



Pipeline Report » 2020

Tuberculosis Preventive Therapy

TAG

Treatment Action Group

TUBERCULOSIS PREVENTIVE THERAPY

Mike Frick

Introductory Note

“Open a window” is an old tuberculosis (TB) prevention adage, one that remains good advice for preventing TB in the household and, now, SARS-CoV-2/COVID-19 too.¹ While I was writing this year’s *TB Prevention Pipeline Report* at home in New York City—a time spent mostly indoors due to the COVID-19 pandemic—my open window and its view of a small square of dirt with a ginkgo tree, standing solitary yet resilient amid a stretch of concrete, reminded me that prevention can arise from the simplest of natural things: a breeze, a patch of soil, the trunk and foliage of a tree. The nature metaphors invoked throughout this year’s *TB Prevention Pipeline Report* are not incidental. Like so much of medical science, recent advances in TB preventive therapy (TPT) and TB vaccines originate in the natural world. Rifapentine and rifampicin, the drugs at the center of shorter TPT regimens, were first synthesized from a compound discovered in a soil sample taken from the pine forests of southern France.² A key component of the M72/AS01E TB vaccine candidate—the QS-21 molecule—comes from the soapbark tree, a medicinal resource recognized in the traditional knowledge of Indigenous Andean peoples.³

Tracing things back to their source is instructive for demonstrating how much a field has grown from its roots. In recent years, TB prevention science has traveled by leaps. Researchers developing new TPT regimens are processing a bounty of data from recently concluded clinical trials that have established a new standard of care (reviewed in this chapter). For TB vaccine developers, successful phase II studies have tilled the ground for larger efficacy trials, most notably a phase III trial of M72/AS01E (reviewed in a separate chapter available [here](#)). Whatever our vantage point, it is a good time to watch the TB prevention pipeline closely, keeping our gaze on where prevention science is going without forgetting where it all began.

The Tuberculosis Preventive Therapy Pipeline

“The first hay is in and all at once / in the silent evening summer has come”

—After the Spring, W.S. Merwin⁴

Regular readers of TAG's *Pipeline Report* will notice the absence of familiar study names from **Tables 1** and **2**. TAG last published a review of research on TPT in 2018. That was the year the harvest came in with the conclusion of several long-running TPT clinical trials. The bumper crop started with positive results from the BRIEF-TB/A5279 phase III study. Conducted by the AIDS Clinical Trials Group (ACTG), BRIEF-TB found that a one-month regimen of daily isoniazid and rifapentine (1HP) was **non-inferior to** nine months of daily isoniazid (9H) in preventing TB, death from TB, or death from unknown cause.⁵ Other large preventive therapy trials bore fruit soon after. The IMPAACT Network's phase IV TB Apprise/P1078 study raised new questions about the standing recommendation to give isoniazid preventive therapy (IPT) to pregnant women with HIV.⁶ And a series of trials supported by the government of Canada—which took over 15 years to complete—showed that four months of daily rifampicin (4R) is a safe and effective alternative to 9H for preventing TB in both adults and children.⁷

The absence of these large trials from Tables 1 and 2, many of which TAG has followed for the better part of the last decade, signals that the TB preventive therapy field has entered a new season. The current moment is less about anticipating long-awaited results and more about making sense of the substantial clinical trial data already on hand. The primary findings from the three studies summarized above have already spurred revisions to World Health Organization (WHO) **guidelines on TPT**, which the agency updated in March 2020.⁸ Putting primary outcomes into normative guidance is just the first pass at unpacking the knowledge generated by these clinical trials. Some of the most exciting advances in TB preventive therapy in the past two years have come from secondary analyses (of P1078 and BRIEF-TB), pharmacokinetic investigations (P2001), drug-drug interaction studies (DOLPHIN), biomarker research (CORTIS), pediatric studies (TiTi), and studies evaluating the durability of newer TPT regimens (WHIP3TB).

Results from the studies italicized in the previous paragraph are reviewed below. These studies share a commitment to carefully designed, detail-oriented investigation into the effectiveness and safety of using newer TPT regimens in vulnerable populations: in the case of these studies, people living with HIV (PLHIV) and pregnant women. Collectively, the studies discussed here and many of those listed in Tables 1 and 2 are about making TPT work for everyone. HIV positive or HIV negative, pregnant or not, young or old, drug user or abstainer, drinker or teetotaler, exposed to drug-resistant or drug-sensitive TB—everyone has a right to the highest attainable standard of TB prevention. Honoring this entitlement means expanding the range of TPT options available to people at risk of TB in all of their diversity.

Non-inferior to means testing whether an intervention is no worse than the control by a prespecified amount (called a noninferiority margin). This is different from testing superiority or equivalence.

TAG's *Statement on WHO Updated TB Preventive Therapy Guidance* overviews major takeaways from the updated **WHO guidelines on TPT**.

Results from the **CORTIS** study will be presented at the 51st Union World Conference on Lung Health in late October 2020 and will be discussed in the next issue of TAG's *Pipeline Report*.

Table 1. Recently Completed Clinical Trials of TB Preventive Therapy

Study Name (Registry number)	Status	Regimens and Study Design	Population	Study Location(s)
WHIP3TB (NCT02980016) <ul style="list-style-type: none"> ▪ Sponsor and major collaborators: Aurum Institute, KNCV, USAID ▪ Phase: III ▪ Sample Size (N =): 4,027 	Completed; <u>results presented</u> at CROI in March 2020	Part A: treatment completion of 3HP versus 6H Part B: effectiveness of 3HP once versus 3HP once a year for two years (p3HP)	PLHIV ≥2 years living in high-TB-incidence settings	Ethiopia, Mozambique, South Africa
P2001 (NCT02651259) <ul style="list-style-type: none"> ▪ IMPAACT ▪ Phase I/II ▪ N = 50 	Completed; <u>results presented</u> at CROI in March 2020	PK and safety of 3HP	Pregnant and postpartum women with and without HIV and with TB infection	Haiti, Kenya, Malawi, Thailand, Zimbabwe
DOLPHIN (NCT03435146) <ul style="list-style-type: none"> ▪ IMPAACT4TB (Aurum Institute/JHU/Unitaid) ▪ Phase I/II ▪ N = 60 	Completed; <u>results presented</u> at CROI in March 2019	PK and safety of 3HP given with DTG-based ART	Adults with HIV on stable DTG-based ART	South Africa
CORTIS (NCT02735590) <ul style="list-style-type: none"> ▪ Phase II/III ▪ University of Cape Town ▪ N = 2,927 	Completed; results to be presented at TB Union Conference in October 2020	3HP versus no intervention and active surveillance for TB	HIV-negative adults with a gene-based correlate of risk suggestive of incipient TB	South Africa
DORIIS (NCT03886701) <ul style="list-style-type: none"> ▪ Phase I ▪ Merck Sharp & Dohme ▪ N = 11 	Completed; <u>results published</u>	Drug-drug interaction study of 3HP and doravirine , a novel NNRTI	HIV-negative, QFT-negative adult volunteers	United States
ART: antiretroviral therapy CROI: Conference on Retroviruses and Opportunistic Infections DTG: dolutegravir IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group JHU: Johns Hopkins University		NNRTI: non-nucleoside reverse transcriptase inhibitor PLHIV: people living with HIV PK: pharmacokinetics QFT: QuantiFERON TB: tuberculosis USAID: U.S. Agency for International Development		

In short: the TB preventive therapy field is anything but a monoculture.

