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Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

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ABSTRACT

BACKGROUND

Patients with highly drug-resistant forms of tuberculosis have limited treatment options and historically have had poor outcomes.

METHODS

In an open-label, single-group study in which follow-up is ongoing at three South African sites, we investigated treatment with three oral drugs — bedaquiline, pretomanid, and linezolid — that have bactericidal activity against tuberculosis and to which there is little preexisting resistance. We evaluated the safety and efficacy of the drug combination for 26 weeks in patients with extensively drug-resistant tuberculosis and patients with multidrug-resistant tuberculosis that was not responsive to treatment or for which a second-line regimen had been discontinued because of side effects. The primary end point was the incidence of an unfavorable outcome, defined as treatment failure (bacteriologic or clinical) or relapse during follow-up, which continued until 6 months after the end of treatment. Patients were classified as having a favorable outcome at 6 months if they had resolution of clinical disease, a negative culture status, and had not already been classified as having had an unfavorable outcome. Other efficacy end points and safety were also evaluated.

RESULTS

A total of 109 patients were enrolled in the study and were included in the evaluation of efficacy and safety end points. At 6 months after the end of treatment in the intention-to-treat analysis, 11 patients (10%) had an unfavorable outcome and 98 patients (90%; 95% confidence interval, 83 to 95) had a favorable outcome. The 11 unfavorable outcomes were 7 deaths (6 during treatment and 1 from an unknown cause during follow-up), 1 withdrawal of consent during treatment, 2 relapses during follow-up, and 1 loss to follow-up. The expected linezolid toxic effects of peripheral neuropathy (occurring in 81% of patients) and myelosuppression (48%), although common, were manageable, often leading to dose reductions or interruptions in treatment with linezolid.

CONCLUSIONS

The combination of bedaquiline, pretomanid, and linezolid led to a favorable outcome at 6 months after the end of therapy in a high percentage of patients with highly drug-resistant forms of tuberculosis; some associated toxic effects were observed. (Funded by the TB Alliance and others; ClinicalTrials.gov number, NCT02333799.)

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THE VISION OF THE END TB STRATEGY OF the World Health Organization (WHO) is of a world free of tuberculosis by the year 2035.¹ However, extensively drug-resistant (XDR) tuberculosis (i.e., tuberculosis with resistance to isoniazid, rifampin, any fluoroquinolone, and at least one injectable drug [amikacin, capreomycin, or kanamycin]) and complicated forms of multidrug-resistant (MDR) tuberculosis (i.e., tuberculosis with resistance to isoniazid and rifampin that does not respond to treatment or for which treatment is discontinued because of side effects) pose threats to the achievement of this goal because of the lack of effective treatment for these forms of the disease.²

Five years ago, the typical duration of treatment of MDR tuberculosis ranged from 18 months to more than 2 years, with some patients receiving up to seven medications, including a second-line injectable. The incidence of side effects with these regimens is high, with 45% of patients having moderate-to-severe adverse events.³ Patients with XDR tuberculosis had few treatment options and no standard treatment regimen. The published success rates for treatment of XDR tuberculosis were low and consistent across South Africa, averaging 14% and ranging from 2 to 22%.^{4,5}

Bedaquiline is a diarylquinoline that inhibits mycobacterial ATP synthase.⁶ In a phase 2 study of bedaquiline added to a background regimen, 23 of 38 patients with XDR tuberculosis (61%) had had a response at 120 weeks after the initiation of treatment.⁷ There has been increased early access to this medication, especially in South Africa. In the cohort of patients with XDR tuberculosis who started treatment between July 2014 and March 2016, bedaquiline-containing regimens were associated with a lower risk of death from any cause than were regimens that did not contain bedaquiline (hazard ratio, 0.26, 95% confidence interval [CI], 0.18 to 0.38).⁸

Linezolid, an oxazolidinone that has been approved in many countries for the treatment of drug-resistant, gram-positive bacterial infections, inhibits bacterial protein synthesis.⁹ Resistance of *Mycobacterium tuberculosis* to linezolid is rare, since this drug has not been widely used to treat tuberculosis. A recent evaluation of 420 XDR and MDR *M. tuberculosis* strains in South Korea showed 1 strain (0.3%) with resistance at the WHO-recommended cutoff value.¹⁰

