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Esmail A, Oelofse S, Lombard C, et al. An All-Oral 6-Month Regimen for Multidrug-Resistant Tuberculosis: A Multicenter, Randomized Controlled Clinical Trial (the NExT Study). Am J Respir Crit Care Med. 2022;205(10):1214-1227. doi:10.1164/rccm.202107-1779OC

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ORIGINAL ARTICLE

An All-Oral 6-Month Regimen for Multidrug-Resistant Tuberculosis
A Multicenter, Randomized Controlled Clinical Trial (the NExT Study)

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Abstract

Rationale: Improving treatment outcomes while reducing drug toxicity and shortening the treatment duration to ∼6 months remains an aspirational goal for the treatment of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB).

Objectives: To conduct a multicenter randomized controlled trial in adults with MDR/RR-TB (i.e., without resistance to fluoroquinolones or aminoglycosides).

Methods: Participants were randomly assigned (1:1 ratio) to a ∼6-month all-oral regimen that included levofloxacin, bedaquiline, and linezolid, or the standard-of-care (SOC) ⩾9-month World Health Organization (WHO)-approved injectable-based regimen. The primary endpoint was a favorable WHO-defined treatment outcome (which mandates that prespecified drug substitution is counted as an unfavorable outcome) 24 months after treatment initiation. The trial was stopped prematurely when bedaquiline-based therapy became the standard of care in South Africa.

Measurements and Main Results: In total, 93 of 111 randomized participants (44 in the comparator arm and 49 in the interventional arm) were included in the modified intention-to-treat analysis; 51 (55%) were HIV coinfected (median CD4 count, 158 cells/ml). Participants in the intervention arm were 2.2 times more likely to experience a favorable 24-month outcome than participants in the SOC arm (51% [25 of 49] vs. 22.7% [10 of 44]; risk ratio, 2.2 [1.2–4.1]; $P = 0.006$). Toxicity-related drug substitution occurred more frequently in the SOC arm (65.9% [29 of 44] vs. 34.7% [17 of 49]; $P = 0.001$)], 82.8% (24 of 29) owing to kanamycin (mainly hearing loss; replaced by bedaquiline) in the SOC arm, and 64.7% (11 of 17) owing to linezolid (mainly anemia) in the interventional arm. Adverse event–related treatment discontinuation in the safety population was more common in the SOC arm (56.4% [31 of 55] vs. 32.1% [17 of 56]; $P = 0.007$). However, grade 3 adverse events were more common in the interventional arm (55.4% [31 of 56] vs. 32.7 [18 of 55]; $P = 0.022$). Culture conversion was significantly better in the intervention arm (hazard ratio, 2.6 [1.4–4.9]; $P = 0.003$) after censoring those with bedaquiline replacement in the SOC arm (and this pattern remained consistent after censoring for drug replacement in both arms; $P = 0.01$).

Conclusions: Compared with traditional injectable-containing regimens, an all-oral 6-month levofloxacin, bedaquiline, and linezolid–containing MDR/RR-TB regimen was associated with a significantly improved 24-month WHO-defined treatment outcome (predominantly owing to toxicity-related drug substitution). However, drug toxicity occurred frequently in both arms. These findings inform strategies to develop future regimens for MDR/RR-TB.

Clinical trial registered with www.clinicaltrials.gov (NCT 02454205).

Keywords: drug-resistant tuberculosis; all-oral regimen; shortened regimen; bedaquiline; linezolid

Am J Respir Crit Care Med Vol 205, Iss 10, pp 1214–1227, May 15, 2022
Copyright © 2022 by the American Thoracic Society
Originally Published in Press as DOI: 10.1164/rccm.202107-1779OC on February 17, 2022
Internet address: www.atsjournals.org

Despite a global decrease in tuberculosis (TB) incidence over the last decade, it remains one of the leading causes of mortality due to an infectious disease, claiming approximately 1.5 million lives in 2020 (1). Approximately one-third of this mortality was attributed to multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) denoting resistance to rifampicin (R) with or without resistance to isoniazid (H), respectively (2). Rifampicin and isoniazid are two key first-line TB drugs. MDR/RR-TB threatens to derail TB control efforts in several parts of the world. Moreover, it is associated with substantial morbidity and severe economic consequences; almost a third of the projected 2050 global cost associated with antimicrobial resistance (∼$50 trillion) will be attributable to drug-resistant TB (3).

Despite increasing access and availability of newer and repurposed TB drugs such as linezolid and bedaquiline (4), successful treatment outcomes in patients with MDR-TB in 2019 were achieved in only ∼57% of patients globally (1). Several reasons are posited, including prolonged treatment regimen of between 9 and 20 months and the use of toxic, painful injectable drugs, both of which contribute to poor treatment adherence (5, 6). The STREAM I (Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB) study showed that a 9- to 11-month regimen including clofazimine with an injectable (but not including bedaquiline or linezolid) was noninferior to the traditional 18- to 20-month injectable-based regimen recommended by the World Health Organization (WHO) at the time (7). An 18- to 20-month all-oral regimen including bedaquiline, linezolid, and fluoroquinolone is now recommended by WHO (8), and a shorter 9- to 11-month regimen has been conditionally endorsed for use in an operational research setting (9). However, the 9- to 11-month injectable-based regimen (also approved in the 2019 WHO guidance [8]) remains the standard of care in many parts of the world where access to bedaquiline and linezolid is limited or nonexistent. For example, it is estimated that in India <5% of eligible patients with MDR/RR-TB (∼25% of the global population with MDR/RR-TB) had access to bedaquiline in 2019, and until recently, bedaquiline was only accessible to patients with MDR-TB with additional resistance to fluoroquinolones (10, 11).

The goal of MDR-TB treatment research is to improve treatment outcomes, reduce drug toxicity, avoid the need for injectable agents, and shorten the treatment duration to ∼6 months (approximating that of rifampicin-susceptible TB) using a multidrug oral regimen (as exemplified in the NixTB study) (12). To address the unmet need for an all-oral short-course treatment regimen for MDR/RR-TB, we evaluated the efficacy of a ∼6-month all-oral regimen containing five drugs, three WHO group A drugs (levofloxacin, bedaquiline, and linezolid) and two group B or C drugs (pyrazinamide and either high-dose isoniazid or ethionamide, or terizidone [a cycloserine analogue] selected on the basis of either a mycobacterial *katG* or *inhA* mutation or presence of both mutations, respectively). This novel regimen was compared with the standard-of-care (SOC) 18- to 20-month injectable-based regimen recommended since 2016 (13). During the course of the trial, this regimen was replaced by the WHO-endorsed shorter 9- to 11-month injectable-based regimen in 2018 (14) (*see* Figure 1 for a study overview).

Neither of the SOC injectable-based regimens contained bedaquiline or linezolid, but both regimens were recently conclusively shown to be noninferior to one another in the STREAM study (7).

Methods

Design and Oversight

We conducted an open-label multicenter randomized controlled trial at five sites within South Africa, in adult participants with MDR/RR-TB, comparing an all-oral short-course regimen with a longer injectable-based regimen that followed the WHO treatment guidelines at the time. The trial was registered on clinicaltrials.gov (NCT 02454205), and additional trial methods are provided in the appendix of the online supplement.

Participants

Participants were eligible for inclusion if they were 18 years or older and had newly diagnosed MDR/RR-TB with susceptibility to fluoroquinolones and aminoglycosides on phenotypic drug susceptibility testing and/or using standardized genomic methods (GeneXpert MTB/RIF; Cepheid, and GenoType MTBDRplus or sl; Bruker). All of the samples/isolates from the patients in the intention-to-treat population (intervention arm or the SOC arm; $n = 111$) underwent susceptibility testing (either genotypic or phenotypic, or both) for rifampicin, isoniazid, fluoroquinolones, and aminoglycosides.

Participants were ineligible if they received MDR/RR-TB treatment for more than 2 weeks before randomization, were known to have an allergy to any of the trial drugs, or were pregnant or breastfeeding at

(Received in original form July 29, 2021; accepted in final form February 15, 2022)

Supported by the South African Medical Research Council (MRC-RFA-UFSP-01-2013/NEXT-RCT), Pfizer, the European and Developing Country Clinical Trials Partnership (TMA 2015-CDF-1052), Wellcome Trust (MR/S027777/1), and the Medical Research Council (MR/S03563X/1).

