INT J TUBERC LUNG DIS 24(10):1095–1102

http://dx.doi.org/10.5588/ijtld.20.0082

Bedaquiline and delamanid result in low rates of unfavourable outcomes among TB patients in Eswatini

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SUMMARY

SETTING: Since 2015, Eswatini has been scaling up bedaquiline (BDQ) and delamanid (DLM) based drug-resistant TB treatment regimens under programmatic conditions.

OBJECTIVE: Identification of factors associated with treatment outcomes in patients receiving BDQ and/or DLM either as a new treatment initiation or drug substitution.

DESIGN: This is a retrospective cohort study of patients receiving BDQ and/or DLM in Eswatini between March 2015 and October 2018. We describe factors associated with unfavourable treatment outcomes (death, lost to follow-up, treatment failure and amplification of resistance) and culture conversion using multivariable flexible parametric survival and competing-risks regression analyses.

RESULTS: Of 352 patients receiving BDQ and/or DLM, 7.8% and 21.2% had an unfavourable treatment outcome at 6 and 24 months, respectively. Predictors were age $\geq$ 60 years (adjusted hazard ratio [aHR] 4.49, 95%CI 1.61–12.57) vs. age 20–39 years, and a treatment regimen combining both drugs (aHR 4.49, 95%CI 1.61–12.57) vs. BDQ only. The probability of culture conversion was increased for two health facilities and patients with a poly resistance profile (adjusted sub-hazard ratio 2.01, 95%CI 1.13–3.59) vs. multidrug resistance.

CONCLUSION: Single use of BDQ or DLM was associated with low rates of unfavourable outcomes, suggesting that these medications may be effectively adopted at scale under routine programmatic conditions. Combined use of BDQ and DLM was a risk factor for unfavourable outcomes and should prompt for collection of more data on the combined use of these medications.

KEY WORDS: BDQ; DLM; multidrug-resistant tuberculosis

IN 2018, ONLY 186 772 of the estimated 484 000 multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) cases were notified globally, representing a case detection gap of 62%.[1,2] In addition, global treatment success remains low at 56–61%.[1,2] Main barriers to improving treatment outcomes are prolonged duration of treatment, severity and irreversibility of side effects associated with the injectable medications, particularly in people living with HIV, and a lack of patient-centred models of care.[3–6]

To improve treatment outcomes, in 2013 the WHO provided interim policy guidance for the implementation of bedaquiline (BDQ),[7] followed by interim policy guidance on the use of delamanid (DLM) in 2014.[8] These recommendations were based on evidence from phase II randomised clinical trials, which demonstrated higher rates of culture conversions in patients receiving BDQ and DLM.[9,10] Although both drugs were also introduced into routine clinical care under close clinical monitoring,[11,12] internationally overall uptake remained far below estimated needs.[13]

In 2015 and 2016, the National TB Control Program (NTCP) of Eswatini (formerly Swaziland) phased-in the use of BDQ and DLM at four pilot sites.[14] The program was overseen for the initial year by a clinical expert committee, which reviewed the care of each patient started on these medications. Approximately 400 patients have been started on

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Article submitted 14 February 2020. Final version accepted 24 June 2020.

BDQ and/or DLM since the program began, the majority of whom were living with HIV. This analysis describes the outcomes of patients initiated on BDQ and/or DLM under programmatic conditions, building on the previous study reporting on the implementation experience in this setting.[14]

METHODS

Setting

Eswatini is a lower-middle income country in southern Africa with a population of 1.1 million. It has a high burden of MDR/RR-TB (25 cases per 100 000 population) and 79% of MDR/RR-TB cases are HIV-positive.[1] MDR/RR-TB cases represent 8.6% of new TB cases and 17.5% of previously treated cases.[1] The treatment success rate in 2017 (2014 cohort) was 58% for MDR/RR-TB.[15] Responding to high rates of adverse events to injectable medications, particularly among people living with HIV, as well as an emerging extensively drug-resistant TB (XDR-TB) epidemic, the Eswatini NTCP decentralised MDR/RR-TB treatment to 12 treatment sites in 2016.

BDQ and DLM were piloted at four health facilities: The National TB Hospital, Mankayane Government Hospital, Matsapha Health Centre and Nhlangano Health Centre. These sites were selected because of the availability of trained MDR/RR-TB physicians, equipment for clinical monitoring (electrocardiograms and audiometers) and additional structures and procedures for providing comprehensive support to ambulatory patients. Medical doctors initiated BDQ and/or DLM to patients meeting predefined criteria which prioritised pre-XDR and XDR-TB, and MDR/RR-TB with treatment failure, medication intolerance, or pre-existing medical conditions such as hearing loss.

