EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Chesov D, Heyckendorf J, Alexandru S, *et al*. Impact of bedaquiline on treatment outcomes of multidrug-resistant tuberculosis in a high-burden country. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.02544-2020).

Impact of bedaquiline on treatment outcomes of multidrug-resistant tuberculosis in a high-burden country

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Article summary line: Used under programmatic condition in a high-burden MDR-TB setting bedaquiline-based MDR-TB treatment regimens result in faster and more sustained disease resolution than bedaquiline-sparing MDR-TB treatment regimens.

Running title: Bedaquiline for MDR-TB

Key words: MDR-TB, treatment outcome, WHO, bedaquiline

Abstract:

Evaluation of novel anti-tuberculosis (TB) medicines for the treatment of multidrug-resistant (MDR)-TB continues to be of high interest on the TB research agenda. We assessed treatment outcomes in patients with pulmonary MDR-TB who received bedaquiline containing treatment regimens in the Republic of Moldova, a high-burden country of MDR-TB.

Method We systematically analyzed the "SIMETB" national electronic TB database in the Republic of Moldova and performed a retrospective propensity score matched comparison of treatment outcomes in a cohort of patients with MDR-TB who started treatment during 2016-2018 with a bedaquiline-containing regimen (bedaquiline cohort) and a cohort of patients treated without bedaquiline (non-bedaquiline cohort).

Results Following propensity score matching, 114 patients were assigned to each cohort of MDR-TB patients. Patients in the bedaquiline cohort had a higher 6 month sputum culture conversion rate than those in the non-bedaquiline cohort, (66.7% vs. 40.3%, $p < 0.001$). Patients under bedaquiline containing regimens had a higher cure rate assessed by both WHO and TBNET definitions (55.3% vs. 24.6%, $p = 0.001$ and 43.5% vs. 19.6% $p = 0.004$, correspondingly), as well, a lower mortality rate (8.8% vs. 20.2%, $p < 0.001$, by WHO and 10.9% vs. 25.2%, $p=0.01$, by TBNET). In patients who previously failed on MDR-TB treatment, more than 40% of patients achieved cure with a bedaquiline-containing regimen.

Conclusions Bedaquiline-based MDR-TB treatment regimens result in better disease resolution when compared to bedaquiline-sparing MDR-TB treatment regimens under programmatic conditions in a country with a high-burden of MDR-TB.

Introductions

Tuberculosis (TB) is the leading infectious cause of death worldwide [1]. Poor disease outcomes are being reported in patients with multidrug-resistant tuberculosis (MDR-TB) [2], defined by bacillary resistance to rifampicin and isoniazid, the two drugs considered to be the best available medicines for the treatment against TB [3]. The number of patients annually identified with MDR-TB has continuously increased during the last decades [4]. This is partially due to better diagnostic capacities, but also because of the increased spread of MDR strains of *Mycobacterium tuberculosis* [5,6]. This situation generates an imperious need for development of new TB drugs for the treatment of MDR-TB.

In the Republic of Moldova, an Eastern European country with one of the highest rates of MDR-TB worldwide (the overall rate of MDR among all TB cases ~34%) [2], bedaquiline has been used for selected patients since the first availability in September 2016. In view of the 2019 recommendations for bedaquiline-based MDR-TB treatment regimens by the World Health Organization (WHO) and the American Thoracic Society (ATS)/Centers of Diseases Control and Prevention (CDC)/European Respiratory Society (ERS)/Infectious Diseases Society of America (IDSA), universal availability of bedaquiline for all patients with MDR-TB will be expected in Moldova soon [7,8]. In this context, data on the use of the bedaquiline in routine clinical practice for the treatment of patients with MDR-TB continue to be a topic of high interest. Therefore, in the present study we have assessed treatment outcomes in MDR-TB patients who received bedaquiline-based treatment regimens and compared them with the outcomes in MDR-TB patients treated with bedaquline-sparing regimens under programmatic conditions.

Methods

We performed a retrospective propensity score matched cohort study based on data collected in the national electronic TB data base SIMETB (Sistemul infromațional de monitorizare și evaluare al tuberculozei). Our objective was to analyse treatment outcomes in the first cohort of patients who started a bedaquiline-based MDR-TB treatment regimens in the Republic of Moldova during 2016 - 2018 (bedaquiline cohort) and to compare them with those from an MDR-TB cohort treated without bedaquiline (non-bedaquiline cohort) from the same setting and period. In the study cohorts we assessed the rate of sputum culture conversion at 6 months of treatment, time to sputum culture conversion, and final TB treatment outcomes applying WHO [3] and TBNET definitions [9].