The studies reviewed here will be succeeded in a few years' time when ongoing clinical trials report results. Some of the most anticipated studies are three evaluating preventive therapy for people exposed to drug-resistant TB (**Table 3**), an area of practice completely barren of clinical trial data. Looking even further ahead, scientists are sowing ideas that, when matured, will radically alter TPT past its familiar form of daily pill taking involving isoniazid, rifampicin, rifapentine, or combinations thereof. Preparations are now underway to study long-acting, injectable formulations of existing drugs and to apply drugs approved for other TB indications as prophylaxis (e.g., bedaquiline, delamanid). The chapter closes with an overview of these exciting developments.

WHIP3TB: is taking a single round of 3HP enough to prevent TB in PLHIV?

The **3HP regimen** is poised to supplant IPT as the preferred TPT regimen (for TB programs that can access it, anyway: see TAG's *An Activist's Guide to Rifapentine* for a discussion of rifapentine accessibility challenges). The expected shift from IPT to 3HP became more likely when the WHIP3TB trial reported results at the 2020 Conference on Retroviruses and Opportunistic Infections (CROI). WHIP3TB was a two-part, randomized, pragmatic trial funded by the US Agency for International Development, sponsored by the KNCV Tuberculosis Foundation, and conducted by the Aurum Institute. The trial enrolled 4,027 PLHIV in Ethiopia, Mozambique, and South Africa. Most participants were adults, though anyone age two years and older living with HIV and on antiretroviral treatment (ART) was eligible to enroll.⁹ Part A of the study was an observational, randomized comparison of 3HP to six months of daily isoniazid (6H) in terms of treatment completion (secondary objectives evaluated the two regimens with respect to TB incidence and all-cause mortality over 12 months). Investigators measured completion by pill counts self-reported by study participants. Results showed that a far greater percentage of people taking 3HP completed therapy compared with those on 6H: 90.4% versus 50.5%, a risk difference of 39.5 (95% confidence interval [CI]: 35–44.9). In other words, participants taking 3HP were 1.79 (95% CI: 1.62–1.97) times as likely to complete therapy as those receiving 6H.¹⁰

Part B of WHIP3TB was a randomized, controlled trial that evaluated the effectiveness and safety of giving 3HP once versus giving 3HP twice—once a year for two years, an approach called periodic 3HP, or p3HP. (Secondary objectives of part B compared 3HP and p3HP in terms of TB incidence over months 12–24 of follow-up, all-cause mortality, serious adverse events, and incidence of rifampicin-resistant TB.) Investigators observed similar TB incidence among participants taking p3HP and 3HP over 24 months of follow-up.¹¹ In the p3HP arm, there were 37 cases of TB per 3,070 **person-years** of follow-up (an incidence rate of 1.12/100 person-years) compared to 39 cases per 3,094 person-years of follow-up (1.26/100 person-years) in the 3HP arm. TB incidence did not differ by subgroups (country, CD4 count, **QFT** status). There were more study-defined serious adverse events (SAEs) reported in the p3HP group than among participants taking either 3HP or 6H, and the most common SAE was hepatitis.

The **3HP regimen** consists of 12 once-weekly doses of rifapentine and isoniazid.

Person-years is a type of measurement that looks at both the number of people in a study and how much time each person spent in the study. It estimates how much “time at risk” participants contributed to a study.

QFT refers to the QuantiFERON-TB Gold (or Gold Plus) test, an interferon-gamma release assay (IGRA) manufactured by Qiagen. IGRAs are used to test for TB infection. They detect cell-mediated immune responses to TB antigens (but do not measure infection directly).

The WHIP3TB results provide yet another demonstration that people are more likely to complete 3HP than either of the longer isoniazid-only options (6H, 9H). The part B findings further suggest that there is no need for PLHIV to take more than one course of 3HP, even if they live in countries with high TB incidence. (Importantly, all WHIP3TB study participants were taking ART to treat HIV. As with earlier studies of IPT in PLHIV, the combination of ART and TPT will better protect against TB than either intervention alone.) A press release by the Aurum Institute during the CROI Conference put it this way: “A single course of 3HP provides lasting protection against TB and does not need to be repeated year after year.”¹² This is good news for the prospects of TB elimination, because it will be easier and cheaper to scale up 3HP given as a single, rather than repeat, course of therapy.

Table 2. Ongoing and Planned Clinical Trials of TB Preventive Therapy

Study Name (Registry number)	Status	Regimens and Study Design	Population	Study Location(s)
3HP vs 1HP (NCT03785106) <ul style="list-style-type: none"> Phase III HIV-NAT N = 2,500 	Enrolling	Safety and efficacy of 3HP vs. 1HP (sub-study: PK of rifapentine, DTG, and TAF)	Adults with HIV and TB infection (QFT or TST positive or HHC)	Thailand
TBTC Study 35 (NCT03730181) <ul style="list-style-type: none"> TBTC, IMPAACT4TB (Aurum Institute/ JHU/Unitaid), Sanofi Phase I/II N = 72 	Enrolling	PK and safety of 3HP using dispersible HP formulations (Sanofi)	Children aged 0–12 years with TB infection (HHC with positive TST or IGRA) with and without HIV (children with HIV on EFV- or RAL-based ART)	South Africa
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)	United States
2R2 (NCT03988933) <ul style="list-style-type: none"> McGill University, CIHR Phase II N = 1359 	Enrolling	Safety and treatment completion of two high-dose rifampicin regimens (20 or 30 mg/kg) taken daily for 2 months vs. 4R	People ≥ 10 years of age with positive TST or IGRA, or other indication for TPT (PLHIV eligible)	Canada, Indonesia, Vietnam

