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MAJOR ARTICLE

Characteristics, Treatment Strategies, and Long-term Health Outcomes of People With Bedaquiline-resistant Tuberculosis in Karakalpakstan, Uzbekistan—A Retrospective Cohort Study

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Background. Bedaquiline resistance is increasing globally, threatening effectiveness of short regimens for rifampicin/multidrug-resistant (RR/MDR)-tuberculosis. Limited data exist describing the treatment and long-term outcomes of people with bedaquiline-resistant tuberculosis.

Methods. We did a retrospective cohort study of patients with bedaquiline-resistant tuberculosis in Karakalpakstan, Uzbekistan, from January 2017 until June 2025. Clinical and laboratory records were reviewed to describe treatment regimens, drug sensitivity profiles, and sputum results. We measured time to sustained sputum culture conversion (SCC), mortality, and the proportion of patients who had tuberculosis-free survival (alive, and had completed treatment or were in care, and had SCC) 18 months after bedaquiline resistance was detected.

Results. Among 50 patients with bedaquiline-resistant tuberculosis who received treatment, the median age was 41 years (IQR: 27–52), 64% (32/50) were male, 69% (34/49) had fluoroquinolone resistance, and 32% (16/50) had not previously received bedaquiline. The median treatment duration was 18.8 months (IQR: 9.0–22.4), with bedaquiline prescribed for 84% for a median 5.6 months (IQR: 2.2–12.9), imipenem for 66% for a median 8.1 months (IQR: 4.5–11.3), and amikacin for 50% for a median 7.9 months (IQR: 4.4–11.1). The median time to SCC was 5.9 months (IQR: 2.1–15.9) and the probabilities of survival to 18 months and 5 years were 79.7% (95% CI: 69.2–91.8) and 63.4% (95% CI: 48.8–82.4). Of 48 patients who had an assessable 18-month outcome, 60.4% (29/48) had tuberculosis-free survival.

Conclusions. Management of bedaquiline-resistant tuberculosis in Uzbekistan required prolonged antituberculosis therapy, often with injectables, resulting in delayed culture conversion and poor long-term health outcomes.

Keywords. Tuberculosis; bedaquiline; RR-TB; MDR-TB; XDR-TB; treatment outcomes.

Tuberculosis is the world's leading cause of death from a single infection, killing 1.25 million people in 2023 [1]. Drug resistance is a particularly enduring challenge for both people with tuberculosis and their health systems [2]. Identifying resistance appropriately requires timely access to diagnostics, many of which need complex laboratory infrastructure, and treatment strategies have historically involved long, toxic, and expensive combinations of drugs, including injectable agents [3]. Together with the many psychosocial and economic challenges faced by people with tuberculosis, which are amplified in people with drug-resistant tuberculosis, this results in worse outcomes and increased community transmission of resistant strains [4, 5]. In 2023, approximately 400 000 people were estimated to have tuberculosis resistant to the first-line antibiotic rifampicin, with or without resistance to isoniazid—rifampicin/multidrug-resistant (RR/MDR)-tuberculosis [1]. Less than half of these were diagnosed and enrolled on treatment, and in 2021, the last year with global data available, only 68% of people with RR/MDR-tuberculosis were successfully treated [1].

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Nevertheless, there has been much optimism in recent years because of the introduction of all-oral regimens for RR/MDR-tuberculosis based on the diarylquinoline drug bedaquiline [6]. Bedaquiline works through a novel mechanism, inhibiting mycobacterial ATP synthesis, which made it the first new tuberculosis drug with a unique target in over 40 years [7]. Based on high-quality clinical trial evidence showing substantial improvements in outcomes (>90% treatment success) [8, 9], World Health Organization (WHO) recommended 6-month bedaquiline-linezolid-pretomanid (BPaL)-based regimens for most people diagnosed with RR/MDR-tuberculosis in 2022 [10]. These regimens were being used in nearly 60 countries in 2023, and 100 countries were using a bedaquiline-containing 9-month regimen [1].

Alarmingly, expanded bedaquiline use has been associated with rapid emergence of resistance because of both selection of resistant mutations during prolonged drug elimination, and subsequent community transmission of resistant strains [11–13]. A recent meta-analysis estimated a baseline prevalence of bedaquiline resistance among people with RR/MDR-tuberculosis of 2.4%, and a prevalence of resistance emerging during treatment of 2.1% [14]. Programmatic data has revealed higher levels of emerging resistance and, concerningly, in Mozambique, prevalence of genotypic bedaquiline resistance in isolates resistant to isoniazid or rifampicin increased from 3% in 2016% to 14% in 2021 [11, 15].

Treatment options for bedaquiline-resistant tuberculosis are scarce and involve complex, individualized regimens constructed from remaining drugs in WHO Groups A (fluoroquinolones, bedaquiline, linezolid), B (clofazimine, cycloserine/terizidone), and C (multiple drugs, including injectable agents, with unclear efficacy), ideally guided by extended drug sensitivity testing [16]. Evidence to guide clinical management is extremely limited, but a recent study of 82 people with bedaquiline-resistant tuberculosis in South Africa, a high HIV-prevalence setting, described the complexity of treatment regimens used and found strikingly poor microbiological and clinical outcomes compared to people with bedaquiline-sensitive tuberculosis [17]. The median time to sputum culture conversion (SCC) was approximately 6 months, only around half of the cohort were alive and had a negative sputum culture 18 months after detection of bedaquiline resistance, and nearly all the survivors were still on treatment.

In Uzbekistan, a low HIV-prevalence setting with historically high rates of drug resistance, we previously estimated a prevalence of bedaquiline resistance of 6.2% in people with RR/MDR-tuberculosis between 2019 and 2023 [18]; and described baseline characteristics and interim outcomes among people with both primary and acquired bedaquiline-resistant tuberculosis [19, 20]. In this study, we aimed to build on this previous work and comprehensively describe the characteristics, treatment strategies, and long-term health outcomes of a larger cohort of people with bedaquiline-resistant tuberculosis.

