To Test or Not to Test? Ending the Age-Old Debate for Drug-Resistant Tuberculosis

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The coming decade has the potential for significant victories in the battle against the age-old scourge of tuberculosis (TB). Although TB has recently regained its position as the leading infectious killer of adults—and drug-resistant forms of the disease are predicted to be one of three bacterial pathogens that will kill more people than cancer and cost the global economy more than 100 trillion dollars by the year 2050—\textsuperscript{1}—the introduction of novel diagnostic and therapeutic approaches have led to a commitment by the global health community to “End TB” by 2030. This is an ambitious goal that will require radically new strategies to be implemented efficiently and effectively, including shorter and more effective therapeutic approaches for individuals affected by drug-resistant TB (DR-TB).

In their article in this issue of \textit{Clinical Infectious Diseases}, Dowdy and colleagues review the potential of one such therapeutic approach—implementation of a standardized, shortened 9-12 month treatment regimen for DR-TB—to contribute to TB elimination.\textsuperscript{2} As noted in the article, this shortened regimen was recommended by the World Health Organization (WHO) in 2016 based on an unpublished meta-analysis of observational cohort data.\textsuperscript{4} Given the dire state of access to effective treatment for drug-resistant TB globally, there is understandable excitement around rolling out a regimen that is shorter, potentially more efficacious and importantly, considerably cheaper than the conventional regimen of 18-24 months duration.\textsuperscript{5} While Dowdy and his co-authors critique a number of aspects of this conditional recommendation, they focus on one particularly thorny area: the need for drug-susceptibility testing (DST) to determine the appropriateness of the regimen for the treatment of people suffering from DR-TB.

This same issue regarding the need for DST in the optimal management of persons with TB was raised almost twenty years ago, when there was great global debate about the necessity of diagnosing and treating DR-TB. In a 1999 editorial in the \textit{International Journal of Tuberculosis and Lung Disease} called “Systematic Drug Susceptibility Testing: A Necessary Component of the DOTS-Plus Strategy”, Grosset asks “Should we therefore conclude...that systematic drug susceptibility tests should be performed on all initial isolates of \textit{M. tuberculosis}? Of course the answer is yes, if the following two limitations are overcome: the scarcity of specialists of drug resistance and the high running costs of a laboratory performing reliable susceptibility tests to first- and second-line drugs in a turnaround time short enough to be clinically relevant.”\textsuperscript{6}
And yet in 2015 only 16% of notified TB patients globally received DST for rifampicin and only 36% of these patients received DST for key second-line TB drugs. As in 1999, the challenges remain with the high costs, perceived complexity, timeliness and validity of the currently available drug susceptibility tests. Because of this lack of progress, we are still reliant on the use of standardized regimens to treat rifampicin-resistant or multidrug-resistant TB in most high burden settings. The use of standardized regimens after the diagnosis of rifampicin-resistance is likely to result in suboptimal treatment for significant proportions of patients in many settings and likely contributes to resistance amplification.

Similarly, the debate around individualized second-line treatment, guided by individual-level DST versus standardized treatment can also trace its roots to the late-1990s. Those arguing for a standardized approach again noted the lack of access to and fallibility of DST and argued that while not all persons with DR-TB would be cured using such regimens, demanding individualized regimens based on DST would deny a significant population of patients access to a regimen that could benefit them. In contrast, those supporting the use of DST to offer persons with DR-TB individualized regimens now appear prophetic in their arguments. They stressed that DST information was essential to providing optimal care and a failure to use DST to individualize treatment would result in poor therapeutic outcomes (current global success rates hover at 50%) and lead to amplification of drug-resistance (i.e. extensively drug-resistant TB).

There is little doubt that there will be patients who benefit from shortened regimens. And those who stand to benefit deserve access to such regimens since the current treatment for DR-TB is likely unnecessarily long. But if not carefully selected, people with DR-TB may face dire consequences if treated with the shortened regimens in the presence of resistance to the component medications. In the 2016 WHO guidelines, emphasis is placed on the high rates of treatment success seen with the shortened regimens in some settings, although reported success rates are significantly lower in persons with resistance to the fluoroquinolones, PZA, or both, and data remain limited from countries outside of Bangladesh. There are also limited data available on relapse outside of the Bangladesh cohort—with relapse being one of the biggest concerns with regimens that are shorter in duration.

WHO recommends that ideally, the shorter regimen be accompanied by individual level DST to exclude resistance to fluoroquinolones and/or second-line injectable drugs. However, as noted by Dowdy et al, such a requirement, given the limitations of currently available DST methods for these drug classes, may
be counterproductive to the aim of improving treatment access. In acknowledgment of this, the WHO 2016 guidance states that in settings without access to second-line DST, the likelihood of resistance can be inferred by the patients’ clinical history and surveillance data. This vague recommendation opens the door for widespread rollout of the shorter regimen in the absence of second-line DST, and is particularly concerning given that almost all the studies on which the guidance was based utilized second-line DST. Expanding access to DST is an urgent priority in order to scale up access to both diagnosis and effective treatment for DR-TB. In failing to emphasize the importance of second-line DST for the use of the shorter regimen, WHO have missed an opportunity to leverage the shorter regimen to improve diagnostic capacity – improvement that will be an even greater priority when shorter regimens incorporating the new TB drugs become available.

Trying to treat DR-TB without further DST is like trying to perform a complicated surgical procedure with a blunt kitchen knife. Unfortunately, global TB policy has a long history of such a minimalist approach. And while we have successfully co-opted the goals of the HIV community and adopted their language around elimination\(^\text{11}\), we have yet to adopt one of their most successful strategies—demanding the funding we need to make a serious attempt at turning the tide against TB, including universal DST for all patients diagnosed with TB and second-line DST for all those diagnosed with rifampicin resistance. As Dowdy and colleagues conclude, we must ensure all patients on the shortened regimen have, at a minimum, documented resistance testing to the injectable agents and fluoroquinolones. Otherwise, 20 years from now—when we are wondering why we have failed to “End TB”—we may still be trying to settle this DST debate.

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References:


