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Adverse events among people on delamanid for rifampicin-resistant tuberculosis in a high HIV prevalence setting

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SUMMARY

SETTING: Patients with rifampicin-resistant tuberculosis (RR-TB) in the township of Khayelitsha, South Africa, were offered delamanid (DLM) within a decentralised RR-TB treatment programme.

OBJECTIVE: To describe adverse events (AEs) among HIV-positive and negative people receiving DLM for RR-TB in a programmatic setting.

DESIGN: Patients were followed up monthly for blood, electrocardiography and clinical monitoring and AEs were assessed for severity grade, seriousness and relationship to DLM.

RESULTS: Fifty-eight patients (55% male; median age 35 years, interquartile range [IQR] 28–42) started DLM; 46 (79%) were HIV-positive, median CD4 count 173 cells/mm^3 (IQR 70–294). Fifty (86%) patients experienced ≥1 new or worsening AE after starting DLM, most commonly vomiting, QTcB >450 ms and/or myalgia. Serious and/or severe AEs were experienced by 22 (38%) patients; three HIV-positive patients died (not related to DLM). HIV status was not significantly associated with number ($P = 0.089$) or severity/seriousness ($P = 0.11$) of AEs during exposure to DLM. Two (3%) patients had DLM withdrawn due to AEs.

CONCLUSION: AEs during RR-TB treatment, both before and during DLM exposure, were common, with relatively few serious/severe AEs considered related to DLM and no significant association with HIV status. Clinical and electrocardiography monitoring should be prioritised in the first two months after starting DLM.

KEY WORDS: DLM; Khayelitsha; rifampicin; multidrug-resistant

DELAMANID (DLM), a nitroimidazo-oxazole derivative, is a relatively new anti-tuberculosis drug with a novel mechanism of action.[1] In the World Health Organization (WHO) Rapid Communication regarding new evidence related to treatment of rifampicin-resistant tuberculosis (RR-TB), the revised grouping of anti-tuberculosis drugs (into three categories, ranked based on the latest evidence for safety and effectiveness), includes DLM (in Group C due to limited available data).[2]

DLM was first registered in Europe in 2014, but global access under programmatic conditions has been limited.[3] Otsuka's international Compassionate Use Programme allows for inclusion of DLM within salvage regimens on a case-by-case basis for patients with limited other treatment options.[4] The endTB Project, a global initiative set up by Médecins Sans Frontières (MSF), Partners in Health (PIH), and Interactive Research and Development (IRD) under the funding of UNITAID[5–7] has facilitated access to DLM across 17 countries.[8]

There are limited published data on the use of DLM outside of clinical trial settings and particularly among individuals infected with human immunodeficiency virus (HIV). The patients described below were included in an analysis of a larger cohort ($n = 103$) published by Mohr et al., which focused on 12-month interim outcomes, sputum culture conversion and QTcF profiles.[9] In this paper, we present a description and analysis of all AEs experienced by patients receiving DLM in the first year that MSF introduced the drug for RR-TB in a high HIV burden programmatic setting in South Africa.

METHODS

Setting

The study was conducted in the peri-urban township of Khayelitsha, near Cape Town, where patients with RR-TB are diagnosed, initiated on treatment and managed by clinicians in government-run primary or secondary care facilities. MSF provides clinical, psychosocial and administrative expertise and support. MSF initially facilitated access to DLM through

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Otsuka's Compassionate Use Programme in November 2015. From January 2016, DLM was procured by MSF and offered as part of the global endTB Project.[9]

Cohort selection and eligibility to receive delamanid

Patients potentially eligible for DLM were identified and screened by MSF doctors using criteria in WHO guidelines[10,11] and the endTB Clinical Guide v3.3.[12] Patients fell into three broad categories: those in whom second-line TB treatment was failing and treatment options were limited; those with RR-TB susceptible to fluoroquinolones but where injectable agents were contraindicated due to drug resistance, ototoxicity, renal impairment, age <18 years or intolerance; and those with RR-TB resistant to fluoroquinolones and treatment options were limited due to underlying comorbidities, drug-drug interactions or previous serious AEs.