METHODS

Study Design and Population

We did a retrospective cohort study of people with bedaquiline-resistant tuberculosis in Karakalpakstan, Uzbekistan. Uzbekistan is a lower middle-income country in Central Asia with a high burden of RR/MDR-tuberculosis—30% of previously treated cases and 16% of new cases were estimated to have RR/MDR-tuberculosis in 2023 [1]. Karakalpakstan is an autonomous republic in northwestern Uzbekistan, and Médecins Sans Frontières (MSF) has worked with the Uzbekistan and Karakalpakstan Ministries of Health (MoH) since 1998 to strengthen tuberculosis prevention and care. This has included supporting a centralized regional laboratory in Nukus [18], the TB-PRACTECAL clinical trial of BPaL-based regimens for RR/MDR-tuberculosis [8, 9], the subsequent programmatic implementation of these regimens as standard of care [21], and the management of people with RR/MDR-tuberculosis who have extensive drug resistance [22]. Phenotypic drug sensitivity testing (pDST) for bedaquiline was introduced in Karakalpakstan in September 2019 and initially performed on samples from people with RR/MDR-tuberculosis who had failed to culture convert, and retrospectively on some baseline previous samples from these individuals stored since 2017. In January 2020, pDST for bedaquiline was incorporated into routine testing algorithms for all people with RR/MDR-tuberculosis.

In this cohort study we included people of any age who had sputum culture-positive pulmonary tuberculosis with a *Mycobacterium tuberculosis* isolate resistant to bedaquiline on pDST between 1 January 2017 and 31 December 2024. People who had evidence of bedaquiline resistance but received no treatment after the sample was taken were excluded.

Procedures

All people included in the cohort were treated within the MoH Karakalpakstan tuberculosis program, collaboratively with MSF physicians and nurses. Treatment was directly observed, either in-person with a healthcare provider or through video, and adherence was supported through a comprehensive package of psychosocial and economic support including food parcels and/or reimbursement for clinic visits. Hospitalization was at the discretion of treating clinicians based on microbiological and clinical criteria. Sputum was collected monthly during treatment episodes.

We reviewed routine clinical and laboratory records to identify people for inclusion in the cohort and extracted data on demographics, tuberculosis treatment history before detection of bedaquiline resistance, comorbidities, treatment regimen (including changes during treatment), drug sensitivity profiles, and sputum smear and culture results. We extracted data for all treatment episodes recorded for each person until June

2025 to capture the full timeline of their illness. In addition, for people who were not on treatment or in care at the end of the study (either because they had completed treatment successfully or because they were lost to follow-up on treatment), we conducted telephonic follow-up to ascertain vital status and whether they had received further tuberculosis treatment, including outside of Karakalpakstan.

Laboratory Tests

Sputum samples were processed at the regional laboratory in Nukus for routine testing, including with smear microscopy and Xpert MTB/RIF Ultra, Xpert MTB/XDR (Cepheid, Sunnyvale, CA, USA) or GenoType MTBDR*plus* (Hain Lifescience, Nehren, Germany) initially. Culture was performed using the BD BACTEC Mycobacterial Growth Indicator Tube (MGIT) SIRE kit with the 960 system (Becton Dickinson, Frankline Lakes, NJ, USA), with pDST for rifampicin, isoniazid, pyrazinamide, and ethambutol done at critical concentrations of 0.5, 1.0, 100, and 5.0 mg/L respectively. Phenotypic drug sensitivity testing for bedaquiline was done using the proportion method on the MGIT with a critical concentration of 1.0 mg/L; [23] and was repeated for all samples with resistance before results were released from the laboratory. Phenotypic drug sensitivity testing was performed for other second-line drugs using the Sigma Aldrich (St Louis, MI, USA) system, with a critical concentration of 1.0 mg/L used for clofazimine, linezolid, and amikacin; and both 0.25 and 1.0 mg/L for moxifloxacin (with 0.25 mg/L used to define resistance). Between January 2019 and May 2022, a technical error in the laboratory meant that the pDST for clofazimine was performed at a critical concentration of 2.5 mg/L, and so any results occurring during this period were not considered as definitive and are not reported here. Internal quality control is performed for each specimen batch using the H37Rv-susceptible strain as a positive control and sterile phosphate buffer as a negative control. Annual external quality assessment is provided by the WHO Supranational Reference Laboratory of Tuberculosis, Gauting, Germany. Due to variations in procedures and guidelines during the study period, not all people in the cohort received all tests [18].

In addition, in 2024, MSF implemented targeted next generation sequencing (tNGS) using the Illumina and GenoScreen Deeplex Myc-TB Combo Kit (Illumina, San Diego, CA, USA) in the regional laboratory in Nukus. Where sputum samples from people with bedaquiline-resistant tuberculosis had been stored, we retrospectively sequenced their *M. tuberculosis* isolates.

Outcomes

We considered 3 outcomes, all defined relative to the date of collection of the first sputum sample showing bedaquiline resistance (referred to as the index sputum hereon)—sustained SCC, survival, and tuberculosis-free survival. SCC was defined as the date of the first of 2 consecutive sputum samples with negative culture results, without any single subsequent positive culture result indicating reversion. Tuberculosis-free survival was a composite of being alive, SCC, and either having completed treatment successfully or being in care.

Statistical Analysis

All analyses were performed using RStudio version 2025.05.0 +496 (Lucent Technologies, Jasmine Mountain, USA). Baseline demographic and clinical characteristics were summarized using descriptive statistics. An individual timeline for each person was constructed to visualize their treatment history (specifically whether they received a bedaquiline-containing regimen or not) and their culture status from the date of the index sputum. Periods of culture positivity/negativity were determined from the date each sample was collected until the date a subsequent sample showing a different result was collected. We tabulated and described pDST and tNGS results, including the mutations detected for bedaquiline with reference to the WHO 2023 mutation catalogue [24].

To describe the antituberculosis regimens used in more detail, we calculated the duration of treatment with each antituberculosis drug per person and visualized the median and interquartile range (IQR) for the 10 mostly frequently prescribed drugs in a boxplot. Then, for each day from the date of the index sputum, we calculated the median and IQR for the number of antituberculosis drugs each person was prescribed (if they were on treatment); and created a visualization showing the proportion of people who were on treatment receiving different antituberculosis drugs.

