Title

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Authors

Govender, Thiloshini
Jham, Menal A
Zhang, Justin C
et al.

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Decentralized, integrated treatment of RR/MDR-TB and HIV using a bedaquiline-based, short regimen is effective and associated with improved HIV disease control

Thilo Govender[1], **Menal A. Jham, MD**[2], **Justin C. Zhang, MD**[3], **Selvan Pillay, MSc**[4], **Youngju Pak, PhD**[5], **Prenisha Pillay, Dip IT**[4], **Jennifer Furin, MD, PhD**[6], **Jason Malenfant, MD, MPH**[7], **Richard A. Murphy, MD, MPH**[8,9]

[1]King Dinizulu Hospital Center, Durban, South Africa

[2]UMMA Community Clinic, Community Clinic Association of Los Angeles County, CA, USA

[3]University of California at San Francisco, CA, USA

[4]Adrenergy Research Innovations, Durban, South Africa

[5]Lundquist Institute for Biomedical Innovation, CA, USA

[6]Harvard Medical School, MA, USA

[7]David Geffen School of Medicine at UCLA, CA, USA

[8]Geisel School of Medicine at Dartmouth, NH, USA.

[9]White River Junction Veterans Affairs Medical Center, VT, USA

Abstract

Background: In decentralized sites, with fewer resources and a high prevalence of advanced HIV, the effectiveness of the new short-course, bedaquiline-based regimen for rifampicin-resistant and multidrug-resistant tuberculosis (RR/MDR-TB) is not well-described.

Setting: Adults with pulmonary RR/MDR-TB initiating the short-course regimen in KwaZulu-Natal, South Africa were prospectively enrolled at a decentralized program that integrated person-centered TB care.

Methods: In addition to standard of care monitoring, study visits occurred at enrollment and months 1, 2, 4, 6 and 9. Favorable RR/MDR-TB outcome was defined as cure or treatment completion without loss to follow-up, death or failure by treatment. In patients with HIV, we assessed ART uptake, virologic and immunologic outcomes.

Results: Among 57 patients, HIV was present in 73.7% (95% CI: 60.3—84.5), with a median CD4 count of 170 cells/mm^3 (intraquartile range (IQR) 49—314). A favorable RR/MDR-TB

CORRESPONDING AUTHOR (AND REPRINTS): Richard A. Murphy, MD, MPH. VA White River Junction Medical Center, Medicine Service 163 Veterans Drive White River Junction, VT 05009 Phone: (802) 295-4318 / Fax: (802) 291-6257 / ramurphy@gmail.com.

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outcome was achieved in 78.9% (CI: 67.1—87.9). Three deaths occurred, all in the setting of baseline advanced HIV and elevated viral load. Overall, 21.1% (95% CI: 12.1–32.9) experienced a severe or life-threatening adverse event, the most common of which was anemia. Among patients with HIV, enrollment resulted in increased ART uptake by 24% (95% CI: 12.1–39.4%), a significant improvement from baseline (P=0.004); virologic suppression during concomitant treatment was observed in 71.4% (n=30, 95% CI: 55.4–84.3).

Conclusion: Decentralized, person-centered care for RR/MDR-TB in patients with HIV using the short-course, bedaquiline-based regimen is effective and safe. In patients with HIV, enrollment led to improved ART utilization and reassuring virologic outcomes.

Keywords

adverse event; toxicity; drug-resistant tuberculosis; multidrug resistant tuberculosis; rifampin-resistant tuberculosis; bedaquiline

Introduction

In Southern Africa, rifampicin-resistant and multidrug-resistant tuberculosis (RR-TB and MDR-TB) remain a significant cause of morbidity and mortality, particularly among persons with HIV.[1] The treatment of RR-TB and MDR-TB has evolved considerably with the availability of bedaquiline and the repurposing of linezolid, allowing for fully-oral, multidrug regimens that are shorter in duration and result in high rates of treatment success.[2] Fully-oral regimens have also facilitated the expansion of RR/MDR-TB care to decentralized treatment settings. However, in these sites, where resources and patient characteristics differ from referral hospital settings, treatment outcomes and adverse events are not well described.[3] In addition, in these sites, a more precise understanding of outcomes as well as the frequency and severity of adverse events (AEs) has the potential to guide more evidence-based monitoring and treatment support. Studying outcomes and AEs in decentralized sites – where RR/MDR-TB is chiefly an HIV-associated opportunistic infection – may ultimately inform an approach to drug-resistant TB care in decentralized sites that is increasingly person-centered and evidence-based.[4]

Person-centered care is an approach to TB that contrasts with the historical response to TB treatment and control which was driven by a “public health approach,” with the result being that TB remains one of the leading infectious killers of adults worldwide.[5] This is especially true for drug-resistant forms of TB (DR-TB) that have been characterized by strict models of service delivery, emphasis on a “one-size-fits-all” approach, and poor outcomes, with success rates of just over 60% reported globally.[6] Recently, calls for more person-centered approaches to TB and DR-TB care, grounded in a human rights model of service delivery, have led to programs that are more holistic, individualized, empowering, and respectful.[7, 8]

A critical aspect of the management of RR/MDR-TB in southern Africa is the comanagement of HIV. Among persons with RR/MDR-TB in KwaZulu-Natal, HIV is present in approximately 70%.[9] It has been demonstrated that the use of ART is critical to successful RR/MDR-TB outcome in patients living with both conditions.[10] Yet more than half of patients with both RR/MDR-TB and HIV present with uncontrolled HIV with

markers of advanced HIV disease, anemia, and weight loss.[11,12] While bedaquiline-based, short -course regimens have been widely deployed amongst this patient group, little is known about key HIV-specific endpoints such as ART uptake and subsequent virologic suppression during concomitant decentralized treatment.[13,14] Thus, we sought to investigate, among a prospective cohort initiating RR/MDR-TB treatment at a decentralized site, both tuberculosis and HIV treatment outcomes across the 9 month, short-course regimen.

