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Early View

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Delamanid for Rifampicin–Resistant Tuberculosis: A Retrospective Study from South Africa

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Summary

Rifampicin-resistant TB patients treated with delamanid had good treatment response and cardiotoxicity was rare.

Abstract:

Background

Experience with delamanid (Dlm) is limited, particularly among HIV-positive individuals. We describe early efficacy and safety from a programmatic setting in South Africa.

Methods

This was a retrospective cohort study of patients receiving Dlm-containing treatment regimens between November 2015 and August 2017. Twelve-month interim outcomes, sputum culture conversion (SCC) by months-2 and 6, serious adverse events (SAEs), and QTcF data were reported.

Results

Overall, 103 patients initiated Dlm; 79(77%) were HIV-positive. The main indication for Dlm was intolerance to second-line anti-TB drugs (n=58, 56%). Forty-six patients had 12-months of follow-up; 28(61%) had a favorable outcome (cure, treatment completion, or culture negativity). Fifty-seven patients had positive cultures at Dlm initiation; 16/31(52%) and 25/31(81%) had SCC within 2 and 6-months, respectively. There were 67 SAEs reported in 29(28%) patients. There were four instances of QTcF prolongation >500ms in 2(2%) patients, leading to permanent discontinuation in one case, however no cardiac arrhythmias occurred.

Conclusions

This large cohort of difficult-to-treat patients receiving Dlm for rifampicin-resistant tuberculosis treatment in a programmatic setting with high HIV prevalence had favorable early treatment response and tolerated treatment well. Dlm should remain available, particularly for those that cannot be treated with conventional regimens and/or with limited treatment options.

Introduction

In 2016, an estimated 600,000 new cases of rifampicin-resistant tuberculosis (RR-TB) emerged globally, defined as *Mycobacterium tuberculosis* with demonstrated resistance to at least rifampicin, including mono- and poly-resistant strains of TB, multidrug-resistant (MDR) TB, and extensively drug-resistant (XDR) TB.[1],[2] This represents a significant public health threat.[3] RR-TB requires prolonged treatment with multiple toxic agents, resulting in poor treatment outcomes. [4],[5]

A novel anti-tuberculosis agent from the nitroimidazole class, delamanid (Dlm) (Deltyba, Otsuka Pharmaceuticals, Rockville, MD, USA), was recommended for use in RR-TB by the World Health Organization (WHO) in 2014 after receiving conditional approval by the European Medicines Agency in 2013.[6],[7] These recommendations were based on Phase IIB trial data, which demonstrated efficacy and safety of the drug.[8],[9] Additionally, Dlm has no drug-drug interactions when given with antiretroviral therapy (ART), including efavirenz (EFV).[10][11] Despite these promising results and early recommendations, uptake of Dlm globally has been poor, with only 976 persons having received the drug under programmatic conditions as of October 2017.[12]

At the 48th Union World Conference on Lung Health, preliminary Phase III clinical trial data were presented, in which Dlm was compared with placebo when added to a multidrug backbone regimen for 6-months. The primary endpoint was time to sputum culture conversion (SCC) at 6-months. Patients in the Dlm arm had 6-13 days faster time to SCC over 6 months compared to the placebo, depending on three different analytic methods used (p-values ranging from 0.0052 – 0.0562). Long term outcomes at 24 months- one of the secondary endpoints- did not differ significantly in the Dlm arm compared to the placebo, although the study was not powered to detect differences in final outcomes. Safety data were encouraging as only 5.3% of patients in the Dlm arm experienced a QTcF interval >500 ms.[13] These results have called into question the role of Dlm in the treatment of RR-TB and there is an urgent need for data on Dlm use under programmatic conditions to better define the role of this drug in the treatment of RR-TB especially among populations that were underrepresented in the Phase III trial, including adolescent patients, those with HIV, extra-pulmonary TB, and intolerance to the drugs in the standard MDR regimen.[14] In fact the WHO recently released a position statement on the use

of Dlm for the treatment of RR-TB stating that use should be continued as indicated and that there is a need for more data from programmatic settings.[15]

In South Africa there were close to 20,000 cases of RR-TB confirmed in 2016.[16] Bedaquiline (Bdq) is registered in the country and is being used widely, along with other repurposed drugs such as linezolid and clofazimine, for treatment of RR-TB in line with WHO recommendations.[17][18] To date, Dlm is not registered or readily available in South Africa outside of an expanded access programme with strict criteria.[19] Médecins Sans Frontières (MSF), a humanitarian non-governmental organization, was able to procure Dlm for a subset of patients with RR-TB in a decentralised treatment programme in Khayelitsha, South Africa since 2015. The aim of this study was to describe early efficacy and safety of Dlm-containing RR-TB treatment regimens in a cohort of patients with high rates of HIV co-infection.

Methods

Study Design

This was a retrospective, descriptive cohort study of patients with RR-TB patients who received Dlm within an individualised treatment regimen, using routinely collected programmatic data.

Setting

Khayelitsha is a peri-urban township outside of Cape Town, South Africa with a population of approximately 450,000 people, most of whom reside in informal structures. The annual case notification rate of RR-TB is 55/100,000 population, the HIV prevalence among RR-TB patients is 70%, and patients with RR-TB are managed mostly as out-patients across 11 primary health care facilities, as previously described.[20] Most patients treated for RR-TB receive self-administered treatment (SAT), accompanied by enhanced adherence support from a dedicated team of counselors.