Finally, we used a Kaplan–Meier estimator to plot survival curves for SCC and mortality. For the SCC analysis, people were censored at the end of their last treatment episode if they did not have sustained culture conversion by that time, and the graph was truncated at 18 months. For the overall survival analysis, people were censored at their last known follow-up date if they were still alive, and the graph was truncated at 5 years. We calculated the median time to SCC, and the survival probabilities with 95% CI at 18 months and 5 years. The proportion of people achieving tuberculosis-free survival was measured 18 months after the index sputum.

Ethics

This study met MSF's Independent Ethical Review Board exemption criteria as a retrospective review of routinely collected data following Uzbekistan's National Tuberculosis Program guidelines.

RESULTS

We identified 56 people with bedaquiline-resistant tuberculosis. 89% (50/56) received treatment after resistance detection

Table 1. Baseline Characteristics of People With Bedaquiline-resistant Tuberculosis (n = 50)

Characteristic		People With Bedaquiline-Resistant Tuberculosis
Demographics and determinants		
Age in years (median; IQR)		41 (27–52)
Sex, self-reported	Female	36% (18/50)
	Male	64% (32/50)
Occupation	Employed	6.0% (3/50)
	Unemployed	52% (26/50)
	Retired	14% (7/50)
	Student	2.0% (1/50)
	Unable to work because of disability	26% (13/50)
Number of people living in the same household (median; IQR)		4 (3–6)
Ever been incarcerated		6.0% (3/50)
Injecting drug user		0.0% (0/50)
Homeless		0.0% (0/50)
Health worker		2.0% (1/50)
Prison worker		0.0% (0/50)
History of travel out of Karakalpakstan		22% (11/50)
Reported tobacco use		10% (5/50)
Reported alcohol use	None	92% (46/50)
	Moderate	8.0% (4/50)
Body mass index (median; IQR)		17.9 (15.6–20.8)
Weight category	Severe underweight (BMI < 16.0)	26% (13/50)
	Moderate underweight (BMI = 16.0–16.9)	12% (6/50)
	Mild underweight (BMI = 17.0–18.4)	20% (10/50)
	Normal weight (BMI = 18.5–24.9)	32% (16/50)
	Overweight/obese (BMI ≥ 25.0)	10% (5/50)
Tuberculosis history		
Received tuberculosis treatment prior to current treatment episode		80% (40/50)
Bedaquiline treatment	Resistance emerged during treatment with bedaquiline	56% (23/50)
	Previously received bedaquiline[a]	12% (6/50)
	Never received bedaquiline	32% (16/50)
Previously received clofazamine[a]		62% (31/50)
Current tuberculosis episode		
Cavities on chest radiography at diagnosis		78% (39/50)
Index sputum smear result	Negative	50% (25/50)
	Scanty	8.0% (4/50)
	+	24% (12/50)
	++	10% (5/50)
	+++	8.0% (4/50)
Known comorbidities	HIV	0.0% (0/50)
	Diabetes	16% (8/50)
	Cardiological diagnosis	8.0% (4/50)
	Renal diagnosis	6.0% (3/50)
	Psychiatric diagnosis	2.0% (1/50)
	Epilepsy	0.0% (0/50)
	Hepatitis	14% (7/50)
	Anemia	32% (16/50)

Abbreviation: IQR, interquartile range.

[a]For at least 1 mo.

and were included in our cohort. Of the 11% (6/56) who did not, 67% (4/6) were known to have subsequently died.

Among those included, the median age was 41 years (IQR: 27–52), 64% (32/50) were male, 58% (29/50) were underweight (body mass index <18.5 kg/m^2), and none had HIV (Table 1). Forty-four percent (22/50) had a previous sensitive pDST result for bedaquiline, and resistance to bedaquiline emerged during treatment with it for 56% (28/50) after a median treatment duration of 7.0 months (IQR: 4.4–14.0). 32% (16/50) had not previously been treated with bedaquiline prior to the index sputum and 20% (10/50) of the cohort had never received tuberculosis treatment prior to their current treatment episode. Individual

