y-axis. Median time to bedaquiline start 2.7 months (IQR 1.5 to 4.2).

APPENDICES

Appendix 1: Research protocol

Purpose of the study:

Overall aim:

To determine the 12-month treatment outcomes of patients with multidrug-resistant tuberculosis (MDR-TB) when second line aminoglycoside antibiotics are substituted with bedaquiline because of contra-indication or toxicity.

Primary outcome measures:

Survival, retention in care, and sputum culture conversion of patients with MDR-TB accessing bedaquiline as a substitute for second line injectables, including HIV-infected patients on antiretroviral therapy (ART), as compared to patients on a standard MDR-TB regimen.

Secondary outcome measures:

1. Baseline characteristics of MDR-TB patients accessing bedaquiline.
2. Timing of bedaquiline substitution.
3. Serious adverse events related to bedaquiline use.

Hypothesis

Substituting bedaquiline (6-month course) for aminoglycosides in the treatment of MDR-TB leads to non-inferior outcomes in terms of survival, retention in care and sputum culture conversion rates at 12 months of MDR-TB treatment compared with patients who remain on aminoglycosides (standard of care).

Background

Globally, 9.6 million people were estimated to have active tuberculosis in 2014. The African Region had 28% of the global cases in 2014, representing the worst global disease burden relative to population with 281 cases for every 100,000 people compared with the global average of 133.[1] South Africa has the 6th highest caseload of tuberculosis cases in the world,

and the second highest annual incidence per 100,000 people (after Lesotho). The global fight against TB has resulted in positive advances. TB prevalence and mortality in 2015 were 42% and 47% lower respectively than in 1990.[1] Unfortunately, while the number of drug-susceptible TB cases appears to be decreasing, the proportions of new and previously treated TB cases with MDR-TB (defined as resistance to at least two first-line drugs: isoniazid and rifampicin)[1,8] have remained virtually unchanged in recent years. Globally, an estimated 3.3% of new TB cases and 20% of previously treated cases have MDR-TB, and in South Africa, these figures are 1.8% and 6.7% respectively.[1] This is likely an underestimate. The lower reported proportion of MDR-TB among patients with TB in the African region is contributed to by poor laboratory facilities for drug-susceptibility testing, poor surveillance and reporting, outdated databases and sub-optimal surveys.[8] In 2014, there were an estimated 480,000 new cases of MDR-TB worldwide. Of those 480,000 new cases, only 123,000 (approximately a quarter) were detected and reported; this large 'diagnosis gap' fuels ongoing transmission by undetected cases.[1] The spread of MDR-TB is threatening to undermine the goal of TB control and elimination by the year 2050 set out by the Millennium Development Goals (MDGs) and Stop TB Partnership.

With timely diagnosis and initiation of correct treatment, most people with TB can be cured. But despite the availability of effective treatment TB has remained a leading cause of death worldwide. In 2014, TB killed 1.5 million people, of which 1.1 million deaths were among HIV-positive people. An estimated 190000 people died of MDR-TB in that year, representing a case fatality rate of 40%.[1] Treatment success rate among MDR-TB patients have remained consistently low since the start of global monitoring. Globally, treatment success rate (defined as cure or treatment completion)[1] for new and relapse drug-susceptible cases was 86% in 2013, whereas the treatment success rate for MDR-TB was much lower, at 50% in the 2012 cohort.[1] Of the 50% of MDR-TB patients who were treated unsuccessfully, 16% died, 16% were lost to follow-up, treatment failed for 10% and 8% had no outcome information.[1] An individual patient data meta-analysis of 9,153 patients showed 54% treatment success rate, whereas 15% died, 23% defaulted and 8% failed treatment or relapsed.[10] In South Africa, 78% of new and relapse cases treated with first line TB therapy in 2013, and 49% of MDR-TB cases started on standard National Department of Health MDR therapy in 2012 were successfully treated.[1] A retrospective review of MDR cases from Johannesburg, South Africa showed 46% treatment success rate, 22% mortality rate and

22% were lost to follow-up.[13] Additionally, this 50% of treatment success rate is actually an over-estimate because of the treatment cascade: only a quarter of MDR cases were detected, and only 50% of these cases were treated successfully.

The use of more toxic drugs with poorer efficacy than those used in drug-susceptible TB contributes to the poor treatment success rate in drug-resistant TB. It is largely a result of high mortality rates, loss to follow-up, and treatment interruptions due to drug toxicity. The frequency of adverse events in XDR-TB patients in a South African study was as high as 60%, and associated with interruption of therapy, life-threatening reactions, or death in 40% of patients. The interruption of key second-line drugs, specifically capreomycin, resulted in poorer sputum culture conversion outcomes.[11] In a study of a cohort of patients from five DOTS-Plus sites in resource-limited settings, 30% of the patients required removal of drug(s) from second-line regimen due to adverse events.[14] Drug resistance, poor adherence to therapy and insufficient treatment duration also result in failure of therapy. Failure to cure MDR-TB leads to further amplification of drug resistance leading to the development of XDR-TB.[8] The treatment of MDR-TB needs to be administered for much longer duration and costs substantially more. The optimal duration of treatment is not known, but a minimum of 18 months after sputum culture conversion has been recommended by WHO 2015 guidelines. In a meta-analysis, the proportion of patients achieving treatment success was better when treatment duration was longer than 18 months and patients received directly observed therapy throughout treatment.[9] Improved treatment success was also associated with the use of at least four effective drugs in the intensive phase and the use of later generation quinolones.[10] The drug regimens used to treat MDR-TB in South Africa (as per 2011 and updated 2013 NDoH guidelines) involve the use of second line injectable drugs – SLIs (amikacin, kanamycin, capreomycin) for a minimum of 6 months, and for at least 4 months after sputum culture conversion,[4] in line with international guidelines.

Aminoglycosides have significant adverse effects, notably ototoxicity and nephrotoxicity. A retrospective review of 263 HIV-uninfected MDR-TB patients in Turkey showed that 41.8% patients developed ototoxicity, occurring at a mean of 4.7 months into treatment. Ototoxicity led to the withdrawal of SLIs in up to 50% of cases. Nephrotoxicity was less common, occurring in 0.7% of cases.[7] Aminoglycoside ototoxicity targets sensory neuroepithelium of the cochlea, resulting in loss of hair cells and secondary degeneration of the auditory nerve. Hearing loss may progress for weeks after aminoglycosides being

stopped owing to its long half-life, and the damage is permanent. Risk factors for developing ototoxic hearing loss include cumulative drug dose, duration of treatment, bacteraemia, renal or liver failure, certain polymorphisms in mitochondrial DNA, and concomitant administration of drugs with a synergistic ototoxic effect.[6] A prospective cohort study of 153 MDR-TB patients with normal hearing at baseline at Brooklyn Chest Hospital, Cape Town, showed that 57% developed high-frequency hearing loss following aminoglycoside treatment. Furthermore, HIV-infected patients (70%) were more likely to develop hearing loss than HIV-uninfected patients (42%).[6] Capreomycin is likewise associated with high toxicity. It was the likely cause of 44% of drug withdrawal, over 40% of severe adverse events, and all adverse event (AE)-related death (hypokalaemia in 1 patient and renal failure in 5 others) in a cohort of 115 South African XDR-TB patients.[11] Having to withdraw aminoglycosides or capreomycin because of toxicity substantially weakens an already poor regimen, and essentially results in pre-XDR TB (MDR strains resistant to aminoglycosides or fluoroquinolones). Treatment success is lower in MDR-TB with resistance to second-line injectable drugs than those without additional resistance.[15]

