



AN ACTIVIST'S GUIDE TO

RIFAPENTINE

TB PREVENTIVE TREATMENT: 3HP AND 1HP



Updated April 2024

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I. INTRODUCTION AND BACKGROUND

This guide summarizes information on rifapentine, an essential drug for treating **tuberculosis (TB) infection**. Treatment of TB infection is referred to as TB preventive treatment (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 can be transmitted from one person to another. Preventive treatment keeps individuals and families safe from active TB disease, which in turn helps communities become TB free.

The primary goal of TPT is to protect people who are already infected with TB from getting sick with active TB disease. Taking TPT is especially important for people who come in close contact and have been exposed to TB because they live or work and share the same air with someone who has active TB disease. TPT is not the only way to prevent TB and is more powerful when used with the other prevention tools shown in **Figure 1**.

There are multiple TPT regimens recommended by the World Health Organization (WHO). The shortest ones rely on a drug called rifapentine, which belongs to a class of drugs called the **rifamycins**. Rifapentine is the backbone of newer, short-course TPT options. When combined with a second TB drug, isoniazid, rifapentine forms the **3HP** regimen (taken once weekly for 12 weeks [three months]) 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**), which people take every day for between six and 36 months.

We wrote this guide to equip advocates with the knowledge they need to educate their communities about how to prevent TB with 3HP and 1HP and to hold their governments accountable for providing the highest standard of TB prevention. People at risk of TB deserve 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 3HP and 1HP. We need to give more people access to TPT regimens like 3HP and 1HP if we hope to end TB in our families and communities.

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.

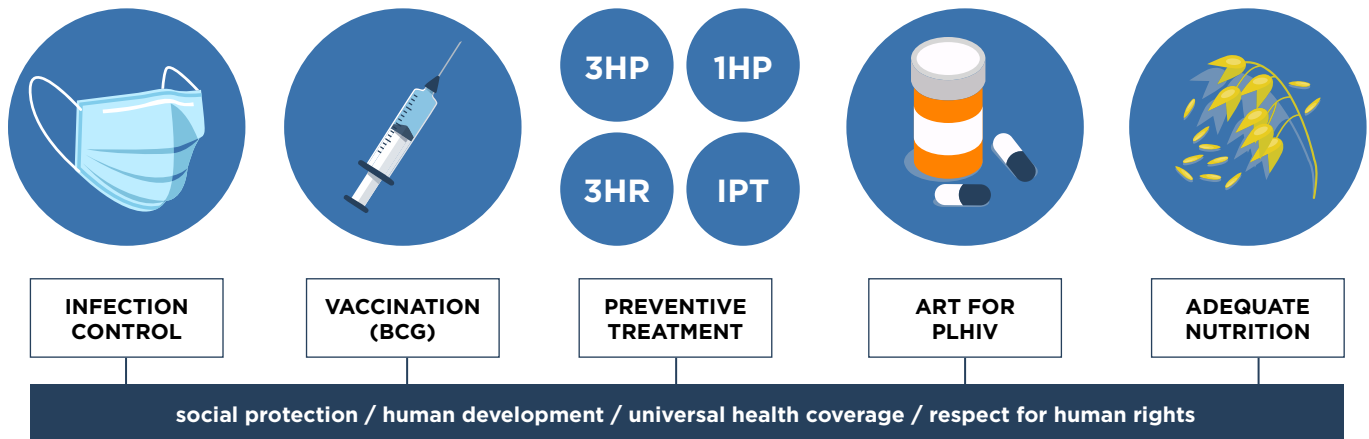
KNOW YOUR TPT REGIMENS:

When abbreviating TB drug regimens, **H** = isoniazid; **P** = rifapentine; and **R** = rifampicin

The WHO 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

FIGURE 1: TPT IS ONE OF MANY WAYS TO PREVENT TB



II. THE EFFICACY OF 3HP AND 1HP

Large, multicountry clinical trials have established the efficacy of 3HP and 1HP in preventing TB disease. PREVENT-TB, a phase III clinical trial led by the TB Trials Consortium (TBTC) at the U.S. Centers for Disease Control and Prevention (CDC), evaluated the efficacy of 3HP against nine months of daily isoniazid (9H). The trial enrolled over 8,000 participants and found that 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 existing HIV treatment guidelines when the study started, trial participants with HIV 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 PREVENT-TB also did well and were more likely to complete treatment than those receiving 9H.³ Children as young as two years old can take 3HP, and soon children of all ages, including infants, will be able to receive this regimen (read “*What about children and young people?*” below).

The BRIEF-TB trial, conducted by the **ACTG**, evaluated the efficacy of 1HP compared with 9H. This phase III trial enrolled 3,000 adults and adolescents 13 years of age and older 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 are now assessing the safety, tolerability, and effectiveness of 1HP in other populations, including **HIV-negative adolescents and adults**, children, and pregnant people.

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

ACTG, or Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections, is a clinical trials network funded by the U.S. National Institutes of Health (NIH).

Although the BRIEF-TB trial only studied 1HP in PLHIV, WHO guidelines allow for the regimen to be used in **HIV-NEGATIVE ADOLESCENTS AND ADULTS**:

“When taking also into account the good safety profile of 1HP and its much shorter length . . . the Guideline Development Group recommended that this regimen may also be used in high TB-burden settings and in people without HIV infection.”

3HP and 1HP look efficacious in clinical trials, but do they work in the real world? Yes! Programmatic experience with 3HP in Cambodia, Ethiopia, Pakistan, Taiwan, Uganda, the United States, and many other places indicates that the regimen is safe, is well accepted by most people who take it, and has high completion rates. 3HP has performed well in diverse settings ranging from HIV clinics, prisons, large cities, small villages, migrant health programs, homeless shelters, and households affected by TB. Programmatic experience with 1HP is growing, with countries like India, Nigeria, Pakistan, and Zambia piloting the regimen.

III. THE SAFETY OF 3HP AND 1HP

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.^{5,6} A systematic review of 15 studies comparing 3HP to other TPT regimens (mostly 9H) found that 3HP has “equal safety and effectiveness” to other regimens.⁷ A separate analysis looking at the efficacy and toxicity of various TPT regimens reached similar conclusions about the safety and efficacy of 3HP.⁸ Compared with IPT, rifamycin-based TPT may carry a higher risk of **hematologic toxicity**.

Overall, 3HP and 1HP are safe enough for people to take themselves (self-administration). Prescribing practices differ across countries, but 3HP is safe enough that many programs provide the full 12 weeks of treatment all at once without making people come to the clinic every month for refills. Some programs recommend that people taking 3HP have a monthly visit — either virtual or in person — with a health care worker to identify any adverse events and receive adherence support.⁹ At one month in duration, 1HP is almost always given to the patient as a full treatment course (see section V. “3HP and 1HP Dosing Information”).

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.

