

The background of the cover is black, featuring several thin, flowing orange lines that curve across the page from the top left towards the bottom right. The lines vary in thickness and create a sense of movement and depth.

Pipeline Report » 2021

Tuberculosis Preventive Treatment

Tuberculosis Preventive Treatment

Background becomes foreground

By Mike Frick

Introduction

The rifamycin drug family remains firmly ensconced at the center of research to develop new and optimize existing TB preventive treatment (TPT) regimens. The locus of activity continues to center on rifapentine, usually paired with isoniazid (as in the 3HP and 1HP regimens) and occasionally standing on its own (as with the 6P regimen being evaluated in Study 37 of the TB Trials Consortium). Rifampicin has not ceded the entire pipeline to rifapentine. The Canadian-funded 2R2 trial is comparing two high-dose regimens of rifampicin to the 4R regimen. For people exposed to drug-resistant TB, the coming year will mark the long-awaited conclusion of the first-ever randomized controlled clinical trials of preventive treatment. Investigators from the V-QUIN and TB CHAMP studies expect to announce results in 2022 and 2023, respectively. Both trials compare the safety and efficacy of six months of levofloxacin to placebo among household contacts of people with drug-resistant TB.

To summarize the state of the TB preventive treatment pipeline in 2021 in a single phrase: background has become foreground. This inversion in focus is evident however one looks at the research landscape:

- From the perspective of work on rifapentine, the original efficacy trials of rifapentine-isoniazid combinations that defined the last decade of TPT research have concluded and receded from the center of attention. In their wake a bevy of clinical trials have arisen to sort out the details of how 3HP and 1HP can best prevent TB among specific populations and under what stipulations and conditions. Current research efforts are comparing the two regimens to each other, determining their compatibility with antiretroviral agents (ARVs) for HIV, clarifying the adverse event profile of rifapentine-isoniazid, and establishing the safety and optimal dosing of 3HP and 1HP in children, pregnant people, people with diabetes, and other groups at risk of TB.
- In terms of rifampicin, old questions have returned to the fore: namely, is rifampicin under-dosed? Studies of rifampicin for the treatment of active TB disease indicate yes;¹ the 2R2 trial asks a similar question about rifampicin dosing when used as preventive therapy by studying two two-month regimens of daily rifampicin given at higher doses than the one used in a previous clinical trial that showed the noninferiority of 4R to 9H in preventing TB.²

TPT drug and regimen abbreviations:

H = isoniazid,
P = rifapentine,
R = rifampicin

- 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 (6H), nine (9H), 12 (12H), or up to 36 months.

- Long relegated to the background and late to attract clinical trial activity, preventive treatment of infection caused by drug-resistant TB is finally preparing to take the spotlight with the anticipated publication of results from V-QUIN and TB CHAMP. If successful, V-QUIN would give many of the estimated 19 million people living with **latent MDR-TB infection** worldwide an option for preventive treatment backed by high-quality evidence.³ A positive result from TB CHAMP would do the same for infants and children under five, including children living with HIV. Meanwhile, the PHOENIX study continues to advance a potential six-month regimen of delamanid as preventive therapy for high-risk adult, adolescent, and child contacts of people with drug-resistant TB.

Treatment Action Group's 2021 *TB Preventive Treatment Pipeline Report* describes this shifting scene in four tables that outline ongoing and planned clinical trials of TPT. Table 1 focuses on efficacy, effectiveness, and safety studies in adolescents and/or adults; table 2 looks at drug-drug interaction studies between 3HP and 1HP and ARVs; table 3 pulls out TPT studies in children; and table 4 reviews the three trials of TPT for people exposed to drug-resistant TB. Table 1 is summarized in detail with a shorter encapsulation preceding tables 2 and 3. The studies in table 4 will be reviewed in next year's *Pipeline Report* if results from V-QUIN and TB CHAMP become available in 2022. Two text boxes titled "In the background" overview nascent work to develop **long-acting formulations** of TPT and discuss the implications that the arrival of long-acting ARVs for HIV treatment and prevention has for the future of drug-drug interaction work between TB and HIV medicines.

One caveat: this *Pipeline Report* installment does not attempt to summarize the quickly multiplying universe of implementation science studies seeking to optimize the delivery of rifamycin-based TPT regimens under real-world conditions. This active field of work has already produced many persuasive demonstrations that the preventive effects of 3HP, 1HP, 3HR, and 4R can travel far beyond the clinical trial setting to reach homeless persons in Seattle,⁴ homeless and incarcerated persons in Mississippi,⁵ Indigenous communities in Nunavut,⁶ multi-generational households in Karachi,⁷ Tibetan boarding school students in Dharamshala,⁸ and household contacts in urban Taiwan,⁹ to name just a few of the places where such operational research has taken place. Watch this terrain—more operational evidence is on the way. For example, the Unitaid-funded IMPAACT4TB consortium is supporting three large TPT demonstration studies: **CHIP-TB**, **CAT**, and **OPT4TPT**.

