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Treatment Action Group

AN ACTIVIST'S GUIDE TO SHORTER TREATMENT

FOR DRUG-SENSITIVE TUBERCULOSIS

October 2021

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October 2021
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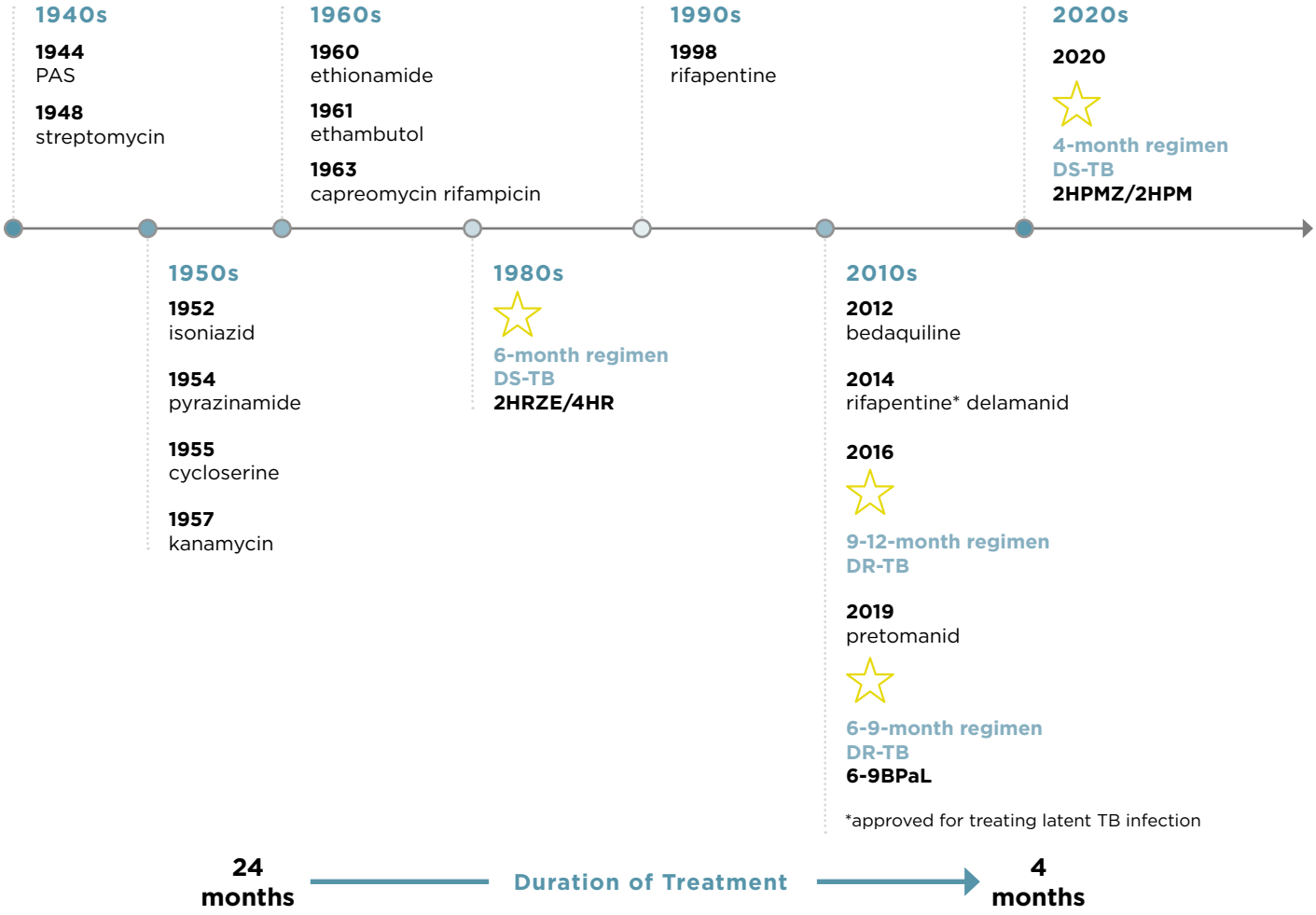
I. INTRODUCTION AND BACKGROUND

After a decades-long wait, shorter treatment for drug-sensitive tuberculosis (TB) for adults and children is finally possible. This Activist's Guide reviews two landmark clinical trials (S31/A5349 and SHINE) showing that adults, adolescents, and some children can be cured of TB in as little as four months. These results, first presented in late 2020, follow closely behind a series of dramatic improvements to treatment regimens for drug-resistant TB (see Figure 1).

FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES



It took multiple attempts to demonstrate that drug-sensitive TB treatment can be shortened to less than six months. Three large phase III trials sought to shorten treatment by introducing a fluoroquinolone (REMoxTB, OFLOTUB)—one of them also introduced rifapentine (RIFAQUIN)—and all failed to demonstrate **noninferiority** to the six-month standard of care.[1,2,3] It's unsurprising that shortening treatment for drug-sensitive TB has been more difficult than shortening treatment for drug-resistant TB. The six-month standard of care for drug-sensitive TB in place since the 1980s: (1) contains rifampicin and isoniazid, two powerful drugs which each have strong **bactericidal and bacteriostatic activity**; (2) has a treatment success rate of up to 95 percent in clinical trials (closer to 80 percent under program conditions); and (3) is safe and well-tolerated by most people. Combined, these factors have made shortening TB treatment further a daunting challenge.

In 2020, more than 40 years after the advent of the six-month regimen, the tide was finally turned by TBTC Study 31/ACTG A5349 (S31/A5349), a phase III randomized controlled study conducted by the **TBTC** and **ACTG**. Conducted in 13 countries in Africa, the Americas, and Asia, S31/A5349 found a four-month rifapentine- and moxifloxacin-containing regimen noninferior to the six-month standard of care in adults and adolescents.[4] The new four-month regimen has been tagged "4-Short TB" by the **Community Research Advisors Group (CRAG)**.[5] In the same year, the SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children), a phase III randomized controlled study sponsored by University College London, determined that the continuation phase of the standard six-month treatment regimen for drug-sensitive TB could be shortened from four to two months for children with **non-severe TB**.[6]

It's important for activists to know the details of shorter TB treatment regimens (see Figure 2) because the coming years will bring results from even more treatment-shortening research. Don't get too comfortable—several ongoing phase III clinical trials are similarly seeking to shorten treatment for drug-sensitive TB by optimizing the rifamycin selection and dose (RIFASHORT, NCT02581527), introducing new and repurposed medicines (SimpliciTB, NCT03338621), or a combination of both strategies (TRUNCATE-TB, NCT03474198; CLO-FAST, NCT04311502). Using even newer drugs, including those with novel mechanisms of action, and potentially in combination with **host-directed therapies,** researchers hope to shorten treatment regimens for TB even further in the future.

NONINFERIORITY means that the experimental treatment intervention does not perform worse than the control. Said differently, the difference between the experimental treatment intervention and the control falls within a prespecified acceptable range (called the noninferiority margin). Testing noninferiority is different from testing for either superiority or equivalence.

A TB drug is considered to have **BACTERICIDAL** activity when it effectively kills mycobacteria.

A TB drug is considered to have **BACTERIOSTATIC** activity when it effectively prevents mycobacteria from replicating.

THE TUBERCULOSIS TRIALS CONSORTIUM (TBTC) is an international clinical trials network funded by the U.S. Centers for Disease Control and Prevention (CDC).

