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Early View

Original article

High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen

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Title: High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen

Summary (max 117 characters): The use of bedaquiline with at least three other active drugs is associated with high treatment success rate among MDR-TB, pre XDR-TB and XDR-TB patients in South Africa, a high HIV prevalence region.

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Declaration of interests
N Ndjeka is an official within the South African Department of Health; his responsibilities include recommending guidelines for DR-TB treatment.
Key words: Extensively drug-resistant tuberculosis; treatment success rate; South Africa; adverse events.

ABSTRACT
Background: South African patients with rifampicin-resistant tuberculosis and resistance to fluoroquinolones and/or injectables (pre/XDR-TB) were granted access to bedaquiline through a Clinical Access Programme with strict inclusion and exclusion criteria.

Methods: Pre/XDR-TB and XDR-TB patients were treated with 24 weeks bedaquiline within an optimised, individualised background regimen that could include levofloxacin, linezolid and clofazimine as needed.

Results: 200 patients were enrolled: 87 (43.9%) with XDR-TB, 99 (49.3 %) were female, median age 34 years (IQR 27, 42). 134 (67.0%) were living with HIV; median CD4+ 281 (IQR 130; 467) and all on antiretroviral therapy.

16/200 patients (8.0%) did not complete 6 months of bedaquiline of which 8 were lost to follow up, 6 died, 1 stopped for side effects and 1 patient was diagnosed with drug-sensitive TB.

146/200 (73.0%) patients had favourable outcomes: 139/200 were cured (69.5%) and 7 completed treatment (3.5%). 25 died (12.5%), were lost from treatment (10.0%), 9 had treatment failure (4.5%).

22 adverse events were attributed to bedaquiline: including QTcF >500ms (n=5), QTcF increase >50ms from baseline (n=11), paroxysmal atrial flutter (n=1).

Conclusion: Bedaquiline added to an optimised background regimen was associated with a high rate of successful treatment outcomes for this MDR-TB and XDR-TB cohort.

INTRODUCTION
The World Health Organization estimated during the year 2016 that there were 600,000 incident cases of rifampicin-resistant tuberculosis (RR-TB) and multidrug-resistant tuberculosis (MDR-TB) in the world, of which only 129,689 cases of RR/MDR-TB (22 % of global estimate) were initiated on treatment[1]. During the same period, treatment was initiated in 11,192 cases of MDR/RR-TB in South Africa, approximately 10% of the global treatment cohort, and in 628 cases of MDR-TB with additional resistance to fluoroquinolones (FLQ) and second-line injectable drugs, i.e. extensively drug resistant (XDR-TB)[1].

Overall poor treatment success rates, high loss to follow up and high mortality have been the key features of RR-TB, especially for patients with XDR-TB or MDR-TB with resistance to either fluoroquinolones or second-line injectable drugs (pre/XDR-TB). There are several factors linked to poor treatment success rates for

RR-TB, including the use of more toxic drugs with poorer efficacy than those used for drug-susceptible TB. In addition, the treatment duration has been until recently a minimum of 18 months compared to the 6-month regimen for drug-susceptible TB. Globally, while the rate of successful treatment for all TB was 83% (2015 cohort), the success rate for RR/MDR-TB patients (2014 cohort) was 54%; among patients with XDR-TB it was only 30%[1]. For the same year, South Africa reported a success rate of 54% for RR/MDR-TB patients and 27% for XDR-TB patients[1]. Mortality was high for the 2014 cohort in South Africa; 21.7% of RR/MDR-TB patients and 42.5% of XDR-TB patients died during treatment[2]. A recent individual patient-level data meta-analysis indicated that treatment outcomes were significantly better with use of new and repurposed drugs including linezolid, later generation fluoroquinolones, bedaquiline, clofazimine, and carbapenems, compared to the standard treatment regimens for MDR-TB[3].

