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Treatment Action Group

TB PREVENTION PIPELINE REPORT 2018

Dispatches from the TB Prevention Pipeline

The past year brought plenty of good news for TB prevention science. Among the highlights: intriguing results from a phase IIa trial of TB vaccine candidate H4:IC31 and BCG revaccination, plus positive results from a phase III clinical trial comparing a preventive regimen of one month of daily isoniazid and rifapentine (1HP) to nine months of daily isoniazid (9H). Thanks to these scientific advancements and others discussed here, TB prevention is finally breaking through decades of stubborn inattention and coming into the foreground of global and national efforts to eliminate TB. This year's *Pipeline Report* offers two dispatches from the TB prevention pipeline. The first provides a detailed review of the phase IIa study of H4:IC31 and BCG revaccination, the TB vaccine field's first prevention-of-infection trial. The second discusses important developments in the availability, accessibility, acceptability, and quality of rifapentine-based TB preventive therapy, including findings from the clinical trial of 1HP versus 9H (skip to p. 10). Each dispatch contains tables giving a comprehensive overview of candidate vaccines or preventive regimens in the pipeline as well as recently completed, ongoing, or planned clinical trials.

Results from a Phase IIa Trial of H4:IC31 and BCG Revaccination: a Signal of More to Come

> *"A new TB vaccine is an inevitability; the question is how long it will take us to get there."*[1]

Start paying attention: tuberculosis (TB) vaccine research and development (R&D) is entering its most productive and promising period, maybe ever. Until now, one could make excuses for not watching closely: the field has launched few large efficacy trials since its revitalization at the turn of the century, today's clinical pipeline looks little changed from five years ago, and TB scientists devoted the bulk of recent years to going 'back to basics' to rethink prevailing scientific models, following important lines of inquiry that sometimes devolved into internecine debates tangential to the bigger picture.[2] The full story, it turns out, always contained more latent possibility than readily acknowledged.

The more optimistic narrative coming into focus is composed of several converging storylines that warrant attention. First, the release of intriguing results from the field's first prevention-of-infection trial, which are reviewed in detail here. Second, the imminent completion or initiation of eight clinical trials with efficacy endpoints,[3] a body of work that promises to generate a wealth of data in humans—still a relatively scarce resource compared with *in vitro* and animal model investigations. Third, a stronger, more confident political voice, on show at the 5th Global Forum on TB Vaccines in New Delhi, India, where the Indian government described plans for a massive efficacy trial of two vaccine candidates: VPM1002 and **MIP**.[4] With an anticipated enrollment of 19,000 participants, this will be the largest efficacy trial of a TB vaccine since the Chingleput **BCG** study, which opened in south India in 1968.[5]

MIP stands for *Mycobacterium indicus pranii*, a whole-cell vaccine first studied in India for use against leprosy.

Bacillus Calmette-Guérin (BCG) is the only licensed TB vaccine and was first introduced in 1921. It offers little protection to adolescents and adults against pulmonary TB.

The government of India's investment in such an ambitious trial is a symbol of its emboldened commitment to supporting TB R&D in what it calls a "mission mode."[6] The recently constituted India TB Research Consortium—coordinated by the Indian Council of Medical Research and crossing government agencies, academia, and the private sector—will oversee the VPM1002 and MIP trial as well as TB diagnostic and drug development projects.[7] To take full advantage of the present scientific opportunities, the TB vaccine field will need more funders to follow the government of India's example. A recent review of the field, quoted in the epigraph above, expressed the field's more self-assured outlook in calling a new TB vaccine an "inevitability," but one whose timeline is conditional on how much the world invests.[8] The authors rightly described the overriding risk aversion that has steered TB vaccine R&D efforts as both consequence and cause of limited funding, arguing:

> *"We have undervalued the knowledge gained from our 'failed' trials and fostered a culture of risk aversion that has limited new funding for clinical TB vaccine development. The unintended consequence of this abundance of caution is lack of diversity of new TB vaccine candidates and stagnation of the clinical pipeline."*

For this stagnation to give way, funders will need to become a little braver. TB vaccine R&D is a long road, but epidemiological modeling suggests it is the only one that will lead to TB elimination within the timeframe United Nations member states set in the 2030 Agenda for Sustainable Development and the World Health Organization (WHO) End TB Strategy.[9] Many trials along the way may not succeed, or may not be judged unambiguous successes, but these same trials will be necessary to make progress toward the new vaccines the world needs to end TB.