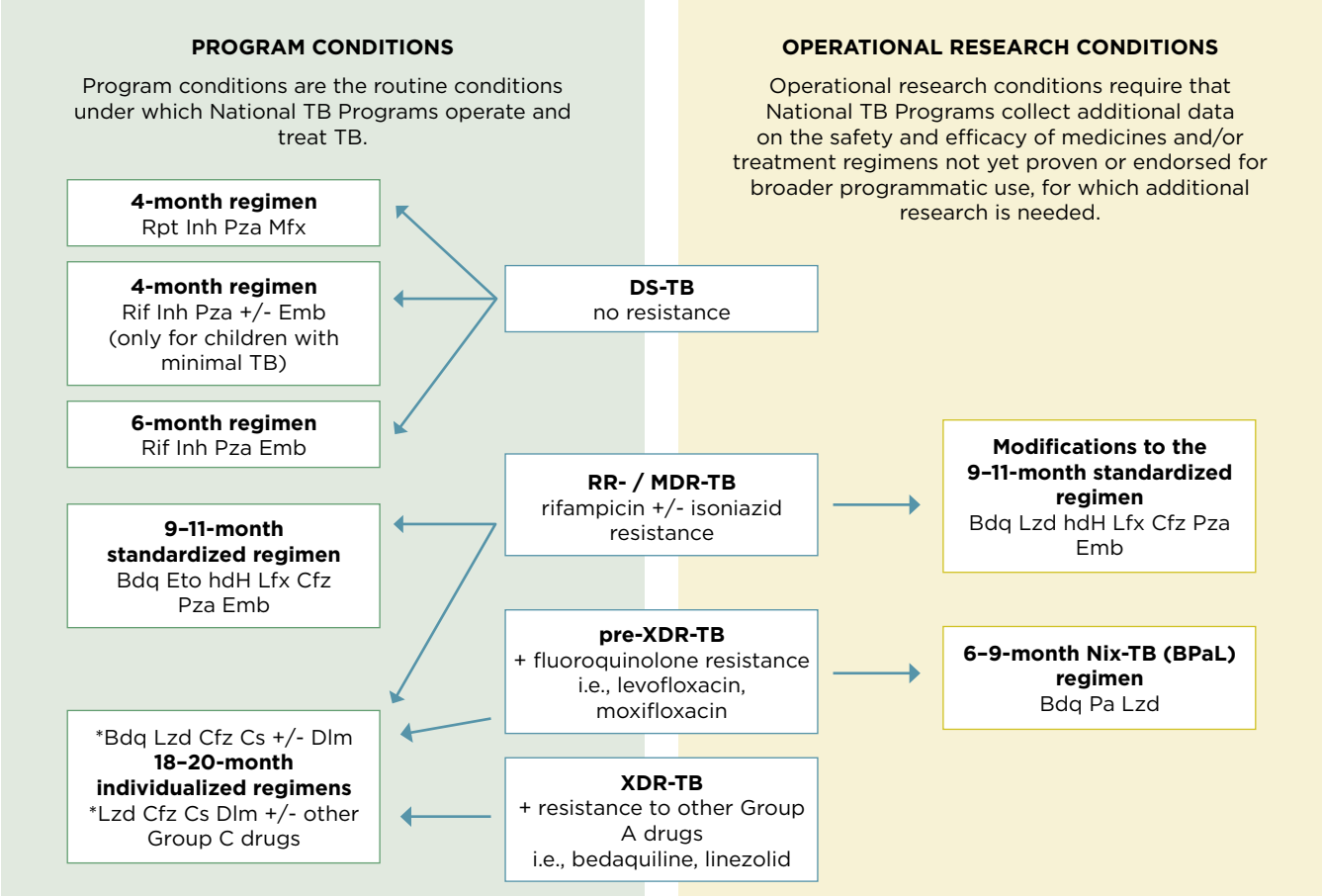
THE AIDS CLINICAL TRIALS GROUP (ACTG) is and international clinical trials network funded by the U.S. National Institutes of Health (NIH).

The **CRAG** is the community advisory board to the TBTC and has been closely involved in S31/A5349 since its inception, influencing key parts of the trial design, implementation, and approach to results dissemination.

NON-SEVERE TB is TB that is both smear negative and non-severe in form, i.e., in lymph nodes outside of the chest ("extra-thoracic lymph node TB") or, if inside of the chest ("intrathoracic TB"), confined to one lobe of the lungs with no cavities or to lymph nodes without significant airway obstruction and no bilateral airway narrowing (as determined on chest X-ray).

HOST-DIRECTED THERAPIES aim to enhance the human (host) immune response or to modulate host factors that may improve the ability of antibiotics to reach and kill TB bacteria in the body, potentially increasing the speed at which TB cure is achieved, and/or reducing lung damage and/or the likelihood of relapse.

FIGURE 2. TREATMENT REGIMENS FOR TUBERCULOSIS RECOMMENDED BY THE WORLD HEALTH ORGANIZATION



*these are examples of individualized regimens containing 4-5 medicines selected according to the WHO table of priority medicines; the composition of individualized regimens will vary depending on the individual's profile of drug-resistance and potentially other factors.

HIGHLIGHT BOX 1: HOW TO USE THIS GUIDE

We wrote this guide to provide activists with information about shorter treatment regimens for drug-sensitive TB, including recent trial results, key considerations for special populations, and anticipated access barriers. The guide also equips activists with actions they can take and arguments they can use to advocate for access to shorter treatment regimens for TB.

Throughout this guide, regimens are represented in short form where numbers represent the duration of treatment in months, letters represent the individual drugs that make up each regimen, and slashes are used to separate the intensive and continuation phases of treatment. For example, 2HRZE/4HR represents the six-month standard of care regimen for drug-sensitive TB: two months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by four months of isoniazid and rifampicin. 2HPZM/2HPM represents the four-month regimen that successfully demonstrated noninferiority in S31/A5349: two months of isoniazid, rifapentine, pyrazinamide, and moxifloxacin, followed by two months of rifapentine, pyrazinamide, and moxifloxacin. The cheat sheet below provides commonly used abbreviations for each TB medicine.

TB MEDICINES ABBREVIATIONS CHEAT SHEET

amikacin	Am	**meropenem**	Mpm
bedaquiline	J, Bdq	**moxifloxacin**	M, Mfx, Mx
clofazimine	C, Cfz	**p-aminosalicylic acid**	PAS
cycloserine	Cs	**pretomanid**	Pa
delamanid	D, Dlm	**prothionamide**	Pto
ethambutol	E, Emb	**pyrazinamide**	Z, Pza
ethionamide	Eto	**rifabutin**	B, Rfb
high dose	Hd	**rifampicin**	R, Rif
imipenem-cilastatin	Imp-Cln	**rifapentine**	P, Rpt
isoniazid	H, Inh	**streptomycin**	S
levofloxacin	L, Lfx, Lx	**terizidone**	Trd, Tzd
linezolid	Lzd, Lz		

