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Individualized Treatment Duration in Tuberculosis Treatment
Precision versus Simplicity

In 1991, the World Health Organization (WHO) introduced the Directly Observed Treatment–Short course strategy for global tuberculosis (TB) control (1, 2) This strategy simplified TB diagnosis and standardized TB treatment so that this could be decentralized to peripheral Heath centers in resource-limited settings. Front line workers, who are usually not physicians, ask one simple question ("Have you ever been treated for TB before?"), perform one simple test (Sputum Acid-Fast Bacilli Smear), and then initiate a standardized 6-month regimen. This "one size fits all" approach has been successful from a global public health perspective. WHO has estimated that between 2000 and 2019, 60 million deaths were averted because of the Directly Observed Treatment–Short course strategy (3).

To an observer from outside the TB community, the designation of a 6-month regimen as "short-course therapy" may seem like an oxymoron. Compared with the progress made over the last three decades with shortening treatment of other infectious diseases to as little as one dose, there has been little progress in shortening treatment in TB despite multiple large-scale trials (4–7). If anything, increased rates of failure and/or relapse with 6 months of therapy have been described in patients with various indicators of more extensive disease, suggesting that there is an identifiable subgroup of patients for whom the current 6-month regimen is too short (8–11).

In this issue of the *Journal*, Imperial and colleagues (pp. 1086–1096) analyzed individual patient data from four randomized trials to identify patient clinical characteristics that can accurately predict the duration of TB therapy required for relapse-free cure (12). Using pretreatment (baseline) HIV status, body mass index, Acid-Fast Bacilli sputum smear grade, and chest X-ray, plus 2-month culture results, patients were accurately allocated into three risk groups. The lowest risk group had excellent TB treatment outcomes with only 4 months treatment, whereas those in the moderate risk category had optimal results with 6 months duration. On the other hand, 29% of patients at high risk of treatment failure or relapse appeared to require more than 6 months of therapy. The authors conclude that this risk categorization may be useful for clinical care and for planning further randomized trials. They have also provided a web-based calculator for the determination of risk to help plan clinical trials.

Strengths of this study are that it is based on a sophisticated analysis of carefully collected and complete data from participants in four trials conducted in many different settings and populations. The prediction model was derived from the data in three trials and validated with the data from the fourth as well as validated in a randomly selected sample from all data. The prediction algorithm is simple and based on readily available clinical information, at least in high-income countries. The concept of individualized therapy based on an accurate estimate of need is very attractive. The finding that almost a third of all patients were at high risk of poor outcomes with 6 months of treatment is a sobering reminder of the limitations of the current standardized regimen.

We see some important limitations in the application of these findings in resource-limited settings in which improved TB treatment is most needed. For example, in Benin, the national TB program does not recommend routine performance of chest radiography before or during TB treatment for Smear- or GeneXpert-positive patients. At the moment, patients must pay out of pocket for the X-rays—a substantial financial barrier. Because culture facilities are not available in many parts of the country, sputum cultures are done only if treatment failure is suspected. More importantly, active TB is detected and treatment initiated in peripheral health centers throughout the country by frontline workers following simple algorithms, as recommended by WHO. Hence, the applicability of a more complex treatment algorithm would be limited in Benin and likely in other resource-limited settings without substantial additional training.

How many patients in high-burden settings would be eligible for a shortened 4-month regimen? Based on the findings from the

three trials that enrolled all types of patients, it is expected that about one-quarter of patients may be eligible for shorter therapy. Based on this, and some "back of the envelope" calculations, in resource-limited settings, it is likely that it would be more cost effective to continue the current practice of 6 months of treatment for all patients than to perform the necessary tests as well as training to initiate risk-stratified treatment duration.

But rather than looking at those who could receive shorter therapy, what about using this predictive tool to accurately identify those who need more than 6 months? In high-income countries, this could be an immediate use, but in resource-limited settings, the lack of chest radiography and 2-month culture information remains an important barrier.

In the design of clinical trials, it is clear that risk stratification would be very useful for accurate prediction of failure and relapse based on the anticipated characteristics of study participants, improving the precision of accurate sample size estimations. This study has highlighted that in a large group of patients with TB, their clinical characteristics and associated risks of treatment failure or relapse are very heterogeneous. This increases the difficulty of assessing novel regimens. Risk stratification could therefore be used to randomize participants in different risk strata to different sets of alternate regimens. This could lower the risk of failure of a novel short regimen by restricting enrollment to only those in lower categories of risk. Alternatively, only patients at high risk of failure or relapse could be randomized; the high rate of events may enhance feasibility of testing multiple regimens using novel adaptive trial designs (13). However, if such risk-stratified trials demonstrate that certain regimens should be given only to certain patients, this brings us back to the difficulties of individualized risk stratification in resource-limited settings. If more testing and more complex decision-making are required, this may be less cost effective or simply not feasible.

Enhanced precision in predicting individual patient responses is an important goal for patient care and clinical research. However, let's keep it simple. The ultimate goal is to develop a well-tolerated and safe regimen that will achieve a high rate of cure for all patients in all settings. ■

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