Study design

This is a descriptive analysis of a retrospective established cohort of patients initiating the single drugs of (BDQ/DLM), or both drugs (BDQ+DLM) for MDR/RR-TB, as well as for poly drug-resistant (PDR-TB), pre-XDR and XDR-TB, at the four treatment sites in Eswatini, between 10 March 2015 and 31 October 2018. These drugs were used for: 1) new treatment initiations in the case of baseline pre-XDR or XDR-TB or contraindications to injectable drugs (e.g. baseline hearing impairment); 2) drug substitutions due to adverse events (e.g. ototoxicity) during treatment for MDR/RR-TB; and 3) treatment modifications due to amplification of drug resistance or treatment failure. These eligibility criteria for BDQ/DLM adhered to existing WHO guidelines for the introduction of new drugs for the treatment of MDR-TB.[7,8,16]

In the primary analysis, patients were followed from the time of initiation of the new drugs until identification of a comprehensive composite unfavourable outcome including death, lost to follow-up, treatment failure and treatment discontinuation for any reason. Observations were censored at the last documented clinic visit in case of transfer out, treatment success (cured and completed combined) or at the time of database closure (31 January 2019) for patients still on treatment.

In the secondary analysis, the cohort was restricted to patients without documented culture conversion prior to initiation of BDQ/DLM. The outcome was time to culture conversion or treatment completion in the absence of documented culture conversion. The date of culture conversion was assumed to be two months before the date of cure if the date of culture conversion was not recorded in the patient file. Death, lost to follow-up, treatment discontinuation and treatment failure were treated as competing risks. Censoring occurred for other outcomes (transfer-out, treatment completion) or at database closure for patients still on treatment without recorded culture conversion. Sensitivity analyses were performed 1) assuming culture conversion 6, 12 and 18 months prior to treatment completion, and 2) treating only death as a competing risk. Routine programmatic definitions of drug resistance, culture conversion and treatment outcomes were used as recommended by WHO.[17]

Statistical analysis

Descriptive statistics were performed including frequencies and proportions for categorical variables, and medians and interquartile ranges (IQRs) for continuous variables. Kaplan-Meier plots and estimates described time to unfavourable outcome and culture conversion.

Multiple imputation by chained equations was used to address missing values of covariates in regression analyses using 10 imputed data sets. In primary analysis, we used a flexible parametric survival model to describe associations between baseline factors and the risk of an unfavourable outcome. Factors for inclusion in regression analyses were determined a priori using directed acyclic graphs. In secondary analysis, we then fitted a competing-risks regression model and plotted the cumulative incidence function for time to culture conversion. In a supplementary analysis, we used penalised maximum likelihood logistic regression to assess predictors of combined use of BDQ+DLM compared with their single use. All analyses were performed with Stata 14.1 (StataCorp, College Station, TX, USA).

Ethics approval for this analysis was obtained from the Eswatini National Health Research Review Board, Mbabane, Eswatini.

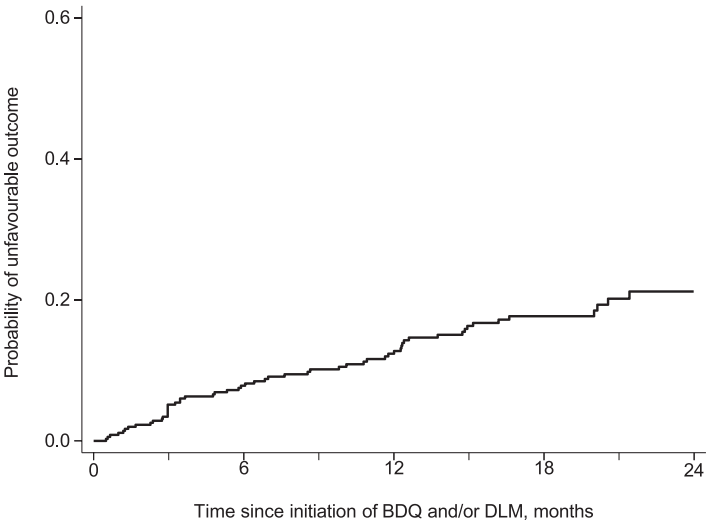

Figure 1 Kaplan-Meier plot of time from initiation of BDQ and/or DLM to composite unfavourable outcome (death, lost to care, treatment failure and treatment discontinuation for any reason). BDQ = bedaquiline; DLM = delamanid.