Bedaquiline was the first new anti-tuberculosis drug developed in five decades and it has a novel mechanism of action[4]. It was registered in the United States in late 2012 for MDR-TB based upon 72-week data from a Phase 2 trial[5]. In the Phase 2b trial, treatment with 24 weeks of bedaquiline, in addition to a standard background regimen, resulted in increased culture conversion at 24 weeks (79% vs 58%) and an increased rate of cure at 120 weeks (62% vs 44%) compared to the background regimen with placebo[6]. However, the study also reported a statistically significant imbalance in mortality; ten deaths occurred among the 79 patients exposed to bedaquiline (12.7%), but most occurred after bedaquiline was stopped and two deaths (2.5%) in the 79 patients in the placebo arm (p=0·02)[6]. In 2013, the WHO issued interim guidelines on the use of bedaquiline, indicating that it should be added to the long-course regimen only in cases where no other effective regimen could be designed[7].

Prior to bedaquiline registration in South Africa, pre/XDR-TB patients were granted access through the Bedaquiline Clinical Access Programme (BCAP) which was a donation from Janssen Pharmaceutica[8]. This program stopped enrolling patients around mid-March 2015 because bedaquiline was registered in October 2014 and the South African National TB Programme (SA NTP) was able to purchase the drug. We published an interim report of the BCAP cohort between March 2013 and July 2014[9]. This report showed that individuals responded well to bedaquiline-based regimens regardless of HIV status. It was also reported that 76% of patients who had completed at least 6 months of bedaquiline -based treatment regimens had at least two negative TB culture results. An updated interim analysis was shared with the WHO and included in the systematic review for the 2017 update to its interim guidelines[10]. This paper reports final clinical outcomes and adverse events of patients enrolled under BCAP.

Methods:

Inclusion and exclusion

Eligible patients had a laboratory confirmed diagnosis of pulmonary XDR-TB or preXDR-TB. Other criteria included: 18 years or older, negative pregnancy test, and no history of habitual TB treatment interruption. Patients with unstable medical conditions were excluded. Patients with any of the following were also excluded: serum creatinine grade 1 or greater (> 1.0 x upper limit of normal (ULN); lipase (> 1.5 x ULN); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (≥ 2.0 x ULN); total bilirubin (> 1.0 x ULN). Patients with a baseline QT interval corrected using the Fredericia formula (QTcF) of >450 msec, clinically significant ECG abnormality at screening, or a family history of prolonged QT syndrome were excluded.

Patients not eligible for BCAP received standard of care individualized treatment regimens and were excluded from analysis. No patients received delamanid while enrolled in BCAP. The need to be able to combine bedaquiline with at least 3 other active drugs was necessary for inclusion. The selection of these three active drugs was based on the drug sensitivity tests as well as prior exposure to medicines.

HIV and ART regimens

In accordance with the South African national HIV treatment guidelines, all patients living with TB and HIV are eligible for initiation of antiretroviral therapy (ART) regardless of baseline CD4 count[11]. The standard first-line ART regimen in South Africa at the time of BCAP was tenofovir, emtricitabine and efavirenz[11]. Patients in whom a first-line regimen failed were eligible to be switched to a second-line regimen containing lopinavir/ritonavir with two appropriate nucleoside reverse transcriptase inhibitors[11]. However, efavirenz co-administration significantly reduces bedaquiline exposure[12,13]; therefore, BCAP patients on efavirenz were switched to either nevirapine or lopinavir/ritonavir.

Pre/XDR-TB treatment and monitoring

Bedaquiline was prescribed at 400 mg once daily for two weeks followed by 200 mg three times a week for 22 weeks[12] alongside an individualized, optimized background regimen which included at least three second-line drugs to which the patient's TB had proven or likely susceptibility. OBR included a combination of some or all of: linezolid, clofazimine, pyrazinamide, ethambutol, high dose isoniazid, p-aminosalicylic acid, capreomycin, kanamycin, levofloxacin, ethionamide, or terizidone as per the SA NTP guidelines[14] and according to availability. Levofloxacin was used instead of moxifloxacin as it has less of an effect on the QT interval[15]. As per the interim WHO recommendations[7], QTcF intervals were measured at baseline, two times in the first month and then monthly while on bedaquiline, and liver function tests at regular intervals. Serious adverse events were reported as per the South African regulatory authority requirements; other adverse events were indicated in the medical files and graded on a scale of mild, moderate, severe, life threatening or fatal. Sputum cultures were performed monthly. Additional laboratory monitoring (e.g. electrolytes, kidney or liver function, haemoglobin) was followed depending on the individualized regimen and ART prescribed, as per the as per the SA NTP guidelines[14].

