TAG
Treatment Action Group

Overcoming Barriers to Adopting the Four-Month Regimen

A Pathfinding Mission to Improve Access to Newer TB Treatments

Written By: Lindsay McKenna
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Background

After 40 years of using the same six-month regimen, a landmark study found that the treatment of drug-sensitive tuberculosis (TB) could be reduced to four months by replacing rifampicin with rifapentine and ethambutol with moxifloxacin.[1] For people with TB, shortening the time on treatment by a third means less time away from work or school, a faster return to life without TB, and less healthcare visits and out-of-pocket costs along the way. The World Health Organization (WHO) endorsed the four-month **"HPMZ"** regimen in 2021, but its use has been limited by pill burden, price, and tolerability concerns.[2,3]

What does HPMZ stand for?

Each letter represents a drug in the regimen:

H = isoniazid
P = rifapentine
M = moxifloxacin
Z = pyrazinamide

In its prioritization guidance for TB in grant cycle eight (GC8), the Global Fund signaled its willingness to support the use of the four-month regimen in "specific populations where programmatic needs justify the additional costs compared with the standard six-month regimen".[4] The concurrence of the GC8 application window with the availability of new fixed-dose combination tablets (more on this below) presents National TB Programs (NTPs) with a fresh opportunity to introduce the four-month regimen.

Here we review barriers to the adoption of the four-month regimen and how they might be addressed and offer a narrative framework communities can use to advocate for the regimen in GC8 and beyond.

Overcoming Barriers to Adoption

Access to the six-month regimen is well established by decades of use, the availability of fixed-dose combination (FDC) tablets, high and predictable volumes, and multiple generic manufacturers supplying the global market at affordable prices. Additionally, NTPs, clinicians, and other healthcare workers are comfortable and familiar with the six-month regimen.

Upending any long-standing practice is difficult, but the initial introduction of the four-month regimen was further challenged by a lack of available fit-for-purpose formulations. The **pill burden** with the four-month regimen was six to nine pills per day, compared to just four pills per day with the six-month regimen.

Excitingly, in 2026, FDCs of HPMZ will be available on the global market, and the pill burden for the four-month regimen will be equivalent to that of the six-month regimen.

Figure 1. New fixed-dose combinations address pill burden

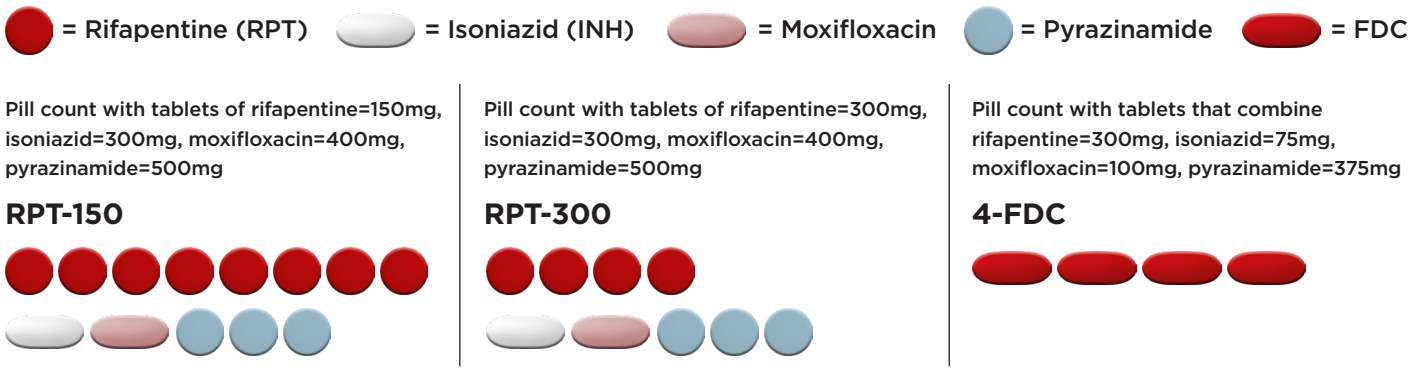

Figure 1 is adapted from *An Activist's Guide to Shorter Treatment for Drug-Sensitive Tuberculosis* (Figure 5), available here.

Another issue is the **price** of the medications. The new FDCs are expected to cost three to four times the US$43 that governments currently pay for the six-month regimen.[5] Most high-TB-burden countries buy medicines for drug-sensitive TB using domestic funds. The dramatic reduction in foreign aid spending globally is putting more pressure on domestic health budgets in high-TB-burden countries. This leaves little room for introducing more costly medications within existing budgets.