Participants

All patients initiated on Dlm in Khayelitsha between November 2015 and August 2017 were included in the study. Indications for Dlm included i) intolerance to specific second-line (SL) drugs in the treatment regimen (i.e. fluoroquinolone susceptible RR-TB but high risk of hearing loss); ii) limited options to design a regimen with at least five effective drugs; iii) patients in whom previous RR-TB treatment had failed. Patients were further eligible to receive the combination of Bdq and Dlm if there was i) the inability to construct a regimen with at least four effective drugs; ii) suspected resistance due to previous drug exposure; iii) intolerance to drugs in the MDR regimen. As patients on the combination of Bdq and Dlm have been previously reported on, we did not assess safety or efficacy outcomes for these patients separately.[21]

Criteria that were considered when designing a Dlm-containing RR-TB treatment regimen were: HIV co-infection, EFV-based ART (therefore Bdq contra-indicated); allergy, intolerance, or prior treatment with Bdq; > 2 months exposure to clofazimine (Cfz); age ≤18 years; pregnancy; extensive drug resistance; high risk of treatment failure (i.e. diabetes and extensive cavitation).

Patient Monitoring

As per WHO recommendations[6], Dlm was administered for a period of 6-months, although some patients required prolonged administration of the drug. Reasons for prolonged administration of Dlm included interruptions in Dlm throughout the course of treatment or the lack of other therapeutic options to devise a treatment regimen with at least four effective drugs following the completion of the intensive phase of treatment with Dlm. Clinical monitoring of patients on Dlm occurred monthly, while electrocardiogram (ECG) monitoring was carried out every 2-weeks for the first 12 weeks and monthly thereafter. In cases of QTcF prolongation (> 500 ms) patients were managed according to WHO guidelines and local expert advice.

Study Outcomes

Standard WHO definitions were used for RR-TB treatment outcomes, including success, loss to follow-up (LTFU), death, and treatment failure.[22] Favorable outcomes were defined as cure, treatment completion, or culture negativity if still on treatment.

Efficacy

Efficacy was assessed using SCC measured 2 and 6-months after Dlm initiation (conducted on liquid media using MGIT). SCC was defined as two consecutive negative cultures taken at least 30 days apart in a patient with a positive specimen at baseline.[22] Sputum reversion to positive was defined as two consecutive positive cultures at least 28 days apart occurring after SCC. Baseline refers to the time-point when Dlm was added to the regimen, even if background RR-TB treatment was ongoing.

Safety

Serious adverse events (SAEs) were defined according to the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines as events: resulting in death; that are life-threatening; that require inpatient hospitalisation or prolongation of existing hospitalisation; resulting in persistent or significant disability/incapacity; or that were congenital anomaly/birth defect.[23]

In our cohort, QT intervals were corrected using the Frederica formula (QTcF).[24] QTcF prolongation was defined as any absolute QTcF interval ≥500 ms *or* as any QTcF interval increase of >60 ms from the baseline.

Data sources, Analysis, and Statistics

Data were obtained from the South African Electronic RR-TB Register (EDR.web), RR-TB registers, patients' medical records (including ECG readings) and the National Health Laboratory Service Database (TrakCare). Data on SAEs were obtained from the central MSF Pharmacovigilance (PV) unit in Geneva, Switzerland who compile SAE reports which are reported by the MSF clinical field team within 24 hours of becoming aware of the event. Data entered in EDR.web were validated using information captured in patient medical records and RR-TB registers.

Clinical and demographic characteristics were stratified by HIV-status. Categorical variables were described using proportions and continuous variables using medians and interquartile range (IQR). Chi square or Fisher tests and Wilcoxon rank-sum tests were used to determine differences in clinical and demographic characteristics based on HIV-status. Interim outcomes for patients who had 12-months of follow-up and culture conversion by 2 and 6-months were reported. A Kaplan-Meier curve was used to show time to 6-month culture conversion; data were censored for LTFU and mortality. Bivariate logistic regression and Cox proportional hazards models were used to determine the strength of association between culture conversion and patient characteristics. SAEs were reported using descriptive statistics. Changes in QTcF values over time at the cohort level were reported as the median of the difference between each follow-up time point and the baseline value for each individual. Box plots were used to show the median QTcF values over time and the median change from baseline for the 6-month follow-up period. Factors were considered statistically significant if there was a two-tailed *P-value of* <0.05. Stata version 14 (College Station, Texas, USA) package was utilized for statistical analysis.

Ethics

Ethical approval for this study was obtained from the University of Cape Town Human Research Ethics Committee (*HREC 499/2011*). The study fulfilled the MSF Ethics Review Board

(Geneva, Switzerland) exemption criteria for *a posteriori* analyses of routinely collected clinical data. Patients provided written informed consent to receive Dlm.

Results

Patient and Treatment Characteristics

Overall, 103 patients were initiated on Dlm for RR-TB treatment, of which 79 (77%) patients were HIV positive (**Table 1**). The median (IQR) CD4 count was 141 (61-252) cells/mm^3 (n=45, 57% with CD4 count< 200 cells/mm^3) and 72 (94%) HIV positive patients were on anti-retroviral therapy (ART) at Dlm initiation. The five patients not on ART at Dlm initiation were started on ART within a median (IQR) of 2.7 (1.0-8.0) weeks after Dlm initiation. The majority of patients had pulmonary TB (PTB; n=97, 94%); of the five patients with extra-pulmonary TB (EPTB) two had peri-anal abscesses and the remaining three had disseminated TB, a pericardial and pleural effusion, and a pleural effusion, respectively. One patient with both PTB and EPTB had disseminated TB. The median (IQR) time from RR-TB treatment to Dlm initiation, and the total time on Dlm, was 1.5 (0.8-3.2) and 6.0 (3.6-7.8) months, respectively; 54 (52%) of patients received treatment with Dlm for > 6 months.

The differences based on HIV-status are shown in **Table 1**. A higher proportion of HIV-negative patients were <18 years of age or diabetic when compared with HIV-positive patients (21% vs. 4% and 12% vs. 1%, P<0.05); additionally greater than 50% of HIV-negative patients had MDR-TB plus additional SL resistance compared with HIV-positive patients (58% vs. 29%, P<0.05).