Selection process

Pre/XDR-TB patients were enrolled from seven approved sites across South Africa. Each site was managed by a principal investigator and a co-investigator. All investigators, pharmacists and clinical nurse practitioners working at selected sites were trained on good clinical practice. Each potential participant was presented to a National Clinical Advisory Committee consisting of eight clinicians with expertise in RR-TB. Three members' approval were required before approaching Janssen Pharmaceutica. This Advisory Committee, Janssen Pharmaceutica, and the South African regulatory authority in turn approved the bedaquiline treatment and the optimized background regimen. The approval process took 4 weeks at the beginning of the programme, and later 2 weeks on average, during which time clinicians could initiate the optimized background regimen and optimize treatment for other co-morbid conditions.

Analysis and reporting

Medical files were reviewed in June 2016 by clinicians and cases record forms were captured in a longitudinal database using Research Electronic Data Capture (REDCap) hosted at University of the Witwatersrand[16]. Medical files for patients who had not completed treatment by June 2016 were reviewed in April 2017 and outcomes updated in the database. The vital status for patients who were lost to follow-up was confirmed or updated through the national vital statistics register for those patients who had a valid South African national identity number in their medical record. We report summary statistics for patient characteristics and treatment outcomes, following the STROBE statement (http://www.strobe-statement.org) for observational cohort studies. Poisson regression was used to test for patient or treatment characteristics associated with treatment success and incidence rate ratios (IRR) and 95% confidence intervals (CI) presented. Multi-variate analysis having adjusted for bedaquiline completion, HIV status (negative or positive) and second-line resistance category (XDR-TB, preXDR-TB with resistance to fluoroquinolones, and preXDR-TB with resistance to second-line injectables) is also reported with adjusted IRR (aIRR). Statistical analysis was done in Stata version 14.2 (College Station, TX).

Ethical approval

Human research ethics committee approval was secured from the University of Witwatersrand, the University of Cape Town, and Pharma-Ethics (www.pharma-ethics.co.za).

RESULTS

Patient characteristics

From March 2013 to March 2015, 200 patients started bedaquiline in addition to a background regimen of 5 to 8 additional anti-TB drugs at the BCAP sites; patient characteristics by HIV status are presented in Table 1. Half (n=99, 49.3%) were female and the median age was 34 years (interquartile range (IQR) 27, 42). For those enrolled, 87 (43.5%) had laboratory confirmed XDR-TB, 33 (16.5%) had preXDR-TB (injectable), and 78 (39.0%) and preXDR- TB (FLQ). Laboratory reports on the resistance pattern for 2 (1.0%) patients were missing at the time of data extraction.

For the background regimen, clofazimine was given to 164 (82.0%) patients, levofloxacin to 166 (83.0%), and linezolid to (128, 64.0%). Among all patients, 67.0% (n=134) were living with HIV with median CD4+ 281 (IQR 130; 467). All individuals living with HIV were on ART consisting of tenofovir, emtricitabine or lamivudine with nevirapine (n=101, 75.4 %) or lopinavir/ritonavir (n=33, 24.6 %).

Table 1. Bedaquiline Clinical Access Program, patient characteristics at bedaquiline initiation, by HIV status. Row proportions.