Bedaquiline, a diarylquinoline that inhibits mycobacterial ATP synthase, is the first anti-tuberculosis drug with novel mechanism of action to be approved for use in TB in 40 years. WHO issued interim guidance on the use of bedaquiline in 2013, and by the end of 2014, at least 43 countries have reported to have used bedaquiline to treat MDR-TB patients in efforts to expand access to treatment. 75% of these patients were from the Russian Federation and South Africa.[1] This was largely based on a phase 2b trial which showed that the addition of bedaquiline to a standard 5-drug MDR-TB background regimen for 24 weeks resulted in faster culture conversion and significantly more favorable treatment outcome at 120 weeks, as compared with those given placebo.[2] In this trial bedaquiline was added to an aminoglycoside-containing regimen rather than replacing the aminoglycosides. Of concern, there were ten deaths in bedaquiline group and only two in the placebo group; its reason is unclear.[2] The use of bedaquiline is associated with moderate prolongation in the QT interval, and the risk is increased when bedaquiline is used in combination with other QT-interval-prolonging drugs, such as moxifloxacin and clofazimine. Bedaquiline is primarily metabolized in the liver by the cytochrome P450 isoenzyme 3A4. Coadministered drugs that inhibit CYP3A4 could result in higher bedaquiline concentrations, potentially increasing the risk of toxicity such as the QT prolongation. Lopinavir/ritonavir is a potent inhibitor of

CYP3A4, and when coadministered with bedaquiline, results in higher plasma bedaquiline exposure.[16]

Few participants in the phase 2b trial had HIV co-infection, and there is very limited data on bedaquiline pharmacokinetics when coadministered long term in patients on antiretroviral therapy (ART). This is particularly relevant in sub-Saharan Africa, which has the highest global prevalence of HIV co-infection among TB patients, at over 60%. Of the 9.6 million people infected with TB in 2014 worldwide, 12% were HIV-infected. The African Region accounted for 74% of these cases. In 2014, HIV-associated TB deaths accounted for one quarter of all TB deaths and one third of the estimated 1.2 million deaths from HIV/AIDS. In South Africa, an estimated 61% of TB cases in 2014 were HIV-infected, and an estimated 79% of these patients were on or started ART.[1] ART improves survival and results in higher rates of TB cure in HIV co-infected patients with drug-resistant TB.[17] A retrospective cohort study from Khayelitsha, South Africa showed no significant difference in treatment response among MDR-TB patients with and without HIV infection in a programmatic setting with access to ART.[12] On the other hand, overlapping toxicities of anti-TB drugs and ART often complicate treatment. Nephrotoxicity with the use of tenofovir and aminoglycosides and hepatitis when nevirapine and pyrazinamide are coadministered have been reported.[17] Drug-drug interactions with ART, as well as different pharmacokinetics in HIV-infected patients on ART are likely to influence bedaquiline treatment outcomes in this population. Nevirapine is a moderate inducer of CYP3A4 and may potentially reduce its efficacy, however study showed no nevirapine effect on bedaquiline concentrations.[16] There are high levels of acquired drug resistance in HIV-infected adults with failure of first-line ART in South Africa, necessitating switch to second-line therapy.[18] The increasing number of patients on lopinavir/ritonavir impose a challenge on the use of bedaquiline, as lopinavir/ritonavir increases bedaquiline exposure two-fold[16].

The Bedaquiline Clinical Access Programme (BCAP) has made bedaquiline available for patients with XDR- or pre-XDR-TB in SA.[5] The interim outcomes for the first 91 pre-XDR and XDR-TB patients enrolled in the BCAP in SA showed high rates of early sputum culture conversion. 76% of patients with 6 months of follow-up had either culture-converted or remained culture-negative at 6 months after initiation of bedaquiline. 59% of patients were HIV-infected and all patients were on ART at initiation of bedaquiline. Mortality rate was 5%, and none of the three deaths were probably or possibly related to bedaquiline. In

addition, no serious adverse events attributed to bedaquiline were reported. QTc interval did not change significantly from baseline, and no severe hepatotoxicity or renal dysfunction occurred.[3]

In an expanded access programme within the national TB programme in SA, modeled on the BCAP, MDR-TB patients who have limited treatment options have now been allowed access to bedaquiline (from 2015).[5] Within this programme one of the indications for bedaquiline is that clinicians can request it for patients with baseline hearing or renal impairment or who develop these toxicities while on MDR-TB treatment. Recent SA guideline updates now allow for patients who develop these toxicities while on the injectable or who have baseline hearing or renal impairment to have the aminoglycoside substituted in their MDR treatment regimen with bedaquiline.[4] The outcomes of patients in the expanded programme have not been formally evaluated. Our hypothesis is that substituting bedaquiline (6 months course) for aminoglycosides in the treatment of MDR-TB leads to non-inferior outcomes in terms of survival, retention in care and sputum culture conversion rates at 12 months of MDR-TB treatment compared with patients who remain on aminoglycosides. The results of this study will inform the expanded roll-out of bedaquiline in SA by evaluating its use in routine clinical settings in a population with high rates of HIV co-infection. In none of the bedaquiline MDR trials to date did bedaquiline replace the injectable, thus this will be the first study (albeit retrospective) to report on this strategy.

Methodology:

Study design

Retrospective observational cohort study

Characteristics of the study population

We will include all patients with a laboratory-confirmed diagnosis of pulmonary MDR-TB who have been prescribed bedaquiline as part of the expanded access programme in the Western Cape because of aminoglycoside contra-indication or intolerance. The outcomes of these patients will be compared with those of patients attending the same clinics during the same study period, with a laboratory-confirmed diagnosis of MDR-TB, who received the standard second-line anti-TB treatment.

Inclusion criteria:

Age ≥18 years

Documented intolerance to second line injectables at baseline or during MDR-TB treatment necessitating switch to bedaquiline.

Exclusion criteria:

Patients with MTB strains resistant to aminoglycosides and/or fluoroquinolones (pre-XDR or XDR-TB)

Data acquisition

Patients will be identified using electronic forms submitted to the provincial BCAP committee when clinicians request access to bedaquiline. (Appendix A) The committee comprises a number of experts in the treatment of DR-TB, who approve the use of bedaquiline as part of an appropriate regimen. Information from these forms are entered into an electronic database and stored in the Western Cape Department of Health. Provincial DR-TB managers have access to this database, and are co-investigators in this study. We will include all adult patients with MDR-TB who receive BDQ as a replacement for second-line injectables, from 1st March 2015 till 31st January 2016. The control group will be MDR-TB patients attending the same clinics during the same study period, who remain on aminoglycosides (standard of care). An existing electronic DR-TB database captures information on control patients and is stored with provincial DR-TB managers in provincial Department of Health.