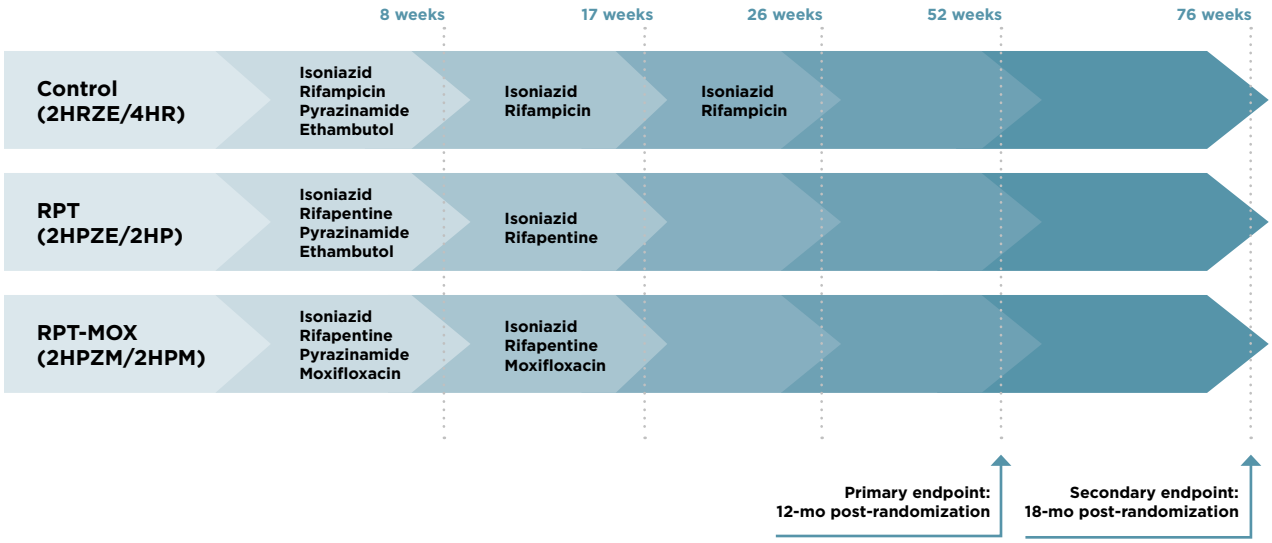
II. THE EFFICACY AND SAFETY OF FOUR-MONTH REGIMENS FOR DRUG-SENSITIVE TB

TBTC Study 31/ACTG A5349 (S31/A5349)

The objective of S31/A5349 was to evaluate the efficacy, safety, and tolerability of two rifapentine-based four-month regimens for the treatment of adults and adolescents with drug-sensitive pulmonary TB. S31/A5349 enrolled 2,516 participants from 34 sites in **13 countries**. Trial participants represented a diverse range of people with TB, including adolescents down to 12 years of age (2.7%), people living with HIV with CD4 counts down to 100 cell/mm^3 (8.5%), and people with cavitary disease (73%). The trial compared two four-month regimens, both with rifapentine (1,200 mg daily) in place of rifampicin, and one with moxifloxacin (400 mg daily) in place of ethambutol (2HPZE/2HP and 2HPZM/2HPM) to the six-month standard of care for drug-sensitive TB (2HRZE/4HR).

The **13 COUNTRIES** included in S31/A5349 are Brazil, China (Hong Kong), Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, the United States, Vietnam, and Zimbabwe.

FIGURE 3. S31/A5349 STUDY SCHEMA



The four-month rifapentine- and moxifloxacin-containing regimen (2HPZM/2HPM) was shown to be noninferior to the six-month standard of care (2HRZE/4HR). Said another way, unfavorable treatment outcomes (i.e., treatment failure, relapse, death) observed among people randomized to receive the four-month rifapentine- and moxifloxacin-containing regimen were no worse than those observed among people randomized to receive the six-month standard of care. In terms of safety, which is measured by all-cause mortality and grade three or higher **adverse events**, no significant differences were observed between the two treatment regimens (Table 1).[7]

In clinical trials, **ADVERSE EVENTS** are often "graded" using standard scales so they can be compared among sites and studies. The scale usually ranges from 1 to 5, with 1 being a mild event and 5 being death.

TABLE 1. EFFICACY AND SAFETY OUTCOMES IN S31/A5349

	EFFICACY		SAFETY	
Regimen	**Favorable outcomes**	**Unfavorable outcomes**	**Grade 3 or higher AEs**	**All-cause mortality**
Control (2HRZE/4HR)	90.4% (656/726)	9.6% (70/726)	19.3% (159/825)	0.8% (7/825)
RPT-MOX (2HPZM/2HPM)	88.4% (668/756)	11.6% (88/756)	18.8% (159/846)	0.4% (3/846)

Percentages of favorable and unfavorable outcomes represented in this table are based on the assessable population, which excludes participants who experience an event that is unlikely related to TB disease or the intervention (e.g., death from violent or accidental cause, loss to follow-up after completing treatment). The safety analysis includes all participants, which is why the denominators are different in the columns for grade 3 or higher adverse events (AEs) and all-cause mortality (safety endpoints) compared with the columns for favorable and unfavorable outcomes (efficacy endpoints).

What about people living with HIV?

S31/A5349 enrolled 214 people living with HIV (8.5% of the trial population) with a CD4 T-cell count of at least 100 cells per cubic millimeter (the median CD4 T-cell count was 344 [223–455] cells/mm^3). PLHIV were enrolled using a phased approach, starting with people already on an efavirenz-based regimen and then expanding to include PLHIV initiating an efavirenz-based regimen within the first eight weeks of TB treatment to evaluate drug-drug interactions between efavirenz and rifapentine. The investigators found that the four-month moxifloxacin- and rifapentine-containing regimen performed similarly to the six-month standard of care among PLHIV and was safe and well-tolerated (Table 2).[8]

TABLE 2. EFFICACY AND SAFETY OUTCOMES IN S31/A5349 AMONG PLHIV

	EFFICACY				SAFETY			
Regimen	**Favorable outcomes**		**Unfavorable outcomes**		**Grade 3 or higher AEs**		**All-cause mortality**	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Control (2HRZE/4HR)	84.7% (50/59)	90.8% (605/666)	15.3% (9/59)	9.2% (61/666)	21.4% (15/70)	19.1% (144/755)	2.9% (2/70)	0.7% (5/755)
RPT-MOX (2HPZM/2HPM)	91.4% (53/58)	88.1% (615/698)	8.6% (5/58)	11.9% (83/698)	13.9% (10/72)	19.3% (149/774)	0% (0/72)	0.4% (3/774)

Percentages of favorable and unfavorable outcomes represented in this table are based on the assessable population, which excludes participants who experience an event that is unlikely related to TB disease or the intervention (e.g., death from violent or accidental cause, loss to follow-up after completing treatment). The safety analysis includes all participants, which is why the denominators are different in the columns for grade 3 or higher adverse events (AEs) and all-cause mortality (safety endpoints) compared with the columns for favorable and unfavorable outcomes (efficacy endpoints).

There were no significant drug-drug interactions between rifapentine (1,200 mg daily) and efavirenz.[9] Studies to evaluate drug-drug interactions between other antiretroviral (ARV) medications (e.g., dolutegravir, tenofovir alafenamide) and rifapentine administered in the context of the **3HP** and **1HP** regimens for TB prevention are ongoing.[10] When dosed at 900 mg weekly in the context of the 3HP regimen for TB prevention in adults, rifapentine can be safely administered with dolutegravir without any dose adjustments.[11] The ACTG plans to evaluate drug-drug interactions between dolutegravir and rifapentine administered at a higher dose (1,200 mg daily) (ACTG A5406) to determine whether any dose adjustments are required while PLHIV on dolutegravir-based regimens are taking TB treatment with this new regimen.

What about children and young people?

S31/A5349 enrolled 68 adolescents (12–17 years old, 2.7% of the trial population) from 10 sites in seven countries. Although numbers were small, the four-month rifapentine- and moxifloxacin-containing arm performed similarly in adolescents, of which 59 (87%) were 15 years or older and 59 (87%) had cavitary disease.[12] No adolescents enrolled in the study were living with HIV. Studies are ongoing to determine the dose and safety of rifapentine administered to children 12 years of age and younger with and without HIV in the context of the 3HP and 1HP regimens for TB prevention.[13] Further investigations will be required to determine the dose and safety of rifapentine administered to children in the four-month moxifloxacin- and rifapentine-containing regimen, and whether dose adjustments will be required for certain ARV medications when administered alongside higher daily doses of rifapentine to children living with HIV.

What about pregnant people?