RESULTS

Baseline characteristics

Between 10 March 2015 and 31 October 2018, a total of 355 patients initiated BDQ and/or DLM. Three patients with unknown treatment outcome were excluded, leaving 352 (98.6%). The largest number of patients initiated treatment in 2017 (n = 159, 45.2%) and at the National TB Hospital (63.6%). The median age was 35 (IQR 29–44) years, 145 (41.3%) were women and 272 (77.3%) were living with HIV, of whom all except for one was on antiretroviral therapy (ART). The predominant resistance profile was MDR-TB (n = 196, 56.8%), followed by monoresistance (n = 47, 13.6%), pre-XDR-TB (n = 46, 13.3%), XDR-TB (n = 44, 12.8%) and PDR-TB (n = 12, 3.5%). Among cases with monoresistance, one had isoniazid monoresistance and the rest rifampicin monoresistance.

Overall, 292 (83.0%) patients received BDQ, 40 (11.4%) DLM and 20 (5.7%) a combination of both drugs. The main reasons for receiving the new drugs were 1) new treatment initiations as per clinicians' discretion (n = 199, 56.5%), of whom 51 (25.6%) had pre-XDR- or XDR-TB and 27 (13.6%) had pre-existing hearing loss; 2) treatment modification (n = 100, 28.4%), of whom 18 (18.0%) had amplification of resistance, 15 (15.0%) had treatment failure and 67 (67.0%) were drug substitutions because of adverse events, mainly due to ototoxicity (n = 61) and nephrotoxicity (n = 4). The remaining 53 (15.1%) patients also had drug substitutions but the reasons were not documented.

Unfavourable treatment outcomes

The median follow-up time from initiation of BDQ/DLM was 1.4 years (IQR 0.7–1.7). At the end of the observation period, 139 (39.5%) patients had been cured, 1 (0.3%) completed treatment, 7 (2.0%) transferred out and 148 (42.1%) were still on treatment. Overall, 57 (16.2%) patients had an unfavourable outcome (51 deaths, 3 treatment failure, 2 lost to follow-up and 1 treatment discontinuation). Restricted analysis to patients enrolled on treatment from 2015 to 2016 with at least 24 months' follow-up time (n = 109) and from these, 73.4% (n = 80) had a successful treatment outcome, 16.5% (n = 18) died, 0.9% (n = 1) had treatment failure, 0.9% (n = 1) were lost to follow-up and 8.3% (n = 9) still received treatment. The crude cumulative probability of an unfavourable outcome was respectively 5.1%, 7.8%, 12.7% and 21.2% at 3, 6, 12 and 24 months (Figure 1). Probabilities of an unfavourable outcome by covariate factor are presented in Supplementary Table S1.

In multivariate analysis (Table 1, Figure 2), predictors of an unfavourable treatment outcome were age $\geq$ 60 years (adjusted hazard ratio [aHR] 3.85, 95% confidence interval [CI] 1.49–9.98) compared with age 20–39 years, and a treatment regimen combining BDQ+DLM (aHR 4.49, 95%CI 1.61–12.57) compared with BDQ only. Associations of other factors (calendar year, treatment location, sex, resistance classification, reasons for new drug, and HIV/ART status) with an unfavourable treatment outcome were not detected.

Culture conversion

In 46 patients, culture conversion occurred before the initiation of BDQ/DLM, leaving 306 (86.9%) patients for analysis. Distribution of baseline characteristics was comparable to that of the entire cohort (Table 2). Figure 3 shows the plot of the cumulative incidence function for time to culture conversion accounting for competing outcomes.

Table 1 Baseline characteristics of patients initiated on BDQ- and/or DLM-based treatment regimens, and associations with unfavourable treatment outcome* in univariate and multivariate analysis