Individually, such studies are context-rich and seek to pull out general lessons from the experiences of delivering TPT in specific places and to certain populations. Collectively, they add up to a growing effort to make shorter, safer, simpler TPT regimens available to everyone. These studies are critical to understanding TPT as part of a human right to TB prevention located in the rights

Latent MDR-TB infection (or MDR LTBI) refers to infection with TB caused by multidrug-resistant/rifampicin-resistant strains of *M. tuberculosis*.

To learn more about **long-acting formulations** of medicines, see TAG's resources on the topic, including an *Illustrated Glossary for Long-Acting Technologies* and a clinical trials tracker.

CHIP-TB is a cluster-randomized comparison of providing TPT to child contacts of adults with TB in communities versus at clinics.

CAT is a cluster-randomized evaluation of a choice architecture approach in which prescribing TPT to PLHIV becomes the default unless contraindicated.

OPT4TPT will assess TPT delivery in Ethiopia, South Africa, and Zimbabwe using a continuum-of-care approach with funding from the Gates Foundation.

to health and scientific progress.¹⁰ Realizing this right to TB prevention requires that governments get it right with TPT: the right regimen, offered to the right individual in the right setting at the right time, based on the right diagnosis or indication of risk, with the right information and counselling provided.

TPT Efficacy, Effectiveness, and Safety Studies in Adolescents and/or Adults

Setting aside studies of TPT for people exposed to drug-resistant TB, there is little to suggest that preventive treatment of TB will leave behind rifapentine or rifampicin anytime soon. Every study listed in Table 1 involves either rifapentine or rifampicin in some iteration. Missing for now are trials making use of newer drug agents. Signs that such compounds—for example, bedaquiline—may soon be studied as preventive treatment are all around, if one knows where to look. Take the patent record: among Johnson & Johnson’s nine separate patent applications on bedaquiline to date, two relate to prevention: a patent on bedaquiline for the treatment of latent TB (WO 2006/067048), and a patent on long-acting formulations of bedaquiline (WO 2019/012100). Preclinical work in a paucibacillary mouse model of TB also suggests that bedaquiline would work well as a treatment for TB infection.^{11,12}

More remarkable than the absence of new drugs from Table 1 is the lack of studies involving isoniazid preventive therapy (IPT). In fact, IPT barely features at all in the TPT clinical trials landscape, not even as a control arm in ongoing studies. Rifamycin-based regimens are now the standard of care and have supplanted IPT as the control arm comparator of TPT trials. Most of the studies in Table 1 assess one or more short-course, rifamycin-based regimens against one another. (Interestingly, and perhaps controversially, a few placebo-controlled studies and trials without active comparators have returned to the field; read on.) To quote a common refrain among activists agitating for better TB prevention services: “The IPT-only era is over.”¹³ Or is it? The **constrained supply** of rifapentine means that IPT continues to reign over most national TPT programs in contrast to the research pipeline where rifapentine-based regimens dominate.

The studies in Table 1 fall into three broad categories: comparisons of 3HP and 1HP; trials of TPT in special populations; and trials of novel rifamycin-based regimens not yet reviewed and recommended by the World Health Organization (WHO).

Constrained supply of rifapentine caused by several factors has slowed the uptake of 3HP and 1HP. IMPAACT4TB maintains a [webpage](#) showing which countries have started programmatic implementation of 3HP.

