



AN ACTIVIST'S GUIDE TO

RIFAPENTINE

FOR THE TREATMENT OF TB INFECTION

Updated April 2020

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I. INTRODUCTION AND BACKGROUND

This guide summarizes information on rifapentine, an important drug for treating **tuberculosis (TB) infection**. Treatment of TB infection is referred to as TB preventive therapy (TPT) and is one of the most powerful ways to prevent TB. If left untreated, TB infection can develop into active TB disease, the form of TB that makes people sick and is capable of being transmitted from one person to another. Yet only a very small proportion of the people who may benefit from TPT receive it.

Rifapentine belongs to a class of drugs called **rifamycins** and is the backbone of newer short-course TPT. When combined with a second TB drug, isoniazid, rifapentine forms the **3HP** regimen (taken once weekly for 12 weeks) and the **1HP** regimen (taken once a day for one month). The 3HP and 1HP regimens offer shorter alternatives to the older standard of care, called isoniazid preventive therapy (IPT), in which people take isoniazid every day for between six and 36 months.

TPT has two major goals: 1) protect people who are already infected with the TB bacterium from falling ill with active TB disease, and 2) shield people who are uninfected but at risk of TB exposure from getting infected in the first place. Preventive therapy is one of the best ways to keep individuals and families safe from TB, which in turn helps communities become—and remain—TB free.

We wrote this guide to provide people at risk of TB, as well as their family members and caregivers, with the knowledge they need to make an informed choice about whether to take rifapentine-based TPT. For this choice to be meaningful, rifapentine must be available, accessible, and affordable, so this guide suggests actions people can take to promote equitable access to rifapentine. We need to give more people access to newer TPT regimens like 3HP and 1HP if we hope to end TB in our families and communities.

II. THE EFFICACY OF RIFAPENTINE-BASED TB PREVENTIVE THERAPY

Large, multicountry clinical trials have established the efficacy of the 3HP and 1HP regimens in preventing TB disease. PREVENT-TB, a phase III clinical trial conducted by the U.S. Centers for Disease Control and Prevention, evaluated the efficacy of 3HP against nine months of daily isoniazid (9H). The trial enrolled over 8000 participants and found that

KEY TERMS

TB INFECTION, sometimes referred to as latent TB infection (LTBI), is caused by infection with *Mycobacterium tuberculosis*.

RIFAMYCINS are a class of antibiotics that includes the drugs rifampicin, rifapentine, and rifabutin. They share a similar chemical structure and method of action.

KNOW YOUR TPT REGIMENS:

When abbreviating TB drug regimens, **H** = isoniazid; **P** = rifapentine; and **R** = rifampicin (sometimes called rifampin).

The World Health Organization recommends the following TPT regimens:

- **3HP** = 12 weeks of isoniazid and rifapentine taken together once a week
- **1HP** = one month of isoniazid and rifapentine taken together once a day
- **3HR** = three months of isoniazid and rifampicin taken together once a day
- **4R** = four months of daily rifampicin
- **IPT** = isoniazid taken daily for six, nine, 12, or up to 36 months

3HP was **noninferior** to (no worse than) 9H in preventing TB disease.¹ Participants taking 3HP were more likely to complete treatment than those on 9H.

PREVENT-TB also assessed the effectiveness of 3HP in nearly 400 people living with HIV (PLHIV) and over 900 adolescents and children as young as two years old. Among PLHIV, 3HP was noninferior to 9H in preventing TB disease, and people taking 3HP were more likely to complete treatment.² Based on when the study started, participants with HIV in the trial were not on antiretroviral therapy (ART). Today, TPT should always be offered together with ART (read “*What about people living with HIV?*” below.) Children taking 3HP in the PREVENT-TB study also did well and were more likely to complete treatment than those receiving 9H.³

The BRIEF-TB trial, conducted by the AIDS Clinical Trials Group at the U.S. National Institutes of Health (NIH), evaluated the efficacy of 1HP compared with 9H. This phase III trial enrolled 3000 adults living with HIV and assessed safety, treatment completion, and efficacy over three years of follow-up.⁴ The trial found that 1HP was noninferior to 9H in preventing TB and death from either TB or unknown cause. Participants taking 1HP were significantly more likely to complete treatment than those on 9H. Further studies to assess whether 1HP is effective in other populations, including HIV-negative people, children, and pregnant women, are planned.

3HP and 1HP look efficacious in clinical trials, but do they work in the real world? Yes! Programmatic experience with 3HP in the **United States**, Australia, Taiwan, Pakistan, and other places indicates that the regimen is safe, is well accepted by most people who take it, and has higher completion rates than IPT.^{5,6} Evaluations of 1HP among PLHIV in program settings will begin soon.

III. THE SAFETY OF RIFAPENTINE-BASED TB PREVENTIVE THERAPY

Rifapentine-based TPT is safe and well tolerated. Across studies, 3HP appears to pose less risk of **hepatotoxicity** than IPT, and the BRIEF-TB trial suggests 1HP is also less hepatotoxic.^{7,8} A systematic review of 15 studies comparing 3HP to other TPT regimens (mostly 9H) found that 3HP has “equal safety and effectiveness” to other preventive regimens.⁹ A separate analysis looking at the efficacy and toxicity of various TPT regimens reached similar conclusions about the safety and efficacy of 3HP.¹⁰ Compared with IPT, rifamycin-based TPT may carry a higher risk of **hematologic toxicity**.