The median (IQR) number of drugs included in RR-TB regimens at Dlm initiation was 6 (6-7) including Dlm. The most commonly co-administered drugs at Dlm initiation included pyrazinamide (Pza, 91%), levofloxacin (Lfx, 86%), terizidone (Tzd, 86%) and ethambutol (Emb, 70%) (**Figure 1**). Bdq was co-administered in 32 (31%) of patients. The majority of patients (97%) received at least one other QT prolonging drug in addition to Dlm, as follows: Bdq and Cfz (n=24, 23%), Cfz only (n=10, 10%), Bdq only (n=8, 8%), moxifloxacin (Mfx) only (n=6, 6%). Clinical and demographic characteristics for the 32 patients treated with regimens containing both delamanid and bedaquiline stratified by HIV-status can be seen in Table 2.

Efficacy

Interim outcomes

The median (IQR) follow-up time for the 103 patients included in this study was 7.8 (4.6-12.9) months. Overall, 12 (12%), 11 (11%), 7 (7%), and 2 (2%) patients had outcomes of LTFU, death, cure or treatment completion, and failure of the SL regimen within a median (IQR) of 2.3 (0.9-3.8), 3.1 (1.0-7.6), 10.3 (7.1-16.6), and 10.9 (8.1-12.6) months after Dlm initiation, respectively. At the time of this analysis 57 (55%) patients were still on RR-TB treatment without or without Dlm and culture negative; 64 (62%) of patients had a favorable outcome.

Overall, 46 (45%) patients had 12-months of follow-up time; of these patients 28 (61%) had a favorable outcome, including either treatment completion and cure or culture negativity, 7 (15%) were LTFU, 5 (11%) died, 2 (4%) were declared to have a failure in treatment, 1 (2%) was transferred out and the remaining 3 (7%) patients were still on RR-TB treatment (2 culture positive and 1 with an unknown culture status). Twelve month outcomes did not significantly differ based on HIV status (P>0.05, **Table 3**).

Culture conversion

Fifty-eight (56%) out of 103 patients had positive cultures at Dlm initiation; 57 (98%) of those had pulmonary TB. Time to culture conversion is displayed in **Figure 2** for these patients. Of the 57 patients, 31 (54%) had month 2 and 6 culture data available; of them 16 (52%) and 25 (81%) had SCC within 2 and 6-months, respectively. SCC and time to SCC did not differ based on HIV status, RR-TB resistance profile, and indication for Dlm (P >0.05).

Of the 25 patients with SCC within 6-months, 3 (12%) reverted to culture positive at 2.2, 3.6, and 4.0 months after the date of culture conversion, which was 5.0, 7.1, and 4.9 months after Dlm initiation, respectively. All of these patients were HIV-positive and still on Dlm at the time of reversion.

Safety

Serious Adverse Events

Overall there were 67 SAEs reported in 29 (28%) patients; each patient had a median (IQR) of 2 (1-3) SAEs. Of these, 22 (33%) were attributed to Dlm. The most common SAEs were QT prolongation (n=7; 100% attributed to Dlm) and vomiting (n=4; 75% attributed to Dlm). There were three hepatic SAEs of which 67% were attributed to Dlm.

QTcF safety profile

The median (IQR) QTcF values observed during the monitoring visits can be seen in **Figure 3a**. Overall, there were four instances of QTcF prolongation >500 ms in 2 (2%) patients; in one of these patients Dlm was permanently withdrawn due to QTcF prolongation.

Median (IQR) QTcF change from baseline values for each monitoring visit can be seen in **Figure 3b**. There were 14 instances in which the QTcF value increased >60 ms from baseline in 9 (9%) patients; none of these instances led to known cardiac arrhythmias or the permanent discontinuation of Dlm, and none led to QTcF >500 ms. Eight of these patients were receiving other potentially QT prolonging drugs along with Dlm: Bdq only (n=1), Cfz only (n=2), and Bdq and Cfz (n=5). A significantly higher proportion of patients on combination treatment with Bdq, Cfz, and Dlm experienced QTcF increase >60 ms from baseline (5/24, 21%) compared to those not on all three of these drugs (4/79, 5%) (Risk ratio 4.1, 95% CI 1.2-14.1, *P*=0.030).

Discussion

We report on a cohort of 103 patients who received Dlm for the treatment of RR-TB in a routine programmatic setting. Notably, more than one third of patients in the cohort were infected with highly resistant strains, more than three out of four patients were HIV positive, and eight were aged ≤ 18 years; these populations have been underrepresented in clinical trials.

The high rates of culture conversion in this population were encouraging, and were similar to rates reported among RR-TB patients treated with Dlm-containing regimens in other programmatic and trial settings (67.6%-94.4%).[13],[25],[26],[27] Data from a programmatic setting in South Korea showed 24-week SCC rates of 94.4% and 92.9% in solid and liquid media, respectively, which are higher than our SCC rates however there are setting specific differences that likely impacted the variability in these findings.[26] In our study one of the three patients whose cultures reverted to positive after initial conversion to negative was given Dlm within an optimised regimen following prior RR-TB treatment failure, and therefore was already at considerably higher risk of a poor outcome.[28] This highlights the need for wider access to more effective treatment regimens including new drugs at initial diagnosis of RR-TB. Treatment with Dlm for greater than 6 months might assist in improving long term outcomes for RR-TB patients with poor early treatment response.[29],[30]

Overall, 11% of patients treated with RR-TB regimens including Dlm died; these findings are similar to those reported for 53 patients treated with Dlm-containing regimens of which 13.2% died by 6-months.[25] Given the high rate of HIV co-infection, high proportion of patients with low CD4 counts, high levels of SL drug resistance, and prior TB treatment history these results are not surprising as previously reported.[31],[32] Time to death was rapid, within approximately three months, and may have been due to severe and extensive disease at time of Dlm initiation as Dlm was often offered to those patients with limited treatment options. Data on final treatment outcomes for RR-TB patients treated with Dlm-containing regimens in a programmatic setting in Latvia showed cure and LTFU rates of 84.2% and 15.8% among 16 patients, respectively.[33] We need more follow-up time for patients enrolled in our cohort before we can make comparisons between our findings and those previously reported. Our data further highlight the

need for early diagnosis and prompt initiation of robust treatment regimens, improved integrated management of HIV/TB, and management of other risk factors for poor outcomes at the time of RR-TB diagnosis and throughout follow-up.

