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Safety and Tolerability of a Short Course of Linezolid for the Treatment of Predominantly Moderate to Severe Tuberculous Meningitis in Adults With Human Immunodeficiency Virus

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Background. Tuberculous meningitis (TBM)–related deaths occur early, often within weeks after treatment initiation. Enhanced treatment early in the disease course with agents that effectively penetrate the central nervous system may improve outcomes in TBM.

Methods. We conducted a phase 2, open-label, randomized trial in Masaka, Uganda, to assess the safety and tolerability of linezolid 1200 mg once daily versus no linezolid with high-dose (35 mg/kg/d) or standard-dose (10 mg/kg/d) rifampin for 4 weeks in participants with definite or suspected TBM. The primary endpoint was any grade ≥3 adverse event during the interventional period. Secondary endpoints included overall survival and functional independence adjusted for TBM disease grade.

Results. We randomized 40 participants (98% with human immunodeficiency virus [HIV]). One-fourth had microbiologically confirmed TBM. Nearly 75% had moderate to severe disease (Medical Research Council grades II and III). No significant difference in grade ≥3 adverse event–free survival was observed across the 4 treatment arms ($P = .18$) or by linezolid ($P = .97$) or rifampin ($P = .46$) treatment group. More favorable overall survival at 12 and 24 weeks (odds ratio, 0.28 [$P = .10$] and 0.43 [$P = .24$], respectively) and functional outcome at 12 and 24 weeks (OR for lower modified Rankin Scale score [ie, less disability], 2.22 [$P = .18$] and 2.00 [$P = .24$]) were observed in the linezolid group.

Conclusions. The addition of a short course of linezolid to treat predominantly moderate to severe TBM in adults with HIV did not introduce excess toxicity. Our findings add to growing evidence that linezolid is a safe and acceptable treatment for TBM that merits further investigation in larger multisite trials.

Keywords. Tuberculous meningitis; linezolid; safety and tolerability; HIV.

Tuberculous meningitis (TBM) is universally fatal without treatment. Even among patients who receive recommended therapy, 25%–50% will die [1]. In those who survive, neurologic disability is common [2–4]. Despite these poor outcomes, there is a paucity of data on how to optimize antituberculosis therapy for TBM, including for people living with human immunodeficiency virus (HIV). The highest proportion of deaths occurs within the first month after treatment initiation [5–9], suggesting that there may be a critical window early in the disease course during which enhanced treatment could have the greatest impact on clinical outcomes.

In the absence of compelling data to guide treatment, the same standard drug regimens and dosing used for pulmonary tuberculosis are empirically used for TBM, except with a longer continuation phase to complete 9–12 months of therapy. This approach assumes that the efficacy of tuberculosis drugs is equivalent at all sites of infection, disregarding the unique challenges of infection of the central nervous system (CNS) [10]. Effective drugs for TBM must penetrate the blood-brain barrier and remain in the CNS to achieve bactericidal drug

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concentrations for an adequate duration [8]. At standard dosing recommended in current guidelines, rifampin, a key drug in the treatment of *Mycobacterium tuberculosis*, seldom reaches minimal inhibitory concentrations for *M. tuberculosis* in the cerebrospinal fluid (CSF) [11], which may jeopardize treatment efficacy in TBM.

Several recently completed or ongoing clinical trials are investigating the effect of high-dose rifampin on mortality rates in TBM [11, 12]. However, even in one small trial that suggested a favorable effect of high-dose rifampin on the treatment of TBM [5], the mortality rate still exceeded 33% in the experimental arm, arguing that additional drugs may be needed to augment the potential benefit of high-dose rifampin. Adjunctive linezolid, given for the first month of treatment of TBM, may enhance bactericidal activity during the rapid growth phase of *M. tuberculosis* while minimizing toxicity. In observational studies, the addition of linezolid to treat TBM in adults and children has been associated with better neurologic outcomes and lower mortality rates [13, 14].

In the Adjunctive Linezolid for the Treatment of TubERculous Meningitis (ALTER) trial, we (1) assessed the safety and tolerability of 4 weeks of linezolid 1200 mg once daily administered with high-dose or standard-dose rifampin and (2) compared mortality rates and functional independence between participants randomized to linezolid versus no linezolid for the treatment of definite or suspected TBM.

METHODS

This was a phase 2, open-label, randomized, controlled trial. Participants were assigned to linezolid 1200 mg once daily versus no linezolid with high-dose (35 mg/kg/d) or standard-dose (10 mg/kg/d) oral rifampin for 4 weeks, followed by standard treatment per local guidelines (Supplementary Figure 1). The study was approved by the institutional review boards or ethics committees of the University of California, San Francisco (UCSF), Uganda Virus Research Institute, and London School of Hygiene and Tropical Medicine. An independent data and safety monitoring board reviewed the study after the first 12 participants were enrolled and twice annually until completion of the trial. Written informed consent was obtained from participants or their surrogates. The trial was registered at clinicaltrials.gov (NCT04021121).