Research procedures and data collection methods

Data will be obtained from the BCAP application source documents, as well as from patient medical and National Health Laboratory Service (NHLS) records. The following data will be imported from an existing electronic DR-TB database and entered onto an electronic database specifically designed for this project:

- Demographic information and medical co-morbidities
- Details of TB diagnosis and drug-susceptibility testing
- HIV status, details of ART, CD4 count and HIV viral loads at start of MDR-TB treatment
- Details of previous and current TB treatment

- Baseline and follow-up renal function and hearing assessments
- Timing of aminoglycoside withdrawal
- Timing of BDQ initiation and duration of use
- Documented ECG QTcF values
- Serious adverse events
- Monthly sputum culture results
- Vital status, treatment status, and sputum TB culture status at 12 months after initiation of therapy

Analysis plan

For the primary objective, we will compare the proportion of patients switched to BDQ with those on standard MDR-TB treatment that reach the composite outcome of death, loss to follow up, and failure to culture convert after 12 months of therapy. We will also describe these outcomes individually. The Kaplan Meier method will be used for this comparison of the combined death and loss to follow-up outcome. Logistic regression analysis will be performed to determine the impact of timing of BDQ substitution and patient characteristics on the primary outcomes. We will also describe the frequencies of serious adverse events between the two groups. Additional analyses will include time to sputum culture conversion over 24 weeks of treatment with bedaquiline, the proportion of patients with sputum culture conversion at 24 weeks and 12 months, and the rates of acquired resistance to second-line drugs at 12 months.

Power calculations

As the purpose of this non-inferiority study is to demonstrate that death, culture conversion and LTFU are not worse in patients who switched to BDQ from standard treatment (aminoglycosides), the sample size estimation was calculated using death as an outcome with a non-inferiority limit of 10%, a significance level of 0.05 and 80% power. To achieve 80% power to demonstrate non-inferiority difference in proportion of deaths at 12 months between BDQ group (estimated at 15%) and standard treatment group (15%), it is estimated that a minimum of 158 patients would be required in each treatment group. It is anticipated that the study will enroll a minimum of 158 in each treatment group (total n =

316) thus the probability of type 2 error will be minimized.

Ethical issues

Privacy and confidentiality

All data will be anonymized on entry into the study database. Each participant will be allocated a unique study number for identification, which will be stored in a different spreadsheet separate from the database. Confidentiality will be maintained as only the MMed candidate will have access to patient medical information after relevant ethical and provincial approvals. We will ensure the safety of data by using password-protected desktop/laptops as well as encrypted USB flash drives. Once data has been collected, all documents with patient identifiers will be removed.

As this is a retrospective analysis, we request a waiver for the requirement of informed consent. No treatment decisions will be changed or influenced by the study.

Risks and benefits

The benefits of the study will include understanding of the outcomes of MDR-TB patients accessing bedaquiline compared with those who remain on standard second-line therapy, and filling the knowledge gap of the efficacy of bedaquiline in HIV co-infected population on concomitant ART. Furthermore, this study will inform the expanded roll-out of bedaquiline in SA by evaluating its use in routine clinical settings in a population with high rates of HIV co-infection.

Oversight

We will seek formal provincial approval for this study. We do not foresee major costs being incurred during the study.

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Appendix 2: Ethics approval letter

446/2016

Prof G Meintjes
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IIDMM

Prof Meintjes

PROJECT TITLE: THE USE OF BEDAQUILINE WHEN SUBSTITUTED FOR AMINOGLYCOSIDES IN THE TREATMENT OF MULTIDRUG RESISTANT TUBERCULOSIS: A RETROSPECTIVE COHORT STUDY (MMed-candidate- Dr Y Zhao)

Thank you for submitting your study to the Faculty of Health thics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th June 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed with the approval period.
(Forms can be found on our

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Dr Ying Zhao will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Clinical Infectious Diseases

MAJOR ARTICLE

Improved Treatment Outcomes With Bedaquiline When Substituted for Second-line Injectable Agents in Multidrug-resistant Tuberculosis: A Retrospective Cohort Study

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Background. Bedaquiline is used as a substitute for second-line injectable (SLI) intolerance in the treatment of multidrug-resistant (MDR) tuberculosis, but the efficacy and safety of this strategy is unknown.

Methods. In this retrospective cohort study adults receiving bedaquiline substitution for MDR tuberculosis therapy, plus a matched control group who did not receive bedaquiline, were identified from the electronic tuberculosis register in the Western Cape Province, South Africa. The primary outcome measure was the proportion of patients with death, loss to follow-up, or failure to achieve sustained culture conversion at 12 months of treatment.

Results. Data from 162 patients who received bedaquiline substitution and 168 controls were analyzed; 70.6% were infected with human immunodeficiency virus. Unfavorable outcomes occurred in 35 of 146 (23.9%) patients in the bedaquiline group versus 51 of 141 (36.2%) in the control group (relative risk, 0.66; 95% confidence interval, .46 –.95). The number of patients with culture reversion was lower in those receiving bedaquiline (1 patient; 0.8%) than in controls (12 patients; 10.3%; $P = .001$). Delayed initiation of bedaquiline was independently associated with failure to achieve sustained culture conversion (adjusted odds ratio for every 30-day delay, 1.5; 95% confidence interval, 1.1–1.9). Mortality rates were similar at 12 months (11 deaths in each group; $P = .97$).

Conclusions. Substituting bedaquiline for SLIs in MDR tuberculosis treatment resulted in improved outcomes at 12 months compared with patients who continued taking SLIs, supporting the use of bedaquiline for MDR tuberculosis treatment in programmatic settings.

Keywords. bedaquiline; drug-resistant tuberculosis; HIV-associated tuberculosis.

Multidrug-resistant (MDR) tuberculosis, defined as resistance to rifampicin and isoniazid, is associated with increased mortality rates and worse treatment outcomes than drug-susceptible tuberculosis [1]. Second-line injectables (SLIs), core agents used in the treatment of MDR tuberculosis [2], cause substantial toxicity, which leads to treatment discontinuation and contributes to the low success rates with conventional MDR tuberculosis treatment [3, 4].

There is a stepwise decline in the success of tuberculosis treatment as drug resistance patterns advance [5], and the presence of resistance to SLIs has been a significant predictor of poor long-term survival in some studies [5, 6]. Therefore, discontinuing SLIs from MDR tuberculosis regimens without replacement by an effective drug may put patients at risk of worse outcomes and ongoing transmission of drug-resistant tuberculosis.

The novel diarylquinoline, bedaquiline, improves culture conversion rates when added to conventional MDR tuberculosis treatment in clinical trials [7–9], and it has also been shown to improve treatment outcomes in observational studies [10]. However, there are safety concerns related to its effect on QT interval prolongation and the increased mortality rate associated with the bedaquiline arms in pooled data from phase 2 clinical trials [11]. The World Health Organization (WHO) has made a conditional recommendation for the use of bedaquiline in adults with MDR tuberculosis who have limited treatment options [12], which may occur in up to two-thirds of cases [13]. Bedaquiline is now being widely used as a substitute in MDR tuberculosis regimens for patients unable to tolerate SLIs [14], but the efficacy and safety of this strategy is unknown. We conducted a retrospective cohort study to determine outcomes

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for South African patients who received bedaquiline as a substitution for SLIs in conventional MDR tuberculosis therapy, with the hypothesis that this would not result in inferior outcomes at 12 months compared with patients who did not discontinue SLIs.