Methods

Study design

This was a prospective, cohort study that recruited patients ≥18 years of age referred to Charles James Hospital with pulmonary RR/MDR-TB who initiated short-course, bedaquiline-based RR/MDR-TB therapy between July 4, 2019 and July 30, 2020. We included patients who had RR/MDR-TB confirmed using either Xpert MTB/RIF or culture. Advanced HIV was defined as a baseline CD4 cell count less than 200 cells/mm.[3]

Setting

Charles James TB Hospital is a 120-bed treatment unit located 25 km southwest of Durban; it was one of the first decentralized drug-resistant tuberculosis treatment units in South Africa. Patients from nearby clinics with tuberculosis-compatible symptoms were evaluated using sputum smear and culture, x-ray and Xpert MTB/RIF, and if found to be ill with pulmonary RR/MDR-TB, were referred for initiation of therapy with the fully-oral, bedaquiline-based, short-course regimen.

Bedaquiline-based, short-course RR/MDR-TB regimen

In 2018, South Africa revised its guidelines for the treatment of patients with RR/MDR-TB, recommending that the injectable agent be replaced by bedaquiline and that linezolid be employed for the first 2 months of multidrug therapy.[15] The short-course, RR/MDR-TB regimen consisted of bedaquiline, levofloxacin, clofazimine, high-dose isoniazid, ethambutol, and pyrazinamide for the first 4–6 months followed by levofloxacin, clofazimine, ethambutol and pyrazinamide for the remaining 5 months. Linezolid is dosed at 600 mg/day. Initially patients were hospitalized for the first 2–3 months (until sputum smear conversion), and were discharged to follow-up monthly at the Charles James clinic. The requirement for initial admission was changed in 2020 and thereafter most patients were initiated without hospitalization. There was also on-site HIV care, CD4 and viral load monitoring, as well as a single pharmacy dispensing both ART and RR/MDR-TB medicines.

Person-centered TB care

Key elements of person-centered care were integrated into the program including an emphasis on treatment accessibility, care quality, patient autonomy and individualized care. In the domain of accessibility, the hospital was decentralized and geographically proximate to patients. As a small hospital, the waiting times at the clinic and pharmacy were limited. On-site care for noncommunicable diseases (NCDs) – including diabetes mellitus and hypertension – was available and NCD medication was dispensed from the same pharmacy. Patients who missed an appointment were contacted the following day to avoid treatment

interruption. In the domain of care quality, deficits in disease and treatment literacy were addressed. Nursing staff engaged patients consistently on symptoms of adverse events and treatment adherence. Additionally, medical care from month to month was provided by a small, consistent team of physicians and nurses. In the domain of patient autonomy, inpatient hospitalization was – by study year 2 – not required and outpatients received community-based adherence support rather than strict DOT. Last, in the psychosocial domain, the social worker was actively engaged in psychological support and assisted patients in applying for financial support.

Patient longitudinal follow-up

Research visits took place at enrollment and at months 1, 2, 4, 6, 9 and, if necessary, 11. Extension of therapy to month 11 occurred in patients who—at month 4 – remained sputum smear positive. As per South African clinical guidelines, patients underwent protocolized monitoring which included routine laboratory testing, ECG, and monthly sputum samples for microscopy, culture and sensitivity testing. At baseline and follow-up research visits, patients participated in structured interviews with a research nurse which included a review of symptoms for AEs and lab monitoring. At month 15 patients received a post-treatment completion questionnaire by phone.

AEs were graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1.[16] AEs of Grade 3 and 4 were considered severe or life-threatening, respectively. For the entire duration, the same treating clinician graded AEs. Symptoms or abnormal laboratory values present at baseline were considered not related to the RR/MDR-TB regimen. If abnormalities within a given clinical condition category spanned more than one grade, they were captured according to highest severity. A 12-lead ECG was obtained at each study visit to monitor for QT prolongation. The Fridericia formula was used to correct the QT interval for heart rate. We followed convention that defined a Fridericia-corrected QT interval (QTcF) > 500 ms as a severe adverse event and, >500 ms with signs or symptoms of arrhythmia as life-threatening.[17]

Biostatistics and outcome definitions

Kaplan-Meier analysis was used to describe treatment outcome. The endpoint of interest was unfavorable final treatment outcome – death, loss to follow up, or failed by treatment – using standardized WHO classifications. Favorable outcome was defined as cure or treatment completion, without an unfavorable outcome (censored). Treatment outcomes were evaluated for patients who had Grade 3 or 4 AEs during treatment and compared to outcomes among patients who had no severe/life-threatening AE, using the logrank test. On-treatment culture conversion was calculated excluding those who died or were lost to follow-up before the time point of interest. The paired two-sample t-test and the McNemare's test were used to compare CD4 counts and the percentage of ART coverage (defined as proportion of HIV positive patients receiving ART), respectively. Virologic outcomes were reported using a "missing=failure" definition; those who, at month 6, were lost to follow-up or deceased or had a missing value were presumed not to be suppressed.