Patients initiating DLM between 2 November 2015 and 1 December 2016 were included (allowing for 6 months follow up until the censor date 1 June 2017). Patients gave written informed consent to receive DLM. Specific approvals were obtained from the MSF/PIH/IRD endTB committee to use DLM in children or in co-administration with bedaquiline (BDQ). DLM was dosed at 100 mg twice daily over 6 months, and the composition of background regimens was modified depending on indication for DLM and background risk of AEs. DLM was never added in isolation to a failing regimen and regimens always included at least three other second-line drugs (SLDs) still considered to be effective, in addition to pyrazinamide.

Access to delamanid and regulatory approval

DLM was imported under approval from the national regulatory authority of South Africa. Monitoring and evaluation of patients on DLM was included within an MSF-designed protocol that was approved by the University of Cape Town Human Research and Ethics Committee (499/2011). MSF ethical review board exemption criteria for analysis of routinely collected programmatic data were met.

Treatment monitoring

Routine RR-TB monitoring comprised monthly clinical assessment, sputum microbiology, audiometry screening and blood monitoring for haematology, hepatic and renal function (monthly) and thyroid function (every three-to-six months). Additional required monitoring for the duration of exposure to DLM included at least monthly assessment of electrocardiography (ECG), serum albumin and electrolytes and medical assessment of AEs thought to be related to DLM (particularly headache, nausea, vomiting, insomnia, cardiac symptoms). More frequent monitoring was carried out as considered necessary by the treating clinician. ECG monitoring was primarily intended to detect QT interval prolongation and involved a single ECG reading at each visit using machines that were routinely available at healthcare facilities.

Adverse events definitions and reporting

All AEs were recorded at each doctor visit, and serious adverse events ('death, life-threatening, hospitalisation, significant disability, congenital anomaly, medically significant')[12] were reported to regulatory authorities and ethics committees. All AEs were graded for severity, between 1 (mild) and 4 (life-threatening), according to the scale used by the MSF pharmacovigilance unit, based on the National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases grading system and the National Cancer Institute Common Terminology Criteria for Adverse Events.[12] Causality of AEs was assessed as 'related' or 'unrelated' to DLM by MSF clinicians.[12] Assessment of QT interval prolongation was based on corrected QT values that were recorded in clinic notes and acted upon by treating clinicians. Most machines automatically corrected for heart rate using Bazett's (QTcB) rather than Fridericia's (QTcF) formula and, as clinicians were unfamiliar with calculating QTcF values manually, QT interval prolongation (as assessed by the clinician) was defined as QTcB >450 ms.

Data collection and analysis

Routine demographic, clinical and interim outcomes data were obtained from multiple sources – the South African Electronic RR-TB Register (EDR.web), paper-based facility registers, individual medical records and the National Health Laboratory Service database. Information on AEs experienced by patients who had been on SLD treatment for at least one day before DLM start was collected retrospectively from existing medical records. As some of these 'baseline AEs' persisted after DLM initiation, the main analysis of AEs (during DLM exposure) included 'new' AEs (occurring for the first time after starting DLM) and those that 'worsened by ≥1 grade in severity' after starting DLM. Data on 'new' and 'worsening' AEs occurring after DLM initiation were collected retrospectively from routine medical records and detailed clinical records maintained by MSF doctors.

Data analyses were conducted using Excel and STATA v 14.1 (Stata Corp, College Station, TX, USA). Differences in clinical and demographic characteristics based on HIV status were assessed using Chi-squared, Fisher's or rank-sum tests. Chi-squared tests were used to test for differences between the occurrence of serious and severe AEs based on HIV status.

Table 1 Characteristics of 58 patients initiating DLM, 2 November 2015–1 December 2016