Overall, 3HP is safe enough for people to take themselves (self-administration). Some programs recommend that people taking 3HP have a monthly visit with a health care worker to identify any adverse events and receive adherence support.¹¹

Rare adverse events called hypersensitivity reactions have been reported in both clinical trials and programmatic use of rifapentine.¹² These reactions are often characterized by **flu-like symptoms**. There are some reports of people experiencing **hypotension** or **syncope** after taking 3HP. Hypersensitivity episodes are uncommon and usually resolve quickly after medication is stopped without any long-term effects. In some

NONINFERIORITY means that the intervention is no worse than the control by a prespecified amount (called a noninferiority margin).

One study of 3HP in **16 U.S. TB PROGRAMS** reported a higher treatment completion rate than observed in the PREVENT-TB trial (see Sandul A, et al.).

HEPATOTOXICITY, or liver toxicity, occurs when drugs or other chemicals damage the liver.

HEMATOLOGIC TOXICITIES are those that affect the blood and its components (e.g., anemia).

FLU-LIKE SYMPTOMS can include fever, chills, headaches, dizziness, and fatigue.

HYPOTENSION is abnormally low blood pressure.

SYNCOPE is a temporary loss of consciousness due to a fall in blood pressure.

cases, people experiencing hypersensitivity have been hospitalized. In the PREVENT-TB trial, 3.5% of participants who received 3HP had a hypersensitivity reaction, with many occurring several hours after taking the third 3HP dose (i.e., in the third week of the 12-week treatment course).¹³

Hypersensitivity may be linked to the intermittent, once-weekly dosing schedule of 3HP.¹⁴ The cause of these reactions is unknown—they could be due to rifapentine, isoniazid, or the combination of the two. Several TB drugs can cause hypersensitivity. Flu-like symptoms have been observed with intermittent, high-dose rifampicin and, less commonly, with isoniazid. People taking 3HP should be informed about the small risk of experiencing hypersensitivity and taught to recognize its signs (flu-like symptoms) and contact a health care provider immediately if experiencing them.

Like other rifamycin class drugs, rifapentine interacts with many medications for other conditions. In addition, there are some important things to consider when using 3HP in special populations such as pregnant individuals, children, and people who use drugs.

What about people living with HIV? Rifapentine is safe to use in PLHIV, but interactions between rifapentine and certain antiretrovirals must be managed (or avoided altogether either by using other TPT options or by switching antiretroviral regimens). 3HP is safe to use with efavirenz-, raltegravir-, and dolutegravir-based ART. Many countries are transitioning from efavirenz- to dolutegravir-based first-line therapy (i.e., the TLD regimen composed of dolutegravir, lamivudine, and tenofovir disoproxil fumarate). A recent study assessed the safety and **pharmacokinetics (PK)** of giving 3HP with dolutegravir (see box). Importantly, PLHIV in areas where malaria or severe bacterial infections are common should receive 3HP together with **cotrimoxazole**.

What about children and young people? 3HP can be given to adolescents and children as young as two years of age. A study looking at safety and optimal dosing of 3HP in children under two years with and without HIV has started in South Africa and is expected to report results in 2021. The study is using a child-friendly formulation of 3HP developed by Sanofi that dissolves in water and tastes like mango. While waiting for the results of this study, infants and children under two years who need TPT can receive either three months of daily isoniazid and rifampicin (3HR) or six months of daily isoniazid (6H). Kids with HIV on efavirenz-based ART can take 3HR, which is available in a child-friendly, water-dispersible formulation. 6H is preferred for children with HIV taking nevirapine, lopinavir-ritonavir, or dolutegravir because it does not require ARV dose adjustments. Isoniazid also comes in a child-friendly dispersible tablet. Until Sanofi's pediatric 3HP product becomes available, even children over two years may prefer 3HR or 6H if they have trouble swallowing pills, due to the 3HP regimen's high pill burden (see "*Rifapentine Dosing Information*" below).

What about pregnant individuals? Pregnancy increases the risk of TB infection progressing to active TB disease, making pregnant individuals a priority population for TPT. Rifapentine is currently not recommended for use in individuals who are pregnant due to a lack of data on the safety of giving rifapentine during pregnancy. Research is starting to fill this critical knowledge gap. In March 2020, investigators from the **IMPAACT** Network presented results of a study showing that pregnant people can receive

PHARMACOKINETICS involves studying what the body does to a drug by looking at things like how a drug moves throughout the body or how the concentration and distribution of a drug changes across space and time.

COTRIMOXAZOLE is an antibiotic that consists of two drugs—trimethoprim and sulfamethoxazole—and is taken by PLHIV to prevent serious bacterial infections such as pneumonia or toxoplasmosis.