	(*n* = 352)		Univariate analysis‡			Multivariate analysis‡		
Patient characteristic†	*n*	%	cHR	95%CI	*P* value	aHR	95%CI	*P* value
Calendar year								
2015	37	10.5	Reference			Reference		
2016	72	20.5	1.08	0.43–2.70	0.876	0.94	0.32–2.78	0.911
2017	159	45.2	1.33	0.58–3.06	0.505	1.08	0.33–3.52	0.900
2018	84	23.9	1.31	0.46–3.80	0.613	1.31	0.31–5.45	0.711
Treatment location								
National TB Hospital	224	63.6	Reference			Reference		
Matsapha Health Centre	66	18.8	0.83	0.41–1.65	0.589	0.50	0.19–1.31	0.160
Mankanyane Hospital	29	8.2	0.52	0.16–1.69	0.281	0.50	0.14–1.79	0.287
Nhlangano Health Centre	33	9.4	0.36	0.09–1.48	0.156	0.29	0.06–1.29	0.103
Sex								
Female	145	41.3	Reference			Reference		
Male	206	58.7	0.73	0.44–1.23	0.239	0.65	0.37–1.16	0.143
Age, years								
≤19	17	4.8	0.98	0.30–3.19	0.972	0.63	0.14–2.94	0.560
20–39	208	59.3	Reference			Reference		
40–59	97	27.6	0.76	0.39–1.46	0.402	0.68	0.34–1.38	0.286
≥60	29	8.3	2.35	1.12–4.91	0.023	3.85	1.49–9.98	0.005
New drug								
BDQ	292	83.0	Reference			Reference		
DLM	40	11.4	2.61	1.33–5.12	0.005	1.88	0.86–4.11	0.116
BDQ and DLM	20	5.7	4.00	1.93–8.30	<0.0005	4.49	1.61–12.57	0.004
Reason for new drug								
New initiation	199	66.6	Reference			Reference		
Toxicity	67	22.4	0.51	0.20–1.28	0.152	0.67	0.23–1.93	0.463
Resistance/treatment failure	33	11.0	1.51	0.72–3.16	0.270	2.70	0.90–8.13	0.077
Resistance classification								
Monoresistance§	47	13.6	1.34	0.58–3.08	0.494	1.07	0.39–2.96	0.899
Poly drug-resistant TB	12	3.5	1.33	0.32–5.62	0.697	1.08	0.23–4.96	0.924
MDR-TB	196	56.8	Reference			Reference		
Pre-XDR-TB	46	13.3	1.10	0.52–2.34	0.798	0.82	0.29–2.33	0.706
XDR-TB	44	12.8	1.19	0.58–2.45	0.643	0.74	0.27–2.03	0.563
HIV and ART status								
HIV-negative	80	22.7	Reference			Reference		
HIV-positive, on ART	271	77.0	1.50	0.74–3.07	0.262	1.83	0.80–4.19	0.153
HIV-positive, not on ART	1	0.3	31.16	3.84–252.93	0.001	13.79	0.76–250.67	0.076

* Composite outcome of death, lost to follow-up, treatment failure or treatment discontinuation.
† Missing: sex (*n* = 1), age (*n* = 1), reasons for new drug (*n* = 53), resistance classification (*n* = 7).
‡ Model specifications: We used multiple imputations for covariates with missing values. The proportional hazards assumption was satisfied. Using 10 imputed data sets, crude and adjusted flexible parametric survival models were built with two degrees of freedom (one internal and two external knots).
§ There were 46 cases of rifampicin monoresistance and one case of isoniazid monoresistance.
BDQ = bedaquiline; DLM = delamanid; cHR = crude hazard ratio; CI = confidence interval; aHR = adjusted hazard ratio; TB = tuberculosis; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB; HIV = human immunodeficiency virus; ART = antiretroviral therapy.

In multivariate analysis (Table 2), the probability of culture conversion was increased for the year 2017 (adjusted sub-hazard ratio [aSHR] 2.02, 95%CI 1.15–3.55) vs. 2015, for Mankayane Government Hospital (aSHR 2.17, 95%CI 1.31–3.60) and Nhlangano Health Centre (aSHR 1.70, 95%CI 1.08–2.68) vs. the National TB Hospital, and for patients with a poly resistance profile (aSHR 2.01, 95%CI 1.13–3.59) vs. MDR. Other factors (sex, age, new drug initiated, reason for new drug, HIV/ART status) were not associated with time to culture conversion. All sensitivity analyses confirmed main findings (Supplementary Table S2).

Supplementary analysis

Details of baseline characteristics and regression analysis of patients receiving both BDQ+DLM vs. single use can be found in Supplementary Table S3. Overall, only 20 patients initiated a combined BDQ+DLM treatment regimen. While clinical factors (HIV status) did not increase the odds of combined BDQ+DLM treatment, programmatic determinants (e.g. facility, later calendar year) and resistance patterns (e.g. XDR-TB) increased the odds (Supplementary Table S3).