Variable	Total ($n = 58$, 100%) *n* (%)	HIV-positive ($n = 46$, 79%) *n* (%)	HIV-negative ($n = 12$, 21%) *n* (%)	*P* value
Age at DLM start, years, median [IQR]	35 [28–42]	35 [30–43]	32 [18–39]	0.18
Male	32 (55)	24 (52)	8 (67)	0.37
CD4 count at DLM start, cells/mm^3,* median [IQR]	—	173 [70–294]	—	—
On ARVs before DLM, *n* (% of HIV-positive)	—	38 (83)	—	—
ARVs at DLM start, number of patients (% of above)				
EFV and NRTIs	—	26 (68)	—	—
NVP and NRTIs	—	6 (16)	—	—
Ritonavir plus ATZ/lopinavir and NRTIs	—	6 (16)	—	—
Time to ARVs after DLM start, weeks,† median [IQR]	—	2.7 [0.8–12.7]	—	—
Indication for DLM				
Second-line TB treatment failure, with limited effective drug options	4 (7)	3 (6)	1 (8)	0.34
RR-TB and FQ-susceptible, injectable contraindicated	39 (67)	33 (72)	6 (50)	
RR-TB and FQ-resistant, and limited effective SLD options	15 (26)	10 (22)	5 (42)	
Started SLD treatment before DLM start	54 (93)	44 (95.6)	10 (83.3)	0.19
Time on SLD treatment before DLM start, weeks, median [IQR]	7.6 [3.1–23.1]	8.6 [3.6–23.6]	5.9 [2.6–11.1]	0.22
Patients with extra SLDs added to regimens at or after DLM start				
≥2 extra SLDs	15 (26)	11 (23.9)	4 (33.3)	0.48
1 extra SLD	29 (50)	25 (54.3)	4 (33.3)	
No extra SLDs	14 (24)	10 (21.7)	4 (33.3)	

* Latest known CD4, closest to DLM start, within 6 months before or after DLM start, $n = 2$ missing CD4 count.
† Among seven patients who initiated ART after DLM was started; one patient did not start ART and was lost from RR-TB treatment 4 weeks after starting DLM.
DLM = delamanid; HIV = human immunodeficiency virus; IQR = interquartile range; ARV = antiretroviral; EFV = efavirenz; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; ATZ = atazanavir; TB = tuberculosis; RR-TB = rifampicin-resistant TB; FQ = fluoroquinolone; SLD = second-line drug.

RESULTS

Cohort description, time to delamanid start and background drug regimens

Table 1 describes 58 patients initiating DLM over the study period; only four (two HIV-positive) initiated DLM at the start of RR-TB treatment. Each of the 54 (93%) patients already on second-line treatment before DLM start were experiencing at least one 'baseline' AE by the time DLM was introduced. The frequencies of SLDs used in regimens to support DLM are demonstrated in Figure 1. Twenty-seven (47%) patients received ≥1 other QT-prolonging TB drug (i.e. clofazimine, BDQ, moxifloxacin) along with DLM.

'Baseline' adverse events at time of delamanid start

There was a total of 199 'baseline' AEs among the 54 patients exposed to SLDs before DLM initiation—a median of three (interquartile range [IQR] 1–4) per person across the whole cohort, but significantly more among HIV-positive, than HIV-negative, individuals ($P = 0.038$). After DLM initiation, 31 (16%) of the 199 'baseline' AEs worsened by at least one grade in severity, among 19 patients; the rest either improved, resolved or persisted at the same grade of severity during DLM exposure.

New and worsening adverse events during delamanid exposure

Figure 2 outlines the duration of exposure to DLM among all 58 patients. Overall, a total of 285 AEs (31 worsening and 254 new) were reported among 50 (86%) patients after DLM initiation; a median of four AEs (IQR 2–7) per patient. There was no significant difference in number of AEs per patient ($P = 0.089$) or proportion of patients experiencing any AE ($P = 0.34$) based on HIV status. Of the eight (14%) patients with no recorded AEs, three were only exposed to DLM for 4 weeks before being lost from treatment or transferring to another facility; the other five patients completed 6 months of DLM with regular monitoring at monthly clinic visits. The frequency of AEs, stratified by HIV status and time to event for AEs considered potentially related to DLM are listed in Table 2. Over one quarter of the cohort experienced vomiting, QTcB prolongation and/or myalgia while receiving DLM along with other SLDs. Overall, 63 (22%) of all new and worsening AEs (predominantly nausea, vomiting, dizziness, headaches and QTcB prolongation) were considered to be related to DLM and occurred among 37 (74%) of the patients; 12 (19%) of the 63 related AEs were serious and/or severe. The median time from DLM start to onset or worsening of all DLM-related AEs was 2.7 weeks (IQR 1.3–4.1).