H4:IC31 and BCG Revaccination Phase IIa Results

Background

In February 2018 at the 5th Global Forum on TB Vaccines, Mark Hatherill of the South African TB Vaccine Initiative (SATVI) presented results from a phase IIa trial of vaccine candidate H4:IC31 and BCG revaccination.[10] H4:IC31 is a subunit vaccine first developed by the Statens Serum Institute of Denmark that combines a fusion of two **MTB** antigens (Ag85b and TB10.4) with IC31, an adjuvant licensed from the French company Valneva. The trial assessed the safety, immunogenicity, and efficacy of H4:IC31 and revaccination with BCG in preventing MTB infection.

MTB stands for *Mycobacterium tuberculosis*, the causative agent of TB disease.

Sponsored by Aeras and Sanofi Pasteur, the trial was conducted at the Desmond Tutu HIV Foundation in Cape Town and at SATVI in Worcester, South Africa, an area known for its incredibly high TB incidence (1,400 per 100,000 persons compared with South Africa's national incidence rate of 781 per 100,000 and the global average of 140 per 100,000).[11,12] The trial enrolled 990 adolescents aged 12–17; all were vaccinated with BCG at birth, HIV negative, and uninfected with MTB at study entry, as indicated by a negative **IGRA** test. The trial excluded two groups known to have a higher-than-average risk of TB: anyone previously treated for TB or MTB infection and individuals living in the same household as someone with TB (i.e., household contacts).[13]

IGRA = interferon-gamma release assay. These blood-based tests detect cell-mediated immune responses to MTB antigens (but do not measure MTB infection directly).

Study design

The trial randomized participants into three arms: one-third received placebo (saline), one-third received H4:IC31 (two intramuscular doses given 56 days apart), and one-third were revaccinated with a single dose of BCG. The first 90 participants enrolled (30 from each arm) comprised the safety and immunogenicity cohort and underwent more intensive collection of safety data and provided samples for additional immunogenicity assays.[14]

The primary efficacy endpoint was IGRA conversion (the trial used Qiagen's QuantiFERON-TB Gold test [QFT]) from negative to positive after three months post-randomization. A secondary efficacy endpoint looked at sustained QFT conversion. Investigators defined this as a positive QFT on three consecutive tests over six months. An exploratory efficacy endpoint assessed sustained QFT conversion through the end of the study (24 months).[15]

Several elements of the study design merit elaboration:

- First, the prevention-of-infection (POI) design. As documented in previous *Pipeline Reports*, the TB vaccine field has pivoted to conducting POI and prevention-of-recurrence (POR) studies in phase II, as these studies are more efficient than traditional prevention-of-disease (POD) trials. This comparative efficiency stems from the higher rates of MTB infection and recurrence of active TB following treatment compared with the rates of TB disease, allowing POI and POR studies to enroll more quickly and follow participants for less time. Without validated **biomarkers** that can act as **surrogate endpoints**, POD trials must obtain microbiological confirmation of disease and follow enough participants for long enough to observe the number of TB disease events required to have sufficient statistical power to investigate differences between study arms. POI and POR trials are intended to help developers select which vaccine candidates to advance to late-stage POD trials by yielding glimpses of vaccine efficacy at earlier points on the clinical development pathway.[16]

- Second, the use of preset go/no-go criteria for deciding whether to continue to develop either H4:IC31 or BCG revaccination based on the trial's results. The trial was designed to compare H4:IC31 to placebo and BCG revaccination to placebo with 80% power. The somewhat low statistical power was selected in light of the desire to use the nimble POI design to detect a signal of efficacy to explore in future studies, and the investigators acknowledged that with lower power comes a higher likelihood of picking up **false positive** results.[17] The go/no-go criteria set before the trial established parameters for deciding what to do next with regard to H4:IC31 and BCG revaccination, taking into account scientific, public health, and commercial considerations.

