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Safety and Effectiveness of an All-Oral, Bedaquiline-Based, Shorter Treatment Regimen for Rifampicin-Resistant Tuberculosis in High Human Immunodeficiency Virus (HIV) Burden Rural South Africa: A Retrospective Cohort Analysis

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Background. At the end of 2018, South Africa updated its all-oral regimen, to include bedaquiline (BDQ) and 2 months of linezolid (LZD) for all patients initiating the shorter 9–12 months regimen for rifampicin-resistant tuberculosis (RR-TB). We assessed a group of patients in rural KwaZulu-Natal for safety and effectiveness of this treatment regimen under programmatic conditions.

Methods. We conducted a retrospective cohort analysis on RR-TB patients treated with a standardized all-oral short regimen between 1 July 2018 and 30 April 2019 in 3 facilities in King Cetshwayo District. An electronic register (EDR web) and facility-based clinical charts were used to collect variables, which were entered into an Epi-Info database.

Results. Our cohort included 117 patients; 68.4% (95% confidence interval [CI]: 59.3–76.3) tested positive for human immunodeficiency virus (HIV). The median time to culture conversion was 56 days (95% CI: 50–57). Treatment success was achieved in 75.2% (95% CI: 66.5–82.3) of patients. Mortality within the cohort was 12.8% (95% CI: 7.8–20.3). Anemia was the most frequent severe adverse event (AE). The median time to develop severe anemia was 7.1 weeks (interquartile range [IQR] 4.0–12.9) after treatment initiation. LZD was interrupted in 25.2% (95% CI: 17.8–34.5) of participants.

Conclusions. An all-oral shorter regimen, including BDQ and LZD as core drugs for the treatment of RR-TB, shows good outcomes, in a high HIV burden rural setting. AEs are common, especially for LZD, but could be managed in the program setting. Support is needed when introducing new regimens to train staff in the monitoring, management, and reporting of AEs.

Keywords. multidrug resistant; all-oral short regimen; bedaquiline; linezolid; adverse event management.

Rifampicin-resistant tuberculosis (RR-TB) affects over half a million of people each year. South Africa remains among the countries with the highest TB and RR-TB burden in the world, with an estimated incidence of 520 TB cases per 100 000 in 2018, up to 7% of which are rifampicin-resistant [1]. The treatment of RR-TB can be long and complex, associated with toxic agents, yet with treatment success rates remaining at just over 60% [2–4]. New and repurposed drugs are now available, with South Africa rolling out new regimens in recent years. South African programmatic data were used to update the World Health Organization (WHO) recommendations for the treatment of RR-TB in 2018 and 2019. This led to the most recent WHO recommendation for an all-oral shorter regimen in which bedaquiline (BDQ) replaces the injectable [5]. This regimen, however, still includes ethionamide (ETH), a drug with doubtful efficacy, poorly tolerated by patients, and ranked lower than linezolid (LZD) in the WHO RR-TB drug hierarchy. Linezolid, a drug shown to be associated with better outcomes and lower mortality, is currently still excluded from the WHO-recommended shorter regimen [5, 6]. At the end of 2018, South Africa modified its all-oral regimen, recommending 6 months of BDQ and 2 months of LZD for all patients initiating the shorter 9–12 months RR-TB regimen [7]. We assessed a group of patients in rural KwaZulu-Natal for safety and effectiveness of this "newest" treatment regimen under programmatic conditions.

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METHODS

Study Design

This is a retrospective cohort analysis of routinely collected programmatic data of RR-TB patients eligible for a short standardized BDQ-based regimen between 1 July 2018 and 30 April 2019 [7]. Study was conducted at 3 RR-TB facilities in King Cetshwayo District, KwaZulu Natal, South Africa.

Study Setting

King Cetshwayo District has a human immunodeficiency virus (HIV) prevalence of 26.4% in the general population and RR-TB rates of 9–12% among all TB cases [8, 9]. In 2011, Médecins sans Frontières (MSF) began working with the National Department of Health (NDoH) and District Health teams to support decentralization of RR-TB care and to improve access to new regimens. Since 2016, RR-TB treatment is provided at 3 ambulatory sites with a centralized in-patient unit if admission is clinically indicated.

RR-TB Treatment Protocol

On diagnosis of rifampicin resistance (by nucleic acid amplification test [GeneXpert; Cepheid] or line probe assay test [GenoType MTBDRplusV2.0; Hain Lifescience]), patients receive clinical evaluation, baseline examinations, and treatment initiation according to NDoH Guidance at a RR-TB treatment site [7]. One sputum sample is collected for smear, culture, and first- and second-line genotypic resistance testing (culture, GenoType MTBDRplus and GenoType MTBDRsl assay are processed by the referral laboratory of the National Health Laboratory Service [NHLS]). This forms the baseline culture for the patient and is taken within the timeframe of 3 months before to 1 month after treatment start.