PATIENTS AND METHODS

Study Population and Eligibility Criteria

In September 2015, the Western Cape Provincial Department of Health expanded and decentralized bedaquiline access for adults who had confirmed MDR tuberculosis without additional second-line drug resistance who were unable to tolerate SLIs. Under this expanded program, which is ongoing, local clinicians made requests for bedaquiline access for individual patients to a Provincial Clinical Advisory Committee using a standardized application form. If the request was approved, bedaquiline was provided for a minimum of 24 weeks (with a loading dose of 400 mg once daily for the initial 2 weeks, followed by 200 mg 3 times per week for 22 weeks). Other drugs in the MDR tuberculosis regimen included moxifloxacin (which was replaced by levofloxacin at bedaquiline initiation, due to the greater QT-prolonging effect of moxifloxacin), pyrazinamide, ethionamide, high-dose isoniazid, ethambutol, and terizidone. Until late 2017, this standardized MDR tuberculosis regimen was generally administered for a total of 18–24 months, including the use of an SLI for 6 to 8 months, according to South African National Treatment Program guidelines (the WHO shorter MDR tuberculosis regimen was introduced in the Western Cape Province in late 2017, after the enrollment window for this study).

We screened all applications to the Provincial Clinical Advisory Committee and included consecutive patients who received bedaquiline as a substitution for SLIs between October 2014 and October 2016. We also included a group of control patients with MDR tuberculosis who did not receive bedaquiline, matched 1:1 for clinic location and time of treatment initiation within a window of ±6 months. These patients were identified from the South African Electronic Drug-Resistant Tuberculosis Register, a Web-based network used in the surveillance and management of drug-resistant tuberculosis in South Africa. Patients <18 years old were excluded, as were those with *Mycobacterium tuberculosis* strains known to be resistant to aminoglycosides and/or fluoroquinolones (pre–extensively drug-resistant or extensively drug-resistant tuberculosis).

Outcome Measures

The primary outcome measure was the proportion of patients with unfavorable outcomes at 12 months, defined as a composite of death, loss to follow-up, or treatment failure (failure to achieve sustained culture conversion). Sustained culture conversion was defined as ≥2 consecutive negative cultures, with the last culture performed 12 months (±2 months) after starting antituberculosis treatment, including cultures from patients with negative or absent baseline sputum cultures. To account for missing data in the primary outcome measure, we created a secondary composite outcome of death, loss to follow-up, and a modified definition of treatment failure wherein any positive sputum culture result between 6 and 12 months after initiation of MDR tuberculosis treatment was regarded as treatment failure. Outcomes were censored at 12 months owing to limited availability of sputum culture data beyond that time.

Time to initial sputum culture conversion was defined as 2 consecutive negative cultures taken ≥30 days apart, in a patient with a positive baseline sputum culture, with the collection date of the first negative culture specimen reported as the conversion date. Culture reversion was defined as 2 positive cultures, taken ≥30 days apart, after initial sputum culture conversion at any time after starting MDR tuberculosis treatment, according to WHO criteria. Patients were considered lost to follow-up when there was a gap of >1 month in clinic visits or dispensing of antiretroviral therapy (ART) or antituberculosis treatment after the last recorded healthcare contact and no further contact by 12 months. Outcomes data at 18 months were collected for those patients with sufficient follow-up time.

Sample Size Estimation

The sample size estimation was calculated using death as an outcome. This was chosen because of the signal of excess mortality in the bedaquiline arm in a clinical trial [9], and because our composite primary end point of unfavorable outcomes at 12 months has not been previously assessed for bedaquiline to our knowledge. Mortality assumptions were based on a comparative mortality analysis from South Africa, published in the 2016 WHO Bedaquiline Guideline Development Group report [10]. With a sample size of 330 patients, we estimated that we would have sufficient power (>80%), at a 1-sided significance level of 2.5%, for a noninferiority margin of 10% in the proportion of deaths at 12 months between the bedaquiline group and the standard treatment group (estimated at 20%).

Analysis and Reporting

We calculated the proportions of case patients versus controls with the composite primary and secondary end points of unfavorable outcome at 12 months and compared these outcomes using the χ^2 test. We also analyzed individual components of the composite outcome as binary variables, as well as the proportions with culture reversion and 18-month outcomes where data were available. Logistic regression analysis was performed to adjust for potential confounders in the primary outcome and to evaluate predictors for failure to achieve sustained culture conversion in the bedaquiline group. The time to initial sputum culture conversion and death was displayed with Kaplan-Meier plots and compared using the log-rank test; censoring was performed at 12 months, as well as for patients who were lost to follow-up or died, for the analysis of time to culture conversion. We used a Cox proportional-hazards model with adjustment

for baseline smear positivity and human immunodeficiency virus (HIV) status to compare the time to culture conversion in the 2 study groups. Statistical analysis was performed using Stata software, version 14.2 (StataCorp).

Ethical Approval

This study was approved by the Human Research Ethics Committee at the University of Cape Town (reference 446/2016).

RESULTS

Patient Characteristics

Data from 330 patients with laboratory-confirmed pulmonary MDR tuberculosis (70.6% HIV infected) were analyzed; these included 162 case patients with bedaquiline substitution and 168 controls who did not receive bedaquiline. Demographic and clinical characteristics at the time of initiation of MDR tuberculosis therapy are summarized in Table 1. The groups were well matched other than for age, which was higher in the bedaquiline group, and CD4 cell count, which was lower among HIV-infected patients in the bedaquiline group.

Management in the Bedaquiline Group

Twenty-nine patients (18.6%) did not receive any SLI treatment and started bedaquiline a median of 29 days (interquartile range [IQR], 18–49 days; range, 0–161 days) after the start of MDR tuberculosis treatment. In the other 127 patients for whom this was documented, SLIs were stopped a median of 54 days (IQR, 25–82 days) after initiation of tuberculosis treatment. There was a 44-day delay (IQR, 29–70 days, range, 11–161 days) from SLI withdrawal to the start of bedaquiline. Hearing loss was the most common reason for SLI discontinuation, present in 115 (74%) of patients who switched. SLIs were also discontinued because of renal impairment in 28 patients (18%) and hypokalemia in 13 (8%).