Table 1. Ongoing and Planned Clinical Trials of TPT in Adolescents and/or Adults

Study Name (Registry number) <ul style="list-style-type: none"> ▪ Sponsor and major collaborators ▪ Phase ▪ Sample Size (N =) 	Status	Regimens and Study Design	Population	Study Location(s)
3HP vs 1HP (NCT03785106) <ul style="list-style-type: none"> ▪ HIV-NAT ▪ Phase III ▪ N = 2,500 	Enrolling	Safety and efficacy of 3HP vs. 1HP (sub-study: PK of P, DTG, and TAF)	Adults ≥18 years with HIV and evidence of TB infection: positive TST/IGRA, HHC, or residing in high-TB-burden area (pregnant people ineligible)	Thailand
ASTERoid/TBTC Study 37 (NCT03474029) <ul style="list-style-type: none"> ▪ TBTC ▪ Phase III ▪ N = 3,400 	Enrolling	Safety and effectiveness of 6P vs. rifamycin-based standard-of-care regimens (3HP , 4R , or 3HR)	People ≥12 years of age with positive TST or IGRA and at high risk of disease progression (PLHIV eligible; pregnancy eligibility pending)	USA
SDR Risk Study (NCT04094012) <ul style="list-style-type: none"> ▪ National Taiwan University Hospital ▪ Phase III ▪ N = 490 	Enrolling	Risk of systemic drug reactions with 3HP vs. 1HP	People ≥12 years who are HHCs with positive TST/IGRA (PLHIV eligible)	Taiwan
2R2 (NCT03988933) <ul style="list-style-type: none"> ▪ McGill University, CIHR ▪ Phase II ▪ N = 1,359 	Enrolling	Safety and treatment completion of high-dose R (20 or 30 mg/kg) taken daily for 2 months vs. 4R	People ≥10 years with positive TST/IGRA, or other indication for TPT (PLHIV eligible; pregnant people ineligible)	Canada, Indonesia, Vietnam
SCRIPT-TB (NCT03900858) <ul style="list-style-type: none"> ▪ Huashan Hospital ▪ Phase III ▪ N = 566 	Completed enrollment	1H₃P₃ * vs no intervention *1 month of P (450 mg) and H (400 mg) given thrice weekly (12 doses total)	Adult men 18–65 years with silica exposure/ diagnosed with silicosis (women and PLHIV ineligible; positive TST/IGRA not required)	China
SCRIPT-LGTB (NCT04528277) <ul style="list-style-type: none"> ▪ Huashan Hospital ▪ Phase III ▪ N = 1,050 	Enrolling	Safety and efficacy of 1H₃P₃ + IVF vs. no treatment + IVF as preventive treatment for latent genital TB preceding IVF	Adult women with and without latent genital TB and experiencing recurrent implantation failure	China
TPT and Rheumatic Disease (ChiCTR1800018242) <ul style="list-style-type: none"> ▪ Peking Union Medical College ▪ Phase IV ▪ N = 500 	Enrolling	Safety, effectiveness, and treatment completion of 3HP vs. 9H in people with rheumatic disease	Adults 18–70 years diagnosed with rheumatic disease and IGRA positive (PLHIV and pregnant people ineligible)	China

Study Name (Registry number) <ul style="list-style-type: none"> ▪ Sponsor and major collaborators ▪ Phase ▪ Sample Size (N =) 	Status	Regimens and Study Design	Population	Study Location(s)
PROTID (NCT04600167) <ul style="list-style-type: none"> ▪ PROTID consortium, NIMR, EDCTP ▪ Phase III ▪ N = 3,000 	Active, not enrolling	Safety and efficacy of 3HP vs. placebo to prevent TB in people with diabetes	Adults ≥18 years with diabetes and positive TST/IGRA (PLHIV ineligible)	Uganda, Tanzania
Ultra Curto (NCT04703075) <ul style="list-style-type: none"> ▪ JHU, NIH ▪ Phase IV ▪ N = 500 	Active, not enrolling	Treatment success and safety of 1HP vs. 3HP	HIV-negative adult and adolescent HHCs (aged ≥15 years) with positive TST/IGRA and documented conversion within 2 years	Brazil
One to Three (NA) <ul style="list-style-type: none"> ▪ IMPAACT4TB ▪ Phase IV ▪ N = 1,000 	Planned	Treatment success (completion) and safety of 1HP vs. 3HP	Adults and adolescents (aged ≥13 years) either HHCs (any HIV status) or PLHIV on EFV- or DTG-based ART	India, Indonesia, Mozambique, South Africa
DOLPHIN Moms/ IMPAACT P2025 (NA) <ul style="list-style-type: none"> ▪ IMPAACT4TB, IMPAACT ▪ Phase IV ▪ N = 252 	Planned	Safety/tolerability and PK of 3HP and 1HP with DTG-based ART	Pregnant women (20–34 weeks gestation) with HIV on DTG-based ART (DTG twice daily initially, once daily potentially)	Select IMPAACT4TB project countries
BALANCE (NA) <ul style="list-style-type: none"> ▪ UCL ▪ Phase IV ▪ N = 3,100 	Planned	Safety and efficacy of 1HP vs. standard of care for diabetes	Adults ≥18 years with diabetes and positive TST/IGRA (PLHIV ineligible)	Philippines, South Africa
ART: antiretroviral therapy CIHR: Canadian Institutes of Health Research DTG: dolutegravir EDCTP: European and Developing Countries Clinical Trials Partnership EFV: efavirenz H: isoniazid HHC: household contact HIV-NAT: HIV Netherlands-Australia-Thailand Research Collaboration IGRA: interferon-gamma release assay IVF: in vitro fertilization IMPACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group IMPACT4TB: Unitaid-funded collaboration led by the Aurum Institute with research projects led by JHU		JHU: Johns Hopkins University NIH: National Institutes of Health NIMR: National Institute for Medical Research, Tanzania NNRTI: non-nucleoside reverse transcriptase inhibitor P: rifapentine PLHIV: people living with HIV PK: pharmacokinetic(s) R: rifampicin TAF: tenofovir alafenamide TB: tuberculosis TBTC: TB Trials Consortium TPT: TB preventive treatment TST: tuberculin skin test UCL: University College London		