The South African standard of care for RR-TB changed during 2018. In July, a BDQ-based regimen was implemented. ETH was removed during the following months (some still receiving ETH initially), and it was advised to treat with LZD until second-line resistance could be excluded. This led to variable durations of LZD among patients. In November 2018, a generalized recommendation of 2 months of LZD for all patients initiating RR-TB treatment was released [7] (Figure 2). In patients with hemoglobin levels <8g/dL, LZD initiation is deferred until anemia improves, sometimes requiring blood transfusion.

First follow-up of patients happens 2 weeks after initiation. Specific laboratory tests, including full blood and neutrophil count, are recommended, as well as electrocardiogram (ECG) monitoring. Further follow-ups are at week 4 and then monthly, with regular ECG while on BDQ and laboratory tests indicated by the prescribed medications. Monthly bacteriological monitoring consists of both smear and culture (SC) samples for all patients on treatment. Cultures are done by liquid medium (BACTEC MGIT®). Phenotypic drug susceptibility testing (DST) for first- and second-line drugs happens on all positive cultures. Adverse events (AEs) are managed according to their clinical significance and national guidelines [7].

Study Population

We included all RR-TB patients over 18 years of age, eligible for the short standardized all-oral BDQ-based regimen as per NDoH guidance [7], at Eshowe, Mbongolwane, and Catherine Booth hospitals in King Cetshwayo District between 1 July 2018 and 30 April 2019.

Study Variables and Definitions

WHO and national guidelines were used to define RR-TB resistance type and outcome variables such as time to SC conversion, end-of-treatment outcomes, and AEs [7, 10]. Time to SC conversion was defined as the time from initiation of RR-TB treatment to time of SC conversion. SC conversion was reached with 2 consecutive negative SC results on samples collected at least 30 days apart with conversion date being the collection date of the first negative SC sample [10].

End-of-treatment outcomes were assigned by the treating clinician, in line with both NDoH and WHO definitions [7]. An AE is defined as any "untoward medical occurrence in a patient receiving any kind of treatment" [11]. We looked at AEs up until the end of the 24-week BDQ course. AEs are graded on a scale of 1 to 4, with 1 being mild and 4 being life-threatening [11]. AEs of grade 3 and higher are considered severe. AEs occurring more than once in the same patient were recorded by the date of highest severity. AEs leading to persistent disability or hospitalization were noted as serious AEs. It was difficult, however, to conclude occurrence of AEs as causes of death due to incompleteness of AE reporting, to polypharmacy and comorbidities of patients, and unspecified recording on death certificates. QT intervals are calculated according to Frederica's formula (QTcF) as recommended per national guidelines [7]. Specific cutoff values for numeric variables of laboratory tests to define grading are taken from the Clinical and Programmatic Guide for Patient Management with New TB Drugs (Common Terminology Criteria for Adverse Events [CTCAE] v.4.03 classification) [11]. For the entire cohort, 2 same medical doctors interpreted treating clinicians' notes for grading of AEs. All proformas were checked for completeness by the principal investigator before final recording.

Data Collection and Analysis

Source documents for our study were NDoH Electronic Drug-resistant Tuberculosis Register (EDRWeb), NHLS results, and facility-based clinical charts. Data were extracted by using a standardized data collection tool (see the Supplementary material). All data were entered into an Epi-Info (Centers for Disease Control and Prevention [CDC], Atlanta, GA, USA) database. Continuous variables are presented as medians with interquartile range (IQR). Categorical variables are presented as

frequencies and proportions. A χ^2 test was used to compare categorical variables. Time to SC conversion was estimated using Kaplan-Meier (KM) curves. For the analysis of time to SC conversion, the outcome of interest was SC conversion achieved within 3 or 6 months of treatment. If the outcome of interest was not achieved, it was considered as censored.

Censoring occurs when the patient is lost to follow-up (LTFU) or died before achieving SC conversion. The time of censoring was the date of death or LTFU. Censoring also occurred when the patient did not SC convert within 6 months of treatment or transferred or moved out (TMO) before SC conversion was achieved. In our cohort, however, no patient TMO before SC conversion was achieved, and SC conversion status at month 6 was known for all those with positive baseline SC samples. Log-rank test was used to investigate the difference between survival curves. The median time to SC conversion was reported using 95% confidence interval (CI). Data were analyzed using STATA version 15 (StataCorp, College Station, TX, USA).

Ethics

Ethics approval was obtained by MSF Ethics Review Board (Geneva, Switzerland) and the Biomedical Research Ethics Board of the University of KwaZulu-Natal, South Africa.

RESULTS

Patient Characteristics

From 1 July 2018 to 30 April 2019, 194 patients were notified with RR-TB in our district. The short regimen was initiated in 151 patients, yet 19.9% (30/151) were switched to a longer regimen, when their baseline resistance profiles became available, as per NDoH guidelines. Figure 1 shows the patients eligible for the short standardized BDQ-based course included in the final analysis.