DISCUSSION

Our programme data suggest that patients initiated on BDQ/DLM can achieve favourable treatment outcomes and high rates of culture conversion, regardless of indication for the drug(s) or resistance pattern. This uniformity across different patient categories likely reflects the potency and tolerability

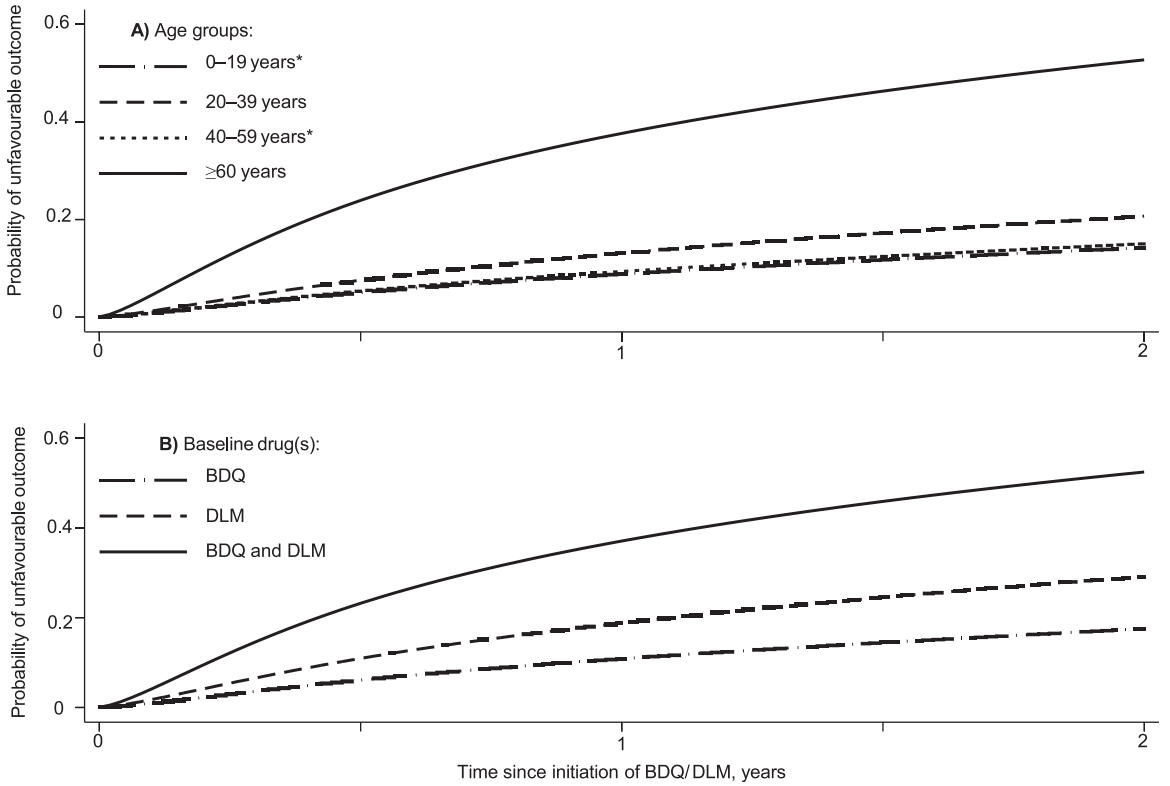

Figure 2 Standardised failure curves by **A)** age group, and **B)** baseline drug after fitting the covariate adjusted flexible parametric model. * The 0–19 and 40–59 years age groups overlap. BDQ = bedaquiline; DLM = delamanid.

of BDQ and is consistent with the recent WHO recommendation to include it as a key drug for all patients with MDR/RR-TB. These findings are also consistent with other recent BDQ implementation experiences from high HIV and TB burden settings.[13,18,19] The programmatic use of BDQ has resulted in reductions in mortality and treatment failure attributable to MDR/RR-TB.[20–22]

In this setting, age $\geq$ 60 years was associated with an almost four-fold increased risk of an unfavourable treatment outcome, although this group had the same probability of culture conversion when compared with younger age groups. This finding may be related to age- associated comorbidities (e.g. cardiac disease, hypertension, diabetes mellitus) which possibly may have aggravated the overall health condition and increased the risk of medication adverse events, which were not captured by this study.[23] Further studies may be required to establish the safety of these new drugs in the elderly.

