Clinical Infectious Diseases

MAJOR ARTICLE

Effectiveness and Safety of Varying Doses of Linezolid With Bedaquiline and Pretomanid in Treatment of Drug-Resistant Pulmonary Tuberculosis: Open-Label, Randomized Clinical Trial

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Background. Treatment of drug-resistant tuberculosis with bedaquiline-pretomanid-linezolid regimen has demonstrated good treatment efficacy. Given linezolid's toxicity profile, prudence suggests reconsidering its dose and duration. We determined the effectiveness and safety of structured dose reduction of linezolid with bedaquiline and pretomanid in adults with pre–extensively drug-resistant (pre-XDR) or treatment-intolerant/nonresponsive multidrug-resistant ($MDR_{TI/NR}$) pulmonary tuberculosis.

Method. Adults with pre-XDR or $MDR_{TI/NR}$ pulmonary tuberculosis were enrolled in a multicenter, parallel-group, randomized clinical trial in India. Patients were randomized to 26 weeks of bedaquiline, pretomanid, and daily linezolid, at 600 mg for 26 weeks (arm 1); 600 mg for 9 weeks followed by 300 mg for 17 weeks (arm 2); or 600 mg for 13 weeks followed by 300 mg for 13 weeks (arm 3). Study end points included sustained cure, bacteriological failure, toxicity, and death.

Results. Of 403 patients enrolled, 255 (63%) were <30 years old, 273 (68%) had prior tuberculosis episodes, and 238 (59%) were malnourished. At the end of treatment, after excluding those with negative baseline cultures, cure was seen in 120 (93%), 117 (94%), and 115 (93%) in arms 1, 2, and 3 respectively. Myelosuppression seen in 85 patients each in arms 1 and 2 and 77 patients in arm 3, not significantly different. Peripheral neuropathy was noticed in 66 patients (30, 17, and 19 in arms 1, 2, and 3) at 10–26 weeks ($P = .02$). The linezolid dose was reduced because of toxicity in 13, 2, and 4 patients in arms 1, 2, and 3, respectively.

Conclusions. In adults with pre-XDR or $MDR_{TI/NR}$ pulmonary tuberculosis, structured linezolid dose reduction to 300 mg/d is as effective as the standard 600-mg dose but with fewer cases of peripheral neuropathy when given with bedaquiline and pretomanid.

Clinical Trials Registration. Clinical Trial Registry of India (CTRI/2021/03/032189)

Keywords. structured dose reduction; linezolid; drug-resistant tuberculosis; pretomanid; drug-related toxicity.

Drug-resistant tuberculosis remains a serious public health problem, fueling the global tuberculosis epidemic [1]. The World Health Organization (WHO) recommends all-oral regimens for treating drug-resistant tuberculosis: the first being a short 6-month all-oral regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) for multidrug-resistant/rifampicin resistant (MDR/RR) tuberculosis and a regimen without moxifloxacin (BPaL) for those with additional fluoroquinolone resistance. The second is an all-oral short regimen of 9 months for MDR/RR tuberculosis, and the third is a longer regimen of 18–20 months that may include an injectable drug [2].

Linezolid is a key component of the BPaLM and BPaL regimens. Three clinical trials using linezolid at doses of ≥600 mg daily [3–5] provide evidence for its efficacy when combined with newer drugs. The Nix-TB trial, with a 90% success rate, found a high incidence of peripheral neuropathy (81%) and

Received 08 March 2024; editorial decision 16 July 2024; published online 28 August 2024

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Clinical Infectious Diseases® 2024;79(6):1375–85

https://doi.org/10.1093/cid/ciae388

myelosuppression (48%) with 1200 mg/d of linezolid for 26 weeks, necessitating dose reduction or cessation over the treatment period [3]. In the ZeNix trial, favorable outcomes of 93%, 89%, 91%, and 84% were achieved when linezolid was given at a dose of 1200 mg/d for 26 or 9 weeks or 600 mg for 26 or 9 weeks, respectively, along with bedaquiline and pretomanid [4]. Peripheral neuropathy was reported in 38%, 24%, 24%, and 13%, and myelosuppression in 22%, 15%, 2%, and 7%, respectively [4]. Linezolid increases the bactericidal and sterilizing action of bedaquiline and pretomanid, resulting in quicker *Mycobacterium tuberculosis* clearance before neuropathy develops [6, 7].

Given the high rates of toxicity with a longer duration of high-dose linezolid, there is a need to study the effect of various linezolid doses and durations. The current trial aimed to determine the effectiveness, tolerability, and safety of structured dose reduction of linezolid in combination with bedaquiline and pretomanid in adults with pre–extensively drug-resistant (pre-XDR) or treatment-intolerant/nonresponsive multidrug-resistant ($MDR_{TI/NR}$) pulmonary tuberculosis [8].

METHODS

Study Population and Intervention

During 2021–2023, this multicenter, parallel arm, randomized pragmatic clinical trial recruited adults, aged 18–65 years, with pre-XDR or $MDR_{TI/NR}$ pulmonary tuberculosis at 9 sites in India. Criteria for ineligibility included (1) bedaquiline or linezolid intake for >2 weeks, (2) unavailable results of fluoroquinolone drug susceptibility test (DST), (3) pregnancy or breastfeeding, and (4) grade ≥3 peripheral neuropathy [9]. After providing informed written consent, eligible patients, underwent physical examination, including assessment for peripheral neuropathy, sputum smear microscopy and liquid culture–DST for all drugs, complete hemogram, liver function testing, measurement of serum electrolytes and lipase, and electrocardiography (ECG) (Supplementary Table 1). If test results were not significantly abnormal, patients were randomized to 1 of the 3 arms with different linezolid doses arm 1 (600 mg daily for 26 weeks), 2 (600 mg daily for 9 weeks followed by 300 mg daily for 17 weeks), or 3 (600 mg daily for 13 weeks followed by 300 mg daily for 13 weeks), along with bedaquiline (400 mg daily for 2 weeks followed by 200 mg thrice weekly for 24 weeks) and pretomanid (200 mg daily for 26 weeks).