- Third, the inclusion of an arm to test whether revaccination with BCG in adolescence can prevent MTB infection in this high-transmission setting. A 2018 WHO position paper on BCG noted: "trials, cohort, and case-control studies have shown little or no evidence of an effect of BCG revaccination in adolescents and adults . . . either in protection against MTB infection or on TB disease."[18] However, no randomized controlled trials have examined BCG revaccination in high-risk individuals such as adolescents living in South Africa's Western Cape Province. The question is worth

Biomarkers are measurable biological processes, clinical phenotypes, or gene activities that signify particular infection/disease states or the body's response to vaccination/treatment.

Surrogate endpoints are biomarkers whose measurement stands in for clinical endpoints in clinical trials.

Clinical endpoints directly measure the outcomes that matter most to people—e.g., whether they live longer, feel better, or can function without pain.

False positives are results that indicate a given condition is present when it is not (also called type I error).

answering with the assurance of high-quality evidence. The finding that BCG revaccination does confer protection against either MTB infection or TB disease for particular populations under certain conditions would identify a new public health application for a tool already in hand. BCG is safe, inexpensive, licensed, and the most widely administered vaccine in the world. It could therefore be rolled out without many of the barriers that slow the introduction of new health technologies (at least in principle).

- Fourth, the inclusion of carefully considered secondary endpoints. In designing the field's first POI trial, investigators had to wade into the murky waters of selecting the most appropriate endpoint for MTB infection. The issue is clouded by the lack of a true test for infection. IGRAs such as QFT measure the body's immune response to MTB antigens but do not detect infection itself. QFT converts to positive when infection occurs, but the meaning of QFT reversion (positive to negative) is less well understood. Also unclear: in the event that either H4:IC31 or BCG revaccination has a protective effect, would it work by blocking infection, thereby preventing QFT conversion outright? Or would it clear infection by helping the immune system control bacterial replication? In this case, QFT might convert to positive upon infection before reverting to negative when infection is resolved.[19] The only way out of the fog is to go through, and the inclusion of secondary and exploratory endpoints assessing sustained QFT conversion allowed the trial to look for signals of efficacy against two measures of infection (albeit within the limits of QFT, an important but imperfect tool).

Study outcomes

Both H4:IC31 and BCG revaccination appeared safe and immunogenic. In terms of the primary efficacy endpoint, neither vaccine prevented QFT conversion. The trial reported 134 QFT conversions (14.4% of participants): 49 in the placebo group, 44 among those receiving H4:IC31, and 41 in participants revaccinated with BCG.[20] This translated to an estimated vaccine efficacy of 9.4%, 80% confidence interval (CI) [−18.3, 30.6] for H4:IC31 and 20.1%, 80% CI [−4.8, 39.1] for BCG; neither achieved statistical significance.

Looking at the secondary efficacy endpoint, BCG revaccination and H4:IC31 both reduced the rate of sustained conversion. That is, among participants who initially QFT converted, those receiving BCG and H4:IC31 were significantly more likely to revert to negative at later time points. BCG had an estimated vaccine efficacy of 45.4%, 80% CI [22.3, 61.6] and H4:IC31 of 30.5%, 80% CI [3.0, 50.2].[21] Both BCG revaccination and H4:IC31 achieved statistical significance at the 80% confidence level, and the BCG results were significant at the more stringent 95% level. In total, there were 82 sustained QFT conversions (8.8% of all participants and 62% of those with an initial QFT conversation). Most sustained conversions (36/82) were in the placebo group. The overall rate of QFT reversion was nearly 37% and driven by reversions among participants in the H4:IC31 and BCG revaccination arms.[22]

Implications

What comes next for H4:IC31 and BCG? The low efficacy of H4:IC31 means that it is unlikely to be developed further. Still, the trend toward protection observed for H4:IC31 is, to quote the press release announcing the results, "the first time a subunit vaccine has shown any indication of ability to protect against TB infection or disease in humans."[23] H4:IC31 may soon have company: GlaxoSmithKline's M72/AS01E subunit vaccine candidate has completed a phase IIb POD trial in HIV-negative adults, for which results are expected to be released in 2018.[24] In addition, the Statens Serum Institute is preparing for a phase IIb POR study of its subunit vaccine H56:IC31 (see **Table 1**).[25]

More exciting is the statistically significant effect of BCG revaccination on reducing the rate of sustained QFT conversion. Acknowledging that this was a secondary endpoint in a trial designed with relatively low statistical power, the positive signal nevertheless provides motivation for confirming this finding in future studies. Several choices lie ahead:

- Investigators could conduct a larger, confirmatory POI trial in the same population and consider adding a site or two in a different setting (e.g., one with a lower force of MTB infection) to see whether the efficacy signal remains.
- If the signal is confirmed, investigators could transition the POI study into a POD trial through the use of an adaptive clinical trial design. Such a study might enroll only QFT-negative people until the POI signal is confirmed and then open enrollment to QFT-positive individuals in the POD stage. Participants could be stratified by QFT status in the final analysis.
- Another option would entail moving straight into a phase III POD study. This approach would cost more but would afford the opportunity to identify correlates of protection from TB disease and, if successful, validate the usefulness of employing POI studies to inform POD trials.
- Alternatively, since BCG is already licensed, investigators could conduct a phase IV pragmatic trial to evaluate the effectiveness of BCG revaccination on TB disease incidence. This type of study would likely be integrated into program settings, have less active participant follow-up, and might not require screening individuals for MTB infection at baseline.

These options were discussed at a panel convened at the 5th Global Forum. One of the panelists, Carl Dieffenbach, director of the Division of AIDS at the U.S. National Institutes of Health, emphasized the precious scientific opportunity at hand to take this positive biological signal and fully interrogate its meaning through rigorous basic science. He drew a parallel to the **RV144** trial of a poxvirus vector prime/protein boost HIV vaccine regimen that demonstrated a small but statistically significant reduction in HIV infection risk. Efficacy in that trial was also low—31.2%—but that positive protective signal sparked a collaborative, international effort to analyze stored samples for correlates of risk.[26] Those efforts subsequently informed the design of HVTN 702, a phase III HIV vaccine trial that launched in 2016 and will enroll 5,400 South African men and women.[27] The TB vaccine field is preparing to conduct similar immune correlates discovery work using stored samples from the H4:IC31 and BCG revaccination trial.[28]

The **RV144** HIV vaccine trial was conducted in Thailand and published results in 2009.

In addition to the immediate development choices at hand, the results of this trial raise several long-term considerations that advocates for TB vaccine R&D should watch closely:

- **Whether future TB vaccine trials should offer participants TB preventive therapy as part of an evolving standard of care.** In 2018, the WHO issued consolidated guidelines for the programmatic management of latent TB infection.[29] The updated guidelines expand the recommendation for TB preventive therapy beyond the traditional focus on people with HIV and children under age 5 to all household contacts of persons with pulmonary TB. Depending on the populations studied, future TB vaccine trials may face the ethical requirement of offering participants preventive therapy alongside vaccination—analogous to the much-discussed role of pre-exposure prophylaxis in HIV vaccine trials.[30] Decisions on this point will have major ramifications for everything from trial design to community engagement to the cost of TB vaccine studies, and they must be made with the full and equal participation of TB-affected communities.

- **The fragility of the global market for BCG,** which makes its easy availability something that vaccine developers cannot take for granted as they weigh the public health potential of BCG revaccination. Between 2005 and 2015, countries in all regions and income groups reported BCG supply disruptions that endangered infant health.[31] These recurrent shortages stemmed from the small number of quality-assured suppliers (including some that withdrew from the market), limited investment in production process improvements, and vaccine wastage.[32] There is now sufficient BCG supply to meet forecasted demand, but the WHO has warned that serious structural risks to BCG availability and accessibility remain unresolved.[33]

- **The need to recognize a greater plurality of TB vaccine R&D stakeholders.** Developers involved in TB R&D tend to think of national TB programs as the constituency most likely to drive the implementation of new tools. For vaccines, however, TB programs may not play the lead role. The pipeline contains candidate vaccines being studied in all age groups—from infants to adolescents to adults. The TB program is not in the room with a mother and her child in the moments following birth, nor have most TB programs built strong systems for reaching adolescents or adults who may be at risk of TB but asymptomatic and therefore not seeking care. Developers should start to build relationships with maternal and child health departments, community-based organizations, and other branches of public health systems outside of TB programs. Importantly, R&D efforts should include the meaningful engagement of intended beneficiaries—that is, the individuals and communities at risk of TB who urgently need new prevention options that are safe, effective, quality assured, affordable, and available equitably and without discrimination.