Author Contributions: Conceptualization, funding acquisition, and methodology: A.E. and K.D. Supervision, visualization, validation, and project administration: A.E., K.D., A.G.M., J.B., E.V., P.O., E.N., N.N., G.M., R.W., and N.M. Investigation: A.E., S.O., N.G., T.A., L. Marais, L. Mottay, B.D., and R.W. Software, data curation, validation, and formal analysis: C.L., A.P., S.M., L. Mbithini, E.V., A.E., and K.D. Critical appraisal of data, writing the original draft, review, and editing: all authors.

Data sharing statement: Individual participant data will be made available to researchers who provide methodologically sound proposals beginning 3 months and ending 5 years after publication. Data sharing requests should be directed to K.D. (keertan.dheda@uct.ac.za). A data access agreement will need to be concluded.

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

At a Glance Commentary

Scientific Knowledge on the Subject: A major goal of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) treatment-related research is to shorten the treatment duration (if possible to ~6 months, approximating that of rifampicin-susceptible TB) using an optimal multidrug regimen. We could find no published randomized controlled trials that had evaluated an all-oral bedaquiline, fluoroquinolone, and linezolid–containing multidrug regimen and none that had evaluated a 6-month regimen for the treatment of MDR/RR-TB.

What This Trial Adds to the Field: The data suggest that a shorter 6-month regimen containing the three designated World Health Organization group A drugs (bedaquiline, a fluoroquinolone, and linezolid) and two other group B/C drugs, in an all-oral format, has similar patient-centered outcomes (≥12-month relapse-free cure or treatment success) compared to a ≥9-month injectable-based MDR/RR-TB regimen. Thus, equivalent treatment success or relapse-free cure can be achieved using a ~6-month regimen containing newer drugs compared to a ~12-month regimen using traditional drugs (and including an injectable agent). This represents a paradigm shift in thinking about treatment duration for drug-resistant tuberculosis, and thus the NExT study sets a new aspirational threshold or standard of care for MDR/RR-TB treatment. Nevertheless, a 25% patient-centered unfavorable outcome suggests that there is room for improvement with addition of alternative group B and C drugs, or newer drugs still in early-phase development. Both regimens were associated with considerable toxicity. Thus, less toxic oxazolidinones are urgently needed, and our data have further confirmed the high toxicity of second-line injectable drugs, which ideally should not be used for the treatment of MDR/RR-TB. Trials of alternative 6-month regimens are urgently needed.

the time of screening. We excluded participants with the following baseline abnormalities: symptomatic peripheral neuropathy, hearing loss on pure tone and speech audiometry, relevant ECG abnormalities (prolonged Q_T of >500 m s), laboratory abnormalities, or a Karnofsky score of 50 or less (*see* the online supplement for details and detailed inclusion and exclusion criteria). Chronic medications were reviewed to ensure participants did not use any drugs that could interact with trial drugs or place them at increased risk for adverse effects (*see* Table E1 in the online supplement for restricted medications). All of the participants provided written informed consent. An institutional review board or ethics committee at each participating trial site reviewed and approved the protocol and informed consent documents. A data safety monitoring board empowered to stop the study was involved in study oversight given the equipoise around the safety of bedaquiline when used with other QTcF (QT interval corrected for heart rate using Fridericia's cube root formula)-prolonging drugs (clofazimine in particular) and lack of established bedaquiline-associated clinical outcome and mortality benefit data during the course of the study (the earlier phase 2 bedaqualine study was based on a culture-conversion outcome) (15).

Randomization and Treatment

Enrolled participants were randomized (1:1) to receive either a conventional ≥9-month treatment regimen (and up to 20 mo), or the 6- but up to 9-month interventional regimen (continued for up to 9 months depending on the time of culture conversion [*see* Figure 1 and the online supplement]). Participants in both arms of the study were followed up for 24 months after the initiation of treatment. Thus, participants in the interventional arm were followed up for 15–18 months, whereas participants in the conventional arm were followed up for 6–15 months after completion of treatment depending on the length of their regimen and culture conversion (*see* Figure 1). Block randomization (block size of 4) was undertaken at the site level using a short messaging system. Randomization was not clustered according to HIV or known TB risk factors. The SOC regimen was designed according to the then National TB Program guidance. The interventional regimen consisted of five drugs (i.e., three group A drugs [bedaquiline, linezolid, and levofloxacin] and two group B or C drugs selected using a *Mycobacterium tuberculosis*–specific mutational analysis approach (high-dose isoniazid [*inhA* mutation] or ethionamide [*katG* mutation], or terizidone [in case of both *inhA* and *katG* mutations]). The standard of care arm initially consisted of 9–20 months of a WHO-recommended regimen including daily kanamycin (6 mo), moxifloxacin, ethionamide/high-dose isoniazid/terizidone (depending on the isoniazid mutation present), and clofazimine. However, in November 2018, this was amended to a 9- to 11-month WHO-recommended regimen in keeping with changes in the national guidelines (Figure 1 and Table E2). Patients with rifampicin monoresistant TB, in keeping with programmatic practice, received the same regimen as outlined above including high-dose isoniazid (to prevent confusion).

Procedures

After the initial screening and baseline visits, participants were seen every 2 weeks for the first 4 weeks, then monthly until the end of treatment by the clinical trial team. In addition to these visits, participants were followed up as part of routine care for directly observed therapies (DOTs) and were also reviewed monthly by a clinician appointed by the TB program (these clinician visits were synchronized where possible). Post-treatment follow-up visits were scheduled every 6 months from the end of treatment in each arm until 24 months after treatment initiation. All participants underwent a baseline clinical evaluation, which included physical examination, HIV testing, provision of contraception, screening of concomitant drug exposures, posteroanterior chest radiograph, ECG (with corrected Q_T interval estimation), neuropathy screening, pure tone and speech audiometry, and urinalysis (*see* Table E3 for trial schedule).

Laboratory safety monitoring (full blood count, liver function, kidney function, electrolytes, and thyroid function) was performed at baseline and at prespecified intervals for the duration of the treatment period (*see* the online supplement). Sputum samples were collected for smears and culture at baseline and then fortnightly for the first 4 weeks, monthly until the end of treatment, and then every 6 months

