antimicrobial drug prophylaxis is not known (*5*), and guidelines vary among countries. In the United Kingdom, prophylaxis is recommended for exposed mothers or babies during the neonatal period, for symptomatic close contacts, or for the entire household if there is >1 case (*6*). In Canada, prophylaxis is recommended for persons who had close contact with a person with a confirmed severe case during a specified period (*7*); in France and the United States, prophylaxis is recommended for close contacts with risk factors for invasive infections (*8,9*). In the cases we report here, the second case-patient did not receive prophylaxis because of the short period between the 2 cases.

Both case-patients received NSAIDs during the onset of the disease. The role of these drugs in streptococcal infection outcome is frequently discussed; they seem to cause an increase of severe infection, most probably in children (*10).*

These cases highlight that different life-threatening transmissible types of *S. pyogenes* are circulating in the same area and that transmission can occur rapidly. Clinician and family education about prophylaxis and symptoms requiring medical care is needed.

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Six-Month Response to Delamanid Treatment in MDR TB Patients

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Delamanid, recently available for the treatment of multidrug-resistant tuberculosis (MDR TB), has had limited use outside clinical trials. We present the early treatment results for 53 patients from 7 countries who received a delamanid-containing treatment for MDR TB. Results show good tolerability and treatment response at 6 months.

Outcomes of conventional 18–24-month regimens for multidrug-resistant tuberculosis (MDR TB) (*1*,*2*) and extensively drug-resistant tuberculosis (XDR TB) (*3*,*4*) are notoriously poor. Two recently marketed drugs, delamanid (*5*–*7*) and bedaquiline (*8*), represent hope for better outcomes. Médecins Sans Frontières (MSF) supported national TB programs to introduce delamanid according to World Health Organization recommendations (*9*) for patients lacking 4 effective second-line drugs in the regimen or at high risk for poor treatment outcomes. Delamanid was preferred over bedaquiline to treat TB in patients with hepatitis C (because of less potential hepatic toxicity with delamanid), patients who are taking antiretroviral drugs (because delamanid produces fewer interactions), or patients previously exposed to bedaquiline (and who had previous treatment failure) or clofazimine (because of potential cross resistance with bedaquiline). We present interim treatment response and safety data for patients treated with delamanid within MSF-supported programs.

This retrospective study comprises all patients started on MDR TB regimens containing delamanid in MSF-supported sites before March 1, 2016. Routine programmatic data were collected on site. Information on serious adverse events (SAEs) was retrieved from a central pharmacovigilance database. The study was approved by the relevant health ministries and meets the criteria of the MSF Ethics Review Board for exemption from ethics review.

We defined culture conversion as 2 consecutive negative culture results 1 month apart for culture-positive patients at start of delamanid treatment. We defined patients as having a favorable interim treatment response at 6 months if they completed 24 weeks of delamanid and culture converted or remained culture negative; we classified patients who did not meet these criteria as having an unfavorable interim treatment response. We used unadjusted bivariate odds ratios with 95% CIs to express the magnitude and precision of associations between outcomes and risk factors (the small number of records precluded a multivariable analysis). We defined SAEs as deaths irrespective of cause, hospitalizations, events leading to disability or congenital malformation, and events considered life threatening or otherwise medically noteworthy.

During February 6, 2015–February 29, 2016, a total of 53 patients from 7 countries (online Technical Appendix Table 1, https://wwwnc.cdc.gov/EID/article/23/10/17-0468-Techapp1.pdf) started a delamanid-containing regimen (Table). Of these, 46 (86.8%) received delamanid through a compassionate-use program. Most patients had been treated previously with second-line drugs (48/53, 90.6%), experienced MDR TB treatment failures (32/53, 60.4%), exhibited resistance to second-line TB drugs (41/51, 80.4%), or had extensive pulmonary disease (40/45, 88.9%). Almost all patients (52/53, 98.1%) received delamanid for an indication of <4 effective drugs in the regimen.