Ethics review

The study was approved by the Institutional Review Boards at the University of KwaZulu-Natal in Durban and at the University of California, Los Angeles.

Results

Fifty-seven patients who initiated treatment for RR/MDR-TB at Charles James Hospital between July 4, 2019 and July 30, 2020 were enrolled. The median age was 35 years (IQR 27—44), 31.6% (95% CI: 19.9—45.2) were female, and 73.7% (n=42, 95% CI: 60.3—84.5) were living with HIV. The current episode was the initial tuberculosis episode for 57.9% (n=33, 95% CI 45.0—70.1) of patients, 38.6% (n=22, 95% CI: 26.8—51.5) had previously been diagnosed with drug-sensitive tuberculosis and 3.5% (n=2, 95% CI: 0.7—10.8) had documented prior drug-resistant tuberculosis. Additional characteristics are shown in Table 1.

Bacteriologic and programmatic outcomes

At baseline, 38.6% (n=22, 95% CI:26.8 – 51.5) of patients had positive smear microscopy and 54.4% (n=31, 95% CI:41.5—66.8) had a positive culture. Among patients with a positive baseline culture, culture conversion occurred at a median of 58 days (IQR:37—97) after treatment initiation. By month 3, 67.7% (n= 21, 95% CI: 50.3—82.1) of patients on-treatment had achieved culture conversion, by month 4 among patients on-treatment, 90.3% achieve culture conversion (n=28, 95% CI: 76.4—97.2) (Figure 1). The median follow-up was 477 days.

Favorable treatment outcome was achieved by 78.9% (n=45, 95% CI: 67.1—87.9) of patients; unfavorable outcomes, comprised of loss to follow-up, death and failed by treatment in 14.0% (n=8, 95% CI: 6.9—24.7), 5.3% (n=3, 95% CI: 1.5—13.4), and 1.8% (n=1, 95% CI: 0.2 –7.9), respectively (Table 2). When patients living with HIV (n=42) were considered as a group, outcomes were similar; favorable treatment outcome (cure or treatment completion) was achieved by 78.6% (n=33, 95% CI: 64.5—88.8); unfavorable outcomes, comprised of loss to follow-up, death and failed by treatment occurred in 11.9% (n=5, 95% CI: 4.7—31.1), 7.1% (n=3, 95% CI: 2.1—17.5), and 2.4% (n=1, 95% CI: 0.3 –10.6), respectively. Notably, all 3 deaths occurred in patients who had, at enrollment, advanced HIV disease with elevated viral load, resulting from ART interruption (n=2) or ART failure (n=1). Deaths all occurred more than 6 weeks after RR/MDR-TB treatment initiation, at days 49, 56 and 441.

HIV-related outcomes during RR-TB treatment

HIV was present in 73.7% (n=42, 95% CI: 60.3—84.5) of patients, with a median and mean CD4 cell count at enrolment of 170 cells/mm^3 (IQR 49—314) and 236.7 cells/mm^3 (95% CI: 151.2—322.2), respectively. Among patients with HIV, advanced HIV disease (baseline CD4 count <200 cells/mm^3) was present at enrollment in 59.5% (n=25, 95% CI: 49.5 – 73.3). ART use in patients with HIV at the time of RR-TB diagnosis – including in those with HIV but not yet diagnosed – was 64.3% (n=27, 95% CI: 49.2–77.4). After 6 months of

enrollment in decentralized RR/MDR-TB treatment, ART use increased by 24% (95% CI: 12.1–39.4%), a significant improvement in ART utilization (P=0.004).

As a result of the potential interaction between bedaquiline and efavirenz, patients with HIV who, at baseline, were receiving an efavirenz-based regimen, underwent an ART change. The new regimens consisted of nevirapine-based ART in 32.4% (n=12, 95% CI:18.0 – 49.8), lopinavir/ritonavir-based ART in 37.8% (n= 14, 95% CI:22.5 – 55.2), and dolutegravir-based ART in 29.7% (n=11, 95% CI:15.9 – 47.0). In 2019, the first year of the study, 26.9% of patients living with HIV in the program were receiving dolutegravir-based ART but by 2020, 78.6% were receiving dolutegravir. Median CD4 cell count numerically improved during treatment of concomitant ART and RR/MDR-TB; compared to the baseline mean CD4 cell count of 167 cells/mm^3 (IQR: 37–296), by month 6 of combined treatment the mean CD4 cell count was 283 cells/mm^3 (IQR: 127–444) (P= 0.2). At month 6, virologic suppression (using a “missing=failure” definition) was achieved by 71.4% (n=30, 95% CI: 55.4–84.3). Among those not suppressed, 7.1% (n=3, 95% CI: 1.5 – 19.5) had low-grade viremia (50–999 copies/ul), 4.8% (n=2, 95% CI: 6.0 – 16.2) had virologic failure (>1000 copies/ul), and 16.7% (n=7, 95% CI: 7.8—30.0) were no longer in follow-up (n=5) or had missing data (n=2).