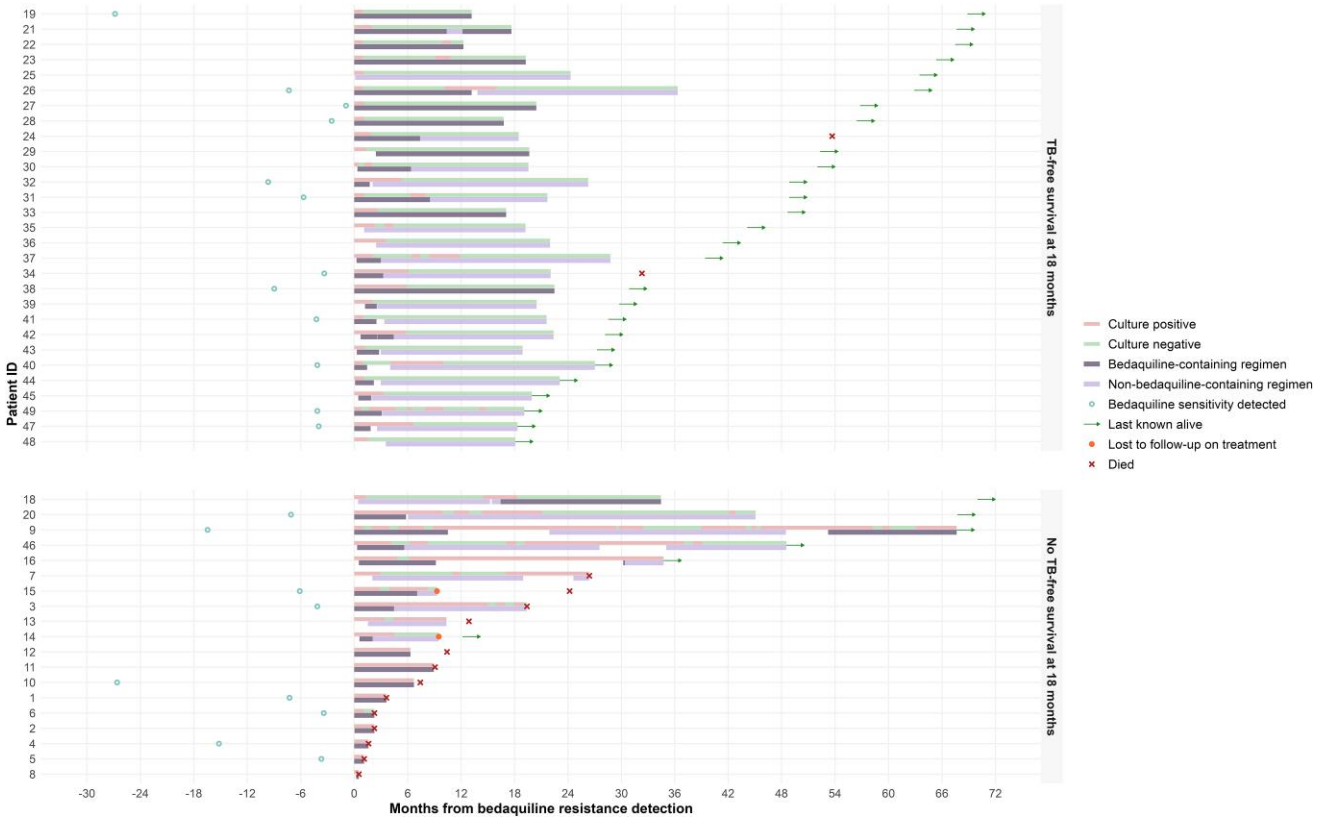

Figure 1. Individual timeline for people with bedaquiline-resistant tuberculosis (TB) stratified by TB-free survival (n = 48). Two patients excluded from this figure as they had not had sufficient follow-up to ascertain TB-free survival at 18 mo.

timelines for each person included in the cohort, stratified by tuberculosis-free survival at 18 months, are shown in Figure 1.

Drug sensitivity profiles are shown in Table 2. On pDST, 69% (34/49) of people had concurrent resistance to a fluoroquinolone and thus had extensively drug-resistant tuberculosis. Thirteen percent (6/47) had resistance to amikacin, and 8% (4/50) had resistance to linezolid. tNGS results were available for 54% of the cohort (27/50). 7.4% (2/27) were reported as resistant to bedaquiline, 11% (3/27) were reported as sensitive, and 81% (22/27) had indeterminate results because of uncharacterized mutations, mutations of uncertain clinical significance, or because mutations were not documented in the 2023 WHO mutation catalogue [24]. The mutations associated with tNGS results for bedaquiline are shown for individual participants in Table 3, demonstrating the diversity and largely uncharacterized nature of bedaquiline resistance in this population. In total, there were 40 mutations detected in 24 people. The most common mutation was a frameshift mutation at genomic position 779130, resulting in an insC codon change in 15% of mutations (6/40). One patient (ID = 50) had a mutation at genomic position 779086 which was associated with bedaquiline resistance but not clofazimine resistance.

The median treatment duration after bedaquiline resistance detection was 18.8 months (IQR: 9.0–22.4), including all treatment episodes and interruptions between episodes. The median active treatment duration (excluding interruptions) was 18.4 months (IQR: 9.0–21.7). After resistance detection, bedaquiline was prescribed for 84% (42/50) of people for a median 5.6 months (IQR: 2.2–12.9); imipenem for 66% (33/50) for a median 8.1 months (IQR: 4.5–11.3), amikacin for 50% (25/50) for a median 7.9 months (IQR: 4.4–11.1), and linezolid for 96% (48/50) for a median 17.1 months (IQR: 8.2–20.4) (Figure 2). Treatment regimens were complex and heterogeneous (Figure 3), with the median number of antituberculosis drugs prescribed per person on any given treatment day being 5 (IQR: 4–5).

The median time to sustained SCC was 5.9 months (IQR: 2.1–15.9) (Figure 4*A*), and the probabilities of survival to 18 months and 5 years were 79.7% (95% CI: 69.2–91.8) and 63.4% (95% CI: 48.8–82.4) respectively (Figure 4*B*). Tuberculosis-free survival at 18 months was 60.4% (29/48) for those who had sufficient follow-up to assess it. 20.8% (10/48) had died, 4.2% (2/48) were lost to follow-up from treatment and not in care, and 14.6% (7/48) were receiving treatment or in care but without SCC. Tuberculosis-free survival at 18 months was lower among those whose treatment started before

Table 2. Drug Sensitivity Profiles for People With Bedaquiline-Resistant Tuberculosis (n = 50)

		Culture-based Phenotypic Drug Sensitivity Testing	Targeted Next Generation Sequencing
First-line drugs, all from testing undertaken on the index sputum or a previous sputum sample			
Rifampicin	Resistant	91% (32/35)	96% (26/27)
	Sensitive	8.6% (3/35)	4.0% (1/27)
	Indeterminate	NA	0% (0/25)
Isoniazid	Resistant	100% (35/35)	100% (27/27)
	Sensitive	0% (0/35)	0% (0/25)
	Indeterminate	NA	0% (0/25)
Ethambutol	Resistant	83% (29/35)	85% (23/27)
	Sensitive	17% (6/35)	15% (4/27)
	Indeterminate	NA	0% (0/25)
Pyrazinamide	Resistant	76% (31/41)	70% (19/27)
	Sensitive	24% (10/41)	22% (6/27)
	Indeterminate	NA	7.4% (2/27)
Second line drugs, all from testing undertaken on the index sputum			
Bedaquiline	Resistant	100% (50/50)	7.4% (2/27)
	Sensitive	0% (0/50)	11% (3/27)
	Indeterminate	NA	81% (22/27)
Clofazamine[a]	Resistant	73% (11/15)	3.7% (1/27)
	Sensitive	27% (4/15)	11% (3/27)
	Indeterminate	NA	85% (23/27)
Linezolid	Resistant	8.0% (4/50)	3.7% (1/27)
	Sensitive	92% (46/50)	89% (24/27)
	Indeterminate	NA	7.4% (2/27)
Amikacin	Resistant	13% (6/47)	7.4% (2/27)
	Sensitive	83% (41/47)	19% (5/27)
	Indeterminate	NA	74% (20/27)
Fluoroquinolone	Resistant	69% (34/49)	67% (18/27)
	Sensitive	31% (15/49)	30% (8/27)
	Indeterminate	NA	3.7% (1/27)
Ethionamide	Resistant	0% (0/50)	30% (8/27)
	Sensitive	0% (0/50)	26% (7/27)
	Indeterminate	NA	44% (12/27)

[a]A technical error in the laboratory between January 2019 and May 2022 meant that clofazimine phenotypic drug sensitivity testing was not reportable.