QT interval prolongation

New or worsening QTcB prolongation occurred in 16 (28%) of the 58 patients and was considered to be related to DLM in all cases. The median time from DLM start to new onset or worsening QTcB prolongation was 4.3 weeks (IQR 2.7–6.6). Ten (37%) of the 27 patients taking ≥1 other QT-prolonging TB drugs experienced QTcB prolongation, compared to 6 (19%) of the 31 patients not exposed to other QT-prolonging drugs ($P = 0.13$). QTcB prolongation was considered both serious

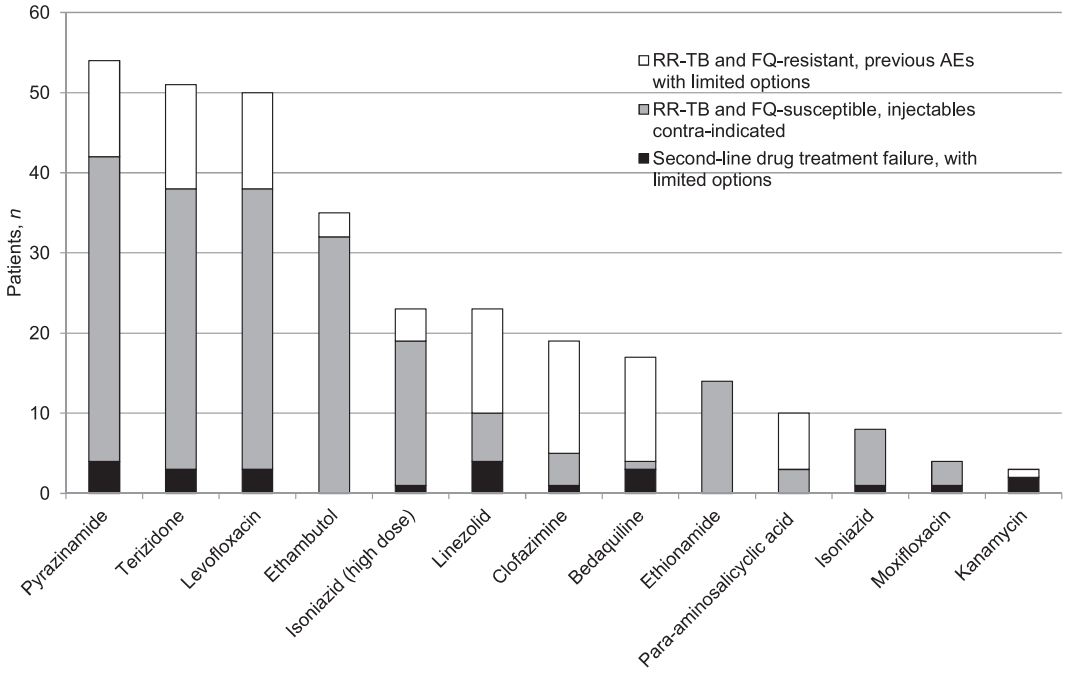

Figure 1 Bar chart showing frequencies of second-line TB medications used at any time during delamanid exposure within RR-TB treatment regimens in 58 patients, stratified by indication for delamanid. RR-TB = rifampicin-resistant TB; FQ = fluoroquinolone; AE = adverse event; TB = tuberculosis.

and severe (i.e. QTcB >500 ms) in six patients; five had already been exposed to at least one other QT-prolonging TB drug and four had experienced mild QTcB prolongation before starting DLM. Two of the six patients had associated cardiac symptoms (chest pain, dizziness, palpitations). There were no cases of cardiac arrhythmia or syncope but all QT-prolonging drugs were temporarily withheld in all six cases; one patient had DLM permanently withdrawn due to the event but the others had DLM successfully reintroduced into the treatment regimen.

Serious and severe adverse events

A total of 33 AEs (12% of all new and worsening AEs after DLM start) were considered serious and/or severe (grade ≥3), and occurred in 22 (38%) patients (Table 3). Twelve (36%) of the 33 serious and/or severe AEs were potentially related to DLM, and occurred among 10 (17%) patients (Table 3). There was no significant difference ($P = 0.11$) in the proportion of HIV-positive individuals (20/46, 43%) experiencing one or more serious and/or severe AE than HIV-negative individuals (2/12, 17%). Three patients (all HIV-positive) died and no deaths were considered potentially related to DLM. The other 19 patients recovered and continued second-line TB treatment; DLM was permanently withdrawn in only two of these patients (Figure 2). Throughout treatment with DLM, at least one of nine SLDs other than DLM was withdrawn due to toxicity or intolerance in 25 (43%) patients.

