FOUR-MONTH TREATMENTS FOR DRUG-SENSISTIVE TUBERCULOSIS

An advocacy guide for NFM4

After decades of waiting, there are finally 4-month regimens for the treatment of drug-sensitive tuberculosis (DS-TB) supported by evidence from randomized controlled trials and endorsed by the World Health Organization (WHO). One regimen is for children with non-severe forms of TB (most children have this type of TB). The other regimen is for adults and adolescents and its implementation is not limited by disease severity. Here, we consider both 4-month regimens for DS-TB and what advocates need to know to push for their urgent inclusion in National Strategic Plans and funding proposals submitted to the Global Fund under NFM4.

Four-Month "SHINE" Regimen for children with non-severe forms of DS-TB

The WHO Guidelines state that in "children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used." This is a strong recommendation based on moderate certainty of evidence. The evidence supporting this recommendation comes from the innovative and pragmatic SHINE trial, one of the only trials specifically carried out for children with clinically diagnosed TB—which is how most children are diagnosed in real-world settings. The SHINE regimen utilizes child-friendly formulations that countries are already using in the standard six-month regimen - dispersible, fixed-dose combinations of isoniazid, rifampicin with and without pyrazinamide (HRZ/HR), sometimes given with a standalone dispersible tablet of ethambutol (E). The SHINE study randomized 1,204 children from sites in Uganda, Zambia, South Africa, and India whose TB met the definition of "non-severe disease" to receive either the standard 6-month TB regimen or a 4-month version of it, with 2 months cut off of the continuation phase. The 4-month SHINE regimen was found to be non-inferior to the 6-month regimen with a 97% success rate. Non-severe disease in the study was identified using smear microscopy and chest X-ray. Ethambutol was included in the first 2 months of treatment for all children with HIV and if it was a standard part of DS-TB treatment for children in the country.

These exciting results should lead to the rapid uptake of this 4-month regimen for children, especially since no new drugs or combination tablets are required. The key, however, will be ensuring that there is a strategy to diagnose children with non-severe disease (see strategies in key arguments below). Country Programs should develop this approach and record the distribution of disease severity in children to support planning and forecasting for implementing the 4-month SHINE regimen for children with non-severe DS-TB in the future.

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Key arguments and messages to leverage in country dialogue on SHINE

Pushback: In line with WHO recommendations for diagnosing TB, our setting is not using smear microscopy anymore.

Response: Smear microscopy is not necessary to identify non-severe disease; in fact, it should not be relied on to diagnose TB in children, since smear microscopy performs poorly in children. Countries using Xpert or Xpert Ultra should consider a reading of "negative," "trace," "very low," or "low" to be the equivalent of a negative smear. The WHO operational handbook provides more implementation strategies in settings that are no longer using smear microscopy to supplement diagnosis of TB in children.

Pushback: Our setting has no or limited access to X-ray.

Response: Unlike smear microscopy, X-ray is a valuable diagnostic tool for children with TB and should be provided free of charge to all pediatric patients with possible TB. Nonetheless, use of the 4-month regimen is not dependent on X-ray. The WHO states that children can be started on the 4-month regimen provided that the following are true: 1) they do not have symptoms that would require hospitalization; 2) they do not have symptoms of extra-pulmonary TB beyond peripheral lymphadenopathy; 3) that their symptoms resolve completely by the end of the first month of treatment; and 4) provided that by the end of 4 months the child is well, including with a normal nutritional status. Treatment can be extended beyond 4 months if the on-treatment milestones are not met. For more information on distinguishing non-severe disease from severe disease, consult the WHO operational handbook.

Pushback: We don't know how to forecast for this regimen.

Response: Countries should plan to order first-line drugs for children with DS-TB as they usually do, and any extra combination HR tablets saved from the implementation of this regimen can be given for preventive therapy (3HR – three months of daily isoniazid and rifampicin is recommended by the WHO as a TB preventive treatment for children). Countries should collect information on proportions of children with non-severe disease for future forecasting.

Pushback: But what about children over 12 years old?

Response: Children over the age of 12 years who weigh more than 40kg can be treated with the 4-month, rifapentine-containing regimen described below. If they are 12-16 years old and have non-severe disease, they can receive either regimen.

Pushback: We need to replicate the SHINE trial in our population / country.

Response: The SHINE trial was a well-designed and conducted study in a heterogeneous population; it provides a high level of evidence. In fact, the WHO recommendation to use the SHINE regimen is rare in that it is a strong recommendation; this is one of the only strong recommendations in WHO Guidelines on TB treatment. Countries should not replicate the trial but rather should focus on factors that can support optimal implementation.