Outcomes

The number of patients assessed for the primary outcome is shown in Figure 1. Unfavorable outcome according to the primary composite measure was assessed in 288 patients (87%; 145 in the bedaquiline group and 143 controls). This outcome occurred in 35 patients (23.9%) in the bedaquiline group versus 51 (36.2%) in the control group (relative risk, 0.66; 95%

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Patients, No. (%)[a]		*P* Value[b]
	Bedaquiline (n = 162)	Control (n = 168)	
Age, median (IQR), y	42 (35–49)	35 (28–42)	<.001
Male sex	93 (57.4)	97 (58.1)[c]	.90
Weight, median (IQR), kg	54 (45–62)	ND	NA
Any comorbid condition	44 (27.2)	ND	NA
HIV infection	110 (67.9)	94 (74.0)[d]	.26
CD4 cell count, median (IQR), cells/μL[e]	97 (45–201)	205 (59–362)	.007
Viral load below detectable limit[e]	46 (63.0)[f]	50 (72.5)[g]	.23
Receiving ART[e]	94 (85.5)[h]	ND	NA
Previous tuberculosis (any)	88 (63.3)[i]	95 (56.6)	.23
Extrapulmonary tuberculosis	18 (11.4)[j]	13 (7.8)[c]	.27
Positive sputum results			
Culture	142 (87.7)	148 (88.1)	.90
Xpert MTB/RIF	111 (68.5)	112 (66.7)	.72
Smear	98 (60.5)	112 (66.7)	.24
Isoniazid mutation[k]			
*inh*A	33 (55.9)	ND	NA
*kat*G	16 (27.1)	ND	NA
Both	2 (3.4)	ND	NA

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not available; ND, no data.

[a]Data represent No. (%) unless otherwise specified.

[b]*P* values calculated using Wilcoxon rank sum test for continuous variables and χ^2 test for binary variables.

[c]Denominator: n = 167.

[d]Denominator: n = 127.

[e]The data for CD4 cell count, viral load, and ART apply only to HIV-infected patients (n = 204) and were recorded at the start of multidrug-resistant tuberculosis or bedaquiline treatment.

[f]Denominator: n = 73.

[g]Denominator: n = 69.

[h]Denominator: n = 110.

[i]Denominator: n = 139.

[j]Denominator: n = 158.

[k]Denominator: n = 59.

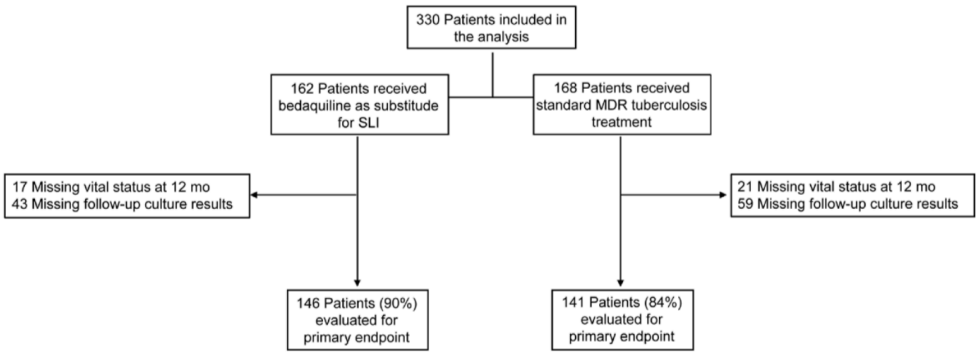

Figure 1. Flow diagram showing screening and inclusion of study population. Culture results required ≥2 consecutive cultures with the last culture performed 12 months (±2 months) after the start antituberculosis treatment, per the definition of sustained culture conversion for this study; outcomes were recorded as missing in cases where culture results were insufficient to evaluate sustained culture conversion, per the prespecified definition. The proportions of patients with missing data were not different between groups ($P = .09$). For the totals of patients evaluated for the primary end points, the missing data do not sum to these values owing to overlap in outcomes (ie, any failure event contributes to the composite outcome, even if another component has a missing outcome). Abbreviations: MDR, multidrug-resistant; SLI, second-line injectable

confidence interval [CI], .46–.95; $P = .02$). The odds of unfavorable outcomes remained significantly lower in the bedaquiline group after adjustment for age, CD4 cell count, HIV status, and baseline smear positivity in a mutivariable logistic regression model (adjusted odds ratio [OR] 0.38; 95% CI, .18–.81). Bedaquiline use was associated with a protective effect of similar magnitude when almost the full cohort (n = 310) was assessed for the secondary composite outcome; 44 patients (27.9%) in the bedaquiline group versus 58 (38.2%) in the control group had unfavorable outcomes at 12 months (relative risk, 0.73; 95% CI, .53–1.0; $P = .053$).

As shown in Table 2, the proportion of deaths in the bedaquiline group (11 deaths; 7.6%) was noninferior to that in the control group (11 deaths; 7.5%) at 12 months (risk difference, 0.1%; 95% CI, −5.9 to 6.1; within the prespecified noninferiority limit of 10%). The reduction in unfavorable outcomes with bedaquiline use was mainly influenced by differences in sustained culture conversion rates: only 7 patients (5.9%) switched to bedaquiline failed to achieve sustained culture conversion at 12 months, compared with 19 (17.4%) in the control group ($P = .006$). The effect of bedaquiline on sustained culture conversion persisted at 18 months (Table 2). A total of 13

Table 2. Treatment Outcomes

Variable	Patients, No./Total No. (%)		*P* Value
	Bedaquiline Group (n = 162)	Control Group (n = 168)	
At 12 mo			
Composite unfavorable outcome (primary)[a]	35/146 (23.9)	51/141 (36.2)	.02
Composite unfavorable outcome (secondary)[b]	44/158 (27.9)	58/152 (38.2)	.053
Death	11/145 (7.6)	11/147 (7.5)	.97
Loss to follow-up	17/162 (10.5)	21/168 (12.5)	.57
Treatment failure[c]	7/119 (5.9)	19/109 (17.4)	.006
Modified treatment failure[d]	16/138 (11.6)	29/131 (22.1)	.02
At 18 mo			
Death	13/79 (16.5)	15/100 (15.0)	.79
Failure to achieve sustained culture conversion	3/93 (3.2)	16/81 (19.8)	<.001

[a]Defined as death, loss to follow-up, or treatment failure. Outcomes were recorded as missing in cases where there was no failure event and ≥1 of the components of the composite end point was absent.

[b]Defined as death, loss to follow-up, or modified definition of treatment failure. Outcomes were recorded as missing in cases where there were no data for all of the components of the composite end point. Note that the components of the secondary composite outcome do not sum in the bedaquiline group owing to overlap in outcomes in 2 patients (modified treatment failure plus death in 1 and modified treatment failure plus loss to follow-up in the other).

[c]Defined as failure to achieve sustained culture conversion (≥2 consecutive negative cultures with the last culture performed 12 months (±2 months) after the start of antituberculosis treatment). Outcomes were recorded as missing in cases where sustained culture conversion, per the prespecified definition, could not be assessed owing to missing sputum culture results. Proportions with missing sputum results were similar between the groups ($P = .09$).

[d]Defined as any positive sputum culture result between 6 and 12 months after initiation of multidrug-resistant tuberculosis treatment. Outcomes were recorded as missing in cases where there were no sputum culture results available after 6 months of therapy. Proportions with missing sputum results were similar between the groups ($P = .09$).

patients (5.4%; n = 241) with a positive baseline culture reverted to culture positive after initial culture conversion (ie, 2 consecutive negative sputum cultures), at a median time of 263 days (IQR, 217–296 days) from the start of treatment. The number of patients with culture reversion was significantly lower in the bedaquiline group (1 patient [0.8%] vs 12 [10.3%] in the control group; $P = .001$). The proportions of patients with missing culture reversion outcome data did not differ between the groups ($P = .10$).