Overall, few patients (2%) experienced QTcF prolongation >500 ms when treated with Dlm in combination with other potential cardio-toxic drugs and less than half experienced SAEs. These data are supported by the recent Phase III Dlm trial results in which only 5.3% of patients who received Dlm experienced QTcF prolongation and Dlm was reported to have a favorable safety profile.[13] Other case reports and studies from programmatic settings utilizing Dlm in RR-TB treatment regimens have reported relatively low rates of QTcF prolongation (>500 ms) or increase >60 ms when Dlm was co-administered with other cardio-toxic drugs (3.7-17.0%).[14],[21] [25],[26],[27],[33],[34][35] In the current study there appeared to be an increased risk of QT interval change >60 ms from baseline when a combination of cardio-toxic drugs, including Dlm, were administered however, none of the episodes reported here led to the permanent discontinuation of Dlm and overall this population included patients treated with multiple drugs all of which are toxic and can cause SAEs. A multi-site study of 28 patients who received RR-TB regimens containing the combination of Bdq and Dlm similarly found that no patients had a QTcF > 500 ms and there were four (14%) patients who experienced 6 instances of a QTcF increase > 60 ms from baseline. However none of these instances led to permanent discontinuation of Bdq or Dlm.[21] One of these instances in a patient from South Africa is also reported on in this study. Given that QTcF prolongation mostly occurred after the eighth week of treatment with Dlm in the current study, the intensive ECG monitoring following Dlm initiation may be overcautious. Given that less than one third of the cohort experienced SAEs, very few of which were attributed to Dlm, our data are further in support of the previous findings regarding the favorable safety profile of Dlm.[13],[26][33] Similar to the favorable safety profile of Bdq, Dlm performed well in RR-TB treatment regimens, with and without Bdq.[36][37][38] A systematic analysis of the evidence regarding Bdq-containing RR-TB treatment regimens showed that Bdq was discontinued in 3.4% and 0.6% of patients due to adverse events and QTc prolongation, respectively.[38]

The first limitation of this study was the retrospective, descriptive cohort design, with a relatively small sample size. There was no control group, and final treatment outcomes were still pending

for the majority of patients in this cohort, therefore statistical inferences for the outcomes of interest could not be made. Multivariate analyses could not be performed, particularly for the analysis of culture conversion, due to the small sample size. There were missing data, particularly on QT intervals, which might have resulted in an underestimation of QTcF prolongation in this cohort, however this reflects the routine monitoring that is carried out in over-burdened and under-resourced facilities in this programmatic setting. Nevertheless, there were no instances of clinically significant cardiac arrhythmias or unexplained sudden deaths reported in this cohort.

This is one of the largest reported cohorts of patients receiving Dlm for RR-TB treatment outside of clinical trial settings, however the generalizability of these findings is limited. Further analyses should include larger numbers of patients and more follow-up time in order to draw conclusions on final outcomes for patients receiving Dlm in programmatic settings. Additionally, further studies are needed to further delineate the possible role of Dlm in populations with limited treatment options, including children, pregnant women, those with drug intolerance, and those who need to remain on EFV-containing regimens.

Overall, this cohort, which included a large proportion of HIV-infected individuals and patients with extensive disease had favorable early treatment response and tolerated Dlm-containing regimens reasonably well. Our data suggest that Dlm should remain available for RR-TB patients, particularly those that cannot be treated with conventional regimens and those with limited treatment options.

Author Contributions: EM, SA, NA, and PI conceived and designed the study. JH, AR, and JF provided clinical services and EM, JD, JH, and AR collected study data. LTD, VA, YK, and AS supervised the implementation of medical activities. EM, GB, JE, and PI performed the analysis. EM, HC, JF, and PI interpreted the results and drafted the manuscript. All authors contributed to the writing of the manuscript. EM and PI undertook the manuscript revisions. All the authors have read and approved the final manuscript.

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We declare that we have no conflicts of interest.

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Table 1. Clinical and demographic characteristics of patients treated with rifampicin resistant tuberculosis regimens containing delamanid, by HIV-status in Khayelitsha, South Africa from 1 November 2015-31 August 2017