Table 1 shows the baseline characteristics of these 117 patients. Of our patients, 59.8% (95% CI: 50.6–68.4) were male, 68.4% (95% CI: 59.3–76.3) living with HIV, and 55.6% (95% CI: 46.3–64.4) had confirmed multidrug resistance (MDR). Of our cohort, 91.5% (95% CI: 84.7–95.4) received both BDQ and LZD; the median time on LZD was 8 (IQR: 6–13) weeks. And 76.9% (95% CI: 68.3–83.6) received their complete RR-TB treatment as out-patients.

Bacteriological Outcomes

Among 117 patients, 44.4% (95% CI: 35.6–53.7) had a positive smear and 57.3% (95% CI: 48.0–66.0) a positive culture at baseline. And 95 patients (81.2%) completed 6 months of treatment and had a median number of monthly follow-up smear and culture results of 6 (IQR 5–6) and 5 (IQR 4–6), respectively (Table 2). Smear conversion was achieved in 92.3% (95% CI: 80.7–97.2), and 7.7% (95% CI: 2.8–19.3) died within 6 months. Culture conversion was achieved in 89.6% (95% CI: 79.3–95.0), 6.0% (95% CI: 2.2–15.2) died, and 4.5% (95% CI: 1.4–13.3) LTFU within 6 months. The median time to smear conversion was 34 days (95% CI: 29–45) and to culture conversion 56 days (95% CI: 50–57) (Figure 3).

The proportion of 6-months culture conversion in HIV-negative patients compared to HIV-positive was 90.0% (95% CI: 64.5–97.8) versus 89.4% (95% CI: 76.2–95.7) ($P = .938$) (Table 3). The median time to culture conversion for HIV-negative and

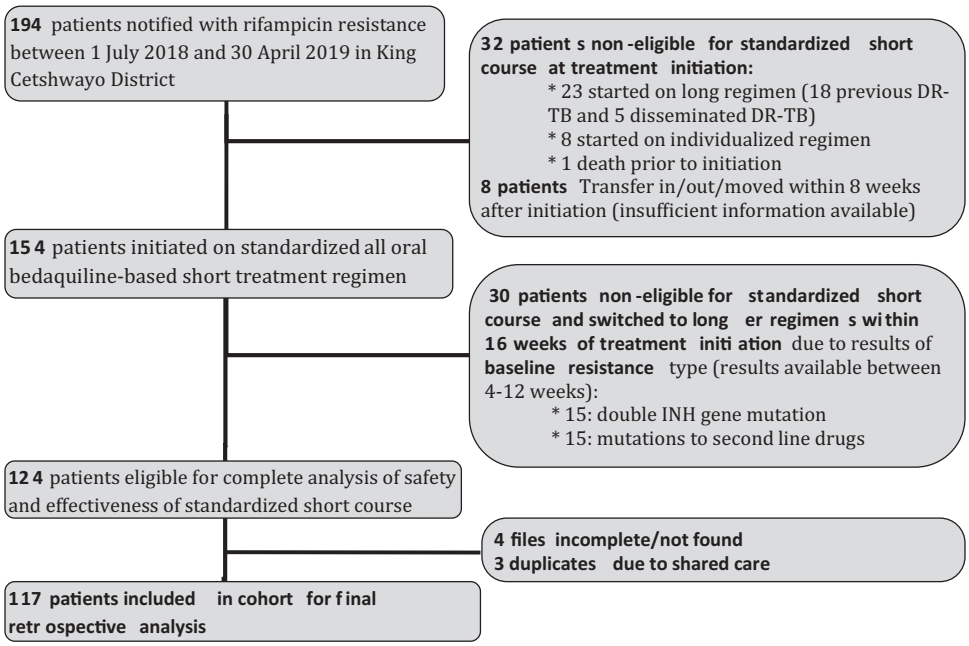

Figure 1. Flow diagram of selection of study participants from patients notified with RR-TB in King Cetshwayo district, Kwa-Zulu Natal, South Africa, 1 July 2018 to 30 April 2019. Abbreviations: DR-TB, drug-resistant tuberculosis; INH, isoniazid; RR-TB, rifampicin-resistant tuberculosis.

Figure 2. Diagrammatic overview of the short standardized Bedaquiline-based regimen, indicating recommended duration of each drug as of November 2018 in South Africa (National Department of Health Interim Guidance for the Implementation of Injectable Free Regimens for Rifampicin-Resistant Tuberculosis).

HIV-positive patients was 36 (95% CI: 29–57) and 57 days (95% CI: 53–64), respectively (P = .104) (Figure 3).