Pregnant people were not eligible to participate in S31/A5349. However, 34 participants became pregnant during study treatment (1.4% of the trial population), including nine people receiving treatment with the rifapentine- and moxifloxacin-containing regimen. In line with the study protocol, people who became pregnant discontinued study treatment and were followed for pregnancy, maternal, and infant outcomes. Analyses of these data were not available at the time of publication. A study conducted in pregnant and postpartum people with and without HIV determined that no dose adjustments are necessary to administer rifapentine in the 3HP regimen for TB prevention during pregnancy.[14] Additional data will be required to determine the *safety* of rifapentine during pregnancy, and whether any dose adjustments are required to administer rifapentine to pregnant people with and without HIV in the four-month moxifloxacin- and rifapentine-containing regimen.

3HP: three months of once weekly rifapentine (900 mg) and isoniazid for TB prevention.

1HP: one month of daily rifapentine (600 mg) and isoniazid for TB prevention.

What about people who want to avoid pregnancy?

S31/A5349 did not evaluate drug-drug interactions between rifapentine and hormone-based contraceptives, however, it is known that rifamycins can decrease their effectiveness. In ACTG study A5338 (NCT02412436), women living with HIV receiving rifampicin-based TB treatment together with Depo-Provera (DPMA) had higher clearance of and reduced exposures to **medroxyprogesterone acetate (MPA)**.[15] In this study, that meant 12 percent of the 42 women enrolled ultimately had levels of MPA that might have been too low to prevent pregnancy. This suggests that to prevent contraceptive failure, more frequent DPMA dosing might be required during TB treatment (e.g., every 8 to 10 weeks instead of every 12 weeks). DPMA has not been studied with rifapentine. Until these data are available, people who want to avoid pregnancy should consider using a non-hormone-based or an additional form of contraception while taking TB treatment with the new four-month rifapentine-containing regimen.

MEDROXYPROGESTERONE ACETATE is the active ingredient in Depo-Provera, an injectable form of contraception that activates the same receptors as the hormone progestin, preventing ovulation and pregnancy.

What about people with diabetes mellitus?

S31/A5349 enrolled 83 people with diabetes mellitus (DM) (3.3% of the trial population). There was no difference in outcomes among people with DM in the trial. Interactions between rifapentine and **hypoglycemic agents** have not been well studied; however, rifampicin is known to interact with them.[16] **Insulin analogs** may be preferentially used to manage DM in people receiving treatment for TB with either the new four-month or standard six-month regimen, given that they do not seem to be affected by rifamycins. Other factors associated with DM, such as age and kidney or renal impairment, may additionally affect hypoglycemic and antituberculosis drug metabolism, necessitating close monitoring for drug and blood glucose levels and adverse effects (e.g., hyperglycemia, hypoglycemia, liver toxicity, gastrointestinal reactions, etc.) during TB treatment.

HYPOGLYCEMIC AGENTS are antidiabetic drugs designed to help people with type 2 diabetes manage their condition by regulating blood sugar levels, e.g., by stimulating insulin secretion, reducing sugar production, enhancing sugar removal, or slowing the absorption of food.

INSULIN ANALOGS are synthetic forms of insulin that are injected under the skin and, once absorbed, act like human insulin.

What about people with extrapulmonary TB?

Extrapulmonary TB can be more severe and difficult to treat than pulmonary TB given variability in the abilities of TB medicines to reach and penetrate sites of TB disease outside of the lungs. Non-severe forms of extrapulmonary TB are generally assumed to be treatable with the same combination of medicines and duration of use as pulmonary TB. People with extrapulmonary TB were not eligible to participate in S31/A5349 so there are no data to support whether the four-month rifapentine- and moxifloxacin-containing regimen will have adequate efficacy against extrapulmonary TB, especially forms that are considered more severe and that currently require treatment for up to 12 months using the standard regimen for drug-sensitive TB.

EXTRAPULMONARY TB is TB outside of the lungs, e.g., in the bones, brain, spine, etc.

What about people being treated for hepatitis C virus?

Rifamycins are known to induce liver enzymes that metabolize direct-acting antiviral drugs (DAAs) used to treat hepatitis C virus (HCV), decreasing their concentrations to subtherapeutic levels. As such, neither rifampicin nor rifapentine are recommended for use together with the DAAs used to treat HCV.[17] People with HCV should consult with their health care providers about starting rifamycin-containing TB treatment regimens either before or after completing treatment for HCV.

What about people who take psychotropic medicines?

Similar to what is observed with DAAs used to treat HCV, rifamycins induce liver enzymes that metabolize many antidepressants and antipsychotic medications. As a result, rifamycins can decrease concentrations of antidepressants and antipsychotic medicines, in some cases to subtherapeutic levels, necessitating dosing adjustments. Most existing information on drug-drug interactions between rifamycins and psychotropic medicines is specific to rifampicin. Interactions between rifapentine and psychotropic medicines can be assumed but have not been as well studied. People who need to take psychotropic medicines should consult with their health care providers about whether their antidepressants and/or antipsychotic medicines can be safely combined with rifampicin- or rifapentine-containing TB treatment regimens and to determine whether any dose adjustments are necessary.

What about people who use drugs?

S31/A5349 enrolled three people who inject drugs and 174 people who use non-injecting drugs (0.1% and 7.4% of the trial population, respectively) but analyses of outcomes and other data specific to people who use drugs (PWUD) enrolled to S31/A5349 are not available or planned. There are limited data available to inform the treatment of TB among people on **opioid substitution therapies (OST)/treatment for opioid use disorders (OUD)**, as PWUD are often excluded from participating in clinical trials. Rifampicin—a rifamycin like rifapentine—is known to reduce exposures to methadone and buprenorphine, which can result in opiate withdrawal if not carefully managed.[18] As such, persons requiring OST while on treatment for TB with either the new four-month rifapentine- and moxifloxacin-containing regimen or the standard six-month regimen should be closely monitored for signs of opiate withdrawal and other adverse events (e.g., liver toxicity, **QT prolongation**) requiring dose adjustments or treatment interruptions. Active drug use is not a reason to withhold treatment for TB.[19]

Shorter Treatment for Minimal Tuberculosis in Children (SHINE)

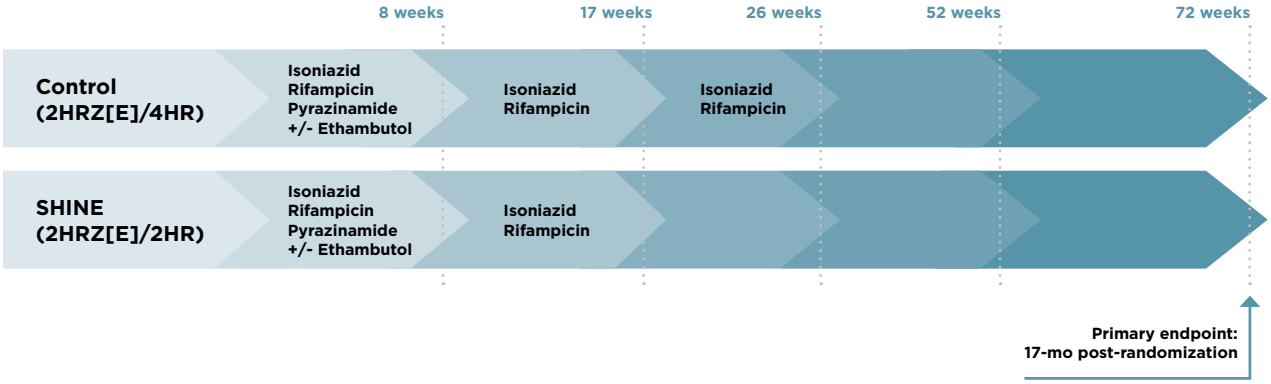
The objective of the SHINE trial was to determine whether the standard six-month regimen for drug-sensitive TB could be shortened by two months without compromising its efficacy or safety in children with non-severe TB. SHINE enrolled 1,204 children 0–16 years old with non-severe TB from five sites in four countries, India, South Africa, Uganda, and Zambia. The trial compared four versus six months of treatment with standard doses of rifampicin, isoniazid, and pyrazinamide plus or minus ethambutol (ethambutol is added in settings with a high prevalence of isoniazid resistance and/or HIV). The **continuation phase** of treatment was shortened from four to two months in the four-month arm (see Figure 4).