Variable	Total Patients N (%) or Median (IQR[a])	HIV-Positive N (%) or Median (IQR[a])	HIV-Negative N (%) or Median (IQR[a])	*P*-value
Number of Patients	103 (100.0)	79 (100.0)	24 (100.0)	----
Age at Dlm[b] initiation, (y)	34 (28-43)	35 (30-43)	31 (21-40)	0.073
<18 years of age	8 (8.8)	3 (3.8)	5 (20.8)	**0.016**
Sex				
Male	63 (61.2)	47 (59.5)	16 (66.7)	0.53
Body Mass Index at Dlm[b] initiation (kg)	20.4 (17.7-23.6)[1]	20.4 (17.8-23.6)[2]	20.2 (17.6-23.7)[3]	0.92
QTcF[c] at Dlm[b] initiation (ms)	412.8 (394.0-433.0)[4]	412.6 (394.0-436.0)	414.0 (394.0-427.0)[4]	0.77
Albumin at Dlm[b] initiation (g/liter)	35.0 (29.0-39.0)[5]	35.0 (29.0-38.0)[6]	38.0 (29.5-40.0)[7]	0.087
Diabetes				
Yes	4 (3.9)	1 (1.3)	3 (12.5)	**0.039**
CD4 count at Dlm[b] initiation (cells/mm^3)		141.0 (61.0-252.0)[8]	----	----
On Anti-retroviral therapy at Dlm[b] initiation			----	----
Yes		74 (93.7)		
RR-TB[d] disease classification				
Presumed RR-TB[e]	1 (1.0)	0 (0.0)	1 (4.2)	
GeneXpert Unconfirmed[f]	3 (2.9)	2 (2.5)	1 (4.2)	
Rifampicin-mono resistant TB[g]	21 (20.4)	18 (22.8)	3 (12.5)	
Multi-drug resistant TB[g]	41 (39.8)	36 (45.5)	5 (20.8)	
Pre-XDR-TB[h] Injectable	5 (4.8)	4 (5.1)	1 (4.2)	
Pre-XDR-TB[h] Fluoroquinolone	15 (14.6)	7 (8.9)	8 (33.3)	
XDR-TB[h]	17 (16.5)	12 (15.2)	5 (20.8)	**0.014**
Previous TB[g] treatment history				
None	44 (42.7)	34 (43.0)	10 (41.6)	
First-line TB[g] treatment	43 (41.8)	36 (45.6)	7 (29.2)	
Second-line TB[g] treatment	16 (15.5)	9 (11.4)	7 (29.2)	0.085
Disease Site				
Pulmonary TB[g]	97 (94.2)	74 (93.7)	23 (95.8)	
Extra pulmonary TB[g]	5 (4.8)	4 (5.0)	1 (4.2)	
Both	1 (1.0)	1 (1.3)	0 (0.0)	1.0
Culture Status at Dlm[b] initiation				
Negative	42 (40.8)	35 (44.3)	7 (29.2)	
Positive	58 (56.3)	42 (53.2)	16 (66.7)	
Contaminated	2 (1.9)	2 (2.5)	0 (0.0)	
Not done	1 (1.0)	0 (0.0)	1 (4.1)	0.16
Indication for Dlm[b]				
Intolerance	58 (56.3)	48 (60.8)	10 (41.7)	
Limited therapeutic options	38 (36.9)	27 (34.2)	11 (45.8)	
Treatment failure	7 (6.8)	4 (5.0)	3 (12.5)	0.16
Time from RR-TB[d] treatment to Dlm[b] initiation (m)	1.5 (0.8-3.2)	1.5 (0.8-3.2)	1.7 (1.2-4.7)	0.35
Received >6 months of Dlm[b]	54 (52.4)	39 (49.4)	15 (62.5)	0.26

[a]IQR, Interquartile range; [b]Dlm, Delamanid; [c]QTcF, QT corrected using the Frederica formula; [d]RR-TB, Rifampicin-resistant Tuberculosis; [e]Presumed RR-TB, rifampicin-resistant tuberculosis diagnosed on presumption without bacteriological confirmation (often children); [f]GeneXpert Unconfirmed, GeneXpert diagnosed rifampicin-resistant tuberculosis with no follow-up second-line testing to confirm resistance; [g]TB, Tuberculosis; [h]XDR-TB, Extensively drug resistant tuberculosis

[1]8 missing baseline body mass index; [2]7 missing baseline body mass index; [3]1 missing baseline body mass index; [4]1 missing baseline QTcF; [5]9 missing baseline albumin; [6]5 missing baseline albumin; [7]4missing baseline albumin; [8]6 missing baseline CD4 count

Table 2. Clinical and demographic characteristics of patients treated with rifampicin resistant tuberculosis regimens containing delamanid and bedaquiline, by HIV-status in Khayelitsha, South Africa from 1 November 2015-31 August 2017

Variable	Total Patients N (%) or Median (IQR[a])	HIV-Positive N (%) or Median (IQR[a])	HIV-Negative N (%) or Median (IQR[a])	*P*-value
Number of Patients	32 (100.0)	18 (100.0)	14 (100.0)	----
Age at Dlm[b] initiation, (y)	35 (30-43)	36 (31-43)	32 (25-42)	0.32
<18 years of age	2 (6.3)	0 (0.0)	2 (14.3)	----
Sex				
Male	19 (59.4)	10 (55.6)	9 (64.3)	0.62
Body Mass Index at Dlm[b] initiation (kg)	20.8 (19.5-24.4)[1]	20.5 (19.5-24.9)	21.7 (19.6-23.6)[1]	0.86
QTcF[c] at Dlm[b] initiation (ms)	410.5 (387.5-429.0)	405.0 (383.0-432.0)	415.5 (404.0-426.0)	0.63
Diabetes				
Yes	2 (6.3)	0 (0.0)	2 (14.3)	0.18
CD4 count at Dlm[b] initiation (cells/mm^3)		91.0 (55.0-215.0)[2]	----	----
On Anti-retroviral therapy at Dlm[b] initiation			----	----
Yes		17 (94.4)		
RR-TB[d] disease classification				
Rifampicin-mono resistant TB[e]	2 (6.3)	2 (11.1)	0 (0.0)	
Multi-drug resistant TB[e]	3 (9.4)	1 (5.6)	2 (14.3)	
Pre-XDR-TB[f] Injectable	1 (3.1)	1 (5.6)	0 (0.0)	
Pre-XDR-TB[f] Fluoroquinolone	12 (37.5)	5 (27.8)	7 (50.0)	
XDR-TB[f]	14 (43.7)	9 (50.0)	5 (35.7)	0.46
Previous TB[e] treatment history				
None	9 (28.1)	3 (16.7)	6 (42.9)	
First-line TB[e] treatment	12 (37.5)	8 (44.4)	4 (28.6)	
Second-line TB[e] treatment	11 (34.4)	7 (38.9)	4 (28.6)	0.26
Disease Site				
Pulmonary TB[e]	30 (93.8)	17 (94.4)	13 (92.9)	
Extra pulmonary TB[e]	2 (4.8)	1 (5.6)	1 (7.1)	1.0
QTcF[c] prolonging drugs co-administered[3]				
Clofazimine	24 (75.0)	13 (72.2)	11 (78.6)	1.0
Moxifloxacin	0 (0.0)	0 (0.0%)	0 (0.0)	-----