The International Maternal Pediatric Adolescent AIDS Clinical Trials (**IMPAACT**) Network at the U.S. NIH is largest clinical trials network devoted to studying HIV and TB in children, adolescents, and pregnant women.

the same dose of rifapentine as non-pregnant people.¹⁵ The study looked at drug exposure levels (measured in blood) and how quickly women clear rifapentine from their bodies during pregnancy and after delivery (postpartum), and assessed whether these differ between women with and without HIV. Pregnant women with HIV on efavirenz-based ART cleared rifapentine faster than pregnant women without HIV, resulting in drug exposures that were 30 percent lower. Importantly, these lower drug exposures remained within the clinically effective range of the drug. Consequently, neither pregnancy status nor HIV status requires a rifapentine dose change.

The study described above was not designed to thoroughly test the safety of giving rifapentine during pregnancy. A randomized clinical trial to determine the optimal timing and safety of 3HP and 1HP during pregnancy is necessary before issuing a broad recommendation that pregnant individuals can safely take rifapentine-based TPT. Until then, pregnant people at risk of TB can take IPT, though

SPOTLIGHT: GIVING 3HP WITH DOLUTEGRAVIR-BASED HIV TREATMENT

In March 2019, investigators from the Johns Hopkins Center for TB Research and the Aurum Institute presented results from a phase I/II study assessing the safety and pharmacokinetics of coadministering 3HP and dolutegravir. The study, which was named DOLPHIN, enrolled 60 adults with HIV who were given dolutegravir-based ART (TLD) and 3HP.

The DOLPHIN study sought to answer two questions: 1) Is it safe to take 3HP with dolutegravir-based ART? 2) If yes, does the dose of dolutegravir need to be adjusted? Answering these questions is important because dolutegravir and 3HP each have advantages over alternative ART and TPT regimens, and so many HIV and TB programs will want to use them together. At the same time, rifamycins such as rifapentine can speed up the body's metabolism of ARVs, including dolutegravir, which could require increasing the dose of dolutegravir to maintain viral suppression of HIV while taking the two treatments together.

1. Safety results: Coadministering 3HP with dolutegravir was safe, with very few adverse events reported. There were no deaths. All 60 participants completed a full course of 3HP.
2. Pharmacokinetic results: Rifapentine reduced dolutegravir concentrations, but not by a clinically meaningful amount, so all participants received the standard dose of dolutegravir (50 mg once a day) without adjustment. All participants saw their HIV remain virally suppressed while taking 3HP. One participant had a detectable HIV viral load reading, but this occurred four weeks after completing 3HP and was judged to be unrelated to rifapentine.

Main takeaway: 3HP can be safely used with dolutegravir-based ART without adjusting dolutegravir doses. With these results, national governments should feel confident introducing 3HP into HIV programs, and donors, including the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund, should support countries in procuring 3HP for TPT as an essential part of the HIV clinical care package.

Future research: the DOLPHIN study enrolled PLHIV who were already on ART, virally suppressed, and switching from an efavirenz-based regimen to the TLD regimen. There is a question about whether 3HP and TLD can be started at the same time in people who are initiating ART for the first time (so-called ARV-naïve persons). A follow-on study called DOLPHIN II will evaluate the safety and pharmacokinetics of simultaneous 3HP and TLD initiation in ARV-naïve people and is expected to start in 2020.

when to start IPT—during pregnancy or after delivery—requires careful consideration. **TB APPRISE**, the only clinical trial of IPT in this population, found more adverse pregnancy outcomes among women with HIV who took IPT during pregnancy compared with those who did so after delivery.¹⁶ This higher risk remained after accounting for whether study participants had known risk factors for adverse pregnancy outcomes (e.g., a low CD4 T-cell count, TB infection, twin pregnancy).¹⁷ The World Health Organization (**WHO**) continues to recommend that pregnant women with HIV take IPT and not delay TPT to the postpartum period.¹⁸ People who receive IPT during pregnancy or postpartum should be closely monitored, especially since the risk of hepatotoxicity is higher during pregnancy and following birth.¹⁹ Rifampicin is also safe in pregnancy, and some clinicians prefer to use rifampicin-based TPT (e.g., 4R). Which TPT regimen to take, and when to start treatment, should be decisions made together by pregnant individuals and their health care providers after openly weighing all the risks and potential benefits.

What about people who wish to avoid pregnancy? Individuals who wish to avoid pregnancy should know that rifapentine (like other rifamycins) decreases the effectiveness of hormonal contraceptives.²⁰ These individuals should consider using a different, or additional, form of contraception when taking rifapentine-based TPT. In one study, 44 women living with HIV received isoniazid and rifampicin during the continuation phase of treatment for active TB disease together with **Depo-Provera (DMPA)**. Rifampicin decreased DMPA levels, and 12 percent of women in the study had subtherapeutic levels of progesterin, indicating possible contraceptive failure.²¹ Increasing the frequency of DMPA injections (e.g., to every 8–10 weeks instead of every 12) may maintain effective contraception with rifampicin.²² DMPA has not yet been studied with 3HP or 1HP, so it is unclear whether giving DMPA more frequently is a possibility for people who are taking rifapentine-based TPT and wish to avoid pregnancy.