Table. Demographic, clinical, and bacteriological characteristics at baseline of 53 patients starting a delamanid-containing MDR TB treatment regimen*

Variable	No. (%) patients or median (IQR)
Sex	
M	36 (67.9)
F	17 (32.1)
Age at delamanid start, y	29.5 (20.0–43.0)
14–17	11 (20.8)
HIV co-infected, n = 48	8 (16.7)
HCV co-infected, n = 42	8 (19.0)
Malnutrition,† n = 51	21 (41.2)
Serum albumin at delamanid start, g/L, n = 46	37.6 (32.0–37.6)
WHO case definition	
New case	4 (7.5)
Relapse	5 (9.4)
Treatment after being lost to follow-up	5 (9.4)
Treatment after failure	32 (60.4)
Other	7 (13.5)
Previously treated	49 (92.4)
With first-line drugs only	1 (2.1)
With second-line drugs	48 (97.9)
MDR TB confirmed	51 (96.2)
Drug resistance subgroups among confirmed MDR TB	
MDR TB only‡	10 (19.6)
Pre–XDR TB FQ	6 (11.8)
Pre–XDR TB Inj	8 (15.7)
XDR TB	27 (52.9)
Radiograph features	
Bilateral, n = 45	35 (77.8)
Cavities, n = 43	26 (60.5)
Bilateral or cavity, n = 45	40 (88.9)
Culture positive at delamanid start	37 (69.8)

*HCV, hepatitis C virus serology; HIV, human immunodeficiency virus; MDR TB, multidrug-resistant tuberculosis; pre–XDR TB FQ, MDR TB with fluoroquinolone resistance; pre–XDR TB Inj, MDR TB with resistance to injectable drugs; WHO, World Health Organization; XDR TB, extensively drug-resistant tuberculosis.
†Malnutrition: either BMI <18.5 kg^2/cm, mid-upper arm circumference <16cm, or weight <50 kg in 3 patients from South Africa without height measurement.
‡Without resistance to fluoroquinolone or injectable drugs.

A total of 31 SAEs were reported in 14 patients (26.4%); most common were hepatotoxicity (5), electrolyte imbalance (5), and QT prolongation (3). The most frequent contributing factors reported were TB disease (6), hepatitis C infection (6), and non–anti-TB drugs, including antiretroviral drugs (ARVs) (8). A possible relation to any TB drug was reported in 80.6% (25/31) of events, including a possible relation to delamanid in 58.6% (18/31). Causes of the 7 reported deaths were advanced TB (2), encephalitis in an untreated HIV patient (1), traumatic pneumothorax (1), sepsis in an HIV patient (1), respiratory failure related to end-stage hepatitis (1), and sudden death of unknown cause (1); a possible relationship to anti-TB drugs was initially reported in the last 2 cases. In 1 patient with hepatitis C and liver cirrhosis, all drugs were permanently discontinued due to hepatotoxicity. No other permanent discontinuation of delamanid was reported (online Technical Appendix Table 2).

Of the patients who were culture positive at delamanid start, 67.6% (25/37) culture converted by 6 months. At 6 months, 73.6% (39/53) of patients had a favorable response, 13.2% (7/53) had died, 7.5% (4/53) remained culture positive, 3.8% (2/53) were lost to follow-up, and 1.9% (1/53) were declared to have a failure in treatment as a result of an SAE. Factors associated with unfavorable response in a univariate analysis were age >35 years (odds ratio [OR] 5.62, 95% CI 1.47–21.57; p = 0.012); hepatitis C infection (OR 7.78, 95% CI 1.45–41.78; p = 0.017); smear positivity at delamanid start (OR 5.21, 95% CI 1.35–20.06; p = 0.016); and serum albumin <34 g/L (OR 7.14, 95% CI 1.6–33.3; p = 0.010) (online Technical Appendix Table 3).

These preliminary results indicate good tolerability and interim treatment response to delamanid at 6 months in a narrow and difficult-to-treat cohort of patients for whom delamanid was preferred to bedaquiline, most of whom had previously failed MDR TB treatment and had extensive disease. Delamanid was used in preference to bedaquiline in this group of patients, despite the programmatic availability of bedaquiline, which may explain the frequency of adverse events in relation to hepatitis C and HIV coinfection, comorbidities that influence this choice, further supporting the need for essential monitoring and treatment of hepatitis C and HIV in MDR TB patients. Limitations of this study include its small numbers and retrospective nature, and data on delamanid treatment outcomes and safety in programmatic conditions with larger indications deserve further studies.