Study Follow-up

After randomization, treatment was supervised by a family member or healthcare professional, determined by patient preference at treatment initiation. Drugs were supplied weekly for the first month, then monthly until the end of treatment. A medical officer performed weekly follow-ups for the first 16 weeks and then switched to monthly follow-ups. These visits included complete physical examination and laboratory investigations for adverse events (AEs), including grading and causality assessments. Two sputum samples were collected for *M. tuberculosis* smear and culture (Supplementary Table 1). All AEs were graded using Division of AIDS criteria (version 2.1) and the Common Terminology Criteria for Adverse Events (CTCAE; version 5.0) for QTc(f) [10, 11]. AE casualties were assessed using the WHO–Uppsala Monitoring Centre (UMC) system [12]. *M. tuberculosis* isolates from pretreatment culture and any positive culture at or after week 16 were subjected to DST for bedaquiline, pretomanid, and linezolid. If sputum culture was positive at week 16, treatment was extended to 39 weeks. Regardless of sputum smear or culture status, structured linezolid dose reduction from 600 to 300 mg was done at protocol-specified time in arms 2 and 3 and for grade 3 toxicity. No further dose reduction beyond 300 mg was permitted.

Study Outcome

The primary study outcome is sustained treatment success 48 weeks after the end of treatment. The effectiveness of the regimen was defined (1) at the end of treatment as favorable (cure defined as completion of 26 or 39 weeks of treatment without evidence of failure and with ≥2 consecutive negative sputum cultures taken 7 days apart) or unfavorable (bacteriological or clinical failure, loss to follow-up, or death) and (2) at 48 weeks after treatment as culture converted or culture reverted (tuberculosis recurrence). Clinical failures were those requiring a change of treatment due to drug-associated toxicity or clinical/radiological deterioration during treatment [9]. The bacteriological failure category included those with persistent culture positivity after 22 weeks of treatment despite a sensitive drug profile and those who reverted after initial culture conversion during the treatment period.

Sample Size and Statistical Analysis

Efficacy of bedaquiline and pretomanid with linezolid (600 mg/d) over 26 weeks was reported as 91% [4]. We expected that the treatment arms with structured linezolid dose reduction would be noninferior to linezolid at 600 mg/d for 26 weeks by about 10%. To illustrate this, with a power of 80%, an α error of 5%, and a 20% loss to follow-up or migration, 133 patients were required in each arm, totaling 399 (approximately 400). Participants were randomly assigned to one of the trial arms in a 1:1:1 ratio, using block randomization performed by the central study team with REDCap software.

Both modified intent-to-treat and per-protocol analyses were performed. The modified intent-to-treat population excluded patient with baseline study drug resistance or culture negativity. The per-protocol analysis included all participants who consumed >80% of the assigned regimen. The primary comparison of effectiveness was between the different arms with varying dosages of linezolid. The Kaplan–Meier survival

analysis was used to determine the time to sputum smear culture conversion and AEs; log-rank tests were used to compare regimens, and χ^2 tests were used to compare the occurrence of peripheral neuropathy between the arms. To determine the predictors of unfavorable outcomes, a Cox regression model was used, considering clinically significant ($P < .20$) covariates in univariate analysis. To compare the frequency and predictors of AEs, a count regression model and log-rank tests were used. Sensitivity analysis was performed for patients excluded at baseline, using multiple imputations with different techniques, and cure rate for the imputed data set was obtained. All participating institutes obtained institutional ethics committee approval. Trial was prospectively registered with India's Clinical Trial Registry (CTRI/2021/03/032189).

RESULTS

We enrolled 403 of 688 patients screened (Figure 1), with equal sex distribution. Table 1 reveals that the 3 arms had similar baseline characteristics. Patients were mostly young (median age, 27 years), with low body mass index (median, 17.5 [calculated as weight in kilograms divided by height in meters squared]), Human immunodeficiency virus was uncommon (1%), and few patients smoked (10%), used alcohol (12%) or had diabetes mellitus (12%). Chest radiography showed cavities in 48%; 68% had prior episodes of tuberculosis treatment with drugs including, but not limited to, isoniazid, rifampicin, pyrazinamide, and fluoroquinolone.

Effectiveness Analysis

Following baseline withdrawals, 378 participants were included in the modified intent-to-treat analysis. At the end of treatment, 352 patients (93%) were declared cured—93% (120 of 129) in arm 1, 94% (117 of 125) in arm 2, and 93% (115 of 124) in arm 3, not significantly different between the arms (Table 2). In the per-protocol analysis, cure was achieved in 368 of 379 patients (97%). There were 26 unfavorable