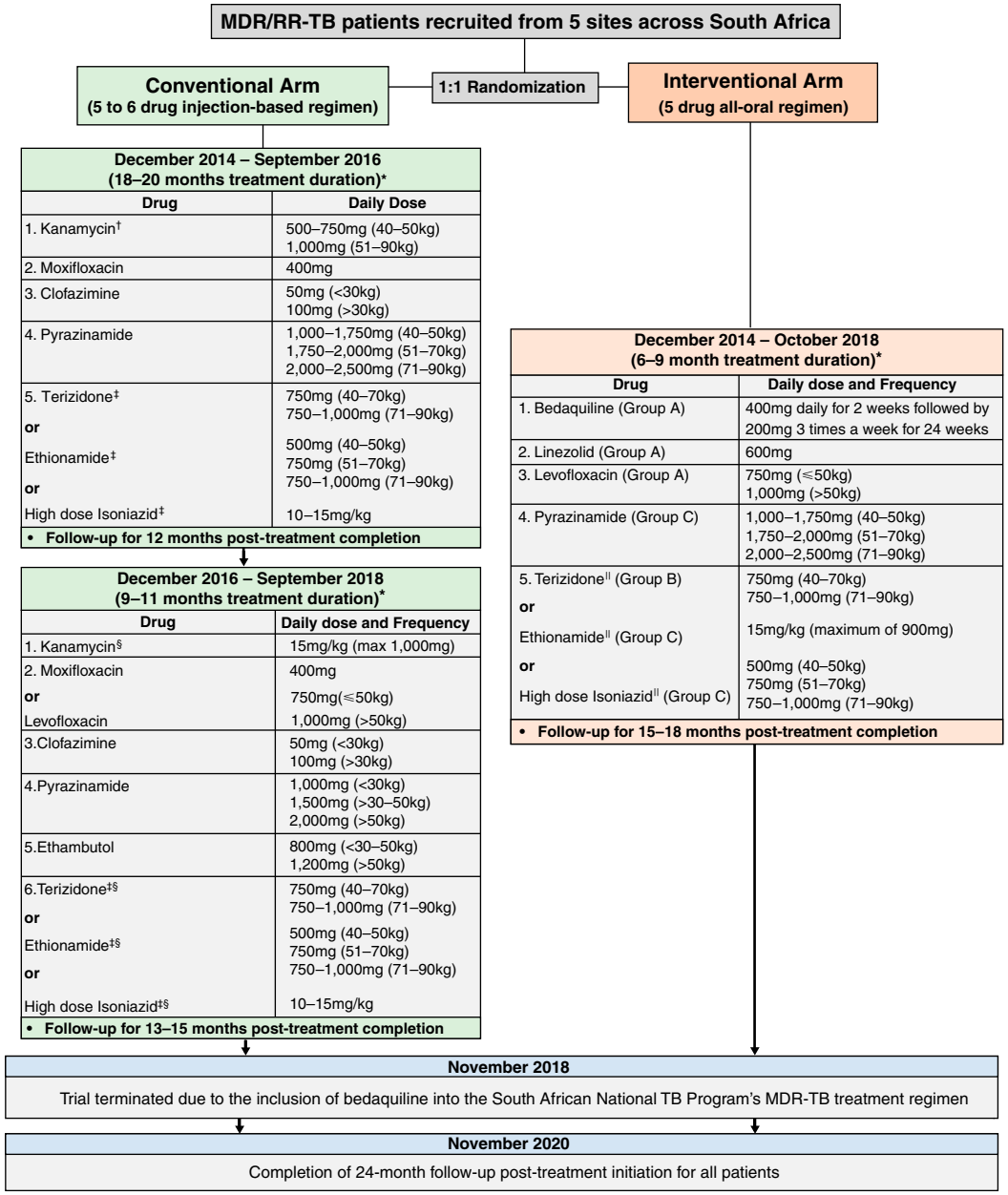


Figure 1. Trial overview. *The length of treatment was dependent on the time to culture conversion (*see* Results section for the proportion that received 6 months vs. 6–9 months of treatment). †In pre-2016 injection-based regimen, kanamycin was given for ~6 months during the intensive phase of treatment (and was continued for up to 8 months, i.e., 2 months after culture conversion occurred), as per WHO and SA MDR-TB treatment guidelines. ‡The conventional regimen mirrored the standard of care at the time of recruitment. The choice of drugs (terizidone, ethionamide, and high-dose INH) was determined by the genotypic resistance profile, i.e., drug selected based on *katG* and/or *inhA* mutations. §In the post-2016 injection-based regimen, kanamycin (in addition to INH and/or ethionamide and/or terizidione) was given for 4–6 months during the intensive phase of treatment as per the SA NTP Guidelines for the shorter treatment of MDR-TB. ‖The choice of the fifth group B/C drug in the interventional arm was determined by the genotypic resistance profile, i.e., drug selected based on *katG*, *inhA*, or both mutations. INH = isoniazid; MDR/RR-TB = multidrug-resistant/rifampicin-resistant tuberculosis; NTP = National Tuberculosis Programme; SA = South African; WHO = World Health Organization.

during the post-treatment follow-up period. Adverse events were graded according to the modified toxicity events criteria by the National Institute of Allergy and Infectious Disease (Division of AIDS [DAIDS] adverse events grading table, version 2.1, July 2017). DAIDS grade 3 and 4 criteria necessitated drug substitution/replacement (*see* the online supplement for details of drug stoppage rules).

Study Outcomes

The primary outcome measure was the 2013 WHO-defined favorable outcome (sum of cured and treatment completed) without any events defining an unfavorable outcome

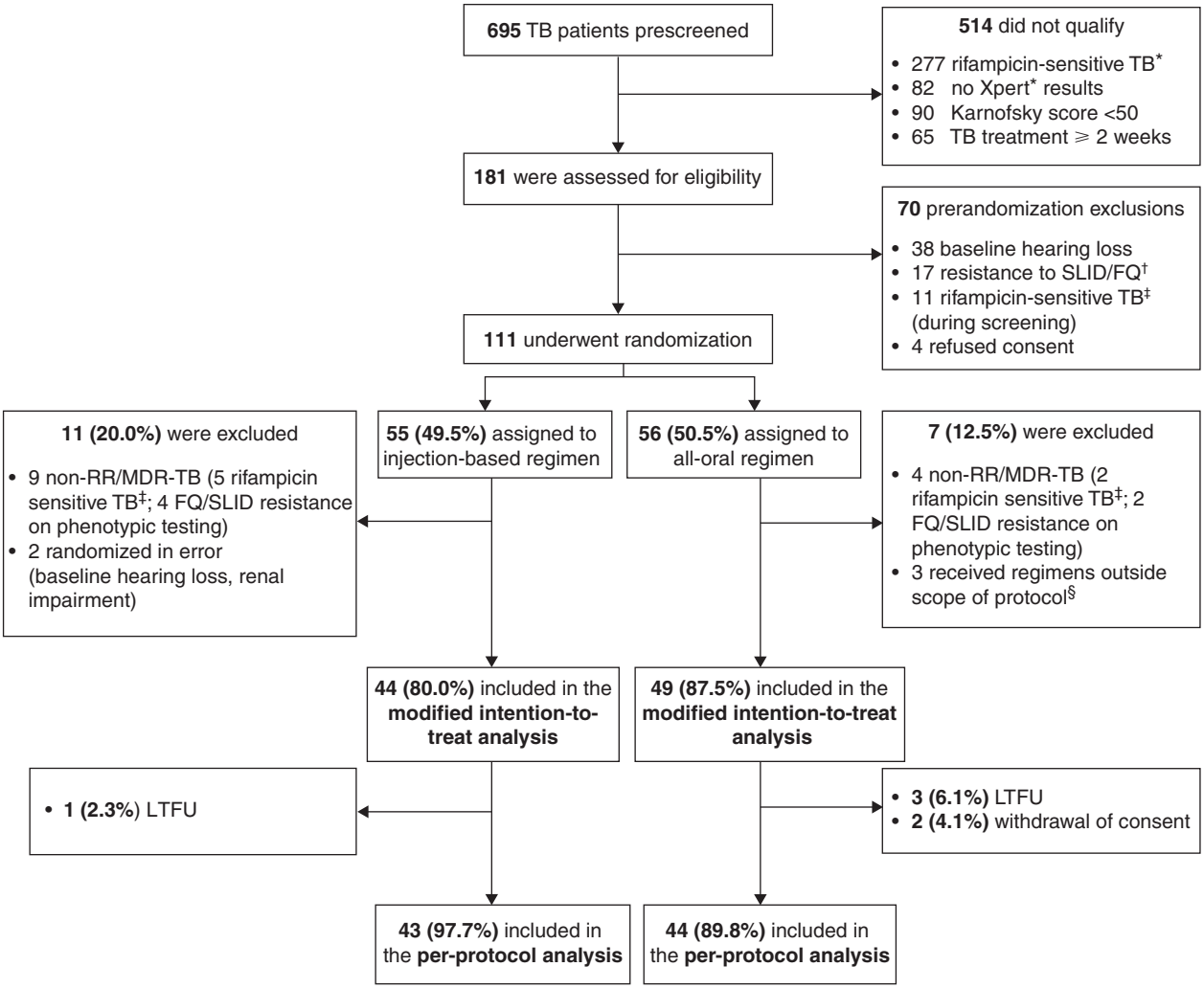


Figure 2. Consolidated Standards of Reporting Trials diagram of the NExT (New and Emerging Therapies for Drug-Resistant Tuberculosis) study. In the conventional arm, 8 of 55 patients (14.5%) received the 18- to 20-month injectable regimen, and 47 of 55 (85.5%) received the 9- to 11-month injectable regimen. The modified intention-to-treat population comprised all participants who underwent randomization, except for those in whom isolates obtained before randomization were subsequently found to be susceptible to rifampicin, or resistant to fluoroquinolones or second-line injectable drugs on phenotypic or genotypic drug-susceptibility testing, or who received treatment regimens outside the scope of the protocol (i.e., erroneously received the intervention regimen for longer than 9 mo). The per-protocol population comprised participants in the modified intention-to-treat population, excluding those participants who did not adhere to protocolized treatment for reasons other than treatment failure or death. *Resistance pattern was detected using Xpert MTB/RIF or Xpert MTB/RIF ULTRA. †Resistance detected using sputum-based genomic tests, i.e., line probe assays (Hain MTBDR*plus*/Hain MTBDR*sl*). ‡Resistance pattern was detected using the Hain MTBDRplus assay using culture isolates. §Participants received the interventional regimen for >9 months. FQ = fluoroquinolone; LTFU = lost to follow-up; MDR-TB = multidrug-resistant tuberculosis; RR-TB = rifampicin-resistant tuberculosis; SLID = second-line injectable drugs; TB = tuberculosis.