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Six-Month Response in MDR TB Patients Treated with Delamanid

Technical Appendix

Pharmacovigilance System of Reporting Serious Adverse Events

All sites mentioned in the report performed active pharmacovigilance (PV) reporting on serious adverse events (SAEs). The site clinicians were trained on systematic collection and reporting of SAEs by the central MSF PV unit (Geneva) either through on site or virtual (web conference) training before the introduction of delamanid-containing regimens. Clinicians were specifically trained on detection of SAEs and on the tools allowing for the recording and reporting of such safety information, including MSF PV guidelines, report forms, and the severity grading scale for the project (Division of Microbiology and Infectious Diseases adult toxicity table, completed by Common Terminology Criteria for Adverse Events, Division of AIDS , and other scales).

SAEs were notifiable to the MSF PV unit within 24 hours of knowledge at the site. The MSF OV unit entered detailed information, including patient demographics and relevant medical background, SAE description, TB regimen information and concomitant drugs, relevant laboratory test results, treating physician's causality assessment, and reporter details, into a central PV database based on the forms transmitted by the sites. The PV unit followed up cases until the SAE outcome was known and organized the medical review by a central team physician for each individual case. Both local and central assessments co-exist in the database; cases judged relevant were additionally reviewed for opinion and signal detection purpose by an expert medical committee at central level (the Medical Review Board).

Copies of SAE report forms were shared with the national authorities by the field clinicians as applicable per national laws. The central PV unit additionally shared SAE information with drug manufacturers, enabling further dissemination to the European Medicine Agency or the US Food and Drug Administration (among other health authorities).

Clinical patient data on treatment including efficacy and safety information were recorded at local site level in local electronic medical record databases; SAE data were reconciled between the local databases and the central PV database. Safety data for this study were taken from the central PV unit database after reconciliation.

Details about patients who developed hepatotoxicity, SAEs of QTcF increase, and SAES with fatal outcomes initially reported as possibly related to TB drugs (see Technical Appendix Table 2) follow.

Details of Hepatoxicity SAEs

Two episodes of hepatotoxicity occurred in 1 patient coinfected with active hepatitis C with cirrhosis (genotype 3 HCV, fibroscan, 13.1 Kpa), which led to permanent discontinuation of all TB drugs, including delamanid and bedaquiline, and a treatment outcome of failure (first episode on bedaquiline: ALT 243 U/L, AST 348 U/L, second episode on delamanid: ALT 304 U/L, AST 241 U/L). The patient was later treated for hepatitis C with direct-acting antiviral drugs (sofosbuvir, daclatasvir, and ribavirin).

In 1 patient co-infected with HIV and on ARVs who had previously had hepatitis C infection but was PCR negative for hepatitis C, all drugs were stopped temporarily. Delamanid was continued with other TB drugs when the hepatoxicity, which was thought to be related to ARVs and prior hepatitis C (ALT 154 U/L, AST 1075 U/L), resolved. The outcome of the hepatoxicity is unknown.

In 1 patient with active hepatitis C (genotype 2, fibroscan metavir score was F0–F1), delamanid was continued after temporarily stopping all drugs. Drug challenge found hepatotoxicity related to other TB drugs (AST 300 IU/L, ALT 461 IU/L). Liver enzymes increased during February 9, 2015–July 4, 2015 until full resolution; however, liver enzymes were not normal at treatment start and recurrent increases and fluctuations occurred during this time as a result of drug challenges.

In 1 patient without any coinfection with HIV or hepatitis C, all drugs were stopped. Drug challenge found hepatotoxicity related to other drugs, and treatment was restarted with delamanid (ALT 183.6 U/L, AST 157.2 U/L). Liver enzymes increased during September 14, 2015–April 14, 2016 for full resolution; however, there were recurrent liver enzyme increases and fluctuations during this time due to drug challenges.

No patients received direct-acting antiviral therapy for active hepatitis C treatment during MDR TB treatment.

Details of QTcF Increase SAEs

Three patients experienced serious adverse events of QTcF increase.

Patient 1: QtcF increase of 592 msec, associated with severe vomiting, severe hypokalemia, moderate hypocalcemia, hypomagnesemia, and hypoalbuminemia; all TB drugs (delamanid-Cm-Eto-Cfz-cs-Lzd-Z-E-Imp-Amox/Clav) and ondansetron were stopped. Adjusted TB treatment including delamanid was restarted after correction of electrolyte imbalances.

Patient 2: QtcF increase of 557 msec, associated with hypoalbuminemia, hypomagnesemia, hypokalemia, nephrotic syndrome, long-standing anemia, and extensive XDR-TB. TB treatment was stopped (delamanid-Cm-Lzd-Cfz-Imp-Amox/Clav-Eto-Cs-Rfb) and reintroduced after correction of electrolytes. The patient later died as a result of complications of traumatic pnuemothorax.