Settings

In the initial phase of therapy, patients in the Republic of Moldova with MDR-TB are usually hospitalized at a single national medical institution, the "Chiril Draganiuc" Phtisiopneumology Institute, with two separate clinic sites in Chisinau and Vorniceni. Following discharge from the hospital, treatment of patients with MDR-TB is provided under direct observation at the place of residency. Anti-TB drugs and all necessary microbiological, laboratory and imaging tests required for the diagnosis of TB and treatment monitoring are provided free of charge by the government of the Republic of Moldova. Decisions regarding the initial treatment regimen and possible treatment adjustments are made by a national committee for the management of patients with MDR-TB, which meets at least once a week. All TB patients notified in the Republic of Moldova are registered in SIMETB. The database contains basic epidemiological, demographic, microbiological and treatment data of all TB patients in the country (http://simetb.ifp.md/SimeTB.ViewDB/default.asp) [10].

Treatment policy

Treatment for patients affected by MDR-TB in the Republic of Moldova is provided according to the National TB Treatment Protocol in accordance with the MDR-TB treatment guidelines of the WHO [11,12]. During the study, all patients with MDR-TB initially started treatment with a standardized regimen of five 2nd-line TB drugs including a fluroquinolone (levofloxacin or moxifloxacin), a 2nd-line injectable (capreomycin or amikacin), ethionamide, cycloserine and pyrazinamide), which was adjusted, when necessary, once results of phenotypic drug susceptibility testing (DST) became available. The treatment duration is linked to the time of sputum culture conversion and consists of an initial 6-8 months of intensive phase followed by a continuation phase with a duration of 12-16 months. Usually, the MDR-TB treatment is initiated in TB hospital where the patients is admitted at least until the sputum smear conversion is achieved and the final treatment scheme is decided. The treatment during hospital admission is supervised by a pneumologist specialized in treatment of TB patients (phtisio-pneumologist). The average time of hospital admission is 2-3 months after which the patient continues to receive his treatment in outpatient conditions. In outpatients, treatment is provided by the patient's family doctor or phtisio-pneumologist who has his office closest to the patient domicile. The patient must come to the medical office daily to receive his medication. The standard treatment follow-up in MDR-TB patients includes monthly sputum culture, quarterly chest radiography, and a set of blood test on request of the treating physician [10].

Since September 2016 bedaquiline became initially available for a limited number of the most severely affected patients. Once bedaquiline became more largely available, more patients with MDR-

TB with resistance to later generation fluoroquinolones or those who failed treatment on a non-bedaquiline containing regimen benefit of the drug. After revision by WHO of the treatment recommendations for MDR-TB patients in 2019, indications for drug prescription became more permissive, particularly bedaquiline started to be included also in treatment regimens for newly diagnosed patients with MDR-TB, also without additional resistance to 2nd-line anti-TB drugs. All patients treated with bedaquiline received a systematic ECG monitoring (on 2nd, 4th, 8th and 24th weeks of treatment, after that only on physician requests).

Study cohort selection

We used SIMETB to identify all MDR-TB patients who were diagnosed and have initiated treatment during 2016 - 2018 in the Republic of Moldova. The selected study period was determined by the probability of MDR-TB treatment completion at the time of data extraction. Of the identified cases, adult patients (age $\geq$ 18 year old), with culture confirmed pulmonary TB who have finished their MDR-TB treatment at the time of data extraction (including patients who were lost-to-follow-up or died) were included in the study. MDR-TB patients without culture confirmed TB, paediatric patients, patients with extrapulmonary TB, and patients who were still on treatment at the time of data extraction were excluded from the study. MDR-TB patients who qualified to the above inclusion and exclusion criteria were divided in to bedaquiline and non-bedaquiline treatment cohorts. The resulting cohorts were matched by applying a propensity score matching algorithm [13] using age, sex, area of residence, cavitary lesion, HIV-status, sputum smear positivity at baseline, fluoroquinolone resistance, past history of TB and used drugs as matching variables.

Ethical statement

The study protocol for this analysis was approved by Ethical Committee of the Chiril Draganiuc Institute of Phthisiopneumology Chisinau, Republic of Moldova, no.1/ 05.07.2019