- **The narrow window of opportunity to increase funding for TB vaccine R&D.** Funding for TB research has languished under decades of complacency, and TB vaccine R&D has been particularly starved of adequate financing.[34] Several nascent political processes have raised the prospect of securing much-needed new resources. Under Germany's leadership, the G20 countries recently launched the AMR R&D Collaboration Hub to tackle antimicrobial resistance (AMR), and the BRICS countries have taken steps to form a **BRICS** TB Research Network.[35,36] The 2018 United Nations High-Level Meeting on TB offers an unprecedented opportunity to raise the profile of TB R&D before political leaders globally. TB vaccine researchers and their advocates must ensure TB vaccine R&D is supported by these new initiatives and reflected in any commitments made by United Nations member states at the High-Level Meeting.

BRICS = Brazil, Russia, India, China, and South Africa. Together, these upper middle-income countries account for nearly half of the world's notified TB cases.

Table 1. TB Vaccines in Clinical Development

Agent	Type	Sponsor(s)	Status*
Notable recently completed, ongoing, or planned clinical trials.			
M. vaccae	Whole-cell *M. vaccae*	Anhui Zhifei Longcom	Phase III
Completing a phase III POD trial in 10,000 MTB-infected, HIV-negative adults (aged ≥15 years) in China (NCT01979900); results expected 2018.			
MIP	Whole-cell *M. indicus pranii*	Indian Council of Medical Research (ICMR), Cadila Pharmaceuticals	Phase III
Preparing to begin a phase III POD trial among 19,000 household contacts of people with TB in India (no clinical trials register entry; information from ICMR).[1]			
VPM1002	Live rBCG	Serum Institute of India, Vakzine Projekt Management, Max Planck Institute for Infection Biology, TuBerculosis Vaccine Initiative (TBVI), European and Developing Countries Clinical Trials Partnership (EDCTP), ICMR, Global Health Investment Fund	Phase II/III
1. Preparing to begin a phase III POD trial among 19,000 household contacts of people with TB in India (see above entry for MIP). 2. Initiating a phase II/III POR study in 2000 HIV-negative adults successfully treated for DS-TB in India (NCT03152903). 3. Recently completed a phase II study in 416 BCG-naïve, HIV-exposed and HIV-unexposed newborn infants in South Africa (NCT02391415) and planning a phase III POD trial in the same population (N = 7,500) in South Africa, Uganda, Kenya, Tanzania, and Gabon.[2]			
M72/AS01E	Protein/adjuvant subunit vaccine	GlaxoSmithKline, Aeras	Phase IIb
Currently completing a phase IIb POD study in 3506 HIV-negative, MTB-infected adults in Kenya, South Africa, and Zambia (NCT01755598); results expected 2018.			
DAR-901	Inactivated whole-cell M. obuense	Dartmouth University, Global Health Innovative Technology Fund	Phase IIb
Currently completing a phase IIb POI study in 650 BCG-vaccinated, HIV-negative, MTB-uninfected 13- to 15-year-old adolescents in Tanzania (NCT02712424); results expected 2019.			
H56:IC31	Protein/adjuvant subunit vaccine	Statens Serum Institut (SSI), Aeras, Valneva—IC31 adjuvant	Phase IIb
1. Preparing to begin a phase IIb POR study in 900 HIV-negative adults successfully treated for DS-TB in South Africa and Tanzania (NCT03512249). 2. Undergoing a phase I study as a therapeutic vaccine given with and without etoricoxib, a COX-2 inhibitor, to adult patients with TB in Norway (NCT02503839).			
H4:IC31	Protein/adjuvant subunit vaccine	Aeras, Sanofi Pasteur, SSI, Valneva—IC:31 adjuvant	Phase IIa
1. Completed a phase IIa POI study in 990 HIV-negative adolescents in South Africa (NCT02075203). 2. Completed a phase I/II safety/immunogenicity study in 243 BCG-vaccinated infants assessing concomitant administration with EPI vaccines (NCT01861730).			