Rare adverse events called hypersensitivity reactions have been reported in both clinical trials and programmatic use of rifapentine.¹⁰ These reactions, which are sometimes also called systemic drug 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 the medication is stopped, without any long-term effects. In some 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).¹¹ In another TBTC trial of 3HP, systemic drug reactions were more common among participants who were female sex, older age (>45 years), or taking other non-TB medications.¹²



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



HEMATOLOGIC TOXICITIES are those that affect the blood and its components by decreasing red blood cells (anemia) or white blood cells (neutropenia), for example.



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.

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. Hypersensitivity may be linked to the intermittent, once-weekly dosing schedule of 3HP.¹³ 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 community health worker or health care provider immediately if experiencing them.

IV. USING 3HP AND 1HP IN PRIORITY POPULATIONS

Like other rifamycin class drugs, rifapentine interacts with many medications for other conditions that people at risk of TB may be taking. In addition, there are some important things to consider when using 3HP in priority populations such as pregnant individuals, children, and people who use drugs.

What about people living with HIV? 3HP and 1HP are safe to use in PLHIV, but interactions between rifapentine and certain antiretrovirals must be managed (or avoided altogether by using other TPT options or by switching ART regimens). 3HP is safe to use with efavirenz-, raltegravir-, and dolutegravir-based ART. Most countries have transitioned from efavirenz- to dolutegravir-based first-line therapy for HIV (e.g., the **TLD** regimen). A pair of studies called **DOLPHIN** and **DOLPHIN Too** showed that 3HP is safe to use with dolutegravir without the need to adjust dolutegravir doses.^{14,15} Importantly, PLHIV in areas where malaria or severe bacterial infections are common should receive 3HP together with **cotrimoxazole**.

Because the dose of rifapentine in 1HP is different than in 3HP and the regimen is taken daily (rather than once weekly) there is a need to look separately at giving 1HP with dolutegravir. Studies of 1HP and dolutegravir are ongoing. One clear takeaway so far: PLHIV can take 1HP and remain virologically suppressed if they take a second dose of dolutegravir (i.e., doubling the standard dose). Supporting evidence comes from an ACTG study called A5372.¹⁶ However, 1HP would be easier for PLHIV to take (and more affordable to programs) if it did not require a second dolutegravir dose; several studies are looking at this possibility.

A trial comparing 3HP with 1HP among PLHIV in Thailand taking either efavirenz- or dolutegravir-based HIV treatment found that most participants remained virally suppressed at 24 weeks after starting TPT (including the 185 people who received 1HP with TLD).¹⁷ A substudy among 13 PLHIV included in the larger trial looked more closely at how 1HP affected dolutegravir drug levels.¹⁸ It found that 1HP substantially reduced dolutegravir concentrations, as expected, but that concentrations did not drop below the point where the drug's efficacy against HIV would be compromised. At the end of 1HP treatment, 12 of 13 participants were virologically suppressed.

These data from Thailand are reassuring but not definitive. Studies to date primarily looked at dolutegravir drug levels in the body but were not designed to assess the outcome that matters most for the health of PLHIV: virological suppression. To this end, the ACTG's A5372 trial will

TLD is an HIV treatment regimen composed of dolutegravir, lamivudine, and tenofovir disoproxil fumarate given once a day as an FDC tablet.

For more information on the **DOLPHIN** and **DOLPHIN TOO** studies of 3HP with dolutegravir, see Appendix.

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.

open a second stage evaluating 1HP with once-a-day dolutegravir with virological suppression as the primary outcome. Once available, these results will provide a better indication of whether PLHIV can take 1HP with standard, once-daily dolutegravir. Until then, programs can offer PLHIV taking dolutegravir either the 3HP regimen (no dose adjustment) or 1HP (with an extra dolutegravir dose).

Some PLHIV take an ART regimen built around the drug **bictegravir**. As with dolutegravir, bictegravir drug levels are reduced by rifapentine. Studies from Taiwan suggest that it may be okay to give 3HP and 1HP with bictegravir under careful monitoring for HIV virologic response — but more research is required before making a general recommendation.^{19,20}

BICTEGRAVIR is a type of HIV medicine called an integrase inhibitor and is closely related to dolutegravir.

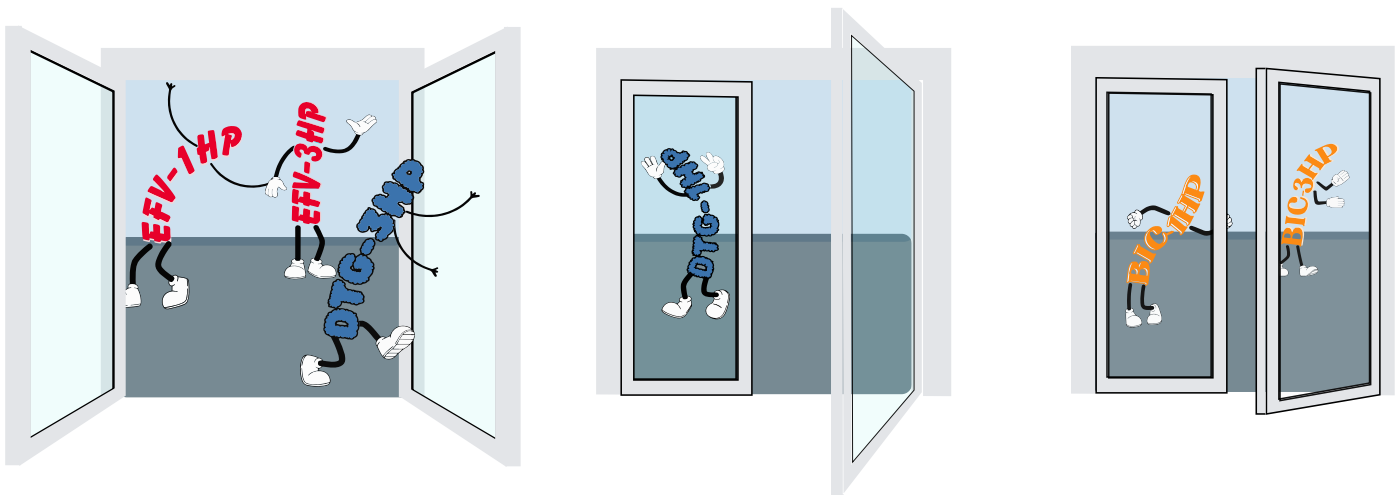
Figure 2 summarizes current knowledge of drug-drug interactions between either 3HP or 1HP and key antiretrovirals using the metaphor of an open door. The door is wide open for using 3HP with dolutegravir, less open for 1HP and dolutegravir, and more closed for rifapentine-based TPT and bictegravir.