What about people being treated for hepatitis C virus (HCV)? Rifamycins, including rifapentine, are not recommended for use together with many of the direct-acting antiviral drugs (**DAAs**) used to treat HCV.²³ This is because rifamycins can decrease the concentration of HCV drugs to subtherapeutic levels. People with HCV should consult with their health care providers about starting rifapentine-based TPT either before or after completing treatment for HCV.

What about people who use drugs (PWUD)? PWUD have a higher prevalence of TB infection and incidence of TB disease.²⁴ Rifapentine has not been systematically studied in PWUD. However, rifampicin is known to reduce exposures to **opioid substitution therapies (OST)** such as methadone and buprenorphine.²⁵ In some people, this results in opiate withdrawal. For this reason, people taking 3HP with OST should be closely monitored for signs of opiate withdrawal and other adverse events. Increasing the dose of methadone or buprenorphine when taking rifamycins can lessen the risk of withdrawal. IPT is safe to use in PWUD, although careful monitoring for liver toxicity is important.²⁶ Drug use should never be taken as a blanket rationale for denying someone TPT; it is the responsibility of health care providers to proactively manage drug-drug interactions for PWUD in a safe way.

TB APPRISE found that pregnant women with HIV who took IPT during pregnancy had a higher risk of adverse pregnancy outcomes when different outcomes including preterm delivery, low birth weight, fetal demise, and congenital anomalies (birth defects) were evaluated together. Risk was not higher when different outcomes were evaluated alone, with the exception of low birth weight.

Regarding IPT and pregnancy, **WHO** guidance on TPT states: “A systematic deferral of IPT to the postpartum period in pregnant women living with HIV would deprive them of significant protection when they are highly vulnerable to TB.”

DMPA is an injectable form of contraception containing the hormone progesterin.

The body processes many **DAAs** in the liver using enzymes such as cytochrome P450. These enzymes play a major role in drug metabolism and are induced by rifamycins, resulting in faster metabolism and lower drug levels.

OST is a type of harm reduction intervention for drug use. OST treats opioid dependence by replacing opioids (like heroin) with prescribed drugs that can manage or reduce opioid cravings and prevent sudden withdrawal.

IV. RIFAPENTINE DOSING INFORMATION

In the **3HP** regimen for adults, 900 milligrams (mg) of rifapentine is taken with 900 mg of isoniazid, along with a **vitamin B6** supplement. Each dose of 3HP is taken once a week. The entire 3HP regimen consists of 12 doses to be completed within 12 weeks.

In the **1HP** regimen for adults, 600 mg of rifapentine is taken with 300 mg of isoniazid together with vitamin B6. Each dose of 1HP is taken once a day. The entire regimen has 30 doses intended to be completed within one month (30 days).

The isoniazid used in the 3HP and 1HP regimens comes in 300 mg tablets. Rifapentine is currently available in two formulations:

1. Sanofi manufactures rifapentine as 150 mg tablets. These 150 mg rifapentine tablets are packaged together with 300 mg tablets of isoniazid to form a 3HP dose. If using the Sanofi product, this means each dose of 3HP requires taking 10 pills: six rifapentine tablets, three isoniazid tablets, and one vitamin B6 tablet (see illustration).
2. Macleods makes a fixed-dose combination (FDC) that combines 300 mg of rifapentine and 300 mg of isoniazid into a single tablet. If using the Macleods product, each dose of 3HP requires taking four pills: three rifapentine-isoniazid FDC tablets and one vitamin B6 tablet (see illustration).

VITAMIN B6 is given with 3HP and 1HP to prevent peripheral neuropathy, a feeling of numbness, tingling, or pain in the hands and feet that indicates nerve damage. Peripheral neuropathy is a side effect of taking isoniazid and is usually reversible.

ILLUSTRATION: Per-Dose Pill Count of 3HP and 1HP by Different Formulations of Rifapentine and Isoniazid

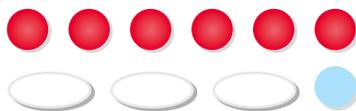
3HP = 900 mg isoniazid (INH) with 900 mg rifapentine (RPT), plus vitamin B6

1HP = 300 mg of INH with 600 mg of RPT, plus vitamin B6

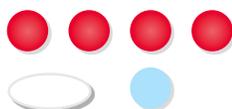
 = Rifapentine (RPT)  = Isoniazid (INH)  = Vitamin B6  = INH/RPT

*Pill count with the Sanofi product:
standalone tablets of INH = 300
mg and RPT = 150 mg*

3HP



1HP



*Pill count with the Macleods product:
INH/RPT fixed-dose combination
(INH 300 mg, RPT 300 mg)*

3HP



1HP



By combining rifapentine and isoniazid in a single pill, the Macleods FDC lowers the pill burden of 3HP. This promises to improve the acceptability of the regimen by making it easier for people to take every dose in full. Other generic drug manufacturers are developing new formulations of rifapentine that would similarly reduce the pill burden e.g., by offering rifapentine as a 300 mg tablet (instead of the current 150 mg option). A 300 mg tablet of rifapentine would be especially well suited to reducing the pill burden of the 1HP regimen. With 300 mg tablets of rifapentine and isoniazid, each dose of 1HP would require four pills: two rifapentine 300 mg tablets, one isoniazid 300 mg tablet, and one vitamin B6 tablet.