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)
DOLPHIN Too (NCT03435146) <ul style="list-style-type: none"> ▪ IMPAACT4TB (Aurum Institute/ JHU/Unitaid), ViiV ▪ Phase I/II ▪ N = 75 	Planned	PK and safety of 3HP and IPT given with DTG-based ART	Adults with HIV starting ART for the first time	South Africa
YODA (NCT03510468) <ul style="list-style-type: none"> ▪ Phase I ▪ NIH Clinical Center ▪ N = 75 	Enrolling	Drug-drug interaction study of 3HP and TAF	HIV-negative, QFT-negative adult volunteers	United States
3HP with DTG + DRV/c (NCT02771249) <ul style="list-style-type: none"> ▪ Phase I ▪ NIH Clinical Center ▪ N = 75 	Enrolling	Drug-drug interaction study of 3HP and DTG + DRV/c	HIV-negative, QFT-negative adult volunteers	United States
A5372 (NCT04272242) <ul style="list-style-type: none"> ▪ ACTG, ViiV ▪ Phase II ▪ N = 72 	Enrolling	PK and safety of 1HP given with DTG-based ART (twice daily vs. once daily)	Adults with HIV on stable DTG-based ART with positive TST or IGRA, or other indication for TPT	Brazil, Thailand, United States
One to Three (NA) <ul style="list-style-type: none"> ▪ IMPAACT4TB (Aurum Institute/ JHU/Unitaid) ▪ Phase III ▪ N ≈ 686 	Planned	Treatment completion of 1HP vs. 3HP	Adults and adolescents (aged ≥13 years) either HHCs (any HIV status) or PLHIV on EFV- or DTG-based ART	Select IMPAACT4TB project countries
Rifapentine with bictegrovir and TAF (NCT04551573) <ul style="list-style-type: none"> ▪ Yale University, Gilead ▪ Phase I ▪ N = 24 	Planned	Drug-drug interaction study of rifapentine (daily and once-weekly) with bictegrovir and TAF	HIV-negative, QFT-negative adult volunteers	United States

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)
Ultra Curto (NA) <ul style="list-style-type: none"> ▪ NIH, JHU, Fiocruz, FMT-HVD, Sanofi ▪ Phase IV ▪ N = 500 	Planned	Treatment success and safety of 1HP vs. 3HP	HIV-negative adults and adolescents (aged ≥ 15 years) with positive TST or IGRA	Brazil
DOLPHIN Kids (NA) <ul style="list-style-type: none"> ▪ IMPAACT4TB (Aurum Institute/ JHU/Unitaid), 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	South Africa
IMPAACT P2024 (NA) <ul style="list-style-type: none"> ▪ IMPAACT ▪ Phase I/II ▪ N = NA 	Planned	PK and safety of 1HP given with DTG- and EFV-based ART	Children ≤ 15 years with and without HIV (children with HIV on DTG- or EFV-based ART)	NA
IMPAACT P2025 (NA) <ul style="list-style-type: none"> ▪ IMPAACT ▪ Phase IV ▪ N = 1104 	Planned	Safety, PK, and optimal timing of 3HP and 1HP	Pregnant and postpartum women with HIV and QFT-positive or recent HHC on EFV- or DTG-based ART (possible subset of HIV-negative women for safety and efficacy)	NA
ACTG: AIDS Clinical Trials Group ART: antiretroviral therapy DTG: dolutegravir DRV/c: darunavir boosted with cobicistat EFV: efavirenz HHC: household contact (of people with TB disease) HIV-NAT: HIV Netherlands Australia Thailand Research Collaboration IGRA: interferon-gamma release assay IPT: isoniazid preventive therapy IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group		JHU: Johns Hopkins University NA: Not available NIH: U.S. National Institutes of Health NNRTI: non-nucleoside reverse transcriptase inhibitor PK: pharmacokinetics QFT: QuantiFERON RAL: raltegravir TAF: tenofovir alafenamide TB: tuberculosis TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention TST: tuberculosis skin test		

DOLPHIN: Is 3HP safe to take with dolutegravir-based ART?

Just as 3HP is increasingly seen as the preferred TPT option, dolutegravir-based ART (i.e., the **TLD regimen**) is fast becoming first-line therapy for HIV in most countries.¹³ Preventing TB in PLHIV will therefore require using TPT regimens that are compatible with dolutegravir. The compatibility of TPT and ART must be demonstrated, not assumed. All of the currently available short-course TPT regimens incorporate either rifapentine (3HP, 1HP) or rifampicin (3HR, 4R). Rifapentine and rifampicin belong to the rifamycin family of drugs; these drugs can speed up the body's metabolism of antiretrovirals (ARVs), including dolutegravir.¹⁴ Consequently, it may be necessary to increase the dose of dolutegravir while taking rifamycin-based TPT in order to keep drug levels high enough to maintain viral suppression of HIV.

The single-arm phase I/II **DOLPHIN study** assessed the safety and **PK** of coadministering 3HP and TLD in adults with HIV on stable ART. As summarized in TAG's *An Activist's Guide to Rifapentine*, the DOLPHIN study sought to answer two questions: (1) Is it safe to take 3HP with dolutegravir-based ART? (2) If yes, does the dose of dolutegravir need to be adjusted?¹⁵ In answer to the first question, the study showed that giving 3HP with TLD is safe. Investigators recorded only three grade 3 AEs (one involving a participant who withdrew before starting 3HP). The remaining 60 participants all completed a full course of 3HP; there were no deaths in the study.¹⁶

Regarding the second question: 3HP increased dolutegravir clearance by 37%, which resulted in an average decrease in daily dolutegravir exposures of 26% (measured as **AUC**).¹⁷ This drop in dolutegravir exposures was not enough to warrant increasing the dose of dolutegravir. More specifically, the mean trough concentrations of dolutegravir in the presence of 3HP, while reduced, exceeded the average concentration corresponding to a 10 mg dose of dolutegravir in the **SPRING-1 study**.¹⁸ Even a 10 mg daily dose of dolutegravir—40 mg lower than the currently recommended dose—is associated with substantial antiviral effect.¹⁹ Therefore, the fact that dolutegravir trough concentrations in DOLPHIN were above those achieved with 10 mg in earlier studies suggests there is no need to raise dolutegravir doses in the presence of 3HP. All participants received the standard once-a-day 50 mg dose of dolutegravir throughout the study and maintained viral suppression while taking 3HP. (One participant had a detectable HIV viral load during the follow-up phase of the study, but this occurred four weeks after completing 3HP.)²⁰

The DOLPHIN study provides reassurance that 3HP and TLD can be coadministered with relative ease, but the story does not end here. Participants entered the study already on ART and with viral suppression. The compatibility of 3HP and dolutegravir in this population does not necessarily apply to people

The **TLD regimen** is composed of the antiretroviral drugs dolutegravir, lamivudine, and tenofovir disoproxil fumarate.

The **DOLPHIN study** was funded by Unitaid under the [IMPAACT4TB project](#) and conducted by investigators at Johns Hopkins University and the Aurum Institute.

PK stands for pharmacokinetics, which involves studying what the body does to a drug by looking at things like how a drug moves through the body or how the drug concentration and distribution change over time.