Pretomanid, a nitroimidazooxazine that inhib-

its mycolic acid biosynthesis and thereby blocks mycobacterial cell-wall production, also acts as a respiratory poison against nonreplicating bacteria after nitric oxide release under anaerobic conditions.^{11,12} Pretomanid has in vitro activity against both drug-susceptible and drug-resistant (including XDR) strains of *M. tuberculosis* and has in vivo activity in animal models of tuberculosis.^{13,14} Phase 2 studies to evaluate the early bactericidal activity of pretomanid over 14 days of daily oral monotherapy showed that the lowest dose to produce a maximal effect for early bactericidal activity was 100 mg per day.¹⁵ Pretomanid was recently approved by the Food and Drug Administration (FDA) under the Limited Population Pathway for Antibacterial and Antifungal Drugs as part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary XDR tuberculosis or with complicated MDR tuberculosis. Here, we present the results of the Nix-TB study, which evaluated the safety, side-effect profile, efficacy, and pharmacokinetics of this oral regimen.

METHODS

STUDY DESIGN

Nix-TB is an open-label, single-group study involving patients with XDR tuberculosis and patients with MDR tuberculosis that is not responsive to treatment or for which a second-line regimen had been discontinued because of side effects. All patients received 26 weeks of daily oral treatment, with an option to extend treatment to 39 weeks if they were culture-positive at week 16. An interim analysis for safety was conducted after every 15 enrollments.

STUDY PATIENTS

Patients were enrolled from three study sites in South Africa: Sizwe Tropical Disease Hospital, Johannesburg; Task Applied Science at Brooklyn Chest Hospital, Cape Town; and King DiniZulu Hospital Complex, Durban. Patients 14 years of age or older were eligible for enrollment. The major inclusion criteria were pulmonary XDR or MDR tuberculosis documented on culture or molecular testing within 3 months before screening, with drug resistance documented by phenotypic or genotypic testing followed by, in patients with MDR tuberculosis, documentation of nonresponse to treatment with an available regi-

men for 6 months or more before enrollment or an inability to continue a second-line drug regimen because of documented side effects from treatment. Human immunodeficiency virus (HIV)–infected patients with a CD4+ cell count of greater than 50 per cubic millimeter could be enrolled and appropriate antiretroviral treatment given (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients with baseline peripheral neuropathy of grade 3 or 4 were excluded. Detailed inclusion and exclusion criteria are provided in the protocol, available at NEJM.org. All patients provided written informed consent.

ENROLLMENT AND INTERVENTION

Patients received orally administered treatment as follows: bedaquiline at a dose of 400 mg once daily for 2 weeks followed by 200 mg three times a week for 24 weeks, plus pretomanid at a dose of 200 mg daily for 26 weeks and linezolid at a dose of 1200 mg daily for up to 26 weeks (with dose adjustment depending on the toxic effects). The total daily dose of linezolid of 1200 mg was changed from 600 mg twice daily to 1200 mg once daily during the study to evaluate whether a single daily dose, which would reduce the exposures above the potential threshold for mitochondrial protein synthesis toxicity, would have less clinical toxicity. More details are provided in the protocol. All patients underwent screening within 9 days before receiving the first dose of the study treatment (day 1) and were seen weekly thereafter to week 16, at weeks 20 and 26, and then at months 1, 2, and 3 after the end of treatment and every 3 months thereafter, to 24 months after the end of treatment.

MICROBIOLOGIC ASSESSMENTS

Two sputum samples were obtained for smear microscopy and culture (performed by means of the Mycobacteria Growth Indicator Tube [MGIT] method) at screening; baseline; weeks 1, 2, 4, 6, 8; and then monthly through week 26 and in follow-up months 1, 2, 3 and every 3 months through month 24. *M. tuberculosis* was identified by molecular methods. *M. tuberculosis* isolates obtained at baseline and at the end of treatment or during follow-up were transferred to a central laboratory for the determination of the minimum inhibitory concentration (MIC) of bedaquiline, pretomanid, and linezolid; for MGIT drug-sus-

ceptibility testing for rifampin, isoniazid, streptomycin, ethambutol, moxifloxacin, and kanamycin; and for paired whole-genome sequencing. The laboratory manual includes full details of the microbiologic procedures.