OPIOID SUBSTITUTION THERAPIES/ TREATMENT FOR OPIOID USE DISORDERS: a type of harm reduction intervention that treats opioid dependence by replacing opioids (like heroin) with prescribed drugs that can manage or reduce opioid cravings and prevent sudden withdrawal.

QT PROLONGATION is a disturbance in the heart's electrical activity that can lead to serious (and sometimes fatal) rhythmic disturbances

TB treatment is often broken out into two phases: (1) the initial two-month intensive phase, during which more drugs are taken to rapidly kill TB bacteria, and (2) the **CONTINUATION PHASE**, during which fewer drugs are taken to eliminate any remaining TB bacteria and prevent relapse.

FIGURE 4. SHINE STUDY SCHEMA



Four months of treatment was shown to be noninferior to six months of treatment for non-severe drug-sensitive TB in children. Said another way, treatment outcomes observed among children with non-severe TB randomized to receive four months of treatment were no worse than those observed among children with non-severe TB randomized to receive six months of treatment.[20] In terms of safety, measured by all-cause mortality and grade three or higher adverse events, no significant differences were observed between four versus six months of treatment (Table 3).[21]

TABLE 3. EFFICACY AND SAFETY OUTCOMES IN SHINE

	EFFICACY		SAFETY	
Regimen	**Favorable outcomes**	**Unfavorable outcomes**	**Grade 3 or higher AEs**	**All-cause mortality**
Control (2HRZE/4HR)	92.7% (558/602)	7.3% (44/602)	8.0% (48/602)	3.2% (19/602)
SHINE (2HRZ[E]/2HR)	92.7% (558/602)	7.3% (44/602)	7.8% (47/602)	2.0% (12/602)

Percentages of favorable and unfavorable outcomes represented in this table are based on the intention to treat population; it includes all participants randomized to the trial.

What about children living with HIV (CLHIV)?

SHINE enrolled 127 children living with HIV (10.5% of the trial population). Given known interactions between rifampicin and ARV medications, children living with HIV enrolled in the study three years of age or older received an efavirenz-based ARV regimen, and children younger than three years either received boosted lopinavir/ritonavir dosing or an ARV regimen composed of three nucleoside reverse transcriptase inhibitors (NRTIs).[22] A prespecified sub-group analysis comparing outcomes among children with and without HIV enrolled in the study found no significant differences. More in-depth analyses of the available data on children living with HIV (e.g., adverse events by HIV status) were not available at the time of publication but are expected in 2022.

What about children with more severe forms of pulmonary TB?

Children with severe TB were not eligible for the SHINE trial. As such, all children enrolled in the SHINE trial were judged by local treating clinicians to have non-severe TB. Radiologists later reviewed the chest X-rays of all children enrolled in SHINE and judged 71 children as having severe TB (34 children treated for four months and 37 children treated for six months), though their adjudication did not influence participation or the treatment received in the trial. Outcomes among children judged to have severe TB by central radiology review were similar between those who received four versus six months of treatment, with 94% of children in each group achieving a favorable treatment outcome. Two children treated for four months and two children treated for six months had unfavorable outcomes; one child in each group died. The numbers of children judged to have severe TB by central radiology review enrolled in the SHINE trial are too small to draw any definitive conclusions about whether treatment can be shortened to four months for children with more severe forms of pulmonary TB.

III. WORLD HEALTH ORGANIZATION TREATMENT GUIDELINES

In June and August 2021, respectively, the World Health Organization (WHO) issued rapid communications on the four-month S31/A5349 and SHINE regimens.[23,24]

In its rapid communication, the WHO signaled its support for the four-month rifapentine- and moxifloxacin-containing regimen (2HPMZ/2HPM), positioning it as an alternative to the current six-month standard of care. The WHO also recognized the potential benefits of and barriers to the regimen's implementation. The potential benefits the WHO recognized include a faster cure and reduced burden on both patients and the health care system. The potential barriers include the cost and availability of rifapentine and access to **drug susceptibility testing (DST)**. Access to DST is important given that the four-month regimen includes moxifloxacin, a fluoroquinolone and key component of regimens for the treatment of drug-resistant TB. Putting moxifloxacin into a regimen used to treat drug-sensitive TB may necessitate earlier and wider testing for fluoroquinolone resistance to ensure its appropriate use and to support antibacterial stewardship efforts (more on these issues in the next section, IV. Determining Access Barriers).

DRUG SUSCEPTIBILITY TESTING: tests used to determine resistance to medicines.

The WHO also signaled its support for the four-month SHINE regimen (2HRZ[E]/2HR) for the treatment of children with non-severe, presumed drug-sensitive TB, recommending that it be used in place of the six-month regimen (2HRZ[E]/4HR). In its rapid communication, the WHO flagged implementation considerations important to determining eligibility for the SHINE regimen, i.e., how to define and diagnose non-severe TB in children (more on this in section IV). Luckily, the SHINE regimen can be implemented using pediatric formulations already on the market. SHINE uses the same pediatric formulations in the same dosages as those used in the six-month standard of care regimen; it's just the duration of treatment that changes.

Full WHO guidance is expected before the end of 2021. Look out for updates to the *WHO Consolidated Guidelines on Tuberculosis Module 4: Treatment - Drug-Susceptible Tuberculosis Treatment and Module 5: Co-morbidities, Vulnerable Populations and People-centered care: Management of tuberculosis in children and adolescents.*

IV. POTENTIAL ACCESS BARRIERS

Rifapentine Price, Supply, and Pill Burden

Making the four-month regimen from S31/A4349 accessible is complicated by the formulations available for rifapentine. There are currently two **quality-assured** rifapentine products on the market: (1) a 150 mg stand-alone tablet, commercialized by Sanofi for $15 per box of 24 tablets, and (2) a 300/300 mg fixed-dose combination (FDC) with isoniazid, commercialized by Macleods for $15 per box of 36 tablets. Of these two formulations, only the 150 mg stand-alone tablet is compatible for dosing the S31/A5349 regimen. This is because isoniazid is dosed at 300 mg daily; using enough 300/300 mg FDC tablets to reach 1,200 mg rifapentine would therefore overdose isoniazid. The 300/300 mg FDC is used for TB prevention.

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

150 mg tablet price: The 150 mg rifapentine tablets are currently being offered to over 100 eligible countries at a discounted price of $5.25 per box under an agreement that Unitaid and the Global Fund negotiated with Sanofi to discount the price of rifapentine through the end of 2021.[25] This discounted price may not last; it seems increasingly likely that Sanofi will raise the price of rifapentine after 2021 given expected investments that manufacturers of rifapentine will need to make to reduce **nitrosamine impurities** to acceptable levels.[26,27]

300/300 mg FDC price: A separate agreement between Unitaid, the Clinton Health Access Initiative, and Macleods set a ceiling price of $15 per box for the 300/300 mg rifapentine FDC, enough for one course of 3HP.[28] A recent volume guarantee negotiated by MedAccess will extend this discounted price for the Macleods FDC.[29]

Future formulation prices: A third quality-assured rifapentine product, a 300 mg stand-alone tablet, is expected to enter the market soon and improve rifapentine's availability, accessibility, and affordability by introducing additional supply and competition. The 300 mg stand-alone tablet will be compatible for dosing the S31/A5349 regimen and will help reduce the daily pill burden (see Figure 5). The price of the 300 mg table is not yet known.