AUC or area under the curve is a PK measure of how much drug reaches the bloodstream in a given period of time. Mostly simply, it can be thought of as total drug exposure.

SPRING-1 (NCT00951015) was a phase IIb dose-ranging study that compared 10 mg, 25 mg, and 50 mg daily doses of dolutegravir.

who may be starting ART for the first time together with 3HP. For this so-called ART-naïve population, DOLPHIN Too will assess the safety and PK of initiating 3HP and TLD simultaneously. **DOLPHIN Too** will enroll two additional groups of participants: 25 people will receive TLD plus daily IPT, and a separate cohort of 50 will take TLD with 3HP.²¹ Investigators will then compare safety, PK, and HIV viral loads among people starting TLD for the first time taking either IPT (the old TPT standard of care) or 3HP (the newer standard of care) over 24 weeks. A separate study, DOLPHIN Kids, will examine drug-drug interactions between 3HP and dolutegravir in children.²²

Aside from 3HP, there is a need to study whether other rifamycin-based TPT regimens are safe to take with dolutegravir. Toward this end, ACTG study A5372 will evaluate potential drug-drug interactions when giving dolutegravir with 1HP.²³ The 1HP regimen may have different effects on dolutegravir than 3HP because of its daily dosing and higher total quantity of rifapentine taken (because the 1HP regimen is taken daily, it requires more rifapentine than 3HP).

P2001: Does the dose of 3HP need to be adjusted for pregnancy?

Other recent PK investigations have looked at the effects of pregnancy on 3HP. Pregnant individuals were excluded from earlier 3HP trials.²⁴ The resulting gap in evidence has preempted the WHO from recommending 3HP during pregnancy, though the regimen would be ideal in this context as its 3-month duration means women could complete it in full before delivery. To fill this evidentiary gap, the IMPAACT Network conducted P2001, a phase I/II study of the PK, tolerability, and safety of 3HP in pregnant and postpartum **women**. The trial enrolled 50 women, 20 of whom were living with HIV. All participants had a risk factor for TB, either because they shared a household with someone with TB or were living with HIV and had a positive QFT test.²⁵

In presenting P2001 results at the 2020 CROI Conference, primary investigator Jyoti Mathad described the study's purpose as "providing the data needed to extend the use of the 3HP regimen to pregnant women."²⁶ To accomplish this, P2001 sought to determine the effect of pregnancy on rifapentine PK and to collect some initial safety data. It is important to note that the study was not powered to demonstrate safety (more on this later). The primary objective of the study was to estimate the population PK of rifapentine and **desacetyl-rifapentine** in pregnant women (second or third trimester) and postpartum women. The analysis compared rifapentine clearance in participants to **historical controls**. Investigators hypothesized that rifapentine clearance in pregnant and postpartum women would be within 25% of the clearance observed in non-pregnant cohorts. The researchers also looked at whether results varied by HIV status and stage of pregnancy.²⁷

DOLPHIN Too is an extension of the DOLPHIN study protocol and listed under the same ClinicalTrials.gov identifier number (NCT03435146).

TAG is using the word "**women**" to review P2001 and P1078 findings and not the gender-neutral "pregnant individuals/persons" preferred by our style guide because this is the term the trialists themselves used in designing, conducting, and analyzing the two studies.

Desacetyl-rifapentine is the active metabolite of rifapentine.

A **historical control** involves comparing newly collected data to data from older studies (as opposed to a study enrolling a concurrent control group). The data used as historical controls in P2001 came from two studies of 3HP conducted by the TB Trials Consortium in non-pregnant individuals: TBTC Study 26 (NCT00023452) and TBTC Study 29B (NCT00694629).

P2001 enrolled participants into two cohorts of 25 people, 10 PLHIV in each. Women in cohort 1 entered the study in their second trimester, and those in cohort 2 entered during their third trimester. The study found that in both the second and third trimesters, women living with HIV cleared rifapentine faster than HIV-negative women.²⁸ On average, women with HIV had 30% lower drug exposure (measured as AUC). Despite this higher clearance, rifapentine exposures remained within the drug's therapeutic range. Among HIV-negative participants, rifapentine clearance was 35% higher postpartum compared with during pregnancy. Among HIV-positive women, there was no difference in rifapentine clearance during pregnancy versus postpartum. In both groups, clearance was similar to that in non-pregnant historical controls. Consequently, investigators concluded that there is no need to change the dose of rifapentine for either pregnant or postpartum women irrespective of HIV status.²⁹ Further analyses of isoniazid exposures as well as PK data on the two drugs in breastmilk and among infants born to women in the trial are forthcoming.

Although not powered for safety, the study did collect information on maternal and infant outcomes. In terms of maternal safety, all 50 women completed 3HP in full, no women developed TB disease, and there were no deaths or drug-related SAEs. One woman in the study died from trauma (placental abruption); her death occurred 10 weeks after completing 3HP. In terms of infant safety, 22 infants were born to women still taking 3HP at the time of birth. No infants developed TB or had an SAE related to 3HP. Rates of low birth weight and premature birth in P2001 were similar to the frequency of these events among women in the general population of the **countries** where the study took place.³⁰

P2001 provides reassurance that pregnant and postpartum women can receive the same dose of rifapentine as non-pregnant people when taking 3HP. As TAG's TB project co-director Lindsay McKenna commented, "These findings bring us closer to unlocking a new, potentially safer TPT option for pregnant women, a population especially vulnerable to TB."³¹ Closer, yes—but not yet all the way. McKenna continued: "A randomized clinical trial powered to determine optimal timing and safety of 3HP and other rifapentine-containing TB prevention regimens during pregnancy is necessary and should be initiated with urgency. Such a study should be a priority for the IMPAACT network to carry forward."³² The PK data collected in P2001 are convincing; the safety data are encouraging, but preliminary. Thoroughly characterizing the safety of 3HP in pregnant women will require a larger study. It will also be important to study 3HP in pregnant women taking dolutegravir-based ART, as all of the participants in P2001 were on efavirenz-based regimens. At this point, it is unclear whether the higher rifapentine clearance seen in women with HIV was due to HIV status or perhaps an effect of efavirenz-based ART.³³ The planned P2025 study by the IMPAACT Network will investigate many of these questions in a four-arm trial of 3HP and 1HP in pregnant and postpartum women living with HIV who are taking either efavirenz- or dolutegravir-based ART.³⁴

P2001 took place in the following **countries**: Haiti, Kenya, Malawi, Thailand, and Zimbabwe.

P1078 secondary analyses: should pregnant women with HIV start IPT during pregnancy or after delivery?