(including treatment failure, relapse, reinfection, default, or death) 24 months after initiation of treatment in either arm (*see* Table E4 for details of the definitions of each type of outcome event) (16–18). A 24-month patient-centered outcome (⩾12-mo relapse-free cure) was defined as treatment success 24 months after treatment initiation in the absence of any unfavorable outcome (treatment failure, death, relapse, or default) but specifically excluding a drug substitution–related unfavorable outcome (the latter was included in the WHO-defined outcome). Treatment failure was defined in the protocol as the need for permanent regimen change (⩾2 group B/C drugs or ⩾1 group A drug) because of either lack of culture conversion (defined in detail in Table E4), bacteriological reversion, acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse events resulting in permanent drug substitution (*see* Table E4 for details). Thus, participants in the SOC arm had toxicity-related kanamycin substitution (i.e., replacement with bedaquiline), and in the intervention arm, linezolid was substituted (there were no cases of bedaquiline substitution). Patients in both arms with microbiological failure were presented to an independent committee of TB experts, who recommended an empiric salvage regimen consisting of at least three to four likely effective new agents (drugs not

Table 1. Baseline Characteristics of the Participants in the Modified Intention-to-Treat Population

Demographic Characteristics	Overall *n* = 93	SOC *n* = 44	BDQ/LZD *n* = 49
Age, yr, median (IQR)	37 (30.0–44.0)	36 (29.0–46.5)	37 (31.0–43.0)
Weight, kg, median (IQR)	54.8 (50.0–62.0)	53.7 (49.3–61.4)	55 (50.3–62.6)
35–50 kg, *n* (%)	23 (25)	13 (30)	10 (20)
⩾50 kg, *n* (%)	70 (75.3)	31 (70.5)	39 (79.6)
Male sex, *n* (%)	62 (67)	28 (64)	34 (69)
Active smoking, *n* (%)	46 (49.0)	22 (50)	24 (49)
History of previous TB, *n* (%)	42 (45.0)	23 (52)	19 (39)
HIV infected, *n* (%)*	51 (55)	24 (55)	27 (55)
CD4 cell count, cells/ml, median (IQR)†	158 (78.0–305.0)	128.5 (54.5–285.3)	163.0 (81.0–317.0)
Smear positive status, *n* (%)	57/92 (61.9)	27/43 (62.8)	30/49 (61.2)
Time to positivity on sputum culture, d, median (IQR)	11.0 (6.5–14.0)	12.0 (7.5–14.5)	10.0 (6.0–13.3)
Isoniazid resistance, *n* (%)‡	49/76 (64.5)	18/31 (58.9)	31/41 (75.6)
Presence of cavitary disease, *n* (%)	48/93 (51.6)	22 (50)	26 (53)
Bilateral disease, *n* (%)	84/93 (90)	28/35 (80)	31/44 (70.5)
Extent of disease score on chest radiograph (median score)§	6.00 (4.31)	6.25 (3.0)	6.00 (4.6)

Definition of abbreviations: BDQ/LZD = bedaquiline and linezolid–based regimen; IQR = interquartile range; SOC = standard of care; TB = tuberculosis.
P values for all comparisons between groups were >0.1.
*All HIV-infected participants received antiretroviral therapy.
†Only performed in individuals infected with HIV.
‡Detected using genotypic and/or phenotypic tests; this was unavailable in 17 samples owing to indeterminate sputum-based readouts or an unculturable isolate using bio-banked sputum.
§Chest X-ray extent of disease score documented by two observers using a validated zonal scoring system (24); *see* Figure E4.

previously used in the program and/or that patient was previously unexposed to). This approach was used because bedaqualine, linezolid, terizidone, delamanid, and carbapenem susceptibility testing was unavailable (at the time) within the program or research setting.

Statistical Analysis

Given the uncertainty of expected treatment outcomes owing to use of a novel regimen and audiometry-based monitoring, we estimated that for a power of 80% and an α level of 0.05, sample sizes of 147, 235, 235, 235, and 207 would be required to detect differences of 25% versus 50%, 30% versus 50%, 40% versus 60%, 50% versus 70%, and 60% versus 80% between the SOC arm and the intervention arm, respectively (*see* Table E5).

All analyses (including safety) were performed using the modified intention-to-treat (mITT) population (*see* Figure 2 and the online supplement for breakdown and definition of the mITT and per-protocol populations). Fisher exact test was used for comparisons of proportions, *t* tests were used to analyze continuous data, and odds ratios were computed to describe effect size. Unadjusted univariate Cox proportional hazards regression and the restricted mean survival time and restricted mean time lost (RMTL) models were used to estimate the relative intervention effect, which are reported with 95% confidence intervals (19).

Results

Participants

A total of 695 participants were screened, 181 were eligible for the trial, and 111 underwent randomization at five centers in South Africa between November 2015 and October 2019 (Figure 2). The trial was stopped prematurely when bedaquiline-based therapy became the SOC in South Africa for MDR/RR-TB and thus randomization was no longer ethically possible.

The leading reasons for ineligibility were the presence of baseline hearing loss, drug resistance beyond MDR-TB, rifampicin-susceptible TB, a low Karnofsky score, and exposure to rifampicin-resistant TB treatment for more than 2 weeks at the time of the eligibility assessment. We excluded a further 18 participants after randomization owing to violation of entry criteria and exposure to regimens outside the scope of the study protocol. Overall, retention until the end of follow-up was high (94%), 98% in the standard of care arm and 90% in the interventional arm. To monitor adherence, all patients received daily DOT in the first ~6 months of treatment. Subsequently, treatment was supervised in the community by the DOT supporter, patient families, and community leaders. Accountability logs were maintained (pill counting and packaging review) on a monthly basis, and home visits were undertaken when appropriate. The demographic, clinical, microbiological, and radiological characteristics of study participants were similar between study arms (Table 1). Extended phenotypic susceptibility testing of bio-banked isolates is shown in Table E6.

Efficacy Outcomes

In the modified intention-to-treat event-free survival analysis, participants in the intervention arm were less likely to experience an unfavorable outcome than participants in the SOC arm over a 24-month period (hazard ratio, 0.4; 95% confidence interval [CI], 0.2–0.6; $P < 0.001$). This is also supported by an RMTL ratio of 0.5 (95% CI, 0.4–0.8; $P = 0.001$) (Figure 3A and Table 2). An exploratory subanalysis including only HIV-infected individuals showed similar results (Figure 3B and Table E7).