Adverse Events

There were a total of 95 AEs and 78.9% (n=45, 95% CI: 67.1–87.9) of patients experienced at least one AE. There were 16 severe and 1 life-threatening Aes; 21.1% (n=12, 95% CI: 12.1–32.9) of patients experienced an AE of severe or life-threatening severity. Severe or life-threatening AEs consisted of severe anemia in 14.0% (n=8, 95% CI: 6.9–24.7) of patients, severe ALT elevation in 5.3% (n=3, 95% CI: 1.5–13.4), severe musculoskeletal toxicity in 5.3% (n=3, 95% CI: 1.5–13.4), other severe hematologic adverse events in 3.5% (n=1 thrombocytopenia and n=1 neutropenia, 95% CI: 0.7–10.8) and a life-threatening psychiatric adverse event in 1.8% (n=1, 95% CI: 0.2–7.9) (Figure 5). Overall, 3.5% (n=2, 95% CI: 0.7 –10.8%) of patients reported symptoms of peripheral neuropathy during linezolid treatment. One of these patients received a shortened course of linezolid, consisting of 1 month of linezolid. Neither reported long-term symptoms of neuropathy at treatment completion, and among patients with a post-treatment interview at month 15 (70.2% of patients), none had symptoms of peripheral neuropathy.

Patients were systematically evaluated for QTc prolongation with ECG. The median (SD) baseline QTcF was 412 ms (34.5). The baseline QTcF was ≤450 ms in 96.5% (n=55, 95% CI: 89.2 – 99.3%) of patients. No patient experienced a QTcF >500ms at any point in the study and no Grade 3 or 4 cardiovascular events were detected. The median QTcF (SD) was 412 ms (34.5) at baseline, 427 ms (24.1) at 1 month, 430 ms (33.6) at 2 months, 437 ms (27.1) at 4 months, 438 ms (25.3) at 6 months, 433 ms (23.3) at 9 months, and, for patients remaining on treatment at 11 months, 428 ms (15) (Figure 4). Median change from baseline at 2 and 6 months were +18 ms and +26 ms, respectively.

We sought to explore the relationship between development of a severe or life-threatening AE and unfavorable RR/MDR-TB treatment outcome; using Kaplan-Meier analysis, we

found no evidence that an AE of this severity was associated with unsuccessful outcome (P=0.23, log-rank test, Figure 3).

Discussion

The treatment of RR/MDR-TB with a short-course, fully-oral, bedaquiline-based regimen in a decentralized setting, was effective and well-tolerated in a patient population with a substantial burden of advanced HIV. Programmatic outcomes were reassuring with a 78% rate of treatment success and, among patients with a positive culture at baseline, all converted to negative. Severe and life-threatening AEs that did occur – notably anemia, ALT elevations and musculoskeletal toxicities – were not frequent. Outcomes in patients living with HIV were notable for excellent ART uptake, significant immunologic recovery and a high rate of virologic suppression, as well as a shift towards the use of dolutegravir-based ART. However, 3 deaths were observed, all among patients who at enrollment had advanced HIV and an elevated HIV viral load, suggesting that for this particularly vulnerable group, novel approaches are needed.

While it has been established that the use of ART in patients with drug-resistant TB and HIV reduces mortality, the effectiveness of ART in this setting – as evidenced by virologic suppression during concomitant treatment – has not been described.[10] Reassuringly, for patients living with HIV in this cohort, enrollment in the RR/MDR-TB program led to improvement in ART utilization as well as a high rate of month 6 virologic suppression with only 4.8% experiencing virologic failure. Important potential reasons for favorable HIV-specific outcomes were that clinicians assertively utilized ART in patients who were eligible, a single pharmacy dispensed both ART and tuberculosis therapy, and there was no separate HIV-related medical visit required. An additional potential reason was the inclusion – alongside routine RR/MDR-TB treatment monitoring – of HIV disease monitoring (viral load and CD4 cell count) to help detect HIV treatment failure. Despite these program components, there was a group of patients who presented with advanced HIV and uncontrolled viremia – among whom all 3 observed deaths occurred – suggesting an opportunity for further innovation.

Another key development for patients with HIV and RR/MDR-TB – that was observed in this cohort – was the wider utilization of dolutegravir. It is a critical development because patients living with HIV receiving efavirenz-based ART undergo an ART switch at initiation of RR/MDR-TB treatment – as recommended by the South African national protocol – to ART with a lower potential for drug-drug interaction with bedaquiline. As an option for patients initially on efavirenz-based ART, the utilization of dolutegravir (DTG)-based ART increased beginning in 2020. Dolutegravir-based ART for patients with RR/MDR-TB presents several advantages including superior potency, reduced pill burden, and likely reduced overall treatment-related toxicity, giving it potential to improve outcomes in both diseases. There is early evidence more broadly that the use of dolutegravir-based ART in RR/MDR-TB programs is increasing.[20] In patients with HIV initiating RR/MDR-TB treatment, the use of DTG-based ART should be expanded.

