ONE-MONTH AND ONCE-WEEKLY REGIMENS FOR TUBERCULOSIS PREVENTION:

An advocacy guide for NFM4

Treatment of tuberculosis (TB) infection is necessary to end TB. An estimated one quarter of the global population is infected with TB, and 5–10% of people infected will develop active TB disease in their lifetime. Ending TB by 2030 requires going beyond finding and treating active TB disease to preventing TB disease from developing among those already living with TB infection.

If left untreated, especially among key vulnerable populations (people living with HIV, household contacts of people with TB, and children), TB infection can develop into active TB disease, the form of TB that makes people sick and is transmitted from one person to another. A range of TB preventive therapy (TPT) regimens have been proven to be safe and effective in people living with HIV (PLWH) and other groups at risk for TB disease. Yet only a very small proportion of the people who may benefit from TPT receive it. In 2018, during the United Nations High Level Meeting on TB, global leaders committed to ensuring access to TPT to at least 24 million contacts of people with active TB and 6 million people living with HIV by 2022; millions more could benefit from TPT. To date, only a fraction of the target of 30 million has been reached.

Here, we share information about safe, effective one-month and once-weekly TPT regimens that can dramatically reduce:

1) **the individual risk of developing active TB;**
2) **morbidity and mortality due to TB; and**
3) **transmission of TB to other people.**

We also share what advocates need to know to push for urgent inclusion of shortened TPT regimens in National Strategic Plans and funding proposals submitted to the Global Fund under NFM4.

The World Health Organization (WHO) Guidelines state: "The following options are recommended for the treatment of LTBI regardless of HIV status: 6 or 9 months of daily isoniazid, or a **3-month regimen of weekly rifapentine plus isoniazid**, or a **3-month regimen of daily isoniazid plus rifampicin**. (Strong recommendation, moderate to high certainty in the estimates of effect). A **1-month regimen of daily rifapentine plus isoniazid** or 4 months of daily rifampicin alone may also be offered as alternatives. (Conditional recommendation, low to moderate certainty in the estimates of effect)."

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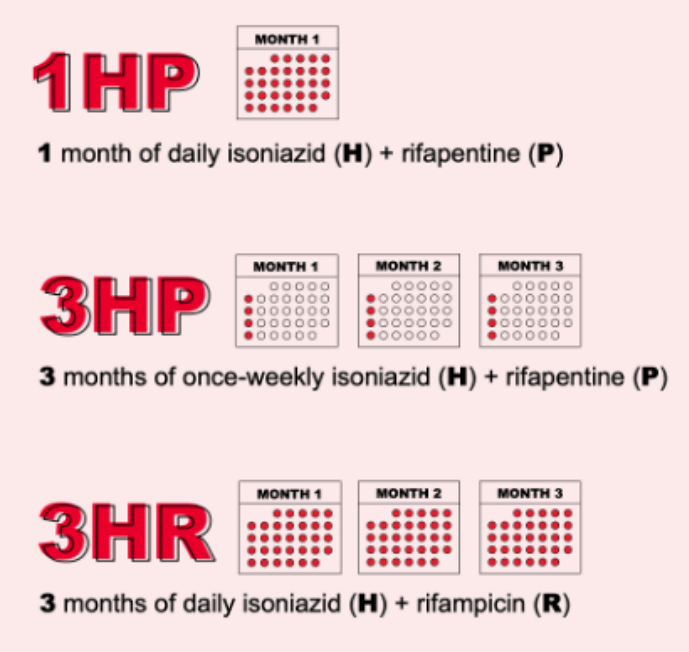
The 3-month regimen of weekly rifapentine plus isoniazid (**3HP**) and 1-month regimen of daily rifapentine plus isoniazid (**1HP**) are the "once-weekly and one-month" regimens referred to by the "1" in the 1/4/6x24 Campaign. The 3-month regimen of daily isoniazid plus rifampicin (**3HR**) is also recommended as a shorter, effective treatment, compared to 6 or 9 months of daily isoniazid, and is commonly used among children and younger adolescents.