NITROSAMINES are chemical compounds considered potentially carcinogenic in humans (i.e., they can cause cancer). Everyone is exposed to some level of nitrosamines in daily life, as they are present in drinking water, certain foods, and other products. In 2020 nitrosamine impurities were identified in rifapentine and rifampicin. For more information, see TAG's *Nitrosamines and TB Medicines Information Note and Patient FAQs*, reference 27.

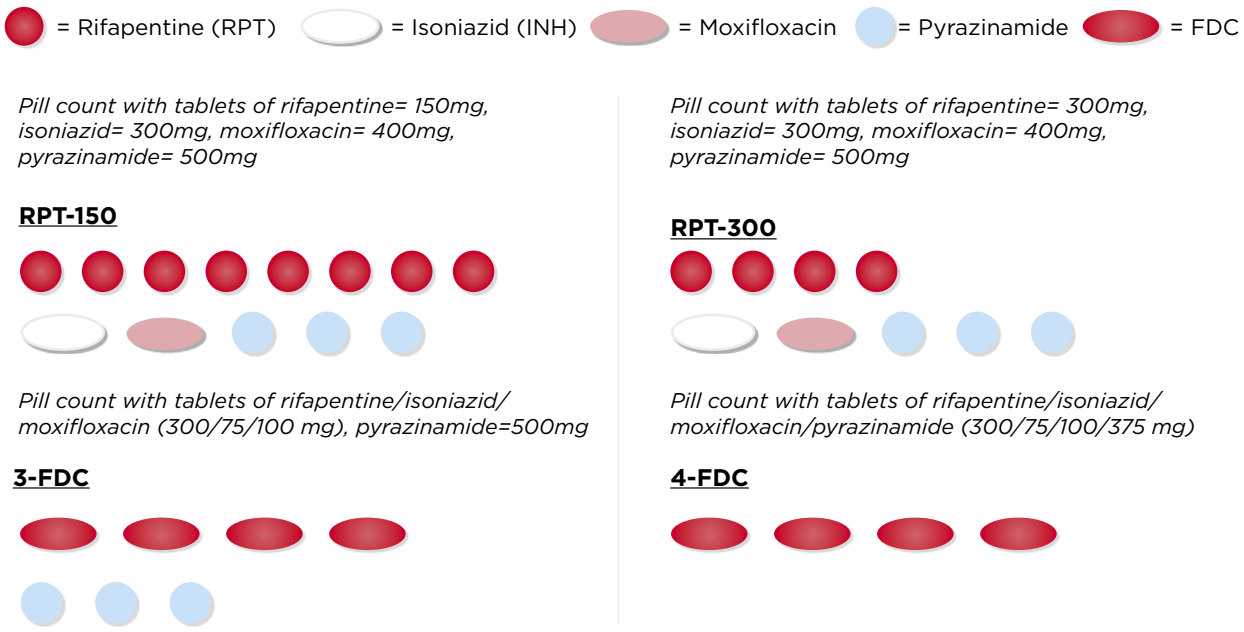
HIGHLIGHT BOX 2: PEDIATRIC RIFAPENTINE DATA AND FORMULATIONS NEEDS

There are no pediatric formulations of rifapentine available outside of clinical trials. The WHO Prequalification Program and Global Fund Expert Review Panel regularly put out Expressions of Interest, intended to signal to manufacturers the medicines and formulations for which there is an urgent unmet need globally. Both entities list a 150 mg scored dispersible rifapentine tablet as an urgent priority given its ability to support pediatric dosing across rifapentine-containing regimens and indications.[30,31] Such a formulation could be used for the 3HP and 1HP preventive treatment regimens as well as the four-month regimen from S31/A5349 for TB treatment once these regimens are recommended by the WHO for children.[32] Currently, rifapentine is recommended in children only in the context of the 3HP regimen for TB prevention, and this recommendation is limited to children two years and older. Rifapentine is recommended for adolescents in the context of the 1HP regimen for TB prevention, but this recommendation does not yet extend to adolescents or children younger than 13. Studies are ongoing or planned to determine the safety and optimal dosing of rifapentine in children less than two years old in the context of 3HP and less than 13 years old in the context of 1HP for TB prevention. Because the four-month regimen from S31/A5349 gives rifapentine at a higher daily dose (1,200 mg daily) than 3HP (900 mg once weekly) or 1HP (600 mg daily), researchers must complete additional dosing and safety research before children and adolescents younger than 12 years old can benefit from access to the four-month S31/A5349 regimen.

Using weighted average prices, the Stop TB Partnership Global Drug Facility calculated the price of the new four-month regimen at $235–$265 per treatment course. (This assumes that the discounted price of the Sanofi rifapentine product holds beyond 2021.) This is more than five times the price of the standard six-month regimen ($43). Ninety percent of the price of the new four-month regimen is driven by the price of rifapentine. The price of rifapentine must fall and the supply must increase for the four-month regimen to be widely adopted and made equitably accessible.

Reducing the daily pill burden for the four-month regimen will require that manufacturers develop new rifapentine formulations, including fixed-dose combinations. Using existing fixed-dose combinations for TB treatment (H75-R150-Z400-E275 and H75-R150), the standard six-month regimen requires four tablets per day. Using the existing 150 mg rifapentine formulation from Sanofi, the pill burden for the new four-month regimen ranges from as many as 13 tablets per day during the intensive phase of treatment to 10 tablets per day during the continuation phase. The introduction of a 300 mg rifapentine stand-alone tablet would reduce the pill burden for the four-month regimen to six to nine tablets per day. The daily pill burden could be reduced to as low as four to seven pills per day with the introduction of three- and four-drug* fixed-dose combinations (H75-P300-M100 and H75-P300-M100-Z375) (see Figure 5).

FIGURE 5: ILLUSTRATION OF DAILY PILL BURDEN FOR FOUR-MONTH S31/A5349 REGIMEN WITH DIFFERENT RIFAPENTINE FORMULATIONS FOR ADULTS



Pill counts for the new four-month regimen (2HPMZ/2HPM) represent the intensive phase of treatment (the first two months of the regimen); during the continuation phase of treatment (the final two months of the regimen), the daily pill count is 3 pills less for the RPT-150, RPT-300, and 3-FDC scenarios (i.e., eliminating pyrazinamide).

*The possibility of a four-drug FDC depends on the ability to use a flat dose of pyrazinamide. In S31/A5349, the investigators used weight-based dosing for pyrazinamide; the other medicines in the 2HPMZ/2HPM regimen were flat dosed.

Drug Susceptibility Testing

The four-month S31/A5349 regimen brings moxifloxacin, which is otherwise a second-line drug and key component of regimens for the treatment of drug-resistant TB, into first-line treatment. This shift may affect how TB programs test for drug resistance. Currently, testing for rifampicin resistance determines eligibility for the standard six-month regimen. People who have TB that is rifampicin-sensitive are eligible for the six-month standard regimen. People found to have TB that is rifampicin-resistant require a different regimen and additional drug susceptibility testing to determine the presence of resistance to other TB medicines. Key among these other medicines are the fluoroquinolones (moxifloxacin or levofloxacin), as susceptibility or resistance to the fluoroquinolones determines which second-line treatment regimen(s) for drug-resistant TB a person is eligible to receive (see Figure 2).