In the bedaquiline group, the proportion of HIV-infected patients with unfavorable outcomes at 12 months (20 [20.0%]; n = 100) was not significantly different from that in HIV-uninfected patients (15 [32.6%]; n = 46; $P = .14$). This included mortality outcomes, with 5 (5.1%) deaths among HIV-infected and 6 (12.8%) deaths among HIV-uninfected patients ($P = .18$). At univariate analysis, shown in Table 3, the timing of initiation of bedaquiline from the start of MDR tuberculosis treatment was the only factor associated with failure to achieve sustained sputum culture conversion at 12 months (unadjusted OR for every 30-day delay, 1.4; 95% CI, 1.1–1.9). This remained an independent predictor after adjustment for comorbid conditions and HIV status (adjusted OR, 1.5; 95% CI, 1.1–1.9).

Among those with positive sputum cultures at baseline (n = 290), 87.4% (95% CI, 81.1%–92.4%) in the bedaquiline group had achieved sputum culture conversion by 6 months versus 78.3% (95% CI, 71.0%–85.0%) in the control group; the crude hazard ratio for culture conversion in the bedaquiline group was 1.32 (95% CI, 1.02–1.71; $P = .03$; Figure 2). This effect persisted after adjustment for HIV status and baseline sputum smear positivity (adjusted hazard ratio, 1.32; 95% CI, 1.00–1.76; $P = .048$). The median time to death within 12 months of initiation of tuberculosis treatment was not different between bedaquiline-exposed and bedaquiline-unexposed patients ($P = .96$; Figure 3).

DISCUSSION

In this population with MDR tuberculosis and a high burden of HIV coinfection, substituting bedaquiline for SLIs resulted in fewer unfavorable outcomes after 12 months of treatment compared with regimens containing an SLI for its full course. To our knowledge, this is the first study to specifically evaluate a strategy of bedaquiline substitution for SLIs in conventional MDR tuberculosis therapy.

Our results are consistent with those from other observational studies assessing the efficacy of bedaquiline in clinical practice [15, 16]. A WHO meta-analysis evaluating the use of bedaquiline among 391 patients with drug-resistant tuberculosis, including extensively drug-resistant tuberculosis, showed that almost 80% had culture converted at 6 months and that treatment success was achieved in 69% [10]. Importantly, in our study the number of patients with culture reversion was significantly lower in those switched to bedaquiline, suggesting a persistent effect after stopping the 6-month course, in keeping with its long terminal elimination half-life [17]. These findings lend support to the use of bedaquiline in shorter MDR tuberculosis regimens, although this needs to be evaluated in prospective studies with longer-term follow-up to assess true relapse.

The 12-month outcomes observed in the control arm of our study were better than the expected treatment success rates with conventional MDR tuberculosis therapy of approximately 54% in programmatic settings [1, 18]. However, the standard definition of treatment success involves a longer follow-up duration to treatment completion, which was not assessed in our cohort and could account for this discrepancy [19]. The external validity of our findings is supported by a 2017 systematic review, which found similar 6-month culture conversion rates (75%; 95% CI, 60%–90%) with the use of standardized treatment regimens for MDR tuberculosis [18].

The mortality rate associated with MDR tuberculosis is consistently about 15% [1, 20], similar to the proportion of deaths observed in our cohort at 18 months. The meta-analysis conducted by WHO found a 10.6% overall mortality rate with the use of bedaquiline [10], but with a large degree of heterogeneity between populations, ranging from about 6.8% in a French cohort [15] to about 20% in the South African Bedaquiline Clinical Access Program [10]. Unlike in our study, which included only patients with MDR tuberculosis, most patients in those cohorts had MDR tuberculosis with additional resistance to second-line agents, limiting conclusions that can be drawn from direct comparison.

It is reassuring that there were no differences in the 12- and 18-month mortality rates between bedaquiline-exposed and

Table 3. Predictors of Failure to Achieve Sustained Culture Conversion at 12 Months in the Bedaquiline Group

Variable	Univariate OR (95% CI)	*P* Value	Mutivariable OR (95% CI)[a]	*P* Value
Sputum smear positive at baseline	1.4 (.3–7.8)	.67	…	…
Comorbid illness	2.1 (.5–10.2)	.34	1.6 (.3–9.5)	.61
HIV infection	0.3 (.06–1.4)	.12	0.3 (.5–1.7)	.17
Per 30-d delay from start of treatment	1.4 (1.1–1.9)	.007	1.5 (1.1–1.9)	.01

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

[a]Goodness-of-fit test $P = .11$ for final multivariate model (baseline smear status did not influence the effect size of the estimates in the mutivariable model and was dropped to improve fit).

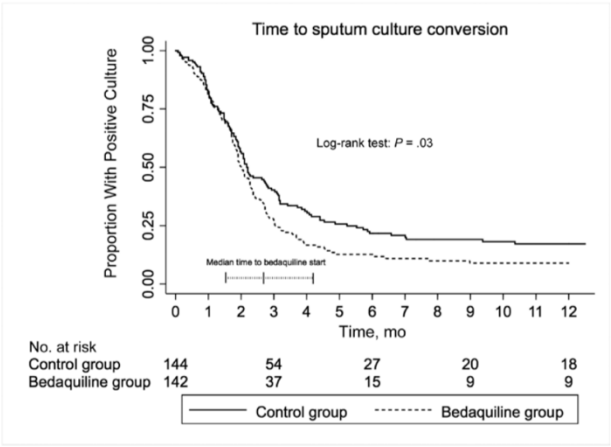

Figure 2. Kaplan–Meier graph of time to initial sputum culture conversion in each study group during the first 12 months of therapy. Superimposed on the graph is a plot of the median (interquartile range) time to initiation of bedaquiline after the start of multidrug-resistant tuberculosis therapy. This analysis includes only patients with a positive baseline culture. There was no difference between groups in the proportion of patients who were culture negative at baseline ($P = .90$). The median time to bedaquiline start was 2.7 months (interquartile range, 1.5–4.2 months).

bedaquiline-unexposed patients in our study. In a phase 2b trial, which found a significantly higher mortality rate with bedaquiline use compared with placebo, almost all deaths occurred after 6 months, at a median time of 49 weeks after stopping bedaquiline [9]. Bedaquiline undergoes extensive tissue distribution with intracellular accumulation, resulting in an extremely long elimination half-life [17, 21]. The impact of these pharmacokinetic characteristics on QT prolongation and other toxic effects is unknown, and this is an important area for future research and pharmacovigilance.

