NEW REGIMENS FOR TREATMENT OF TB

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NRITLD

SBMU

- One of the great satisfactions of managing infectious diseases is the remarkable and rapid efficacy of antibiotics.
- The first uses of penicillin in the treatment of pneumococcal pneumonia produced near miraculous results, and most bacterial infections can be cured with a few days of therapy.
- However, tuberculosis has been an outlier

- A series of landmark studies performed over several decades showed that combination therapy could result in high rates of cure among patients with tuberculosis, but the best “short course” regimen — and the one that remains in use to this day — still requires 6 months of therapy with multiple drugs

- This treatment has cured more than 95% of persons with tuberculosis in the context of clinical trials but has underperformed in national treatment programs, in which long-term adherence is difficult for some persons and resource constraints limit the provision of adherence support

- Many efforts have been made to shorten this period. There is good evidence that this may be possible, because most patients who receive standard therapy are cured well before 6 months.
- The longer duration is driven by a minority of patients for whom extended therapy is warranted.
- In clinical trials, at least 85% of participants have been cured with 3-month and 4-month regimens, and the percentage is likely to be higher when these regimens contain fluoroquinolones or rifapentine
- A similar probability of cure has also been observed with 2-month regimens that are administered for the treatment of smear negative tuberculosis

- The current 6-month regimen may lead to overtreatment in the majority of persons in order to prevent relapse in a minority of persons
- A “stratified medicine” approach proposed recently would entail identifying those in need of longer treatment

- The alternative approach is to replace the standard regimen with one that provides a durable cure for all patients in less time.
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- Higher doses of rifamycins could increase the rate of clearance of infecting bacteria in tuberculosis.
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ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

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ABSTRACT

BACKGROUND

Rifapentine-based regimens have potent antimycobacterial activity that may allow for a shorter course in patients with drug-susceptible pulmonary tuberculosis.

METHODS

In an open-label, phase 3, randomized, controlled trial involving persons with newly diagnosed pulmonary tuberculosis from 13 countries, we compared two 4-month rifapentine-based regimens with a standard 6-month regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol (control) using a noninferiority margin of 6.6 percentage points. In one 4-month regimen, rifampin was replaced with rifapentine; in the other, rifampin was replaced with rifapentine and ethambutol with moxifloxacin. The primary efficacy outcome was survival free of tuberculosis at 12 months.

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RESULTS

Among 2516 participants who had undergone randomization, 2343 had a culture positive for *Mycobacterium tuberculosis* that was not resistant to isoniazid, rifampin, or fluoroquinolones (microbiologically eligible population; 768 in the control group, 791 in the rifapentine–moxifloxacin group, and 784 in the rifapentine group), of whom 194 were coinfected with human immunodeficiency virus and 1703 had cavitation on chest radiography. A total of 2234 participants could be assessed for the primary outcome (assessable population; 726 in the control group, 756 in the rifapentine–moxifloxacin group, and 752 in the rifapentine group). Rifapentine with moxifloxacin was noninferior to the control in the microbiologically eligible population (15.5% vs. 14.6% had an unfavorable outcome; difference, 1.0 percentage point; 95% confidence interval [CI], –2.6 to 4.5) and in the assessable population (11.6% vs. 9.6%; difference, 2.0 percentage points; 95% CI, –1.1 to 5.1). Noninferiority was shown in the secondary and sensitivity analyses. Rifapentine without moxifloxacin was not shown to be noninferior to the control in either population (17.7% vs. 14.6% with an unfavorable outcome in the microbiologically eligible population; difference, 3.0 percentage points [95% CI, –0.6 to 6.6]; and 14.2% vs. 9.6% in the assessable population; difference, 4.4 percentage points [95% CI, 1.2 to 7.7]). Adverse events of grade 3 or higher occurred during the on-treatment period in 19.3% of participants in the control group, 18.8% in the rifapentine–moxifloxacin group, and 14.3% in the rifapentine group.

CONCLUSIONS

The efficacy of a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in the treatment of tuberculosis. (Funded by the Centers for Disease Control and Prevention and others; Study 31/A5349 ClinicalTrials.gov number, NCT02410772.)

- Both rifapentine and moxifloxacin are widely available and could probably be packaged appropriately for use by national tuberculosis programs.
- Shortening a regimen by 2 months would make treatment somewhat less cumbersome and probably make it more cost-effective.