Notably, patients receiving both BDQ+DLM had an increased risk of an unfavourable outcome when compared with BDQ as a single drug, which is increasingly recognised as a safe and highly effective medication.[24,25] Several potential explanations exist. First, there may be overlap and accumulation of toxicities, resulting in adverse events that were not adequately captured in our dataset, and indicating the ongoing need for strengthening active drug safety monitoring.[11,25] In contrast, emerging data suggest that BDQ+DLM can be used in combination safely without synergistic QTc prolongation, suggesting that findings may be attributable to possible overlapping toxicities with other drugs or residual confounding.[26–28] Second, supplementary analysis showed that XDR-TB and treatment modifications due to amplification of drug resistance or treatment failure were the main clinical predictors for initiation of both medications combined, which may have contributed to the association with unfavourable outcomes.

This analysis further demonstrated that health facility and calendar year were associated with probability of culture conversion, indicating that facility-level factors and temporal trends may play a role in the provision of quality care, referral bias or data collection with respect to culture. In addition, patients with a poly resistance profile were also more likely to convert, possibly due to the combined efficacy of BDQ/DLM with other more potent companion drugs with more limited resistance. In Eswatini, patients with mono-isoniazid or poly resistance may be more likely to be treated with an MDR drug regimen because of the very high prevalence of the rifampicin resistance conferring I491F mutation, not detected by Xpert or Mycobacteria Growth Indicator Tubes drug susceptibility testing.[29,30] To note, these factors were not associated with an unfavourable treatment outcome.

Table 2 Associations with time to culture conversion for patients who did not culture convert before initiation of the BDQ- and/or DLM-based regimen*

	Baseline characteristics ($n = 306$)		Univariate analysis ($n = 306$)			Multivariate analysis ($n = 306$)		
Patient characteristics†	*n*	%	cSHR	95%CI	*P* value	aSHR	95%CI	*P* value
Calendar year								
2015	35	11.4	Reference			Reference		
2016	65	21.2	1.05	0.70–1.57	0.814	1.21	0.73–2.02	0.455
2017	133	43.5	2.02	1.32–3.09	0.001	2.02	1.15–3.55	0.015
2018	73	23.9	1.53	0.93–2.53	0.094	1.05	0.52–2.15	0.884
Treatment location								
National TB Hospital	198	64.7	Reference			Reference		
Matsapha Health Centre	55	18.0	1.42	0.93–2.15	0.101	1.42	0.88–2.31	0.150
Mankanyane Hospital	27	8.8	2.19	1.36–3.54	0.001	2.17	1.31–3.60	0.003
Nhlangano Health Centre	26	8.5	1.65	1.13–2.39	0.009	1.70	1.08–2.68	0.021
Sex								
Female	127	41.6	Reference			Reference		
Male	178	58.4	1.06	0.82–1.36	0.647	0.97	0.74–1.29	0.851
Age, years								
≤19	13	4.3	1.64	0.93–2.91	0.090	1.68	0.85–3.33	0.134
20–39	177	58.0	Reference			Reference		
40–59	86	28.2	0.99	0.75–1.31	0.941	0.81	0.60–1.09	0.160
≥60	29	9.5	1.12	0.75–1.66	0.585	0.71	0.41–1.23	0.215
New drug								
BDQ	251	82.0	Reference			Reference		
DLM	36	11.8	1.07	0.72–1.58	0.736	0.91	0.57–1.46	0.691
BDQ and DLM	19	6.2	0.87	0.44–1.75	0.703	0.77	0.34–1.73	0.529
Reason for new drug								
New initiation	199	75.7	Reference			Reference		
Toxicity	37	14.1	1.22	0.88–1.71	0.236	1.03	0.69–1.55	0.886
Resistance/treatment failure	27	10.3	1.11	0.62–1.99	0.725	1.28	0.67–2.45	0.458
Resistance classification								
Monoresistance‡	46	15.4	1.24	0.81–1.89	0.331	1.53	0.90–2.60	0.117
Poly drug-resistant TB	12	4.0	1.54	0.91–2.63	0.110	2.01	1.13–3.59	0.018
MDR-TB	157	52.5	Reference			Reference		
Pre-XDR-TB	41	13.7	0.80	0.56–1.15	0.230	0.85	0.52–1.37	0.500
XDR-TB	43	14.4	0.65	0.45–0.94	0.021	0.84	0.53–1.31	0.436
HIV and ART status								
HIV-negative	72	23.5	Reference			Reference		
HIV-positive, on ART	233	76.1	0.74	0.57–0.97	0.026	0.79	0.57–1.09	0.149
HIV-positive, not on ART	1	0.3	1.22	0.95–1.56	0.112	0.97	0.28–3.33	0.965

* Percentages may not total 100 due to rounding.
† Missing: sex ($n = 1$), age ($n = 1$), reason for new drug ($n = 53$), resistance classification ($n = 7$).
‡ There were 45 cases of rifampicin monoresistance and one case of isoniazid monoresistance.
BDQ = bedaquiline; DLM = delamanid; cSHR = crude sub hazard ratio; CI = confidence interval; aSHR = adjusted sub hazard ratio; TB = tuberculosis; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB; HIV = human immunodeficiency virus; ART = antiretroviral therapy.