3HP and 1HP Comparisons

Five studies are directly comparing 3HP to 1HP. Already underway is the HIV-NAT study of the efficacy and safety of 3HP vs. 1HP among adults with HIV in Thailand. Preparing to open are the Ultra Curto study (safety and treatment success of 3HP and 1HP among HIV-negative adult and adolescent household contacts in Brazil) and the IMPAACT4TB One to Three study (treatment completion of 3HP and 1HP among adults and adolescents of any HIV status in India, Indonesia, Mozambique, and South Africa). Related to this last endeavor, the IMPAACT4TB partners are collaborating with the IMPAACT Network on a study called DOLPHIN Moms to establish the safety and tolerability of 3HP and 1HP in pregnant people living with HIV on dolutegravir-based antiretroviral treatment (ART).¹⁴ The study will generate important safety data on 3HP and 1HP started during pregnancy (20–34 gestational weeks) using a composite measure of maternal all-cause mortality, permanent drug discontinuation due to toxicity, and particular maternal/infant serious adverse events and pregnancy outcomes. The study will begin by dosing dolutegravir twice daily with the possibility of once-daily dosing dependent on results from an interim analysis.¹⁵ In Taiwan, a trial at the National Taiwan University Hospital is comparing the risk of systemic drug reactions among household contacts taking either 3HP or 1HP. The goal is to better understand the hypersensitivity reactions reported among three to five percent of people taking 3HP in previous clinical trials and programmatic evaluations and to test the hypothesis that participants taking 1HP will have a lower rate of such reactions.

Studies in Special Populations

Two trials are evaluating 3HP among people with diabetes. People with diabetes count among the most underserved populations for preventive therapy given their three-times higher risk of developing TB disease than non-diabetic people.¹⁶ Funded by the EDCTP, the PROTID study is comparing the safety and efficacy of 3HP to placebo among 3,000 adults with diabetes and a positive test for TB infection in Uganda and Tanzania. The use of placebo is justified, in part, by the fact that PROTID will be the first-ever randomized controlled trial to evaluate the safety and efficacy of TPT in people with diabetes.¹⁷ In essence, there is no established standard of TB preventive treatment recommended for this population, a gap in normative guidance the PROTID trial aims to fill. Additionally, isoniazid may alter blood glucose control and decrease the effectiveness of common antidiabetic drugs such as metformin, making the choice of IPT as a control regimen less attractive.¹⁸ Still in the planning stages is the BALANCE trial, which will study the safety and efficacy of 1HP compared to standard-of-care management for diabetes with respect to microbiologically confirmed TB disease over two years of follow-up. The BALANCE trial will take place in the Philippines and South Africa and will afford the opportunity to examine the immunological effects of metformin, which some evidence suggests may act as a host-directed therapy for TB.¹⁹

Taking an unexpected tack, investigators at Huashan Hospital in Shanghai, China are studying a rifapentine-isoniazid regimen consisting of 450 mg of rifapentine taken with 400 mg of isoniazid three times a week for one month (for a total of 12 doses). Called 1H₃P₃, the **drug doses** and frequency of pill taking in this regimen differ from 1HP and 3HP. Clinical trials registries do not contain any previous studies of this regimen; this atypical combination of rifapentine and isoniazid came together after a previous study in China found that 3HP among people with silicosis “had a high protective efficacy but an unsatisfactory completion rate.”²⁰ Among 254 participants randomized to receive 3HP in that study, 70% experienced an adverse event, 8% reported a grade 3 or 4 event, and 11% had a flu-like hypersensitivity reaction.²¹ In the end, 28% of people receiving 3HP stopped treatment early (the study used the same adverse event grading criteria as TBTC Study 26 in which 4.9% of participants discontinued 3HP due to an adverse event).²² The finding of poor 3HP completion from the Chinese study stands apart from other clinical trials and programmatic evaluations of 3HP outside of China, nearly all of which show the regimen to have a lower adverse event rate and significantly higher completion rate than isoniazid-only alternatives such as 6H or 9H.²³

Huashan Hospital is undertaking two studies of 1H₃P₃, each among a group excluded from most previous TPT research. The SCRIPT-TB study is comparing rates of TB disease among adult men with silicosis or silica dust exposure randomized to receive either 1H₃P₃ or no active intervention. The SCRIPT-LGTB study is evaluating the safety and efficacy of 1H₃P₃ among women with and without latent genital TB (LGTB) who have experienced recurrent implantation failure following in vitro fertilization (IVF). The hypothesis is that a course of TPT preceding IVF may increase the success of fertility treatment for women with LGTB (diagnosed via an endometrial polymerase chain reaction test).