- The need to take rifapentine after meals to maximize absorption could introduce new issues with adherence.
- Moreover, one of the advantages of the currently used tuberculosis drugs is that they are not widely used in other infections.
- In addition to necessitating rapid drug-susceptibility testing for moxifloxacin, widespread use of this antibiotic for the treatment of tuberculosis could promote resistance to fluoroquinolones in other bacteria

- This trial does, however, establish an important principle: there is no magic with 6 months of therapy.
- Although the development of the standard 6-month regimen resulted from trials in humans, the rifapentine–moxifloxacin therapy was first shown to be effective in shortening therapy in animals

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Treatment Strategy for Rifampin-Susceptible Tuberculosis

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ABSTRACT

BACKGROUND

Tuberculosis is usually treated with a 6-month rifampin-based regimen. Whether a strategy involving shorter initial treatment may lead to similar outcomes is unclear.

METHODS

In this adaptive, open-label, noninferiority trial, we randomly assigned participants with rifampin-susceptible pulmonary tuberculosis to undergo either standard treatment (rifampin and isoniazid for 24 weeks with pyrazinamide and ethambutol for the first 8 weeks) or a strategy involving initial treatment with an 8-week regimen, extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse. There were four strategy groups with different initial regimens; noninferiority was assessed in the two strategy groups with complete enrollment, which had initial regimens of high-dose rifampin–line-

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TRUNCATE-TB trial

- Participants were randomly assigned to undergo either standard treatment or a strategy involving initial treatment with an 8-week regimen, extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse.
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TRUNCATE-TB trial

- In the four strategy groups, initial treatment consisted of the following 8-week regimens: a high dose of rifampin and linezolid, a high dose of rifampin and clofazimine, rifapentine and linezolid, and bedaquiline and linezolid, each in combination with isoniazid, pyrazinamide, and ethambutol.
- In the strategy group with an initial rifapentine–linezolid regimen, ethambutol was replaced with levofloxacin

TRUNCATE-TB trial

- The high dose of rifampin was 35 mg per kilogram of body weight initially and was reduced to 20 mg per kilogram starting on November 1, 2019
- When a participant had persistent clinical disease (symptoms and a positive sputum smear) at week 8 or had missed doses, treatment with the five-drug regimen could be extended through week 12

TRUNCATE-TB trial

- When a participant had persistent clinical disease at week 12 or had adverse events at an earlier point, the five-drug regimen could be switched to standard treatment to complete a 24-week course of treatment

Table 2. Primary Efficacy Outcome.*

Outcome	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Linezolid vs. Standard Treatment Adjusted Difference (97.5% CI)†	Strategy with Bedaquiline–Linezolid (N=189)	Strategy with Bedaquiline–Linezolid vs. Standard Treatment Adjusted Difference (97.5% CI)†
Intention-to-treat population‡					
Primary outcome: composite of death, ongoing treatment, or active disease at wk 96 — no. (%)§	7 (3.9)	21 (11.4)	7.4 (1.7 to 13.2)	11 (5.8)	0.8 (–3.4 to 5.1)
Death before wk 96	2 (1.1)	5 (2.7)	—	1 (0.5)	—
Ongoing treatment at wk 96	2 (1.1)	8 (4.3)	—	5 (2.6)	—
Active disease at wk 96¶	1 (0.6)	4 (2.2)	—	3 (1.6)	—
Evaluation by telephone at wk 96 with no evidence of active disease but insufficient evidence of disease clearance when last seen	2 (1.1)	3 (1.6)	—	1 (0.5)	—
No evaluation at wk 96 and insufficient evidence of disease clearance when last seen	0	1 (0.5)	—	1 (0.5)	—
Outcomes classified as unassessable — no. (%)	1 (0.6)	1 (0.5)	—	2 (1.1)	—
Single positive culture at wk 96 but no other evidence of active disease‖	0	1 (0.5)	—	0	—
Death from a cause that was definitively unrelated to tuberculosis**	1 (0.6)	0	—	0	—
No evaluation at wk 96 and sufficient evidence of disease clearance when last seen	0	0	—	2 (1.1)	—
No primary outcome or outcome classified as unassessable — no. (%)	173 (95.6)	162 (88.0)	—	176 (93.1)	—
Assessable population††					
Primary outcome — no./total no. (%)	7/180 (3.9)	21/183 (11.5)	7.5 (1.7 to 13.2)	11/187 (5.9)	0.8 (–3.4 to 5.1)
Per-protocol population‡‡					
Primary outcome — no./total no. (%)	6/177 (3.4)	17/160 (10.6)	6.9 (0.9 to 12.8)	9/176 (5.1)	0.9 (–3.3 to 5.1)