Bringing moxifloxacin into first line raises the importance of earlier and wider testing for fluoroquinolone resistance. Rapid molecular diagnostic technologies (e.g., GeneXpert, Truenat), recommended as the initial test for TB, also test for rifampicin resistance. These same molecular platforms are capable of rapid testing for fluoroquinolone (and isoniazid) resistance, but this requires a separate cartridge or chip, such as the Xpert MTB/XDR cartridge, for which Cepheid is currently charging $20 per test. Additionally, the Xpert MTB/XDR cartridge can't run on the widely available GeneXpert 6-color modules. To use Xpert MTB/XDR cartridges, programs must upgrade to a new 10-color module, which costs at least $3,860 per module, or buy a satellite instrument starting at $6,420.[33] A Truenat chip for testing resistance to fluoroquinolones (and isoniazid) is under development. TB programs have access to other technologies capable of testing for fluoroquinolone (and isoniazid) resistance, such as **line probe assays (LPA), high-throughput testing platforms,** or **culture.** However, in most countries, these platforms are not available at or close to the point of care and take longer to provide results. The WHO's latest target product profile (TPP) for peripheral DST prioritizes testing for fluoroquinolone resistance as a minimal requirement for new tests in development, so fluoroquinolone resistance testing is likely to become more accessible at more decentralized levels of the health system in the future.[34]

In the immediate term, to make rapid fluoroquinolone resistance testing available earlier and closer to the point of care, the price of Xpert MTB/XDR and the cost of transitioning to 10-color modules must come down. Since 2019, the Time for $5 Coalition, comprising more than 150 civil society organizations working across countries and diseases to improve access to rapid diagnostic testing, has called for Cepheid to lower the price of Xpert tests to $5 per test across diseases, inclusive of service and maintenance, based on the available evidence of Cepheid's cost of production of Xpert tests.[35,36,37] Cepheid continues to refuse these demands, charging low- and middle-income countries two to four times what it costs the company to make Xpert tests and greedily enjoying a 54–85% profit margin.[38] The WHO's latest TPP recommends that the optimal price of DST for fluoroquinolones and other core TB drugs should be a maximum of $5 per test.[39]

For more information on DST or other TB tests, see TAG's *An Activist's Guide to Tuberculosis Diagnostic Tools.*[40]

LINE PROBE ASSAY: tests that detect drug resistance by introducing probes that bind to and change color in the presence of bacterial DNA with mutations that confer resistance to specific medicines (a genotypic test).

HIGH-THROUGHPUT TESTING PLATFORMS: platforms positioned in centralized laboratories capable of running molecular tests on multiple samples simultaneously (a genotypic test).

CULTURE: tests that detect TB and drug resistance by attempting to grow TB bacteria, including in the presence of TB medicines (a phenotypic test).

HIGHLIGHT BOX 3: WHAT ABOUT ISONIAZID RESISTANCE?

Isoniazid acts by dramatically reducing the TB bacterial load early in treatment, increasing the likelihood that cure will be achieved and protecting other drugs in the regimen from **spontaneously occurring resistant bacteria**. This makes isoniazid an important part of treatment for drug-sensitive TB and an especially critical component of the shorter four-month S31/A5349 regimen. Rates of **isoniazid mono-resistance** have been on the rise, yet routine testing remains rare. This is in part because guidelines, diagnostic algorithms, and rapid molecular tests have positioned rifampicin resistance as a gatekeeper to further drug susceptibility testing. It's also because there is limited evidence for how to optimally treat isoniazid monoresistant TB. The WHO conditionally recommends a six-month regimen composed of rifampicin, ethambutol, pyrazinamide, and levofloxacin.[41]

S31/A5349 did not include people with isoniazid mono-resistant TB, so we don't know how the four-month S31/A5349 regimen performs in this population. We can, however, make a rational assumption that the shorter regimen will be less effective, increasing the likelihood of an unfavorable treatment outcome and the opportunity for spontaneously occurring bacteria resistant to other drugs in the regimen to survive and replicate. The introduction of the shorter regimens and the increasing prevalence of isoniazid monoresistant TB raises the importance of earlier and wider testing for isoniazid resistance alongside testing for resistance to rifampicin and fluoroquinolones.

Certain bacterial mutations can inactivate or prevent a medicine from entering the TB bacterial cell or from carrying out the mechanism of action it uses to kill TB bacteria or to prevent them from replicating. Mutations that confer resistance can be **SPONTANEOUSLY OCCURRING** or can develop over time following inadequate or irregular drug exposures.

ISONIAZID MONO-RESISTANCE is TB that is resistant to isoniazid but not to rifampicin or other TB drugs.

Diagnosing Non-Severe TB in Children

The SHINE trial defined non-severe TB as TB that is both smear-negative and non-severe in form, diagnosed using **smear microscopy** and chest X-rays. The trial was designed so that programs could move to implement the four-month regimen right away, as the tools used to diagnose non-severe TB (smear microscopy and X-ray) should already be widely accessible and available to TB programs.

Defining non-severe TB when molecular tests (i.e., GeneXpert, Truenat) are used as the initial test (as opposed to smear microscopy) in line with WHO guidelines is possible using Xpert cycle threshold (C_T) values, a quantitative output reflecting the number of **polymerase chain reaction (PCR)** cycles required to detect TB. A strong association between Xpert MTB/RIF C_T values and smear status has been demonstrated, with higher Xpert C_T values associated with smear negativity and lower Xpert C_T values associated with smear positivity.[42] A study conducted in high-HIV-burden settings in southern Africa found that Xpert C_T can be used as a measure of **bacillary burden** and a surrogate for smear status, recommending a C_T cutoff of 28 to rule out smear positivity.[43] Additional research is required to evaluate the correlation between Xpert Ultra's C_T and smear status, including on pediatric pulmonary and extrapulmonary samples, and to determine Xpert MTB/RIF and Ultra C_T cutoffs that can be used to rule out smear positivity in children. Many children with pulmonary TB are Xpert negative; practically, these children can be considered to have smear-negative TB.

SMEAR MICROSCOPY is a method of diagnosing TB in which technicians directly look for TB bacteria in samples using a microscope. Though this diagnostic method is widely available and cheap, it has limited sensitivity, especially in children, detecting TB in only 50% of samples with TB bacteria present (for comparison, Xpert MTB/RIF Ultra detects TB in 90% of samples with TB bacteria present).

POLYMERASE CHAIN REACTION is a method used to rapidly and exponentially multiply specific DNA sequences, so that they might be more easily detected.

BACILLARY BURDEN (or bacterial load) is the amount of TB bacteria in a sputum or other sample. Historically, bacillary burden has been measured using **SMEAR GRADE**, a ranked indicator (+4, +3, +2, +1) of how severe and infectious a person's TB is based on the number of bacilli observed in a sample when examined under a microscope.

The WHO recommends chest X-rays as a screening test for TB, followed by rapid, molecular diagnostic testing (e.g., GeneXpert, Truenat) for people with abnormal chest X-rays suggestive of TB.[44] In addition to clinical and other criteria, chest X-rays are also used to help determine the severity of disease once TB is diagnosed. Digital imaging has helped to expand access to chest X-rays by reducing costs and enabling the use of **computer-aided detection (CAD)** software in adults.[45] Still, chest X-rays are not widely available,[46] especially at more decentralized levels of the health system where sick children often initially present to care. And CAD software systems have largely been trained on images from adults, so they are not currently recommended for use among children.[47] Investments to improve access to portable, digital X-ray technologies[48] and train CAD software systems on pediatric images are necessary to support the diagnosis of non-severe TB in children according to the definition used in the SHINE trial at more decentralized levels of the health care system. In the meantime, programs can refer children to health care centers where chest X-rays are available. Without improved and validated tools, appropriate training, and access to chest X-rays and smear microscopy or Xpert, health care providers may lack the confidence and/or ability to diagnose non-severe TB in children, opting instead to prescribe the standard six-month regimen.