		HIV-negative	**HIV-positive**	**All (column proportions)**
All patients		66 (33.0%)	134 (67.0%)	200
Age	Median (IQR)	27 (IQR: 23,41)	36 (IQR: 31,42)	34 (IQR: 27,42)
	Age 18-29	24 (66.7%)	12 (33.3%)	36 (18.0%)
	Age 30-49	31 (23%)	104 (77.0%)	135 (67.5%)
	Age 50+	11 (37.9%)	18 (62.0%)	29 (14.5%)
Sex				
	Female	31 (31.3%)	68 (68.7%)	99 (49.3%)
	Male	35 (34.7%)	66 (65.4%)	101 (50.7%)
Resistance				
	preXDR-TB (FLQ)	29 (33.3%)	58 (66.7%)	87 (43.5%)
	preXDR-TB (SLI)	11 (33.3%)	22 (66.7%)	33 (16.5%)
	XDR-TB	25 (32.1%)	53 (68.0%)	78 (39.0%)
	Missing	1 (50.0%)	1 (50.0%)	2 (1.0%)
Weight	Median (IQR)	53.5 (IQR: 49,65)	55 (IQR: 48,62)	54 (IQR: 48,64)
	50kg or less	25 (34.7%)	47 (65.3%)	72 (36.0%)
	More than 50kg	41 (32.3%)	86 (67.7%)	127 (63.5%)
	Missing		1 (100%)	1 (0.5%)
HIV status				
	CD4 count; median (IQR)	N/A	281 (IQR 130; 467)	N/A
	On ART	N/A	134 (100%)	N/A
	Viral load > 1000 copies	N/A	24 (17.9%)	N/A
Province				
	Eastern Cape	3 (50.0%)	3 (50.0%)	6 (3 %)
	Gauteng	6 (24.0%)	19 (76.0%)	25 (12.5 %)
	KwaZulu Natal	13 (19.7%)	53 (80.3%)	66 (33 %)
	North West	6 (17.1%)	29 (82.9%)	35 (17.5 %)
	Western Cape	38 (55.9%)	30 (44.1%)	68 (34 %)

IQR: interquartile range; preXDR-TB: pre-extensively drug resistant tuberculosis; XDR-TB: extensively drug resistant tuberculosis; FLQ: fluoroquinolone resistant; SLI: second-line injectable drug resistant; N/A: not applicable

Treatment outcomes

Among the 200 BCAP patients, 146 (73.0%) patients had a favourable outcome (Table 2); 139 were cured (69.5%) and 7 successfully completed treatment (3.5%). Among the 87 patients with the most extensive resistance (XDR-TB), 70 (80.5%) had a successful outcome.

Twenty-two patients experienced at least one treatment interruption for bedaquiline; 16/200 patients (8.0%) did not complete 24 weeks of bedaquiline: 8 were lost from care (50.0%), 6 died (37.5%), 1 stopped for side effects other than QTcF prolongation (6.3%), and 1 patient was determined to have drug-sensitive TB. Among the 184 BCAP patients who completed the 24 weeks of bedaquiline, 145 had successful outcome (78.8%).

During the 18-24 months of follow-up after bedaquiline initiation, 25 patients died (12.5%), 20 patients were lost from treatment (10.0%), and 9 patients experienced treatment failure with continued culture positive sputa (4.5%). Subsequent to discharge from BCAP, 2 of the 9 patients in whom treatment had failed (22.2%) died.

Table 2. Treatment outcomes, by patient and treatment characteristics, row proportions