A favorable outcome at the end of 24 months from treatment initiation was reported in 22.7% (10 of 44) of the participants in the SOC arm and 51.0% (25 of 49) of the participants in the intervention arm, a relative risk of 2.2 (95% CI, 1.2–4.1) and risk difference of 28.3% (9.6–46.7); $P = 0.006$ (Table 2; Table E8

Table 2. Comparison of Primary and Secondary Endpoints in Each Arm Using the Modified Intention-to-Treat Population ($n = 93$) Unless Otherwise Specified

Description of Endpoint	SOC	BDQ/LZD	Relative Risk Ratio (95% CI)	Risk Difference % (95% CI)	*P* Value*
Primary endpoint					
Favorable outcomes at 24 mo after initiation of treatment, *n* (%)	10/44 (22.7)	25/49 (51.0)	2.2 (1.2 to 4.1)	28.3 (9.6 to 47.0)	0.006
Time to unfavorable outcome (event-free survival) over 24-mo	N/A	N/A	Hazard ratio, 0.4 (95% CI, 0.2 to 0.6)		<0.001
Restricted mean time lost, mo†	15.8 (13.0–18.5)†	8.6 (5.9–11.2)	RMTL ratio, 0.5 (95% CI, 0.4 to 0.8)†		0.001†
Secondary endpoints					
Time point–specific WHO-defined favorable outcomes after treatment initiation‡					
Favorable outcomes at 24 mo after treatment initiation in the per-protocol population	10/43 (23.3)	25/44 (56.8)	2.4 (1.3 to 4.5)	33.6 (14.2 to 52.9)	0.002
Favorable outcomes after treatment completion§					
Favorable outcome at treatment completion (specifically at the time point of treatment cessation)					
mITT population	11/44 (25.0)	28/49 (57.1)	1.9 (1.3 to 2.7)	4.0 (1.7 to 9.7)	0.003
Per-protocol population	11/43 (25.6)	27/44 (61.4)	2.0 (1.3 to 3.2)	4.6 (1.9 to 11.5)	0.001
Favorable outcome 12 mo after treatment completion (specifically at the time point of treatment cessation)					
mITT population	10/44 (22.7)	25/49 (51.0)	2.2 (1.2 to 4.1)	28.3 (9.6 to 47.0)	0.006
Per-protocol population	10/43 (23.3)	25/44 (56.8)	2.4 (1.3 to 4.5)	33.6 (14.2 to 52.9)	0.002
Favorable patient-centered outcomes (treatment success or ⩾12-mo relapse-free cure) at 24-mo (i.e., a non–WHO-defined outcome)¶					
Patient-centered outcomes at 24 mo after treatment initiation in the mITT population¶	30/44 (68.2)	33/49 (67.4)	1.0 (0.8 to 1.3)	−0.8 (−19.9 to 18.2)	1
Patient-centered outcomes at 24 mo after treatment initiation in the per-protocol population¶	30/43 (69.8)	33/44 (75.0)	1.1 (0.8 to 1.4)	5.2 (−13.5 to 24.0)	0.637
Culture conversion outcomes (reported for culture-positive participants at baseline)					
2-mo sputum culture conversion	29/41(70.7)‖	37/43 (86.1)‖	1.2 (1.0 to 1.5)	15.3 (−2.0 to 32.7)	0.113
6-mo sputum culture conversion	39/41 (95.1)‖	41/43 (95.4)‖	1.0 (0.9 to 1.1)	0.2 (−8.9 to 9.3)	1
All-cause mortality					
All-cause mortality at 24 mo after initiation of treatment	4/44 (9.0)	4/49 (8.2)	1.0 (0.3 to 3.9)	0.1 (−5.9 to 6.1)	0.91

Definition of abbreviations: BDQ/LZD = bedaquiline and linezolid–based regimen; CI = confidence interval; mITT = modified intention-to-treat; N/A = not applicable; RMTL = restricted mean time lost; SOC = standard of care; WHO = World Health Organization.

Odds ratios are shown in Table E8.

*Fisher exact test comparing the proportions in the two groups.

†An RMTL analysis was performed, as the proportional hazard assumption of the effect being constant over time was not met.

‡Six-, 12-, and 18-month outcomes shown in Table E8.

§Outcomes were identical to the 24-month post-treatment initiation time point, as there were no unfavorable outcome events at the outer limits of the differential follow-up periods.

¶In contradistinction to the WHO-defined 24-month favorable outcome, the patient-centered 24-month favorable outcome (treatment success) excluded treatment failure owing to regimen change (i.e., drug substitution during the course of treatment [thus only microbiological treatment failures were counted]); thus, the patient-centered 24-month outcome better captures how well the regimen performed in reality and at patient level after accounting for drug substitution.

‖Any difference in time-specific culture conversion between the arms was mitigated by bedaquiline substitution in a significant proportion of the SOC cohort owing to kanamycin-induced high-frequency hearing loss. Thus, the conversion rate in the SOC arm was augmented by BDQ substitution.

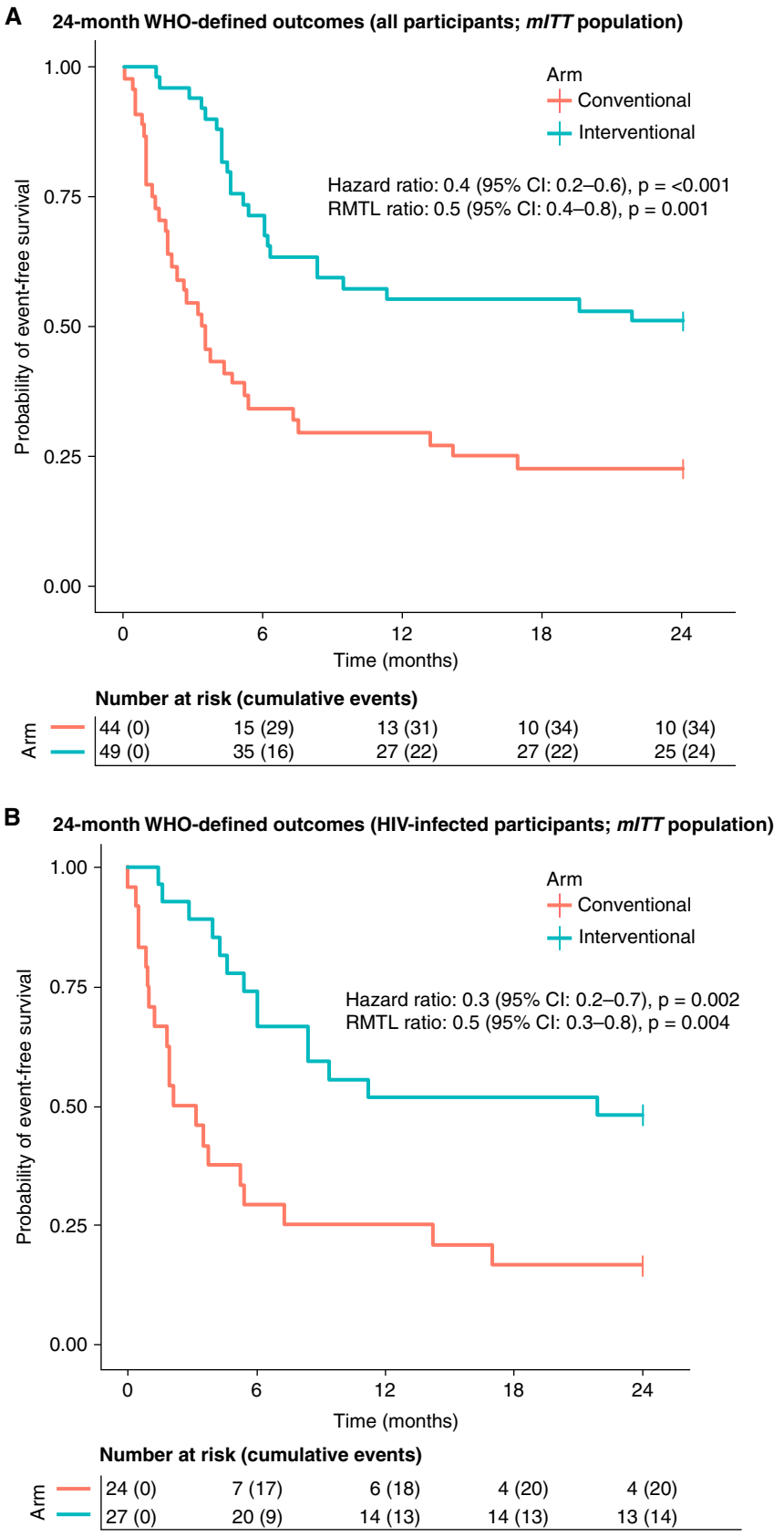


Figure 3. Summary of favorable and unfavorable outcomes in the modified intention-to-treat (mITT; $n = 93$) population. Kaplan-Meier curves indicating the probability of attaining a World Health Organization (WHO)-defined favorable outcome (event-free survival [i.e., absence of an

shows the odds ratio). In the per-protocol analysis, a favorable outcome at 12 months after treatment completion was reported in 23.3% (10 of 43) of participants in the SOC arm and 56.8% (25 of 44) of participants in the intervention arm, a risk difference of 33.6% (95% CI, 14.2–52.9; $P = 0.002$).

