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Treatment Outcomes of Adolescents With Drug-Resistant Tuberculosis in Resource-Constrained Settings

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Dear Editor

There are very few data on the treatment of drug-resistant tuberculosis (DR-TB) in adolescents. A study by Moyo et al. (1), published in the January issue of the archives of pediatric infectious diseases, described patient outcomes and factors associated with outcomes of adolescents diagnosed with DR-TB between January 2008 and August 2013 in Khayelitsha, South Africa. This study represents one of the most extensive series of adolescents with DR-TB reported in the literature.

Khayelitsha is a township with one of the highest rates of human immunodeficiency virus (HIV) infection, tuberculosis (TB), and DR-TB in South Africa and worldwide (2, 3). Since 2007, Medecins Sans Frontieres, the city of Cape Town, and the provincial government of the Western Cape are working on an ambitious project to provide treatment to DR-TB patients at the primary care level (4). Although there exist a number of challenges, the program has been gradually implemented successfully. The details of the entire DR-TB cohort in Khayelitsha and a description of the methodology have been previously published (2-4).

The retrospective study by Moyo et al. (1) described treatment outcomes in 71 adolescents who underwent treatment for DR-TB between 2008 and 2013. Of these patients, 6 (8%) did not start treatment. The HIV co-infection rate was 27.7% and 94% of the HIV-infected adolescents were receiving antiretroviral therapy at the time of DR-TB diagnosis. The drug susceptibility patterns of the 65 adolescents who started treatment were as follows: 20 (30.8%) had rifampicin monoresistance, 30 (46.2%) had multidrug-resistant TB (MDR-TB) with no second-line anti-TB drug resistance, 12 (18.5%) had MDR-TB and second-line resistance, 1 (1.5%) had presumed MDR-TB, and 2 (3.1%) had MDR-TB and unknown second-line resistance. In all the treated patients, a standard treatment regimen for at least 18 months was used, and this was adapted according to the second-line drug sensitivity testing results or when treatment was failing.

Final treatment outcomes were available in 44 adolescents. Sixteen (36.4%) patients achieved treatment success, 19 (43.2%) patients did not complete treatment, and 4 (9.1%) patients died during treatment. All 4 patients showed resistance to first- and second-line drugs and were HIV negative. Treatment failed in 5 (11.4%) patients.

This study demonstrated very poor outcomes in HIV-infected and uninfected adolescents, with very high rates of loss to treatment, treatment failure, and mortality.

When the Khayelitsha DR-TB program started, the median time from diagnosis to initiation of treatment was 54 days, during which patients died or their clinical situation worsened. During this period, drug susceptibility testing was available only for TB patients at a high risk of DR-TB (1, 3). Late in 2011, Xpert MTB/RIF testing was introduced for all individuals with suspected TB. The MTB/RIF test, funded by the Foundation for Innovative New Diagnostics, allows the sensitive detection of TB and rifampin resistance directly from sputum in < 2 hours. If this technology had been available at the time when the study was conducted, then treatment could have been initiated as soon as the diagnosis was made. This could have reduced mortality and increased therapeutic success. Accessibility to new diagnostic tests for confirmation of TB and drug susceptibility testing is the key to ensuring that adolescents with DR-TB are correctly diagnosed and treated.

The second relevant factor for improving treatment success in adolescents with DR-TB is to adopt the best available standard of care. Healthcare professionals must be aware

of the high prevalence of low adherence to treatment in adolescents. Many different factors have an impact on adherence; however, the critical factors to consider in adolescents are their developmental stages and challenges, emotional issues, and degree of family dysfunction (5). In addition, standard services, which are usually aimed at adults, are not always well accepted by adolescents. All these reasons contribute to the high rates of refusal and loss to anti-TB treatment. Multiple interventions to improve adherence have been proposed, as follows: appropriately managing mental health issues; building a strong relationship; customizing the treatment regimen, if possible; empowering adolescents to deal with adherence issues; providing relevant information; ensuring family and peer support; and applying motivational enhancement therapy (5). It is crucial to design new DR-TB treatment strategies targeted at specific adolescent needs and challenges.

Finally, the third and most important factor for improving treatment success is determination of the type of drugs used and length of treatment administration. In the study by Moyo et al. (1), the treatment success rate (cure or treatment completion) was only 36.5%, which was comparable to that reported in HIV-positive adolescents in India; likewise, the rate of loss to treatment (45%) was higher in this study than in the Mumbai cohort (6). The rates of loss to treatment and treatment success did not significantly differ between HIV-infected and uninfected adolescents. The mortality and loss to treatment rates of DR-TB patients are generally high but depend on the study population, HIV status, and drugs administered, and these rates vary in different countries (7). A treatment success rate of $\geq$ 75% in DR-TB patients was achieved in only 30 of 107 countries that reported treatment outcomes to the world health organization (7).

The primary reason for poor treatment outcomes for DR-TB is the use of second-line drugs, as those used in the Khayelitsha study (1-3). These drugs are costly, poorly tolerated, suboptimally effective, and require a prolonged treatment duration (7). Second-line drug treatment for DR-TB might also increase the risk of acquired drug resistance.

DR-TB represents a substantial challenge to TB control (7). New drugs are required to shorten and simplify the current treatments for drug-sensitive TB and DR-TB, especially in HIV patients. News drugs could also help to treat latent TB infection (7).

An ideal new anti-TB drug should have a novel mode of action with bactericidal and sterilizing efficacy and should be low cost, orally dosed once daily, and well tolerated. It should demonstrate efficacy against both drug-sensitive TB and DR-TB and should not interfere with antiretroviral treatment.

No new drugs for TB treatment were approved for over 50 years until 2012. Recently, there has been considerable progress in drug development. At present, several promising new or repurposed anti-TB drugs are in clinical trials (8): bedaquiline (TMC207), an inhibitor of *Mycobacterium tuberculosis* ATP synthase; delamanid (OPC-67683) and other nitroimidazoles (PA-824 and TBA-354) that inhibit mycolic acid synthesis; sutezolid (PNU-100480), a new oxazolidinone; faropenem, an orally bioavailable β-lactam antibiotic; and other new anti-TB agents (7, 9, 10). Besides individual compounds, new combinations of drugs are being tested in several human clinical trials (7, 8). At present, 10 new or repurposed drugs are in the late phases of clinical development (7). Two trials, which are expected to be completed in 2017, are under way to evaluate new anti-TB drugs in children (7).

Novel regimens could transform therapy by shortening and simplifying the treatment of both drug-sensitive TB and DR-TB. Novel treatment regimens for DR-TB have the potential to be considerably less expensive than the currently recommended therapies.

Authors' Contributions

Vicente Ausina and Carlos Rodrigo contributed equally to this letter to the editor.

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