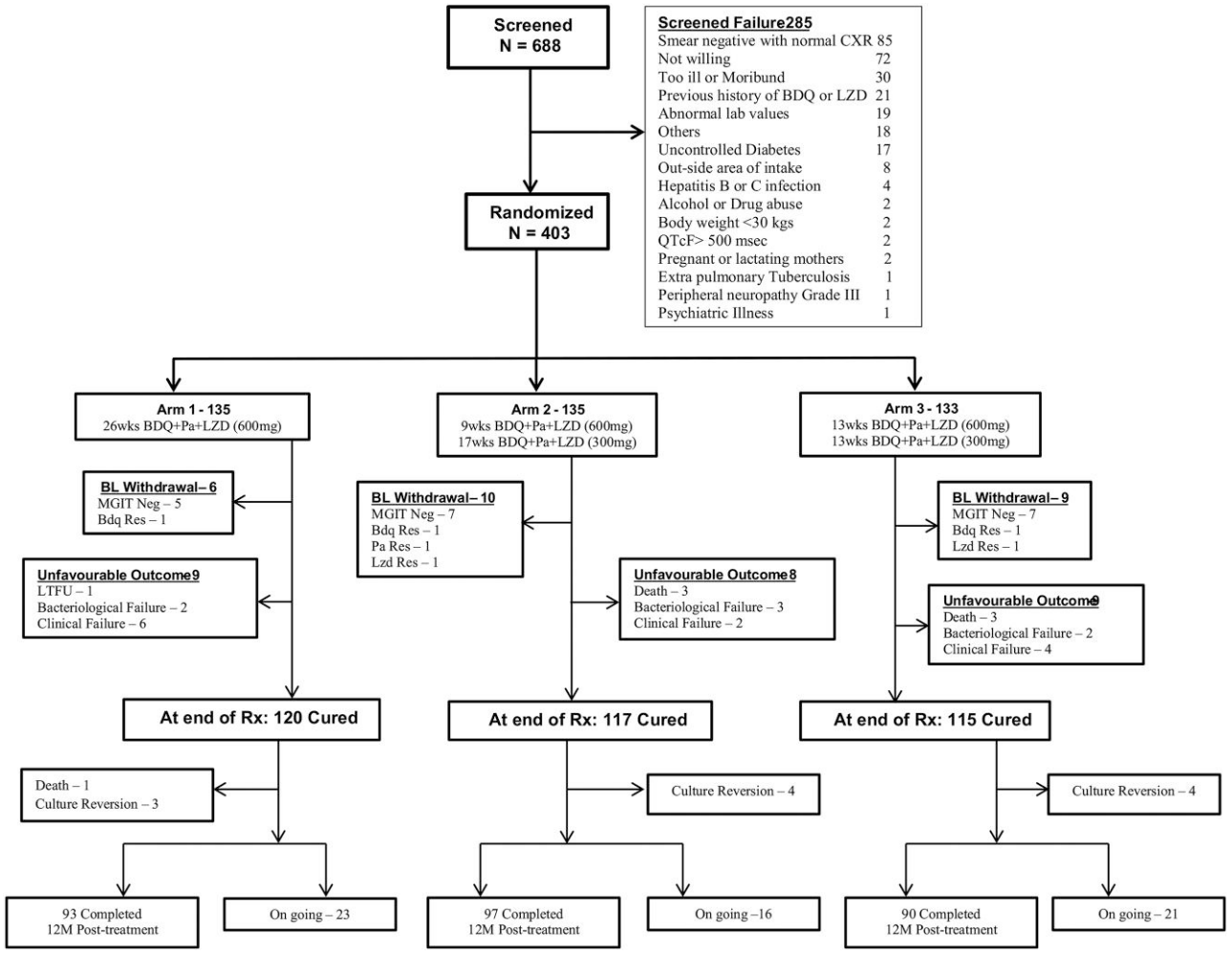

Figure 1. Consort checklist of mBPaL trial participants. Abbreviations: BDQ, bedaquiline; BL, baseline; CXR, chest radiography; LTFU, loss to follow up; LZD, Linezolid; mo, months; MGIT, mycobacterial growth indicator tube; Neg, negative; Pa, pretomanid; PN, peripheral neuropathy; Res, resistant.

Table 1. Baseline Characteristics of Trial Participants

Characteristic	Participants, No. (%)[a]			
	Arm 1 (n = 135)	Arm 2 (n = 135)	Arm 3 (n = 133)	All Arms (n = 403)
Male sex	67 (50)	75 (56)	67 (50)	215 (53)
Weight, median (IQR), kg	45.0 (40.0–51.5)	45.0 (38.7–51.4)	47.8 (40.0–55.0)	45.1 (39.8–52.0)
BMI, median (IQR)[b]	17.3 (15.6–20.3)	17.3 (15.6–19.8)	17.9 (15.8–20.5)	17.5 (15.6–20.2)
Age, median (IQR), y	28 (23–38)	26 (21–40)	27 (22–37)	27 (22–38)
Age group				
≤30 y	82 (61)	84 (62)	89 (67)	255 (63)
>30 y	53 (39)	51 (38)	44 (33)	148 (37)
HIV status				
Positive	0	1	1	2
Negative	135 (100)	134 (99)	132 (99)	401 (99)
Smoking status				
Never	123 (91)	123 (91)	117(88)	363 (90)
Current	1	0	0	1
Former	11(8)	12 (9)	16(12)	39 (10)
Current alcohol use[c]				
Yes	16 (12)	14 (10)	17 (13)	47 (12)
No	119 (88)	121 (90)	116 (87)	356 (88)
Diabetes mellitus				
Yes	22 (16)	14 (10)	13 (10)	49 (12)
No	113 (84)	121 (90)	120 (90)	354 (88)
Chest radiographic findings				
Abnormal	133 (99)	134 (99)	130 (98)	397 (99)
No. of zones involved				
≤3	82 (62)	90 (67)	88 (68)	260 (65)
>3	51 (38)	44 (33)	42 (32)	137 (35)
Unilateral	56 (42)	48 (36)	48 (37)	152 (38)
Bilateral	77 (58)	86 (64)	82 (63)	245 (62)
Cavitation	68 (51)	65 (49)	60 (46)	193 (49)
No cavitation	65 (49)	69 (51)	70 (54)	204 (51)
Type of resistance				
Pre-XDR tuberculosis	133 (98)	133 (98)	130 (98)	396 (98)
MDR tuberculosis–treatment intolerant	2 (2)	2 (2)	3 (2)	7 (2)
Previous tuberculosis episodes				
Yes	95 (70)	85 (63)	93 (70)	273 (68)
No	40 (30)	50 (37)	40 (30)	130 (32)
Sputum smear at baseline[d]				
Negative	8 (6)	9 (7)	14 (10)	31 (8)
Scanty	5 (4)	7 (5)	10 (8)	22 (5)
1+	59 (44)	62 (46)	49 (37)	170 (42)
2+	21 (15)	25 (18)	21 (16)	67 (17)
3+	42 (31)	32 (24)	39 (29)	113 (28)
Liquid culture (MGIT) at baseline				
Positive	130 (96)	128 (95)	126 (95)	384 (95)
Negative	5 (4)	7 (5)	7 (5)	19 (5)

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; MGIT, mycobacterial growth indicator tube; XDR, extensively drug resistant.

[a]Data represent no. (%) of participants unless otherwise specified. Arm 1 received bedaquiline, pretomanid, and linezolid at 600 mg/d for 26 weeks; arm 2, bedaquiline, pretomanid, and linezolid at 600 mg/d for 9 weeks, followed by 300 mg/d for 17 weeks; and arm 3, bedaquiline, pretomanid, linezolid at 600 mg/d for 13 weeks, followed by 300 mg/d for 13 weeks.