BCG revaccination	Whole-cell M. bovis	Aeras	Phase IIa
Recently completed a phase IIa POI study in 990 HIV-negative adolescents in South Africa (see entry above for H4:IC31).			
MTBVAC	Live genetically attenuated MTB	University of Zaragoza, Biofabri, TBVI, Aeras	Phase IIa
1. Completed a phase I safety/immunogenicity study in adults (NCT02013245) and a phase Ib/IIa dose escalation, safety and immunogenicity study comparing MTBVAC to BCG in infants (N=36) with a safety arm in adults (N=18) (NCT02729571); results expected 2018/2019. 2. Preparing to begin a phase IIa dose-defining safety/immunogenicity study in 99 South African infants (NCT03536117). 3. Preparing to begin a phase Ib/IIa study in 120 adults with and without MTB infection in South Africa (NCT02933281).			
ID93/GLA-SE	Protein/adjuvant subunit vaccine	Infectious Disease Research Institute, Wellcome Trust, Quratis	Phase IIa
1. Completed a phase IIa safety/immunogenicity study in 60 HIV-negative adults successfully treated for DS-TB (NCT02465216). Now planning for a phase IIb POR trial in 840 adult patients with TB. 2. Preparing for phase I/II studies as a therapeutic vaccine given to adult patients with DS- or MDR-TB (no clinical trials register entry; information from IDRI).[3] 3. Preparing for a phase IIa POI trial in 180 BCG-vaccinated, MTB-uninfected healthcare workers in South Korea (no clinical trials register entry; information from IDRI).[3]			
RUTI	Fragmented MTB	Archivel Farma	Phase IIa
Undergoing a phase IIa therapeutic vaccination study in 27 adult patients with MDR-TB (NCT02711735).			
TB/FLU-04L	Viral vector	Research Institute for Biological Safety Problems, Kazakhstan	Phase IIa
Completed a phase I safety/immunogenicity study in BCG-vaccinated healthy volunteers (NCT03017378; results presented at 5th Global Forum on TB Vaccines) and planning for a phase IIa study in MTB-infected adults.			
Ad5Ag85A (aerosol)	Viral vector	McMaster University, CanSino	Phase I
Undergoing a phase I safety/immunogenicity study in BCG-vaccinated healthy volunteers (NCT02337270).			
MVA85A (aerosol)	Viral vector	Oxford University, TBVI	Phase I
Undergoing a phase I safety/immunogenicity study comparing MVA85A aerosol vs. intramuscular vaccination in MTB-infected adult volunteers (NCT02532036).			
ChAdOx1.85A + MVA85A	Viral vector	Oxford University	Phase I
Completed a phase I safety/immunogenicity study of ChAdOx1 85A with and without MVA85A boost in BCG-vaccinated adult volunteers (NCT01829490).			
GamTBvac	Protein/adjuvant subunit vaccine	Ministry of Health of the Russian Federation	Phase I
Completed a phase I safety/immunogenicity study in BCG-vaccinated adult volunteers (NCT03255278).			
AEC/BCO2	Protein/adjuvant subunit vaccine	Anhui Zhifei Longcom	Phase I
Undergoing a phase I safety/immunogenicity study in adult volunteers (NCT03026972).			
rCMV	Viral vector	VirBio	preclinical
Published results from preclinical evaluations in rhesus macaques.			

NCT: ClinicalTrials.gov entry of the ongoing or recently completed clinical trials; N: estimated/actual enrollment
*Status indicates the most advanced phase of either ongoing or recently completed trials.

ChAd: chimpanzee adenovirus vector; BCG: bacillus Calmette-Guérin; COX-2: cyclooxygenase-2; DS-TB: drug-susceptible TB; EPI: Expanded Programme on Immunization; *M. bovis: Mycobacterium bovis*; MDR-TB: multidrug-resistant tuberculosis; MIP: *Mycobacterium indicus pranii*; *M. obuense: Mycobacterium obuense*; MTB: *Mycobacterium tuberculosis*; *M. vaccae: Mycobacterium vaccae*; MVA: modified vaccinia virus Ankara; POD: prevention of disease; POI: prevention of infection; POR: prevention of recurrence; rBCG: recombinant bacillus Calmette-Guérin; rCMV: recombinant cytomegalovirus

Information compiled from ClinicalTrials.gov, checked against pipeline summaries published by Aeras and TBVI, and augmented by additional information provided by sponsors. Candidates without activity in the last two years (i.e., no published results, ongoing studies, or publicly available plans for future work) are not included.

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Rifapentine-based TB preventive therapy—technically available, but where is it?