It will be interesting to see whether either study informs global guidelines given the divergent approach to rifapentine and isoniazid dosing. The comparison of 1H₃P₃ to no intervention rather than to an existing WHO-recommended TPT regimen raises an important ethical consideration about the lack of an active comparator. Chinese national guidelines have not established a standard of care for preventing TB in these populations; consequently, rather than take another preventive treatment regimen, individuals in the control arms of these two studies will receive close monitoring (informed consent to participate is, of course, a requirement as well).²⁴ An additional consideration: China has historically manufactured its own rifapentine rather than buy from the two quality-assured manufacturers that supply the international market: Sanofi and Macleods. Since the two SCRIPT trials employ locally manufactured drug product,²⁵ bioequivalence between the Chinese-supplied rifapentine and the Sanofi product will need to be demonstrated before the WHO and regulatory authorities outside of China can recommend or approve the regimen. Initial work raises doubts: a study published in Chinese tested the bioequivalence of rifapentine manufactured by Sichuan Med-Shine Pharmaceutical Co., the supplier of drug product for the SCRIPT studies, and rifapentine manufactured by Sanofi and concluded that “the two preparations...are not bioequivalent.”²⁶

Drug doses for rifapentine-isoniazid TPT regimens:

- 3HP = 900 mg rifapentine, 900 mg isoniazid (taken once-weekly for 12 weeks).
- 1HP = 600 mg rifapentine, 300 mg isoniazid (taken daily for one month).
- 1H₃P₃ = 450 mg rifapentine, 400 mg isoniazid (taken three times a week for one month; under study in China).

Novel Rifamycin-based Regimens

In addition to the two trials of the 1H₃P₃ regimen in China, Table 1 contains two other novel rifamycin-based TPT regimens under study. The TB Trials Consortium (TBTC) Study 37 is evaluating a six-week regimen of rifapentine taken daily at a dose of 600 mg. The trial is testing the noninferiority of 6P in relation to a composite control arm consisting of other rifamycin-based regimens 3HP, 3HR, and 4R. Led by McGill University, the 2R2 trial is testing whether rifampicin alone can effectively prevent TB in less time than the four-month 4R regimen if given at higher-than-standard doses (20 mg/kg or 30 mg/kg per day as opposed to 10 mg/kg per day). Both trials are enrolling adolescents and adults (12 years and older in Study 37 and 10 years and older in 2R2). People living with HIV (PLHIV) may participate in both studies, though most participants in each will be HIV-negative individuals deemed at risk of TB and with a positive test for infection. Pregnant women are ineligible to participate in 2R2 and Study 37. TBTC investigators have committed to reconsider pregnancy inclusion pending an interim safety analysis. If successful, Study 37 and 2R2 would give the world choices for TPT using isoniazid-sparing regimens.

In the background—long-acting rifamycin-based TPT: Long-acting formulations of rifapentine and isoniazid may enter clinical trials in coming years if efforts by the Unitaid-funded LONGEVITY project meet success. The LONGEVITY team has taken initial steps to formulate rifapentine as a long-acting agent using the solid drug nanoparticle technology platform owned by Tandem Nano Ltd, a University of Liverpool spin-off.²⁷ The goal is to pair long-acting rifapentine with an isoniazid pro-drug to create an injectable regimen of rifapentine-isoniazid that could be administered as few as one or two times. The basic idea is that the injection would deliver a drug depot into either muscle or subcutaneous tissue thus allowing for gradual, extended release of drug substance into the body. The 2021 issue of *TAGline* contains a thoughtful discussion of the science behind long-acting TPT and the need for robust community engagement in this area.²⁸

See *TAGline* article “Injectables Redux: developing acceptable long-acting formulations for TB prevention amidst a push for all-oral treatment.”