[b]BMI calculated as weight in kilograms divided by height in meters squared.

[c]Current alcohol use defined as use of alcohol at the time of study enrollment.

[d] International Union Against Tuberculosis and Lung Disease/WHO smear grading for acid-fast bacilli.

outcomes, including 6 deaths, 1 loss to follow-up, 7 bacteriological failures, and 12 clinical failures (Table 2). Among the clinical failures, 7 were due to clinical/radiological deterioration (2 each in arms 1 and 2 and 3 in arm 3) and 5 due to AEs (4 in arm 1 and 1 in arm 3). Two of the 6 deaths occurred during the first 5 weeks of treatment (Supplementary Table 2). At

Table 2. Effectiveness Analysis at the End of Treatment

Population and Treatment Outcome	Participants, No. or No. (%)[a]			
	Arm 1 (n = 135)	Arm 2 (n = 135)	Arm 3 (n = 133)	Total (n = 403)
ITT population				
Assessable population	135	135	133	403
Cure at end of treatment	125 (93)	124 (92)	122 (92)	371 (92)
CI for cure at end of treatment, %				
95% CI	87–97	86–96	86–96	89–95
97.5% CI	88–98	85–96	85–96	89–95
Unfavorable outcome	10 (7)	11 (8)	11 (8)	32 (8)
Death	0	3	3	6
Loss to follow-up	1	0	0	1
Bacteriological failure	2	3	2	7
Clinical failure	6	2	4	12
Withdrawal due to study drug resistance	1	3	2	6
mITT population				
Not assessable (baseline withdrawal n = 25)				
MGIT negative	5	7	7	19
Baseline study drug resistance	1	3	2	6
Total	6 (4)	10 (7)	9 (7)	25 (6)
Assessable population	129	125	124	378
Cure at end of treatment	120 (93)	117 (94)	115 (93)	352 (93)
CI for cure at end of treatment, %				
95% CI	87–97	88–97	87–97	90–95
97.5% CI	86–97	87–98	86–97	90–96
Unfavorable outcome	9 (7)	8 (6)	9 (7)	26 (7)
Death	0	3	3	6
Loss to follow-up	1	0	0	1
Bacteriological failure	2	3	2	7
Clinical failure	6	2	4	12
Per-protocol-population				
Not assessable n = 24 (<80% drug received)[b]				
Assessable population	125	130	124	379
Cure at end of treatment	123 (98)	124 (95)	121 (98)	368 (97)
95% CI for cure at end of treatment, %				
95% CI	94–99	90–98	94–99	95–98
97.5% CI	95–99	91–99	95–99	95–99
Unfavorable outcome	2	6	3	11 (3)
Death	0	1	0	1
Bacteriological failure	2	3	2	7
Clinical failure	0	2	1	3

Abbreviations: CI, confidence interval; ITT, intent-to-treat; MGIT, mycobacterial growth indicator tube; mITT, modified intent-to-treat.

[a]Data represent no. (%) of participants unless otherwise specified. Arm 1 received bedaquiline, pretomanid, and linezolid at 600 mg/d for 26 weeks; arm 2, bedaquiline, pretomanid, and linezolid at 600 mg/d for 9 weeks, followed by 300 mg/d for 17 weeks; and arm 3, bedaquiline, pretomanid, linezolid at 600 mg/d for 13 weeks, followed by 300 mg/d for 13 weeks.

[b]The per-protocol analysis excluded participants who took less than 80% of prescribed drugs. The analysis included those who were culture negative or drug resistant at baseline.

the time of death, sputum smear and culture were positive in 3 patients and negative in 2, while 1 patient had missed treatment after 2 weeks and died without further treatment in week 17. According to Cox proportional hazards model, female patients had a 3-fold higher chance of unfavorable outcomes (adjusted hazard ratio, 3.28 [95% confidence interval, 1.3%–8.3%]; $P = .01$) (Supplementary Table 3).

The median time to culture conversion in arm 1 was 9 weeks, compared with 4 weeks in the other 2 arms. The log-rank test was used to assess the median time to culture conversion across the arms ($P = .88$ for arms 1 vs 2; $P = .76$ for arms 2 vs 3, and $P = .88$ for arms 1 vs 3), which did not differ significantly (Figure 2). At week 9, culture conversion occurred in 316 (86%) patients (111 [87%], 105 [86%], and 100 [85%] in arms 1, 2, and 3, respectively). At week 16, sputum culture was positive in 17 patients (4%) (7 in arm 1; 5 each in arms 2 and 3), and treatment was extended to 39 weeks. Of these patients, 11 converted by week 20 and 3 by week 24. Two had persistent culture