Statistical analysis

Statistical analysis was performed using R Version 3.6.3. Continuous variables were described as median with interquartile interval (IQR). Categorical variables were presented as frequencies (percentages). Patients receiving bedaquiline were matched with patients without bedaquiline using Propensity Score. Using the R package MatchIt, the logit-based Propensity Score was calculated using the variables age, gender, residential area (rural/urban), presence of cavities, previous TB history, HIV, flouroquinolone resistance, smear microscopy for tuberculosis at baseline as well as the use of the drugs: fluoroquinolone, capreomycin, amikacin, linezolid, ethionamide, cycloserine, imipenem, para-aminosalicylic acid, pyrazinamide, ethambutol, isoniazid (high dose), clofazimine and delamanide, for each of the patients and on the basis of this, a comparison patient with the greatest possible overlap of the propensity was identified for each bedaquiline receiving patient. The propensity score matching procedure was tested using the R packet table one and the resulting standardized mean differences (SDM). Continuous variables were checked for their distribution using the Shapiro-Wilk test. Statistical analysis was performed after matching using univariate logistic regressions to determine statistical significance. Afterwards, a post-hoc power analysis for logistic regression was performed based on the achievement of culture conversion after six months for patients with and without bedaquiline with an alpha of 0.05 and a power of >0.8 was achieved. For the graphical presentation of the data the GraphPad Prism version 8.0 software was used.

Results

Study cohorts

A total of 2966 patients who started MDR-TB treatment during 2016-2018 was identified in the SIMETB database (inclusively 203 cases with bedaquiline as part of the treatment regimen). The following were excluded from the study: 332 patients who were still on treatment at the time of data extraction, 96 pediatric patients (none of them received bedaquiline), 35 patients with extrapulmonary TB and 434 patients with negative or missing culture results at the time of diagnosis (**Figure 1**). Thus, 2069 MDR-TB patients were included into the study analysis. Of them 115 patients were attributed to the bedaquiline cohort and the other 1954 to the non-bedaquiline cohort. After the propensity score matching 114 MDR-TB patients were assigned to each one of the study cohorts. There were no significant differences among the cohorts by main demographic and clinical features such as: age, sex, place of residence, positive smear microscopy, radiographic cavitary lesion, resistance to fluoroquinolone and previous history of TB (**Table 1**).

Treatment regimens

Drugs included into the treatment schemes of the patients from both cohorts are presented in **Table 2**. After propensity score matching both cohorts were comparable by all used drugs, except bedaquiline.

In all patients bedaquiline was started during hospital admission. In 21 patients bedaquiline was part of the initial treatment scheme, while in the other 93 it was used for the adjustment of the initial treatment scheme once DST results became available. Fifty-point nine percent of the patients who received bedaquiline were treated after at least one MDR-TB treatment episode failure. In 50 out of 93 (53,8%)

patients in whom bedaquiline was used for adjustment of the initial treatment scheme it was the single drug added to or substituted in the regimen. The median time of bedaquiline administration was 34 (IQR, 24-40) weeks. An extended duration of bedaquiline intake was decided by the Committee for the management of MDR-TB cases on an individual approach base in patients with slow radiographic improvement, particularly in the case of persistent cavities, and also in those with persistent positive sputum culture results at 5 or 6 months of treatment, as well as in case of previous history of repeated MDR-TB treatment failure. In 15 patients bedaquiline administration was stopped during the first 20 weeks of drug intake (in 10 patients it was interrupted on patients' initiative after hospital discharge, in 4 patients it was stopped by local TB physicians and in 1 patient it was due to adverse events).

Bedaquiline associated adverse drug events

Only adverse events that lead to stop of the drug intake are recorded in the SIMETB database. Fifty-five of such episodes (in 43 patients; 37.8%) were registered in the database for patients from the bedaquiline cohort and 50 episodes (in 38 patients; 43.8%) in the non-bedaquiline cohort. Of these only one was attributed to bedaquiline. That was a case of dizziness that led to discontinuation of bedaquiline after 7 weeks of treatment. No critical prolongation of QTc interval (Fredericia corrected QTc > 500 ms) was observed in any of 114 patients who received bedaquiline.

Comparison of treatment outcomes

The rate of sputum culture conversion at 6 months of treatment in the bedaquiline cohort were higher than that in the non-bedaquiline cohort (66.7% versus 40.3%, $p < 0.001$, **Table 3**). As well, sputum culture conversion was achieved significantly faster in the bedaquiline cohort (during the first month of treatment), than in the non-bedaquiline cohort, median time to sputum culture conversion in the

bedaquiline cohort was less than one month [IQR, 0-1] versus 1 month [IQR, 0-3] in the non-bedaquiline cohort, $p < 0.001$ (**Figure 2**).

When final treatment outcomes were assessed by the latest WHO definitions (**Table 3**), a higher treatment success rate and a lower mortality rate was found in the bedaquiline cohort (55.3% versus 24.6%, $p < 0.001$ and 8.8% versus 20.2%, $p < 0.001$, correspondingly). At the same time, treatment failure rate was similar (27.2% versus 29.8%, $p = 0.7$).