Ongoing and Planned Drug-Drug Interaction Studies of TPT with ART and Trials of TPT in Children

At times it can feel like TB drug development is caught in a perpetual eddy of conducting pharmacokinetic (PK) and safety studies on the compatibility of TB and HIV medicines only to find that newly approved ARVs mean the process must start all over again. The TB drugs stay the same; only the ART regimens change. Tables 2 and 3 suggest that when it comes to 3HP and 1HP, at least, TB researchers have done an admirable job of keeping pace with changing norms

in HIV treatment. Safety and PK evaluations of short-course TPT regimens and ARVs in children are farther behind, not due to lack of effort by researchers, but instead owing to an obstacle course of bureaucratic, industrial, and regulatory hurdles. A particular challenge is the lack of a pediatric formulation of rifapentine, which would allow for studying 3HP and 1HP in the youngest children. **TPMAT** and **PADO TB** have called for a 150 mg dispersible, functionally scored rifapentine tablet, a recommendation now amplified by the WHO Expression of Interest to manufacturers of TB medicines.²⁹

For both adults and children with HIV, the immediate need centers on establishing the safety and optimal dosing of rifapentine-based TPT with dolutegravir-based ART. A dispersible dolutegravir formulation, approved by the U.S. Food and Drug Administration in June 2020, means that dolutegravir can now be given to infants as young as four weeks old.³⁰ New WHO consolidated guidelines on managing HIV recommend a first-line regimen of dolutegravir plus a backbone of two **NRTIs** for adults and children (with a raltegravir-based regimen recommended for neonates).³¹ While dolutegravir occupies the foreground, just as important is work taking place in the background to test drug-drug interactions between short-course TPT regimens and other ARVs such as **bictegravir**. Here is a summary of key activities:

- For 3HP: The DOLPHIN study showed that 3HP can be used with dolutegravir-based ART without need for dose adjustment.³² Ongoing work promises to generate safety and PK data on 3HP in people initiating dolutegravir-based ART for the first time (DOLPHIN Too); in children and adolescents aged four weeks and older taking dolutegravir (DOLPHIN Kids); and in children on efavirenz- or raltegravir-based regimens (TBTC Study 35). Researchers are also studying 3HP with **TAF**, darunavir/cobicistat, and bictegravir.
- For 1HP: The ACTG study A5372 is assessing the PK and safety of 1HP with dolutegravir (given once a day as standard, or twice a day to account for the possible need to increase dolutegravir dosing). The IMPAACT network will follow with P2024, a study of 1HP in children 13 years and younger with and without HIV.³³ The inclusion of HIV-positive children in the study will afford the opportunity to study 1HP among children on dolutegravir-based ART. Investigators at Yale University had planned to study rifapentine at the doses used in 1HP (600 mg/daily) and 3HP (900 mg/weekly) with TAF and bictegravir but withdrew the study in September 2021 citing delays due to the COVID-19 pandemic. The DOLPHIN Moms study (described above and listed in Table 1) will generate safety and PK data on 3HP and 1HP in pregnant people with HIV taking dolutegravir.

The TB Market Shaping Action Team (**TPMAT**) is an initiative of the Global Drug Facility.

PADO TB is the Paediatric Antituberculosis Drug Optimization forum.

NRTIs are nucleoside reverse transcriptase inhibitors, an HIV drug class that includes **TAF** (tenofovir alafenamide) and TDF.

Bictegravir (BIC) is an integrase inhibitor developed by Gilead Sciences.

Table 2. Ongoing and Planned Drug-Drug Interaction Studies of TPT with ART*

Study Name (Registry number) ▪ Sponsor and major collaborators ▪ Phase ▪ Sample Size (N =)	Status	Regimens and Study Design	Population	Study Location(s)
1HP with BIC/FTC/TAF (NA) ▪ National Taiwan University Hospital ▪ Phase I/II ▪ N = 50	Completed	PK and safety of 1HP and BIC	Adults with HIV on BIC/FTC/TAF and IGRA-positive	Taiwan
DOLPHIN Too (NCT03435146) ▪ IMPAACT4TB, ViiV ▪ Phase I/II ▪ N = 75	Enrolling	PK and safety of 3HP and IPT given with DTG-based ART	Adults ≥18 years with HIV starting ART for the first time	South Africa
YODA (NCT03510468) ▪ NIH Clinical Center ▪ Phase I ▪ N = 75	Enrolling	Drug-drug interaction study of 3HP and TAF	HIV-negative, IGRA-negative adult volunteers 18–65 years	USA
3HP with DTG + DRV/c (NCT02771249) ▪ NIH Clinical Center ▪ Phase I ▪ N = 37	Completed enrollment	Drug-drug interaction study of 3HP and DTG + DRV/c	HIV-negative, IGRA-negative adult volunteers 18–65 years	USA
A5372 (NCT04272242) ▪ ACTG, ViiV ▪ Phase II ▪ N = 72	Enrolling	PK and safety of 1HP given with DTG-based ART (twice daily & once daily)	Adults with HIV 18–65 years on stable DTG-based ART with positive TST/IGRA, or other indication for TPT	Botswana, Brazil, Malawi, Peru, Thailand, USA, Zimbabwe
Rifapentine with BIC/FTC/TAF (NCT04551573) ▪ Yale University, Gilead ▪ Phase I ▪ N = 24	Withdrawn	Drug-drug interaction study of RPT (dosed daily/600 mg and once-weekly/900 mg for four weeks) with BIC and TAF	HIV-negative, IGRA-negative adult volunteers	USA
* Some studies in Table 1 include PK/PD sub-studies between TPT regimens and ARVs not listed in this table. Pediatric PK/PD studies are listed in Table 3.				
ACTG: AIDS Clinical Trials Group ART: antiretroviral therapy BIC: bictegravir DTG: dolutegravir DRV/c: darunavir boosted with cobicistat FTC: emtricitabine TAF: tenofovir alafenamide				
For abbreviations and acronyms not listed here, see footnote to Table 1.				