The proportion of 6-months culture conversion in CD4 count <200 cells/μL compared to CD4 count ≥200 cells/μL was 85.0% (95% CI: 59.6–95.6) versus 96.0% (95% CI: 73.7–99.5) (P = .198) (Table 3). We looked at time to culture conversion up to 3 months considering that 3-months culture conversion was known for 82.2% (95% CI: 67.9–92.0) of patients living with HIV with documented baseline CD4. There was no significant difference between KM survival curves of CD4 groups within 3 months of follow-up (P = .826) (Figure 3). The median time to culture conversion within 6 months follow-up in CD4 levels <200 cells/μL was 64 days (95% CI: 32–113) and with CD4 levels ≥200 cells/μL was 57 days (95% CI: 57–68).

Seven patients had a positive culture during their treatment course after achieving culture conversion. Four of the 7 positive cultures occurred after month 6. The positive cultures showed similar resistance patterns to baseline and patients continued the same regimen. All 7 patients reconverted; 5 successfully completed treatment, 1 patient had TMO, and 1 patient was LTFU. Of patients with negative baseline culture samples, 7 developed a positive culture during treatment. Of these 7, 2 patients had culture results with amplified resistance profiles, compared to baseline line probe assay results.

End-of-Treatment Outcomes

Treatment success was achieved in 75.2% (95% CI: 66.5–82.3) of patients. Mortality was 12.8% (95% CI: 7.8–20.3), and 80% (95% CI: 51.9–95.7) of deaths occurred in the first 4 months of treatment. LTFU, treatment failure, and TMO was recorded in 10.3% (95% CI: 5.9–17.3), .9% (95% CI: .01–6.0), and .9% (95% CI: .01–6.0), respectively.

Adverse Events

A total of 298 AEs was recorded; 108 (92.3% [95% CI: 85.8–96.0]) patients experienced at least 1 AE (grade 1–4) during the BDQ course, with a median of 2 (IQR 2–4) AEs per patient. Looking at severe AEs only, a total of 62 severe AEs were recorded in 43 (36.8% [95% CI: 28.4–46.0]) patients. Anemia was the most frequent and accounted for 27 (43.5% [95% CI: 31.0–56.7]) of all severe AEs (Figure 4). For these 27 patients, the median time to severe anemia was 7.1 (IQR 4.0–12.9) weeks after treatment initiation. Of 107 patients who received LZD, 27 (25.2% [95% CI: 17.3–34.6]) developed severe anemia. Of 15 patients who died, severe anemia occurred in 10 (66.7% [95% CI: 38.4–88.2]) patients. In our cohort, grade 3 and 4 QT prolongation occurred in 7 (6.0% [95% CI: 2.4–11.9]) patients. Other severe AEs documented were hepatotoxicity in 9 (14.5% [95% CI: 6.9–25.8]) patients, QT prolongation in 7 (11.3% [95% CI: 4.7–21.9]) patients, nausea and vomiting in 5 (8.1% [95% CI: 2.7–17.8]) patients, and nephrotoxicity in 4 (6.5% [95% CI: 1.8–15.7]) patients. One patient developed optic neuritis and lost all vision. A different patient developed peripheral neuropathy of the lower limbs and fractured her ankle following gait disturbances. These last 2 AEs met the definition of serious AEs.

Management of Adverse Events

Supportive medication was given for symptom control for 103 (34.6% [95% CI: 29.2–40.3]) AEs. No specific management actions were taken for 119 (39.9% [34.3–45.7]) AEs, due to their transient course, clinical insignificance, and/or planned

Table 1. Demographic and Clinical Characteristics of RR-TB Patients Initiated and Continued the Short Standardized BDQ-based Regimen in King Cetshwayo District, South Africa, 1 July 2018 to 30 April 2019, n = 117

Patients Characteristics	n	%/Median	95% CI/IQR
Gender			
Female	47	40.2	31.6–49.4
Male	70	59.8	50.6–68.4
Median age (IQR)	117	35	27–44
Age group			
14–24	22	18.8	12.6–27.0
25–34	33	28.2	20.7–37.2
35–44	34	29.1	21.5–38.0
45–54	17	14.5	9.2–22.3
≥55	11	9.4	5.2–16.3
Previous TB history			
New	63	53.8	44.7–62.8
Had DSTB	50	42.7	34.0–52.0
Had DRTB	4	3.4	1.7–8.9
HIV status			
Negative	37	31.6	23.7–40.7
Positive	80	68.4	59.3–76.3
ART status during RR-TB Tx (n = 80)			
Lost to follow-up	6	7.5	3.3–15.9
Newly diagnosed	12	15.0	8.6–24.8
Stable on antiretroviral	62	77.5	66.8–85.5
Median CD4 at RR-TB initiation (IQR)	76	243	93–459
CD4 at RR-TB initiation (n = 80)			
<100	20	25.0	16.6–35.9
100–200	16	20.0	12.5–30.4
200–350	14	17.5	10.5–27.7
≥350	26	32.5	23.0–43.7
CD4 not done	4	5.0	1.8–12.8
RR-TB type			
Rif Res on GXP only	39	33.3	25.3–42.5
Rif monoresistance	11	9.4	5.2–16.3
GXP: Rif Res and 1st line LPA sensitive	2	1.7	.4–6.7
Confirmed MDR[a]	65	55.6	46.3–64.4
Baseline smear results			
Negative	63	53.8	44.7–62.8
Positive	52	44.4	35.6–53.7
Test not done	2	1.7	.4–6.7
Baseline culture results			
Negative	32	27.4	19.9–36.3
Positive	67	57.3	48.0–66.0
Contaminated	12	10.3	5.9–17.3
Test not done	6	5.1	2.3–11.1
Hb at baseline			
<7.9	9	7.7	4.0–14.2
7.9–9.9	26	22.2	15.5–30.8
≥10	82	70.1	61.1–77.8
QTcF at baseline			
<450	112	95.7	90.0–98.2
≥450	4	3.4	1.3–8.9
Missing	1	0.9	.1–6.0

Abbreviations: ART, antiretroviral therapy; BDQ, bedaquiline; CI, confidence interval; GXP, GeneXpert (first line test for any presumptive TB case); Hb, hemoglobin; HIV, human immunodeficiency virus; INH, isoniazid; IQR, interquartile range; LPA, line probe assay; MDR, multidrug resistant (resistant to both rifampicin and isoniazid); QTcF, calculated QT interval according to Frederica's formula; Rif Res, rifampicin resistant; Rif S, rifampicin sensitive; RR-TB, rifampicin-resistant tuberculosis; TB, tuberculosis.

[a]Isoniazid resistance in these patients was limited to the presence of a single gene mutation (either katG or inhA), because patients with both mutations do not qualify to receive the shorter regimen [7].

Table 2. Smear and Culture Conversion Status at Month 6 for RR-TB Patients Initiated and Continued the Short Standardized BDQ-based Regimen in King Cetshwayo District, South Africa, 1 July 2018 to 30 April 2019.

Smear and Culture Follow-up and Conversion Status at Month 6 of Treatment	n	%/Median	95% CI/IQR
Median number of follow-up smears for all	95	6	5–6
Median number of follow-up smears for smear positive at baseline	41	6	5–6
Smear conversion status (n = 52)			
Converted negative	48	92.3	80.7–97.2
Died before conversion	4	7.7	2.8–19.3
LTFU before conversion	0	0.0	N/A
Median number of follow-up cultures for all	95	5	4–6
Median number of follow-up cultures for culture positive at baseline	56	5	4–6
Culture conversion status (n = 67)			
Converted negative	60	89.6	79.3–95.0
Died before conversion	4	6.0	2.2–15.2
LTFU before conversion	3	4.5	1.4–13.3

Of total cohort (n = 117), 95 completed 6 months treatment. Of 67 culture positive at baseline, 56 completed 6 months treatment. Of 52 smear positive at baseline, 48 completed 6 months treatment.
Abbreviations: BDQ, bedaquiline; CI, confidence interval; IQR, interquartile range; LTFU, lost to follow-up; N/A, not applicable; RR-TB, rifampicin-resistant tuberculosis.

completion of the course of the causative drug. For 21 (7.0% [95% CI: 4.4–10.6]) AEs, patients were hospitalized for further monitoring and treatment.

Hospitalization after treatment initiation occurred in 26 (22.2% [95% CI: 15.1–30.8]) of our patients for various reasons. Among hospitalizations, 18 (69.2% [95% CI: 48.2–85.7]) were attributed to an AE and the need for inpatient management. Of these AE-linked admissions, 8 (44.4% [95% CI: 21.5–69.2]) were due to severe anemia, and 2 (11.1% [95% CI: 1.4–34.7]) were due to a prolonged QT interval.

LZD was interrupted by the provider in 27 (25.2% [95% CI: 17.8–34.5]) participants; the median time on LZD for these patients was 8 (IQR 4–11) weeks. LZD was reintroduced at a reduced dosage of 300 mg/day in 8 occurrences; 1 patient reinitiated the dosage of 600 mg/day; in the remaining 18 cases, LZD was permanently discontinued and not replaced. This was due to various reasons, including receipt of DST results showing an absence of second-line resistance or clinical improvement of the patient on the regimen, where the risks of LZD were felt to outweigh the benefit of continued use. BDQ was interrupted in 3 patients and reinitiated in all, after review and supportive therapy.