However, while the cost of the medication is higher, the shorter duration of the four-month regimen is expected to generate savings for programs and people receiving TB care.[6]

Modeling suggests that the HPMZ regimen could already be considered cost effective in some settings (see Figure 2).[7]

Figure 2. Price thresholds for 4HPMZ cost neutrality and cost effectiveness in India, Philippines, and South Africa

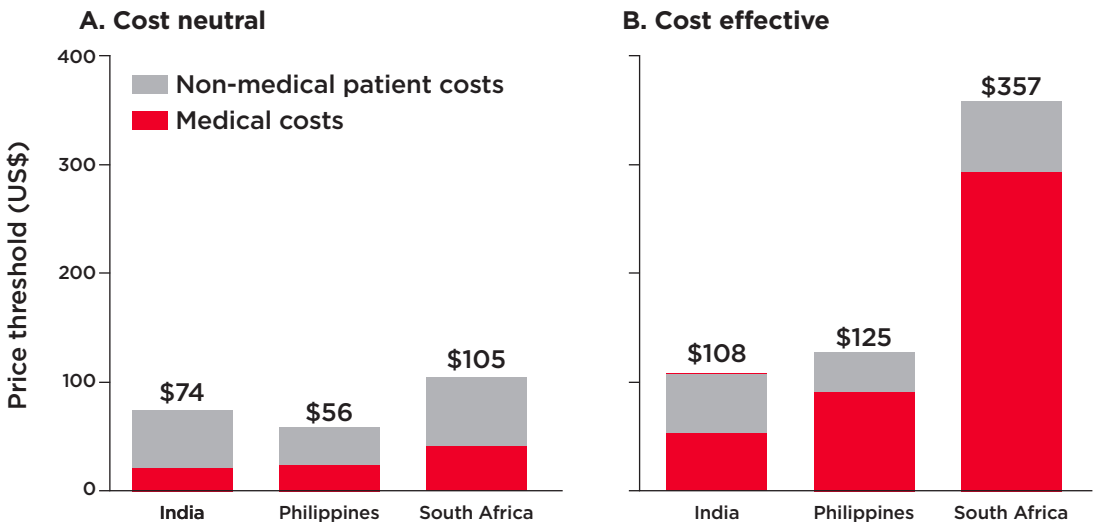

Figure 2 is adapted from "Scientific Advances and the End of Tuberculosis: a Report From the *Lancet* Commission on Tuberculosis" (Figure 2), available here.

Programmatic experience implementing the four-month regimen is still in its early days. The few data published from these experiences raise concerns about **tolerability**, especially in older people.[8,9] No regimen is perfect, but clinicians are used to the side effects of the six-month regimen and know how to handle them, for example the fatigue, nausea, vomiting, and rash that people taking TB treatment experience.[10,11] Gastrointestinal upset and liver toxicity commonly reported among people on the six-month regimen have also been reported among people treated with the four-month regimen.[12,13] The four-month regimen has its own tolerability issues, and because it is newer, they may feel different and less familiar to TB programs and clinicians, and implementation support tools with practical guidance on how to manage side effects and issues like missed doses may not exist yet. The clinical trial found slightly higher rates of hyperbilirubinemia, a specific type of liver abnormality that can result in jaundice, in people taking the four-month regimen (see Figure 3). Flu-like hypersensitivity reactions have been observed with rifapentine (specifically with once-weekly rifapentine and isoniazid administered for TB prevention) but were reassuringly uncommon in the clinical trial of the four-month treatment regimen.[14]

Figure 3. A side-by-side comparison of the four- and six-month regimens

Duration	Four months	Six months
Drug components	isoniazid, rifapentine, moxifloxacin pyrazinamide	isoniazid, rifampicin, pyrazinamide, ethambutol
Age cut-off	12 years old	None; all ages eligible
Pill burden	4 pills per day	4 pills per day
Rate of treatment success	84.5%	85.4%
Rate of treatment discontinuation	7.0%	7.9%
Rate of severe adverse events (grade 3 or higher)	18.8%	19.3%
Rate of elevated liver enzymes (grade 3 or higher)	1.9%	2.9%
Rate of elevated bilirubin levels (grade 3 or higher)	3.3%	1.0%
Rate of gastrointestinal toxicity (grade 3 or higher)*	0.2%	0.4%
Rate of hypersensitivity reaction (grade 3 or higher)**	0.2%	0%

Rates of treatment success and adverse events are from the phase III trial, Study 31/A5349, ClinicalTrials.gov number **NCT02410772**.[15]

*Reported in supplementary appendix as gastrointestinal disorders.

**Reported in supplementary appendix as adverse drug reactions.

Side effects of the four-month regimen are not necessarily worse than those associated with the six-month regimen. But some of them are different and less familiar to TB programs and clinicians. Parallels can be drawn to program and clinician hesitancy with the initial introduction of new medicines for drug-resistant TB. While bedaquiline was generally safer and better tolerated than existing second-line medicines, its QT-prolonging potential (affecting the heart rhythm) and the lack of prior TB program experience conducting electrocardiograms (EKGs) to monitor for this side effect dramatically slowed implementation and access. Programs and clinicians tend to prefer "the devil [they] know" – regimens with well-known and commonly managed side effects versus those that are less familiar and may require new systems to monitor for and address them.

Conclusion

The process of introducing something new for the treatment of drug-sensitive TB is a pathfinding opportunity against inertia and other barriers that may hamper access to future innovations in TB treatment. ***Conditioning the program muscles that support change will be critical to accelerating the introduction of the next generation of TB treatment innovations like long-acting TB medications.***

As you help your country coordinating mechanism (CCM) write its Global Fund proposal for GC8, ask that funding be set aside to introduce the four-month regimen among some specific populations, like people without underlying liver disease not available to complete treatment within six months or at risk for not completing for other reasons. Make sure to build in training and other resources necessary to manage side-effects and other anticipated implementation concerns. Leveraging Global Fund funding to introduce the four-month regimen will diffuse scientific benefits to the communities that NTPs serve and help them to prepare in practice for what comes out of the research and development pipeline next.

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