We enrolled participants from Masaka Regional Referral Hospital (MRRH) in Masaka, Uganda. The hospital, located in southern Uganda, serves a catchment area of >3 million people spanning 12 districts and 1 city. All participants were ≥18 years of age with ≥1 of the following: headache, fever, neck stiffness, convulsions, focal neurologic deficits, or altered consciousness. In addition, participants had either a positive CSF acid-fast bacilli smear, positive CSF GeneXpert result, CSF glucose-to-plasma ratio <0.5, or clinical suspicion for TBM, wherein the participant was being committed to a course of antituberculosis therapy. Exclusion criteria are shown in Supplementary Box 1. All eligible patients admitted to MRRH were invited to participate. Participants were classified as having definite, probable, or possible TBM, using a uniform case definition developed for research [15].

Participants were randomized to linezolid 1200 mg once daily versus no linezolid for the first 4 weeks of therapy with high-dose (35 mg/kg/d) or standard-dose (10 mg/kg/d) rifampin. Weight bands were used to assign the dose of rifampin. Randomization was stratified by TBM Medical Research Council (MRC) grade. All participants received a backbone of isoniazid, pyrazinamide, and ethambutol in addition to corticosteroids (dexamethasone 0.4 mg/kg/d for week 1 and 0.3 mg/kg/d for week 2, followed by a prednisone taper over 6 weeks) and vitamin B_6 (50 mg/d). For participants receiving high-dose rifampin, the dose was reduced to 10 mg/kg/d after 4 weeks. Pyrazinamide and ethambutol were discontinued once the 8-week intensive treatment phase concluded, after which rifampin and isoniazid were continued. After 24 weeks, participants were referred to local tuberculosis clinics to complete standard of care treatment in accordance with Uganda National Tuberculosis Program guidelines. Participants with HIV who were not on antiretroviral therapy (ART) at the time of presentation were started on ART after completing 8 weeks of antituberculosis treatment, per national guidelines.

Initiation of study treatment occurred within 24 hours of randomization. After randomization, participants were followed through 24 weeks with follow-up evaluations (eg, symptom assessment and neurologic examination with Glasgow Coma Scale) at day 2, weeks 1, 2, 4, 8, 12, 18, and 24, and as clinically indicated. Complete blood count, chemistry panel, and liver function tests were performed at randomization, at weeks 1, 2, and 4, and as clinically indicated. We followed participants with the Brief Peripheral Neuropathy Screen (BPNS) [16] and vision testing.

The primary endpoint was the proportion of participants with a treatment-emergent grade ≥3 adverse event during the interventional period. A treatment-emergent adverse event was defined as any condition new in onset or aggravated in severity, frequency, or character compared with at entry. The primary endpoint comprised targeted grade ≥3 laboratory abnormalities associated with linezolid or rifampin use, including hematologic changes and elevated liver function test results, and any grade ≥3 clinical sign or symptom (eg, focal weakness), including death. With the exception of peripheral neuropathy and visual changes, clinical and laboratory adverse events were graded according to the US National Institutes of Health Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [17]. Peripheral neuropathy was defined as any grade ≥2 symptom (of 3 possible grades)

or a ≥2-level decline in vibratory sensation on the BPNS. A decline in vision was defined as (1) loss in visual acuity of >2 lines on the Snellen chart; (2) decrease in color perception by ≥3 Ishihara cards, or (3) a decrement in contrast sensitivity by ≥0.50 log units or an absolute score of <1.0 log units on the Pelli-Robson test.

Secondary endpoints included the proportion of participants who experienced serious adverse events during the 24-week observational period; the proportion who completed linezolid treatment; time to death; and death and disability, as measured by the modified Rankin Scale (mRS), at 12 and 24 weeks. All deaths and nonfatal serious adverse events were reviewed by the study team and by the DSMB, which provided input on classification of severity, expectedness, and causality of events. A structured questionnaire [18, 19] combined with the Rankin Focused Assessment [20] were used to assign an mRS score, which ranged from 0 to 5 (0 indicates no symptoms; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; and 5, severe disability). Participants who died were assigned a score of 6. In a post hoc analysis, the mRS was dichotomized with a score of 0–2 defined as a favorable outcome.

Power calculations for the trial were based on quantification of pharmacokinetic parameters (to be published separately) for a planned sample size of 60 participants. However, with trial start-up and recruitment hampered by the coronavirus disease 2019 pandemic, we ultimately stopped recruitment before reaching this target due to cessation of funding. In the statistical analysis, we compared the proportions of participants who experienced any treatment-emergent grade ≥3 adverse event and individual grade ≥3 adverse events, using χ^2 or Fisher exact tests. We then compared grade ≥3 adverse event–free survival over 4 weeks and overall survival over 24 weeks (1) by treatment arm, (2) between participants who did and those who did not receive linezolid, and (3) between those who received high-dose versus standard-dose rifampin, using the log-rank test and visualization with Kaplan-Meier curves. In a post hoc analysis, we compared survival rates, restricted to participants with moderate to severe disease. We evaluated additional secondary clinical endpoints with logistic regression models and a proportional odds analysis for the 7-level mRS, adjusted for baseline MRC grade.

RESULTS

Of 264 potentially eligible participants, 40 were randomized between 10 September 2021 and 7 June 2023 (Figure 1). No participants were lost to follow-up. Demographic and clinical characteristics of participants are in Table 1. Almost all participants (98%) were living with HIV. The majority (67%) were HIV treatment experienced, about half of whom had discontinued ART. One-fourth had microbiologically confirmed TBM, 70% were classified as having probable TBM, and 5% as having possible TBM. Nearly 75% of participants had moderate to severe TBM (MRC grades II and III). No rifampin resistance was identified.