Only 138 HIV-infected patients were included in the WHO meta-analysis, and it is of concern that these patients seemed to have a higher mortality rate than HIV-uninfected patients receiving bedaquiline (13% vs 9%, respectively) [10]. In our

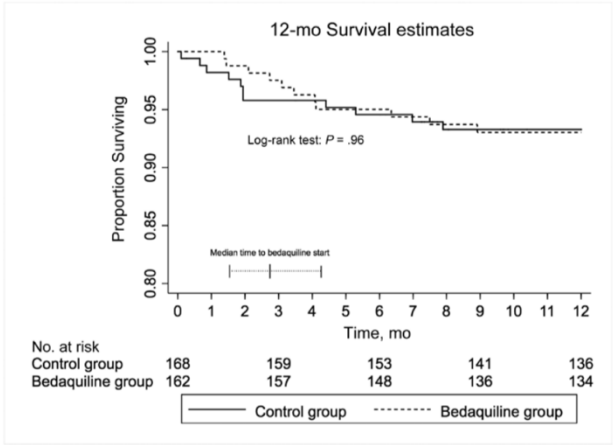

Figure 3. Kaplan-Meier graph of time to death in each study group during the first 12 months of therapy. Superimposed on the graph is a plot of the median (interquartile range [IQR]) time to initiation of bedaquiline after the start of multidrug-resistant tuberculosis therapy. Note the truncated scale on the y-axis. The median time to bedaquiline start was 2.7 months (IQR, 1.5–4.2 months).

study, which included 110 HIV-infected patients receiving bedaquiline, we found no difference in 12-month mortality rate compared with those who were HIV uninfected. This finding may be related to the relatively high proportion of patients receiving ART (85%), and it is consistent with a previous report from the South African Bedaquiline Clinical Access Program that bedaquiline can be used successfully in HIV-infected patients receiving ART [16].

In our cohort, later initiation of bedaquiline after the start of MDR tuberculosis treatment was independently associated with failure to achieve sustained culture conversion at 12 months. Maintaining effective systems for decentralized bedaquiline implementation is challenging and will require continuous monitoring and review.

The current study has important limitations. The retrospective design introduces sources of bias, particularly in the selection of cases. For example, the process used by the Provincial Clinical Advisory Committee to evaluate applications may have systematically allocated patients with different disease characteristics to the bedaquiline group; this is possibly reflected by the older age and lower CD4 cell counts in those patients. However, this would tend to bias toward worse outcomes in the bedaquiline group, raising the possibility that bedaquiline could have an even larger effect on treatment efficacy in an unselected population. Adjustment for potential confounders did not change the effect of bedaquiline on reduction of unfavorable outcomes. We minimized selection bias by including consecutive applications for bedaquiline substitution and by matching cases with control patients for time of starting MDR tuberculosis treatment and for clinic location, which would tend to reduce confounding related to variations in quality of care between clinics. Although baseline characteristics were similar, our inability to perform matching for variables known to have prognostic significance (such as radiographic abnormalities and weight) is an additional limitation.

This study involves one of the largest published cohorts to describe the programmatic use of bedaquiline, but difficulties in ascertaining outcomes data retrospectively limited the power and accuracy of our primary end point. Data on the composite primary end point were missing for 43 patients (13%), mainly because of restricted access to the national death registry and incomplete follow-up culture results. However, the proportions of patients with missing outcomes data were similar between the groups, and we were able to verify the internal validity of the primary outcome by showing similar results with the use of a secondary outcome measure, which included a more conservative definition of treatment failure (any positive sputum culture result after month 6 of treatment) that evaluated almost the entire cohort (n = 310).

Another limitation is the possibility of immortal time bias conferring an early survival advantage on the bedaquiline group [22]. This is due to the initial period of observation time before SLI substitution when the primary outcome cannot occur in the bedaquiline group, as opposed to controls who entered the study from start of MDR tuberculosis treatment. However, the early mortality rate (as shown in Figure 3) was relatively low and did not differ significantly between the groups, suggesting limited bias toward survival in the bedaquiline group.

We were not able to obtain specific safety data related to bedaquiline use. Although pharmacovigilance is in place, the decentralization of bedaquiline use across many sites made obtaining electrocardiographic recordings unfeasible with the available resources for this study. Reassuringly, accumulating safety data from prospective observational studies suggest that the association with QT prolongation has not translated into adverse clinical outcomes [10, 23].

In conclusion, substituting bedaquiline for SLIs in the programmatic treatment of MDR tuberculosis is not associated with increased mortality rate and results in fewer unfavorable outcomes at 12 months than in patients who remain continue taking SLIs. The improved outcomes with bedaquiline use were driven by differences in sustained culture conversion, and reflected by the significantly lower rates of culture reversion among those patients. Notwithstanding the limitations of the study design, these findings provide additional evidence to support the routine inclusion of bedaquiline in MDR tuberculosis regimens [24].

Notes

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Appendix 4: Reviewer comments and response

Reviewer #1:

1. I am wondering why no adverse event data is presented in the paper. I imagine that since the authors were using an electronic database for cases and controls there was probably not great reporting of adverse events (a chronic problem with DR-TB records everywhere). If the authors do have adverse event data, it would be important to see it reported here. If not, they should mention why not.

Response

We were not able to obtain adverse event data related to bedaquiline use, specifically information on QT prolongation and hepatotoxicity. The decentralization of bedaquiline use across many sites (patients from 51 clinics across the Province were included in the study) made obtaining ECG recordings impossible with the available resources for this study, and monitoring of liver enzymes is not systematically done. We have mentioned this limitation in the revised manuscript as follows:

"*We were not able to obtain specific safety data related to bedaquiline use. Although pharmacovigilance is in place, the decentralization of bedaquiline use across many sites made obtaining ECG recordings unfeasible with the available resources for this study. Reassuringly, accumulating safety data from prospective observational studies suggest that the association with QT prolongation has not translated into adverse clinical outcomes.*[10,23]"

2. While the authors clearly define their endpoints, I did not see a rationale for looking at 12 month outcomes. Was this because most patients would have completed both the injectable or BDQ after 6 months and then there were an additional 6 months for follow up? I am assuming this is why--and also why the authors looked at culture reversion as a potential "proxy" for relapse. But it would be good to see an explicit rationale stated in the paper.

Response

The main reason for selecting 12-month outcomes as the primary endpoint was because of our expectation that data quality would deteriorate beyond that time point, reducing power

to observe meaningful differences between the groups. This was borne out in the data, with substantially more missing outcomes data at 18 months due to missing culture results and vital status. An explanatory statement has been included in the revised manuscript:
"*Outcomes were censored at 12 months due to limited availability of sputum culture data beyond that time.*"

Data from the Preserving Effective TB Treatment Study suggest that 12-month sputum culture conversion has reasonable diagnostic performance for predicting treatment success in MDR-TB [Kurbatova EV, et al. The Lancet Respiratory medicine. 2015;3(3):201-9]. We therefore feel that assessing outcomes at 12 months allowed for a relatively robust comparison of outcomes a number of months after completion of bedaquiline (or injectables). Culture reversion was chosen as a secondary outcome measure because of its recognized use to assess treatment outcomes in MDR-TB [Günther, G., et al. New England Journal of Medicine. 2016;375(11): 1103-1105 and Pietersen E, et al. Lancet. 2014;383(9924):1230-1239], and because we did not ascertain end-of-treatment outcomes.

3. The authors also note that outcomes data at 18 months were collected for some of the patients, but I did not see this reported anywhere.