	Successful (Cure or completion)	**Died**	**Lost from treatment**	**Treatment failed**
All patients	146 (73.0%)	25 (12.5%)	20 (10.0%)	9 (4.5%)
Age category				
Age 18-29, n=36	27 (75.0%)	3 (8.3%)	4 (11.1%)	2 (5.6%)
Age 30-49, n=135	102 (75.6%)	17 (12.6%)	12 (8.9%)	4 (3.0%)
Age 50+, n=29	17 (58.6%)	5 (17.2%)	4 (13.8%)	3 (10.3%)
Sex				
Female, n=99	80 (80.8%)	10 (10.1%)	5 (5.1%)	4 (4.0%)
Male, n=101	66 (65.4%)	15 (14.9%)	15 (14.9%)	5 (5.0%)
Resistance				
preXDR-TB (FLQ), n=78	50 (64.1%)	15 (19.2%)	8 (10.3%)	5 (6.4%)
preXDR-TB (SLI), n=33	25 (75.8%)	2 (6.1%)	6 (18.2%)	0 (0.0%)
XDR-TB, n=87	70 (80.5%)	8 (9.2%)	5 (5.7%)	4 (4.6%)
Missing resistance report, n=2	1 (50.0%)	0	1 (50.0%)	0
Weight category				
50kg or less, n=72	54 (75.0%)	9 (12.5%)	5 (6.9%)	4 (5.6%)
More than 50kg, n=127	91 (71.7%)	16 (12.6%)	15 (11.8%)	5 (3.9%)
Missing weight, n=1	1 (100%)			
HIV status				
Negative, n=66	44 (66.7%)	6 (9.1%)	12 (18.2%)	4 (6.1%)
Positive, n=134	102 (76.1%)	19 (14.2%)	8 (6.0%)	5 (3.7%)
HIV viral load > 1000 copies, n=24	14 (58.3%)	4 (16.7%)	4 (16.7%)	2 (8.3%)
Bedaquiline				
Completed 24 weeks, n=184	145 (78.8%)	15 (8.2%)	15 (8.2%)	9 (4.9%)
Incomplete, n=16	1 (6.3%)	10 (62.5%)	5 (31.3%)	0 (0%)
Other drugs included in the background regimen				
Clofazimine, n=164	120 (73.2%)	19 (11.6%)	18 (11.0%)	7 (4.3%)
Kanamycin, n=40	32 (65.3%)	10 (20.4%)	4 (8.2%)	3 (6.1%)
Levofloxacin, n=166	122 (73.5%)	20 (12.1%)	16 (9.6%)	8 (4.8%)
Linezolid, n=128	98 (76.6%)	14 (10.9%)	8 (6.3%)	8 (6.3%)

PreXDR-TB: pre-extensively drug resistant tuberculosis; XDR-TB: extensively drug resistant tuberculosis; FLQ: fluoroquinolone resistant; SLI: second-line injectable drug resistant

In unadjusted Poisson regression, completion of bedaquiline was associated with a 1.05 incident risk ratio (IRR) for success (95% CI: 1.03, 1.08). When adjusted for HIV status (negative or positive) and resistance status (XDR-TB, preXDR-TB (FLQ) or preXDR-TB (SLI)), the IRR and confidence interval was unchanged (Table 3). In both univariate and adjusted regression, patients with preXDR-TB with fluoroquinolone resistance were statistically significantly less likely to have a successful treatment outcome (aIRR: 0.81, 95%CI: 0.67-0.99).

Table 3. Poisson regression results, characteristics associated with successful treatment outcome, incident rate ratio (IRR) and adjusted IRR (aIRR) with 95% confidence intervals (95% CI)

	IRR (95% CI)	**aIRR (95% CI)^**
Age category		
Age 18-29	0.99 (0.80-1.23)	1.03 (0.82-1.30)
Age 30-49	Reference	Reference
Age 50+	0.78 (0.56-1.07)	0.80 (0.59-1.09)
Sex		
Female	Reference	Reference
Male	**0.81 (0.68-0.96)**	**0.83 (0.71-0.98)**
Resistance		
preXDR-TB (FLQ)	**0.80 (0.65-0.97)**	**0.81 (0.67-0.99)**
preXDR-TB (SLI)	0.94 (0.76-1.17)	0.97 (0.80-1.17)
XDR-TB	Reference	Reference
Missing resistance report	0.62 (0.50-2.50)	0.68 (0.20-2.32)
Weight category		
50kg or less	1.05 (0.88-1.24)	1.02 (0.86-1.20)
More than 50kg	Reference	Reference
HIV status		
Negative	Reference	Reference
Positive	1.14 (0.94-1.39)	1.18 (0.98-1.42)
HIV viral load > 1000 copies	0.78 (0.55-1.10)	0.87 (0.62-1.20)
Bedaquiline		
Completed 24 weeks	**1.05 (1.03-1.08)**	**1.05 (1.03-1.08)**
Incomplete	Reference	Reference
Other drugs included in the background regimen		
Clofazimine	1.01 (0.81-1.27)	0.94 (0.76-1.16)
Kanamycin	0.87 (0.69-1.08)	0.96 (0.74-1.24)
Levofloxacin	1.04 (0.82-1.32)	0.99 (0.79-1.24)
Linezolid	1.15 (0.95-1.39)	1.14 (0.94-1.39)

^ Adjusted for second-line drug resistance, HIV status, and whether completed 24 weeks of bedaquiline.