The urgency behind McKenna’s call for a randomized clinical trial to determine the safety and optimal timing of 3HP in pregnant and postpartum women originates in the experience of an earlier IMPAACT study. P1078 was a phase IV trial that evaluated the safety of immediate (during pregnancy) versus deferred (postpartum) IPT in 956 HIV-positive women. Most TB in women occurs in women of reproductive age. When TB and pregnancy coincide, there is a higher risk of adverse maternal, pregnancy, and infant outcomes. Although vulnerable to TB, pregnant women were excluded from earlier clinical trials of IPT.³⁵ This exclusion held across decades of research on IPT.³⁶ Despite the resulting lack of safety and efficacy data from clinical trials, the prevailing medical consensus and longstanding WHO recommendation were that pregnant women, particularly those with HIV or TB infection, receive IPT. Generating high-quality evidence to back up this recommendation is especially important since physiological changes during pregnancy and the early postpartum period alter how the body processes many drugs.³⁷ Medicines that work one way in non-pregnant people may have different safety profiles, may require different dosing strategies, or may be contraindicated entirely in pregnant people.

P1078 sought to close this decades-long evidence-practice gap. Investigators hypothesized that starting IPT during pregnancy would be noninferior to deferring IPT to 12 weeks after delivery. And it was; the trial’s primary outcome was a **composite safety measure** of maternal adverse events. There were 72 of these events in the group of women starting IPT during pregnancy (15.1%) and 73 in the deferred group (15.2%) for a risk difference of 0.10 (95% CI: -4.77 to 4.98).³⁸ This met the trial’s definition of noninferiority. Additionally, both groups had low rates of TB. However, things got more complicated when it came to secondary outcomes, particularly a **composite adverse pregnancy outcome**. Here, more women in the group starting IPT during pregnancy experienced an event considered an adverse pregnancy outcome than in the deferred group (23.6% versus 17.0%, a risk difference of 6.7 [95% CI: 0.8–11.9]).³⁹ When analyzed individually, the various adverse pregnancy outcomes did not differ significantly between the immediate and deferred IPT groups, but when analyzed together, as the composite outcome, they did.

Some may interpret this finding to mean that pregnant women should wait to start IPT until after they give birth—the opposite of long-established practice. For their part, the study investigators reacted in the reasonable, understated prose of academic medicine: “This was a new finding.... that highlights a safety concern that warrants further examination.”

Composite measures combine different endpoints of interest into a single outcome measure.

The **composite adverse pregnancy outcome** in P1078 included the following events: still birth, spontaneous abortion, low birth weight, preterm delivery, and infant congenital anomalies.

To further interrogate this finding, P1078 investigators presented a secondary analysis of the adverse pregnancy outcomes at the 2020 CROI Conference.⁴⁰ The secondary analysis adjusted for factors (covariates) associated with the different pregnancy outcomes. (These covariates included things like maternal age, ARV regimen, CD4 count, QFT status, twin pregnancy, mid-upper arm circumference, etc.) The adjusted analysis evaluated three composite outcomes comprised of different combinations of adverse pregnancy events. For all three composite adverse pregnancy outcomes, the odds of experiencing an event were higher in the group of women starting IPT during pregnancy compared to the deferred group. In other words, starting IPT during pregnancy was independently associated with a higher risk of adverse pregnancy outcomes after adjusting for known risk factors. The adjusted analysis also indicated that the odds of low birth weight were 1.68 times higher among women in the immediate versus deferred IPT group (odds ratio = 1.68 [95% CI: 1.10–2.59]).⁴¹

The P1078 study team presented an additional set of secondary analyses at the AIDS2020 conference looking at the risk of **hepatotoxicity**.⁴² Sixty-three women in the trial experienced a hepatotoxic event; most events occurred at least one week postpartum. The effect of immediate versus deferred IPT on risk of hepatotoxicity differed by ARV regimen. Women taking efavirenz-based ART were more likely to experience hepatotoxicity if they initiated IPT postpartum rather than during pregnancy (the opposite was true for women taking nevirapine-based ART). Starting **cotrimoxazole** therapy after 12 weeks post-delivery was also associated with a higher risk of liver toxicity. Most importantly, investigators observed a 2.5-fold higher risk of hepatotoxicity among women with a CYP2B6 genotype associated with slow efavirenz metabolism compared with women with a CYP2B6 genotype associated with moderate or fast efavirenz clearance (risk ratio = 2.5, 95% CI: 1.42–4.56).⁴³ The two major takeaways from this analysis are (1) the importance of monitoring for hepatotoxicity in the postpartum period and (2) the need to consider ARV regimen, CYP2B6 genotype, and cotrimoxazole use when deciding whether to use IPT in pregnant and postpartum women living with HIV.

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

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

Where does this leave pregnant women with HIV at risk of TB? The WHO reviewed data from the P1078 primary analysis for its updated TPT guidance released in March 2020. Ultimately, the WHO guideline development group did not change the original recommendation that pregnant women with HIV receive IPT during pregnancy to prevent maternal and infant TB. Pregnancy does not disqualify women with HIV from receiving IPT. In making this decision, the GDG evaluated the P1078 findings alongside the totality of other evidence (most of it from observational studies that did not confirm the findings of P1078). The group

considered that “a systematic deferral of IPT to the postpartum period in pregnant women living with HIV would deprive them of significant protection when they are highly vulnerable to TB.”⁴⁴ Although the P1078 results did not change WHO guidance, the primary and secondary analyses add important context to a choice many women will have to make. Women and their healthcare providers may weigh the risks and benefits of deferring IPT differently knowing that there may be higher odds of adverse pregnancy outcomes when IPT is started during pregnancy. One day, hopefully soon, pregnant women will have the option to choose from a wider array of TPT regimens with well-characterized safety and PK data.

The results of P1078 are complex and nuanced, but the trial’s larger implication is clear: more research in pregnant women, earlier. The field is playing catch-up with regimens like 3HP and 1HP, which are already approved but have just recently been studied in pregnant women.⁴⁵ Future TPT regimens must be developed in a way that generates safety and PK data in pregnant and postpartum women as soon as feasible. Women at risk of TB cannot afford to repeat the experience of IPT where 66 years separates the introduction of a regimen and its systematic study in pregnant women. The consequences of this exclusion, which applies to other research areas including HIV, is summarized by the opening statement of a report from the **PHASES project** (Pregnancy + HIV/AIDS Seeking Equitable Study): “Pregnant women are among those most in need of safe and effective preventives and treatments for HIV and its co-infections. Yet, because they are commonly excluded from research, they are among the least likely to have robust, timely evidence to inform decisions around the use of needed medications. The resulting evidence gaps have put pregnant women and their children in harm’s way.”⁴⁶

The **PHASES project** report contains 12 recommendations for generating more research in pregnant women on HIV and its coinfections in ways that uphold the ethical values of protections, access, and respect.