FIGURE 2: RIFAPENTINE-ART DRUG-DRUG INTERACTIONS

Open doors = Co-administer without concern

Partially closed doors = Caution warranted — adjustments may be necessary and monitoring is recommended

Mostly closed doors = More research is needed and close monitoring is required



EFV = efavirenz; DTG = dolutegravir; BIC = bictegravir; 3HP = 12 weeks of once-weekly isoniazid and rifapentine; 1HP = one month of daily isoniazid and rifampicin

What about children and young people? 3HP can be given to adolescents and children as young as two years of age. A study called TBTC Study 35 is looking at the safety and optimal dosing of 3HP in children under two years in South Africa and will report results in 2024. Once available, these results are expected to show that 3HP can be used in children of all ages. Most participants in TBTC Study 35 are HIV-negative, but the study will also generate data on 3HP given to a few children living with HIV on dolutegravir-based ART. For children who cannot swallow pills, both rifapentine and isoniazid are available in child-friendly formulations that disperse in water (read section V. “3HP and 1HP Dosing Information”). While waiting for these results, infants under two years who need TPT can receive either three months of daily isoniazid and rifampicin (3HR) or six months of daily isoniazid (6H).

The WHO recommends dolutegravir-based HIV treatment for all infants and children for whom approved dolutegravir dosing information is available.²¹ Several studies are assessing the safety

and **pharmacokinetics** (PK) of giving 3HP or 1HP to children with HIV on dolutegravir-based treatment. In addition to TBTC Study 35, the DOLPHIN Kids trial is evaluating the PK and safety of 3HP in children and adolescents ages 3 months to 17 years taking dolutegravir. The **IMPAACT Network** will conduct a similar study of 1HP and dolutegravir in children ages 2–13 years. Until these studies are completed, 6H is preferred for children on dolutegravir (as well as for kids still taking nevirapine or lopinavir-ritonavir). Any children with HIV still on efavirenz-based ART can take either 3HP or 3HR, which is available in a child-friendly, water-dispersible formulation.

What about pregnant individuals? Pregnant and postpartum women have a higher risk of developing TB than nonpregnant people, making pregnancy an important time to offer preventive services to women. Rifapentine is currently not recommended for use in individuals who are pregnant due to a lack of data. In other words, an absence of evidence — rather than evidence of harm — keeps pregnant people from enjoying the protection of 3HP and 1HP. This may soon change thanks to previous and ongoing research:

- Previous research: An analysis of participants who became pregnant after joining the PREVENT-TB trial and another CDC-funded trial of 3HP found no unexpected fetal loss or congenital anomalies (birth defects) among 87 women who were exposed to 3HP or 9H during pregnancy.²² An IMPAACT Network study showed that pregnant people can receive the same dose of rifapentine as nonpregnant people.²³ The study looked at how quickly women cleared rifapentine from their bodies during pregnancy and after delivery (postpartum). It also assessed whether drug exposure and clearance differed between women with and without HIV. All women in the study — whether pregnant or postpartum, HIV-negative or living with HIV — had drug exposures associated with effective TPT in nonpregnant people. This study showed that pregnant and postpartum people of any HIV status can receive the same dose of rifapentine as nonpregnant people, but it did not fully answer the question of 3HP safety during pregnancy because it was not large enough to do so or designed for that purpose.
- Ongoing research: A trial run by **IMPAACT4TB** called DOLPHIN Moms is evaluating the safety, tolerability, and potential drug-drug interactions of 3HP and 1HP in pregnant people (20–34 weeks gestational age) who are taking dolutegravir-based ART. The first 25 participants in the 1HP and 3HP groups will take dolutegravir twice a day (a double dose); if dolutegravir drug levels look good in these initial participants, then subsequent participants may receive the standard dose.

Positive results from the DOLPHIN Moms study could lead WHO to update its guidelines to recommend 3HP and 1HP for pregnant and postpartum people at risk of TB. Until then, pregnant women can take IPT. However, deciding when to start IPT — during pregnancy or after delivery — requires careful consideration (see “*Spotlight: TB APPRISE Study of IPT in Pregnancy*” below). 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.

PHARMACOKINETICS studies what the body does to a drug by looking at things like how a drug moves through the body or how the concentration of a drug changes over time. Understanding how a medicine is absorbed, metabolized, and eliminated by the body informs decisions about appropriate dosing.

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

Funded by Unitaid and led by the Aurum Institute, the **IMPAACT4TB** project catalyzed the global scale-up of rifapentine-based TPT by supporting 12 countries in Africa, Asia, and South America in introducing 3HP and 1HP. Learn more at www.impaact4tb.org.

SPOTLIGHT: TB APPRISE STUDY OF IPT IN PREGNANCY

More than 60 years elapsed between when IPT was first introduced and when it was first studied systematically in pregnant women. When TB APPRISE, the only clinical trial of IPT in this population, published results in 2019, the findings upended prevailing expert opinion. 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, except for low birth weight.²⁴

In other words, researchers observed more adverse pregnancy outcomes among women with HIV who took IPT during pregnancy compared with those who did so after delivery. On the other hand, women who started IPT after delivery had a higher risk of hepatotoxicity than those who started during pregnancy. Even with the data from TB APPRISE, the **WHO guidance** continues to recommend that pregnant women with HIV take IPT and not delay TPT to the postpartum period.²⁵ 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.²⁶

The risks uncovered by TB APPRISE could have been recognized earlier if pregnant people had not been excluded from prior studies of TPT. Identifying the risks of IPT for pregnant women could have motivated researchers to develop better therapies — not only for pregnant people but also for others at risk of TB. Efforts are now underway to mainstream the early inclusion of pregnant people in TB research: the WHO is developing a consensus position on this topic, and representatives of TB-affected communities, including women who were treated for TB during pregnancy, have published their own **community position statement**.²⁷

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.”

The **COMMUNITY POSITION STATEMENT** on TB research and pregnancy says: “It is critical that all those involved in TB research move toward the routine inclusion of pregnant and breastfeeding women and persons in research.”

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.²⁸ People taking hormone-based contraception should consider using a different, or additional, form of contraception when taking rifapentine-based TPT. No studies have looked specifically at how 3HP and 1HP affect contraception, but two trials of TB treatment with rifampicin offer guidance relevant for rifapentine-based TPT.

- **Depo-Provera (DMPA) injection:** In the first study of its kind, 44 women living with HIV received isoniazid and rifampicin during the continuation phase of treatment for active TB disease together with DMPA. Rifampicin decreased DMPA levels, and 12 percent of women in the study had subtherapeutic levels of progestin, indicating possible contraceptive failure.²⁹ Increasing the frequency of DMPA

DEPO-PROVERA (DMPA) is an injectable form of contraception containing the hormone progestin.

injections (e.g., to every 8–10 weeks instead of every 12) may maintain effective contraception with rifampicin. DMPA has not yet been studied with 3HP or 1HP, but based on what is known about rifampicin, similar dose adjustments may be required.