Assessment of treatment outcomes by simplified TBNET definitions was possible in patients in whom at least one year after treatment completion was passed; that was the case in 92/114 (80.7%) patients in the bedaquiline cohort and 107/114 (88.6%) patients in non-bedaquiline cohort. Patients from the bedaquiline cohort had a higher cure rate and a lower mortality rate (43.5% versus 19.6% $p = 0.004$ and 10.9% versus 25.2%, $p=0.01$, **Table 3**). When applying TBNET treatment outcome definitions, the cure rate was lower compared to WHO criteria assessment and treatment failure rates were significantly higher in both bedaquiline and non-bedaquiline cohorts.

Treatment success in previous treatment failures in the bedaquiline cohort

The bedaquiline cohort included 58 (50.9%) patients with previous failure of at least one MDR-TB treatment regimen. The culture conversion rate at 6 months in these previously failing patients was 55.2% (32/58), while the cure rate was 41.4% (24/58) by WHO definitions and 31.4% (16/51) by TBNET definitions (**Table 4**).

The six months culture conversion rate in patients treated with bedaquiline without a history of previous MDR-TB treatment failure (56 patients) was 82.1% and the cure rate in these patients was 69.6% (39/56) when assessed by WHO definitions and 58.5% (24/41) when assessed by TBNET definitions (**Table 4**); both were significantly better than for those in patients with previous treatment failure ($p = 0.003$ and $p = 0.01$, respectively).

Discussion

We evaluated treatment outcomes in patients with MDR-TB in the Republic of Moldova, a high-burden MDR-TB country in Eastern Europe, who received bedaquiline as part of their treatment regimen and compared them with treatment outcomes observed in patients with MDR-TB from the same country treated without bedaquiline. We found that patients treated with a bedaquiline-based treatment regimen had a faster and higher 6 months sputum culture conversion rate, a higher cure rate and a lower mortality rate compared with those in patients treated without bedaquiline. Patients who failed previous MDR-TB treatment regimens had a higher chance for getting cured when they received a bedaquiline-based treatment regimen.

In previous studies, the rate of 6 months sputum culture conversion in patients treated with beadquiline containing regimen varied from 64 to 100% with treatment success rates ranging between 52-85% both outcomes being higher in patients treated with bedaquiline when compared to those without bedaquiline [14–26]. Similarly, patients treated with bedaquiline in our study had a better 6 months sputum culture conversion rates and higher treatment success rates than those who did not received bedaquiline. The added value of our data consists in the comparison of primary and final treatment

outcomes in bedaquiline-treated patients with propensity score-matched MDR-TB patients treated without bedaquiline-containing regimens from the same setting and comparable treatment regimens. Missing of a such comparator was reported as a limitation of previously published observational cohort studies [20,22,24]. Data from the present analysis support the efficacy and feasibility of the use of bedaquiline-containing regimens when applied under programmatic conditions in a high-burden MDR-TB setting.

The observed treatment success rate in the present cohort is among the lowest of those previously reported (55,3%), despite treatment regimens that also included linezolid and imipenem, drugs which are known to be associated with a higher rate of treatment success [27]. Patients from both cohorts could be characterized as exceedingly difficult to treat patients. Thus, 73% of the patients were infected with a strain of *M. tuberculosis* resistant to fluoroquinolones, 81% had cavitary lesions on the chest radiography and 80% were retreatment cases, all these factors being known as predictors for poor treatment outcomes in patients with MDR-TB [27]. Also, treatment outcomes could have been influenced by the poor patient adherence to the treatment, an important challenge for the TB treatment in Eastern Europe. Even though TB treatment within the National TB Program (NTP) in the Republic of Moldova is provided under direct observation of the medical staff, it is hard to be confident about the swallowing of the pills by the patients, particularly in the outpatient setting [28]. A poor adherence during the previous and current episodes of TB could also explain repetitive failure among previously treated cases in both study cohorts, 64% of which are retreatments after failure. To improve TB treatment adherence several interventions were implemented during the last years in the Republic of Moldova, but their scale up to the level of the entire countries is not achieved, yet [29,30].

One of the factors which could also have an influence on the treatment outcome is the duration of hospital admission in both study cohorts. Due to retrospective nature of the study the data on these were not available for the analysis and represent a limitation of the presented results.

We applied WHO outcome definitions, which are currently used by the National TB Program in the Republic of Moldova, and those proposed by the TBNET [9]. Application of TBNET definitions allowed to address possible disease relapse during the first year of post treatment follow-up in both cohorts [31–34]. The higher rate of failure observed when the TBNET definitions were applied was generated by reassessment of loss of follow up cases which had positive sputum culture when they restarted treatment after several months of interruption [34].

Bedaquiline-containing MDR-TB regimens were associated with an increased risk of death in a phase 2b clinical trial [14]. On the other hand, a later cohort analysis from South Africa reported a significantly lower mortality rate associated with bedaquiline containing regimens, compared with a standard regimen [35]. We also observed a lower mortality rate in our bedaquiline patients, that was not previously reported in bedaquline treated patients from an Eastern European setting.