SAFETY

Assessments of safety included regular electrocardiography and examination of blood samples, with particular attention paid to expected hematologic toxic effects. Ophthalmologic examination, including assessment of visual acuity and color vision, was performed every 4 weeks, and a slit-lamp examination for cataracts performed at screening, at the end of treatment, and 3 months later. Changes were noted in signs and symptoms of peripheral neuropathy, including any changes from baseline, with the use of a Brief Peripheral Neuropathy rating scale that evaluated subjective symptoms and objective measures of deep-tendon reflexes and vibration sense.¹⁶

OUTCOME MEASURES AND END POINTS

The primary end point was the incidence of an unfavorable outcome, defined as treatment failure (bacteriologic or clinical) or disease relapse. Clinical treatment failure was defined as a change from the protocol-specified tuberculosis treatment as a result of a lack of clinical efficacy, retreatment for tuberculosis, or tuberculosis-related death through follow-up until 6 months after the end of treatment. Patients were considered to have had a favorable outcome if their clinical tuberculosis disease had resolved, they had a negative culture status at 6 months after the end of therapy, and they had not already been classified as having had an unfavorable outcome. Secondary end points included the time to an unfavorable outcome and the time to sputum culture conversion through the treatment period. Culture conversion was defined as at least two consecutive culture-negative samples collected at least 7 days apart.

Safety and adverse-event end points included all-cause mortality and the incidence of adverse events that occurred or worsened during the treatment period, defined here as the period from the start of treatment through 14 days after the end of treatment. The severity of adverse events was categorized according to grade, as defined by the Division of Microbiology and Infectious Diseases,¹⁷ as well as according to whether

they were judged by the investigators to be related to the study medication.

STUDY OVERSIGHT

An independent data and safety monitoring committee oversaw the safety of the study and provided advisement about whether to continue without changes after each review. Although there were no formal stopping rules, recommendations for early stopping or modification of the study were left to the discretion of the data and safety monitoring committee. National and local ethics committees approved the study. The Food and Drug Administration and the Medicines Control Council in South Africa reviewed the protocol. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

STATISTICAL ANALYSIS

No formal statistical power calculation was performed; however, we prespecified that the regimen would be determined to be effective if the lower bound of the 95% confidence interval of the percentage of patients with a favorable outcome was greater than 50% (see Section 7 of the Efficacy Statistical Analysis Plan, available with the protocol at NEJM.org). Although the protocol allowed enrollment of up to 200 patients, enrollment stopped after 109 when ZeNix, a randomized trial investigating linezolid dosing and duration in the context of treatment with bedaquiline, pretomanid, and linezolid (ClinicalTrials.gov number, NCT03086486), was started. All analyses were performed with Stata software, version 15.1 (StataCorp).

Intention-to-treat and modified intention-to-treat analyses were prespecified as the primary analyses, and a per-protocol analysis was also performed. However, the populations were similar, and for ease of interpretation we report the intention-to-treat analysis with no exclusions. More details on the definitions of the analysis populations are provided in the protocol.

We calculated percentages (with exact 95% confidence intervals) of the assessable patients who had a favorable outcome. Subgroup analyses of the primary outcome according to the type of tuberculosis (XDR or MDR), HIV status, and dosing schedule of linezolid were performed to evaluate the consistency of the results. No formal statistical tests were performed. The time to an

unfavorable outcome and time to culture-negative status were analyzed with standard time-to-event analysis techniques, including Kaplan–Meier plots.

RESULTS

PATIENTS

In total, 34 potential participants were excluded during screening (Table S2), and 109 patients were enrolled in the study between April 16, 2015, and November 15, 2017, and included in the analysis of efficacy and safety. The first 44 patients were started on linezolid at 600 mg twice daily, and the remaining 65 were started on 1200 mg daily. Two patients who had positive cultures during treatment (one at month 4 and one at month 5) had their treatment extended for an additional 3 months. Follow-up to 24 months after the end of treatment is ongoing.