Large, randomized, controlled clinical trials conducted across multiple countries have established the efficacy of the 3HP and 1HP regimens in preventing TB disease. The PREVENT-TB trial evaluated the efficacy of 3HP against nine months of daily isoniazid (9H). The trial enrolled over 8,000 participants, including people living with HIV, adolescents, and children as young as two years old. It found that 3HP was noninferior to (no worse than) 9H in preventing TB disease. The BRIEF-TB trial evaluated the efficacy of 1HP compared with 9H. This phase III trial enrolled 3,000 adults and adolescents living with HIV and found that 1HP was noninferior to 9H in preventing TB disease and death from either TB or from other, unknown causes. In both trials, participants taking the rifapentine-based short-course regimens were significantly more likely to complete treatment than those on 9H.

Studies necessary to inform the dose of rifapentine in young children are ongoing, but kids can still benefit from access to shorter TPT: 3HR – three-months of daily isoniazid plus rifampicin. A systematic review combined data from three studies that compared 3HR to 6H or 9H in children. It found 3HR to be as good as 6H or 9H at preventing TB in adolescents and children < 15 years old, and to have lower risk of adverse events and better adherence.

The 1HP, 3HP, 3HR regimens assume exposure to a drug-sensitive strain of TB. High-risk household contacts of people with drug-resistant TB can receive TPT based on "individualized risk assessment and sound clinical justification." For people exposed to drug-resistant TB, the WHO recommends "the regimen should be individualized and based on reliable information on the drug resistance profile of the presumed source." One possible option for people exposed to drug-resistant TB is to take six months of levofloxacin. This regimen is currently being studied in two clinical trials that will report results in 2023.



Key arguments and messages to leverage in country dialogue discussions on TPT

(adapted from An Activist's Guide to Rifapentine for the Treatment of TB Infection by Treatment Action Group)

Pushback: Taking TPT encourages the development of drug-resistant TB.

Response: There is no evidence that TPT promotes the development of drug-resistant TB. A review of six trials of rifamycin-based TPT regimens (e.g., 3HP, 3HR) found no statistically significant increased risk of rifamycin resistance in people taking these regimens compared with people taking TPT without a rifamycin or placebo. Similarly, a review of 13 IPT studies published since 1951 found no significantly increased risk of isoniazid-resistant TB among people receiving IPT versus placebo. The vast majority of drug-resistant TB arises from inadequate treatment of active TB disease. Rather than withhold TPT out of fear of drug-resistant TB, TB programs should 1) ensure all people starting TPT are first screened for active TB; 2) promote treatment completion by offering short-course TPT options like 3HP and 1HP; and 3) diagnose and treat all people with drug-resistant TB to halt its spread.

Pushback: TB programs are overwhelmed with treating active TB. TPT will divert attention and resources away from TB treatment.

Response: Treatment versus prevention is a false conflict. We must abandon the austerity mindset that tells TB programs they can do only one thing at a time; the late Paul Farmer, in whose honor this campaign was launched, referred to this as "socialization for scarcity." Denying people interventions like TPT that are proven to reduce suffering is a violation of their human rights to health and scientific progress. TB programs must do more than diagnose and treat active disease. TB programs should actively identify TB in the community (active case finding), perform contact tracing after diagnosing someone with TB, offer TPT to contacts of people with TB, and support people to complete TPT.

Pushback: Rifapentine isn't available or it's too expensive.

Response: The benefits of TPT are multifold: it avoids the cost of treatment of active TB disease, the lost wages during its treatment, and the additional sickness and death caused by transmission. With generic manufacturers recently entering the market and receiving prequalification by WHO, rifapentine products will be produced by at least 3 manufacturers. And, a single course of 1HP currently costs less than US $20 and a course of 3HP costs less than US $15. At this price point, research has shown that these regimens can be a cost-effective alternative to longer TPT regimens.

Pushback: National guidelines do not include 1HP or 3HP for TPT and/or rifapentine does not have regulatory authorization and/or is not on the national formulary in country.

Response: These treatments are the standard of care. WHO has recommended 3HP and 1HP for select populations since 2018. The 2020 WHO recommendations expanded the populations in whom these regimens are recommended. It is an inexcusable violation of the human right to science to continue withhold these regimens. These regimens should urgently be added to national guidelines and rifapentine authorized and added to national formularies. Countries can purchase rifapentine using Global Fund resources even if rifapentine is not registered with national authorities.