At 24 months after treatment initiation, treatment success or favorable patient-centered outcomes (for which drug substitution was not considered a criterion for an unfavorable outcome) is shown in Table 2 and Figures 4A and 4B (mITT and per-protocol populations, respectively). In the per-protocol population, it was 69.8% (30 of 43) in the SOC arm and 75.0% (33 of 44) in the intervention arm. The breakdown of unfavorable outcomes, including relapse/reinfection, are shown in Figure 4. The median duration of treatment in the interventional arm was about 6 months (interquartile range, 5–7) with the proportion of participants in the intervention arm who received treatment for 6, 7, 8, and 9 months being 61.4% (27 of 44), 15.9% (7 of 44), 11.4% (5 of 44), and 11.4% (5 of 44), respectively as outlined in Table E9.

Given that bedaquiline often replaced kanamycin because of toxicity, sputum culture conversion rates did not differ significantly between the SOC arm and intervention arm at 2 months (70.7% vs. 86.1%; $P = 0.113$) and 6 months (95.1% vs. 95.4%) after treatment initiation. However, when censoring the data for participants in the control arm who received bedaquiline owing to a toxicity-related drug substitution, the rate of sputum culture conversion was greater in the intervention arm than the SOC arm (hazard ratio, 2.6; 95% CI, 1.4–4.9) (Figure 5). The rate of sputum culture conversion in HIV-infected versus HIV-uninfected subjects are shown in and Figure E1. The effect of linezolid discontinuation on culture conversion in the intervention arm is shown in Figure E2.

Safety

In the safety population (participants receiving at least one dose of study medication), 31 toxicity-related drug stoppage events occurred in the SOC arm, 27 of which were owing to kanamycin, and 19 were related to ototoxicity detected by pure tone audiometry (only 5 of 19 [26.3%] had measurable loss within the hearing frequency range, i.e., patient-discernible impairment). Seventeen toxicity-related drug stoppage events occurred in the intervention arm, 11 of which were owing to linezolid-induced hematological toxicity or peripheral neuropathy (Table 3). A breakdown of serious adverse events and those of special interest are shown in Table 3 and Tables E10 and E11. *See* Table E12 for a summary of drug interruption (substitution and replacement of drugs owing to adverse events). Eight participants died during the treatment or follow-up period (four [9.1%] in the control arm and four [8.2%] in the intervention arm); two deaths in the control arm and three deaths in the intervention arm were TB related. Significant prolongation of the QTc interval (DAIDS grade 3/>500 m s) was identified in one participant in the SOC arm and in none of the participants in the intervention arm.

Discussion

We evaluated the efficacy of an all-oral 6-month regimen (containing three WHO group A drugs and two group B or C drugs) compared with a ⩾9-month injectable regimen without linezolid or bedaquiline (at the outset). The key findings were that *1*) patient-centered outcome (⩾12-month relapse-free cure) was similar between the regimens despite the intervention regimen being considerably shorter; *2*) the all-oral 6-month regimen achieved significantly better WHO-defined outcomes than the injectable-based longer regimens (despite ∼87% of the latter group receiving bedaquiline at a median of 1.5 months after treatment initiation); *3*) toxicity remained considerable (in the interventional arm, ∼37% of participants were classified as treatment failures, and hence an unfavorable outcome, largely because of linezolid toxicity, whereas in the SOC arm, audiometry-defined hearing loss was substantial); and *4*) about one-quarter of the interventional arm still had an unfavorable outcome even after toxicity-related regimen modification was accounted for. Notably, the rapidly changing drug-resistant TB treatment landscape meant that during the course of the study, the longer 18- to 20-month injectable-based regimen in the control arm was replaced nationally by the shorter standardized 9- to 11-month injectable-based regimen. Nevertheless, both SOC arms represented a ⩾9-month injectable regimen not containing bedaquiline or linezolid, and both regimens were recently conclusively shown to be noninferior to one another in the STREAM study (including in our own analysis) (Figure E3) (7). Furthermore, the trial was stopped prematurely when bedaquiline-based therapy became the standard of care in South Africa for MDR/RR-TB on the basis of data from observational studies, and thus randomization was no longer ethically possible.

Improved outcomes were seen with this 6-month all-oral regimen. However, a WHO-defined favorable outcome was documented in only 51% of the participants. This was substantially owing to the way in which WHO-approved treatment outcomes are defined (i.e., toxicity-related replacement of drugs during treatment counts as treatment failure when ascertaining the 24-month outcome [1, 16, 17]). In the interventional regimen, this was predominantly driven by interruption of therapy owing to linezolid toxicity with resultant termination of the regimen and the assignment of treatment failure status. However, there is no widely accepted standardized definition of unfavorable outcome because of regimen termination (protocols may define regimen termination based on stoppage of one or 2 or more drugs), and many of these patients still achieve treatment success after drug substitution (what we called 24-month patient-centered outcome or treatment success) (16). We prespecified toxicity-related treatment failure as one drug if it was a WHO group A drug such as bedaquiline or linezolid that was substituted/replaced (a precedent is provided by other protocols [20]

Figure 3. (*Continued*). unfavorable outcome event]) 24 months after initiating the bedaquiline and linezolid–based (intervention) regimen compared with the standard-of-care (conventional) regimen is shown for (*A*) all participants ($n = 93$), and (*B*) in participants infected with HIV ($n = 51$) as part of an exploratory subgroup analysis. Events included death, microbiological and toxicity-related treatment failure, default, and reinfection/relapse. The hazard ratio and restricted mean time lost (RMTL) ratio with 95% confidence intervals (CIs), and *P* values, are indicated in each plot.

