EDITORIAL

Shortening Tuberculosis Treatment — A Strategic Retreat

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Our current treatment regimen for tuberculosis, which goes by the somewhat ironic name of "directly observed therapy, short course," is anything but short. Patients are treated, generally on a daily basis, for 6 months, which necessitates an infrastructure to deliver and observe therapy. This logistic burden has led to a push for shorter treatments. Although many initial attempts failed, a recent study suggested that a newer regimen could lead to a similar probability of cure in 4 months.[1] This is certainly an advantage, and yet the newer regimen, if widely used, would still require a similarly burdensome infrastructure. Can we do even better and get to a point where the logistics would not be so limiting? The investigators of the TRUNCATE-TB (Two-Month Regimens Using Novel Combinations to Augment Treatment Effectiveness for Drug-Sensitive Tuberculosis) trial,[2] the results of which are now published in the *Journal*, attempted to do that. But rather than focusing on a regimen alone, they chose a treatment strategy.

The trial design is a bit complex and initially had five groups. Participants had to have a nucleic acid amplification test that was positive for tuberculosis with no genotypic evidence of rifampin resistance. The investigators excluded some higher-risk patients initially but then changed the entry criteria to include this population. Participants who were randomly assigned to the control group received standard tuberculosis treatment for 24 weeks (8 weeks of isoniazid, rifampin, ethambutol, and pyrazinamide, followed by 16 weeks of isoniazid and rifampin); this group served as a comparator for a planned noninferiority analysis. Participants in the four other groups received an intensified regimen that contained five drugs. The plan was to drop two of these groups on the basis of early stopping rules. In fact, none of these groups met those standards, so enrollment was stopped in two groups on the basis of logistic criteria (pill burden and regulatory concerns) in order to preserve statistical power. The two remaining groups received either high-dose rifampin plus linezolid or bedaquiline plus linezolid, each in combination with isoniazid, pyrazinamide, and ethambutol.

For the groups that received an intensified regimen, the strategy consisted of treatment for 8 weeks and then reassessment for persistent disease (symptoms and a positive sputum smear). If the reassessment was negative, treatment was stopped; if positive, participants continued treatment for another 4 weeks. Those who remained positive could be switched to standard treatment to complete 24 weeks. Those who had a relapse in any group were retreated with a standard regimen with adjustments made according to antibiotic susceptibility testing. Participants were followed closely for evidence of relapse through week 96. The primary outcome was a composite of death, ongoing treatment, or active disease at week 96. For the treatment strategy to be declared noninferior, the upper limit of the confidence interval for the difference between the strategy group and the standard-treatment group in the risk of the primary outcome had to be less than 12 percentage points. This is a somewhat low threshold; for example, a recent treatment-shortening trial used a noninferiority margin of 6.6 percentage points.[1] As it turned out, one of the strategy groups failed to meet even that loose criterion, whereas the other would have succeeded at either margin.

The trial enrolled 675 participants at 18 sites in five countries. Impressively, almost all completed the trial and follow-up period. Altogether, 7 participants (3.9%) had a primary-outcome event in the control group, as compared with 21 (11.4%) in the rifampin–linezolid group (adjusted difference, 7.4 percentage points; 97.5% confidence interval [CI], –1.7 to 13.2) and with 11 (5.8%) in the bedaquiline–linezolid group (adjusted difference, 0.8 percentage points; 97.5% CI, –3.4 to 5.1). With these results, only the strategy involving treatment with the bedaquiline–linezolid regimen was declared noninferior to standard treatment. 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 the standard-treatment group (180.2 days).

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. Although a much larger number of patients would need to be treated to detect any significant difference, the small number of cases of drug resistance in this trial does not pose substantial concerns.

In many ways, the results of this trial are not surprising. We have long known that most patients with tuberculosis who are treated even with standard regimens do not have a relapse after 4 months of treatment; in fact, several appear to be cured after only 2 months of treatment.[3] And the inclusion of bedaquiline and linezolid in regimens for drug-resistant tuberculosis has allowed for shorter regimens.[4-6] What is striking is that each of these drugs has posed considerable concerns about toxic effects in the past. 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. Because of these effects, whether these drugs could be used safely for the treatment of drug-susceptible tuberculosis has been unclear. In the TRUNCATE-TB trial, the toxic effects appeared to be quite limited. In fact, this is one of many trials that suggest that the original concerns about bedaquiline might be overstated, at least for patients who undergo prescreening with electrocardiography.

Will these data change practice? Two months of treatment might not be revolutionary but could be very helpful. However, some obstacles remain. There was a very high degree of adherence to treatment in this trial, far higher than the level likely to occur outside the context of a clinical trial. Lower adherence could mean increased treatment failure at 2 months. In addition, the treatment strategy involved careful assessments of patients to identify those who would receive extended courses of therapy. Although this approach is possible within the confines of a trial, it could require considerable resources that are not now available in many tuberculosis control programs.

Perhaps the biggest accomplishment of this trial is a step forward in the adaptive clinical trial design that may help to accelerate regimen development and to rapidly test many more 2-month therapies that are selected on the basis of recent treatment-shortening trial results.[4-7] For shorter treatments, positive results that are similar to the results for standard treatment and are observed across various patient populations, including those with a high burden of cavitary tuberculosis, would garner the confidence needed to influence practice in lower-resource settings.

Treatment algorithms such as that used in the TRUNCATE-TB trial are fundamental to tuberculosis control. Although implementing them could be a challenge, any added burden might be offset by reduced costs, better adherence, and increased patient satisfaction. Thus, for tuberculosis, a strategy might be more than just a regimen.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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This editorial was published on February 20, 2023, at NEJM.org.

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DOI: 10.1056/NEJMe2300413