DISCUSSION

The South African all-oral short regimen shows good results in a high HIV burden setting. Treatment success was achieved in 75% of our patients, exceeding historical treatment successes of <65% of both the short injectable regimen and the "BLIX" cohort (BDQ and LZD for XDR patients) within the same area [12, 13]. The success rate is similar to that reported from a national cohort in South Africa where BDQ and LZD were combined in a longer regimen [14]. AEs remain common and were often associated with the use of LZD, but some toxicity occurred to other drugs in the regimen. High-dose isoniazid, pyrazinamide, and ethambutol were frequently interrupted following an AE (Figure 5), calling into question the routine use of these drugs for RR-TB treatment, as their effectiveness is also uncertain [6]. Mortality in our cohort remains high, comparable to other oral regimens for RR-TB [14, 16] and happens early during treatment. This can be due to delayed diagnosis and treatment initiation [17]. Most of our patients received their treatment as outpatients, likely reducing costs within a resource-limited healthcare system yet with risk for LTFU, in absence of proper financial and social support.

Table 3. Culture Conversion Status at Month 6 of Treatment for HIV-positive Patients with Positive Baseline Culture by HIV status and CD4 Cell Count of RR-TB Patients Initiated and Continued on the Short Standardized BDQ-based Regimen in King Cetshwayo district, South Africa, 1 July 2018 to 30 April 2019

	HIV negative (n = 20)			HIV positive (n = 45)			CD4 <200 cells/μL (n = 20)			CD4 ≥200 cells/μL (n = 25)		
Culture Conversion Status at Month 6	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Converted negative	18	90.0	64.5–97.8	42	89.4	76.2–95.7	17	85.0	59.6–95.6	24	96.0	73.7–99.5
Died before conversion	2	10.0	2.2–35.5	2	4.3	1.0–16.2	1	5.0	.5–32.3	1	4.0	.4–26.3
LTFU before conversion	0	0.0	0.0–0.0	3	6.4	2.0–18.7	2	10.0	2.0–35.5	0	0.0	0–0

χ^2 and *P* value: HIV-negative vs HIV-positive (.006 and .938). CD4 <200 vs ≥200 (1.66 and .198).
Abbreviations: BDQ, bedaquiline; CI, confidence interval; HIV, human immunodeficiency virus; LTFU, lost to follow-up; RR-TB, rifampicin-resistant tuberculosis.

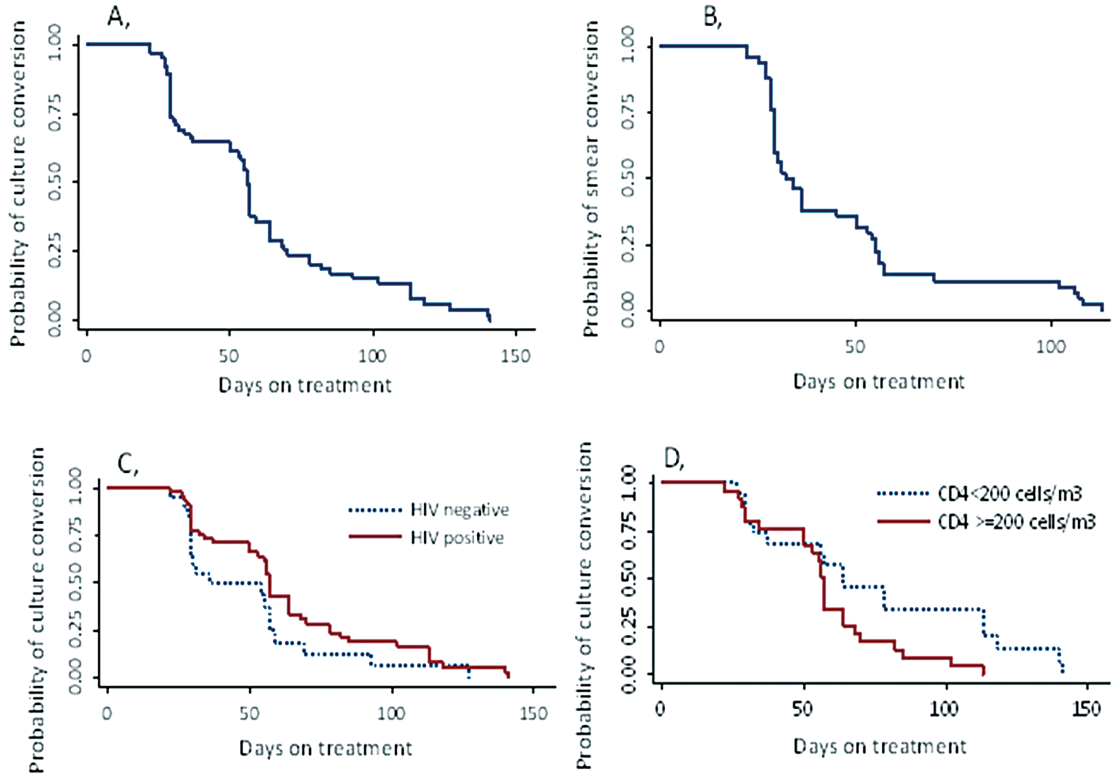

Figure 3. Kaplan-Meier survival estimates for smear/culture positive RR-TB patients at baseline in King Cetshwayo district, 1 July 2018 to 30 April 2019. *A*, Time to culture conversion (n = 67). *B*, Time to smear conversion (n = 52). *C*, Time to culture conversion by HIV status (n = 67); log-rank test within 6 months of follow-up: $P = .104$. *D*, Time to culture conversion by CD4 count (n = 45); log-rank test within 3 months of follow-up: $P = .826$. Abbreviations: HIV, human immunodeficiency virus; RR-TB, rifampicin-resistant tuberculosis.