In the last decade, experts in the treatment of drug-resistant tuberculosis have urged the adoption of “person-centered” tuberculosis treatment derived, not from the standard “public health approach,” but based on principles that place the patient at the center of care. This model, which has been embraced by many decentralized sites, aims to provide care that is individualized and empowering.[21] Implicit is the recognition that drug-resistant TB does not occur randomly but within difficult social contexts that, if simultaneously addressed, may improve the likelihood of a successful outcome. Key elements of this model that were integrated at this decentralized site were in domains of treatment accessibility, care quality, patient autonomy and individualized care. Unfortunately, person-centered care (PCC) has not been the care model employed in large referral hospitals where drug-resistant tuberculosis care has traditionally been located. Although challenging to quantify, PCC may have contributed to the favorable outcomes observed in this cohort and, as national programs act to implement even shorter, fully-oral regimens for RR/MDR-TB, this model should be considered as a key part of drug-resistant TB programs.[22]

Although this study lacked the power to determine risk factors for unfavorable treatment outcome, it is notable that significant economic barriers were present at baseline, with approximately 70% of patients unemployed and reporting no monthly income. Additional barriers present in the psychosocial domain may have included mental illness and high-risk substance use. Among a subset of patients screened at baseline for mental illness and substance use (full data not shown in this report); 57% screened positive for depression, 29% for anxiety, and 29% for problem alcohol use. Additional key factors that may have affected retention were the stigma related to RR/MDR-TB, colloquially known as “big TB,” in South Africa, as well as the economic consequences of illness resulting from loss of work, transport costs and caregiving costs.[18,19] While a goal of person-centered care is to identify and address such barriers, pre-exisiting economic and psychosocial problems are likely to continue to have implications on outcomes.

Overall, the 9-month, bedaquiline-based, fully-oral RR-TB regimen was well-tolerated. The most common severe AE was anemia which occurred in 14% of patients. Anemia, known to be associated with linezolid, is an AE of particular concern in patients with RR/MDR-TB and HIV because it is typically already present at baseline (for example, the mean hemoglobin at enrollment in the cohort was 11.3 mg/dl), and additional hematologic toxicity is poorly tolerated. Notably, anemia was observed using a lower linezolid dose of 600 mg/daily given for a relatively short duration of 2 months. In contrast, within the more novel BPaL and BPaLM oral regimens for RR/MDR-TB endorsed by the WHO, linezolid is given for a considerably longer duration of 6 months. Using these new regimens in decentralized settings should come with the expectation that hematologic toxicity will be even greater.[23] Therefore close hematological monitoring, access to transfusion services and protocols that facilitate rapid regimen adjustments, should remain an essential feature of RR/MDR-TB treatment programs utilizing linezolid. Another adverse event associated with linezolid, peripheral neuropathy, was observed in few patients (3.5%), with no long-term peripheral neuropathy observed. The low rate of peripheral neuropathy may have been related to the limited duration of linezolid use (2 months) and the dose used, which contrasts with a recent trial in which a substantial rate of neuropathy (81% of patients) was observed using a higher dose (1200 mg/daily) for a longer (6 month) period.[24] The overall safety of

this RR/MDR-TB regimen adds to the evidence supporting its use in a variety of settings, including decentralized sites where robust monitoring strategies are in place.

In line with another recent study, we found that despite the use of several agents concomitantly that can prolong the QT interval – bedaquiline, clofazimine and levofloxacin – QT interval changes were modest; none of our patients experienced a QTc >500ms or a clinically evident severe or life-threatening cardiovascular AE during follow-up.[25] Although QT changes were noted – with median changes from baseline at 2 and 6 months of 18 ms and 26 ms, respectively – these excursions had a modest impact, potentially because the baseline QTc interval almost uniformly was below 450ms. The use of regular ECG monitoring in patients receiving this regimen may be more productively aimed at patients with additional risk factors such as older age or pre-existing cardiac disease. The availability of ECG monitoring should not be a prerequisite for the use of this regimen in less-supported treatment sites.

The study has limitations. Although laboratory adverse events were captured with monthly monitoring, serum creatinine was not captured longitudinally in this cohort. Reassuringly, low rates of nephrotoxicity have been previously reported with this – injectable-free – regimen.[11] Second, some adverse events that were mild or moderate may have gone undetected in our programmatic setting as the review of systems at each study visit – by necessity in a busy clinic setting – was brief and focused. Nonetheless, given the close longitudinal patient follow-up, we think that the majority of severe and life-threatening adverse events were captured. Third, the number of patients enrolled fell short of expectations. In the months following the World Health Organization announcing SARS-CoV-2 as a global pandemic, Charles James Hospital was closed and remaining patients were required to complete the study elsewhere at a large referral hospital. Our study team established a presence at the new site but the change was disruptive for patients and led to some missed study visits. Nevertheless, for the patients affected by this change in treatment location, we were able to achieve complete follow-up.

In summary, the use of the bedaquiline-based short-course RR-TB regimen in a decentralized setting where person-centered care was prioritized resulted in a high rate of culture conversion and, for HIV positive patients, high ART uptake and robust virologic outcomes. For patients living with RR-TB and HIV, decentralized, person-centered care is effective and may be the preferable treatment model as new, more potent regimens emerge. To reduce on-treatment mortality, novel interventions aimed at patients who at initiation of RR/MDR-TB treatment have advanced HIV and uncontrolled viremia are needed; given that none of these patients died very early after RR/MDR-TB treatment initiation, this may be a patient subgroup that could benefit from intensive adherence support and closer clinical monitoring.