Poor access to important TB drugs in Eastern European high-burden MDR-TB countries has been previously reported [33]. Limited use of delamanid and clofazimine in both bedaquiline and non-bedaquiline cohorts in this study reflect the same phenomenon. Among the main causes of a slow scale-up of the approved TB drugs in countries like the Republic of Moldova are limited budgets of the public healthcare sector and subsequent high dependence of external funding, as well as high level of bureaucracy and sometimes reticence of public authorities [36]. Of note, only in September 2016

the first patient received bedaquiline as part of MDR-TB regimen in the Republic of Moldova, mostly after three years since its international approval. However, release by the WHO of new treatment recommendation on an all oral treatment regimen for patients with MDR-TB has improved availability of antituberculosis medicines. Delamanid and clofazimine have become available for a larger number of patients recently. Once the new all oral bedaquiline based regimens will be available to all patients with MDR-TB in the Republic of Moldova we expect to observe an increase in treatment success rates.

A critical finding of this study is the high rate of patients who received bedaquiline as a single additive drug for the adjustment of the MDR-TB treatment regimens. This situation is also a consequence of the reduce access to some of the MDR-TB drugs in resource limited settings like the Republic of Moldova. This practice may be associated with the future development of additional resistance against bedaquiline [37]. Unfortunately, we were unable to assess the acquisition of bedaquiline resistance during TB treatment in this cohort due to the study's retrospective nature and missing of DST data on treatment follow-up cultures in routine practice. An additional risk for the development bedaquiline resistance under therapy is represented by patients which discontinuing bedaquiline intake after several weeks of medication after hospital discharge (14 patients (12.3%) in our cohort). Diversification of drugs supply and strengthening of patient management in the outpatient setting are critically important to prevent the development of bacillary resistance to novel anti-TB drugs in the Republic of Moldova and countries with similar settings in the region.

Missing data about all adverse events limit our conclusion regarding the overall safety of the bedaquiline containing regimens. The overall low rate of the adverse events observed in both cohorts could be a consequence of underreporting, a limitation that could not be overcome in this retrospective

study. However, the present data confirm absence of critical cardiac adverse effects in patients receiving bedaquiline despite the concomitant use of other drugs also causing prolongation of QTc intervals. Being in concordance with previously reported data [38,39] this finding confirms the low risk of severe adverse events of bedaquiline and proves its safety under programmatic conditions in a high burden MDR-TB setting.

Conclusions

Bedaquiline-based MDR-TB treatment regimens result in faster and better disease resolution when compared to bedaquiline-sparing MDR-TB treatment regimens under programmatic conditions in a high-burden MDR-TB country, even in exceedingly difficult to treat patients. More than 40% of patients previously failing MDR-TB treatments achieve cure under bedaquiline-based therapy regimens. Efficient antibiotic stewardship measures should be implemented to prevent avoidable cases of newly acquired resistance to novel anti-tuberculosis drugs.

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Table 1: Cohorts characteristics

	Before propensity score matching				After propensity score matching			
Variable	**Bedaquliline (n=115)**	**Non-Bedaquiline (n=1954)**	**p**	**SMD**	**Bedaquliline (n=114)**	**Non-Bedaquiline (n=114)**	**p**	**SMD**
Age (Median; IQR)	37 (31-44)	39 (32-50)	0.02	0.27	37 (31 – 44)	39 (32 – 46)	0.4	0.12
Sex, male	88 (76.5%)	1549 (79.3%)	0.5	0.07	87 (76.3%)	85 (74.6%)	0.8	0.04
Rural domicile	57 (50%)	1066[#] (55.6%)	0.3	0.10	57 (50.0%9	52 (45.6%)	0.5	0.09
Cavitary lesion	94 (81.7%)	1165[#] (60.2%)	<0.0001	0.49	93 (81.6%)	98 (86.0%)	0.4	0.12
HIV status positive	17 (14.8%)	276 (14.1%)	0.8	0.02	17 (14.9%)	19 (16.7%)	0.7	0.05
Smear positive	85 (73.9%)	1122 (57.4%)	0.0005	0.35	84(73.7%)	93 (81.6%)	0.1	0.19
FQ resistance	76 (72.4%)	485 (29.6%)	<0.0001	0.94	76 (73.1%)	73 (69.5%)	0.6	0.08
History of past TB				0.78				0.10
after treatment failure	59 (51.3%)	364 (18.6%)	<0.0001		58 (50.9%)	58 (50.9%)	0.7	
after loss of follow up	18 (15.7%)	271 (13.9%)	0.6		18 (15.8%)	29 (25.4%)	0.2	
relapse case	15 (13.0%)	446 (22.8%)	0.01		15 (13.2%)	7 (6.1%)	0.7	
new case	23 (20.0%)	873 (44.7%)	<0.0001		23 (20.2%)	20 (17.6%)	0.7	

FQ - fluoroquinolone; IQR - inter quartile range; TB – tuberculosis; SMD -standardized mean difference; [#] - 1936 records available.