The demographic and clinical characteristics of the patients are given in Table 1. The median age was 35 years (range, 17 to 60 years), 57 patients (52%) were male, 56 (51%) were HIV-positive, 92 (84%) had cavities on chest radiographs, and the median body-mass index (the weight in kilograms divided by the square of the height in meters) was 19.7. All patients with HIV coinfection were treated with antiretroviral therapy during the trial, and all except 2 had been receiving antiretroviral therapy before enrollment. The median time since the original diagnosis of tuberculosis was 12 months (range, <1 to 141 months). All except 9 patients had received tuberculosis medications in the month before enrollment, with the most common drugs used (by ≥55 patients) being fluoroquinolones, pyrazinamide, terizidone, clofazimine, para-aminosalicylic acid, ethambutol, and ethionamide, with a median of 7 (range, 3 to 13) tuberculosis drugs being taken. A total of 71 cases (65%) were classified as XDR tuberculosis, 19 (17%) were classified as MDR tuberculosis that did not respond to treatment, and 19 (17%) were classified as MDR tuberculosis for which treatment was stopped because of side effects.

MICROBIOLOGIC ASSESSMENT

All patients met the inclusion criterion of having tuberculosis with documented resistance to anti-tuberculosis drugs and were categorized as having either XDR or MDR tuberculosis, although

16 patients did not have positive baseline cultures. Baseline isolates for 57 patients could be evaluated for MICs of all study drugs. In all but three isolates, bedaquiline and linezolid MICs were below or equal to the critical concentration recommended by the WHO (1 μg per milliliter for both drugs).¹⁸ Two baseline isolates had bedaquiline MICs equal to 2 μg per milliliter, and one had a bedaquiline MIC equal to 4 μg per milliliter. All the baseline isolates tested had pretomanid MICs of 1 μg per milliliter or lower. Among the surviving patients, the median number of cultures obtained to determine the primary end point was 29 (range, 20 to 40).

EFFICACY ANALYSIS

At 6 months after the end of treatment in the intention-to-treat analysis, 11 patients (10%) had an unfavorable outcome. The 11 unfavorable outcomes were 7 deaths (6 during treatment; 1 during follow-up from an unknown cause that was not considered by the investigators to be tuberculosis- or drug-related), 1 withdrawal of consent during treatment, 2 relapses during follow-up, and 1 loss to follow-up.

The number of patients classified as having a favorable outcome in the intention-to-treat analysis was 98 (90%; 95% CI, 83 to 95), with similar findings in the modified intention-to-treat and per-protocol analyses (Table 2). These results had a lower bound of the 95% confidence interval that was greater than 50% (Table 2).

SUBGROUP ANALYSES

The results were similar when stratified according to tuberculosis type. Among the 71 patients with XDR tuberculosis in the intention-to-treat population, the number classified as having a favorable outcome was 63 (89%; 95% CI, 79 to 95), and among the 38 patients with MDR tuberculosis, 35 were classified as having a favorable outcome (92%; 95% CI, 79 to 98) (Table 2). The results were also consistent regardless of HIV status and linezolid dosing scheme.

The time to an unfavorable outcome, overall and stratified according to tuberculosis type, HIV status, and linezolid dosing, is shown in Figure 1. Kaplan-Meier estimates of the time to culture-negative status, overall and stratified according to tuberculosis type, are shown in Figure 2. There were two relapses. Whole-genome sequencing performed on the corresponding

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Value (N = 109)
Median age (range) — yr	35 (17–60)
Male sex — no. (%)	57 (52)
Race — no. (%)†	
Black	83 (76)
Mixed race	25 (23)
White	1 (1)
Median BMI (range)‡	19.7 (12.4–41.1)
HIV-positive — no. (%)	56 (51)
Median time since HIV diagnosis (range) — yr	4.0 (0.2–14.3)
Median CD4 cell count (range) — cells/mm ³ §	343 (55–1023)
Cavities present on chest radiograph — no. (%)	
No	17 (16)
Unilateral	51 (47)
Bilateral	41 (38)
Karnofsky score — no. (%)¶	
100	9 (8)
90	50 (46)
80	29 (27)
70	19 (17)
60	2 (2)
<60	0
Median no. of tuberculosis drugs taken in month before enrollment (range)	7 (3–13)
Median time since original tuberculosis diagnosis (range) — mo	12 (<1–141)

* Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus.