Baseline laboratory results from blood and CSF are in Supplementary Table 1. At entry, 85% of participants had hyponatremia, and 35% had elevated alanine aminotransferase levels. Most participants had a lymphocyte-predominant CSF

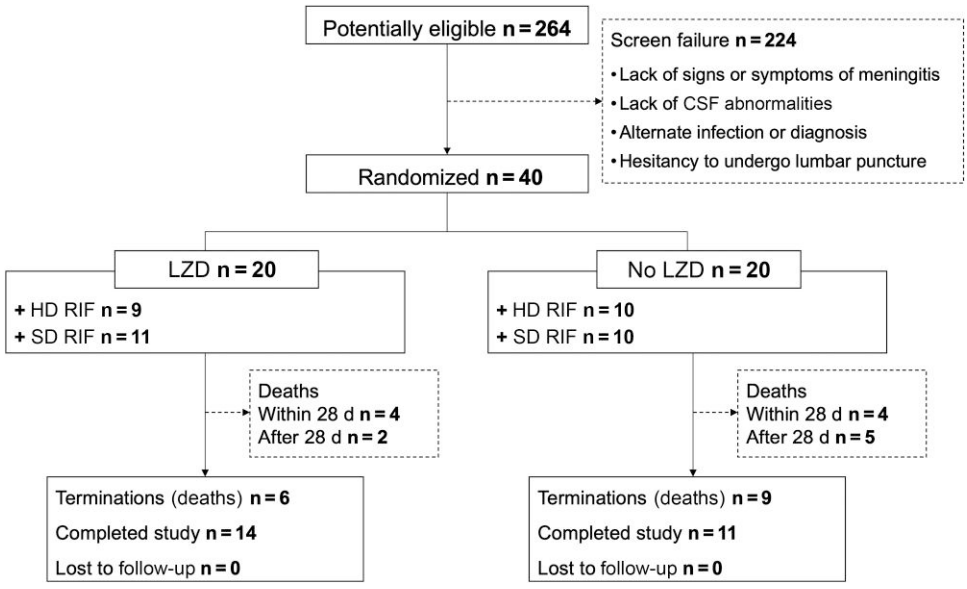

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Diagram. Abbreviations: CSF, cerebrospinal fluid; HD, high-dose; LZD, linezolid; RIF, rifampin; SD, standard-dose.

Table 1. Demographic and Clinical Characteristics at Study Entry

Characteristic, No. of Participants (%)[a]	All Participants (n = 40)	LZD Group			No LZD Group		
		HD RIF (n = 9)	SD RIF (n = 11)	Total (n = 20)	HD RIF (n = 10)	SD RIF (n = 10)	Total (n = 20)
Age, median (IQR), y	37 (29– 42)	39 (36–42)	35 (33–43)	39 (33– 42)	38 (28–42)	33 (27–42)	36 (27–42)
Female sex	22 (55)	2 (22)	8 (73)	10 (50)	6 (60)	6 (60)	12 (60)
Living with HIV	39 (98)	9 (100)	11 (100)	20 (100)	9 (90)	10 (100)	19 (95)
ART status							
On ART	11 (28)	1 (11)	5 (46)	6 (30)	3 (33)	2 (20)	5 (26)
Suboptimal adherence	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	1 (5)
Discontinued ART	14 (36)	4 (44)	3 (27)	7 (35)	3 (33)	4 (40)	7 (37)
ART naive	11 (28)	4 (44)	3 (27)	7 (35)	2 (22)	2 (20)	4 (21)
Unknown	2 (5)	0 (0)	0 (0)	0 (0)	1 (11)	1 (10)	2 (11)
CD4 cell count, median (IQR), cells/μL	149 (63–341)	187 (41–504)	215 (71–351)	201 (68–392)	144 (91–284)	109 (44–154)	138 (50–217)
MRC grade							
Grade I	11 (27.5)	2 (22.2)	3 (27.3)	5 (25)	3 (30)	3 (30)	6 (30)
Grade II	21 (52.5)	5 (55.6)	6 (54.5)	11 (55)	4 (40)	6 (60)	10 (50)
Grade III	8 (20)	2 (22.2)	2 (18.2)	4 (20)	3 (30)	1 (10)	4 (20)
TBM case definition[b]							
Definite	10 (25)	2 (22)	4 (36)	6 (30)	1 (10)	3 (30)	4 (40)
Probable	28 (70)	7 (78)	6 (55)	13 (65)	8 (80)	7 (70)	15 (25)
Possible	2 (5)	0 (0)	1 (9)	1 (5)	1 (10)	0 (0)	1 (5)

Abbreviations: ART, antiretroviral therapy; HD, high-dose; HIV, human immunodeficiency virus; IQR, interquartile range; LZD, linezolid; MRC, Medical Research Council; RIF, rifampin; SD, standard-dose; TBM, tuberculous meningitis.

[a]Data represent no. (%) of participants unless otherwise specified.

[b]Based on uniform case definition from Marais et al [15].

pleocytosis. From entry to week 2, differences in the change in white blood cells, the percentages of lymphocytes and neutrophils, and resolution of hypoglycorrhachia were observed, suggestive of greater improvement in CSF parameters in the linezolid group (Supplementary Table 2 and Supplementary Figure 2).