DISCUSSION

The majority of people in this cohort experienced multiple AEs, both before and after initiating DLM; mild to moderate AEs were very common (affecting >85% of patients). A recent systematic review and meta-analysis of 2776 patients (70% HIV co-infected) receiving second-line treatment for RR-TB (not including DLM) found that 83% of patients experienced one or more adverse drug reactions.[13] Aside from QT interval prolongation, the AEs reported here were similar to those in other cohorts of HIV-coinfected patients on RR-TB treatment without DLM.[14]

Otsuka's phase III clinical trials reported no significant difference in treatment-emergent AEs between participants receiving DLM and those receiving placebo, but AEs considered related to DLM in previous reports include: mild-to-moderate QT interval prolongation, nausea, vomiting, insomnia and headaches.[1,15–17] Although nearly one quarter of all AEs in this observational study were considered potentially related to DLM, this may be an overestimate as many common AEs may be caused or exacerbated by a variety of ART and other second-line TB drugs.[18] Our findings suggest that regular clinical and ECG assessment should be prioritised within the first two months of exposure to DLM within multidrug regimens to identify and address the most common AEs.

Serious and/or severe AEs occurred in a higher proportion of patients (particularly among those

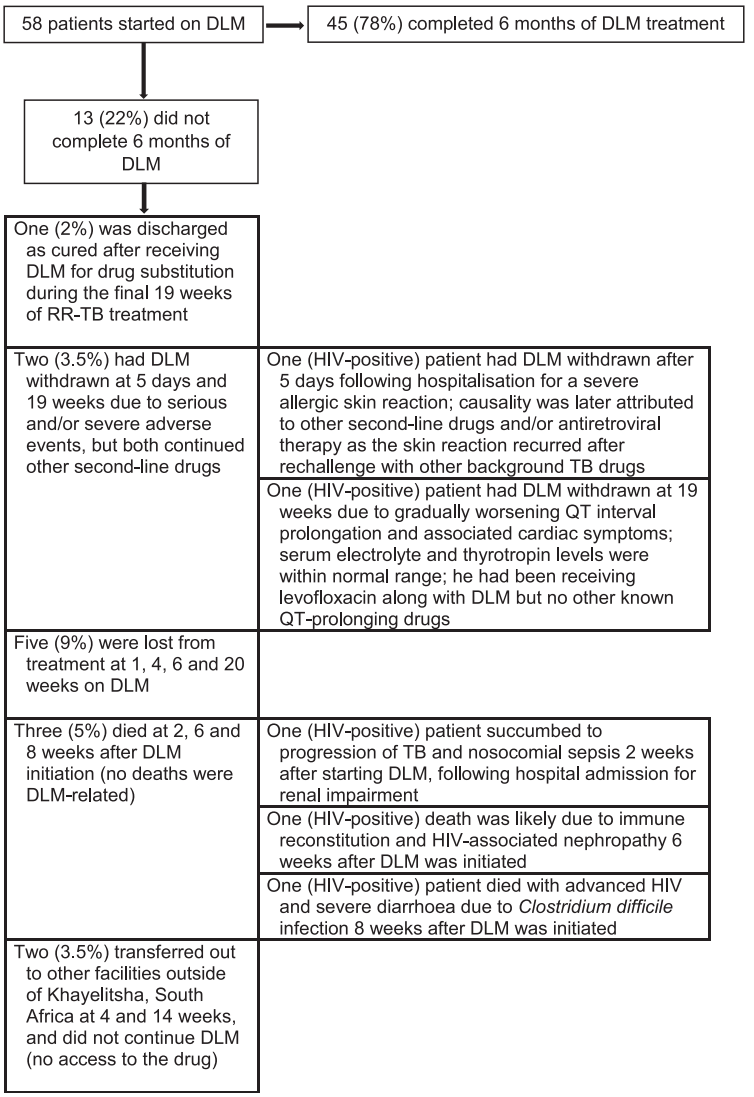

Figure 2 Flow diagram of duration of exposure to DLM among 58 patients initiating DLM between 2 November 2015 and 1 December 2016. DLM = delamanid; IQR = interquartile range; RR-TB = rifampicin-resistant TB; HIV = human immunodeficiency virus; TB = tuberculosis; AE = adverse event; SLD = second-line drug; ART = antiretroviral therapy.