Patient 3: QtcF increase of 510 msec while on TB treatment of bedaquiline-Lzd-PAS-Cfz-Lfx-Trd before starting delamanid associated with vomiting, sepsis, and renal failure. The patient was on ARV treatment of tenofovir, emtricitabine, and efavirenz and later died as a result of complications of sepsis.

Details of SAES with Fatal Outcomes Initially Reported as Possibly Related to TB Drug

One patient experienced cardiogenic shock and respiratory failure: a 47-year-old man who died 36 days after starting delamanid-containing XDR-TB treatment (delamanid- Cfz-Lzd-Lfx-Cs-Cm), in severe condition related to TB and advanced liver disease due to hepatitis C (with cirrhosis, ascites, and encephalopathy). The patient had renal failure, anemia, and prior QT prolongation requiring Cfz discontinuation (17 days before death), and developed respiratory insufficiency and hypotension; the patient died as a result of cardiogenic shock and respiratory insufficiency. This case was initially conservatively considered by the treating physician as possibly related to all drugs. After the data lock point for this analysis and in the light of all the details on the patient's medical history, the treating physician and the central PV review agreed that the events were unlikely to be related to the TB drugs and rather were secondary to the patient's comorbidities, namely hepatitis C cirrhosis and TB.

The second patient was a 21-year-old man who died 21 days after starting adapted delamanid-containing XDR-TB treatment (delamanid-Imp-Amx/Clv added to Cm-Mfx-PAS-Lzd administered for 75 days at time of death). Central venous catheter was placed 3 days before the death. About 1 hour after drug infusion on the day of the death, the patient was at home and developed dyspnea, restlessness, anxiety, and sweating, as reported by his parents. He was brought to a nearby hospital, where he was declared stable and the decision was made to transfer him to another facility (presumably for infection control reasons). The patient went into cardiorespiratory arrest en route to the hospital and was declared dead upon arrival. Retrospectively, the case was reviewed and hypothetical causes of death included pulmonary embolism, pneumothorax/tension pneumothorax, or cardiac arrhythmia. None of these hypotheses could be fully confirmed with the available information. Conservatively, the death was considered of unknown cause and recorded as potentially related to any drug in the absence of sufficient information to fully assess the case.

Technical Appendix Table 1. Country of residence of patients with MDR TB who received delamanid

Country	N (%)
Armenia	8 (15.1)
Belarus	6 (11.3)
Georgia	12 (22.6)
India	11 (20.8)
Russia	8 (15.1)
South Africa	6 (11.3)
Swaziland	2 (3.8)

Technical Appendix Table 2. Serious adverse event terms; frequency; relation to TB drugs, delamanid and non-TB drugs; other causal factors; comorbidities; and outcomes*

SAE term	N	Associated factors	Possibly related to TB drugs	Possibly related to delamanid	Possibly related to non-TB drugs	HIV	Advanced TB	HepC	Outcomes
Electrolyte imbalance: hypokalemia (2), hypomagnesemia (2), hypocalcemia (1)	5	3 associated with ondansetron, omeprazole	5	5	3	0	NA	NA	All resolved/ recovered
Hepatotoxicity (raised transaminases, drug-induced liver injury)	5	4 with HCV, 1 with ARVs	5	3	1	0	NA	4	4 recovered/ resolved, 1 unknown†
End-stage TB (tuberculosis, pulmonary hemorrhage, asphyxia)	3	3 Advanced TB	0	0	0	0	3	NA	3 fatal
QTcF prolongation	3	2 associated with electrolyte imbalance, 1	3	3	1	0	NA	NA	3 resolved/ recovered†