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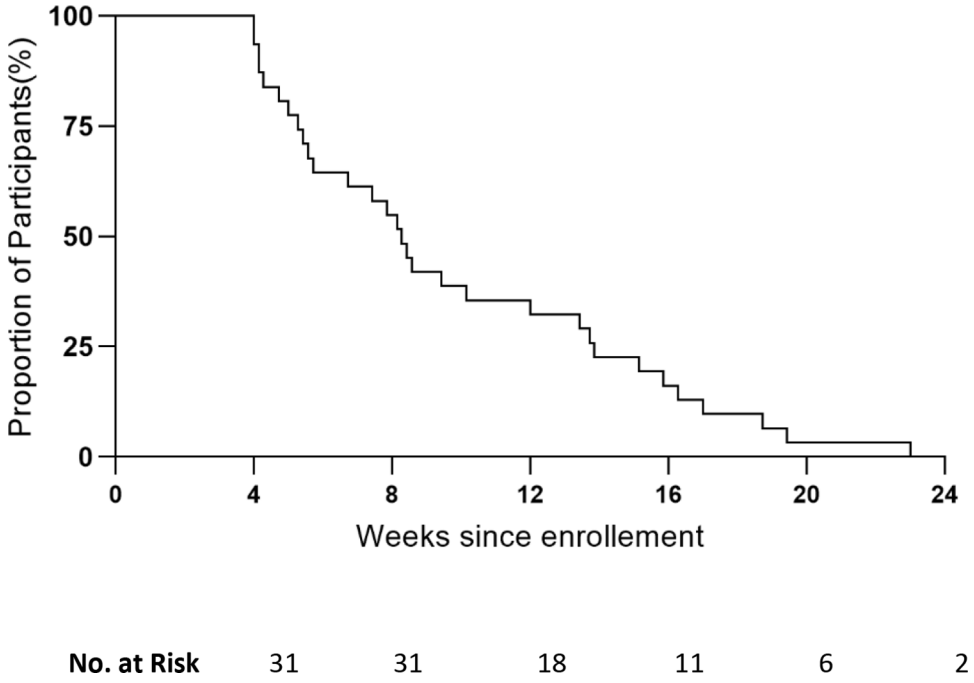
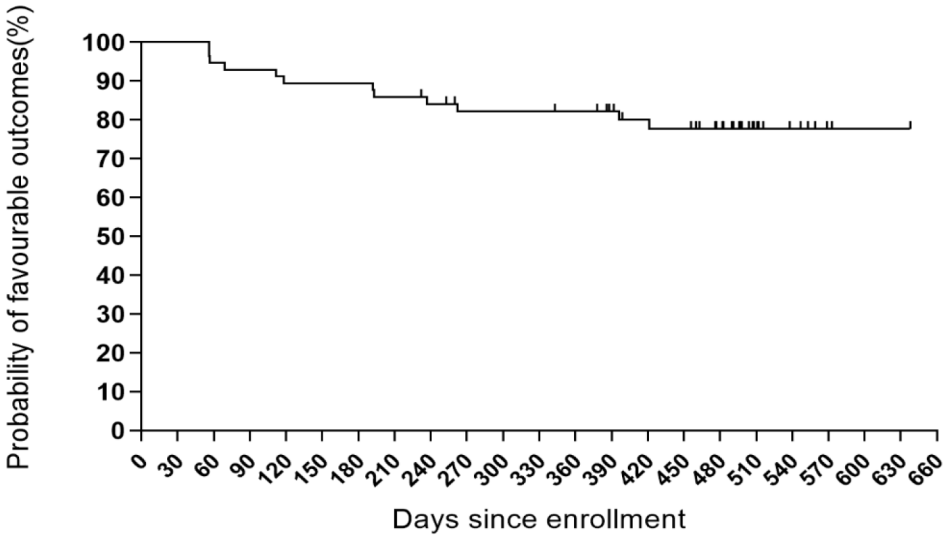


Figure 1.

Kaplan-Meier curve of time to tuberculosis culture-negative sputum; the median time to negative culture was 58 days (N= 31).



Days	0	60	120	180	240	300	360	420	480	540	600	660
Censored	0	0	0	0	2	2	1	6	7	21	5	1
Unfavorable outcome	(0)	(3)	(3)	(0)	(3)	(1)	(0)	(1)	(1)	(0)	(0)	(0)
Number at Risk	57	54	51	51	46	43	42	35	27	6	1	0

Figure 2.

Kaplan-Meier curve of the occurrence of outcomes defined as death, loss to follow up, or failed by treatment. Censored patients experienced favorable outcome, specifically cure or treatment completion without an unfavorable outcome defined as death, loss to follow-up or failed by treatment.