- **Levonorgestrel (Plan B) pill:** Another study looked at how rifampicin given as part of TB treatment affects levonorgestrel (Plan B) drug exposures. The study found that taking a double dose of levonorgestrel (Plan B) while taking TB treatment with rifampicin is enough to overcome the rifampicin-related drug-drug interaction that compromises the efficacy of a single dose of levonorgestrel. Women being treated for TB with rifampicin should take 3.0 mg of levonorgestrel instead of the standard 1.5 mg dose.³⁰ Levonorgestrel (Plan B) has not yet been studied with 3HP or 1HP, but based on what is known about rifampicin, similar dose adjustments may be required.

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)** to treat HCV.³¹ 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.³² Rifapentine has not been systematically studied in PWUD. However, rifampicin is known to reduce exposures to **opioid substitution therapies (OSTs)** such as methadone and buprenorphine.³³ In some people, this results in opiate withdrawal. For this reason, people taking 3HP or 1HP 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.³⁴ Drug use should never be invoked as a blanket rationale for denying someone TPT; it is the responsibility of health care providers to work together with PWUD to proactively manage drug-drug interactions in a safe way.

V. 3HP AND 1HP 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 (pyridoxine). 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 (pyridoxine). Each dose of 1HP is taken once a day. The entire regimen has 28 doses intended to be completed within one month.

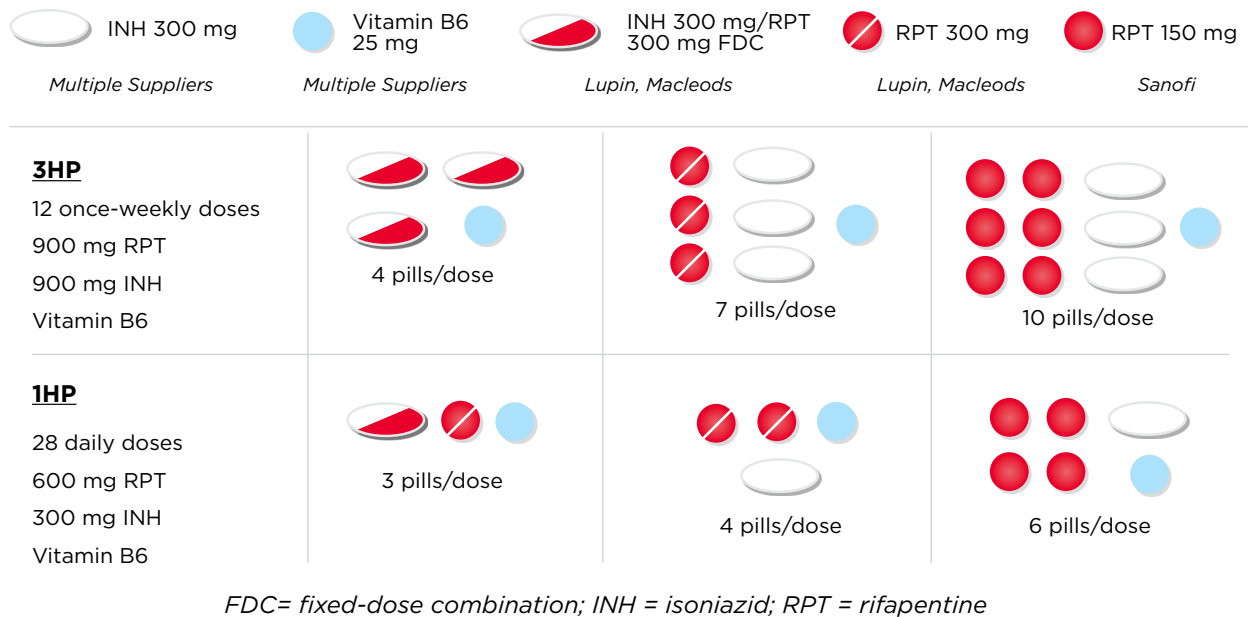
LEVONORGESTREL, commonly called **PLAN B** or sometimes the “morning after pill,” is a form of emergency contraception and a type of progestin hormone.

Similar to HIV drugs like dolutegravir, 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

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

VITAMIN B6 (pyridoxine) prevents 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.

FIGURE 3: PER-DOSE PILL COUNT OF 3HP AND 1HP BY DIFFERENT FORMULATIONS OF RIFAPENTINE



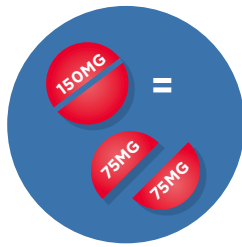
The **pill count** of 3HP and 1HP depends on the formulations of rifapentine and isoniazid (see **Figure 3**). The isoniazid used in 3HP and 1HP usually comes in 300 mg tablets. Rifapentine is currently available in four formulations:

- Fixed-dose combination (FDC) tablet:** A tablet that combines 300 mg of rifapentine with 300 mg of isoniazid in a single pill. The FDC formulation is made by Lupin and Macleods and is particularly well-suited for the 3HP regimen. The FDC is bioequivalent to the same amount of each drug from taking standalone tablets of rifapentine and isoniazid. There are no clinical differences in terms of the efficacy or bioavailability of the FDC and standalone tablets.
- 300 mg tablet:** A tablet that contains 300 mg of rifapentine alone. This formulation is manufactured by Lupin and Macleods and is especially well-suited for 1HP but can also be used for 3HP or even the four-month drug-sensitive TB treatment regimen known as **HPMZ**.
- 150 mg tablet:** Sanofi manufactures a 150 mg tablet of rifapentine. Because this formulation contains less rifapentine than the 300 mg tablet, using it will result in higher pill counts of 3HP and 1HP.
- 150 mg dispersible tablet (children):** This is a child-friendly formulation of rifapentine that is dispersible in water, making it easy to give to young children who cannot swallow pills. In addition, this formulation is functionally scored, meaning it can be split into two equal half doses of 75 mg each — this makes it easier to adjust the dose based on the child’s weight. Lupin makes a 150 mg dispersible functionally scored pediatric rifapentine tablet that is raspberry-mint flavored; the company is developing a dispersible tablet of isoniazid. Macleods is developing its own pediatric dispersible rifapentine formulation and already sells a dispersible isoniazid tablet that is strawberry flavored (**Figure 4**).

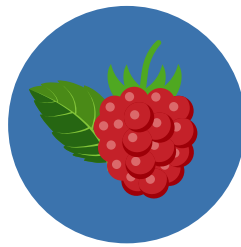
PILL COUNT refers to the number of pills a person must swallow when taking each dose. Lower pill count is associated with improved acceptability by making it easier for people to take every TPT dose in full.

HPMZ is a four-month regimen for treating drug-sensitive TB that combines isoniazid (H), rifapentine (P), moxifloxacin (M), and pyrazinamide (Z). Read TAG’s *An Activist’s Guide to Shorter Treatment for Drug-Sensitive TB* for more information.