SAE term	N	Associated factors	Possibly related to TB drugs	Possibly related to delamanid	Possibly related to non-TB drugs	HIV	Advanced TB	HepC	Outcomes
		with non-TB drugs: ondansetron, omeprazole							
Hypoalbuminemia	2	1 non-TB drugs: ondansetron, omeprazole	2	2	1	0	NA	NA	2 resolved/ recovered
Encephalitis	1	Untreated HIV	0	0	0	1	NA	NA	Fatal
Cardiogenic shock and respiratory failure	2	2 advanced hepC and cirrhosis	2	2 (initially)	0	0	1	2	Fatal†
Psychotic disorder	1	Possible tuberculoma or vasculitis	1	0	0	0	1	NA	Not recovered/ not resolved
Systematic inflammatory response	1	TB, other infection	1	0	0	0	NA	NA	Recovered/ resolved
Nephrotic syndrome	1	NA	1	1	0	0	NA	NA	Recovered/ resolved
Renal failure	1	TDF and vomiting/ dehydration	1	0	1	0	NA	NA	Recovering/ resolving
Traumatic pneumothorax	1	Insertion of portacath	0	0	0	0	NA	NA	Fatal
Sepsis	1	Prolonged hospital stay in HIV patient	0	0	0	1	NA	NA	Fatal
Vomiting	1	ARVs	1	0	1	0	NA	NA	Recovered/ resolved
Weight loss	1	Failure of DRTB treatment	1	1	0	0	1	NA	Unknown
Death	1	NA	1	1	0	0	NA	NA	Fatal†
Device-related infection	1	NA	1	0	0	0	NA	NA	Recovered/ resolved
Total	**31**		**25**	**18**	**8**	**2**	**6**	**6**	
%			80.6%	58.1%					

*ARVs, antiretroviral drugs; DRTB, drug-resistant tuberculosis; HepC, hepatitis C; NA, not applicable; SAE, serious adverse effect; TDF, tenofovir disoproxil fumarate

†Details of hepatotoxicity SAEs, QtcF prolongation SAEs, and SAEs with fatal outcomes initially assessed as possibly being related to delamanid are described in the Technical Appendix text.

Technical Appendix Table 3. Factors associated with unfavorable response in a univariate analysis of patients with MDR TB*

Characteristics	Unfavorable outcome n (%)	OR	95% CI	p-value
Age				
<35	4/31 (12.9)	**1**		
≥35	10/22 (45.5)	**5.62**	**1.47–21.57**	**0.012**
Sex				
Male	11/36 (30.6)	1		
Female	3/17 (17.7)	0.49	0.12–2.04	0.326
HIV				
Negative	10/40 (25.0)	1		
Positive	4/8 (50.0)	3.0	0.63–14.27	0.167
Hepatitis C				
Negative	6/34 (17.7)	**1**		
Positive	5/8 (62.5)	**7.78**	**1.45–41.78**	**0.017**
Malnutrition†				
Good	7/30 (23.3)	1		
Poor	5/21 (23.8)	1.02	0.28–3.82	0.969
X-ray changes				
Unilateral	0/10 (0.0)			
Bilateral	9/35 (25.7)	NA	NA	NA
Cavity on X-ray				
No	1/17 (5.9)	1		
Yes	7/26 (26.9)	5.90	0.65–53.11	0.114
Smear at delamanid start				
Negative	4/29 (13.8)	**1**		
Positive	10/22 (45.5)	**5.21**	**1.35–20.06**	**0.016**
Culture at delamanid start				
Negative	2/16 (12.5)	1		
Positive	12/37 (32.4)	3.36	0.66–17.21	0.146
DST profile				
MDR, pre-XDR (Inj, FQ)	6/24 (25.0)	1		
XDR	8/27 (29.6)	4.18	0.48–36.53	0.196
Albumin at delamanid start				
<34	7/14 (50.0)	**1**		
≥34	4/32 (12.5)	**0.14**	**0.03–0.63**	**0.010**
Cfz in regimen				
No	5/12 (41.7)	1		
Yes	7/36 (19.4)	0.34	0.08–1.39	0.133
Mfx in regimen				
No	9/31 (29.0)	1		
Yes	1/15 (6.7)	0.17	0.02–1.53	0.115

*Bold text indicates figures with p < 0.05. Cfz, clofazimine; DST, drug susceptibility testing; HIV: human immunodeficiency virus; MDR, MDR TB without resistance to fluoroquinolone or injectable drugs; MDR TB, multidrug-resistant tuberculosis; Mfx: moxifloxacin; pre-XDR-TB (FQ): MDR TB with fluoroquinolone resistance; pre-XDR-TB (Inj): MDR TB with resistance to injectable drugs; XDR-TB, extremely drug-resistant tuberculosis
†Malnutrition: either BMI <18.5 kg^2/cm, mid-upper arm circumference <16 cm, or weight <50 kg in 3 patients from South Africa without height measurement

*