

## Treating drug-resistant tuberculosis infection: no more excuses

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It is hard to look at Thabos's\* spine with its serpentine twists, the result of the vertebrae being ravaged by a rifampicin-resistant strain of tuberculosis (RR-TB). The six-year old's bright eyes and quick smile belie the tragedy that has marked his young life in rural South Africa. With both his mother and younger sister dead from RR-TB and his father recently admitted to the adult ward of the same hospital where Thabo is being treated, he is part of what his neighbors call a "TB family". His mother was the first to become sick more than a year ago and it took nearly 3 months from the time her symptoms appeared until she was started on appropriate therapy. Her advanced disease meant it was too late to save her life. From her deathbed, she begged anyone who would listen to do something to spare her children from the same fate. After much fretting and consulting guidelines, health care practitioners counseled the remaining family about the signs and symptoms of TB, advising them to return to the clinic if they "had any concerns". But a dead mother cannot watch over her children and it was only when the children became critically ill that Thabo's father could miss work and take them to the clinic.

Thabo's tragic story is all-too-common, with multiple studies demonstrating the high risks of transmission of RR-TB to household members when an individual becomes sick with the disease<sup>1</sup>. Amplifying the heartbreak of it all is the fact that the subsequent illness of Thabo, his sister, and his father and all the suffering they faced as they fought for their lives could have been completely preventable if only they had been offered treatment for RR-TB infection, or what is commonly referred to as "prophylaxis" or "preventive therapy"<sup>2</sup>. Treatment of TB infection can reduce the TB incidence in contacts by 60-90%.<sup>3</sup> An estimated 19 million people in the world are infected with RR-TB strains<sup>4</sup>, and few of them are offered treatment to stop them from becoming sick. Policy makers, programs, donors and clinicians appear to be comfortable with a "watch and wait" approach. A tepid recommendation from the WHO regarding RR-TB preventive therapy has done little to spark a change in the global approach to caring for vulnerable individuals who have a well-documented exposure to RR-TB<sup>5</sup>. While there are limited data on the use of such therapy—and ongoing randomized trials that may provide additional data in the next 5 to 7 years—the risks inherent in the development of RR-TB are so high that the benefits of RR-TB preventive therapy seem obvious<sup>6</sup>.

There are many reasons given for not implementing RR-TB treatment of infection, but concerns about safety of such therapy are often cited as a key factor<sup>7</sup>. Which is why the paper by Malik and colleagues<sup>8</sup> is so important. Their study published in this issue of *Clinical Infectious Diseases* provides detailed safety information from a cohort of 172 individuals receiving RR-TB preventive therapy in Karachi, Pakistan who were started on a treatment of infection regimen that included a third-generation fluoroquinolone (primarily levofloxacin) and either ethambutol or ethionamide (ethionamide was used when ethambutol was not available) for a total of 6 months<sup>9</sup>. Individuals started on these regimens received a phone call every two weeks from a trained psychologist and were visited in-person by a community health worker monthly to assess adherence and provide support. They were also seen in the clinic every two months. A standard

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interview guide was used to assess for adverse events which were then graded using standard scales from the U.S. National Institutes of Health Division of AIDS. The primary outcome of interest was the development of any clinical adverse events. The authors also assessed self-reported rates of treatment completion.

Overall, the study found that 36 of the 172 treated contacts (21%) developed 64 adverse events, for a total 7.9 events per 100 person-months of follow up. Of note, there were no Grade 3 or 4 adverse events reported. A majority of the people who developed adverse events did so within the first month of treatment (22 of the 36 contacts, 61%) and the most common adverse events were in the gastrointestinal organ class system. Adverse events were much more common among people who received ethionamide than among those who received ethambutol as the companion drug to the fluoroquinolone (16 adverse events versus 4.4 adverse events per 100 person-months, IRR: 3.7, 95% CI: 2.2-6.3). After adjusting for possible confounders in a multivariable analysis, the risk of developing adverse events with ethionamide was two-fold higher than with ethambutol (HR: 2.2, 95% CI: 1.2-3.8). This is in line with reports from other studies that have reported significantly higher adverse events with use of ethionamide compared to ethambutol<sup>2</sup>. The authors also found that younger children (defined as < 5 years of age) appeared to tolerate treatment of RR-TB infection better than older children or adults (5-9 years HR: 2.7, 95% CI: 1.1-6.5; 10-19 years HR: 3.9, 95% CI: 1.8-8.6; > 19 years HR: 4.1, 95% CI: 1.7-9.7), although some of this may have been due to reporting bias, especially since it is a challenge to carry out symptomatic screening in younger populations. Rates of self-reported completion of treatment did not vary between individuals who developed adverse events and those who did not, and of the 172 contacts initiated on treatment for RR-TB infection, 51 (29.7%) did not complete therapy.