FIGURE 4: LUPIN PEDIATRIC RIFAPENTINE FORMULATION CHARACTERISTICS



150 MG FUNCTIONALLY SCORED
(accurately split into two equal half doses
of 75 mg)



**RASPBERRY
MINT FLAVORED**



**DISPERSIBLE
IN WATER**

When and how to take 3HP and 1HP:

- The most important thing is to take every 3HP or 1HP dose in full, according to a set schedule. This is called adherence and is a way to ensure that enough rifapentine and isoniazid remain in the body to be effective.
- If possible, people should take 3HP or 1HP with food, since taking rifapentine with a meal that is rich in fat increases its **bioavailability**.
- 3HP should be taken once a week, on the same day each week. If someone forgets to take 3HP on the usual day, they should take it as soon as they remember and then resume their normal schedule the following week.
 - If more than three days go by before someone realizes they forgot to take 3HP, then they should wait to take their next dose on their usual day. This means that they skipped a week and will need to continue the medication for an additional week.
- 1HP should be taken once a day, at the same time each day. If someone misses a dose, they should take it as soon as they remember and then resume their normal daily routine until completing all 28 doses.
 - If someone forgets to take 1HP for three or more days, they should take their next dose when they remember and then reach out to their health care provider for guidance and adherence support.
- People should *not* make up for a missed dose of 3HP or 1HP by taking two doses at once.

IMPAACT4TB has created **patient information leaflets** on 3HP and 1HP that contain medication trackers, calendars, and other treatment tips.

VI. ACCESS TO 3HP AND 1HP

Three manufacturers produce **quality-assured** rifapentine: Lupin, Macleods, and Sanofi. Two of these companies, Lupin and Macleods, are generic drug makers based in India. Sanofi is one of the world's largest pharmaceutical companies and is headquartered in France. Macleods was the first generic company to offer quality-assured rifapentine when it introduced its 3HP FDC formulation in 2020. Until that point, Sanofi enjoyed a de-facto monopoly on rifapentine, which contributed to the initial high price of the drug.

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

IMPAACT4TB has **PATIENT INFORMATION LEAFLETS** that help patients set a pill taking schedule and record each dose they take: <https://impaact4tb.org/medication-tracker/>.

A **QUALITY-ASSURED** drug is one that has been evaluated and approved by a stringent regulatory authority or the WHO prequalification program.

When TAG last updated this *Activist Guide* in April 2020, the lowest price of 3HP globally was US\$15 per patient-course and offered by Macleods under a deal negotiated by Unitaid and IMPAACT4TB partners.³⁵ Today, the lowest price of 3HP is US\$9.99 per patient-course (using the Lupin FDC tablets), and 1HP costs ~US\$20 (using the Lupin 300 mg rifapentine tablets plus the cost of isoniazid). These prices were announced by USAID and PEPFAR at the 2023 United Nations High-Level Meeting on TB.³⁶ Global production capacity for rifapentine now stands at over 4 million 3HP patient-courses per year. **Table 1** provides an overview of rifapentine pricing as of April 2024.

TABLE 1: RIFAPENTINE PRODUCTS AND GLOBAL PRICING

Which companies make rifapentine?	What rifapentine product(s) do they make?	What does 3HP or 1HP cost?
Lupin	RPT/INH FDC tablet (300 mg rifapentine, 300 mg isoniazid)	US\$9.99/36-tablet pack <i>which equates to</i> US\$9.99 for a full course of 3HP
	RPT 300 mg tablet	US\$33.89/100-tablet pack <i>which equates to</i> ~US\$20 for a full course of 1HP, inclusive of cost of isoniazid
	RPT 150 mg functionally scored, dispersible tablet for children	US\$13.80/100-tablet pack <i>which equates to</i> US\$6.53–US\$15.80 for a full course of 3HP depending on child’s weight, inclusive of cost of isoniazid
Macleods	RPT/INH FDC tablet (300 mg rifapentine, 300 mg isoniazid)	US\$10.96/36-tablet pack <i>which equates to</i> US\$10.96 for a full course of 3HP
	RPT 300 mg tablet	Price forthcoming (expected to be comparable to price of Lupin RPT 300 mg tablet listed above)
	RPT 150 mg functionally scored, dispersible tablet for children	Under development
Sanofi	RPT 150 mg tablet	US\$7.15/24-tablet pack <i>which equates to</i> US\$22 for a full course of 3HP, inclusive of cost of isoniazid ~US\$33 for a full course of 1HP, inclusive of cost of isoniazid

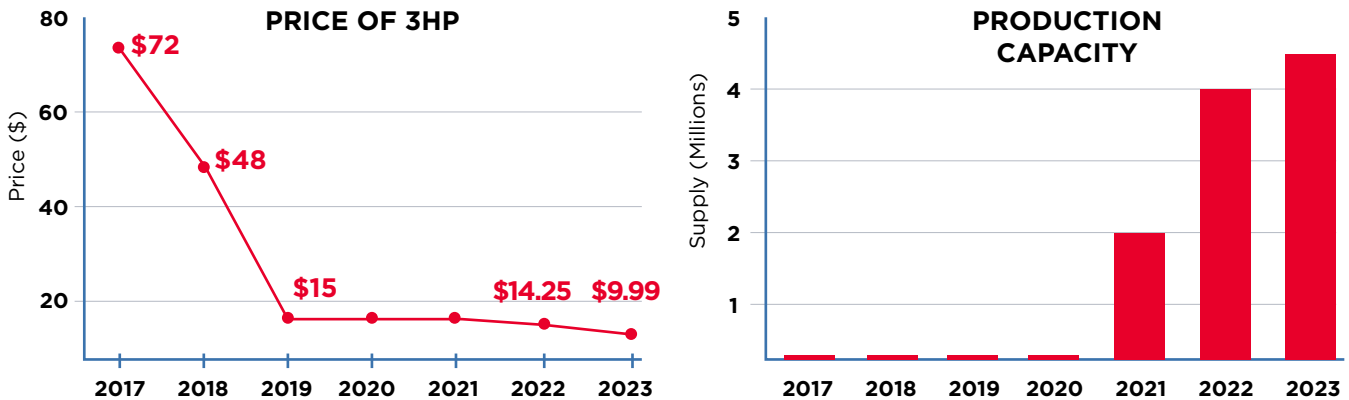
FDC = fixed-dose combination; INH = isoniazid; mg = milligram; RPT = rifapentine; 3HP = 12 weeks of once-weekly isoniazid and rifapentine; 1HP = one month of daily isoniazid and rifapentine

Note: 1HP, because it is taken daily, requires taking more rifapentine than 3HP and therefore will always cost more than the 3HP regimen.

Regimen costs calculated using prices listed in Global Drug Facility catalogue (Jan. 2024).