[a]IQR, Interquartile range; [b]Dlm, Delamanid; [c]QTcF, QT corrected using the Frederica formula; [d]RR-TB, Rifampicin-resistant Tuberculosis; [e]TB, Tuberculosis; [f]XDR-TB, Extensively drug resistant tuberculosis

[1]1 missing baseline body mass index; [2]1 missing baseline CD4 count; [3]Numbers are not mutually exclusive

Table 3. Twelve month outcomes for patients receiving rifampicin-resistant tuberculosis regimens including delamanid from 1 November 2015 to 30 September 2016 stratified by HIV-status

	Total N (%)	**HIV-Positive N (%)**	**HIV-Negative N (%)**	**Median time (m) from Dlm[a] initiation to final outcome (IQR[b])**
Number of patients	46 (100.0)	35 (100.0)	11 (100.0)	8.1 (2.0-12.6)
Still on Treatment & Culture Positive	2 (4.3)	2 (5.7)	0 (0.0)	-----[1]
Still on Treatment & Culture Negative	21 (45.7)	14 (40.0)	7 (63.6)	-----[1]
Still on Treatment & Culture Status Unknown	1 (2.2)	1 (2.9)	0 (0.0)	-----[1]
Cured or Completed Treatment	7 (15.2)	6 (17.1)	1 (9.1)	10.3 (7.1-16.6)
Lost to Follow-Up	7 (15.2)	6 (17.1)	1 (9.1)	7.0 (1.1-10.6)
Died	5 (10.9)	4 (11.5)	1 (9.1)	2.0 (1.4-13.6)
Treatment Failure	2 (4.3)	2 (5.7)	0 (0)	10.4 (8.1-12.6)
Transferred out	1 (2.2)	0 (0.0)	1 (9.1)	5.9 (5.9-5.9)

[a]Dlm, Delamanid; [b]IQR, Interquartile Range

[1]Rifampicin-resistant tuberculosis treatment was ongoing in these patients and therefore time to a final outcome could not be calculated

Figure Legends

Figure 1. Number of rifampicin-resistant tuberculosis drugs co-administered at delamanid initiation between 1 November 2015 and 31 August 2017 in Khayelitsha, South Africa