How scientists include those most vulnerable to a particular disease in a research agenda says a lot about how committed a scientific field is to health equity. The safety, PK, and drug-drug interaction studies reviewed in this year’s dispatch from the TB preventive therapy pipeline are not the sideshow to larger trials but the main event. If PLHIV, pregnant women, and other groups such as children or people who use drugs are most at risk of TB, then they should also be well represented in research to prevent TB. Too often their inclusion comes later—historically, much later. More recently, scientists, funders, activists, and representatives from TB-affected communities have moved closer to realizing the earlier and equitable inclusion of special populations in TPT research. Future installments of TAG’s *Pipeline Report* will reveal whether this progress is momentary or lasting.

Table 3: Clinical Trials of Tuberculosis Preventive Therapy for People Exposed to Drug-Resistant TB

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)
TB CHAMP <u>ISRCTN92634082</u> <ul style="list-style-type: none"> ▪ South African MRC, Wellcome Trust, U.K. MRC, ▪ Phase III ▪ N = 1,556 child HHCs from 778 households 	Active, not enrolling	Safety and efficacy of 6 months of daily levofloxacin vs. placebo	HIV-positive or HIV-negative children (aged 0–5 years) who are HHCs of adults with MDR-TB	South Africa
V-QUIN <u>ACTRN12616000215426</u> <ul style="list-style-type: none"> ▪ Australian NHMRC, government of Vietnam ▪ Phase III ▪ N = 2785 HHCs from 1326 households 	Active, enrolling	Safety and efficacy of 6 months of daily levofloxacin vs. placebo	Household contacts of people with MDR-TB; first phase restricted to people aged ≥15 years (PLHIV eligible)	Vietnam
PHOENIX MDR-TB/ A5300B/I2003B <u>(NCT03568383)</u> <ul style="list-style-type: none"> ▪ ACTG, IMPAACT ▪ Phase III ▪ N = 3,452 HHCs from 1,726 households 	Enrolling	6 months (26 weeks) of daily delamanid vs. 6H	High-risk adult, adolescent, and child household contacts of adults with MDR-TB (PLHIV eligible)	Botswana, Brazil, Haiti, India, Kenya, Peru, Philippines, South Africa, Tanzania, Thailand, Uganda, Zimbabwe
ACTG: AIDS Clinical Trials Group DFID: U.K. Department for International Development HHC: household contact (of people with tuberculosis disease) IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group		MDR-TB: multidrug-resistant tuberculosis MRC: Medical Research Council NHMRC: National Health and Medical Research Council (Australia)		

The future of TPT is long-acting

Since the advent of IPT, preventive therapy for TB has required swallowing pills—a lot of pills. Even the 12-week 3HP regimen requires taking either 120 pills (Sanofi formulation) or 48 pills (Macleods formulation). In the future, familiar TPT regimens such as 3HP and 1HP may assume new forms as long-acting, injectable nanoparticle suspensions. Instead of filling a prescription for pill bottles or blister packs, people taking TPT would receive an injection or two (or perhaps three) into muscle or subcutaneous tissue. The injection would deliver a **drug depot** that would gradually release drug at a rate that provides a meaningful therapeutic concentration for weeks or even months.

Momentum for developing long-acting, injectable (LAI) formulations of TPT and TB treatments has been building slowly but steadily for several years.

The **LEAP** TB working group wrote a target product profile that lays out the minimum expectations and ideal standards for TB LAI technologies.⁴⁷ LEAP and associated investigators also evaluated existing TB drugs for their potential to be repositioned as LAIs. Not every drug is suitable for long-acting applications. Compounds must have the right mix of qualities with respect to low water solubility (water-soluble nanoparticles dissolve and release drug too quickly), high potency (meaning the drug can still work without a high plasma concentration), and a long half-life (which prevents the drug from clearing the body too rapidly). TB drugs that possess the right combination of solubility, potency, and half-life include rifapentine, delamanid, bedaquiline, and rifabutin.⁴⁸ The first three unlock the potential to apply LAI technologies to TPT. Rifapentine is the backbone of existing short-course TPT regimens (3HP, 1HP), delamanid is being studied as prophylaxis for people exposed to MDR-TB (in the PHOENix trial), and there are murmurings of using bedaquiline as preventive therapy (read on).

The momentum pushing forward this work accelerated in 2020 when Unitaid announced a \$32 million, 5-year award to a consortium led by the University of Liverpool and known as **LONGEVITY**. The LONGEVITY project seeks to develop and commercialize long-acting medicines for TB prevention (isoniazid and rifapentine), malaria treatment (atovaquone), and hepatitis C cure (glecaprevir and pibrentasvir).⁴⁹ The TB work will initially focus on creating an LAI version of the powerful rifapentine and isoniazid combination. Reformulating rifapentine as an LAI will be the easy part; isoniazid is trickier. Isoniazid is highly water soluble (among the drugs in the TB LEAP assessment, isoniazid was more soluble than any drug except pyrazinamide). The LONGEVITY team will therefore need to develop a novel isoniazid **prodrug** before beginning phase I trials (scheduled for 2024). Other important issues must be worked out during the development process—for example, can rifapentine and isoniazid nanoparticle suspensions be delivered together in a single vial, or will they require separate injections? The eventual clinical trials will investigate safety, tolerability, and dosing schedules (the team is aspiring toward one or two injections of rifapentine-isoniazid, each designed to work over a month).

A **drug depot** delivered by injection places a localized mass of drug material in muscle or tissue where it is gradually released and absorbed by the body over an extended period of time.

The Long-Acting/Extended Release Antiretroviral Resource Program (**LEAP**) is an NIH-funded effort to support the development of long-acting ARVs for HIV.

The **LONGEVITY** consortium includes the University of Liverpool, CHAI, Tandem Nano Ltd, University of Nebraska, Johns Hopkins University, the Medicines Patent Pool, and TAG.

A **prodrug** is a compound that is converted by the body into active drug substance after its administration

Why long-acting, and why now? Unitaid framed its investment in the LONGEVITY project primarily in public health terms by pointing out that when daily oral medicines “are not taken consistently, treatments fail and illness spreads. Poor adherence can also allow drug-resistant microbes to develop.”⁵⁰ In Unitaid’s vision, long-acting formulations may also “free patients from daily pills, make it easier for them to start and stay on treatment, and reduce the burden on health systems.” For diseases that carry significant stigma, such as TB, “long-acting medicines can provide people with a more discreet treatment.”⁵¹ All of these benefits are potential, and realizing these potentialities will depend on developing long-acting TPT formulations in close consort with communities to ensure that the resulting products meet **3AQ** standards.