The market entry of Macleods in 2020 and then Lupin in 2022 introduced competition between two generic suppliers and Sanofi that has greatly improved the affordability and availability of rifapentine (see **Figure 5**). However, affordability (lower prices) did not simply follow from availability (higher production capacity) and market competition (multiple suppliers). This healthier market had to be created through outside intervention: by activists who campaigned for lower prices, by community advocates who built demand for 3HP and 1HP, by national TB programs that started offering rifapentine-based TPT, and by global buyers who banded together to negotiate successively more favorable deals with manufacturers. What looks like a simple story of market competition is a lesson in the power of activism, demand creation, pooled procurement, collective bargaining, and strategic supplier engagement to shape markets for more equitable outcomes.

FIGURE 5: IMPROVEMENTS TO RIFAPENTINE AFFORDABILITY AND AVAILABILITY



SPOTLIGHT: NO PATENTS ON PREVENTION! KEEPING RIFAPENTINE IN THE PUBLIC DOMAIN

Rifapentine is an old drug, first discovered in the 1960s. This means that any **patents** on rifapentine expired a long time ago. 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. If granted and enforced, these patents could have given 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.³⁷

Patents are intended to reward innovation. In the case of 3HP, combining two decades-old, off-patent drugs was more obvious than innovative. Sanofi’s patent filings were especially indefensible considering that public funding underwrote most of the research behind 3HP and 1HP. To prevent private capture of a public good, in late 2019 activists in India, Thailand, and several other countries lodged pre-grant patent oppositions encouraging national patent authorities to reject Sanofi’s applications. The oppositions argued that Sanofi’s claims did not fulfill basic patentability criteria such as novelty and non-obviousness. Around the same time, Sanofi withdrew its patents from the European Patent Office and in Indonesia and India.³⁸

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.

In a victory for access to medicines activists, in late 2020, Sanofi announced that it was voluntarily withdrawing its 3HP FDC patent applications everywhere they remained pending and would abandon patents in countries where they had already been granted. In a letter to TAG, the company pledged: “Sanofi commits not to reinstate any of the patents/applications, and not to initiate any action against any party who would like to manufacture the specific formulations of the combinations once covered by Sanofi’s two patent families.”³⁹

For more information: The Access to Rights and Knowledge Foundation, an IMPAACT4TB community partner in Nagaland, India, published a guide to help grassroots activists understand how they can push back against pharmaceutical corporation patenting practices that impede access to essential medicines.

FOR MORE INFORMATION on the 3HP patent story, see TAG’s publication *Isoniazid/Rifapentine (3HP) Access Roadmap and Patent Landscape* and a community guide by ARK Foundation, *No Patents on Prevention!*

VII. TAKE ACTION! KEY ADVOCACY MESSAGES

Access to the highest standard of TB prevention is an essential part of the human rights to health and scientific progress. The right to health requires that governments ensure the availability, accessibility (affordability), acceptability, and quality of TB services and commodities, including preventive treatment.⁴⁰ Under the right to science, governments have a duty “to make available and accessible to all persons, without discrimination, especially to the most vulnerable, all the best available applications of scientific progress necessary to enjoy the highest attainable standard of health.”⁴¹ This is the central demand of the **1/4/6x24 Campaign**: that every eligible person with TB infection or disease have access to evidence-based, short-course treatment regimens. Thus the **#RightToPreventTB** hinges on access to the rifapentine-based regimens 3HP and 1HP.

In the spirit of these campaigns, this section provides some key messages advocates can use to hold governments accountable for ‘getting it right’ with TPT: the right regimen, offered to the right person, based on the right diagnosis or indication of risk, available in the right setting, and prescribed with the right information and counselling.



TB preventive treatment 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.⁴² Other compelling evidence comes from modelling studies; one found that by scaling up short-course TPT to PLHIV and close contacts, governments can prevent 850,000 deaths through 2035, including 700,000 averted deaths among children.⁴³ *Activists should call on governments to offer TPT to all people at risk of TB and raise awareness among TB-affected communities so that people demand access to TPT as their human right.*

Launched by TAG and allies in 2022, the **1/4/6x24 CAMPAIGN** aims to accelerate equitable uptake of newly discovered safer, shorter regimens to cure all forms of TB. The “1” in the campaign name refers to 1HP and 3HP.

The **#RIGHTTOPREVENTTB** campaign has resources that activists can use to advocate for 3HP and 1HP.



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. TPT guidelines should look beyond TB/HIV integration (though this remains important!) and address the use of 3HP and 1HP in a broad swath of populations at risk of TB, including children, pregnant people, close contacts, people who use drugs, homeless people, incarcerated persons, people preparing for organ transplantation, and other vulnerable groups. In addition, guidelines should respond to ongoing research; countries must rapidly update guidelines when safety data on using 3HP during pregnancy, in children aged 0–2 years, and with newer antiretrovirals become available. International donors, particularly Global Fund and PEPFAR, should financially support countries in scaling up 3HP and 1HP 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.*



3HP and 1HP should be available and affordable to all. The deals struck by global donors with Lupin, Macleods, and Sanofi have greatly improved the availability and affordability of 3HP for public purchasers in low- and middle-income countries. But the price can come down even further. Based on what it costs to manufacture rifapentine, and assuming sufficient volumes of sales, 3HP could cost well under \$10 per patient. With global targets to put at least 45 million people on TPT by 2028, lower rifapentine prices are not only possible — but necessary. For this to happen, 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.

In addition, many countries do not have access to newer formulations of rifapentine at affordable prices. This is particularly true of low-incidence countries (many high income) that do not regularly procure TB drugs through the GDF. For example, Canada relies on a Special Access Program to obtain rifapentine on an individual patient basis.⁴⁴ In the United States, local TB programs have weathered years of supply shortages of Sanofi’s 150 mg rifapentine tablet — the only rifapentine product registered with the U.S. Food and Drug Administration. In a world where TB programs everywhere are inadequately resourced, equitable access to 3HP and 1HP will depend on ensuring the availability and affordability of rifapentine for all countries regardless of income level or TB burden. *Activists should build community demand for TPT, call on manufacturers to register rifapentine products widely, and ask governments to pool demand by buying rifapentine through mechanisms like GDF.*



The quality of TPT programs matters. In the **global drive** to eliminate TB, there is a risk that countries will move quickly to start many people on TPT without paying sufficient attention to the quality and performance of TPT programs. One of the main advantages 3HP and 1HP had over IPT in clinical trials was that study participants were more likely to complete these shorter regimens. For 3HP and 1HP to live up to their potential, the same should be true outside of clinical trials in real-world settings. It is important that national TB programs track both the number of people who start TPT and the proportion who complete a full course of TPT as prescribed. Programs should also put in place **pharmacovigilance** systems to collect information on the safety of TPT. In addition, TPT should be given with patient supports such as counselling and nutritional supplementation. Communities have an important role to play in quality assurance by making sure people started on TPT receive the services they need. *Activists should devise community-led monitoring structures to track program performance, stockouts, and quality of care while supporting people taking TPT to complete the journey from their first dose to their last.*

The **GLOBAL DRIVE** to scale up TPT responds to a commitment by United Nations member states to provide TPT to 45 million people between 2023 and 2027.

