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Elizabeth Glaser Pediatric AIDS Foundation | Unitaid Innovation in Global Health | IMPAACT4TB PREVENTING TB TO END TB

Catalyzing Pediatric Tuberculosis Innovations (CaP TB):
Short-course Treatment Regimens to Prevent TB: 3HP and 3RH

The current approach to the treatment of TB infection has failed. We can and must do better.

The Context

Latent TB infection (LTBI) is characterized by the presence of immune responses to *Mycobacterium tuberculosis* (M. *tb*) infection without clinical evidence of active tuberculosis (TB)[i]. Infection by M. tb remains difficult to diagnose, which is why the true global burden is unknown. However, it is estimated that approximately one-fourth of the world's population (about 1.7 billion people) have LTBI[ii].

The World Health Organization's (WHO) 2015 End TB Strategy recognized that people with LTBI are an important, but often neglected, reservoir of the disease. Prevention of new M. *tb* infections and their progression to active TB disease is critical in order to reduce the burden of the disease and resulting deaths, as well as to achieve the UN high-level meeting (UNHLM) on TB and End TB Strategy targets for 2022 and 2030/2035.

Approximately 5-15% of adults with LTBI develop active TB disease during their life.[iii]

Provision of preventive treatment has proven itself an effective intervention to avert the development of active TB disease, with efficacy ranging from 60% to 90%.[iv]

The likelihood of progression of TB infection to active disease depends on bacterial, host, and environmental factors.[v] In high TB prevalence and resource-limited settings, the WHO has defined four target populations for preventive treatment: (1) people living with HIV, (2) children <5 years of age, who are household contacts of bacteriologically confirmed pulmonary TB cases, (3) all household contacts of bacteriologically confirmed pulmonary TB cases with TB infection and (4) clinical risk groups (such as patients initiating anti-tumor necrosis factor [TNF] treatment, receiving dialysis, preparing for solid organ or bone marrow transplants and those with silicosis).[vi-ix]

HIV infection is the strongest risk factor associated with the development of active TB, with up to 40% of patients progressing to TB disease after exposure.[x] Treatment of LTBI in people living with HIV (PLHIV) reduces the risk of TB disease development by up to 35%[xi] and plays a synergistic role in further risk reduction when used with antiretroviral therapy (ART).

Children <5 years old are a particularly vulnerable population due to their higher risk of progressing to active TB disease and their greater risk of developing more severe forms of TB (including TB meningitis and disseminated TB), in addition to the difficulty of confirming the diagnosis, given the paucibacillary nature of their disease. Together, these factors result in high TB-associated child morbidity and mortality.[xii, xiii]

As diagnosing active TB disease in young children is a challenge, averting new pediatric TB cases by delivering preventive treatment is of strategic importance to decrease the overall burden of pediatric TB disease.

> LTBI testing by tuberculin skin test (TST) or interferon-gamma release assay (IGRA) is NOT required prior to initiation of contacts <5 years old and PLHIV on TB preventive treatment (TPT) considering the very high risk of acquiring TB infection and progressing to disease.

The WHO End TB Strategy Targets for TB Preventive Treatment (TPT) and Current Gaps

In order to monitor the progress on delivery of TPT, the End TB Strategy has set a specific global targets which call for 90% coverage of LTBI treatment among PLHIV and household

contacts by 2035[xiv]. The UNHLM on TB, in September 2018, has further emphasized the need to strengthen implementation of preventive therapy and called for 30 million people, including 4 million children <5 years of age, to receive TPT by 2022.[xv]

Despite the fact that TPT has been available since 1960s and in spite of evidence demonstrating its effectiveness and recent emphasis on the importance of LTBI management (included in the End TB Strategy), uptake and scale-up have been slow and critical gaps remain in achieving global targets. In 2017, coverage of TPT among patients newly-enrolled in HIV care varied significantly among high TB and TB/HIV burden countries, averaging 36% (range 1-53%) among the few that reported it.[ix]

The gap in TPT provision to children is even more concerning. Globally, about 292,000 children <5 years of age started TPT in 2017; this represents only 23% of the 1.3 million children <5 years old estimated to be eligible for treatment.[xvi]

Key Challenges in Scaling-up TPT

Until recently, 6 months isoniazid was the more widely used regimen for TPT (isoniazid preventive treatment or IPT). However, uptake has been limited by the following challenges and concerns, perceived by health care providers[ix,xix]:

- Poor ability to screen and reliably exclude active TB disease prior to initiation of preventive treatment
- Management of side effects with prolonged IPT and poor adherence
- Increased workload and additional recording and reporting

In 2018, after an exhaustive review of available evidence on the use of different regimens for preventive treatment, the WHO published updated guidelines that recommend TPT options which may help overcome several perceived or experienced challenges. The new guidelines include the use of combination therapies with isoniazid and rifamycins as an alternative to 6 or 9 months IPT. Use of a regimen including isoniazid (INH) and rifapentine (RPT) - also known as the 3HP regimen - has been recommended for adults and for children >2 years of age; while rifampicin (RIF) and isoniazid for 3 months has been recommended for children <15 years of age (also known the 3RH regimen).[ix]

3HP and 3RH: Benefits and Uses

3HP is a short-course TPT regimen that combines two antibiotics active against TB, INH and RPT. 3HP is taken once a week for 12 weeks (12 doses in 3 months). It has proven effective and safe for PLHIV and their household contacts >2 years old.

3RH is also a short-course TPT regimen that combines two antibiotics active against TB, INH and RIF. 3RH is taken once daily, for 12 weeks (90 doses in 3 months). The WHO LTBI guidance document released in early 2018 describes the 3RH regimen as an alternative option to 6H, for treatment of LTBI in children and adolescents <15 years of age, in countries with high TB incidence.[ix]

It is important to note that RIF and RPT are potent inducers of the cytochrome P450 oxidase system. Their administration may affect the pharmacokinetics of other drugs including some antiretrovirals (ARVs). For people living with HIV/AIDS, both 3HP and 3RH are safe to give with efavirenz-based ART without any dosing adjustments. In adults, 3HP is safe to give with dolutegravir-based ART without any dosing adjustment. Both 3HP and 3RH reduce lopinavir-ritonavir and nevirapine levels. Thus, dosing adjustments are needed. So, neither can be used together with lopinavir-ritonavir or nevirapine. As a consequence, for HIV-infected children taking lopinavir-ritonavir, nevirapine, or dolutegravir, the preferred TPT regimen is represented by 6H (preferably with the dispersible formulation), which does not require dose adjustment.

Table 1 provides an overview of key characteristics of the 3HP and 3RH regimens and table 2 provides an overview of key advantages and main limitations of 3HP and 3RH regimens, compared to IPT.

Table 1: Overview of key characteristics of 3HP and 3RH regimens

Regimen	Dosing (mg/kg/day)	Frequency	Duration of treatment	Target population	Availability of FDC	Availability of pediatric dispersible formulation
3HP	Adult: 900mg INH/ 900mg RPT Weight-banded pediatric dosing for 10 kg – 40 kg	Once weekly	12 weeks 12 doses	Adults and children ≥2 years old	NO (pending approval in 2019)	NO (a pediatric FDC has been developed by Sanofi and is under evaluation)
3RH	Weight-banded pediatric dosing. Preventive treatment requires same dosing as recommended for treatment of drug-sensitive TB: < 25kg: Pediatric FDC (RH 75/50mg) > 25 kg: adult FDC (RH)[xix]	Once daily	12 weeks 90 doses	Children of all ages	YES	YES (RH 75/50mg)

Table 2: Advantages and limitations of 3RH and 3HP regimens

Regimen	Improved adherence and increased treatment completion rate compared to isoniazid preventive treatment (IPT)	Safety and adverse events compared to isonizid preventive treatment (IPT)	Compatibility with ART regimen	Cost (USD)
3HP	YES[xx,xxi]	No significant hepatotoxicity. Safety profile similar to that of IPT regimen[xxiii,xxiv]	LIMITED No dose adjustments required for efavirenz and dolutegravir containing regimen For individuals taking lopinavir-ritonavir, or nevirapine, use of the 6H regimen, which does not require dose adjustment, is preferred.	ADULT: US$ 48 per treatment course CHILDREN US$ 27 (treatment course for a 15kg child: 8 tablets/ week, 3 months (12 doses) (cost calculated considering single formulations of RPT + INH) FDC Price- Not yet available Generic single formulation Price- Not Available Yet
3RH	YES[xxiv, xxv, xxvi]	No significant hepatotoxicity Safety profile similar to that of IPT regimen[xxvii,xxviii, xxviv]	LIMITED No dose adjustments required for efavirenz containing regimen For individuals taking lopinavir-ritonavir, dolutegravir or nevirapine, use of the 6H regimen is preferred	CHILDREN: US$ 9 per treatment course (treatment course for a 15 Kg child: 3 tablets/day, 30 days/ month, 3 months)[1]

Why Switch from the 6 or 9 month IPT to Short-course Regimens (3HP or 3RH) for TPT?