Table 3. Ongoing and Planned Clinical Trials of TPT in Children

Study Name (Registry number) ▪ Sponsor and major collaborators ▪ Phase ▪ Sample Size (N =)	Status	Regimens and Study Design	Population	Study Location(s)
iTIPS (NCT02613169) ▪ U. Washington, Thrasher Research Fund ▪ Phase II ▪ N = 300	Completed	Risk of acquisition of TB infection among infants receiving 12H vs. no intervention	HEU infants 6 weeks of age	Kenya
TBTC Study 35 (NCT03730181) ▪ TBTC, IMPAACT4TB, Sanofi ▪ Phase I/II ▪ N = 72	Enrolling	PK and safety of 3HP using dispersible HP formulations (Sanofi)	Children 0–12 years with TB infection (HHC with positive TST/IGRA) with and without HIV (children with HIV on EFV- or RAL-based ART)	South Africa
DOLPHIN Kids (NA) ▪ IMPAACT4TB, ViiV ▪ Phase I/II ▪ N = 100–140	Planned	PK and safety of 3HP given with DTG-based ART	Children and adolescents with HIV aged 4 weeks to 18 years on DTG-based ART	South Africa
IMPAACT P2024 (NA) ▪ IMPAACT ▪ Phase I/II ▪ N = NA	Planned	PK and safety of 1HP given with DTG-based ART ; bioavailability of P given as a crushed or whole tablet	Children aged 2–13 years with and without HIV (children with HIV on DTG-based ART)	NA
HEU: HIV-exposed, uninfected RAL: raltegravir For abbreviations and acronyms not listed here, see footnotes to Tables 1 and 2.				

Regarding bictegravir, investigators at National Taiwan University Hospital presented results of a phase I/II safety and PK study of 1HP and bictegravir among 50 adults with HIV at the 2021 CROI Conference.³⁴ All study participants tested positive for TB infection, were taking BIC/FTC/TAF for at least two weeks prior to 1HP initiation, and **virally suppressed**. Overall, 1HP taken with bictegravir was well tolerated. All but one participant completed 1HP in full; the one individual who discontinued 1HP stopped about halfway through the month-long treatment course due to side effects (fever, rash). However, the PK results offered less assurance about pairing 1HP and bictegravir. Concurrent use of 1HP significantly reduced bictegravir trough concentrations in this population. As a result, while all participants began the study virally suppressed, this was not true at day 15 and day 29. Both bictegravir concentrations and viral suppression recovered in all participants after completing 1HP when assessed during the six-month follow-up period.³⁵

Virally suppressed is defined as having <200 copies of HIV RNA per milliliter of blood.

The study from National Taiwan University Hospital suggests that 1HP may not be the most suitable TPT regimen for PLHIV taking bictegravir. However, the full story is still unwritten. Men made up 98 percent of study participants, motivating the need to conduct further drug-drug interaction work between 1HP and bictegravir in women living with HIV. A Yale University safety and PK study of bictegravir and rifapentine was withdrawn before it started from Clinicaltrials.gov in September 2021. Where the Taiwanese study collected sparse PK data, the study by Yale University had intended to conduct more intensive PK sampling (though among HIV-negative adult volunteers without TB infection).³⁶

In the background—TPT and long-acting ARVs: As detailed in TAG's 2021 *Antiretroviral Therapy Pipeline Report*, January 2021 marked the first approval of a long-acting injectable ARV combination consisting of the integrase inhibitor cabotegravir and the **NNRTI** rilpivirine (branded by ViiV Healthcare as Cabenuva). More long-acting HIV regimens are on the way. Among other ARVs in late-stage development, islatravir (Merck) and lenacapavir (Gilead Sciences) will be studied as oral and long-acting combinations.³⁷ Many ARVs used for HIV treatment and prevention may soon be available in an array of long-acting forms, whether as injectables, oral tablets, or implants.