TRUNCATE-TB trial

- In the bedaquiline–linezolid group, 162 participants (85.7%) did not receive therapy beyond 8 weeks
- According to the definitions used in the trial, extension of therapy was not a “failure” but was part of the treatment strategy. Altogether, the mean total length of treatment in the bedaquiline–linezolid group (84.8 days) was less than half that in thestandard-treatment group (180.2 days)

TRUNCATE-TB trial

- One risk that is associated with a shorter course could be the development of antibiotic resistance. There were two cases of acquired drug resistance in the bedaquiline–linezolid group and none in the standard-treatment group.
- Bedaquiline has a long terminal half-life that generates lingering subtherapeutic concentrations for several months after the end of therapy, which results in de facto monotherapy and a prolonged window for the potential acquisition of drug resistance in cases of relapse

TRUNCATE-TB trial

- Bedaquiline still carries a black-box warning that resulted from very early trials showing increased mortality among treated patients
- Linezolid can lead to dose-limiting toxic effects that have been a substantial issue in other trials

- Tuberculosis is an important cause of death worldwide, and drug resistance is implicated in one third of the almost 2 million deaths from tuberculosis each year.
- Progress accelerated with the Food and Drug Administration approval in 2012 of bedaquiline, the first new antituberculosis agent in decades

- The programmatic rollout of bedaquiline was led by South Africa, where the addition of the drug to standard agents markedly improved survival among patients with drug-resistant tuberculosis

	Drugs	Comments
Step one	Bedaquiline	Given for the first 6 months of treatment; some experts recommend using the drug for 9 months or longer
Step two	Levofloxacin or moxifloxacin	No preference for either fluoroquinolone; although levofloxacin has less QTc prolonging potential than moxifloxacin, discontinuation of bedaquiline in a fluoroquinolone-containing regimen because of QTc prolongation is uncommon
Step three	Linezolid	Linezolid is frequently associated with adverse drug events and requires very close monitoring in long-term treatment
Step four	Clofazimine and cycloserine or terizidone	These drugs are probably more potent than step five drugs and at least one of them should generally be part of the regimen unless contraindicated
Step five	Pyrazinamide* and prothionamide or ethionamide†	Add if steps one to four do not lead to four or more active drugs; use pyrazinamide before prothionamide or ethionamide if pyrazinamide susceptibiity is assured; prothionamide and ethionamide probably not as potent as step four drugs; drug resistance against pyrazinamide* or prothionamide or ethionamide must be ruled out
Step six	Meropenem and amoxicillin-clavulanic acid and amikacin	Add if steps one to five do not lead to four or more active drugs and in case of fluoroquinolone resistance; use meropenem and amoxicillin-clavulanic acid before amikacin for better tolerability; administration via a subcutaneous tunnelled venous catheter is desirable for injectable agents like meropenem or amikacin; amoxicillin-clavulanic acid must be administered simultaneously; amikacin administered for the first 6–8 months of treatment only; capreomycin and kanamycin should be avoided
Step seven	Delamanid, para-aminosalicylic acid, and ethambutol*	Add one or more if steps one to six do not lead to four or more active drugs

The choice of drugs should be guided by drug susceptibility testing. Drugs should be added step by step until the regimen consists of at least four effective (or probably effective) and tolerated drugs. In the absence of a biomarker to guide physicians for an individual duration of therapy, the treatment regimen should be administered for 18–20 months. However, the optimal duration of therapy is not only dependant on the level of drug resistance and choice of the treatment regimen, but also on the extent of the disease, the immune status of the host, and the kinetic of the treatment response. Close monitoring of adverse events is mandatory for second-line antituberculosis drugs. *Depending on the geographical setting most multidrug-resistant tuberculosis strains might be resistant to pyrazinamide and ethambutol. Do not include pyrazinamide or ethambutol in the regimen unless proven by drug susceptibility testing. However, drug susceptibility testing is often unavailable or inaccessible and thus resistance to pyrazinamide must be assumed. †Do not include prothionamide or ethionamide in the initial regimen if molecular drug susceptibility testing shows a mutation in the promotor of the *inhA* gene (mostly positions 8 or 15).