The primary endpoint of any grade ≥3 adverse event during the 4-week interventional period occurred in 27 participants (Table 2). No significant difference in the proportion of participants who experienced a grade ≥3 adverse event or in the time to grade ≥3 adverse event was observed across treatment arms or by linezolid (Table 2 and Figure 2) or rifampin treatment group (Supplementary Figure 3). When examined separately, the frequency of individual grade 3 or 4 adverse events did not differ across treatment arms or by linezolid or rifampin treatment group (Table 2). No participant had to reduce the dose of or discontinue linezolid. Seven participants inadvertently received linezolid at a dose of 600 mg twice daily instead of the per-protocol dose of 1200 mg once daily. The occurrence of grade ≥3 adverse events did not differ by linezolid dosing schedule.

Of grade 3 and 4 adverse events, hyponatremia and anemia were the most common laboratory abnormalities; both occurred more frequently in participants who did not receive linezolid (Table 2). Neuropathy developed in 4 participants, of whom 3 were on linezolid. Two of the 3 participants who received linezolid had resolution of signs and symptoms of neuropathy on the BPNS by week 8; the third participant missed the week 8 visit and did not undergo repeated BPNS. One participant not on linezolid died before repeated BPNS could be performed at week 8. Among those who tolerated vision testing, none experienced a decline in visual acuity, color vision, or contrast sensitivity. Twenty participants experienced 22 serious adverse events over 24 weeks of follow-up (Table 3). None were attributable to a study drug other than a single occurrence of grade 3 hyperbilirubinemia in a participant receiving high-dose rifampin without linezolid (Supplementary Table 3).

The 24-week overall survival rate was higher for participants who received linezolid than for those who did not (Table 3). At 12 weeks, 14 participants (35%) had died, with 5 deaths (25%) in the linezolid group and 9 (45%) in the no-linezolid group (odds ratio [OR] for linezolid group, 0.41 [95% confidence interval (CI), .10–1.52; $P = .19$]; adjusted OR, 0.28 [.06–1.23; $P = .10$]). At 24 weeks, 1 additional participant in the linezolid group had died, for a total of 15 deaths (37.5%) (OR for linezolid group, 0.52 [95% CI, .14–1.90; $P = .33$]; adjusted OR, 0.43 [.10–1.71; $P = .24$]). No significant difference in overall survival was observed across treatment arms or by linezolid (Figure 3) or rifampin (Supplementary Figure 3) treatment group. Most deaths occurred in the first 6 weeks after initiation of antituberculosis therapy in participants with moderate to severe disease (Figure 4 and Supplementary Box 2). In a post hoc analysis restricted to participants with moderate to severe disease, overall

Table 2. Grade 3 or 4 Adverse Events or Death During 4-Week Interventional Period

Adverse Event, No. of Participants (%)	All Participants (n = 40)	LZD Group		No LZD Group		*P* Value[a]	Total LZD Group (n = 20)	Total No LZD Group (n = 20)	*P* Value[b]
		HD RIF (n = 9)	SD RIF (n = 11)	HD RIF (n = 10)	SD RIF (n = 10)				
Laboratory abnormality									
Grade 3 anemia	2 (5)	0 (0)	1 (9)	0 (0)	1 (10)	0.83	1 (5)	1 (5)	0.61
Grade 4 anemia	2 (5)	0 (0)	0 (0)	1 (10)	1 (10)		0 (0)	2 (10)	
Grade 3 or 4 thrombocytopenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	…	0 (0)	0 (0)	…
Grade 3 or 4 neutropenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	…	0 (0)	0 (0)	…
Grade 3 or 4 elevated ALT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	…	0 (0)	0 (0)	…
Grade 3 elevated total bilirubin	2 (5)	0 (0)	0 (0)	2 (20)	0 (0)	0.16	0 (0)	2 (10)	0.49
Grade 4 elevated total bilirubin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Grade 3 hyponatremia	6 (15)	0 (0)	1 (9)	3 (30)	2 (20)	0.21	1 (5)	5 (25)	0.27
Grade 4 hyponatremia	4 (10)	0 (0)	2 (18)	1 (10)	1 (10)		2 (10)	2 (10)	
Clinical sign or symptom									
Grade ≥2 symptoms/signs on Brief Peripheral Neuropathy Screen[c]	4 (10)	1 (11)	2 (18)	0 (0)	1 (10)	0.83	3 (15)	1 (5)	0.61
Decline in visual examination[d]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	…	0 (0)	0 (0)	…
Focal weakness	3 (7.5)	0 (0)	0 (0)	1 (10)	2 (20)	0.34	0 (0)	3 (15)	0.23
Confusion/altered mental status	5 (12.5)	1 (11)	1 (9)	2 (20)	1 (10)	0.92	2 (10)	3 (15)	1.00
Transient loss of consciousness	1 (2.5)	1 (11)	0 (0)	0 (0)	0 (0)	0.23	1 (5)	0 (0)	1.00
Headache	1 (2.5)	0 (0)	1 (9)	0 (0)	0 (0)	1.00	1 (5)	0 (0)	1.00
Fever	1 (2.5)	0 (0)	0 (0)	0 (0)	1 (10)	0.73	0 (0)	1 (5)	1.00
Vomiting/anorexia/dehydration	2 (5)	1 (11)	1 (9)	0 (0)	0 (0)	0.59	2 (10)	0 (0)	0.49
Total no. of participants with any grade 3 or 4 adverse event	21 (53)	4 (44)	7 (64)	5 (50)	5 (50)	0.88	11 (55)	10 (50)	1.00
Total no. of participants with a grade 3 or 4 adverse event or death	27 (68)	6 (67)	9 (82)	7 (70)	5 (50)	0.52	15 (75)	12 (60)	0.50

Abbreviations: ALT, alanine aminotransferase; HD, high-dose; LZD, linezolid; RIF, rifampin; SD, standard-dose.