Four-Month Rifapentine-Containing Regimen for Adults and Adolescents with DS-TB

The WHO Guidelines state "People aged 12 years or older with drug-susceptible pulmonary TB may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (2HPMZ/2HPM). This is a conditional recommendation based on moderate certainty of evidence. The evidence supporting this WHO recommendation comes from TBTC Study 31/ACTG 5349, a randomized controlled trial carried out in 2,343 individuals from 13 different countries. The trial found that the 4-month rifapentine- and moxifloxacin-containing regimen was non-inferior to the 6-month standard regimen for DS-TB. The 4-month regimen consisted of 8 weeks of daily isoniazid, rifapentine, moxifloxacin, and pyrazinamide followed by an additional 9 weeks of daily isoniazid, rifapentine, and moxifloxacin. This regimen reported a success rate of 88% compared to 90% with the standard 6-month DS-TB regimen. The trial included people living with HIV and didn't detect any significant differences in the 4-month regimen's performance or safety in this population, although the numbers enrolled were very small at just 194 people living with HIV.

Key arguments and messages to leverage in country dialogue discussions on the 4-month rifapentine-containing regimen

Pushback: Why should we implement this regimen since it only got a conditional recommendation?

Response: The recommendation was conditional based on considerations such as feasibility, acceptability, and equity, not because of the quality of the evidence. The evidence was convincing, but the guideline committee considered other implementation factors (such as drug and regimen costs and availability of FDCs) when making the recommendation. Many of these issues, however, will be solved or overcome with increased use of the regimen.

Pushback: Rifapentine is too expensive—the 4-month rifapentine-containing regimen is more expensive than the six-month regimen.

Response: Although some of the drug costs for the rifapentine-containing regimen are higher, this is expected to be temporary, and the Global Fund is willing to pay for this regimen. The Global Fund Information Note on Tuberculosis for Allocation Period 2023–2025 encourages applicants to consider several priority interventions, including the 4-month rifapentine-containing regimen. Increased competition and volumes will bring down the price of rifapentine and the cost of the rifapentine-containing regimen. TB programs need to consider trade-offs between the temporarily higher drug costs and shorter duration of the regimen, which provides human resource and other savings and potential benefits. Improving the quality of care by shortening treatment for people with TB is a worthy investment.

Pushback: The daily pill burden for the 4-month rifapentine-containing regimen is too high.
Response: With newer rifapentine formulations, the daily pill burden for the rifapentine-containing regimen is nine tablets, which may be unacceptable to some TB patients. The excellent rate of treatment adherence observed among the 791 participants randomized to receive the rifapentine-containing regimen using formulations that required participants to take up to 13 tablets per day in the phase III trial should, however, provide some reassurance to TB programs regarding feasibility. Future fixed-dose combinations can bring the daily pill burden even closer to that for the standard six-month regimen, but programs must demonstrate willingness to implement this regimen and demand for these formulations to usher suppliers to accelerate their development and market introduction.

Pushback: What about saving the fluoroquinolone (i.e. moxifloxacin) for drug-resistant TB?
Response: People currently living with TB should be offered therapy with the most effective regimens possible and their care should not be compromised based on concerns for theoretical "future" populations. It is true that the fluoroquinolones play an important role in the treatment of rifampicin-resistant TB, but they are also key in the treatment of drug-susceptible TB. There is no evidence from the trial that rates of fluoroquinolone resistance increased with the use of this regimen, and the best way to prevent the selection of resistance is to support people on treatment and rule out resistance to drugs in the regimen prior to using it. Fixed-dose combinations may also help to prevent resistance acquisition.

Pushback: Do we have to do drug resistance testing to rifampicin and the fluoroquinolones?
Response: WHO recommends universal resistance testing for people diagnosed with TB. This applies to people regardless of which DS-TB regimen they receive. However, WHO advises that, in the absence of universal DST "… treatment selection can be guided by clinical judgement and consideration of the epidemiology of TB and its drug-resistant forms in the specific setting." Xpert cartridges (MTB/RIF or Ultra paired with XDR) can test for resistance to rifampin, isoniazid, and fluoroquinolones. The WHO consolidated guidelines module 3: diagnosis describes other approved rapid tests for detecting resistance to rifampin, isoniazid, and/or fluoroquinolones. Countries should plan to procure sufficient supplies of WHO-approved rapid tests for resistance to rifampin, isoniazid, and fluoroquinolones for all patients starting treatment for TB.

For more information on these 4-month regimens, please see Treatment Action Group's An Activist Guide to Shorter Treatment for Drug-Sensitive TB and 1/4/6x24 Community Campaign Training Materials or contact:
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