The Macleods 3HP FDC is **bioequivalent** to a 3HP dose comprised of standalone tablets of rifapentine and isoniazid. This means that there should be no clinical differences in terms of the efficacy or **bioavailability** of the FDC and standalone tablets. The FDC is not recommended for adolescents and children younger than 15 years old. Some TB programs are accustomed to crushing adult drugs in order to administer them to children. Macleods has not done any crushed tablet studies, so the FDC should not be split or crushed with the aim of delivering a partial dose.

When to take rifapentine: if possible, people should take rifapentine with food, since taking the drug with a meal (especially one with some fat) increases the bioavailability of rifapentine.

Don't be surprised: rifapentine tablets are red in color, and people taking rifapentine may notice their urine, sweat, or tears turn red or orange. This effect is harmless and will disappear soon after finishing treatment.

V. ACCESS TO RIFAPENTINE

Until recently, Sanofi was the only **quality-assured** supplier of rifapentine. This monopoly contributed to the initial high price of the drug. In October 2019, Sanofi reached a deal with Unitaid and the Global Fund to discount the price of rifapentine by 66 percent for 100 eligible countries.²⁷ Under the agreement, the price of rifapentine dropped from US\$45/patient-course of 3HP to \$15/patient-course. When factoring in the cost of isoniazid and vitamin B6, this brings the total cost of 3HP to approximately \$17/patient-course. The discount applies for a 12-month period; renewal for 2021 will be confirmed before the end of September 2020. The 1HP regimen, which is taken daily and therefore requires more rifapentine, costs more at \$25/patient-course with the price discount. This discounted price greatly improves the affordability of 3HP, but because it only applies to some countries, it falls short of ensuring that all people at risk of TB can access the highest-available standard of TB prevention.

In 2020, the Indian generic drug manufacturer Macleods Pharmaceuticals will introduce a 3HP FDC. Under an agreement with Unitaid, a full patient-course of the Macleods 3HP FDC will cost US\$15, just slightly lower than the \$17/patient-course price when using the Sanofi product.²⁸ This price applies to governments and international organizations procuring for 138 countries. This \$15 price point is a ceiling price that will remain in effect through December 31, 2021.

Two drugs are **BIOEQUIVALENT** when there is no significant difference in the rate and extent of absorption by which the active ingredient becomes available in the body. Stated simply, bioequivalence compares two products with respect to their bioavailability.

BIOAVAILABILITY is the proportion of a drug that enters circulation after being taken and is therefore able to have an active effect. It measures the rate and extent to which a drug is absorbed and becomes available at the site of action.

A **QUALITY-ASSURED** drug is one that has been evaluated and approved by a stringent regulatory authority (e.g., the Food and Drug Administration, the European Medicines Agency) or the WHO prequalification program.

In terms of quality assurance, the Macleods 3HP FDC is being reviewed by the WHO prequalification program and obtained a positive opinion from the Global Fund Expert Review Panel, meaning countries can purchase the product using Global Fund resources. A separate quality assurance process managed by the United States government will make the product eligible for procurement by **PEPFAR** programs.²⁹

Aside from Macleods, at least one other generic manufacturer is expected to seek prequalification for a rifapentine product soon (likely for a rifapentine-isoniazid FDC and potentially for a 300 mg rifapentine tablet). The introduction of additional quality-assured generic formulations of rifapentine should improve the drug's availability, accessibility, and affordability by introducing competition among multiple suppliers. But ensuring that rifapentine becomes equitably accessible to all who may benefit from this essential TB prevention drug will require vigilance and action on the part of activists (see box).

PEPFAR is the largest source of donor funding for HIV globally and a major supporter of TB/HIV activities including TPT. PEPFAR has named 3HP as "the preferred TPT regimen for adults and adolescents," pending adequate global supply.

WHAT ABOUT INTELLECTUAL PROPERTY BARRIERS?

Rifapentine is an old drug, first discovered in the 1960s. This means that any **patents** on rifapentine have long expired.³⁰ Isoniazid was first approved for TB in the 1950s and never patented. Intellectual property has not posed an obstacle to accessing rifapentine and was not considered a major driver of the initial high price of 3HP. However, in 2014 Sanofi filed for patents on two FDCs of 3HP, one formulated for adults and one for children, in 69 countries/territories.³¹ If granted and enforced, these patents could give Sanofi a monopoly on these 3HP FDC formulations until 2034 by either blocking generic equivalents or forcing generic manufacturers to work around Sanofi's patents by developing alternative, less direct ways of combining rifapentine and isoniazid. This would forestall the potential of generic competition to improve the availability, accessibility, and affordability of 3HP for people at risk of TB.