2020, when bedaquiline resistance testing was performed only after failure to culture convert, than among those starting from 2020 onwards, when testing was routine (42.9% [6/14] vs 67.7% [23/34]); with deaths higher in the pre-2020 cohort (28.6% [4/14] vs 17.6% [6/34]).

Of the 36 people who had survived to 18 months and had not been lost to follow-up, 86% (31/36) were still on treatment or in care at 18 months. The median treatment duration with bedaquiline after resistance was 6.0 months (IQR: 2.5–15.9) for people who had tuberculosis-free survival, and 5.3 months (IQR: 2.2–7.1) for people who did not.

DISCUSSION

In this retrospective cohort study describing the characteristics, treatment strategies, and long-term health outcomes of people with bedaquiline-resistant tuberculosis in Uzbekistan, our findings demonstrate the severe clinical and public health consequences of this emerging form of drug resistance. First, while resistance emerged during treatment with bedaquiline for most of the cohort, a third had never received the drug previously, and a fifth had never been treated for tuberculosis, indicating the growing importance of primary resistance acquired through transmission [4]. Second, treatment required prolonged antituberculosis therapy with a median of 5 drugs, and often included injectable agents used in the prebedaquiline era. These drugs are associated with greater toxicity and administration costs, placing an enormous burden on both people with tuberculosis and their health systems [2]. Finally, around half of our cohort was still culture positive at 6 months, driving community transmission [25]; less than two-thirds were alive and free of tuberculosis at 18 months, with most survivors still on treatment; and only around two-thirds were estimated to be alive after 5 years.

Our results are strikingly similar to the recent South African study where most participants had HIV [17], suggesting that bedaquiline resistance is the dominant factor driving poor microbiological and clinical outcomes, regardless of HIV status. Furthermore, they are particularly concerning when compared to outcomes among people with bedaquiline-sensitive tuberculosis receiving BPaL-based regimens in our setting. Under programmatic conditions in the same health system during a similar period, the median time to culture conversion among these people was 27 days (IQR: 26–31), 94% had treatment success with a low risk of relapse, and 1.6% died [21]. These contrasting outcomes highlight 2 key priorities for the global tuberculosis community—an urgent need for a rapid, sensitive DST for bedaquiline and other second-line drugs; and the development of new antituberculosis drugs and treatment strategies for people with bedaquiline-resistant tuberculosis.

In our cohort, pDST results were used to guide treatment decisions. Because these often take at least 2 to 3 months to be processed, reported, and actioned by clinicians, most people in our cohort continued to receive bedaquiline either because of a previous sensitive result, or empirically while pDST was awaited. Although we do not have data on exactly when clinicians received bedaquiline pDST results, the delay was probably longer in our setting because we repeated pDST before releasing results. Interestingly, many people continued to receive bedaquiline for extended periods after resistance, and in some cases were successfully treated with prolonged continuation of bedaquiline-containing regimens. It is possible that bedaquiline might continue to have an antituberculosis effect against *M. tuberculosis* isolates with moderate minimum-inhibitory-concentration elevations. Further research is required in this area, including to understand the clinical efficacy of continuing bedaquiline in the face of phenotypic resistance at different MICs [26, 27]. While this approach deviates from WHO recommendations to

Table 3. Targeted Next-generation Sequencing Mutation Results for People With Bedaquiline-Resistant Tuberculosis (n = 27)

Patient ID	Validated Result	Gene	Genomic Position	Codon Change	Amino Acid Change	% Variant	Confidence From Deeplex Report	Time To Culture Conversion (months)	Duration of Bedaquiline Prescription After Resistance (months)	Tuberculosis-Free Survival At 18 mo
8	Indeterminate	rv0678	779130	insC	Frameshift	92.43	n/a	Not achieved	0.3	No
41	Indeterminate	rv0678	Gene deletion	…	…	…	Associated with Resistance	1.0	2.5	Yes
44	Indeterminate	rv0678	779358	insGC	Frameshift	90.32	n/a	1.0	2.1	Yes
6	Indeterminate	rv0678	779339	ctg117cgg	L117R	99.27	Uncertain Significance	Not achieved	2.3	No
17	Indeterminate	rv0678	779114	tgg42tag	W42	99.95	n/a	1.1	Not received	Not assessable
29	Indeterminate	rv0678	779111	ggc41gtc	G41V	99.87	Uncharacterized	1.4	17.2	Yes
48	Indeterminate	rv0678	779264	tat92tct	Y92S	99.78	Uncharacterized	1.5	Not received	Yes
45	Indeterminate	rv0678	779130	insC	Frameshift	92.89	n/a	3.3	1.4	Yes
36	Indeterminate	rv0678	778996–9005	del10bp	Frameshift	96.88	n/a	3.6	Not received	Yes
14	Indeterminate	rv0678	779182	delG	Frameshift	25.13	n/a	4.5	1.5	No
			779130	insC	Frameshift	36.42	n/a			
			779181	insG	Frameshift	6.93	n/a			
38	Indeterminate	rv0678	779182	delG	Frameshift	87.47	n/a	5.9	22.5	Yes
47	Indeterminate	rv0678	779129	insTC	Frameshift	7.94	n/a	6.7	1.8	Yes
			779130	insC	Frameshift	59.06	n/a			
			779181	insG	Frameshift	2.93	n/a			
			779314	insGG	Frameshift	6.5	n/a			
			779215	caa76aaa	Q76K	8.74	Uncharacterized			
40	Indeterminate	rv0678	779005	delG	Frameshift	6.25	n/a	10.0	1.4	Yes
			779052	gaa21gat	E21D	7.69	Uncharacterized			
			779197	aat70gat	N70D	6.53	Uncertain Significance			
			779296	ggc103agc	G103S	69.35	Uncertain Significance			
37	Indeterminate	rv0678	779125	insG	Frameshift	6.75	n/a	11.8	2.7	Yes
			779130	insC	Frameshift	80.88	n/a			
49	Indeterminate	rv0678	779182	delG	Frameshift	74.35	n/a	14.7	3.1	Yes
		rv0678	779120	ctg44cgg	L44R	3.06	Uncharacterized			
18	Indeterminate	rv0678	779111	ggc41gtc	G41V	99.81	Uncharacterized	18.3	18	No
46	Indeterminate	rv0678	779029	delC	Frameshift	21.18	n/a	39.1	5.3	No
			779129	insTC	Frameshift	30.14	n/a			
			779263	insA	Frameshift	6.2	n/a			
2	Indeterminate	rv0678	779349	delG	Frameshift	6.89	n/a	Not achieved	2.2	No
			779127	insG	Frameshift	11.57	n/a			
			779130	insC	Frameshift	59.78	n/a			
7	Indeterminate	rv0678	779454	insC	Frameshift	97.23	n/a	Not achieved	Not received	No
13	Indeterminate	rv0678	779181	insG	Frameshift	47.75	n/a	Not achieved	Not received	No
15	Indeterminate	rv0678	779450	ctg154ccg	L154P	100	Uncharacterized	Not achieved	7.1	No
16	Indeterminate	rv0678	779252	gat88ggt	D88G	5.97	n/a	Not achieved	8.8	No