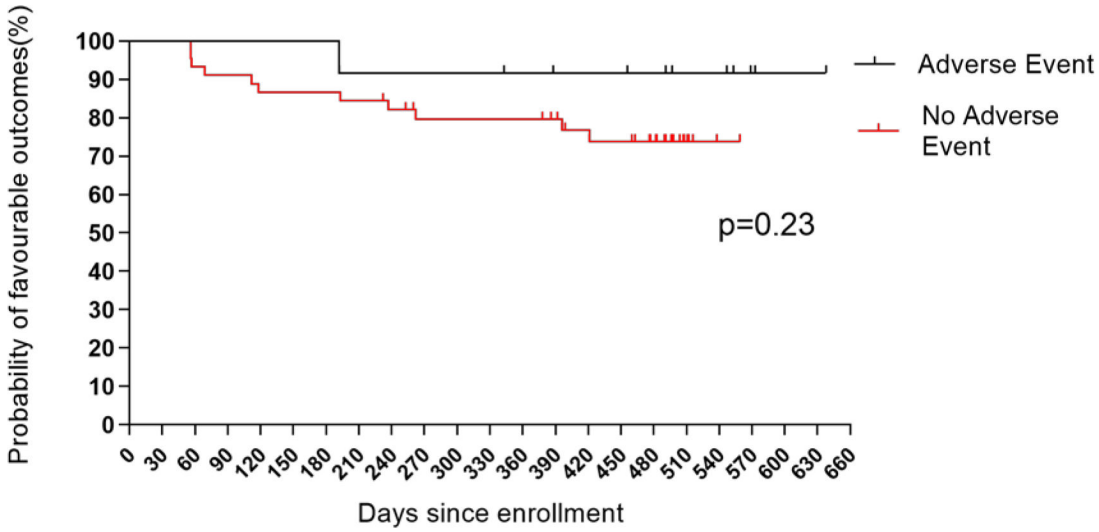


Figure 3.

Kaplan-Meier curve of the occurrence of unfavorable outcome by presence or absence of Grade 3 or 4 adverse event. Censored patients experienced favorable outcome, specifically cure or treatment completion without an unfavorable outcome defined as death, loss to follow-up or failed by treatment.

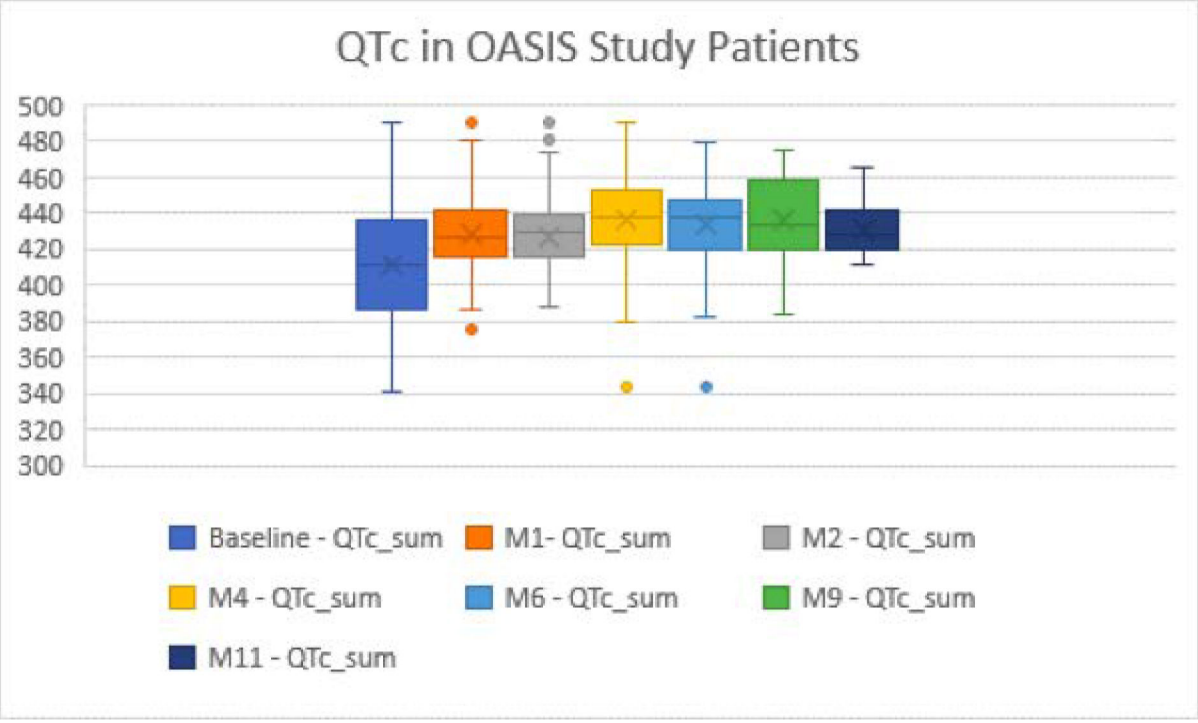


Figure 4:
Median QTcF at study visits occurring at baseline (before initiation of anti-tuberculosis therapy) and at months 1, 2, 4, 6, 9 and 11 with no excursions noted above 500 ms.