IRR: incidence rate ratio; aIRR: adjusted incident rate ratio; CI: confidence interval; PreXDR-TB: pre-extensively drug resistant tuberculosis; XDR-TB: extensively drug resistant tuberculosis; FLQ: fluoroquinolone resistant; SLI: second-line injectable drug resistant

Reported adverse events (AE)

At baseline (initiation of bedaquiline), the median QTcF (n=194) was 403 ms (IQR: 389,422). For the 153 patients with a reported QTcF at the end of 24 weeks of bedaquiline, the median increase from baseline was 11 ms (IQR: -6,27). In total, 10 patients experienced 15 AEs related to QTcF prolongation.

Study investigators recorded a total of 603 AEs for 171/200 (85.5%) patients. Nearly all were assessed by the clinicians as being mild or moderate (n=507 AEs, 84.1%). Of the 603 AEs, investigators attributed 19 (3.2%) to bedaquiline: increased QTcF greater than 500ms (n=5/19 AEs, 26.3%), QTcF increase >50ms from baseline but less than 500ms (8/19, 42.1%), paroxysmal atrial flutter (n=1, 5.3%) and other mild AE (5/19 , 26.3%).

Eighty-seven AEs were reported as serious (death, life-threatening, hospitalisation, significant disability, congenital anomaly, medically significant), all were graded as severe, life threatening or fatal and these occurred in 1/3 of patients (64/200, 32.0%). Among the severe AE, 4 (4.6%) were attributed to bedaquiline (increased QTcF greater than 500ms). The most common severe AE were anaemia (12/87 , 13.6%), peripheral neuropathy (9/87 , 10.2%), and hearing loss or ototoxicity (7/87 , 8.0%). Severe AE were most frequently attributed to linezolid (23/87 , 26.4%), kanamycin (11/87 , 11.4%), and terizidone (8/87 , 9.1%).

DISCUSSION

In 2012, the SA NTP launched the BCAP in order to improve patients' outcomes while simultaneously assessing the effectiveness and safety in routine settings of adding bedaquiline to individualized treatment regimens for persons with pre-XDR-TB and XDR-TB. This cohort of patients was one of the first to receive bedaquiline outside of a clinical trial and 134/200 (67%) patients were living with HIV. The clinicians at the sites selected patients who had few if any other treatment options. Despite this, we found that 146 out of 200 (73.0%) had favourable outcomes and only 25 out of 200 (12.5%) died. Tolerability of the bedaquiline-containing regimens were remarkable in our context: only 16/200 (8.0%) patients did not complete 6 months of bedaquiline. No deaths were attributed to bedaquiline.

It is encouraging that the final cohort results are consistent with the published interim results[9,10]. Based on the clinical trials, interim results and experience of clinicians working with bedaquiline in South Africa, the South African regulatory authority approved bedaquiline for the treatment of RR/MDR-TB at the end of 2014. Following this approval, the SA NTP and the BCAP Clinical Advisory Committee developed guidelines for the use of bedaquiline for patients with pre/XDR-TB or MDR/RR-TB patients for whom an effective regimen could not otherwise be constructed[17]. By June 2018, more than 15,000 patients had been initiated on bedaquiline through the SA NTP. Among the cohort of XDR-TB patients initiating treatment July 2014 to March 2016, bedaquiline-containing regimens were associated with a reduction in the risk of all-cause mortality (hazard ratio [HR] 0.26, 0.18–0.38) compared with non-bedaquiline regimens[18].

The final results of BCAP, despite the high rates of second-line drug resistance and HIV infection, are also consistent with reports from other contexts[19]. At 120 weeks, the open-label trial TMC207-C209 reported 16 deaths out of 233 (6.9%) enrolled patients, all of which were considered not related to bedaquiline[20]. Use of bedaquiline was associated with a 2-fold improvement in treatment success (adjusted odds ratio (aOR), 95%CI: 1.4-2.9) in an individual patient-level data meta-analysis[3]. A multi-centre study reported successful treatment of XDR-TB for patients receiving bedaquiline ranging from 72.6% to 80.4%[21].