> *"A celebrated analysis in 2008 estimated that AIDS denialism under President Thabo Mbeki in South Africa resulted in 330,000 preventable deaths from delays in making ART available. Using the TEMPRANO results, a simple back-of-the-envelope estimate of AIDS mortality since WHO recommended programmatic use of IPT in 2008 suggests that at least several million deaths could have been averted if IPT had been rolled out worldwide."—Richard Chaisson and Jonathan Golub*[37]

Tuberculosis (TB) preventive therapy has historically been a tough sell—both for national TB programs and for the people who could benefit from taking it. This is despite the low cost of isoniazid; the mountain of scientific evidence that isoniazid preventive therapy (IPT) reduces the risk of TB disease and death in people with HIV, children, and other high-risk groups; and the clear public health motivation for averting unnecessary suffering from TB. In an editorial introducing long-term follow-up results from the Temprano study (**Box 1**), which tested early versus delayed initiation of antiretroviral therapy (ART) given with or without IPT, Richard Chaisson and Jonathan Golub drew a provocative comparison between the mortality linked to the AIDS denialism of former South African president Thabo Mbeki, who questioned whether HIV is the cause of AIDS, and the TB deaths that could have been prevented if IPT had been implemented at scale worldwide.[38] The comparison, though startling, appears understated when one focuses on the different scales at hand: several hundred thousand deaths resulting from Mbeki's refusal to establish a robust national ART program versus several million that could have been prevented by wider use of IPT.[39]

Only 1.3 million of the more than 30 million people living with HIV worldwide started TB preventive therapy in 2016.

Chaisson's and Golub's back-of-the-envelope calculation suggests that denial can take many forms. It can manifest through the intransigence and callousness of a willful political figure backed by state power. Or it can build from the ground-up accumulation of many diffuse choices not to act on evidence. The paltry implementation of TB preventive therapy is an example of this type of diffuse failure. But the ground is shifting: shorter, safer rifamycin-based regimens now offer attractive alternatives to IPT, which must be taken for six, nine, or even 36 months and comes with the risk of liver toxicity. Phase III clinical trials have established the safety and efficacy of **3HP** (12 once-weekly doses of isoniazid and rifapentine); 1HP (one month of daily isoniazid and rifapentine); and **4R** (four months of daily rifampicin).

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

These choices have kindled an unprecedented interest in TB preventive therapy, with most attention focused on regimens that include rifapentine. There is a risk, however, that these newer regimens will go the way of IPT and fall short of their promise. Implementation is only part of the challenge; research must continue to ensure these regimens are safe, effective, and acceptable for the groups most in need of improved prevention options, including infants and young children, pregnant women, people with HIV on various ART regimens, and people who inject drugs.

The results of a phase III trial comparing 4R to 9H, led by McGill University, will be published in 2018.

The twin goals of expanding the provision of TB preventive therapy and accelerating the research and development (R&D) of better ones are human rights imperatives. Under

international law, governments are obligated to respect, protect, and fulfill the right to health and the right to enjoy the benefits of scientific progress and its applications (i.e., the **right to science**). Upholding the right to health includes ensuring the **availability, accessibility, acceptability, and quality** of health goods and services.[40] The right to science obligates governments to support research and connect people—particularly marginalized groups—to its benefits, including the tangible products of scientific advancement (e.g., new medicines).[41]

The right to health is established in Article 12 of the International Covenant on Economic, Social, and Cultural Rights (ICESCR) and the right to science in Article 15.

Availability, accessibility, acceptability, and quality are collectively known as the **3AQ**.

New TB prevention options such as 3HP and 1HP represent a significant but partial step toward addressing the longstanding marginalization of people at risk of TB within global health discourse and national TB programs. This dispatch from the TB prevention pipeline uses the rights-based 3AQ framework to discuss important developments in the availability, accessibility, acceptability, and quality of rifapentine-based TB preventive therapy.