The probability of an unfavourable outcome was low at 12 (12.7%) and 24 (21.2%) months after initiation of treatment, despite the high HIV co-infection rate. Although comparison with historical outcome data and other programmes using routine treatment regimens is limited as both drugs were used for a variety of reasons (new treatment initiations vs. drug substitutions) for treatment-naïve and experienced patients, these findings highlight the potential of BDQ/DLM in improving treatment outcomes under routine programmatic conditions.

In addition, new WHO policy guidelines recommend accelerated use of BDQ/DLM in shorter and fully oral treatment regimens for the treatment for MDR/RR-TB as a substitution for the second-line injectable drug, or as part of a novel shorter regimen under operational research conditions.[31,32] This programmatic simplification may enable patients to better adhere to therapy and achieve cure, as well as improve programme outcomes.

Several limitations were identified. First, the use of routine programme data and cohort study design limited the scope of the analyses and thus it is different from a randomised controlled trial. For instance, we could not adjust for all potentially important covariate factors, such as socio-demographic and clinical characteristics (e.g. disease severity, body mass index, CD4 cell count) which may have introduced bias. For instance, clinicians may have decided to prescribe combined BDQ and DLM to sicker patients presenting with advanced TB disease or comorbidities. This may have biased the association with the unfavourable treatment outcome. Second, no data on the safety or adverse events (e.g. QTc interval prolongation, hepatotoxicity) potentially attributable to the new drugs were

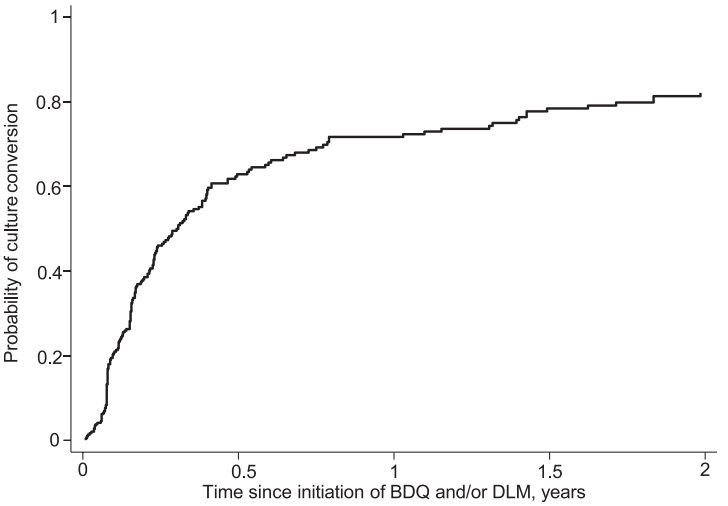

Figure 3 Plot of cumulative incidence function for time from initiation of BDQ- and DLM-based regimen to culture conversion accounting for competing outcomes. Plot of the cumulative incidence function after fitting a competing-risks regression model (Fine-Gray model). The competing risks were death, lost to care, treatment discontinuation and treatment failure, assuming that these events impeded or were likely to impede the outcome event of culture conversion. BDQ = bedaquiline; DLM = delamanid.

available in this dataset. Third, BDQ was more commonly used in this cohort limiting our ability to draw conclusions with respect to the impact of DLM. Finally, it was beyond the scope of this study to compare outcomes of this cohort with outcomes of cohorts from before the introduction of BDQ/DLM or other similar settings. A strength of this study was its conduct under routine programmatic conditions suggesting that the findings may be applicable to similar resource-limited settings in sub-Saharan Africa. Our cohort is also unique with respect to the high prevalence of HIV co-infection.

CONCLUSION

Our data demonstrate the feasibility of providing BDQ/DLM-based treatment regimens under programmatic conditions in a resource-limited setting. The cumulative probability of an adverse outcome was low at 2 years, a considerable achievement where the majority of patients were co-infected with HIV. However, specific populations (e.g. ≥60 years old) remain vulnerable, indicating the need for differentiated service delivery to adequately address the medical comorbidities that increase with age. Notably, the combined use of BDQ+DLM was associated with unfavourable outcomes, calling urgently for more data on the safety of the combined use of these drugs.