PHARMACOVIGILANCE can be thought of simply as the systems to monitor drug safety after a drug is licensed and enters use in routine care. The goal is to identify, understand, and prevent adverse events.



TPT should be offered through 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 health care. One successful approach from the HIV field

is **differentiated service delivery (DSD)**. By putting people at the center of services, DSD models make it easier for people to complete treatment and remain engaged in care. For PLHIV, TPT can be incorporated into existing DSD platforms such as ART refill groups, peer-led adherence support clubs, and expert patient networks. For close contacts, including children, TPT can be offered through family-centered approaches to care (where family can refer to more than biological families and include close-knit groups of people who 'share air' and thus may share risks for TB). Achieving family-centered care may require making it safe for people with TB disease to **disclose** their status to family members, who should then receive encouragement to seek TB screening and TPT. *Activists should work with TB and HIV programs to design flexible and adaptable methods for delivering TPT centered on the holistic health needs of people and their families.*



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 likelihood of TB infection progressing to TB disease is much higher for some groups such as PLHIV, young children, malnourished people, and people who just acquired infection from a recent TB exposure. 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.⁴⁵ *Activists should raise awareness of rifampentine-based TPT, share knowledge of how to prevent TB, and ensure TB prevention programs respect human rights and individual decision-making.*

VIII. QUESTIONS FROM THE COMMUNITY

Through the Unitaid-funded IMPAACT4TB project, TAG has helped civil society and community-based organizations in over 12 countries build demand for 3HP and 1HP. Partners in Brazil, Cambodia, Ghana, Kenya, Indonesia, India, Malawi, Mozambique, Nigeria, Sierra Leone, South Africa, Tanzania, Zambia, and Zimbabwe promoted treatment literacy among PLHIV, TB-affected families, and other groups of people at risk of TB to raise awareness of TPT. Across countries, community members asked similar questions; some of the most frequently asked questions are answered below.



Question: *Why should I take TPT when I am not sick and feel healthy?*

Answer: People with TB infection do not feel sick and are not contagious, but in some people, TB infection will develop into active TB disease. This risk is higher if someone has specific risk factors for TB — for example, they live in a crowded space, do not have enough to eat, or have certain comorbidities such as HIV or diabetes. Disease risk is also higher among people recently exposed to TB (i.e., within the past two years). Taking TPT reduces the risk of TB infection becoming TB disease. It is a way for people who have been exposed to TB but are not yet sick to make sure they stay healthy. The **Global Coalition of TB Advocates** explained it this way: "Treating TB infection even when one is not ill is important and will provide protection, much like fire proofing a house even when there is no fire." In other words, TPT is about getting ahead of TB before it becomes a problem.

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.

TAG and IMPAACT4TB developed two guides to support people with TB **DISCLOSE** their health status and to encourage their family members to seek TB screening and TPT:

After TB Exposure: Tips for Protecting Yourself and the People in Your Life

Sharing Your TB Diagnosis with the People in Your Life: Tips for Engaging Their Support

The **GLOBAL COALITION OF TB ADVOCATES (GCTA)** published a community TPT guide, *How to Protect Ourselves from TB*.



Question: *Does a single course of TPT provide adequate protection against TB?*

Answer: Yes, for most people a single course of 3HP or 1HP provides adequate 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. 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. Importantly, all WHIP3TB participants were on ART. This finding indicates that 3HP provides durable protection against TB among PLHIV on ART for up to two years, even in countries with high rates of TB transmission.⁴⁶ A different study in Brazil found that adults and adolescents who received either the 4R or 9H regimen were protected for up to 12 years. Among this mostly HIV-negative population, “the effects of TPT completion were sustained [and] additional courses or prolonged TPT was not necessary for long-term protection” among participants who completed their initial TPT course with good adherence.⁴⁷ The main takeaway: there is no need to repeat 3HP or any other TPT regimen annually, but there are situations in which someone should receive TPT more than once — keep reading.



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

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



Question: *Since 3HP and 1HP are newer regimens, can someone take these drugs if they have already received IPT in the past?*

Answer: Yes, someone can take 3HP after taking IPT. If someone took IPT in the past but then later has a new TB exposure, they should be screened for TB disease and consider taking another course of TPT if recommended by a health care worker. Based on individual circumstances and medical history, health care workers will determine the most appropriate TPT regimen for someone to receive. **South Africa’s national guidelines** on TPT have clear guidance on this question.

In **ZAMBIA**, national TPT guidelines recommend that PLHIV take TPT every three years: “Due to ongoing exposure to TB, it is recommended that TPT should be repeated 3 years after completion of TPT in PLHIV.”

According to **SOUTH AFRICA’S NATIONAL GUIDELINES**: “TPT is indicated at each new TB exposure.”

and

“TPT should be offered to all people (regardless of age or HIV status) after significant TB exposure and those who are immunocompromised (regardless of known exposure) after TB disease has been ruled out, i.e., a TB test-and-treat approach.”



Question: *Can someone take TPT if they have previously been treated for active TB disease?*

Answer: Yes, people treated for active TB disease in the past can receive TPT. A person who has had TB before is more likely to have TB again compared with someone who has never had the disease. This makes TB survivors an important priority group for prevention efforts. If someone treated for TB disease is newly exposed to TB then they should be screened for TB and offered TPT once TB disease is ruled out. The WHO continues to recommend **secondary preventive treatment** for groups at high risk of recurrent TB, including adults and children with HIV. In practice, few TB and HIV programs provide secondary preventive treatment, though this is an intervention that communities can ask for in national guidelines.



Question: *In our country, 3HP is rarely prescribed with vitamin B6 — is that okay?*

Answer: Vitamin B6 is given with TPT to prevent a side effect called peripheral neuropathy, which is a feeling of numbness, tingling, or pain in the hands and feet that indicates nerve damage. Peripheral neuropathy is most closely associated with isoniazid. It can be very painful, but it is preventable and usually reversible with vitamin B6. Longer courses of IPT are more likely to cause peripheral neuropathy than 3HP and 1HP. For this reason, many people will be able to tolerate 3HP or 1HP without receiving vitamin B6. If someone starts to experience signs of peripheral neuropathy, they should tell a health care worker right away and ask about adding a vitamin B6 supplement to their regimen. PLHIV are at a higher risk of peripheral neuropathy and therefore should receive vitamin B6 together with TPT. Based on the experience of IMPAACT4TB community partners, people who receive vitamin B6 with 3HP report much higher satisfaction with their regimen than those who do not. Vitamin B6 is an inexpensive, simple thing programs can offer to make the experience of taking TPT easier on people. National TB programs should make every effort to provide vitamin B6 together with 3HP or 1HP, but its absence is not a reason to delay TPT initiation in someone at risk of TB.