As indicated in Table 1 and 2 above, the short-course regimens 3HP and 3RH offer clear advantages in terms of improved adherence and completion rates due to the shorter duration of treatment and the child-friendliness, fixed-dose combination (FDC) treatment option available for 3RH.

Compared to the standard IPT regimen, the 3HP and 3RH regimens offer numerous benefits for patients requiring TPT, clinicians and programs. Their introduction will be needed if the UNHLM and End TB Strategy targets are to be met.

Why Consider the 3HP Regimen?

Studies have shown 3HP to be as effective as IPT in preventing progression from TB infection to active TB. In addition, the 3HP regimen is simpler, shorter and requires fewer doses for patients. Evidence shows that people taking 3HP are more likely to complete their course of treatment than those on the longer IPT regimen.[xxx, xxxi]

Compared to IPT, administering a shorter, weekly dose limits the burden on TB and HIV programs. Modeling studies have shown that the 3HP regimen could be cost-effective, thereby reducing the economic burden of TB control efforts.[xxxii]

The shorter duration of treatment with 3HP and the higher rates of treatment completion make it more cost-effective in the long-term. Currently, the cost of RPT drives a higher short-term cost, which will be reduced through the introduction of generic manufacturers over 4 years. This is the principal objective of the IMPAACT4TB project. In the last year alone, the cost of a patient course for RPT decreased from US$ 72 to US$ 46 – a 40% reduction.

Table 3. Pros and Cons of TPT Regimen

Drug Regimen	Pros and Cons
3HP	✓ Shorter regimen, better adherence, cost-effective.
	✗ Potential drug-drug interactions with some antiretroviral drugs (e.g lopinavir-ritonavir and nevirapine), higher cost, FDC and child-friendly formulation still in development phase
3RH (for pediatric population)	✓ Shorter regimen, better adherence, availability of a child-friendly FDC, wide availability
	✗ Potential drug-drug interactions with some ARV (lopinavir-ritonavir, dolutegravir, nevirapine), marginal price increase compared to IPT
6 or 9 months INH[1]	✓ Low cost, effective, compatible with most ART regimens
	✗ Poor adherence, low uptake, more side effects than rifamycin-based regimens (3HP and 3RH)

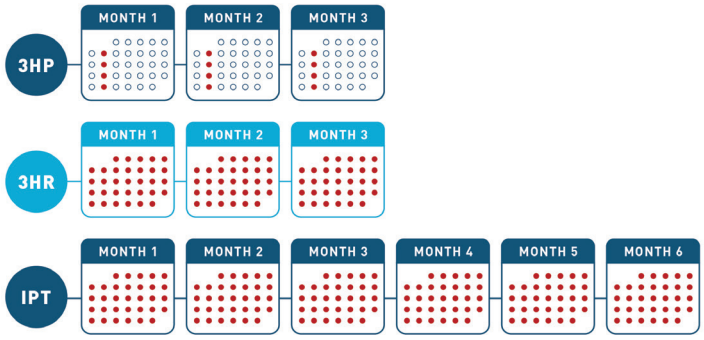
[1] As a comparison, the costs of TPT for children for a 6 months course of INH is US$ 4.60 with the film coated tablet, and US$ 31 with the new dispersible INH (calculated considering a dose of 13mg/kg/ day, 2 tablets/day, 30 days/month, 6 months. Price source: GDF, available at http://www.stoptb.org/gdf/drugsupply/pc3.asp?PID=56 and http://www.stoptb.org/gdf/drugsupply/pc3.asp?PID=1062)"

The results of a study of 3HP in children aged 2 to 17 years indicated that it is well-tolerated and as effective as 9 months of daily isoniazid, only with higher completion rates.[xxxiv]

There are no data available on the safety or dosing of RPT in children <2 years of age — the group with the highest risk of progression to active TB disease following TB infection.