[a] *P* values comparing across 4 treatment arms.

[b] *P* values comparing linezolid versus no linezolid groups.

[c] Findings in 25 participants who were able to participate in testing.

[d] Findings in16 participants who were able to participate in testing.

survival was again observed to be higher for participants who received linezolid than for those who did not (Supplementary Figure 4).

The distribution of functional outcomes measured by the mRS at 12 and 24 weeks favored the linezolid group (Figure 5). In a proportional odds model, the odds of a lower mRS (eg, mRS of 0 vs ≥1 or 0 or 1 vs ≥2) in participants who received linezolid, signifying less disability, was about twice that for participants who did not receive linezolid (OR at 12 weeks, 2.22 [95% CI, .69–7.14; $P = .18$]; OR at 24 weeks, 2.00 [.64–6.25; $P = .24$]). Participants who received linezolid had a 3.69-fold higher adjusted odds of a favorable outcome at 24 weeks (mRS, 0–2) than those who did not receive linezolid (95% CI, .82–20.69; $P = .10$).

DISCUSSION

In this randomized, open-label phase 2 trial, a 4-week course of linezolid 1200 mg once daily with high-dose or standard-dose rifampin was safe and well tolerated in adults with predominantly moderate to severe TBM. Notably, fewer participants receiving linezolid died or had severe disability. These findings add to growing evidence that linezolid is a safe and acceptable treatment for TBM, with sufficient potential to warrant further inquiry in large-scale randomized trials.

The results of our trial align with findings from the Linezolid, Aspirin and Enhanced Dose Rifampicin in HIV-TBM (LASER-TBM; NCT03927313) trial [21], which compared linezolid and high-dose rifampin (35 mg/kg/d) with or without aspirin versus standard of care. In LASER-TBM, no significant difference in the cumulative proportion of participants experiencing adverse events or death during the 8-week interventional period was detected across treatment arms. In that study, however, the majority of participants had mild disease with a low overall mortality rate of 16%, which does not reflect the full spectrum of disease severity in TBM. In contrast, most participants in our study had moderate to severe TBM, with 20% meeting criteria for severe disease. Even in our more neurologically ill population, linezolid administered for 4 weeks was safe and well tolerated, with no participant requiring discontinuation or reduction in the dose of linezolid.

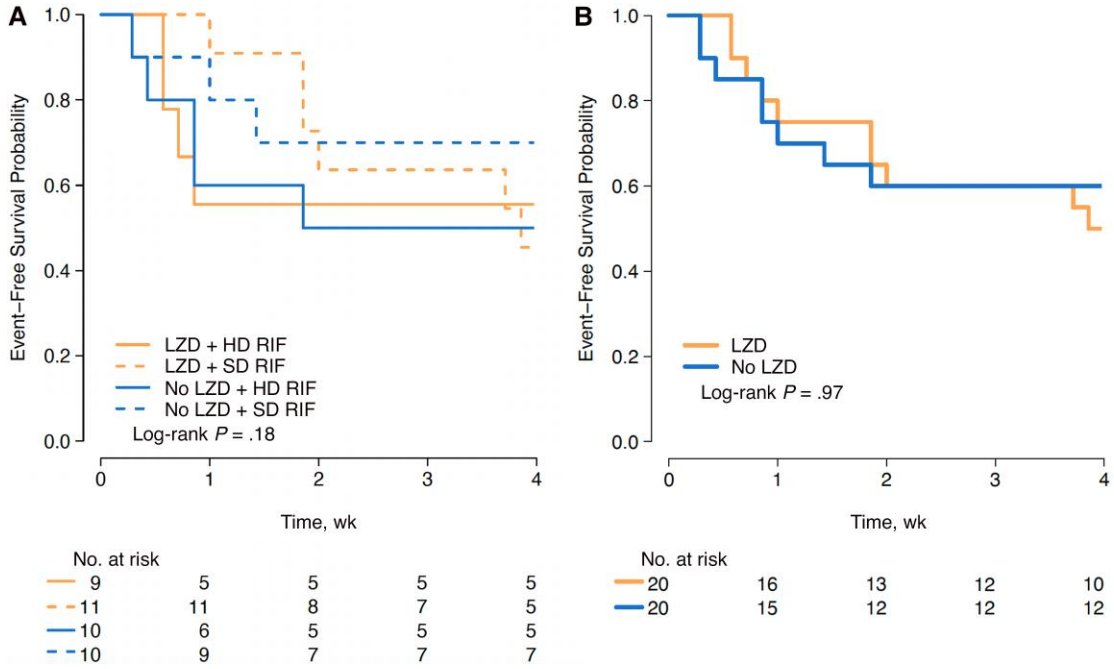

Figure 2. Kaplan-Meier analysis comparing time to grade ≥3 laboratory adverse event or death during the 4-week interventional period by treatment arm (*A*) and between participants who did or did not receive linezolid (LZD) (*B*). Abbreviations: HD, high-dose; RIF, rifampin; SD, standard-dose.