† Race was reported by the patient.

‡ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ Data on CD4 cell count were missing for 5 patients.

¶ The Karnofsky score ranges from 0 to 100, with lower scores indicating greater disability.

baseline and late isolates confirmed that one patient had a relapse with the same strain of *M. tuberculosis* (only 5 single-nucleotide polymorphisms [SNPs] separated the two isolates). One of these SNPs produced a change in the bedaquiline resistance gene *Rv0678*, from wild type at baseline to a 138-139insG variant in the late isolate. The bedaquiline MIC was elevated in the late isolate (4 μg per milliliter, as compared with 0.5 μg per milliliter at baseline).¹⁹ The second patient who had a relapse did not have a baseline isolate available for testing, but the late

Table 2. Primary Efficacy Analysis.*

Outcome	XDR	MDR	Overall
Intention-to-treat population†			
No. of patients	71	38	109
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	89 (79–95)	92 (79–98)	90 (83–95)
Unfavorable outcome — no. (%)	8 (11)	3 (8)	11 (10)
Deaths — no.	6	1	7
Withdrawal during treatment — no.	1	0	1
Lost to follow-up after end of treatment — no.	0	1	1
Relapse — no.	1	1	2‡
Modified intention-to-treat population†			
No. of patients	70	37	107
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	90 (80–96)	95 (82–99)	92 (85–96)
Unfavorable outcome — no. (%)	7 (10)	2 (5)	9 (8)
Deaths — no.	5	1	6
Withdrawal during treatment — no.	1	0	1
Relapse — no.	1	1	2‡
Per-protocol population			
No. of patients	68	37	105
Favorable outcome			
No. of patients	62	35	97
Percent of patients (95% CI)	91 (82–97)	95 (82–99)	92 (86–97)
Unfavorable outcome — no. (%)	6 (9)	2 (5)	8 (8)
Deaths — no.	5	1	6
Relapse — no.	1	1	2‡

* An unfavorable outcome was defined as treatment failure (bacteriologic or clinical) or disease relapse, with clinical treatment failure defined as a change from the protocol-specified tuberculosis treatment as a result of treatment failure, retreatment for tuberculosis, or tuberculosis-related death through follow-up until 6 months after the end of treatment. Patients were considered to have had a favorable outcome if their clinical tuberculosis disease had resolved, they had a negative culture status at 6 months after the end of therapy, and they had not already been classified as having had an unfavorable outcome. All patients in this study had either a favorable or an unfavorable outcome at 6 months after the end of treatment.

† The intention-to-treat and modified intention-to-treat analyses were prespecified in the protocol. Two patients were excluded from the modified intention-to-treat population: one who died from non-tuberculosis-related causes during follow-up, and one who was lost to follow-up after the end of treatment. Two additional patients were excluded from the per-protocol population: one who received an inadequate amount of drug, and one who was withdrawn (not for treatment failure) during treatment.

‡ A baseline isolate was not available for one patient who had a relapse.

isolate was analyzed and was shown to be susceptible to all three study drugs.