HIV-coinfected) in this cohort than in the phase III trials, where serious AEs were recorded in 26.1% of participants (37.5% of HIV-positive) in the DLM arm and 27.6% (31.3% of HIV-positive) in the placebo arm.[17] This could be explained by the higher HIV co-infection rate in this cohort and possible exclusion of non-serious AEs of grade 3/4 severity in the phase III trial report. DLM was not considered causal in any of the three deaths, but could not be ruled out as a potential cause in one third of all serious and/or severe AEs, (mostly QTcB prolongation).

Overall, 10% of the whole cohort experienced QTcB >500 ms. The phase III trial data showed that 2.1% of participants who received DLM and 1.2% of those who received placebo experienced QTcF >500 ms.[17] This difference may be explained partly by the difference in DLM dosing over the 6-month period as well as the overestimation of the corrected QT interval using Bazett's formula at higher heart rates.[19] The previously published paper by Mohr et al. reported QTcF >500 ms in 2% of the larger cohort from this setting, but these QTcF values were calculated retrospectively and did not impact clinical management.[9] QTcB intervals as recorded in clinic notes represented the clinician's assessment of QT interval prolongation which influenced management decisions in real time. Reassuringly, few patients experienced clinical cardiac sequelae or had DLM withdrawn for this reason. Concomitant use of BDQ, clofazimine and/or moxifloxacin probably contributed to the rate of QTcB prolongation in this cohort, however the association was not significant given the small sample size. Our findings support ECG monitoring for at least the first two months of DLM exposure, particularly among patients receiving multiple QT-prolonging drugs. Clinicians should be

Table 2 New and worsening adverse events among 58 patients after starting DLM, 2 November 2015–1 December 2016*

	Number of patients experiencing AE			Causality of AE in relation to DLM	
Adverse event category	Total ($n = 58$) *n* (% of whole cohort)	HIV-positive ($n = 46$) *n* (% of HIV-positive)	HIV-negative ($n = 12$) *n* (% of HIV-negative)	Experienced ≥1 AE related to DLM number of patients (% of row total)	Time from DLM start to onset of first related AE days Median [IQR]
All adverse events	50 (86)	41(89)	9 (75)	37 (74)	19 [9–29]
Vomiting	18 (31)	16 (35)	2 (17)	8 (44)	30 [19–46]
ECG QTcB >450 ms	16 (28)	13 (28)	3 (25)	16 (100)	33 [12–84]
Myalgia	15 (26)	15 (33)	0	0	—
Arthralgia	14 (24)	12 (26)	2 (17)	0	—
Diarrhoea	13 (22)	12 (26)	1 (8)	2 (15)	8 [8–9]
Neuropathies	12 (21)	8 (17)	4 (33)	0	—
Nausea	12 (21)	12 (26)	0	9 (75)	21 [19–81]
Mucocutaneous symptoms	11 (19)	9 (20)	2 (17)	1 (9)	5 [5–5]
Dyspepsia	10 (17)	9 (20)	1 (8)	0	—
Headaches	10 (17)	10 (22)	0	8 (80)	30 [26–37]
ALT/AST increased	8 (14)	7 (15)	1 (8)	6 (75)	68 [37–99]
Hypocalcaemia (not corrected)	8 (14)	7 (15)	1 (8)	0	—
Chest pain	8 (14)	4 (9)	4 (33)	4 (50)	61 [24–102]
Anaemia	7 (12)	5 (11)	2 (17)	0	—
Dizziness	7 (12)	7 (15)	0	7 (100)	14 [7–27]
Hypoalbuminaemia	6 (10)	4 (9)	2 (17)	0	—
Reduced appetite	6 (10)	6 (13)	0	2 (33)	18 [16–19]
Visual disturbance	6 (10)	6 (13)	0	0	—