Table 3. Deaths and Serious Adverse Events During 24-Week Follow-up

		LZD Group		No LZD Group					
Outcome, No. of Participants (%)	All Participants (n = 40)	HD RIF (n = 9)	SD RIF (n = 11)	HD RIF (n = 10)	SD RIF (n = 10)	*P* Value[a]	Total LZD (n = 20)	Total No LZD Group (n = 20)	*P* Value[b]
Total deaths	15 (38)	3 (33)	3 (27)	5 (50)	4 (40)	0.78	6 (30)	9 (45)	0.51
By MRC grade									
Grade I	1	0	1	0	0	…	1	0	…
Grade II	7	2	0	2	3	…	2	5	…
Grade III	7	1	2	3	1	…	3	4	…
All participants with an SAE	20 (50)	5 (56)	4 (36)	6 (60)	5 (50)	0.78	9 (45)	11 (55)	0.75
By MRC grade									
Grade I	2	1	1	0	0	…	2	0	…
Grade II	11	3	1	3	4	…	4	7	…
Grade III	7	1	2	3	1	…	3	4	…
SAE related to investigational drug	1 (5)	0 (0)	0 (0)	1 (17)	0 (0)	1.00	0 (0)	1 (9)	1.00

Abbreviations: HD, high-dose; LZD, linezolid; MRC, medical research council; RIF, rifampin; SAE, serious adverse event; SD, standard-dose.

[a] *P* values comparing across 4 treatment arms.

[b] *P* values comparing linezolid versus no linezolid groups.

Grade 3 or 4 hematologic adverse events occurred in 10% of participants, most of whom did not receive linezolid. Two instances of grade 3 hyperbilirubinemia with grade 2 elevation in alanine aminotransferase occurred, both in participants on high-dose rifampin without linezolid. In one of them, study drugs were temporarily discontinued and successfully resumed without recurrence of liver injury. In the other participant, the abnormal liver function test results occurred at the conclusion of the 4-week interventional period. The incidence of drug-induced liver injury was comparable to that observed in the LASER-TBM study but lower than in the ESCALATE (Linezolid As An Add On Treatment in the Intensive Phase of Tubercular Meningitis) trial (Clinical Trials Registry–India CTRI/2019/06/019501), in which elevated aminotransferase

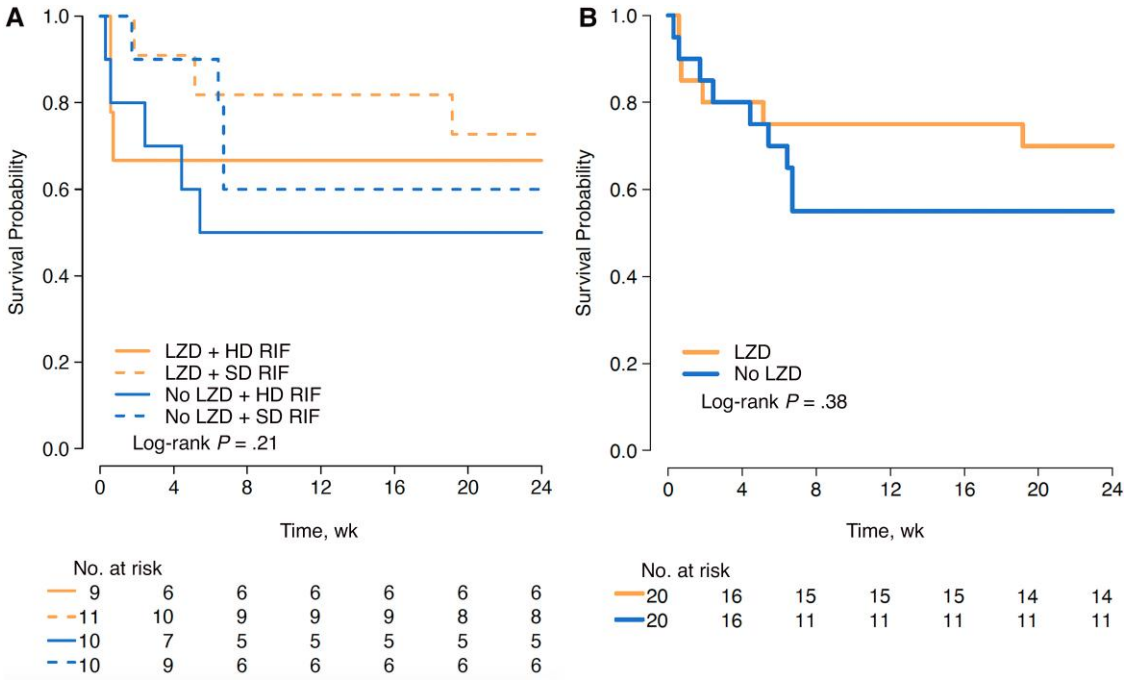

Figure 3. Overall survival among all participants, as shown by Kaplan-Meier analysis comparing time to death over 24 weeks of follow-up by treatment arm (*A*) and between participants who did or did not receive linezolid (LZD) (*B*). Abbreviations: HD, high-dose; RIF, rifampin; SD, standard-dose.

levels developed in 31% of participants receiving conventional antituberculosis therapy with or without linezolid [22]. The higher prevalence of transaminitis in the ESCALATE trial, a single-center study in India, is in line with recent data suggesting that Asian race may be a risk factor for drug-induced liver injury [23]. However, the proportions of participants in the ESCALATE study with liver injury did not differ significantly by linezolid treatment status.