Question: *Many people on TPT report nausea, having headaches, or feeling fatigued. What advice should we give them to ensure that they complete their treatment?*

Answer: Most people tolerate taking 3HP and 1HP with few side effects. But among people who do experience side effects, headache, fatigue, and nausea are among the most common. For most people, these feelings are mild and disappear with time. But if side effects linger, or get worse instead of better, then people should report them to a health care worker and seek medical advice.

In **SECONDARY PREVENTIVE TREATMENT**, 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).

SPOTLIGHT: ADDRESSING TPT DRUG STOCKOUTS

The scale-up of 3HP and 1HP has not come without challenges. One of the obstacles most frequently reported by community advocates is the unreliable supply of 3HP and 1HP, which sometimes manifests as drug shortages or even outright drug stockouts. Advocates have warned that stockouts can decrease the enthusiasm and confidence of health care workers in prescribing TPT. There are several actions that advocates can take to address stockouts.

- **Advocate for equitable distribution.** Health care workers can advocate for a more equitable distribution of essential TPT medicines. This can involve engaging with policymakers, health authorities, and other relevant stakeholders to highlight the importance of providing adequate stock to meet demand.
- **Strengthen supply chain management.** Improving supply chain management is crucial. This can include enhancing forecasting and quantification methods to accurately estimate the demand for TPT in different populations. It may also involve improving procurement processes and distribution systems to ensure a consistent supply of medicines. Advocates should ensure that drugs are not sitting at central medical storage facilities for too long by tracking delivery of 3HP and 1HP in their countries.
- **Monitor and report stock levels through community-led monitoring.** This will help health care workers actively monitor the stock levels of TPT and vitamin B6. The frequency and severity of stockouts can then be reported to higher-level bodies to ensure that shortages are addressed by the appropriate authorities.
- **Explore alternative sources.** In situations where there is limited stock of 3HP or 1HP, health care workers can undertake a prioritization exercise to make sure that people who have already started TPT have enough medicine to complete their regimen. In situations where there are still stocks of isoniazid, people can receive IPT and vitamin B6 as an alternative form of TPT.

IX. OVERCOMING RESISTANCE TO IMPLEMENTING 3HP AND 1HP

Activists will hear many excuses for not implementing TPT. Some common excuses for not using TPT are presented 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 TPT in PLHIV or child household contacts less than five years old. 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 infection** are imperfect, expensive, and come with several important limitations, the biggest being that they do not directly measure infection or the risk of progression to active TB.⁴⁸ Therefore, testing should never be a barrier to offering TPT to PLHIV and young children.

WHO GUIDELINES do not make a test for infection a requirement to start TPT in PLHIV or young child contacts: "TB infection testing is desirable to identify individuals at highest risk for developing active TB. However, it is not required in PLHIV or in household contacts aged under 5 years."

CURRENT TESTS FOR INFECTION include interferon-gamma release assays (IGRAs), tuberculin skin tests (TST), and newer antigen-based skin tests like the C-Tb test.

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 health care workers identify people who are more likely to benefit from TPT (generally speaking, those with a positive test benefit more from TPT than those without). WHO guidelines note: “In HIV-negative household contacts aged 5 years and older, and in other risk groups, TB infection tests are recommended, but their unavailability should not be a barrier to treating people who are judged to be at higher risk.”⁴⁹ Remember: 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 (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.⁵⁰ 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.⁵¹ Most drug-resistant TB arises from inadequate treatment of active TB disease. Rather than withhold TPT out of fear of drug resistance, TB programs should 1) ensure all people starting TPT are first screened to rule out 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.



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 only do one thing at a time. This either/or mentality traps TB-affected communities in a false economy of partial solutions. In fact, the WHO found that a dollar invested in TB screening and TPT has a substantial **return on investment**.⁵² Denying people proven interventions like TPT is a violation of their human rights to health and scientific progress. When considering different TB interventions, we need a both/and mindset change. TB programs must do more than diagnose and treat active TB disease. Programs should actively identify TB in the community (active case finding), conduct contact investigation after diagnosing someone with TB, encourage TB disclosure to eliminate stigma, offer TPT to contacts of people with TB, and support people taking TPT to complete treatment. A TB program without TPT is not living up to its human rights and public health responsibilities.

A WHO investment case found that every dollar spent on TB screening and TPT produces **A RETURN ON INVESTMENT** of US\$27 in Kenya and US\$39 in South Africa by 2050.

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

APPENDIX: GIVING 3HP WITH DOLUTEGRAVIR-BASED HIV TREATMENT

Researchers supported by IMPAACT4TB undertook two studies to see if 3HP can be safely given with dolutegravir-based HIV treatment. The first study, DOLPHIN, assessed the safety and PK of coadministering 3HP and dolutegravir in people who were already taking ART and switching to TLD. The second study, DOLPHIN Too, looked at the safety and PK of 3HP and dolutegravir in people who were ARV naive, meaning they were starting HIV treatment for the first time.

Each study sought to answer two important questions: 1) Is it safe to take 3HP with dolutegravir-based ART? 2) Does the dose of dolutegravir need to be adjusted to achieve HIV viral suppression? Answering these questions was important because 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 HIV viral suppression while taking the two treatments together.

Here is what each study found:

DOLPHIN:⁵³ This phase I/II study enrolled 60 adults who were already on ART, virally suppressed, and switching from efavirenz-based ART to TLD.

- Safety: 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.
- PK: As expected, rifapentine increased how quickly the body cleared dolutegravir, which reduced dolutegravir concentrations and drug exposures, but not by a clinically meaningful amount. All participants received the standard dose of dolutegravir (50 mg once a day) without adjustment and maintained HIV viral suppression. (One participant had a detectable HIV viral load reading, but this occurred four weeks after completing 3HP and was judged unrelated to rifapentine.)

DOLPHIN Too:^{54,55} This phase I/II study enrolled 75 ARV-naive adults: 50 received 3HP and 25 were given 6H. In contrast to the original DOLPHIN study, participants started TPT on the same day as beginning ART for the first time with a dolutegravir-based regimen.

- Safety: Starting TPT and dolutegravir at the same time was safe, with no treatment-related serious adverse events seen in either the 3HP or the 6H group. There were no deaths. All 75 participants completed their TPT.
- PK: As expected, rifapentine significantly reduced dolutegravir drug levels, but all participants receiving 3HP still had enough dolutegravir in their body to achieve and maintain rapid HIV viral suppression.

Main takeaway: 3HP can be safely used with dolutegravir-based ART without adjusting dolutegravir doses. This is true for people who are already on ART and for those who are starting ART for the first time. National governments should feel confident using 3HP in HIV programs, and donors, including the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund, should support countries in procuring 3HP as an essential part of the HIV clinical care package.

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