Acknowledgements

We would like to acknowledge the patients treated for MDR/RR-TB in Eswatini and the diverse array of health professionals involved in their care. In addition, we would like to recognise the political will to End TB in Eswatini.

Conflicts of interest: none declared.

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RÉSUMÉ

CONTEXTE : L'Eswatini a accéléré les protocoles de traitement de la tuberculose pharmacorésistante, basé sur la bedaquiline et/ou le delamanide (BDQ et/ou DLM) dans des conditions de programme depuis 2015.

OBJECTIF : Identifier des facteurs associés aux résultats du traitement parmi les patients recevant de la BDQ et/ou du DLM soit comme mise en route d'un nouveau traitement ou comme substitution à d'autres médicaments.

SCHÉMA : Etude rétrospective d'une cohorte de patients recevant de la BDQ et/ou du DLM en Eswatini entre mars 2015 et octobre 2018. Nous décrivons les facteurs associés à un résultat défavorable du traitement (décès, perte de vue, échec du traitement et amplification de la résistance) et à la conversion de culture avec une analyse de régression multi variable flexible paramétrique de survie et de risque en compétition.

RÉSULTATS : Sur 352 patients recevant de la BDQ et/ou du DLM, 7,8% et 21,2% ont eu un résultat défavorable du traitement à 6 et 24 mois, respectivement. Les facteurs de prédiction ont été un âge $\geq$ 60 ans (risque relatif ajusté [HRa] 4,49 ; IC95% 1,61–12,57) contre un âge de 20–39 ans et un protocole de traitement combinant les deux médicaments (HRa 4,49 ; IC95% 1,61–12.57) contre la BDQ seule. La probabilité de conversion de culture a été augmentée dans deux structures de santé et chez les patients ayant un profil de poly résistance (sous-risque relatif ajusté 2,01 ; IC95% 1,13–3,59) contre une multirésistance.

CONCLUSION : L'usage isolé de la BDQ ou du DLM a été associé à un faible taux de résultats défavorables, suggérant que ces médicaments pourraient être effectivement adoptés à grande échelle dans des conditions de programme de routine. L'utilisation combinée de la BDQ et du DLM a été un facteur de risque de résultat défavorable et devrait amener à recueillir rapidement davantage de données sur l'utilisation combinée de ces médicaments.

RESUMEN

MARCO DE REFERENCIA: En Eswatini se emprendió una ampliación de la utilización de esquemas contra la TB farmacorresistente a base de bedaquilina, delamanid o ambos (BDQ y/o DLM) en condiciones programáticas, desde el 2015.

OBJETIVO: Determinar los factores asociados con el desenlace terapéutico de los pacientes que reciben BDQ y/o DLM, ya sea al iniciar un tratamiento nuevo o como esquema de sustitución.

MÉTODO: Fue este un estudio retrospectivo de cohortes de pacientes que recibieron BDQ y/o DLM en Eswatini, de marzo del 2015 a octubre del 2018. Se describen los factores asociados con los desenlaces terapéuticos desfavorables (muerte, pérdida durante el seguimiento, fracaso del tratamiento y amplificación de la resistencia) y la conversión del cultivo, mediante análisis de supervivencia con modelos paramétricos multivariables y flexibles y modelos de regresión para riesgos en competencia.

RESULTADOS: De 352 pacientes que recibieron BDQ y/o DLM, alcanzaron un desenlace terapéutico desfavorable el 7,8% a los 6 meses y el 21,2% a los 24 meses. Los factores pronósticos fueron la edad $\geq$ 60 años (riesgo relativo [aHR] 4,49; IC95% 1,61–12,57), en comparación con 20–39 años y el esquema de tratamiento que combinaba ambos fármacos (aHR 4,49; IC95% 1,61–12,57), comparado con la BDQ exclusivamente. La probabilidad de conversión del cultivo aumentó en dos establecimientos de salud y en pacientes con un perfil de polirresistencia (subriesgo relativo ajustado 2,01; IC95% 1,13–3,59), en comparación con la multirresistencia.

CONCLUSIÓN: El uso exclusivo de BDQ o DLM se asoció con tasas bajas de desenlaces desfavorables, lo cual indica que estos fármacos se pueden adoptar en amplia escala en condiciones programáticas. El uso combinado de BDQ y DLM apareció como un factor de riesgo de desenlaces desfavorables, lo cual debe exhortar a reunir más datos sobre la utilización combinada de estos medicamentos.