* Less common (occurring in <10% of cohort) adverse events included oral discomfort/dysphagia (9%), constipation (9%), palpitations (9%), hypomagnesaemia (9%), hypothyroidism (7%), itching eyes (7%), pruritis (7%), raised creatinine (5%), seizure (5%), malaise (5%), anxiety (5%), dyspnoea (5%), candidiasis (5%), hypokalaemia (3%), insomnia (3%), photophobia (3%), hyperthyroidism (3%), fatigue/lethargy (3%), weight loss (3%), psychosis (3%), sexually transmitted infection (3%), allergic reaction (3%), hearing impaired (3%); other AEs that occurred in <3% ($n = 1$) of the cohort were as follows: hyponatraemia, hypertension, injection site reaction, raised ALP, tinnitus, urinary tract infection, jaundice, depression, cough, epistaxis, facial flushing, fever, confusion, delirium, pneumothorax, multi-organ failure, renal impairment, other infections, miscellaneous neurological disorders.
DLM = delamanid; AE = adverse event; HIV = human immunodeficiency virus; IQR = interquartile range; ECG = electrocardiograph; ALT = alanine transaminase; AST = aspartate transaminase; ALP = alkaline phosphatase.

Table 3 Serious and/or severe (grade 3 or 4) adverse events, related and not related to DLM in 22 of 58 patients receiving DLM for rifampicin-resistant tuberculosis*

	HIV-positive ($n = 46$) *n* (%)	HIV-negative ($n = 12$) *n* (%)
Related to DLM		
QTcB >500 ms	6 (13.0)	0
Skin rash	1 (2.2)	0
Allergic reaction (angioedema)	1 (2.2)	0
Dyspnoea	1 (2.2)	0
Headaches	1 (2.2)	0
Palpitations	1 (2.2)	0
Not related to DLM		
Seizure	3 (6.5)	0
Psychosis	2 (4.3)	0
Neuropathies	1 (2.2)	1 (8.3)
Anaemia	1 (2.2)	1 (8.3)
Skin rash	1 (2.2)	0
Allergic reaction	1 (2.2)	0
Vomiting	1 (2.2)	0
Renal impairment	0	1 (8.3)
Nosocomial sepsis leading to death	1 (2.2)	0
Urinary tract infection	1 (2.2)	0
Transaminitis	1 (2.2)	0
Arthralgia	1 (2.2)	0
Multi-organ failure leading to death	1 (2.2)	0
Hypokalaemia	1 (2.2)	0
Hypocalcaemia	1 (2.2)	0
Clostridium difficile diarrhoea leading to death	1 (2.2)	0
Delirium	1 (2.2)	0
Arm weakness	1 (2.2)	0

* Some patients experienced >1 serious/severe adverse event.
DLM = delamanid; HIV = human immunodeficiency virus.

aware that QT correction using Bazett's formula may overestimate QT interval prolongation in these patients.

The findings reported here are from a programmatic setting among a population that was considerably underrepresented in the phase III DLM trials (<25% HIV coinfection) where no new or clinically significant drug-drug interactions between DLM and commonly used ARVs were reported.[17] Many HIV-positive patients in our cohort were able to continue on uninterrupted efavirenz-based ART regimens throughout treatment with DLM. In Schnippel's review of 24 observational cohorts, nine of the 16 studies that tested associations between HIV and ADRs found no significant effect of HIV status;[13] in our cohort HIV-coinfection was only significantly associated with a higher rate of AEs before the introduction of DLM.

This study was observational and a number of factors may have significantly affected the nature, rate, severity and/or seriousness of AEs reported before and after DLM initiation. Numbers were small and we could not control for confounding factors such as CD4 count, comorbid conditions, concomitant medications, duration of SLD exposure before starting DLM, and number and type of SLDs in the background regimens. Other limitations include the lack of assessment of causality of AEs to other TB

drugs and ARVs, the use of QTcB instead of QTcF and the low threshold for determining clinically relevant QT prolongation in this study.

In conclusion, although AEs were common, most were likely due to factors or drugs other than DLM. Serious and/or severe AEs rarely led to permanent DLM withdrawal even among HIV-coinfected individuals. As drug-related AEs often contribute to loss to follow up, the most common AEs can and should be detected and addressed early during DLM exposure, particularly in primary and secondary healthcare settings. Access to DLM should be expanded to provide more alternative drug options for treatment of RR-TB, regardless of HIV coinfection.