SAFETY ANALYSIS

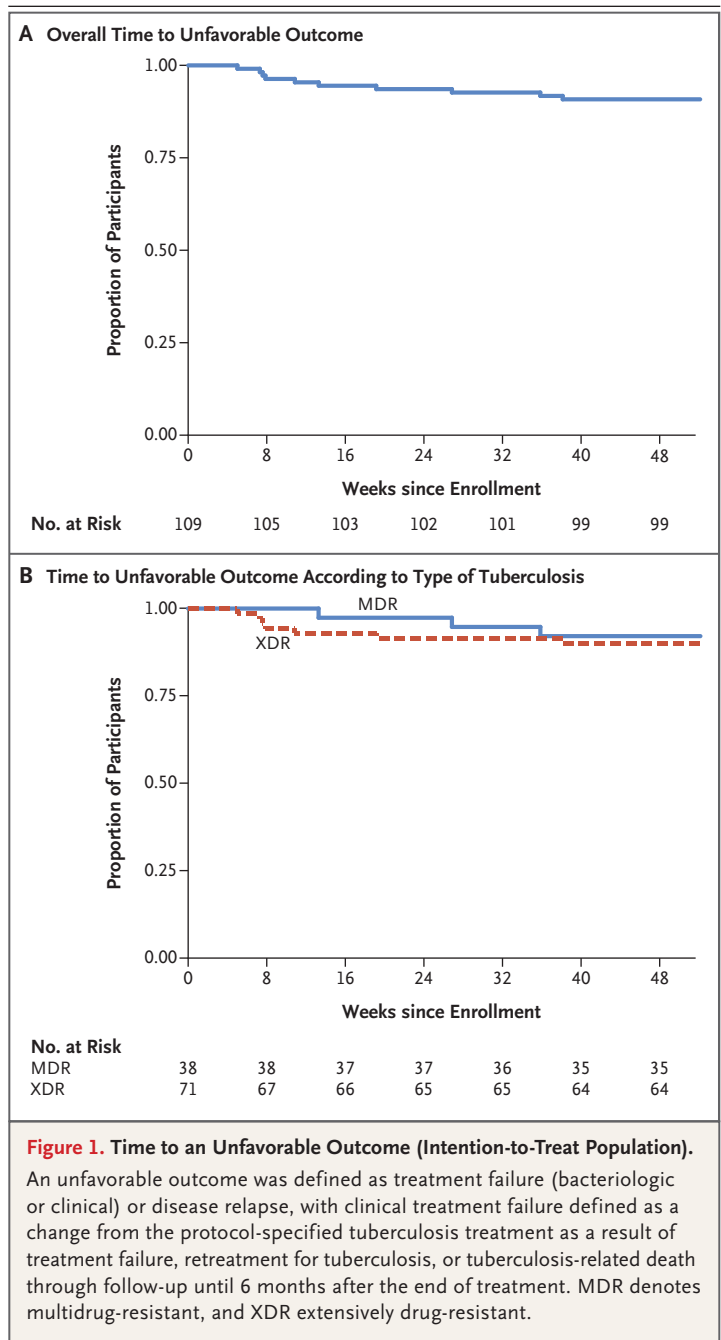
All patients had at least one adverse event that occurred or worsened during treatment, and 19

(17%) had serious adverse events, which were similar in frequency regardless of whether patients were HIV-positive or HIV-negative. Six patients died during the course of treatment (1 patient at month 1, 4 at month 2, and 1 at month 3; an additional patient died from sepsis

and gangrene after relapse of tuberculosis). A total of 62 patients (57%) had adverse events of grade 3 or higher that occurred or worsened during treatment; the percentage of patients with such an event did not differ substantially according to HIV status (Table 3). Details of the adverse events and deaths are provided in Tables S3, S4, and S5.

During treatment, 88 patients (81%) were reported to have peripheral neuropathy; in the majority of cases, the symptoms were mild to moderate. Among patients whose mean score on the Brief Peripheral Neuropathy Screening scale indicated moderate to severe neuropathy, the median time to a return to a score indicating no or mild neuropathy was 3 months. Patients are continuing in follow-up, and the time course of the resolution of neuropathy is undergoing further analysis. Figure S1A shows the time to a first linezolid dose reduction or interruption for neuropathy; the majority of these events occurred after the initial 3 months of treatment. Results were similar for patients who were coinfectd with HIV and those who were HIV-uninfected and for patients who initially received linezolid at 600 mg twice a day and those who received linezolid at 1200 mg daily. Optic neuritis developed in 2 patients, which resolved on withdrawal of linezolid. Blood and lymphatic system disorders were the second most common adverse events that occurred or worsened during treatment: myelosuppression occurred in 52 patients (48%); 40 of these patients (37% of the study population) had anemia, 7 of whom had hemoglobin decreases to less than 8.0 g per deciliter. Figure S1B shows the time to a first linezolid dose reduction or interruption for anemia. In the majority of patients with this event, it occurred during the first 2 months of treatment, with similar results observed in HIV-coinfectd and -uninfected patients and in patients who received different starting doses of linezolid.