Almost 20% of patients initiated on the short regimen were switched to a longer regimen when their baseline resistance profiles became available [7]. We decided not to include these patients in our analysis, as we wanted to assess both tolerability and effectiveness in the "newest" shorter regimen for eligible RR-TB patients. These 30 patients either had isoniazid (INH) mutations and/or levofloxacin or injectable resistance. Although excluded from our analysis, they represent an important population for additional future study, especially to see if the empiric inclusion of LZD as part of the shorter regimen decreases the likelihood of developing resistance to other administered drugs. As patients are currently started on RR-TB treatment before rapid molecular INH and FLQ-resistance results are available, we believe there is benefit in a robust regimen, including LZD, at treatment initiation.

Nearly all of our patients received both BDQ and LZD. The use of these 2 drugs likely contributed to high rates of almost 90% of SC conversion at month 6, exceeding conversion rates in similar settings [18]. LZD has been associated with improved outcomes in RR-TB patients [3, 19] and adding on LZD to the BDQ-based regimen, forming a robust backbone, could have contributed to the rapid time to culture conversion in our cohort. Our results are consistent with those reported under trial conditions, but they are noteworthy, demonstrating what can be achieved in program conditions with high HIV comorbidity [3, 18, 20–25] present. An important finding in our cohort is that HIV status and CD4 levels had no effect on achieving culture conversion, or on time needed to convert within the first 3 months of treatment, even though almost half of our HIV-positive cohort had advanced HIV disease. We acknowledge our small sample size and are cautious drawing conclusions from our findings; nevertheless, this is encouraging for other countries with high HIV/DRTB burden.

Worldwide concern for BDQ-related cardiotoxicity has promoted frequent ECG monitoring [5, 7], yet QT prolongation was observed in <10.0% of the cohort and contributed minimally to hospitalizations. The safety of BDQ has been reinforced in both HIV-negative and HIV-positive patients over the past few years and we see the same reassuring results [20, 26]. LZD-related toxicities, however, remained a challenge, equally noted in other settings [15, 19, 20, 23]. Anemia was the most frequent recorded severe AE, contributing to treatment discontinuation, hospitalization, and possibly mortality within our cohort. Most of the LZD-related toxicities reversed when the drug was discontinued. The overall frequency of peripheral neuropathy in our cohort is low, as LZD exposure was limited to 2 months and possibly underdiagnosis of the pathology. Considering all