While most treatment-limiting toxicities associated with linezolid are reversible, neurologic toxic effects, including painful, sensory-predominant peripheral neuropathy and optic neuropathy, can be permanent [24]. The median time to onset of neuropathy associated with linezolid is often >2 months [25–28], and in some studies >6 months [29]. However, many of these studies have been of patients treated with lower-dose linezolid, typically 600 mg/d. In the ZeNix study, among 46 participants who received linezolid 1200 mg/d for 9 weeks, 15 adverse events suggestive of peripheral neuropathy occurred [30]. Likewise, even with the short duration of linezolid in our trial, signs and symptoms of peripheral neuropathy developed in 4 participants, of whom 3 were on linezolid. Reassuringly, on repeat testing after the conclusion of 4 weeks of linezolid treatment, all evaluable participants experienced complete resolution of signs and symptoms of neuropathy.

Consistent with prior studies showing early mortality in TBM [5, 7, 31, 32], deaths occurred within a short interval after presentation. Of the 15 participants who died, 14 died in the first 6 weeks of the trial, with all but 1 death in participants with moderate to severe disease. The severity of disease at presentation is arguably the strongest predictor of outcome in TBM [4, 33–37]. Although this could point to a critical window during which intensified antituberculosis therapy is most beneficial, a counterargument is that for patients who present with advanced infection, brain injury may be irreversible. Alongside efforts to optimize treatment, strategies that reduce time to presentation, enhance recognition of possible TBM, promote earlier initiation of empiric therapy, and support development of more accessible, higher-yield point-of-care diagnostic, are essential to improving outcomes in this devastating form of tuberculosis.

Fewer than half of participants met criteria for microbiologically confirmed infection, which is standard in TBM trials [21, 36, 38, 39]. Emerging data suggest that a proportion of patients with suspected TBM may have an alternative CNS infection or, particularly for people with HIV, have TBM with another coinfection [40]. Enrolling participants in TBM trials who do not have TBM or have an untreated coinfection could potentially dilute the effect of the treatment under investigation. Alternatively, if a subset of participants in our trial had bacterial infections that were missed, linezolid may have appeared effective due to its gram-positive antibacterial activity. Although a suggestion of greater improvement in CSF parameters in the linezolid group was noted, similar to findings from