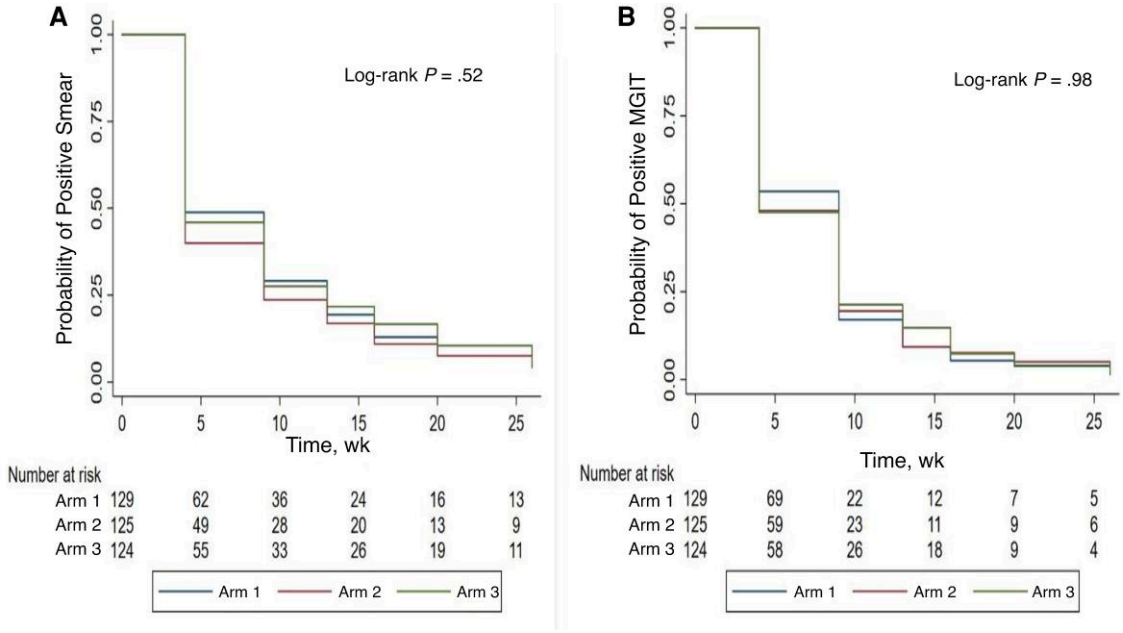

Figure 2. Kaplan–Meier plot showing the time to sputum smear (*A*) and sputum culture (*B*) conversion among trial participants. Abbreviation: MGIT, mycobacterial growth indicator tube.

positivity and were declared as having bacteriological failure, while 1 patient died at week 31 due to extensive nonresponding tuberculosis disease.

Fifteen patients (4%) had ≥1 baseline culture isolate resistant to ≥1 trial drug (bedaquiline in 7, pretomanid in 1, and linezolid in 7). Six were withdrawn from the study and started on DST-guided tailored regimens. In nine, pretreatment DST came after >80% of the treatment doses were completed, with 7 being cured and 2 developing bacteriological failure at week 26 of treatment.

Sensitivity analysis performed on participants excluded at baseline (259 [39%]) had similar results as the primary effectiveness analysis, with no substantial deviation in the cure rate. For those excluded from the trial, treatment was initiated as per the standard of care.

Safety Analysis

During the treatment period, 32 serious AEs were reported in 28 patients (7%) (Supplementary Table 2). A total of 319 patients reported at least 1 AE of any grade between weeks 1 and 9 (106 in arm 1, 112 in arm 2, and 101 in arm 3), while 265 reported an AE between weeks 10 and 26 week of treatment (96, 84, and 85, respectively), not significantly different (Supplementary Figure 1*A* and *B*).

Non–Linezolid-Associated Toxicity

Elevated liver enzymes was the most commonly reported AE, with recurrent episodes in few patients (Table 3). Six patients (3%) had grade 3 or 4 enzyme elevations, with 3 having associated hyperbilirubinemia. All were managed with supportive medicines; 4 of 6 did not require any drug interruption as the elevation was noticed in the final week of treatment. In 1 patient, treatment was interrupted thrice, reintroduced, and completed with dose compensation within 39 weeks; in another, treatment was permanently discontinued and switched to a non–bedaquiline-based regimen. Serum lipase levels were elevated in 143 patients (35%) during protocol-specified investigations (Table 3). None of them were symptomatic, the regimen was continued uninterrupted, and the levels subsided during follow-up. Ninety-nine patients had hypocalcemia, with 8 patients having concomitant QTc(f) prolongation (either >60 msec from baseline and/or an absolute >500 msec). All patients were managed conservatively with calcium and vitamin D3 combination tablets once daily until the serum levels normalized. QTc(f) prolongation of >60 msec from baseline was seen in 96 patients and was managed conservatively as the absolute QTc(f) was <500 msec, except for 1 patient in arm 3 whose treatment was interrupted for 3 days. After return to normalcy, the regimen was resumed and completed at the same dose without additional AEs.

Linezolid-Associated Toxicity

Anemia (of any grade) was the second most prevalent AE, with 258 occurrences in 183 patients (45%), with a median time of occurrence (interquartile range) of 4 (2–6) weeks and more grade 3 severity in arm 1 (Table 3). All cases were managed conservatively, except in 1 patient who required blood transfusion; in 4 patients (arm 1) treatment was withheld temporarily, and linezolid reintroduced at 300 mg daily after resolution of

Table 3. Key Adverse Events With Grading During the Treatment Period

	No. of AEs by Treatment Arm and AE Grade[a]												
	Arm 1				Arm 2				Arm 3				
System	Gr 1	Gr 2	Gr 3	Gr 4	Gr 1	Gr 2	Gr 3	Gr 4	Gr 1	Gr 2	Gr 3	Gr 4	Total
Laboratory investigations													
Anemia	46	23	16	2	64	26	6	…	50	17	8	…	258
Thrombocytopenia	23	4	…	7	20	5	…	2	18	9	…	3	91
Elevated liver enzymes[b]	118	11	2	1	128	15	1	0	130	9	1	1	417
Hyperbilirubinemia	6	…	…	…	6	2	…	…	6	…	…	…	20
Elevated serum lipase	25	34	4	3	22	29	3	1	18	19	3	2	163
Elevated serum amylase	17	11	…	…	28	10	…	…	19	2	2	…	89
Hypocalcemia	25	10	2	2	43	9	5	1	22	2	4	…	125
Hypercalcemia	9	1	…	1	8	3	…	…	9	…	1	…	32
Hypokalemia	15	…	1	…	14	2	1	1	14	…	…	1	49
Hyperkalemia	7	…	…	1	5	3	…	1	5	1	…	…	23
Peripheral nervous													
Peripheral neuropathy	22	4	7	…	17	1	1	…	18	1	1	…	72
Cardiovascular													
QTc(f) prolongation	5	1	45	…	4	…	55	…	4	…	49	…	163
Ophthalmic													
Blurring of vision	2	1	1	…	3	…	…	…	2	…	…	…	9
Gastrointestinal	25	1	1	…	32	1	2	…	23	1	…	…	86
Total	345	101	79	17	394	106	74	6	338	61	69	7	…

Abbreviations: AEs, adverse events; Gr, grade.