Sanofi, the sole manufacturer of RPT, has developed a pediatric FDC of 3HP for trial purposes. This formulation is currently undergoing evaluation and it is not yet commercially available. The IMPAACT4TB project is supporting research to establish the safety and efficacy of this product in children with and without HIV, to determine its safety and dosing among children <2 years. Furthermore, in project countries, 3HP will be rolled-out to children >2 years who can tolerate crushed pills, to further understand the path to wider uptake of this regimen in children.

For adults: 12 doses of HP over 3 months vs a minimum of 180 doses (6 months) of IPT. 3HP entails fewer doses, shorter duration, fewer adverse events, better adherence.



Why Consider the 3RH Regimen for Children?

The shorter 3RH regimen for children offers benefits for patients and health systems. Several studies have demonstrated that 3RH is better tolerated, with fewer side effects and better adherence than 6 or 9 months of isoniazid alone.[xxxiii]

A pediatric FDC that is both dispersible and palatable is currently available for the 3RH regimen, while RPT is not yet available in a child-friendly formulation and dosing is not yet known for children <2 years of age.

The pediatric dispersible FDC for RH is available through the Global Drug Facility (GDF) and has already been introduced in countries for the treatment of drug-sensitive TB. The cost of a full course preventive treatment (3 months, 28 doses/month) is about US$ 8.40.[2] This estimate is calculated with a child in the 12-15 kg weight band in mind. The 3RH regimen offers a significant improvement regarding LTBI treatment for children while 3HP study results and the development of a child-friendly formulation are pending.

For children: 3 months of RH offers a shorter, better tolerated, child-friendly option while awaiting child-friendly formulations and data on 3HP in children

[2] http://www.stoptb.org/gdf/drugsupply/pc3.asp?PID=977

Strategy to Introduce Shorter Regimen for TPT

Introduction of shorter regimens can offer several advantages at both the clinical and programmatic levels. In the short term, the availability of a pediatric FDC for RH makes the 3RH regimen the most feasible and pragmatic option for delivery of TPT to most of the pediatric population.

Once a child-friendly and affordable FDC for HP becomes available, 3HP can become the preferred regimen for TPT across all ages. This will significantly facilitate delivery of TPT and support a family-centered approach to LTBI management.

The proposed strategy for introduction of short-course TPT regimens that countries can consider in order to support an effective scale-up of LTBI management is outlined in Table 3 on the following page.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Short-term strategies for roll-out of shorter TPT regimens	
Adults	**Children (0-14 years)**
Criteria for treatment: • Newly screened PLHIV on ART who have not yet received any TB preventive treatment and are not on nevirapine or lopinavir-based ART • All contacts of TB cases including PLHIV who may have received IPT in the past but are new contacts of a TB case • Newly diagnosed PLHIV not opting for ART immediately	**Criteria for treatment:** • Contacts of TB cases <5 years of age • Children of all ages who are PLHIV and who are not receiving lopinavir or nevirapine-based ART
Treatment option: 3HP	**Treatment options:** *Children < 25 kg :* • 3HR for children <25kg (including children < 2years of age) due to the availability of a child-friendly FDC in country (same formulation as the one used for the continuation phase of TB treatment) *Children > 25 Kg:* • Can receive 3HP if this regimen is being rolled out in country for the adult population • Can receive RH (using the adult RH FDC)
Adults on lopinavir-ritonavir or nevirapine ART • Continue the use of 6 or 9 month INH	**Children on ART or nevirapine-prophylaxis** • Continue use of 6 or 9 month INH for children on lopinavir/ritonavir, dolutegravir, or nevirapine-based ART or who are on nevirapine prophylaxis
Medium /long-term strategies for roll-out of shorter TPT regimens	
Adults	**Children (0-14 years)**
Prioritize introduction and use of 3HP regimen where all PLHIV and family members identified through contact investigation (regardless of HIV status) can access the same regimen	**Children < 25 kg** Switch to use of 3HP regimen in all children once: • Data can inform dosing schedule, safety and tolerability in children < 2 years • A child-friendly, affordable FDC is available Children on lopinavir/ritonavir, dolutegravir or nevirapine-based ART or prophylaxis should continue INH until further data on safety and dosage is available

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