Table 3. Continued

Patient ID	Validated Result	Gene	Genomic Position	Codon Change	Amino Acid Change	% Variant	Confidence From Deeplex Report	Time To Culture Conversion (months)	Duration of Bedaquiline Prescription After Resistance (months)	Tuberculosis-Free Survival At 18 mo
			779282	aac98agc	N98S	7.08	n/a			
50	Resistant	rv0678	779086	act33gct	T33A	100	Minimal	5.6	Not received	Not assessable
42	Resistant	rv0678	779454	insC	Frameshift	98.17	Associated with resistance … Interim	5.8	3.7	Yes
43	Sensitive	…	…	…	…	…	…	1.2	2.5	Yes
35	Sensitive	…	…	…	…	…	…	4.4	Not received	Yes
3	Sensitive	…	…	…	…	…	…	Not achieved	4.5	No

Abbreviation: n/a = Not applicable.

discontinue bedaquiline after resistance detection, the continued use in our cohort likely reflects multiple factors: clinical stability or improvement on bedaquiline-containing regimens (around a quarter of our cohort had culture conversion within 2 months on these regimens); limited alternative options given extensive baseline resistance to other drugs (most of our cohort were resistant to fluoroquinolones and clofazimine); and reduced clinician awareness of results (although we anticipate this to be uncommon in our setting because of the close integration of the regional laboratory with the settings where care is provided).

Relatedly, our tNGS results have important implications. 12% of people with bedaquiline-resistant tuberculosis on pDST were reported sensitive on tNGS, and 81% had indeterminate tNGS results due to uncertain or uncharacterized mutations. This finding broadly aligns with a recent systematic review, which found that only between 49–69% of phenotypic bedaquiline resistance could be detected by even the most sensitive current genomic approaches [28]. If tNGS is implemented without culture-based pDST, as has been suggested in some research because of its high sensitivity and specificity for first-line drugs and fluoroquinolones, this would leave clinicians without reliable bedaquiline susceptibility results to inform treatment decisions, complicating regimen selection and monitoring, with associated risks of resistance amplification and transmission [29–31]. Research to better understand the genetics of bedaquiline resistance is urgently needed, including to investigate the associations between specific resistant variants, MICs, and outcomes. Meanwhile, investment in phenotypic methods such as microscopic observation of drug susceptibility assays for bedaquiline and other second-line drugs, which provide results in days rather than months, is critical to ensuring all people with RR/MDR-tuberculosis have access to a rapid, sensitive DST [32]. Such tests might have particular value for reducing pretreatment loss to follow-up, which may be an underestimated problem in tuberculosis care and prevention [33]—6 people with bedaquiline-resistant tuberculosis in our setting did not receive any treatment following sputum collection, 4 of whom were known to have subsequently died.

The treatment regimens used in our cohort highlight the possibility of a stark reversal in progress toward simpler, less toxic antituberculosis therapy. While BPaL-based regimens have enabled 6-month, all-oral treatment for bedaquiline-sensitive RR/MDR-tuberculosis, our patients required a median of 5 drugs per day for over 18 months, with considerable heterogeneity in regimen composition. Compared to the South African cohort, injectable agents were used much more frequently, possibly because of more established healthcare infrastructure and extensive experience using these drugs given the historically high rates of drug resistance in our setting [17]. 50% of our cohort received amikacin (compared to none in the South African cohort), often for prolonged periods, in a return to the prebedaquiline era of painful daily injections and