[a]Grading was per the Division of AIDS criteria, version 2.1 (dated July 2017) [10] and the

Common Terminology Criteria for Adverse Events (CTCAE) for QTc(f) version 5.0 (dated November 2017) [11]. Arm 1 received bedaquiline, pretomanid, and linezolid at 600 mg/d for 26 weeks; arm 2, bedaquiline, pretomanid, and linezolid at 600 mg/d for 9 weeks, followed by 300 mg/d for 17 weeks; and arm 3, bedaquiline, pretomanid, linezolid at 600 mg/d for 13 weeks, followed by 300 mg/d for 13 weeks.

[b]Elevated liver enzymes included aspartate aminotransferase, alanine aminotransferase, or both.

anemia. Similarly, peripheral neuropathy was reported in 66 patients, with a median time of occurrence (interquartile range) of 11 (4–16) weeks, and grade 1 severity in a majority of patients, managed symptomatically.

Treatment interruption due to linezolid toxicity occurred in 22 patients (12 for peripheral neuropathy, 6 for ophthalmic complication, 4 for grade 3 or 4 anemia) (Table 4). After symptoms resolved, linezolid was reintroduced at a decreased dose of 300 mg in 12 patients. In 3, linezolid was discontinued as it was the end of treatment. Four patients were due for structured dose reduction as per their randomization schedule and hence were started on 300 mg when symptoms subsided. Three patients were switched to a non–linezolid-based regimen due to toxicity. The χ^2 tests showed a statistically significant occurrence of peripheral neuropathy after 9 weeks ($P = .002$), more in arms 1 and 3 than in arm 2 (Figure 3*A*–3*D*). Anemia occurred more frequently during the first 9 weeks than after 9 weeks, though its occurrence did not differ significantly between arms. Anemia was more common in female than in male patients ($P < .001$) throughout this period, while after 9 weeks, more cases of anemia were seen in arm 1 and in female patients (Figure 4*A* and 4*B*). Previous exposure to antituberculosis therapy was associated with higher risk of AEs (adjusted risk ratio, 1.27; $P = .05$) to the given regimen (Supplementary Table 4).

Posttreatment Follow-up

Of 352 patients declared cured at the end of treatment, 1 died at week 32 due to acute exacerbation of chronic obstructive pulmonary disease. At follow-up 12 months after treatment, 280 patients remained culture converted (sputum negative), 11 (4%) were culture-reverted (tuberculosis recurrence; 3 in arm 1 and 4 each in arms 2 and 3), and 60 on follow-up. All 11 cases of tuberculosis recurrence were pansensitive to study drugs at baseline and recurrence. Sputum smear and culture were negative at week 16. Pretreatment chest radiographs of those with recurrent tuberculosis showed bilateral disease with cavity in 5 patients (1 each in arms 1 and 3; 3 in arm 2), and involvement in >2 zones in 7 patients (2 each in arms 1 and 3; 3 in arm 2). At end of treatment, only 3 of 11 patients showed radiographic improvement compared with the pretreatment chest radiograph, and 10 of 11 patients had gained ≤4.0 kg. At recurrence, chest radiographic deterioration was noted in 5 patients. Of 352 patients followed up, there were 19 serious AEs in the posttreatment follow-up period.

DISCUSSION

The efficacy of all the 3 treatment arms at the end of treatment was comparably high in this clinical trial evaluating 26 weeks of

Table 4. Linezolid Dose Interruption During Adverse Event and Tuberculosis Treatment Outcome

Patient[a]	BMI at Baseline[b]	Patient Age/Sex	AE	AE Grade	Week of LZD Interruption	Duration of LZD Withholding, d	LZD Reintroduced at Lower Dose (300 mg)	Treatment Outcome
Arm 1								
1	16.0	27/F	Anemia	4	12	9	Yes	Cured
2	25.8[c]	39/F	Anemia	3	20	30	Yes	Cured
3	17.2	22/F	Anemia	3	3	11	Yes	Cured
4	15.1	35/F	Anemia	4	16	8	Yes	Cured
5	20.3[c]	45/F	PN	2	17	27	Yes	Cured
6.	15.6	35/M	PN	3	23	27	LZD permanently discontinued	Cured
7	16.7	23/M	PN	3	20	34	Yes	Cured
8	13.1	21/M	PN	2	22	31	Permanently discontinued	Cured
9	16.0	28/F	PN	3	25	10	Permanently discontinued	Cured
10	14.8	30/M	PN	3	21	28	Yes	Cured
11	25.0	60/F	PN	3	21	28	Yes	Cured
12	15.2	30/M	PN	3	9	…	Permanently discontinued	Clinical Failure
13	16.2	25/M	PN	3	18	…	Permanently discontinued	Clinical Failure
14	26.9	49/M	ON	2	17	20	Yes	Cured
15	24.2	53/M	ON	1	10	26	Yes	Cured
16	17.3	33/F	ON	3	9	…	Permanently discontinued	Clinical Failure
Arm 2								
17	15.6	26/M	PN	1	17	2	300-mg LZD continued	Cured
18	24.9	33/M	ON	1	10	23	Protocol-defined structured dose reduction	Cured
Arm 3								
19	21.2	42/F	PN	3	3	8	Yes	Cured
20	13.0	18/F	PN	1	14	20	Protocol-defined structured dose reduction	Cured
21	18.2	18/F	Blurring of vision	1	6	25	Yes	Cured
22	15.3	19/F	Papilledema	1	13	5	Protocol-defined structured dose reduction	Cured

Abbreviations: BMI, body mass index; AE, adverse event; F, female; LZD, linezolid; M, male; ON, optic neuritis; PN, peripheral neuropathy.

[a]Patients in arm 1 received bedaquiline, pretomanid, and linezolid at 600 mg/d for 26 weeks; those in arm 2, bedaquiline, pretomanid, and linezolid at 600 mg/d for 9 weeks, followed by 300 mg/d for 17 weeks; and those in arm 3, bedaquiline, pretomanid, linezolid at 600 mg/d for 13 weeks, followed by 300 mg/d for 13 weeks.

[b]BMI calculated as weight in kilograms divided by height in meters squared.

[c]Reduction in BMI at the time of AE occurrence.