The development of TPT LAIs is drafting off the success of similar techniques applied to other diseases. Long-acting/extended-release technologies are commonly used for contraception (e.g., Depo-Provera) and management of schizophrenia (many anti-psychotic drugs are available in LAI forms). More recently, and closer to home for TB, the HIV field is preparing for the first U.S. Food and Drug Administration approval of a once-a-month, LAI ARV combination (**cabotegravir** and **rilpivirine**). In addition, a large clinical trial among 4,570 cisgender men and transgender women who have sex with men showed that long-acting cabotegravir (**CAB LA**) was noninferior to TDF/FTC (Truvada™) as pre-exposure prophylaxis (PrEP) for HIV.⁵²

The TB field should carefully watch the reception of long-acting cabotegravir as ART and PrEP. Just as people experience pill fatigue from having to take daily medication, they may also tire of repeat, large injections. In two clinical trials of long-acting cabotegravir and rilpivirine (ATLAS and FLAIR), 81% and 86% of participants reported injection-site reactions.⁵³ In the CAB LA study, 80% of participants receiving CAB LA experienced injection-site pain or tenderness.⁵⁴ Still, overall acceptability of both approaches was high. In an editorial introducing the ATLAS and FLAIR results in the *New England Journal of Medicine*, Judith Currier wrote, “For many, freedom from the need for daily oral therapy is a major advance, even at the cost of having to receive monthly injections.”⁵⁵ Whether this holds over time remains to be seen. Researchers will also need to demonstrate acceptability in key populations such as people who inject drugs. Since TPT is not taken for life, trading longer oral regimens for shorter injectable regimens may present an even easier choice. But preserving choice is key: not everyone likes getting a shot, and prevention works best when people who receive it—people who are by definition not sick and who by choosing therapy are acting to avert a future potential risk to themselves and others—have a range of options from which to choose.

Developing LAIs guided by **patient preferences and values** is an especially important undertaking in TB, where civil society and community groups only recently won a years-long struggle to drop injectable drug agents from drug-resistant TB therapy. New LAIs for prevention and the decades-old injectable agents for drug-resistant TB are not the same, but negative associations may carry over from past experience.

3AQ is a human rights standard established by the right to health and the right to science. It requires that any health goods and scientific benefits be available, accessible (affordable), acceptable to users, and of quality.

TAG’s 2020 Pipeline Report chapters on *Antiretroviral Treatment and PrEP and Microbicides* review the latest research advancements related to long-acting **cabotegravir/rilpivirine** and **CAB LA**.

The LONGEVITY project is opening with a series of surveys to understand community and **patient preferences** for long-acting TB preventive technologies.

Looking even further ahead, beyond rifapentine-based TPT, the LONGEVITY project may work with bedaquiline and delamanid if either drug is recommended by the WHO as TB prophylaxis within the 2020–2024 project period (possible for delamanid, less likely for bedaquiline). Janssen has already developed a bedaquiline LAI and has funded its early evaluation in a mouse model of TB.⁵⁶ The injectable bedaquiline performed well in a **paucibacillary** mouse model of latent tuberculosis infection that compared giving one, two, or three monthly injections of bedaquiline to the equivalent oral doses. Most notably, a single bedaquiline LAI injection had detectable antibiotic activity out to 12 weeks.⁵⁷ Additional research and development is required before studying bedaquiline LAI in humans, but the initial mouse data are promising. In an interview with TAG conducted in April 2020, Gavin Churchyard, CEO of the Aurum Institute, raised an intriguing idea: “Could we couple the rifapentine injectable with the bedaquiline long-acting formulation, which has been evaluated in mice and shown to have durable protection up to three months?”⁵⁸ Coupling LAI rifapentine and bedaquiline would bring together two drugs that are always used apart due to drug-drug interactions that would need to be overcome.⁵⁹ A lot of work lies ahead, but Churchyard expressed the optimism evident throughout the entire TPT field: “The innovation is not done. We can look forward to many new exciting developments.”

Paucibacillary refers to having a low bacterial count or burden, in this case to simulate the conditions of TB infection (as opposed to the higher bacterial counts of TB disease).

Endnotes

1. World Health Organization. Q&A: ventilation and air conditioning in public spaces and buildings and COVID-19 [Internet]. 2020 July 29. <https://www.who.int/news-room/q-a-detail/q-a-ventilation-and-air-conditioning-in-public-spaces-and-buildings-and-covid-19>.
2. Margalith P, Beretta G. Rifamycin XI taxonomic study on streptomyces mediterranei nov. sp. Mycopathologia et mycologia applicata. 1960;13(4):321–30. doi: 10.1007/BF02089930.
3. For a detailed review of the natural provenance of QS-21 and its application to TB vaccine development, see: Frick M. The TB vaccine pipeline. M72/AS01E: between nature and licensure. New York: Treatment Action Group; 2019. <https://www.treatmentactiongroup.org/resources/pipeline-report/2019-pipeline-report/>.
4. Merwin W.S. “After the spring.” In: Travels. New York: Knopf; 1993.
5. Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. N Engl J Med. 2019;380(11):1001–11. doi: 10.1056/NEJMoa1806808.
6. Gupta A, Montepiedra G, Aaron L, et al. Isoniazid preventive therapy in HIV-infected pregnant and postpartum women. N Engl J Med. 2019;381(14):1333–46. doi: 10.1056/NEJMoa1813060.
7. Menzies D, Adjobimey M, Ruslami R, et al. N Engl J Med. 2018;379(5):440–53. doi: 10.1056/NEJMoa1714283.
8. World Health Organization. WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment. Geneva: World Health Organization; March 2020. <https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment>.
9. Churchyard G, Cardenas V, Chihota V, et al. Effectiveness of 3HP annually vs once for HIV-positive people: the WHIP3TB trial (Abstract 143). Presented at: Conference on Retroviruses and Opportunistic Infections; 2020 March 8–11; Boston, MA. <https://www.croiconference.org>.
10. Ibid.
11. Ibid.
12. Aurum Institute (Press Release). Shorter regimen for preventing TB found to have lasting protective effect in people living with HIV. 2020 April 28. <https://www.auruminstitute.org/component/content/article/46-press-releases/international-news/115-shorter-regimen-for-preventing-tb-found-to-have-lasting-protective-effect-in-people-living-with-hiv>.