Table 2: Drugs included in MDR-TB treatment regimens

Drug	Before propensity score matching				After propensity score matching			
	Bedaquliline (n=115)	**Non-Bedaquiline (n=1954)**	**p**	**SMD**	**Bedaquliline (n=114)**	**Non-Bedaquiline (n=114)**	**p**	**SMD**
Fluoroquinolone	97 (83.4%)	1873 (95.9%)	<0.0001	0.39	96 (84.2%)	100 (87.7%)	0.4	0.10
Capreomycin	87 (75.7%)	1817 (93.0%)	<0.0001	0.49	86 (75.4%)	93 (81.6%)	0.3	0.15
Amikacin	7 (6.1%)	151 (7.7%)	0.5	0.06	7 (6.1%)	5 (4.4%)	0.5	0.08
Linezolid	98 (85.2%)	851 (43.5%)	<0.0001	0.96	98 (86.0%)	103 (90.4%)	0.3	0.14
Ethionamide	66 (57.4%)	1585 (81.1%)	<0.0001	0.53	65 (57.0%)	65 (57.0%)	1.000	<0.001
Cycloserine	112 (97.4%)	1910 (97.8%)	0.8		111 (97.4%)	111 (97.4%)	1.000	
Imipenem	62 (53.9%)	252 (12.9%)	<0.0001	0.96	62 (54.4%)	62 (54.4%)	1.000	<0.001
Para-amino-salicylic acid	54 (47%)	1123 (57.5%)	0.03	0.53	54 (47.4%)	51 (44.7%)	0.7	<0.001
Pyrazinamide	111 (96.5%)	1915 (98%)	0.3	0.09	110 (96.5%)	110 (96.5%)	1.000	<0.001
Ethambutol	2 (1.7%)	235 (12.0%)	0.0007	0.41	2 (1.8%)	1 (0.9%)	0.6	0.08
Isoniazid (high dose)	30 (26.1%)	231 (11.8%)	<0.0001	0.37	29 (25.4%)	23 (20.2%)	0.3	0.12
Clofazimine	10 (8.7%)	9 (0,5%)	<0.0001	0.4	9 (7.9%)	5 (4.4%)	0.3	0.15
Delamanid	3 (2.61%)	3 (0.15%)	<0.0001	0.21	3 (2.6%)	2 (1.8%)	0.6	0.06

SMD -standardized mean difference

Table 3: Treatment outcomes in bedaquiline and non-bedaquiline cohorts by WHO and simplified TBNET definitions

	Bedaquiline (n=114)	non-Bedaquiline (n=114)	p
Six months sputum culture conversion rate	76 (66.7%)	46 (40.3%)	<0.001
Final treatment outcome by WHO			
Cured	63 (55.3%)	28 (24.6%)	<0.001
Fail	31 (27.2%)	34 (29.8%)	0.7
Died	10 (8.8%)	23 (20.2%)	<0.001
Loss of follow up	10 (8.8%)	29 (25.4%)	<0.001
Final treatment outcome by TBNET [#]			
Cured	40 (43.5%)	21 (19.6%)	0.004
Fail	36 (39.2%)	54 (50.5%)	0.1
Died	10 (10.9%)	27 (25.2%)	0.01
Loss of follow up	6 (6.5%)	5 (4.7%)	0.4

[#] - 92 records available for bedaquiline cohort and 107 records available for non-bedaquiline cohort (the not included cases have not completed 1 year posttreatment follow up).

Table 4: Treatment outcomes in patients who failed previous TB treatment episodes in the bedaquiline cohort by WHO and simplified TBNET definitions