600 mg/d of linezolid against structured dose reduction of linezolid to 300 mg/d after 9 or 13 weeks at 600 mg/d along with standardized bedaquiline and pretomanid in the management of pre-XDR and $MDR_{TI/NR}$ pulmonary tuberculosis. The study highlights the effectiveness of the regimens even with less overall linezolid exposure. This was comparable with other trials that used higher doses of linezolid for longer durations, such as the Nix-TB (1200 mg/d for 26 weeks with 90% efficacy) and ZeNix (600 mg/d for 26 weeks with 91% efficacy) trials [3, 4]. In the TB-PRACTECAL trial, the BPaL arm with linezolid 600 mg/d for 16 weeks followed by 300 mg/d for 8 weeks had a 77% favorable outcome at 72 weeks [5]. An individual patient-level meta-analysis of the cumulative incidence of AEs of BPaL-containing regimen demonstrated 600 mg daily linezolid to be well tolerated and efficacious [13].

In our cohort, 22% of patients in the 600 mg daily arm experienced peripheral neuropathy similar to that in the ZeNix trial (24%), compared with 13% and 15% in our other 2 arms. Of patients with reduced linezolid dosage, 92% had a favorable outcome, suggesting that linezolid maintains its efficacy even at lower doses, similar to findings in other studies [14–17]. While linezolid at 600 mg daily for 6 months is safe in many patients, the risk of toxicity can be further reduced with a smaller dose while maintaining high treatment efficacy. Studies have shown an association between plasma levels of linezolid and AEs as well as good efficacy with reduced toxicity at a lower dose [18–20]. Although linezolid at 300 mg daily may achieve an effective therapeutic target, there may be a small group of patients in whom this dosing may fail to achieve the optimal drug levels, requiring a higher dosage [21].

In our cohort, clinical failures were more common due to AEs in treatment arm 1 with daily linezolid dosing of 600 mg for 26 weeks. Among bacteriological failures, only 1 patient who was pan-sensitive at treatment initiation acquired resistance to linezolid. All those who failed to respond to modified BPaL (mBPaL) regimen received an individualized treatment

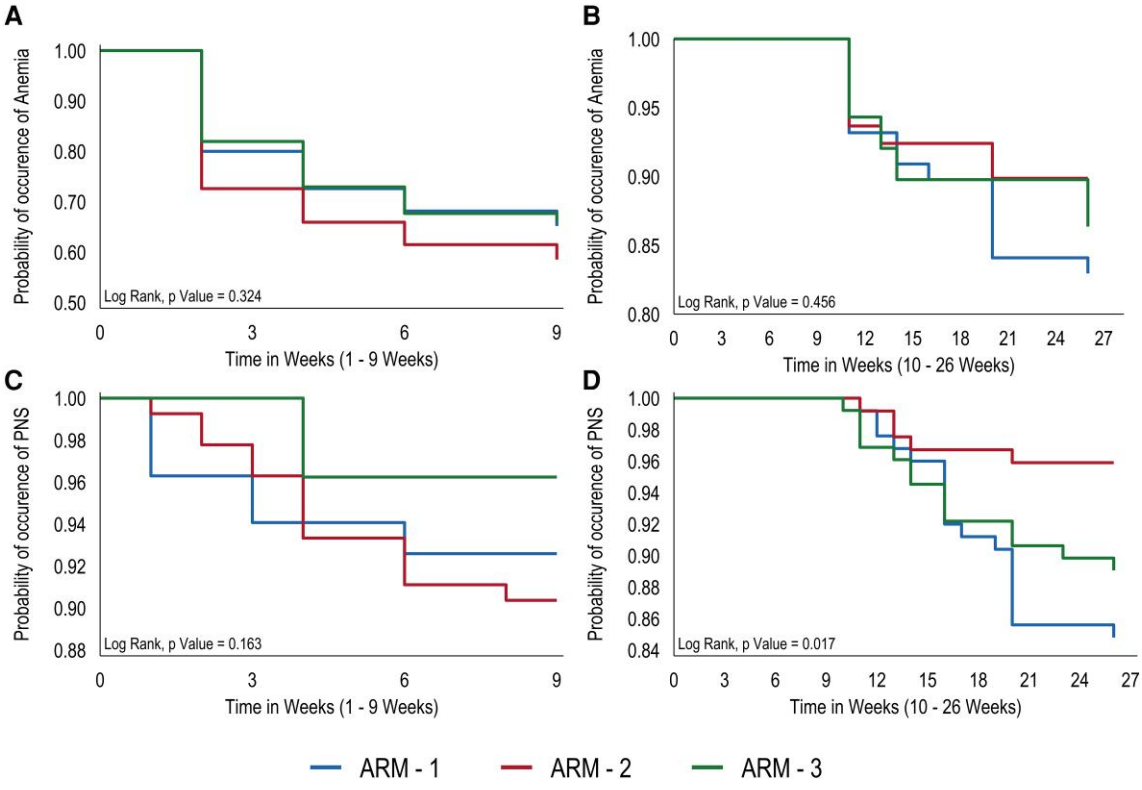

Figure 3. Kaplan-Meier plots showing the time of occurrence of anemia (*A, B*) and peripheral neuropathy (PN) (*C, D*) among trial participants during the treatment period (1–9 and 10–26 weeks).