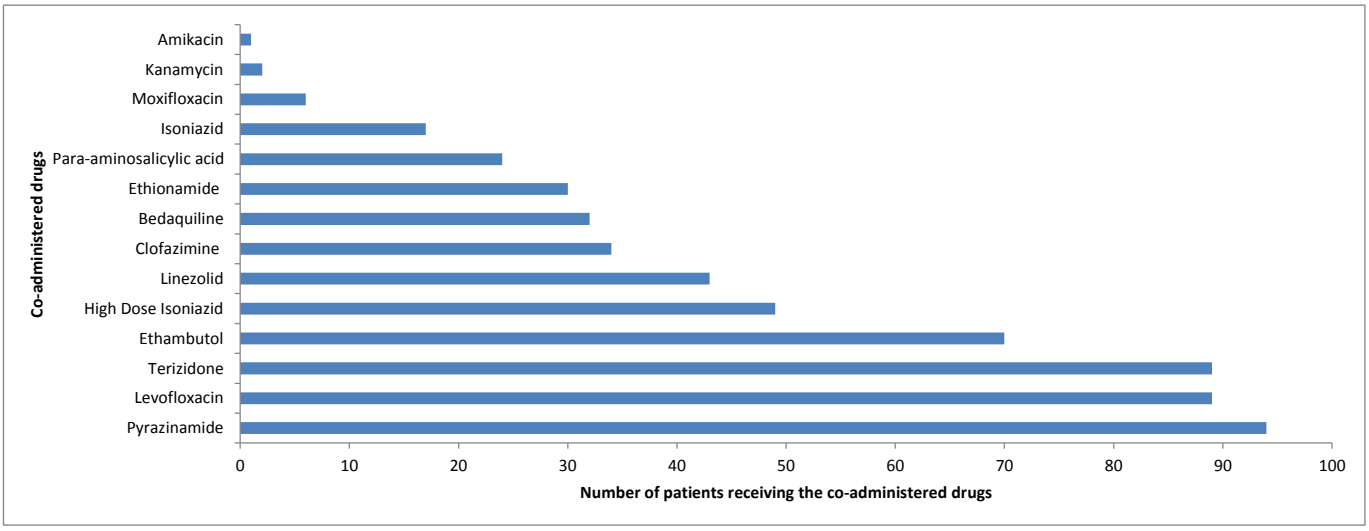
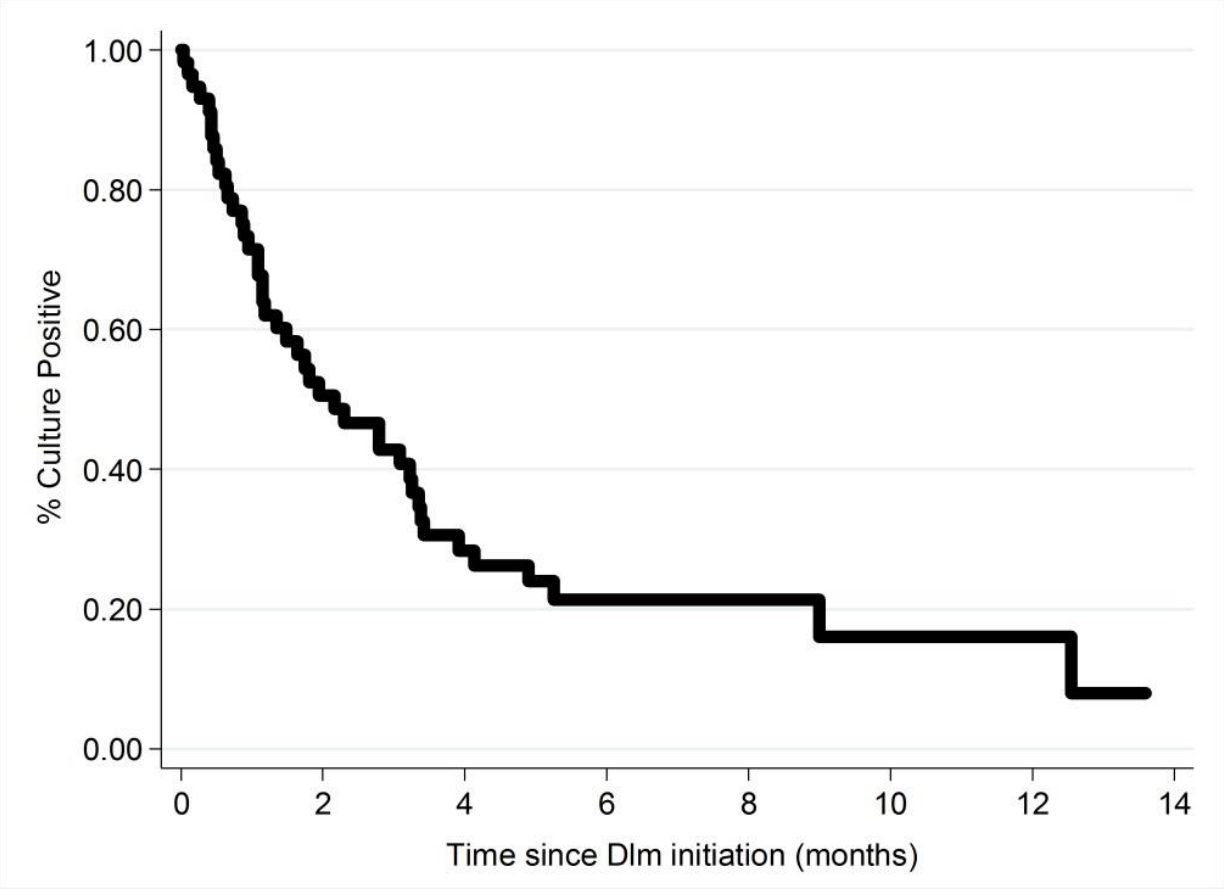
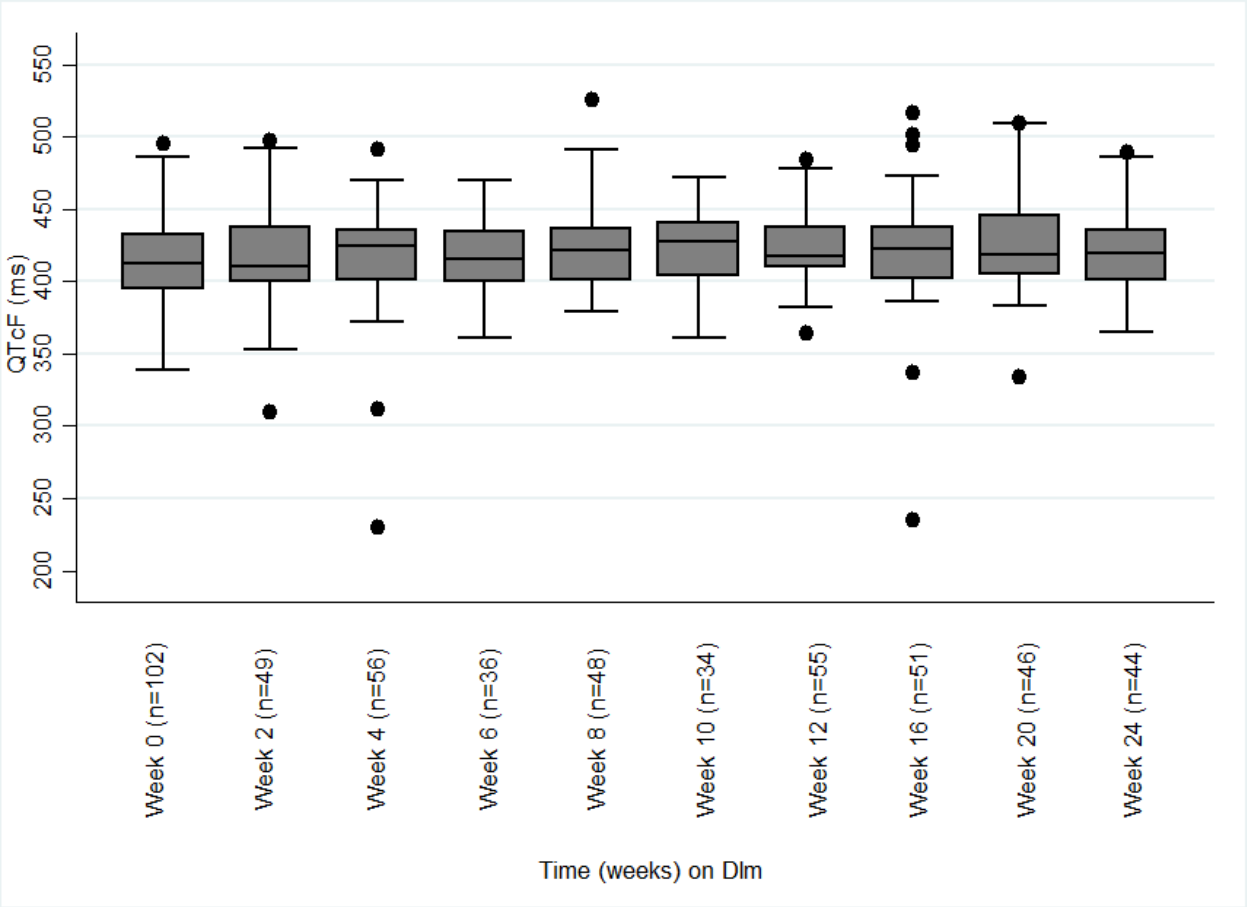