Aminotransferase increases occurred in 17 patients; 12 had an alanine aminotransferase (ALT) elevation and 11 an aspartate aminotransferase (AST) elevation to a level higher than 3 times the upper limit of the normal range. Two of these patients had ALT and AST elevations to more than 3 times the upper limit of the normal range, as well as direct and total bilirubin elevations to more than 2 times the upper limit of the normal range. In both cases, the



study regimen was interrupted. Eight patients had the regimen interrupted for hepatic adverse events, but all resumed and completed the full 26 weeks of treatment. The maximum mean increase in the QT interval, as assessed with Fridericia's formula, was 10 msec at week 16; no patient had an increase of more than 480 msec.

All surviving patients completed 26 weeks of treatment (including two who extended to 39

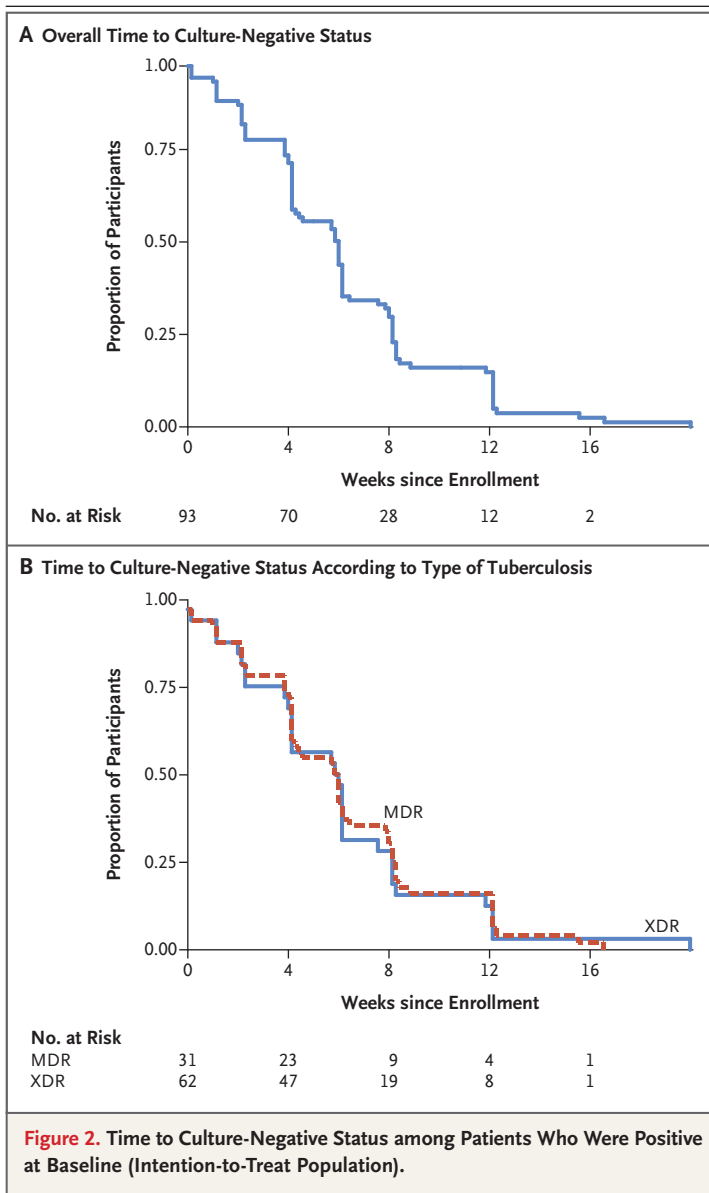
DISCUSSION

At 6 months after the completion of therapy, 98 patients (90%) were found to have a favorable outcome, including 63 of 71 patients (89%) with XDR tuberculosis. Of the 38 patients with MDR tuberculosis who were enrolled in the study, 35 (92%) had favorable outcomes.