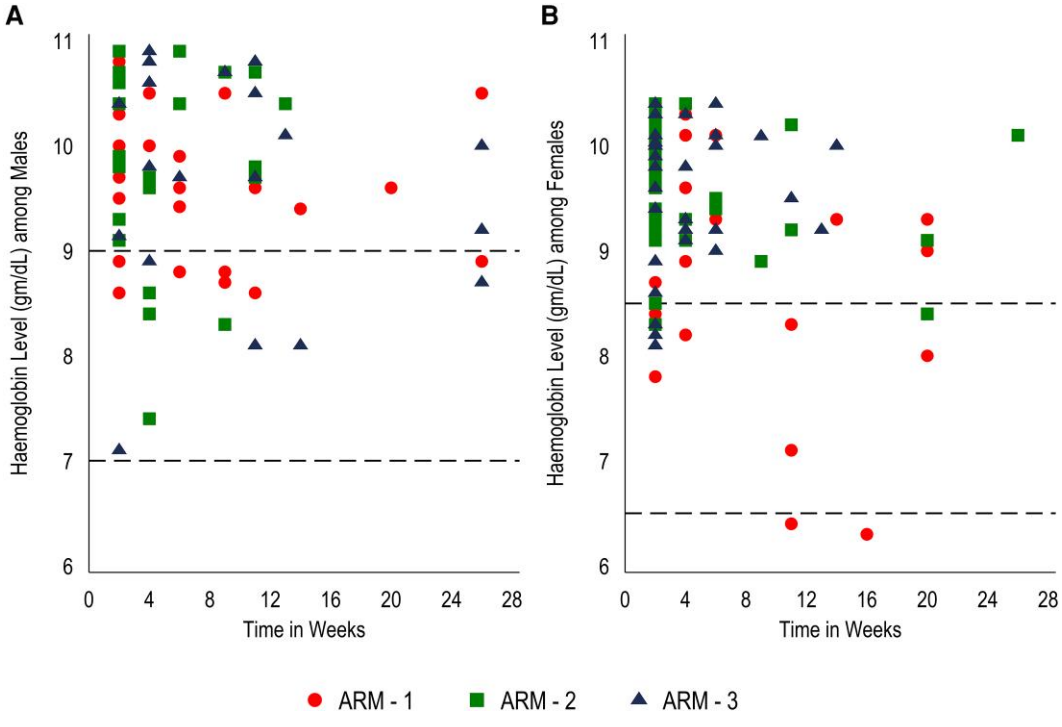

Figure 4. Serum hemoglobin levels in male (*A*) and female (*B*) patients at the time of occurrence of adverse events during the treatment period.

regimen based on their drug susceptibility and clinical profile. Although 9 patients had baseline resistance to study drugs, they continued the same regimen due to delays in receiving baseline DST. This did not adversely affect the treatment outcome in 7 patients, similar to findings in another cohort [22]. The need for pretreatment drug susceptibility profiling cannot be overemphasized, however, especially for long-term outcomes.

Many predefined safety investigations were conducted at regular intervals as part of this trial that detected additional AEs—such as elevated serum liver enzymes, lipase, and hypocalcemia—that might have gone unnoticed as they were asymptomatic. Regular ECG monitoring did not find QTc(f) >500 msec, though isolated >60-msec increases of QTc(f) from baseline were noted. Hence this regimen can be considered safe from a QTc standpoint among those with no preexisting cardiac conditions [23]. National tuberculosis elimination programs can review the emerging evidence and prioritize the follow-up investigations for patients on bedaquiline-containing regimens. A 10% decline in hemogram from baseline can be considered a toxicity indicator if a fortnightly hemogram is done for the first 3 months [24–26]. Similarly, frequent ECG monitoring can be restricted to only those with pretreatment risk factors for cardiac complications, thus minimizing the utilization of resources to those who need them the most while making the regimen available to many.

The strength of this trial is its practicality. Investigational frequency was nearly identical to that in the routine programmatic management of drug-resistant tuberculosis, except for hemograms and liver function tests, which provided information on drug-induced toxicity with the shorter regimen. Trial limitations include the open study design, which may have influenced the management of AEs, drug supervision by family provider, and unreported nonadherence. Furthermore, the lack of pharmacokinetic analysis for various linezolid dosings prevented correlation between the area under the curve and efficacy.

In conclusion, our results show that 600 mg of linezolid daily for a limited period (9–13 weeks) followed by structured dose reduction to 300 mg for the rest of the treatment period, in combination with bedaquiline and pretomanid, is noninferior to the standard 600-mg linezolid dose for 26 weeks. Close monitoring should be done to identify and manage AEs early.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank Ranjani Ramachandran, MD, National Programme Officer-World Health Organization, India, and Central TB Division consultants, Rupak Singla, MD, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, and Rajendra P. Joshi, Deputy Director General-TB, Central TB Division, Ministry of Health and Family Welfare, Government of India. We are grateful to Mylan Pharmaceuticals and to the National Tuberculosis Elimination Programme for supplying pretomanid for this trial and to the nursing staff of ICMR–National Institute for Research in Tuberculosis for drug management at study sites.

The trial was sponsored by ICMR-National Institute for Research in Tuberculosis.

modiifed BPaL (mBPaL) team. The study team included the following: C. P., B. D. D., B. R., S. S., M. V. M., J. Bharathi, Shanmugapriya Kumaravadivelu, Ghazala Shamail, Shakila Shankar, A. Stella Mary, Mangalambal Ganesan, Sreenisha Sreedhar, G. Subhashini, A. Shilna, R. K. D., N. Singla, Rupak Singla, Manpreet Bhalla, SarojMeena, Mukesh Kumar Singh, Renu Kanwar, Gopal Singh Bisht, P. V., Pranav Patel, Vani Jain, Grinish Tamaku Wala, Biswarup Chatterjee, Dipti Rana, Gamit Aishwarya Dipakbhai, Chetan Kumar Jain, Rashi Mehta, N. V. S., Manasvi Nanavare, Tejasvi Parade, Amol Ghadage, A. K. B., Rishikesh Nath Mukherjee, U. M., Shivani Rawat, Alok Rawat, Krishan Kumar, S. Kant, Amita Jain, J. Bajpai, Rohit Kumar Pandey, Sushma Yadav, J. D. D., A. B. S., Amanankur, Mamta Padaya, V. S. O., S. D. M., M. Palav, Vrushali Shete, Santosh Kambli, S. Kumar, A. K. Awasthi, N. Shekh, Vijay Kumar, Praveen Kumar, P. R., D. P., Dhivya Baskaran, Ramesh Kumar, S. C., M. Parmar, J. J., Umesh Alavadi, R. K., and S. K. M.

Financial support. This work is supported by the United States Agency for International Development (USAID), under the iDEFEAT TB Project with the International Union Against Tuberculosis and Lung Disease (The UNION) (cooperative agreement 72038620CA00007).

Potential conflicts of interest. Umesh Alavadi was an employee of the United States Agency for Internation Development (USAID) during the initial period of study conduct and J. J. is an employee of The UNION. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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