13. fhi360. Tenofovir, lamivudine, and dolutegravir (TLD) transition. Durham, NC: fhi360; 2019. <https://www.fhi360.org/sites/default/files/media/documents/linkages-tld-transition-information.pdf>.
14. See, for example, the effects of rifampicin on dolutegravir concentrations: Dooley K, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr*. 2013;62(1):21–7. doi: 10.1097/QAI/0b013e318276cda9.
15. Frick M. An activist's guide to rifapentine.
16. Dooley K, Savic R, Gupte A, et al. Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial. *Lancet HIV*. 2020;7(6):e401–9. doi: 10.1016/S2352-3018(20)30032-1.
17. Ibid.
18. Hans-Jürgen S, Reynes J, Lazzarin A, et al. Dolutegravir in antiretroviral-naïve adults with HIV-1: 96-week results from a randomized dose-ranging study. *AIDS*. 2013;27(11):1771–8. doi: [10.1097/QAD.0b013e3283612419](https://doi.org/10.1097/QAD.0b013e3283612419).
19. In an early monotherapy trial of dolutegravir, the 10 mg dose had “antiviral responses [that] were similar to or higher than those seen in short-term studies of other antiretrovirals...” See: Min S, Sloan L, DeJesus E, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. *AIDS*. 2011;25(14):1737–45. doi: 10.1097/QAD.0b013e32834a1dd9.
20. Dooley K, et al. Once-weekly rifapentine and isoniazid.
21. [ClinicalTrials.gov](https://clinicaltrials.gov/) [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT03435146, Safety, tolerability, DDI short course treatment of LTBI infection with high-dose rifapentine and isoniazid or standard isoniazid preventive therapy in HIV+ patients (DOLPHIN & DOLPHIN TOO) (IMPAACT4TB). Cited: 2020 September 22. <https://clinicaltrials.gov/>.
22. Salazar-Austin N. Pediatric TPT research gaps. Presentation to: WHO HIVTB Implementation for Impact Working Group; 2020 May 20; virtual meeting.
23. [ClinicalTrials.gov](https://clinicaltrials.gov/) [Internet]. Bethesda (MD): National Library of Medicine (U.S.) 2000. Identifier NCT04272242, Drug-drug interactions between rifapentine and dolutegravir in HIV/LTBI co-infected individuals. Cited: 2020 September 22. <https://clinicaltrials.gov/>.
24. Gupta A, Hughes M, Garcia-Prats A, McIntire K, Hesselting A. Inclusion of key populations in clinical trials of new antituberculosis treatments: current barriers and recommendations for pregnant and lactating women, children, and HIV-infected persons. *PLoS Med*. 2019;16(8):e1002882. doi: 10.1371/journal.pmed.1002882.
25. Mathad J, Savic R, Britto P, et al. Rifapentine pharmacokinetics and safety in pregnant women with and without HIV on 3HP (Abstract 144). Presented at: Conference on Retroviruses and Opportunistic Infections; 2020 March 8–11; Boston, MA. <https://www.croiconference.org>.
26. Ibid.
27. Ibid.
28. Ibid.
29. Ibid.
30. Ibid.
31. Lindsay McKenna quoted in: Treatment Action Group. CROI 2020 TB round up [Internet]. 2020 March 16. <https://www.treatmentactiongroup.org/statement/croi-2020-tb-round-up/>.
32. Ibid.
33. Mathad J. Rifapentine pharmacokinetics and safety.
34. McKenna, Lindsay (Treatment Action Group and IMPAACT TB Scientific Committee, New York, NY). Personal communication with: Mike Frick (Treatment Action Group, New York, USA). 2020 September 15.
35. Gupta A, Mathad J, Abdel-Rahman S, et al. Toward earlier inclusion of pregnant and postpartum women in tuberculosis drug trials: consensus statement from an international expert panel. *Clin Infect Dis*. 2016;62(6):761–9. doi: 10.1093/cid/civ991.
36. McKenna L, Frick M, Lee C, et al. A community perspective on the inclusion of pregnant women in tuberculosis drug trials. *Clin Infect Dis*. 2017;65(8):1383–8. doi: 10.1093/cid/cix533.
37. Gupta A, et al. Toward earlier inclusion of pregnant and postpartum women.
38. Gupta A, et al. Isoniazid preventive therapy.

39. Ibid.
40. Theron G, Chakhtoura N, Montepeidra G, et al. Adjusted analysis of the effect of isoniazid preventive therapy on adverse pregnancy outcomes in women with HIV (Abstract 727). Presented at: Conference on Retroviruses and Opportunistic Infections; 2020 March 8–11; Boston, MA. <https://www.croiconference.org>.
41. Ibid.
42. Gupta A. Risk factors for hepatotoxicity in HIV-infected women receiving isoniazid preventive therapy in pregnancy and postpartum (Abstract OAB05). Presented at: AIDS2020; 2020 July 6–10; San Francisco, CA. <https://cattendee.abstractsonline.com/meeting/9289/presentation/74>.
43. Ibid.
44. World Health Organization. WHO consolidated guidelines on tuberculosis.
45. Gupta A. Inclusion of key populations in trials of antituberculosis treatments.
46. PHASES Working Group. Ending the evidence gap for pregnant women around HIV & coinfections: a call to action. Chapel Hill, NC: July 2020. <http://www.hivpregnancyethics.org/>.
47. Swindells S, Siccardi M, Barrett S, et al. Long-acting formulations for the treatment of latent tuberculosis infection: opportunities and challenges. *Int J Tuberc Lung Dis*. 2018;22(2):125–32.
48. Ibid.
49. Unitaid. Repurposing key medicines as long-acting formulations could revolutionize prevention and treatment [Internet]. N.D. <https://unitaid.org/project/long-acting-medicines-for-malaria-tuberculosis-and-hepatitis-c/#en>.
50. Unitaid. Unitaid invests in long-acting medicines to simplify treatment and prevention for HIV, TB, malaria and HCV [Internet]. 2020 January 30. <https://unitaid.org/news-blog/unitaid-invests-in-long-acting-medicines-to-simplify-treatment-and-prevention-for-hiv-tb-malaria-and-hcv/#en>.
51. Ibid.
52. Jefferys R. The antiretroviral therapy pipeline 2020. New York: Treatment Action Group; 2020. <https://www.treatmentactiongroup.org/resources/pipeline-report/2020-pipeline-report/>.
53. Ibid.
54. Jefferys R. PrEP and microbicides pipeline 2020. New York: Treatment Action Group; 2020. <https://www.treatmentactiongroup.org/resources/pipeline-report/2020-pipeline-report/>
55. Currier J. Monthly injectable antiretroviral therapy—version 1.0 of a new treatment approach. *N Engl J Med*. 2020;382(12):1164–5. doi: 10.1056/NEJMe2002199.
56. Kaushik A, Ammerman N, Tyagi S, et al. Activity of a long-acting injectable bedaquiline formulation in a paucibacillary mouse model of latent tuberculosis infection. *Antimicrob Agents Chemother*. 2019;63(4):e00007-19. doi: 10.1128/AAC.00007-19.
57. Ibid.
58. Churchyard, Gavin (Aurum Institute, Johannesburg, South Africa). Interview with: Mike Frick (Treatment Action Group, New York, NY). 2020 May 6.
59. Svensson E, Murray S, Karlsson M, Dooley K. Rifampin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. *J Antimicrob Chemother*. 2015;70(4):1106–14. doi: 10.1093/jac/dku504.