One of the limitations of this study is that there is no randomized control group. At the time of implementing this protocol, there was no standard regimen for the treatment of XDR tuberculosis. Mortality was high, with long-term cure occurring in less than 20% of patients in reports from South Africa, and a single-group study was therefore warranted. However, during the course of this study, both bedaquiline and linezolid have been increasingly used to treat MDR tuberculosis and XDR tuberculosis, and the WHO recently published guidelines that recommend these two drugs as first-line treatment for MDR tuberculosis over an 18-month course of therapy.²⁰ Bedaquiline has been shown recently in a programmatic context to reduce overall mortality when added to treatment for MDR and XDR tuberculosis.^{8,21,22} Among patients with XDR tuberculosis who were treated in Cape Town, South Africa, at one of the sites of the Nix-TB study, the percentage of patients who were cured was below 20% before the use of bedaquiline or linezolid and has improved to 66% more recently, since bedaquiline and linezolid were added to the regimens (all the patients received bedaquiline, and 81% also received linezolid).²³ Of note, these patients had newly diagnosed XDR tuberculosis and were treated for 24 months with a median of eight drugs.

Another limitation of this study is that it was conducted in only one country, which potentially limits the generalizability of the findings. South Africa was selected because it has a robust regulatory framework, good clinical trial capacity, and historically poor outcomes among patients with XDR tuberculosis. In addition, there is a high background prevalence of HIV infection.

The primary end point in this study was based on an unfavorable outcome at 6 months after the end of treatment, since most relapses occur during this period.²⁴ The secondary end point of the incidence of treatment failure is be-



weeks); only one of these patients had a treatment interruption longer than the allowed 35 consecutive days, and none had the regimen permanently discontinued. Most patients had a reduction in dose or an interruption of linezolid during treatment. In total, 37 patients (34%) completed 26 weeks of linezolid treatment without any interruption, although they may have had a dose reduction, and 16 (15%) completed 26 weeks at a total daily dose of 1200 mg of linezolid with no interruptions or dose reductions.

Table 3. Adverse Events That Occurred or Worsened during Treatment.

Event*	HIV Status		Linezolid Regimen		Overall (N = 109)
	Negative (N = 53)	Positive (N = 56)	600 mg Twice Daily (N = 44)	1200 mg Daily (N = 65)	
			<i>number (percent)</i>		
Adverse event	53 (100)	56 (100)	44 (100)	65 (100)	109 (100)
Adverse event leading to death	3 (6)	3 (5)	4 (9)	2 (3)	6 (6)
Serious adverse event	10 (19)	9 (16)	13 (30)	6 (9)	19 (17)
Grade 3 or 4 adverse event	27 (51)	35 (62)	27 (61)	35 (54)	62 (57)

* A patient could have had more than one type of event.

ing measured at 24 months after the end of treatment. It is reassuring that to date there has been only one additional relapse among the 47 patients who have reached this time point in the study with final follow-up and cultures.

For both individual patients with tuberculosis and national tuberculosis programs, a shorter duration of treatment that is effective is beneficial. Visits to health care facilities place a financial and time burden on patients. Income loss often constitutes the largest financial risk for patients. For tuberculosis programs, a shorter duration of treatment translates into fewer patients being in care at any one time, with the potential to reduce loss to follow-up.

A high percentage of patients had adverse events related to linezolid during the study: 81% of the patients reported peripheral neuropathy, and almost half had evidence of hematologic toxic effects. Although patients taking this regimen should be monitored carefully, these toxic effects were manageable in our study. All eight patients who had the regimen interrupted for hepatic adverse events resumed and completed the full 26 weeks of treatment.

This study shows that XDR tuberculosis and

complicated MDR tuberculosis can be treated with a regimen consisting of three oral agents for 26 weeks. Despite these forms of tuberculosis being historically hard-to-treat conditions, treatment success was 90%, which is similar to that obtained with the standard of care (i.e., isoniazid, rifampin, pyrazinamide, and ethambutol) in modern trials of treatment for drug-sensitive tuberculosis.²⁵⁻²⁷

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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