Conflicts of interest: none declared.

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RÉSUMÉ

CONTEXTE : Les patients atteints de tuberculose résistante à la rifampicine (RR-TB) dans le township de Khayelitsha, Afrique du Sud, se sont vus offrir du délamanide (DLM) dans le cadre d'un programme de traitement de RR-TB décentralisé.

OBJECTIF : Décrire les effets secondaires (AE) parmi les patients positifs et négatifs au virus de l'immunodéficience humaine (VIH) recevant du DLM pour une RR-TB dans un contexte de programme.

SCHÉMA : Les patients ont été suivis tous les mois avec un bilan sanguin, un électrocardiogramme et un examen clinique et les FS ont été évalués en termes de degré de gravité et de lien avec le DLM.

RÉSULTATS : Cinquante-huit patients (55% d'hommes ; âge médian 35 ans [IQR] 28–42) ont mis en route le DLM ; 46 (79%) étaient positifs au VIH, le nombre de CD4 médian était de 173 cellules/mm^3 (IQR 70–294). Cinquante (86%) patients ont eu au moins un AE nouveau ou une aggravation d'un AE existant après la mise en route du DLM, le plus souvent des vomissements, un QT > 450 ms et/ou des myalgies. Des AE importants et/ou graves ont affecté 22 (38%) patients ; trois patients positifs au VIH sont décédés (sans rapport avec le DLM). Le statut VIH n'a pas été significativement associé au nombre (P = 0,089) ni à la gravité/l'importance (P = 0,11) des AE durant l'exposition au DLM. Deux (3%) patients ont dû arrêter le DLM en raison des AE.

CONCLUSION : Les AE lors du traitement de la RR-TB, à la fois avant et pendant l'exposition au DLM, ont été fréquents, avec relativement peu d'effets secondaires importants/graves considérés comme liés au DLM et pas d'association significative avec le statut VIH. Le suivi clinique et électrocardiographique doit être une priorité dans les 2 premiers mois suivant l'introduction du DLM.

RESUMEN

MARCO DE REFERENCIA: En el marco de un programa descentralizado de tratamiento de la tuberculosis resistente a rifampicina (RR-TB), se ofreció a los pacientes el delamanid (DLM) en el municipio de Khayelitsha, en Suráfrica.

OBJETIVO: Describir las reacciones adversas (AE) observadas en las personas positivas o negativas frente al virus de la inmunodeficiencia humana (VIH) que recibían DLM para el tratamiento de la RR-TB en un marco programático.

MÉTODO: Se llevó a cabo un seguimiento mensual biológico, electrocardiográfico y clínico de los pacientes y se evaluaron las AE según la intensidad, la gravedad y su relación con el DLM.

RESULTADOS: Ochenta y cinco pacientes iniciaron DLM (55% de sexo masculino, mediana de la edad 35 años; amplitud intercuartílica [IQR] 28–42); de ellos 46 eran positivos frente al VIH (79%; mediana del recuento de linfocitos CD4 173 células/mm^3; IQR 70–294). Cincuenta pacientes (86%) presentaron una o más AE nuevas o agravadas después de haber iniciado el DLM, con mayor frecuencia vómito, prolongación del intervalo QT ajustado a la frecuencia cardíaca (QTcB) > 450 ms y mialgias. En 22 pacientes (38%) se observaron AE intensas, graves o ambas; tres pacientes positivos frente al VIH fallecieron (sin relación con el DLM). La situación frente al VIH no se asoció de manera significativa con el número (P = 0,089) ni la intensidad o gravedad (P = 0,11) de las AE durante la exposición a DLM. En dos pacientes (3%) se retiró el DLM por causa de las AE.

CONCLUSIÓN: Las AE durante el tratamiento de la RR-TB, tanto antes de la exposición al DLM como durante la misma fueron frecuentes y en pocas ocasiones las AE intensas o graves se consideraron relacionadas con este fármaco; no se observó una asociación significativa con la infección por el VIH. Es importante dar prioridad a un seguimiento clínico y electrocardiográfico durante los 2 primeros meses de administración de DLM.