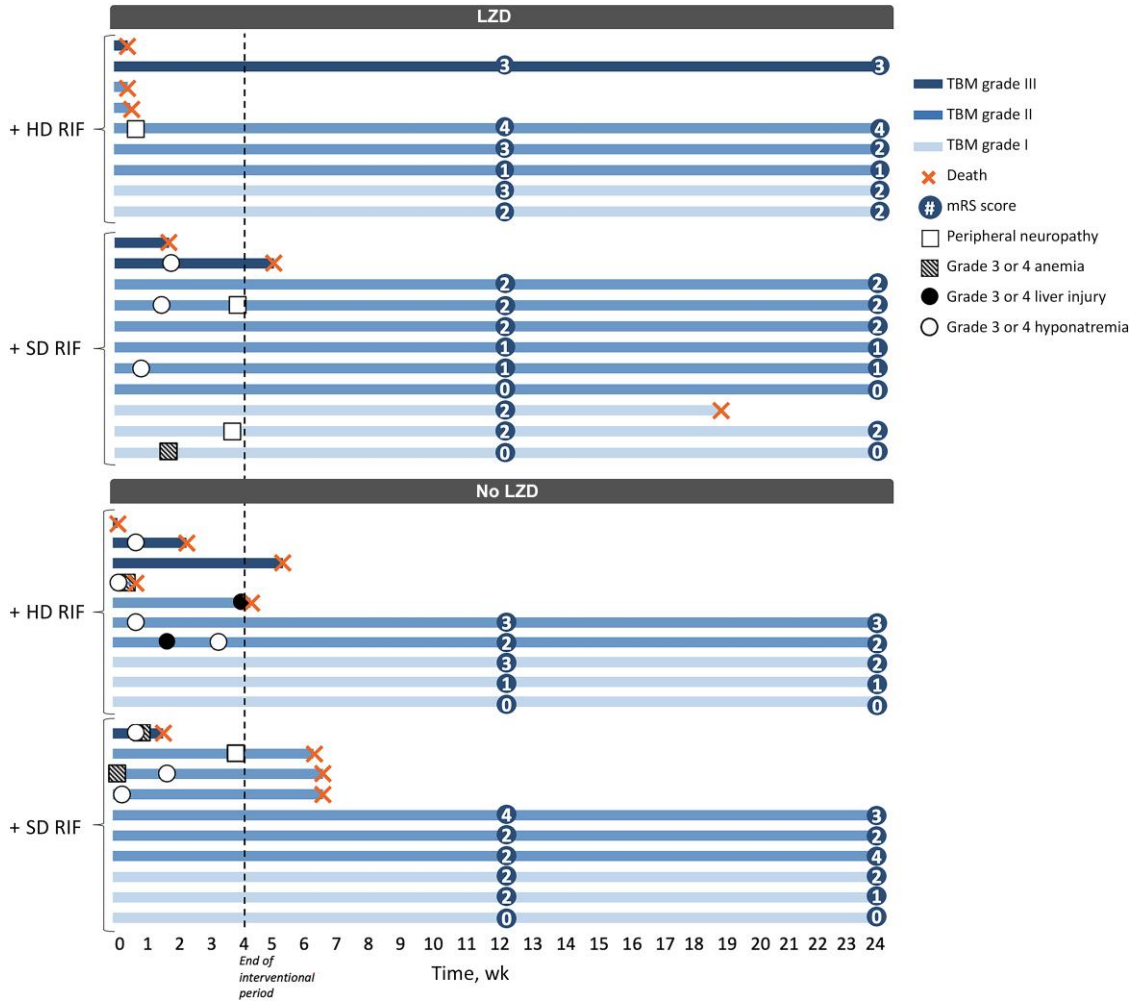

Figure 4. Swimmer plot for all participants. Characteristics and outcomes of all 40 trial participants are depicted, including Medical Research Council disease grade at presentation, study regimen received, timing of adverse events, timing of deaths, and modified Rankin Scale (mRS) score at 12 and 24 weeks. Abbreviations: HD, high-dose; LZD, linezolid; RIF, rifampin; SD, standard-dose; TBM, tuberculous meningitis.

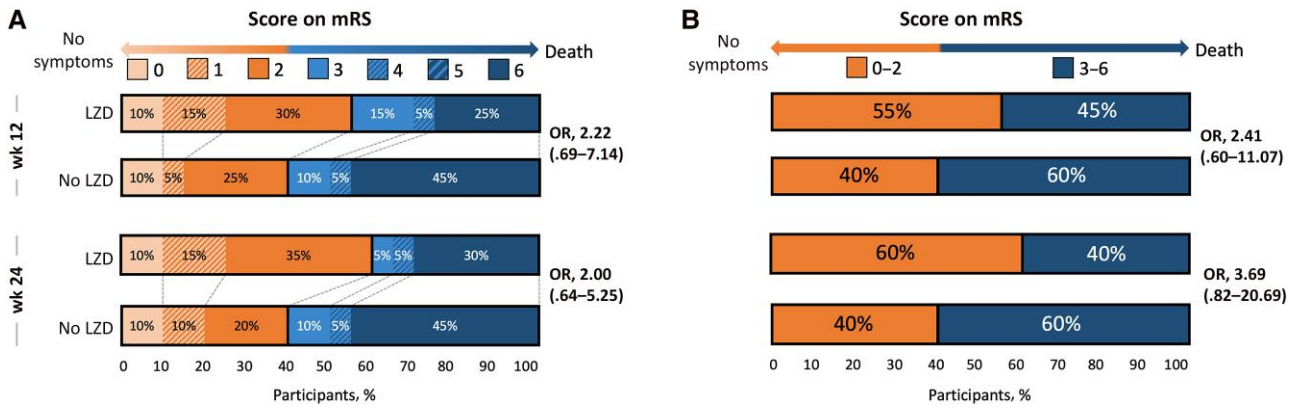

Figure 5. Modified Rankin Scale score (mRS) scores at weeks 12 and 24. *A,* Proportional odds analysis comparing mRS scores at 12 and 24 weeks for participants in the linezolid (LZD) versus no LZD groups. For participants who received LZD, the odds of a lower mRS score at 12 and 24 weeks, signifying less disability, was about twice that for those in the no LZD group. *B,* In a post hoc analysis adjusted for baseline disease grade, participants who received LZD were 3.69-fold more likely than those in the no LZD group to have a favorable outcome at week 24, defined as an mRS score of 0–2. Parenthetical ranges after odds ratios (ORs) represent 95% confidence intervals.

an observational study of linezolid for TBM [13], the tempo of improvement over a short interval could also reflect the expected response to treatment of bacterial meningitis with linezolid.

Our findings should be considered in light of several limitations: a modest sample size, limiting conclusions about clinical outcomes, including across the 4 treatment subgroups; a single-center study design, limiting generalizability; and the large proportion of unconfirmed infections, potentially biasing the observed efficacy of linezolid. Strengths include robust follow-up with no participants lost and the inclusion of mostly moderate to severe TBM cases, unlike in many TBM trials conducted in participants with milder disease and lower mortality rates.

We found that a short course of linezolid to treat primarily moderate to severe TBM disease in a population of neurologically ill people with HIV did not introduce additional toxicity. The results of our study complement mounting data suggesting that linezolid is a safe and well-tolerated medication that should be investigated in larger multisite trials as part of an enhanced regimen for the treatment of TBM.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Data availability. Data from the trial are available from the corresponding author on reasonable request and with the permission of the ALTER study team.

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