Patents are intended reward innovation. In the case of 3HP FDCs, calling two obvious combinations of two decades-old drugs innovative should inspire nothing but incredulity. In late 2019, activists in India and Thailand lodged pre-grant patent oppositions encouraging national patent authorities to reject both applications.³² The oppositions argued that Sanofi's patent claims do not fulfill basic patentability criteria such as novelty and non-obviousness. Around the same time, Sanofi withdrew its patent filings from the European Patent Office and in Indonesia and India.³³ Activists are now calling on Sanofi to withdraw its 3HP FDC patent applications everywhere they remain pending and to surrender their patents in countries where they have already been granted.

PATENTS are a type of intellectual property, a kind of 'right of ownership' that allows the owners of a patented product to exclude others from making or selling it for a period of time.

FOR MORE INFORMATION on Sanofi's 3HP FDC patent filings, see TAG's publication *Isoniazid/Rifapentine (3HP) Access Roadmap and Patent Landscape*.

TABLE: RIFAPENTINE PRODUCTS ON THE MARKET AND IN LATE-STAGE DEVELOPMENT

Which companies make rifapentine?	What rifapentine product(s) do they make?	What does rifapentine cost?	Where is rifapentine registered for treatment of TB infection?
Sanofi	RPT 150 mg tablet	<p><u>Via the global access agreement:</u> RPT 150 mg = \$5/24-tablet blister pack</p> <p>This equates to \$15 for the RPT in a full course of 3HP.</p> <p>This equates to \$25 for the RPT in a full course of 1HP.</p> <p><u>In the United States:</u> RPT 150 mg = \$24/24-tablet blister pack</p> <p>This equates to \$72 for the RPT in a full course of 3HP.</p>	<p>As of March 24, 2020, Sanofi had registered rifapentine in the United States (2014), Taiwan (2017), Hong Kong (2017), the Philippines (2018), Thailand (2018), Indonesia (2018), South Africa (2018), India (2019), Mongolia (2019), Singapore (2019), Myanmar (2019), Democratic Republic of Congo (2019), and Ghana (2020).*</p> <p>This encompasses 6 out of 30 high-TB-burden countries and 6 out of 30 high-TB/HIV-burden countries.</p>
Sanofi	Water-dispersible 3HP FDC tablet for children (150 mg INH, 150 mg RPT) Water-dispersible RPT standalone tablet for children (100 mg RPT)	NA	Under evaluation in a clinical trial; not yet on the market.
Macleods	3HP FDC tablet (300 mg INH, 300 mg RPT)	<p><u>Via the Unitaid agreement:</u> A pack of 36 FDC tablets (one patient course) = \$15</p>	<p>Global Fund ERP endorsement obtained, WHO PQ approval pending.</p> <p>Regulatory filings begun in 10 countries.**</p>
Other generic suppliers	RPT 300 mg tablet 3HP FDC tablet (300 mg INH, 300 mg RPT)	NA	In development; WHO PQ submissions expected in 2020 or 2021.

ERP = Global Fund Expert Review Panel for Pharmaceutical Products; FDC = fixed-dose combination; INH = isoniazid; mg = milligram; NA = not available; PQ = WHO prequalification; RPT = rifapentine

* Sanofi has not shared information on ongoing and planned regulatory submissions.

** Macleods has not publicly shared where it has filed for registration or priority countries for future regulatory submissions.

Notes:

- Rifapentine is also registered in Chile, although this product is not made by either Sanofi or Macleods.
- Rifapentine is produced in China, although this product is not quality assured.

VI. TAKE ACTION! KEY ADVOCACY MESSAGES

TB preventive therapy saves lives. There is no doubt that TPT saves lives, prevents illness, and averts suffering. Some of the strongest proof comes from the TEMPRANO trial, which studied IPT among PLHIV in Cote d'Ivoire. Participants receiving IPT had a 37% reduction in mortality, independent of whether they were also on ART, with those on both IPT and ART enjoying the greatest protection against severe disease and death.³⁴ Several million TB deaths could have been avoided if IPT had been rolled out worldwide when the WHO recommended its programmatic use in 2008.³⁵ Short-course rifapentine-based TPT may have an even greater potential to save lives. *Activists should demand that TPT be offered to all people at risk of TB and raise awareness of TPT among TB-affected communities so that people demand access to TPT as their right.*

Rifapentine is an essential TB medicine and the cornerstone of new TPT regimens. All countries should have guidelines for TPT that include 3HP and 1HP. Countries must rapidly update guidelines when safety data on using 3HP during pregnancy and in children aged 0–2 years become available. Guidelines should respond to ongoing research to develop even safer and shorter regimens. International donors, particularly the Global Fund and PEPFAR, should financially support countries' scale-up of rifapentine-based TPT as a routine and integral part of TB and HIV programs. *Activists should hold country governments and donor agencies accountable for implementing rifapentine-based TPT in line with global guidelines and evolving scientific evidence.*

The supply of rifapentine must increase. Limited supply is the major barrier to rifapentine availability now that the price of the drug has fallen well below its previous prohibitive level. In 2020, demand for rifapentine by countries and donor-funded TB and HIV programs will far outstrip what Sanofi and Macleods are able to produce. Macleods is projected to deliver 800,000 patient courses of 3HP in 2020 and Sanofi has capacity to produce 600,000 treatment courses.³⁶ With global targets to put at least 30 million people on TPT by 2022, existing manufacturers will need to greatly increase production capacity and new rifapentine manufacturers must enter the market. *Activists should support market entry of additional generic manufacturers and call on Sanofi and Macleods to increase production of rifapentine to meet global demand.*