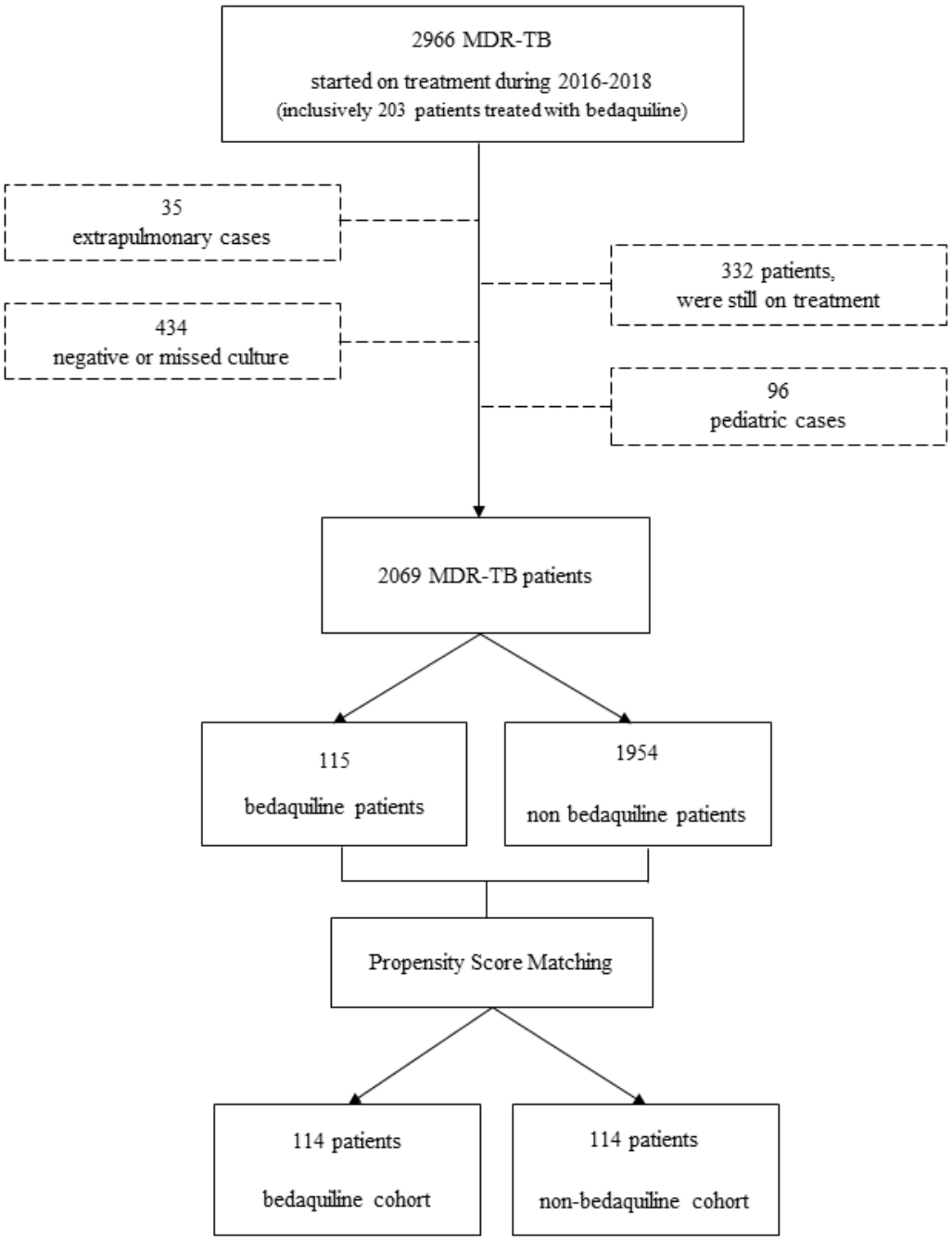
	Past-failure (n=58)	Non past-failure (n=56)	p
Six months culture conversion rate	32 (55.2%)	44 (78.6%)	0.007
Final treatment outcome by WHO			
Cure	24 (41.4%)	39 (69.6%)	0.003