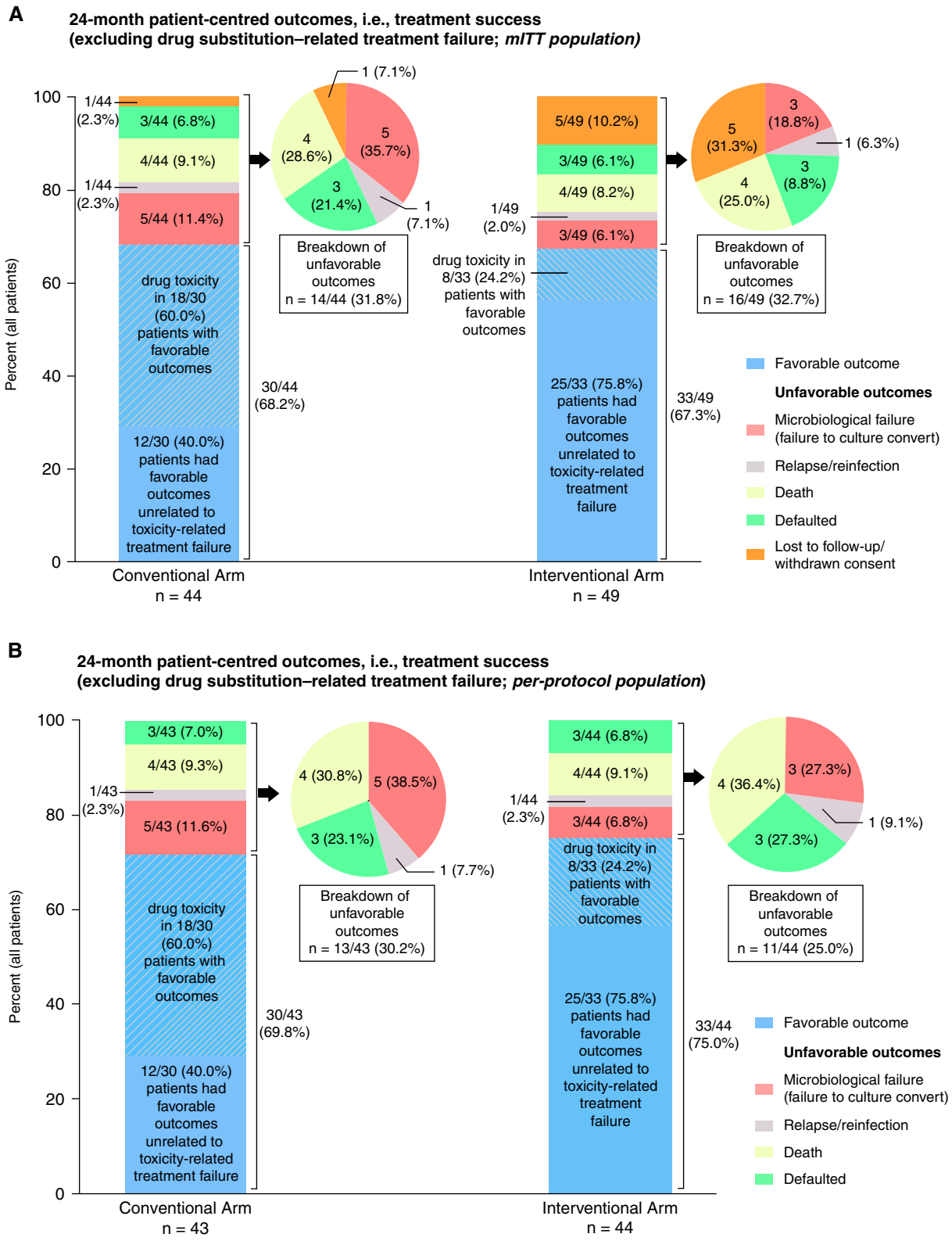


Figure 4. A 24-month breakdown of patient-centered favorable outcomes (treatment success [i.e., taking into account or incorporating the effect of drug replacement (i.e., drug substitution–related treatment failure ignored or excluded, which the WHO definition specifically designates as an unfavorable outcome)]) in the (*A*) modified intention-to-treat (mITT) population and (*B*) per-protocol population. Also shown are loss to follow-up and unfavorable outcomes. In this per-protocol analysis, loss to follow-up, which is an indeterminate outcome, is not shown

and as these drugs are associated with mortality reduction and improved outcomes in controlled trials [8, 9]), and two or more drugs if they were not WHO-defined group A drugs.

By contrast, 24-month treatment success (patient-centered outcomes) or ⩾12-month relapse-free cure, in which toxicity-related drug substitution was ignored or excluded (and the effect of the replacement/substitution was taken into account or incorporated), a favorable outcome was achieved by 75% of the participants in the interventional arm (and ∼70% in the SOC arm). As a patient may achieve cure or treatment completion following toxicity-related drug replacement/substitution, this classification is more likely to reflect the real-world performance of the regimen. Nevertheless, about 25% of participants in the interventional arm still had an unfavorable outcome, suggesting that there is a need for more effective drug combinations to improve outcomes (e.g., at least one or more group B drug or alternative group C drugs). Indeed, 90% of treatment-intolerant MDR-TB or XDR-TB (extensively drug-resistant tuberculosis [resistance to fluoroquinolones and aminoglycosides]) patients, had favorable outcomes using the 6- to 9-month bedaquiline, pretomanid, and high-dose linezolid regimen (12).

Despite improved outcomes with this all-oral regimen, there was still considerable toxicity. Indeed, linezolid treatment was interrupted in almost half of the participants and thus less toxic oxazolidinones or optimized dosing strategies will be required in future regimens. However, toxicity was still greater in the SOC arm when defined by the rate of drug discontinuation (drug withdrawal occurred in 65.9% of the participants and in 82.8% of these, kanamycin was the implicated drug, mostly owing to the development of hearing loss in almost 70% of participants in the mITT population (Table E11). This accounts for the high treatment failure (replacement of kanamycin by bedaquiline) and thus the low proportion of participants with a favorable outcome, a mere 21% in the SOC arm. This contrasts with programmatic conditions, in which favorable outcomes using injectable-based regimens approach ∼50% (21), and the STREAM study, in which it was ∼79% (7). However, audiometry is not routinely performed in most TB endemic settings, and in the STREAM study, audiometry was not undertaken in the overwhelming majority of patients (only one site had access to audiometry). By contrast, in our study, audiometry-detected high-frequency hearing loss was identified predominantly in patients without self-discernible hearing loss (∼75% of cases of those with hearing loss), accounting for a much higher proportion of participants stopping kanamycin than seen in programmatic cohorts or the STREAM study. Indeed, studies have shown that aminoglycoside-associated hearing loss in TB-endemic countries is very high when ascertained by audiometry (∼70% in persons infected with HIV and 42% in those who are uninfected with HIV) (22, 23). Nonetheless, even after allowing for toxicity-related drug substitution in patients who subsequently went on to achieve a cure or treatment completion, only 63% of participants on a control SOC arm regimen achieved a favorable outcome.

There are several strengths to our study. This is the first published randomized control trial to evaluate the efficacy of an all-oral 6-month regimen for MDR/RR-TB, and its pragmatic nature reflects the on-the-ground reality in a TB-endemic setting. We also achieved high participant retention rates, performed audiometry reflecting current best practice and standard of care in South Africa, leveraged sputum-based mycobacterial-specific pharmacogenomics (line probe assays) to add a fifth drug to the regimen, used second-line phenotypic susceptibility testing in tandem with genomic testing to minimize selection bias, controlled for radiological disease extent (which is often ignored in clinical trials), used a 24-month outcome definition biasing against the interventional arm (as relapses and reinfections after 6 months of treatment counted against the interventional arm), and used definitions for unfavorable outcomes that were prespecified in the protocol.

Our study also had several limitations. It was an open-labeled study, which is prone to bias. However, a double-blinded design would have been unfeasible (adding a daily intramuscular injection-based placebo, and the regimens were of different lengths) and laboratory and analytical teams were blinded to the assignment status. The study was only undertaken in South Africa and so has limited external validity (∼50% of participants were infected with HIV). It is possible that outcomes may have been different in settings with a low incidence of HIV, different *Mycobacterium tuberculosis* strains, and a different host genetic background. However, the study involved five sites in four different provinces with wide heterogeneity in TB strains (Beijing in the Western Cape vs. LAM in the Kwa-Zulu Natal province), widely varying race and ethnicity (mixed European and Black African race in the Western Cape vs. Black African in Kwa-Zulu Natal), and the inclusion of participants infected with HIV, which increased the robustness of our findings. The sample size was limited by the premature termination of the study. However, we were still able to show a significant difference between these arms (our study was powered for a ∼20% effect across a range of sample sizes). Our regimen included a one-mutationally selected drug and pyrazinamide (∼50% resistance in South Africa), which are WHO group C designated drugs. However, the NExT (New and Emerging Therapies for Drug-Resistant Tuberculosis) regimen, comprised the three WHO group A drugs and two group B or C drugs, thus providing at least four likely effective drugs as recommended by WHO for the construction of an MDR/RR-TB regimen. We further leveraged mycobacterial-specific pharmacogenomic tools to guide a more

Figure 4. (*Continued*). (no outcomes could be assigned to six participants after being lost to follow-up or withdrawing consent). The hatched areas of the favorable outcome segment (in blue) indicate the proportion of the favorable outcome (treatment success) that could be attributed to regimen change or toxicity-related treatment failure. The breakdown of unfavorable outcomes, expressed as a proportion of the total number of participants with unfavorable outcomes in the conventional and intervention group, is shown in the pie charts indicated for each arm. Events included death, microbiological treatment failure, default, and relapse/reinfection (of the two cases of relapse/reinfection, there was one case of reinfection with a drug-sensitive strain, and whole-genome sequencing revealed relapse in one patient with acquired resistance to bedaquiline and clofazimine [involving the Rv0678 gene]). Figures within the bar graphs indicate the number of participants and percentages are given in parentheses. WHO = World Health Organization.