A lower price for some countries must become an affordable price for all. The deals struck by global donors with Sanofi and Macleods apply, respectively, to 100 and 138 mostly low- and middle-income countries. These agreements have greatly improved the affordability of 3HP for public purchasers in these places, which are home to a majority of people estimated to have TB infection. But there is a difference between a lower price for some and a low price for all. This difference is more than symbolic: the price of rifapentine remains high in many places, particularly low-incidence countries that could have a real shot at eliminating TB with access to shorter TPT regimens such as 3HP. In the United States, for example, Sanofi sells rifapentine for \$72/patient-course of 3HP. Setting one price for one band of countries, and a higher price for another set of countries, for the same product manufactured in the same facility, makes little sense in a world where TB programs everywhere are inadequately resourced. Equitable and sustainable access to rifapentine will depend on further price reductions—for all countries, everywhere.

Based on what it costs to manufacture rifapentine, and assuming sufficient volumes of sales, 3HP could cost as little as \$10 per patient. To reach this more affordable price point, two things must happen:

1. Additional suppliers must enter the market. The introduction of the Macleods 3HP FDC, and the expected market entry other generic manufacturers, has ended Sanofi's longstanding monopoly on quality-assured rifapentine. *Activists should support market entry of additional generic manufacturers and hold all suppliers accountable to pricing rifapentine equitably and affordably by demanding a single global access price for all countries.*
2. Volumes must rise, and buyers should work together to pool demand and negotiate lower prices. Pooling procurement by purchasing rifapentine via the Global Drug Facility (GDF) would help consolidate demand and create positive, predictable market dynamics that would encourage prices to fall as volumes rise. *Activists should build community demand for rifapentine and encourage governments to pool demand by buying rifapentine through the GDF.*

Rifapentine is a global public good. Sanofi's attempt to patent 3HP FDC formulations for adults and children is especially indefensible considering that **public funding** underwrote the vast majority of research behind 3HP and 1HP. Sanofi is not the original innovator behind rifapentine. Traded from one pharmaceutical company to the next over five decades, "rifapentine has had many private owners and mostly public benefactors."³⁷ The public has a right to benefit from public investments in science. Sanofi and other manufacturers therefore have an obligation to make rifapentine accessible to all, in a manner that honors the drug's status as a global good developed primarily with public resources. *Activists should call on Sanofi to withdraw its 3HP patent applications in all countries where they remain pending, and to surrender their patents in places where they have already been granted.*

TPT should be integrated within people-centered systems of care.

Access to pills alone is not enough to prevent TB. TPT will be more powerful and sustainable if integrated into comprehensive systems of healthcare service delivery. One successful approach from the HIV field is **differentiated service delivery (DSD)**. By putting people at the center of service delivery, DSD models make it easier for people to complete treatment and remain engaged in care. For PLHIV, TPT can be incorporated into existing DSD models.³⁸ For example, the Zimbabwe National Network of People Living with HIV has already taken steps to put TPT into DSD platforms such as community ART refill groups, peer-led adherence support clubs, and expert patient networks.³⁹ Public health programs will need to be creative in imagining what DSD looks like for HIV-negative persons taking TPT. *Activists should work with TB and HIV programs to design flexible and adaptable methods for delivering TPT centered on people's holistic health needs.*

Provision of TPT must always be based on human rights and respect for persons.

Whether to take TPT (or not) must always be an individual choice made with full information and without coercion. By definition, people with TB infection are not sick and therefore do not pose any risk to others. The risk of TB infection progressing to TB disease is much higher for some groups, such as PLHIV, very young children, and people who have just recently acquired infection. In general, however, only 5–10% of people with TB infection will develop active TB disease at some point in their lifetime. Treatment always carries some risk of side effects, so understanding the individual risk/benefit tradeoffs of taking TPT is necessary to make an informed decision. The WHO TB Ethics Guidance clearly states that taking TPT should never be compulsory.⁴⁰ *Activists should raise awareness of rifapentine-based TPT, share knowledge of how to prevent TB in communities, and ensure TB prevention efforts are based on human rights and respect for individual decision-making.*

MAJOR PUBLIC FUNDERS of rifapentine development efforts include the U.S. Centers for Disease Control and Prevention, the U.S. National Institutes of Health, the U.S. Agency for International Development, Unitaid, and the European & Developing Countries Clinical Trials Partnership.

DIFFERENTIATED SERVICE DELIVERY adapts HIV services to the needs, preferences, and expectations of PLHIV, while at the same time reducing unnecessary burden on care providers. The International AIDS Society has developed DSD resources, including for TPT, at www.differentiatedservicedelivery.org.