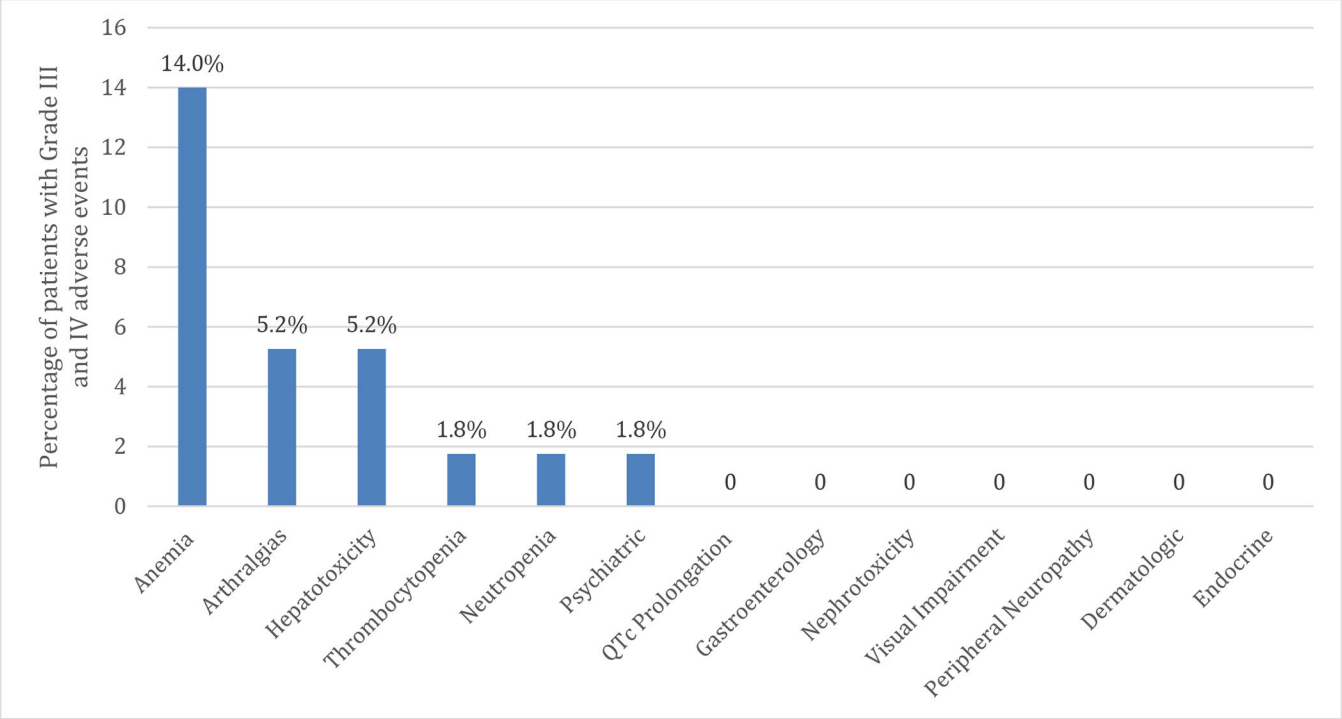


Figure 5:

Percentage of patients who experienced severe (Grade III) and life-threatening (Grade IV) adverse events during the fully-oral, short-course, bedaquiline-based RR/MDR-TB regimen in KwaZulu-Natal, July 2019 – July 2020.

Table 1

Characteristics of patients with RR-TB starting a short-course, fully-oral, bedaquiline-based regimen, Charles James Hospital outside of Durban, South Africa, 4 July 2019 to 30 July 2020

Characteristics	n	% / Median	95% CI / IQR
Gender			
Male	39	68.4	55.7–79.3
Age, median (IQR)	57	36	26—46
Education			
Did not complete secondary school	24	42.1	29.9—55.0
Completed secondary school	32	56.1	43.2—68.5
Employment			
Unemployed	39	68.4	55.7—79.3
Student	1	1.8	0.2—7.9
Employed	17	29.8	19.2—42.5
Monthly income, median rands / month (IQR)[1]	17	3000	2250—4500
Tobacco			
Active	10	17.5	9.4—28.9
Former	7	12.3	5.7—22.6
Alcohol			
1 per day	6	10.5	4.5—20.4
2 per day	4	7.0	2.4—15.8
Heroin (whoonga)			
Current use	1	1.8	0.2—7.9
Tuberculosis history			
New	33	57.9	45.0—70.1
Prior drug-sensitive tuberculosis	22	38.6	26.8—51.5
Prior drug-resistant tuberculosis	2	3.5	0.7—10.8
Smear microscopy results, baseline			
Positive	22	38.6	26.8 – 51.5
Negative	29	50.9	38.1—63.5
Missing	6	10.5	4.5 – 20.4
Culture results, baseline			
Positive	31	54.4	41.5—66.8
Negative or contaminated[2]	26	45.6	33.2—58.5
Bilateral lung disease			
Bilateral	38	66.7	53.8—77.8
Unilateral	19	33.3	22.2—46.2
HIV positive (n=42)			
Newly diagnosed at time of RR/MDR-TB disease	10	24.4	12.4 – 40.3

Characteristics	n	% / Median	95% CI / IQR
Previously diagnosed at time of RR/MDR-TB disease	31	73.8	59.7 – 87.6
CD4 count at initiation of RR/MDR-TB therapy, median cells/mm^3 (IQR)[3]	38	170	49—314
Antiretroviral therapy status at diagnosis of RR/MDR-TB			
Receiving ART	27	64.3	48.0 – 78.4
Not receiving ART	15	35.7	16.3—38.7
Weight, baseline, median in kg	57	55.0	48.0—62.0
Hemoglobin, baseline, mean in mg/dl	57	11.3	9.3—13.4
Albumin, baseline, mean in g/dl	50	2.9	2.2—3.5
QTcF, baseline			
≤ 450 ms	55	96.5	89.2—99.3

1. Income data includes 17 employed patients; 40 unemployed patients reported no monthly income.

2. These patients had a baseline Xpert MTB/RIF positive for rifampicin resistance without baseline positive culture

3. Four patients living with HIV were missing baseline CD4 cell count

Table 2:

Treatment outcomes of patients with RR/MDR-TB who initiated a short-course, fully-oral, bedaquiline-based regimen, Charles James Hospital, South Africa

Tuberculosis treatment outcomes	n	%	95% CI
Completed therapy	45	78.9	67.1—87.9
Lossed to follow-up	8	14.0	6.9—24.7
Died	3	5.3	1.5—13.4
Failure of treatment	1	1.8	0.2 –7.9