Response
18-month outcomes data are reported in Table 2. This has also now been emphasized in the text of the revised manuscript:
"*The effect of bedaquiline on sustained culture conversion persisted at 18 months (Table 2).*"

4. *In terms of minor comments, throughout the abstract and the paper the authors keep referring to MDR-TB patients "who substituted BDQ". The patients themselves did not substitute BDQ but rather they received BDQ as a substitution for the injectable. The authors should correct this throughout.*

Response
Many thanks for pointing this out. It has been corrected in the revised manuscript.

5. *In the introduction, the authors state that "presence of resistance to the injectable is a significant predictor of poor long-term survival" and cite an important reference from Korea.*

However, other studies--including a meta-analysis of more than 9,000 patients on treatment for DR-TB--have not shown it to be a predictor of poor outcomes. Thus the authors might want to note that "some studies" show it to be a predictor of poor outcomes and that the drug is recommended as a core agent in the treatment of MDR-TB.

Response

Thank you for this suggestion. An individual patient meta-analysis including data from over 6,700 patients specifically evaluating this association found a significantly lower odds of treatment success with the presence injectable resistance in MDR-TB (aOR 0.6 (95% CI, 0.5–0.7)). We have included a reference to this study in the revised manuscript and, as suggested, have noted that the association is limited to "*some studies*".

6. *Finally, in the conclusion, the authors note that the data on culture reversion give support for BDQ in shorter regimens. This is an interesting idea but not one addressed by their data. I would either take it out or note that this is an area for further study.*

Response

We point out in the manuscript that our study did not evaluate the use of bedaquiline in the shorter MDR-TB regimen. As suggested, a statement has been added in the discussion to emphasize that additional studies are required to address this:

"*These findings lend support to the use of bedaquiline in shorter MDR-TB regimens, although this needs to be evaluated in prospective studies with longer term follow-up to assess true relapse.*"

Reviewer #2

1. *The 12-month unfavourable outcome rate reaches significance depending on which*

definition was used. It is a pity that the p value is non-significant using the second definition. The difficulty is that culture positivity between 6 and 12 months is high predictive of an unfavourable outcome (at least for patients on MDR treatment not on bedaquiline). Given this consideration, it would be fair to state this upfront in the abstract and modify the conclusions appropriately.

Response

The effect of bedaquiline on reducing the rate of unfavorable outcomes was statistically significant using the prespecified primary composite outcome measure. A secondary composite outcome measure was evaluated, which involved a more conservative modified definition of treatment failure, in order to support our conclusions from the primary endpoint with a larger sample of the cohort. Using this secondary composite outcome measure there was a strong trend in favor of bedaquiline ($p = 0.053$), with a similar magnitude of effect to that observed with the primary composite outcome. Furthermore, when data from the composite outcomes were disaggregated, differences in the treatment failure component remained statistically significant regardless of the definition used. We therefore feel reassured that our conclusions are adequately supported by the data.

2. More detail is required about the patients that were matched. Were standard prognostic features in MDR TB, including HIV status, weight, number of drugs, disease extent taken into account when matching patients?

Response

As described in the manuscript, matching was done for clinic location and timing of initiation of MDR-TB therapy. Data for prognostic factors such as weight and chest x-ray changes were unavailable, and we were therefore unable to perform matching for these variables. However, our matching strategy appeared to be adequate, and as demonstrated in Table 1 other important prognostic baseline characteristics such as HIV status and virological suppression, smear positivity, culture status, extrapulmonary TB, and previous episodes of TB were similar between groups. The table has been updated to report p-values to highlight this, as suggested by the reviewer. During the study period standardized MDR-TB regimens were used and the number of drugs and composition of background regimens was not different for those who received bedaquiline as a substitute for injectables. This has now been emphasized in the revised manuscript.

3. Were chest radiographs available so patients could be matched for disease severity? If not, then this limitation should be stated.

Response

This has been noted as a limitation in revised manuscript:

"*Although baseline characteristics were similar, our inability to perform matching for variables known to have prognostic significance (such as radiographic abnormalities and weight) is an additional limitation.*"

4. Presentation could be improved by including the p-values in table 1.

Response

Thank you for this suggestion: the table has been amended in the revised manuscript.

5. *Several variables bias against the bedaquiline group, e.g. CD4 count, which makes the findings of the authors more significant (they allude to this). Should a multi-variable analysis not be performed, controlling for confounders so that a more accurate assessment of unfavourable outcomes could be made? The same considerations apply for treatment failure.*

Response

A multivariate Cox proportional hazards model was performed for time to sputum culture conversion, which showed that the effect of bedaquiline on earlier culture conversion persisted after adjusting for HIV status and baseline smear positivity. At the suggestion of the reviewer we have now also performed multivariate logistic regression for the composite primary endpoint. The odds of unfavorable outcomes remain significantly lower in the bedaquiline group with the inclusion of age, CD4 count, HIV status, and baseline smear positivity in the model (aOR 0.38; 95% CI, 0.18 to 0.81). This has been reported in the revised manuscript.

6. Figure 2 shows time to initial sputum culture conversion. However, this measure doesn't have a good relationship with treatment outcomes. A much better measure would be 6-month culture conversion and there are several papers recently, including from the Lange group, that evaluated this biomarker as a predictor of outcome in patients on conventional MDR regimens. The 6-month culture conversion rate should be reported. Perhaps the manuscript could be updated to reflect more recent publications and policy?

Response

The proportion of patients achieving 6-month culture conversion was reported in the submitted manuscript, both in the text (final paragraph of the results section) and in Figure 2, showing a consistent effect in favor of the bedaquiline group. As discussed above, data from the Preserving Effective TB Treatment Study suggest that 12-month sputum culture conversion has an acceptable diagnostic performance for predicting treatment success in MDR-TB, and that this is similar to 6-month sputum culture conversion [Kurbatova EV, et al. The Lancet Respiratory Medicine. 2015;3(3):201-9]. The same study also showed that time to culture conversion was significantly associated with end-of-treatment outcomes. We therefore feel that these two prespecified endpoints provide reasonable proxies for treatment outcomes and allow for a meaningful comparison of the two treatment strategies. We acknowledge the limitations of using proxy outcome measures for treatment success in MDR-TB (even 6-month sputum culture conversion has suboptimal specificity) and recognize that prospective studies with longer term follow up are required to reach more definitive conclusions:

"*the standard definition of treatment success involves a longer follow up duration to treatment completion, which was not assessed in our cohort,*" and
"*this needs to be evaluated in prospective studies with longer term follow-up to assess true relapse."*

7. *The failure to match controls to cases based on prognostic features is a major limitation that should be mentioned. Why was this not undertaken?*

Response

This is addressed under points 2 and 5 above.

8. The authors have clearly stated the other limitations. Given these considerations, it might be reasonable to phrase the conclusions appropriately and in a more cautious and preliminary.

Response

As the reviewer points out, we have carefully considered and explained the limitations of

the study design and have attempted to address any modifiable issues with our analysis plan. While we are fully cognisant of the limitations of this study (and have been transparent about this in the manuscript), we are confident to make the claim that these data contribute additional evidence for the wider use of bedaquiline in MDR-TB therapy. To address the reviewer's concern, we have inserted language in the revised manuscript to emphasize the limitations:

"*Notwithstanding the limitations of the study design, these findings provide additional evidence to support the routine inclusion of bedaquiline in MDR-TB regimens.*"