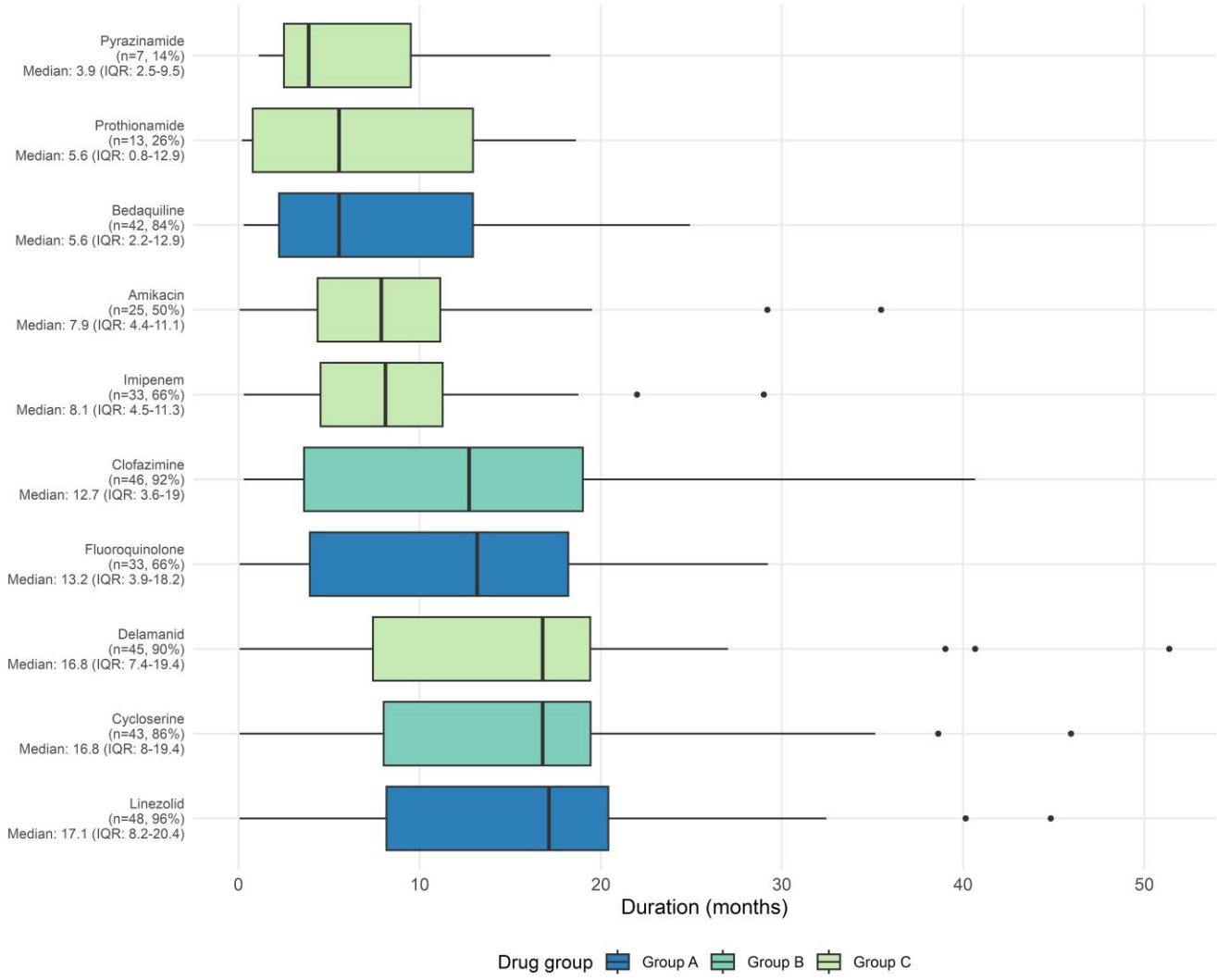

Figure 2. Antituberculosis drug boxplot for people with bedaquiline-resistant tuberculosis (n = 50).

ototoxicity risk. Injectable carbapenems are a potentially more effective drug and were used in 66% of our cohort (compared to 39% in the South African cohort). Whilst carbapenem use in people with extensively drug-resistant tuberculosis has been associated with improved outcomes, these drugs are logistically challenging given they require intravenous administration multiple times daily [34].

Indeed, the complexity of these regimens places enormous strain on both people with bedaquiline-resistant tuberculosis and their health systems: people with bedaquiline-resistant tuberculosis must endure prolonged hospitalization, multiple daily medications with overlapping toxicities, and high pill burdens; while health systems must maintain drug supplies, monitor for adverse events, and provide extensive adherence support. This situation underscores the urgent need for access to novel antituberculosis drugs for this population that are both effective and tolerable. People with bedaquiline-resistant tuberculosis experience disproportionate morbidity and mortality yet have the fewest treatment options available to them. As bedaquiline resistance increases globally, clinical trials into effective treatment strategies, including optimal use of new and pipeline compounds, are essential. While these are awaited, as for bedaquiline in the first years following approval, expanded access and compassionate use programs should be implemented to provide access to promising agents [35, 36]. Without such initiatives, people with bedaquiline-resistant tuberculosis will continue to rely on inadequate regimens with poor outcomes, driving transmission.

Strengths of our study include the long follow-up (over 5 years for some participants), our ability to describe multiple treatment episodes with detailed changes in treatment regimens and culture status, and our use of both genotypic and phenotypic DST. Our study also had limitations. The single-center, retrospective design may limit generalizability and