Prior to the introduction of bedaquiline, the 2012 XDR-TB cohort (n=581) showed a treatment success rate of 19% and death rate of 47%[2]. The 2015 XDR-TB cohort (n=781) had a treatment success rate of 49% and death rate of 28%[2]. We accessed the vital registration data in order to update records of deaths on the BCAP as well as the 2015 XDR-TB cohort.

An analysis of this cohort showed that providing a bedaquiline based regimen to 65% of individuals in the XDR-TB cohort of 2015 has helped significantly increase overall treatment success rate and significantly decrease death rate. Following the phase 2b trial results, safety and tolerability of bedaquiline-containing regimens have been questioned and this has contributed to the slow uptake of bedaquiline. Meanwhile, the global treatment success rate of MDR-TB and XDR-TB have been stagnant and poor. Recently, several studies have shown that bedaquiline is well tolerated, effective with good safety profile[22,23] hence there has been a call for wide use of bedaquiline-containing regimens[24], with background regimens including linezolid, clofazimine and levofloxacin. Gatifloxacin has been recommended and part of the list of fluoroquinolones in all guidelines of the World Health Organization[25] and has shown very good results in the short course MDR TB treatment[26]. Unfortunately, gatifloxacin is not widely available. While moxifloxacin could be used in this regimen, the concern about the increase in QT interval remains[15]. Gatifloxacin or moxifloxacin could be more effective than levofloxacin, although that has to be further investigated.

In addition, the Global TB Alliance trial NIX-TB, patients with XDR TB, MDR TB treatment intolerance or MDR TB failure were started on a combination of bedaquiline, pretomanid and linezolid. The last published results from this trial were in Feb 2017 [27] and in personal communication with the GATB, the high rate of success has remained in excess of 80% with a mortality of less than 10%. *Limitations*

The observational and programmatic design of this study is a limitation, as there was no control arm and patients were seen in implementation rather than study-settings.

The FDA, based on phase 2 data from the trial C 208, approved bedaquiline in December 2012. This was under accelerated approval based on time to sputum culture conversion. Continued approval for this indication is contingent upon verification and description of clinical benefit in confirmatory trials. STREAM Stage 2 was designed as the phase 3 trial for bedaquiline. This is at present a three-arm study comparing the WHO approved 9-11 months treatment regimen for MDR TB to two bedaquiline containing regimens. The first of these is a 9-month injection free regimen and the second is a 6 months injectable containing regimen. This is a multi-center trial being conducted in South Africa, Ethiopia, Uganda, Mongolia and India. Enrolment has been slower than expected and results are expected in late 2021. While randomized controlled clinical trials remain the highest level of medical evidence and still has to be done, the results of this cohort are reassuring.

Conclusion:

The proportion with final successful treatment outcomes of this cohort with resistance to fluoroquinolones and/or second-line injectables treated with bedaquiline- containing regimens was high. While AEs occurred, most were indicated as probably attributed to drugs in the background regimen and not bedaquiline. These encouraging results supported the SA National Department of Health to make the bold decision to remove the injectable agent from MDR-TB regimen and replace with bedaquiline. These results were included in the analysis of evidence that informed the latest recommendation with regard to the use of bedaquiline in MDR-TB and XDR-TB patients. The World Health Organization recently updated their drug-resistant tuberculosis medicines classification: bedaquiline has moved to group A, which is the group of the most potent medicines to

treat drug-resistant tuberculosis, alongside linezolid and latest generation fluoroquinolones and k anamycin is no longer recommended [28]. . Finally, it is not the addition of a single medication to a regimen for the treatment of MDR TB or XDR TB that will prove to be the game changer but rather the design of new regimens combining as many of the new and repurposed agents including linezolid, carbapenem and other companion drugs if we are to decrease the morbidity and mortality associated with rifampicin resistant TB.

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Authors' contributions
NN, FC, JH, NB, AP designed study and obtained approval for BCAP. NN, KS, FC drafted manuscript; GaM, JH, GeM revised. KS, FC, NN analysed data. SA BCAP investigators provided site leadership, medical care and collected data. All authors reviewed and approved manuscript for submission.

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