VII. QUESTIONS FROM THE COMMUNITY

Through the Unitaid-funded **IMPAACT4TB project**, Treatment Action Group has supported civil society and community-based organizations in 12 countries raise awareness of and build demand for 3HP among communities affected by TB and HIV. These efforts have sparked many community dialogues on TPT. Whether in Brazil, Cambodia, or Zimbabwe, community members often ask similar questions. Some of the most frequently asked questions are answered below.

Question: *Is a single course of 3HP enough to protect against TB?*

Answer: Yes, a single course of 3HP provides lasting protection against TB. A randomized controlled trial called WHIP3TB compared the effectiveness and safety of giving 3HP once versus giving 3HP twice (once a year for two years, an approach called periodic 3HP, or p3HP) among PLHIV in South Africa, Ethiopia, and Mozambique. Both 3HP and p3HP were safe, and participants who took a single course of 3HP were no more likely to develop TB disease over two years of follow-up than participants who took 3HP twice.⁴¹ Importantly, all participants in the WHIP3TB study were on ART. This finding indicates that 3HP provides durable protection against TB among PLHIV on ART, even in countries with high rates of TB transmission. There is no need to repeat 3HP annually, knowledge that should make it easier and less expensive to scale-up 3HP globally.

Question: *Is there ever a reason to take TPT more than once?*

Answer: A single course of TPT should offer sufficient protection against TB for most people. However, there are a couple of scenarios where taking TPT more than once may be a good idea. First, if someone completes a course of TPT, and then afterward has a new exposure to TB (for example, maybe someone in their household falls ill with TB) they should take another round of TPT. Generally speaking, every new exposure to TB is an opportunity to prevent TB by taking TPT. Second, some countries have decided to offer 3HP to all PLHIV, even if someone took IPT at some point in the past. PLHIV who have taken IPT may consider taking a short-course TPT regimen such as 3HP or 1HP.

Question: *Can someone take TPT if they have previously been treated for active TB disease, one or more years back? What about taking TPT soon after finishing TB treatment?*

Answer: Yes—people treated for active TB disease in the past can receive TPT. **Secondary preventive therapy** may be especially beneficial for groups at high risk of recurrent TB, including adults and children with HIV. WHO recommendations on TPT clearly state that adults and children living with HIV who have successfully completed treatment for TB disease may receive TPT.⁴² For PLHIV, there may be particular benefit in giving TPT soon after completion of TB treatment. A review of four studies of secondary preventive therapy found that giving TPT after TB treatment greatly reduced the risk of recurrent disease in PLHIV compared to no treatment or placebo.⁴³ Three of these studies used isoniazid alone (6H) and one used isoniazid and rifampicin (HR)—in theory, 3HP would have a similar protective effect. In practice, few TB and HIV programs provide secondary preventive therapy, though this is an important intervention that communities can demand.

Funded by Unitaid and led by the Aurum Institute, the **IMPAACT4TB PROJECT** is supporting 12 countries in Africa, Asia, and South America scale-up rifampentine-based TPT regimens, primarily 3HP. Learn more at www.impaact4tb.org.

In **SECONDARY PREVENTIVE THERAPY**, people successfully treated for TB disease receive TPT to reduce the risk of disease recurrence (through either reinfection with TB or a relapse of the original infection).

VIII. OVERCOMING RESISTANCE TO IMPLEMENTING TPT

Activists will hear many excuses for not implementing TPT. Some common excuses for not using TPT are outlined below, along with the evidence and arguments that activists can use to overcome them.

Excuse: *There isn't a good test for TB infection, or for predicting who with infection will progress to active TB disease, so we don't know whom to treat with TPT.*

Response: WHO guidelines do not require a test for infection before starting PLHIV or child household contacts less than five years old on TPT.⁴⁴ These two groups face a much higher risk of TB, making the risk/benefit tradeoff favor TPT, even without testing for infection. It is true that current tests for TB infection are imperfect and expensive and come with several important caveats, the biggest being that they do not directly measure infection or the risk of progression to active TB (Current tests for TB infection include tuberculin skin tests [TSTs] and interferon-gamma release assays [IGRAs]). Therefore, testing should never be a barrier for offering TPT to PLHIV and young children. For other groups, a test for infection does two useful things: 1) a test result may help individuals decide whether to take TPT, and 2) a positive test may help clinicians identify people who are more likely to benefit from TPT (generally speaking, those with a positive test benefit more from TPT than those without). Active TB disease must always be ruled out before starting TPT in all people, regardless of HIV status or age.

Excuse: *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.⁴⁵ 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.⁴⁶ 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 3) diagnose and treat all people with drug-resistant TB to halt its spread.

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

Response: Treatment versus prevention is an old, tired, and false conflict. We must abandon the austerity mindset that tells TB programs they can do only one thing at a time. This either/or mentality traps TB-affected communities in a false economy of partial solutions. Denying people interventions like TPT that are proven to reduce suffering is a violation of their human rights to health and scientific progress.

When considering different TB interventions, we need to adopt a both/and mindset. 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 taking TPT to complete treatment. A TB program that focuses only on diagnosis and treatment of active disease is living up to only part of its human rights and public health responsibilities.

**Want more information on rifapentine or TB preventive therapy?
Write to communications@treatmentactiongroup.org**

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