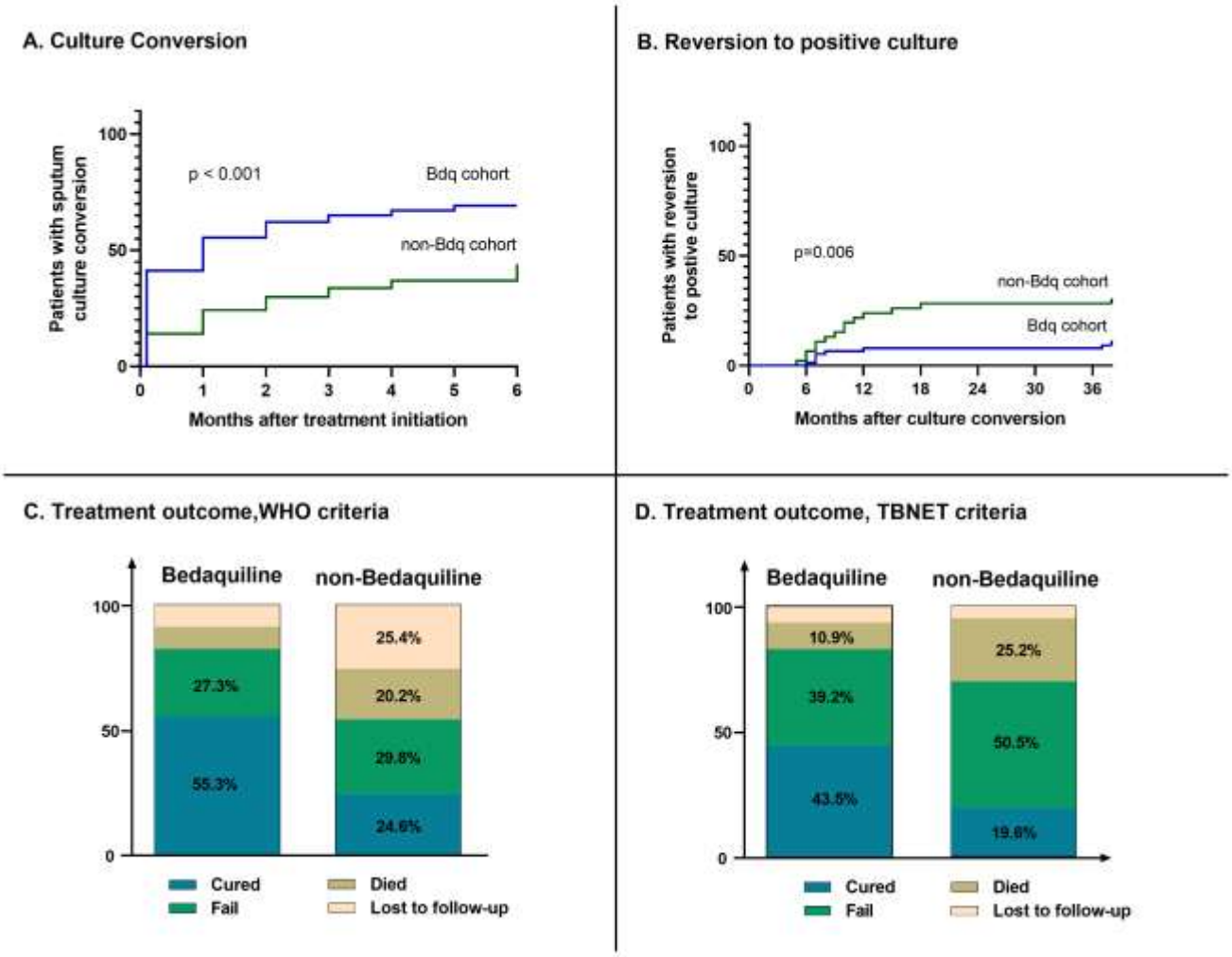
Failure	22 (37.9%)	9 (16.1%)	0.01
Death	4 (6.9%)	6 (10.7%)	0.5
Loss of follow up	8 (13.8%)	2 (3.6%)	0.09
Final treatment outcome by TBNET [#]			
Cure	16 (31.4%)	24 (58.5%)	0.01
Failure	26 (50.1%)	10 (24.4%)	0.01
Death	4 (7.8%)	6 (14.6%)	0.3
Loss of follow up	5 (9.8%)	1 (2.4%)	0.2

[#] - 51 records available for past failure group and 41 records available for non past-failures group (the not included cases have not completed 1year posttreatment follow up).

Figure 1: Study flowchart

Figure 2: Treatment outcomes in patients with MDR-TB who received bedaquiline and non-bedaquiline containing treatment regimens


2966 MDR-TB
started on treatment during 2016-2018
(inclusively 203 patients treated with bedaquiline)
35
extrapulmonary cases
434
negative or missed culture
332 patients,
were still on treatment
96
pediatric cases
2069 MDR-TB patients
115
bedaquiline patients
1954
non bedaquiline patients
Propensity Score Matching
114 patients
bedaquiline cohort
114 patients
non-bedaquiline cohort


A. Culture Conversion
Patients with sputum culture conversion
100
50
0
p < 0.001
Bdq cohort
non-Bdq cohort
0
1
2
3
4
5
6
Months after treatment initiation
B. Reversion to positive culture
Patients with reversion to positive culture
100
50
0
p=0.006
non-Bdq cohort
Bdq cohort
0
6
12
18
24
30
36
Months after culture conversion
C. Treatment outcome,WHO criteria
Bedaquiline
non-Bedaquiline
100
50
0
27.3%
55.3%
25.4%
20.2%
29.8%
24.6%
Cured
Fail
Died
Lost to follow-up
D. Treatment outcome, TBNET criteria
Bedaquiline
non-Bedaquiline
100
50
0
10.9%
39.2%
43.5%
25.2%
50.5%
19.8%
Cured
Fail
Died
Lost to follow-up