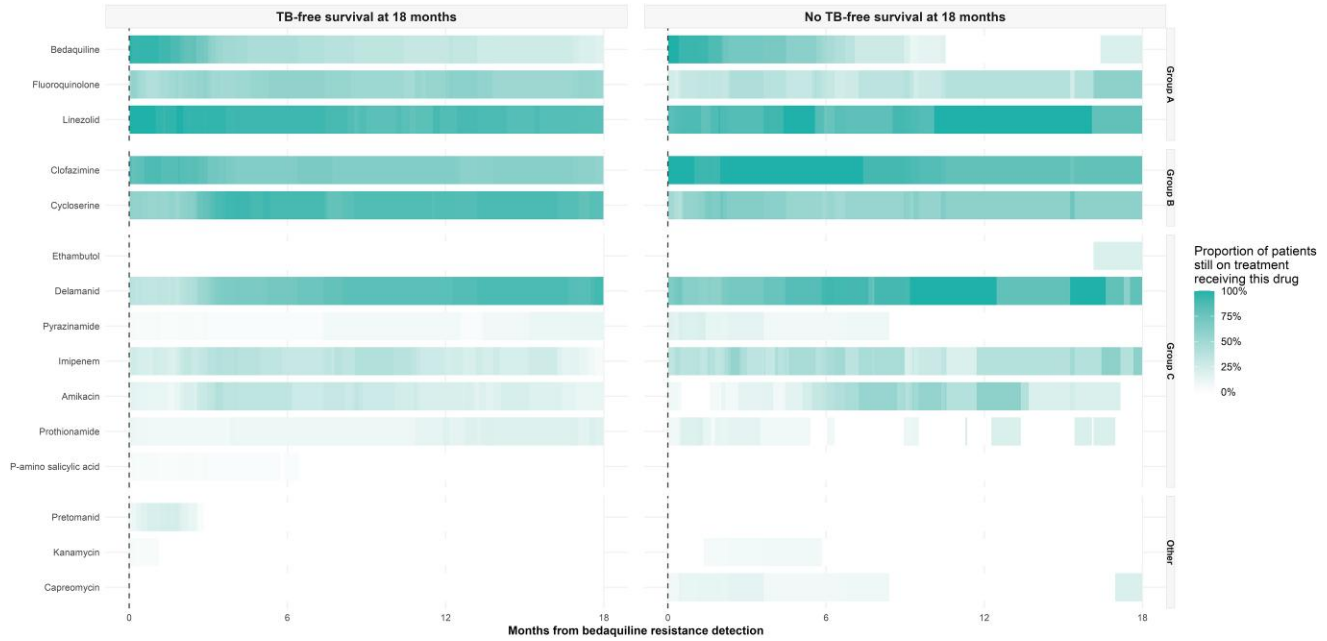

Figure 3. Antituberculosis drug heatmap for people with bedaquiline-resistant tuberculosis (TB), stratified by TB-free survival (n = 48). Two patients excluded from this figure as they had not had sufficient follow-up to ascertain TB-free survival at 18 mo.

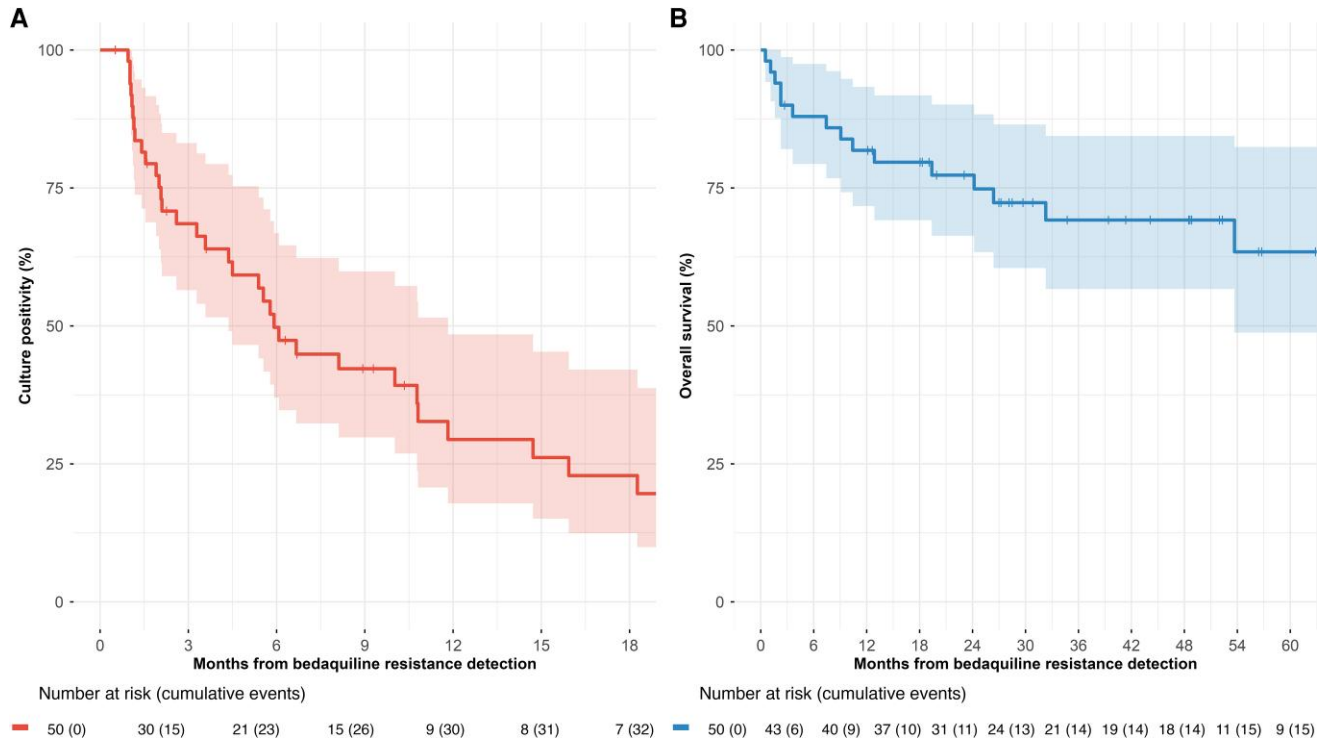

Figure 4. *A.* Kaplan–Meier curve for sustained sputum culture conversion through 18 mo among people with bedaquiline-resistant tuberculosis (n = 50). *B.* Kaplan–Meier curve for survival through 60 mo (5 years) among people with bedaquiline-resistant tuberculosis (n = 50).

restricted our ability to capture clinical decision-making rationale, adverse events, and the timing of when pDST results reached clinicians. Furthermore, the sample size did not permit investigation of determinants of poor outcomes, including detailed chest radiography results, and further research is needed in this area to identify higher-risk people with tuberculosis who can be targeted for interventions and adherence support. Selection bias may have influenced our findings, as pDST was initially performed selectively on patients who failed to culture convert before becoming routine in 2020, potentially enriching for worse outcomes early in the study. In addition, people had to receive treatment after resistance detection to be included; of the 11% (6/56) excluded, 4 died and 2 were lost to follow-up, so our reported outcomes are likely more favorable than those of all people with bedaquiline-resistant tuberculosis. We were unable to ascertain causes of death, limiting our understanding of tuberculosis-attributable versus other-cause mortality, although most deaths occurred during treatment when people were culture positive. Finally, our ability to ascertain tuberculosis recurrence was limited to treatment registers and telephonic follow-up, without universal microbiological testing at the end of the study. This means, if anything, we will have underestimated the burden of poor outcomes among people with bedaquiline-resistant tuberculosis.

In conclusion, our study adds to the growing body of evidence demonstrating that bedaquiline resistance is a phenomenon that threatens to undermine efforts to end the global tuberculosis epidemic.

Notes

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