NNRTI stands for the non-nucleoside reverse transcriptase inhibitors HIV drug class.

For TB, this means that future drug-drug interaction work will need to consider the compatibility of rifamycin-based TPT with long-acting ARVs. The considerations get almost exponentially more complex: how will intermittent TPT regimens (3HP) interact with ARVs administered monthly or bimonthly? What about daily TPT regimens (1HP, 3HR, 4R, 6P)? Do these considerations change for HIV medicines offered in injectable versus other long-acting formulations? What is the feasibility of dose-adjusting long-acting ARVs in the presence of a rifamycin? Would it be easier to avoid the issue altogether by encouraging people to complete TPT before initiating long-acting HIV treatment?

TB and HIV drug developers need to start thinking today about how people taking long-acting ARVs can receive existing formulations of TPT. In some situations, co-administration may not be possible. In others, the old strategy of adjusting dosing to avoid or lessen drug-drug interactions may hold. There is some precedent for this work: an ACTG study of TB treatment taken with one of the oldest long-acting drug agents, the contraceptive Depo-Provera (DMPA). The study showed that increasing the frequency of DMPA injections to every 8–10 weeks (instead of the standard 12-week interval) could overcome the drop in progestin levels caused by rifampicin and thus lower the risk of contraceptive failure during TB treatment among women on DMPA.³⁸

The field needs more work in this vein. To return to Cabenuva, there are currently no PK data on rifapentine and cabotegravir, but work on cabotegravir and rifampicin hints at what might be in store. A small phase I study among 15 participants explored the effects of rifampicin on the

pharmacokinetics of a single dose of oral cabotegravir.³⁹ The study found that rifampicin induced cabotegravir metabolism resulting in faster clearance and decreased drug exposures. The authors further commented that “rifampin is expected to increase cabotegravir clearance following long-acting injectable administration.” The time for dedicated work on the compatibility of rifamycin-based TPT regimens and long-acting ARVs is now. One day, not too far into the future, researchers will need to study the effects of long-acting TPT (either rifapentine-isoniazid, bedaquiline, or perhaps even delamanid) on long-acting ARVs.

Table 4: Ongoing Clinical Trials of TPT for People Exposed to Drug-Resistant TB

Study Name (Registry number) ▪ Sponsor and major collaborators ▪ Phase ▪ Sample Size (N =)	Status	Regimens and Study Design	Population	Study Location(s)
TB CHAMP (ISRCTN92634082) <ul style="list-style-type: none"> ▪ South African MRC, Wellcome Trust, U.K. MRC, Unitaid ▪ Phase III ▪ N = 1,009 child HHCs from 650 households 	Enrolling	Safety and efficacy of 6 months of daily levofloxacin vs. placebo	HIV-positive or HIV-negative children (aged 0–17 years) who are HHCs of adults with MDR-TB	South Africa
V-QUIN (ACTRN12616000215426) <ul style="list-style-type: none"> ▪ Australian NHMRC, Gov. of Vietnam ▪ Phase III ▪ N = 2,048 HHCs from >1,300 households 	Completed enrollment	Safety and efficacy of 6 months of daily levofloxacin vs. placebo	Household contacts of people with MDR-TB with positive TST; first phase restricted to people aged ≥15 years (PLHIV eligible)	Vietnam
PHOENIX MDR-TB A5300B/I2003B (NCT03568383) <ul style="list-style-type: none"> ▪ ACTG, IMPAACT, Otsuka ▪ Phase III ▪ N = 3,452 HHCs from 1,726 households 	Enrolling	Safety and efficacy of 6 months (26 weeks) of daily delamanid vs. 6H	High-risk adult, adolescent, and child HHCs of adults with MDR-TB (PLHIV eligible)	Botswana, Brazil, Haiti, India, Kenya, Peru, Philippines, South Africa, Tanzania, Thailand, Uganda, Zimbabwe
6H: six months of isoniazid preventive therapy ACTG: AIDS Clinical Trials Group HHC: household contact (of people with MDR-TB) IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group		MDR-TB: multidrug-resistant tuberculosis MRC: Medical Research Council (South Africa, United Kingdom) NHMRC: National Health and Medical Research Council, Australia For abbreviations and acronyms not listed here, see footnotes to Tables 1–3.		

Endnotes

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