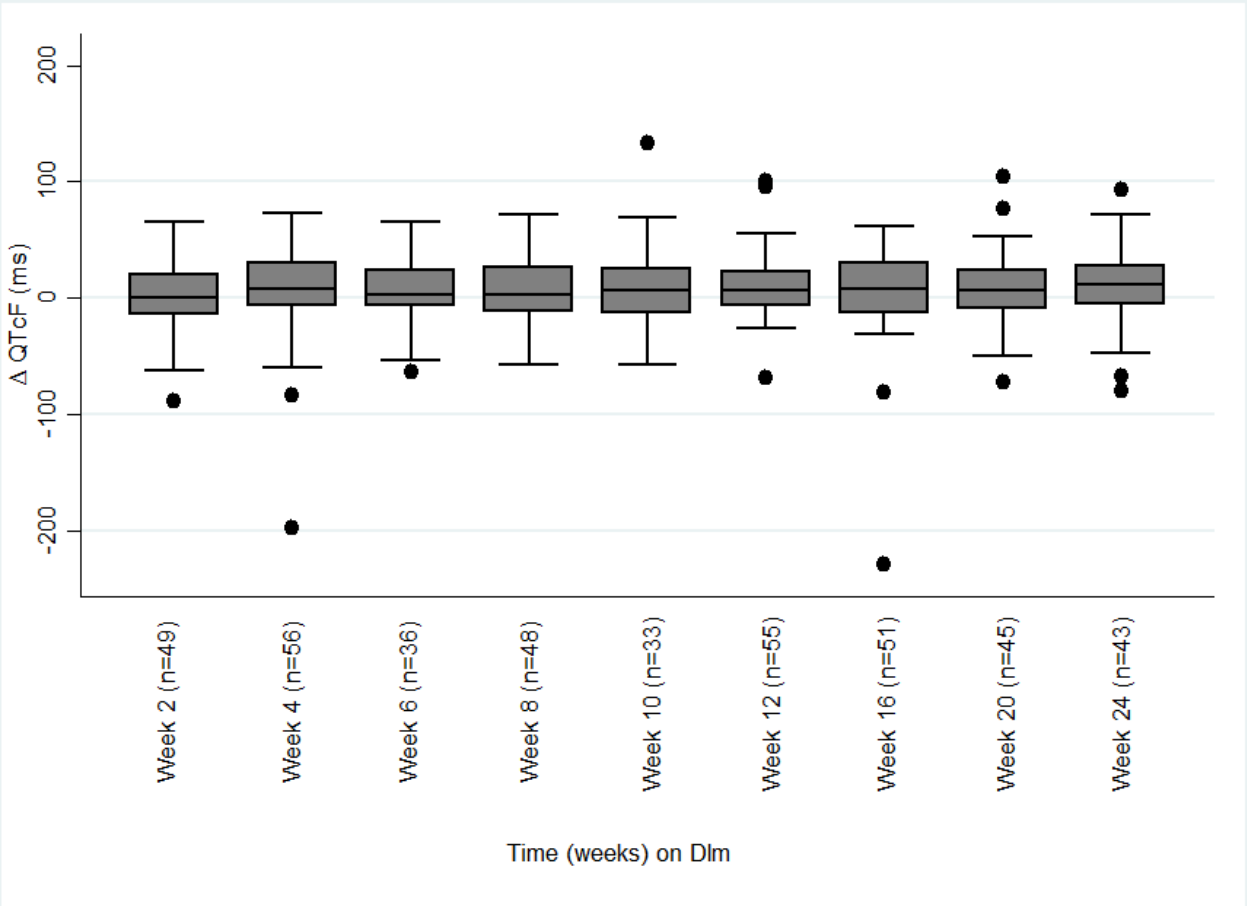
Figure 2. Time to culture conversion among patients with pulmonary tuberculosis initiated on rifampicin-resistant tuberculosis treatment regimens including delamanid before 1 January 2017, in Khayelitsha, South Africa (n=57)
Abbreviations: Dlm, delamanid



Months since Dlm initiation	0	2	4	6	8	10	12
Number of patients at risk (n)	57	26	13	6	5	3	2
Proportion remaining Culture Positive (%)	100.0	50.3	27.9	20.7	20.7	16.1	16.1
Lower Confidence Limit (%)	---	36.4	16.4	10.6	10.6	6.4	6.4
Upper Confidence Limit (%)	---	62.7	40.6	33.2	33.2	29.7	29.7

Figure 3. (a) Median QTcF (interquartile range) in milliseconds at Weeks 0 – 24 after delamanid initiation, regardless of time on delamanid, among patients treated for rifampicin-resistant tuberculosis in Khayelitsha, South Africa from 1 November 2015- 31 August 2017 (b) Median change from baseline QTcF (interquartile range) in milliseconds at Weeks 2 – 24 after delamanid initiation, regardless of time on delamanid, among patients treated for rifampicin-resistant tuberculosis in Khayelitsha, South Africa from 1 November 2015- 31 August 2017





Abbreviations: Dlm, delamanid; QTcF, QT corrected using the Frederica formula; Δ, change