COMPUTER-AIDED DETECTION is artificial-intelligence-based software that assists medical professionals to detect lung abnormalities on chest X-rays and to interpret results.

V. TAKE ACTION!

There are several actions activists can take to overcome the barriers discussed in the previous sections and to promote equitable access to shorter treatment regimens for TB.

1. **Share the trial results with your communities.** Break down the information included in this document for sharing at the community level. Translate this information into local languages and facilitate its dissemination among your civil society and community networks. Identify opportunities to raise awareness about the four-month regimens at community forums. Note the questions from members of your networks that are not answered in this document and share these with TAG (so we can help get you the information you need).

2. **Advocate for national guidelines updates and implementation.** Contact your national TB program to sensitize them to the results of the S31/A5349 and SHINE trials and corresponding updates to WHO treatment guidelines. Ask when your national program plans to update its guidelines and make four-month regimens available. Push your national program to be ambitious with its timeline and approach. Anticipate barriers to national and subnational guidelines change and implementation and identify allies and strategies for overcoming them.

3. **Push research funders to fill data gaps so that everyone can benefit from access to shorter treatment regimens.** For rifapentine in the context of the four-month regimen, additional research is necessary to determine its dose and safety for children and pregnant people and any important interactions with ARVs, opioid substitution therapies, psychotropic, and hypoglycemic medicines. To support the diagnosis of non-severe TB in children and determine eligibility for the SHINE regimen in decentralized settings, research is required to define Xpert MTB/RIF and Xpert Ultra C_T cutoffs that can be used to rule out smear positivity in Xpert-positive children and to train CAD software systems on pediatric images.

4. **Call for increased supply of rifapentine, lower prices, and new formulations that will ease administration.** Existing formulations of rifapentine are too expensive and neither fit for the purpose of the S31/A5349 regimen nor available in adequate supplies. Activists should: hold existing rifapentine manufacturers accountable (and the donors and projects that supported the introduction and scale-up of these products) for maintaining discounted prices beyond the end of existing agreements; and support the market entry of new, affordable formulations that can ease administration of the S31/A5349 regimen by reducing the daily pill burden for adults and dispersing when mixed with liquids for children.

5 **Advocate for country governments and finance mechanisms to allocate additional resources** to support national rollout of the four-month S31/A5349 regimen and decentralized access to drug susceptibility testing. Additional financial resources will be necessary to support the higher cost of the regimen; to increase access to rapid molecular drug susceptibility testing; and to fund guidelines updates, trainings, and other activities associated with introducing new interventions to TB programs.

VI. OVERCOMING OPPOSITION TO IMPLEMENTING SHORTER REGIMENS

Activists will hear many excuses for not implementing the shorter treatment regimens recommended by the WHO. Some anticipated excuses are outlined below, along with the evidence and arguments that activists can use to overcome them.

EXCUSE: Rifapentine is too expensive—the four-month S31/A5349 regimen is five times the cost of the six-month regimen.

RESPONSE: After 40 years and multiple failed attempts, we finally have a shorter regimen for drug-sensitive TB, and to boot, it's composed of medicines that are off-patent, widely available, and familiar to TB programs. Although drug costs for the S31/A5349 regimen are higher, this is expected to be temporary. The market for rifapentine is growing, as is the number of suppliers. Increased competition and volumes will bring down the price of rifapentine and the cost of the S31/A5349 regimen. TB programs need to consider trade-offs between the higher drug costs and shorter duration of the regimen, which provides human resource and other savings and potential benefits. A formal economic analysis is underway that will provide information on the extent to which the higher drug costs are offset by the shorter duration of the regimen. Improving the quality of care and shortening treatment for people with TB is a worthy investment. The lives of our family members and friends with TB are worth it!

EXCUSE: The daily pill burden for the four-month S31/A5349 regimen is too high.

RESPONSE: With existing rifapentine formulations, the daily pill burden for the S31/A5349 regimen may be unacceptable to some TB patients (see Figure 5). The excellent rate of treatment adherence observed among the 791 participants randomized to receive the S31/A5349 regimen using these same formulations in the phase III trial should, however, provide some reassurance to TB programs regarding feasibility. New rifapentine formulations expected soon will help cut the daily pill burden for the S31/A5349 regimen in half, with future fixed-dose combinations bringing the daily pill burden even closer to that for the standard six-month regimen. In the meantime, TB patients should be offered the choice: a shorter regimen with a higher daily pill burden, or a longer regimen with a lower daily pill burden. Give people with TB and their families a chance to decide what matters to them!

EXCUSE: We need to reserve moxifloxacin for drug-resistant TB. We can't risk propagating resistance to the fluoroquinolones.

RESPONSE: Very few people in the rifapentine- and moxifloxacin-containing arm of the phase III trial relapsed and virtually no one with a TB-related unfavorable outcome acquired resistance to fluoroquinolones (or any of the other drugs in the regimen). The improved adherence expected to accompany shorter regimens may help reduce the incidence of drug resistance acquired when longer treatment regimens are interrupted, taken inconsistently, or discontinued too early.

Fluoroquinolone resistance testing has increased with the introduction of shorter regimens for drug-resistant TB, and new rapid molecular tests are bringing DST closer to the point of care. The Xpert MTB/XDR cartridge recommended by the WHO in 2021 tests for resistance to both fluoroquinolones and isoniazid simultaneously, and new tests from other manufacturers are in the pipeline.[49] Implementing rifampicin-, isoniazid-, and fluoroquinolone-resistance testing alongside the

S31/A5349 regimen should ensure appropriate regimen selection. If resistance to fluoroquinolones or other medicines is acquired because of inappropriate regimen selection or poor adherence, a highly effective salvage regimen can still be composed according to WHO guidelines using new and repurposed medicines.

EXCUSE: Moxifloxacin can cause QT prolongation and requires electrocardiogram (ECG) monitoring, which is too expensive and difficult to do.

RESPONSE: In the phase III trial, serious cardiac events were observed in only 0.4% (3/846) of participants randomized to receive the four-month rifapentine- and moxifloxacin-containing regimen. Only one event, reported as palpitations with borderline electrocardiographic QT prolongation, was considered treatment-related.[50] Moxifloxacin has long been administered for the treatment of drug-resistant TB without ECG monitoring. The introduction of other QT-prolonging medicines to treatment regimens for drug-resistant TB has necessitated the introduction of ECG monitoring. In the absence of other QT-prolonging medications and additional risk factors, ECG monitoring is likely not necessary to administer the four-month S31/A5349 regimen. People with increased risk for cardiac events (e.g., with a high baseline QT interval, electrolyte imbalance, underlying family history of cardiac disease, long QT syndrome, etc.), however, may require regular ECG monitoring or may prefer to receive the standard six-month regimen. Recent innovations in ECG monitoring systems have the potential to make ECG testing more accessible and feasible to implement in home, ambulatory, and remote settings.[51]

EXCUSE: We don't have the tools or resources necessary to diagnose non-severe TB to determine whether children are eligible for the SHINE regimen.

RESPONSE: The SHINE trial was designed with the intention that programs could move to implement the four-month regimen right away, as the tools used in the trial to diagnose non-severe TB (smear microscopy and X-ray) should already be widely accessible and available to TB programs. In more decentralized settings, an X-ray referral system could be established. Even if X-rays take several weeks to obtain, the medicines and formulations required for the four-month regimen are the same as those already in use for the six-month standard of care—the continuation phase of treatment just ends two months earlier. As such, treatment initiation would not need to be delayed, and the duration of treatment could always be modified based on X-ray results available at a subsequent patient visit.

WANT MORE INFORMATION?
Write to **communications@treatmentactiongroup.org**

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