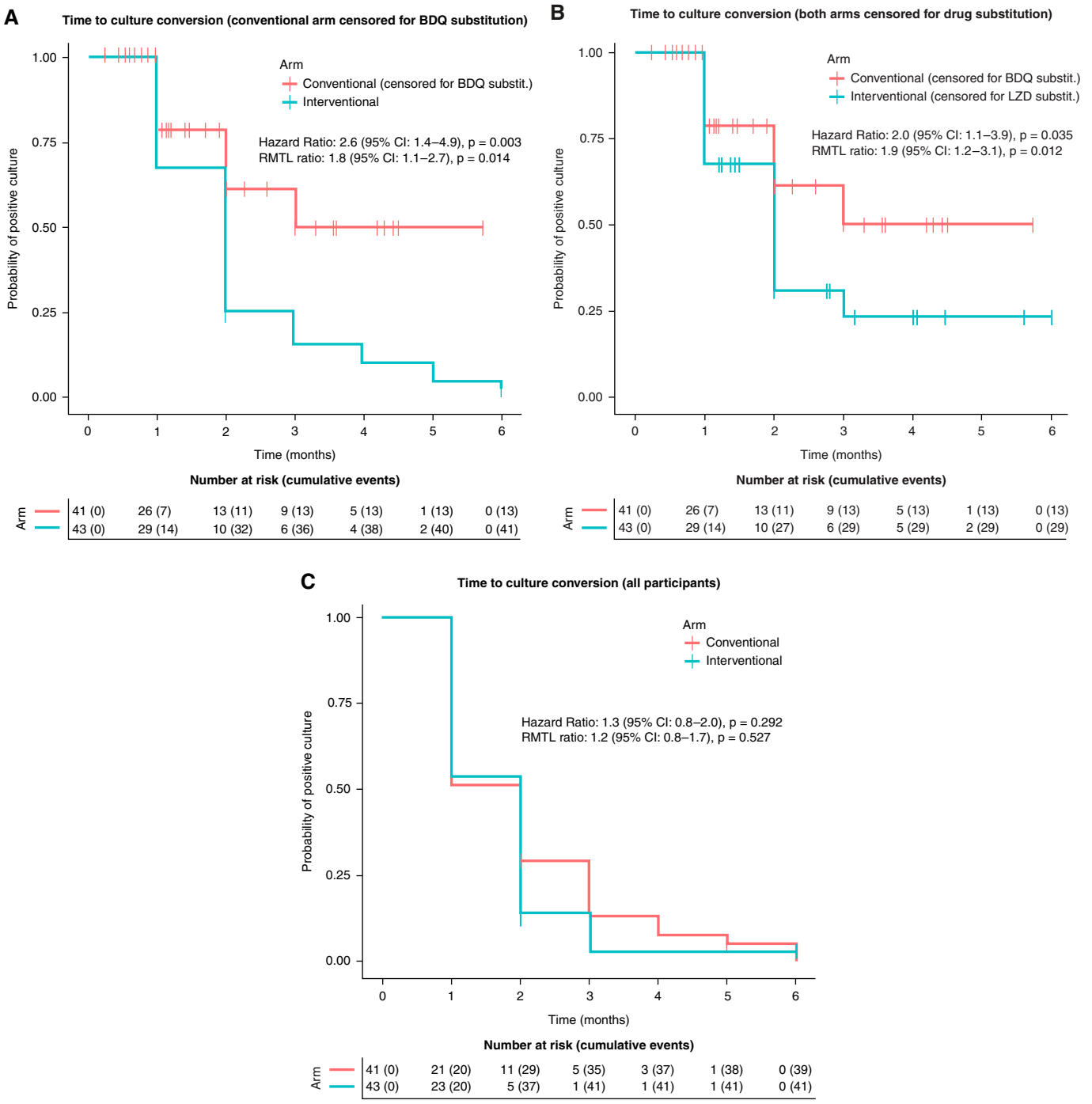


Figure 5. Kaplan-Meier curves indicating the probability of maintaining a positive sputum culture 6 months after initiating the bedaquiline and linezolid–based (BDQ/LZD) (intervention) regimen compared with the standard-of-care (SOC) (conventional) regimen for all participants having a positive sputum culture at the start of the trial ($n = 84$; nine samples failed to grow an isolate from the sputum sample donated at randomization). The probability is shown after (*A*) only censoring participants who had toxicity-related kanamycin substitution (i.e., bedaquiline replacement) in the SOC arm (thus the intervention arm was uncensored), (*B*) censoring participants who had kanamycin substitution (i.e., replacement with bedaquiline) in the conventional arm *and* linezolid substitution (i.e., replacement with terizidone) in the intervention arm (thus the effect of censoring in both arms shown), and (*C*) in the overall population irrespective of drug substitution (effect of all drug replacements and substitutions in both arms are shown). The hazard ratio and restricted mean time lost (RMTL) ratio with 95% confidence intervals (CIs), and *P* values, are indicated in each plot. Culture conversion is defined in Table E4.

Table 3. Summary of Safety Outcomes at 24 Months after Treatment Initiation in the Safety Population

Adverse Event Type	SOC	BDQ/LZD	Odds Ratio (95% CI)	*P* Value*
Adverse event requiring the discontinuation of at least one drug	31/55 (56.4)†	17/56 (30.3.)‡	0.3 (0.2–0.7)	0.007
DAIDS grade 4 or 5 events§	13/55 (23.6)	14/56 (25.0)	1.1 (0.5–2.6)	1
DAIDS grade 3 events§	18/55 (32.7)	31/56 (55.4)	2.55 (1.2–5.5)	0.022
Serious adverse events as per GCP definition	11/55 (20.0)	14/56 (25.0)	1.3 (0.5–3.3)	0.65
All adverse events	79/55	76/56	NA	NA

Definition of abbreviations: BDQ/LZD = bedaquiline and linezolid–based regimen; CI = confidence interval; DAIDS = Division of AIDS; GCP = Good Clinical Practices; NA = not applicable; SOC = standard of care.
Participants who received at least one dose of a trial medication were included in the safety analysis population (i.e., the intention-to-treat population). Safety outcomes for the modified intention-to-treat population are shown in the online supplement.
*For comparison of proportion.
†Kanamycin was identified as a culprit drug in 27 of 31 (87.1%) participants with adverse events where the drug was stopped; the majority of kanamycin-related events (19 of 27; 70.4%) were related to high-frequency hearing loss.
‡Linezolid was identified as a culprit drug in 11 of 17 (64.7%) participants with adverse events where the drug was stopped; the majority of linezolid events (10 of 11; 90.1%) were related to anemia.
§Adverse events were graded according to National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS table for grading the severity of adult adverse events (version 2.1, July 2017 update).

precision medicine–based regimen. Thus, given our findings, four or more suitable drugs including the addition of more potent drugs will be required to design an optimal all-oral regimen. We did not rechallenge with linezolid in the majority of participants who experienced linezolid toxicity, as this was not a widely accepted clinical practice and most clinicians practicing at the trial centers were not comfortable with an aggressive rechallenge approach. Lastly, our study did not perform serial audiometric analysis in the bedaquiline and linezolid–based regimen arm since this arm did not contain any known agents with ototoxic adverse events. However, audiometry was performed on all patients prior to randomization, and patients with baseline hearing loss were excluded from the trial.

In conclusion, an all-oral 6-month regimen containing three group A drugs (bedaquiline, linezolid, and a fluoroquinolone), two group B/C drugs (pyrazinamide and either ethionamide or high-dose isoniazid or terizidone) when compared with traditional ⩾9-month injectable-containing regimen, was associated with significantly improved WHO-defined 24-month treatment outcomes (predominantly owing to toxicity-related drug substitution). Importantly, patient-centered outcomes (⩾12-month relapse-free cure) were similar between the regimens despite the intervention regimen being considerably shorter. Nevertheless, toxicity with the all-oral regimen remained considerable. In essence, if the current WHO-recommended oral regimen is reduced to a ∼6-month duration, ∼25% of patients will still have an unfavorable outcome after accounting for toxicity-related drug substitution. These data inform strategies to develop shorter and improved regimens for MDR/RR-TB in TB-endemic settings. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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