There are several limitations to this study, including a lack of routine laboratory screening for adverse events and a reliance on self-reporting both for adverse events and for treatment adherence. The authors wanted to replicate programmatic conditions as much as possible and in doing so may have missed laboratory abnormalities (i.e. changes in electrolytes or renal function resulting from vomiting) leading to an under-reporting of adverse events. The clinical significance of such events, however, was likely minimal. It is also unclear why the authors used TST alone to identify older children in need of preventive therapy given the limitations of this test of infection. A strength of this study is that it did not just focus on children living with HIV or under the age of five years.

In spite of its limitations, there are several important findings from the paper. First, the study shows that treatment for RR-TB infection is safe and well-tolerated and that the excessive concerns about adverse events with RR-TB preventive therapy are likely unfounded. While such concerns may on the surface appear to be about protecting people who have been exposed to RR-TB, they have enabled programs to deny persons in peril of becoming sick with this deadly infectious disease from receiving treatment that appears to decrease their chances of developing RR-TB and all its attendant risks. The study found a relatively high rate of self-reported treatment completion—although 70.3% is far from ideal—and this may have been due to the

frequent interactions with health workers in the community. Such interactions may have overcome the detrimental impact of adverse events on treatment completion.

The Malik paper, however, does call into question the use of multidrug regimens for the treatment of RR-TB infection, which could be one reason treatment completion rates were not even higher. The historical reasons for using a multi-drug RR-TB prevention regimen<sup>10</sup>—based largely on limited access to drug susceptibility testing (DST), long delays in receiving culture-based results, and fears of generating resistance to the fluoroquinolones—no longer seem relevant in the age of genotypic drug susceptibility testing. There is ample evidence supporting the effectiveness of the fluoroquinolones-based regimens against RR-TB strains<sup>11</sup>—provided those strains are not fluoroquinolone resistant in which case other agents that are safe and effective anti-tuberculosis or treating RR-TB, like delamanid, could be considered (although there is no evidence regarding the use of delamanid for preventive therapy yet). This paper also calls into question the use of ethambutol and ethionamide for the treatment of RR-TB infection. In the majority of programmatic setting – including Karachi, Pakistan where this study took place - reliable DST for ethambutol is not accessible; surveillance data demonstrates that there is a very high level of ethambutol resistance in most RR-TB strains<sup>12</sup>. Thus the use of this drug is likely to add adverse events without protection against development of RR- TB disease. Ethionamide is an anti-TB drug recently relegated by the WHO to category C for use in RR-TB treatment due to limited efficacy data and toxicity concerns. Clinical reasoning supports that such a toxic drug should not be used for healthy individuals without disease.

Many will still advocate waiting for the results of several ongoing randomized trials before implementing treatment for RR-TB on a wider scale. Unfortunately, such trials were only recently launched, and results will not be available for several years. One indicator of the great inequality in the global approach to treatment of RR-TB infection is that wealthy countries routinely provide such therapy<sup>13</sup> even in the absence of randomized controlled trial data, and it is only resource-limited countries that are asked to roll the dice with the fate of their citizens after a high-risk RR-TB exposure. The evidence presented by Malik and colleagues highlight that it is not acceptable to stand by and bear witness as RR-TB exposed individuals become sick. Continuing to delay the global roll out of treatment of RR-TB infection is a human rights violation. For Thabo, if he survives, he will carry the scars of his family's deadly brush with RR-TB forever.

Neither author has any conflicts to disclose.

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