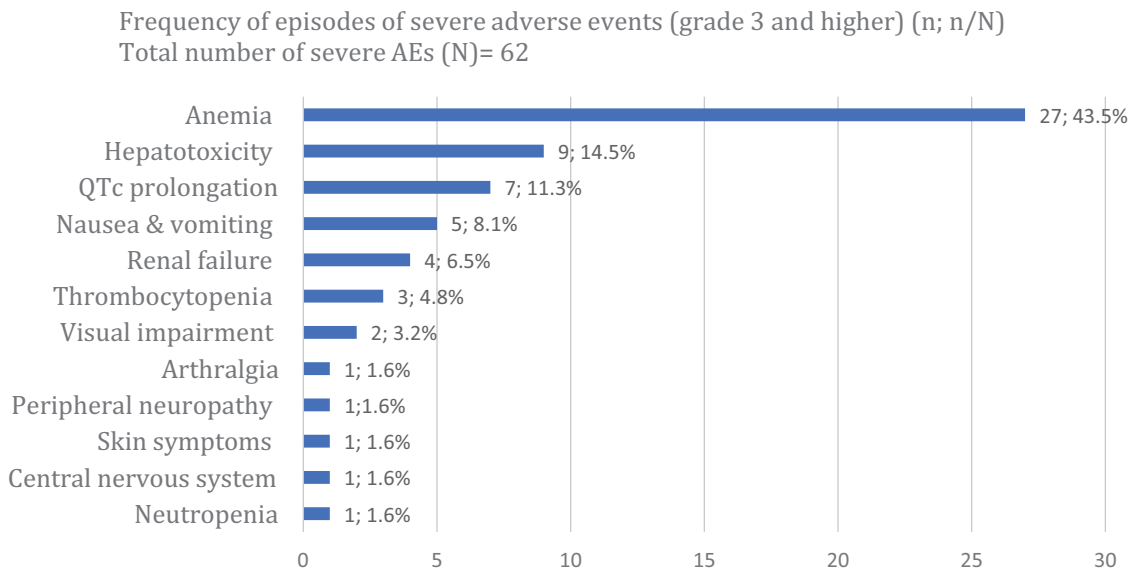

Figure 4. Frequency of severe AEs experienced in RR-TB patients during first 24 weeks after treatment initiation (N = 62), receiving a short standardized BDQ-based regimen in King Cetshwayo district between 1 July 2018 and 30 April 2019. Abbreviations: AE, adverse event; BDQ, bedaquiline; RR-TB, rifampicin-resistant tuberculosis.

LZD-associated toxicities, it is crucial to strictly monitor for myelosuppression and neuropathy and to ensure prompt management happens when toxicity occurs [5, 7, 27].

There are several limitations to our analysis. We look at the cohort retrospectively without any comparison group and therefore cannot exclude a general improvement of care contributing to our results. Our cohort was defined as the patients receiving the newly adopted "all-oral BDQ-based" regimen in South Africa, yet the guidance and final recommendation for this regimen was delayed. This led to variable durations of LZD within our cohort. Our data likely underreport on AEs because we relied on routine program data, characterized by inaccuracies in recording. Trained clinicians performed a systematic audit on all clinical charts and missing laboratory results were retrieved

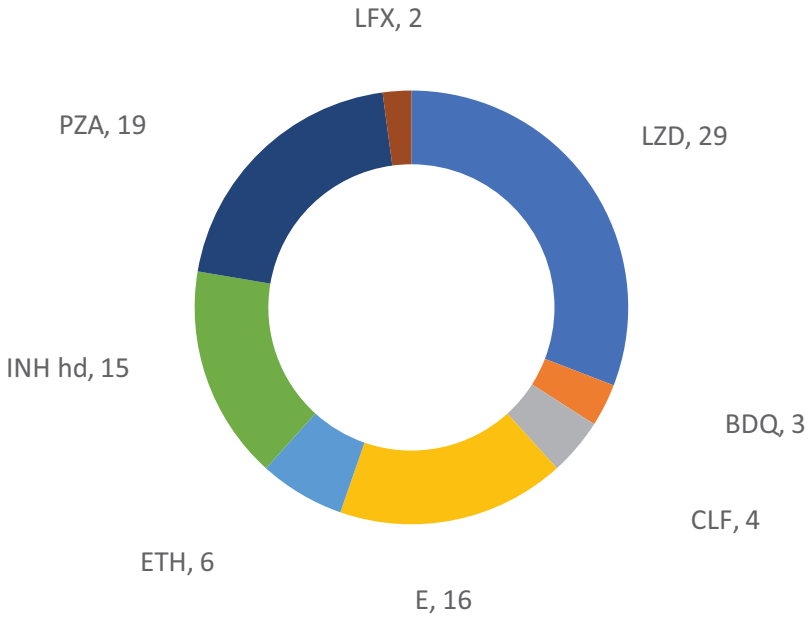

Figure 5. Graphic illustration of episodes of treatment interruption (N = 94) per individual drug (drug name; n) following an AE in patients during the first 24 weeks of the short standardized BDQ-based regimen in King Cetshwayo district, South Africa, 1 July 2018 to 30 April 2019. Abbreviations: AE, adverse event; BDQ, bedaquiline; CLF, clofazimine; E, ethambutol; ETH, ethionamide; INH hd, high dose isoniazid; LFX, levofloxacin; LZD, linezolid; PZA, pyrazinamide.

online to minimize incompleteness. Retrieving information on AEs a posteriori made it difficult to conduct any causality assessment. We assessed end-of-treatment outcomes with no further follow-up of our cohort and have no data on recurrence rates of this regimen; final outcomes could differ. Fourteen patients had a positive culture, mostly late in treatment, and could be at higher risk for relapse. Long-term follow-up of RR-TB patients completing treatment is necessary to evaluate relapse risk and long-term effectiveness of the shorter regimen.

CONCLUSION

An all-oral shorter regimen, containing BDQ and LZD, shows excellent outcomes in a high HIV prevalent population and used under rural programmatic conditions. The most common AEs were related to LZD, and specific screening and management strategies are needed to identify bone marrow toxicity, especially after the first month of treatment, associated with this medication. In spite of the effectiveness of this regimen, mortality remained high and there is additional support needed to reduce LTFU as well.

South Africa has shown a way for rapid implementation of new regimens under programmatic conditions, using WHO group A drugs to combat their RR-TB epidemic. Given the effectiveness and the feasibility of this regimen, the country can hopefully serve as a model for others to improve RR-TB care for patients worldwide.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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