Table 3: **Stepwise design of a treatment regimen for multidrug-resistant tuberculosis**

- The results of the TB-PRACTECAL trial, which was led by Médecins sans Frontières. This open-label, phase 2–3, randomized, controlled trial involving patients with rifampinresistant tuberculosis represents the opening of a new chapter

- A total of 89% of the patients who received the 6-month, all-oral treatment consisting of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) had favorable outcomes, and the safety profile of the regimen was acceptable to the patients and manageable for caregivers.
- BPaLM was superior to a current 9-to-24-month standard-care regimen

- The results of the Nix-TB study, which were published in the Journal in 2020,showed that the combination of two new drugs, bedaquiline and pretomanid, with a repurposed oxazolidinone antibiotic agent, linezolid, given for 6 to 9 months to patients with drug resistant or complicated multidrug-resistant tuberculosis, resulted in a favorable outcome in 98 of 109 patients (90%) at 6 months after the end of treatment.

- The efficacy of the regimen came at a cost — peripheral neuropathy developed in 88 patients (81%), and myelosuppression developed in 52 patients (48%).
- Both these conditions are well-recognized complications of prolonged linezolid treatment.

- Sutezolid and delpazolid are next-generation oxazolidinones that may provide efficacy that is equivalent to that of linezolid, with fewer toxic effects

DELAMANIDE

- In this multicentre, randomised, open-label phase 2/3 non-inferiority trial, we enrolled men and women aged 19–85 years with multidrug-resistant tuberculosis confirmed by phenotypic or genotypic drug susceptibility tests or rifampicin-resistant tuberculosis by genotypic tests at 12 participating hospitals throughout South Korea.

- The investigational group received delamanid, linezolid, levofloxacin, and pyrazinamide for 9 months, and the control group received a conventional 20–24-month regimen, according to the 2014 WHO guidelines

- Between March 4, 2016, and Sept 14, 2019, 214 participants were enrolled, 168 (78·5%) of whom were included in the modified intention-to-treat population.
- At 24 months after treatment initiation, 60 (70·6%) of 85 participants in the control group had treatment success, as did 54 (75·0%) of 72 participants in the shorter-regimen group (between-group difference 4·4% [97·5% one-sided CI –9·5% to ∞]), satisfying the predefined non-inferiority margin.
- No difference in safety outcomes was identified between the control group and the shorter-regimen group.

- 9-month treatment with oral delamanid, linezolid, levofloxacin, and pyrazinamide could represent a new treatment option for participants with fluoroquinolone-sensitive multidrug-resistant tuberculosis.

Clinical Infectious Diseases

MAJOR ARTICLE

Safety and Effectiveness Outcomes From a 14-Country Cohort of Patients With Multi-Drug Resistant Tuberculosis Treated Concomitantly With Bedaquiline, Delamanid, and Other Second-Line Drugs

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- We conducted a multi-centric, prospective observational cohort study across 14 countries among patients receiving concomitant Bdq-Dlm treatment.
- Patients were recruited between April 2015 and September 2018 and were followed until the end of treatment.
- All serious adverse events and adverse events of special interest (AESI), leading to a treatment change, or judged significant by a clinician, were systematically monitored and documented

- Overall, 472 patients received Bdq and Dlm concomitantly.
- A large majority also received linezolid (89.6%) and clofazimine (84.5%).
- Nearly all (90.3%) had extensive disease; most (74.2%) had resistance to fluoroquinolones.
- The most common AESI were peripheral neuropathy (134, 28.4%) and electrolyte depletion (94, 19.9%).
- Acute kidney injury and myelosuppression were seen in 40 (8.5%) and 24 (5.1%) of patients, respectively.
- QT prolongation occurred in 7 patients (1.5%).
- Overall, 78.0% (358/458) had successful treatment outcomes, 8.9% died, and 7.2% experienced treatment failure.

- Concomitant use of Bdq and Dlm, along with linezolid and clofazimine, is safe and effective for MDR/RR-TB patients with extensive disease.
- Using these drugs concomitantly is a good therapeutic option for patients with resistance to many anti-TB drugs.