Box 1: Long-term follow-up results from the Temprano trial

In the **ANRS**-sponsored **Temprano** trial, 2056 people with HIV in Cote d'Ivoire were randomized to receive one of four interventions: deferred ART, deferred ART plus IPT (for six months), early ART, or early ART plus IPT. The study found that early ART and IPT each independently reduced the risk of morbidity over 30 months of follow-up and that the combination of early ART and IPT had the greatest protective effect.[42]

Individuals who completed the main study were invited to participate in a long-term post-trial phase with an average duration of follow-up of 4.9 years. Findings from this post-trial period, published in November 2017, indicate that receiving IPT led to a 37% reduction in mortality, independent of whether someone received ART, and that IPT and ART had an "additive effect, with the maximal benefit in patients who received both therapies."[43] The Temprano investigators described these results as "the first evidence from a randomized trial showing that IPT decreases mortality in HIV-infected adults with high CD4 cell counts and in the ART era."[44] The reduced probability of death associated with IPT six years post-randomization provides powerful confirmation of the importance of IPT, specifically, and TB preventive therapy, generally, in protecting the health of people with HIV.

ANRS is the French National Agency for Research on AIDS and Viral Hepatitis.

Temprano started before the WHO recommended immediate ART for all people newly diagnosed with HIV, hence the early versus deferred ART study arms.

Availability of rifapentine-based TB preventive therapy

The 3AQ framework articulates the obligation of governments to ensure the availability of health facilities, goods, and services.[45] Availability can refer to the quantities of health goods or to whether they exist at all—many important technologies to address TB are simply unavailable (i.e., nonexistent) due to a lack of R&D.[46] Where inadequate or

nonexistent tools hinder an effective public health response, fulfilling the right to health and the right to science requires states to ensure the availability of health technologies by promoting research to develop new or better ones.[47] **Table 2** (see end of section) reviews recently completed and ongoing clinical trials of TB preventive therapy. Nearly all of these studies are supported primarily through public funding, and seven involve the drug rifapentine.

Noninferiority trials test whether the intervention is no worse than the control by a prespecified amount (called a noninferiority margin). This is different than testing whether two interventions are equivalent or whether one is better than (superior to) another.

The year opened with positive news from one of these studies when investigators from the AIDS Clinical Trials Group (ACTG) presented results from the BRIEF-TB (A5279) trial at the February 2018 Conference on Retroviruses and Opportunistic Infections.[48] This phase III **noninferiority trial** randomized 3,000 adults and adolescents with HIV to receive either 1HP or nine months of daily isoniazid (9H). Participants had to either live in an area with a high TB incidence or have MTB infection as indicated by a positive **TST** or **IGRA**. The primary outcome measure was a composite endpoint looking at the incidence rate of active TB disease, death from TB, or death due to unknown cause. Participants were followed for three years from the date the last participant enrolled. Secondary endpoints evaluated safety and treatment completion.

TST = tuberculin skin test
IGRA = interferon-gamma release assays

TST and **IGRA** are tests used to indicate the presence of infection with *Mycobacterium tuberculosis* (MTB), the causative agent of TB disease. However, neither test measures MTB infection directly.

The BRIEF-TB trial found that 1HP was noninferior to (no worse than) 9H in preventing TB, death from TB, or death from unknown cause.[49] In terms of the composite endpoint, there were 33 events among participants receiving 9H compared with 32 among those taking 1HP. There were two deaths from TB, both in the 9H arm. As expected, TB was more common in participants who had a positive TST or IGRA or who had low CD4+ T-cell counts (≤250 cells/mm3) at study entry. Overall, 21% of participants were TST positive at the start of the trial, half were on ART (over 90% by study completion), and very few entered the study with low CD4+ T-cell counts. Among this last group, TB incidence was higher in those taking 1HP than 9H, but this difference was not statistically significant.

Hematologic toxicities are those primarily affecting the blood and its components (e.g., neutropenia, anemia).

Investigators did not observe any significant differences in serious adverse events between regimens, although participants on 9H had more liver toxicity and those on 1HP more **hematologic toxicity**. Participants were significantly more likely to complete 1HP than 9H (97% vs. 91%).[50]

The finding that 1HP is safe, well tolerated, and noninferior to 9H in preventing TB and death from either TB or unknown cause is a landmark achievement for the field. The short duration of 1HP and its lower risk of liver toxicity should attract interest from HIV programs, which were never enthusiastic adopters of IPT, as well as from patients, who often balked at the months of pill-taking IPT required. The once-a-day dosing of 1HP may also appeal to people with HIV who are accustomed to the daily administration of antiretroviral drugs (ARVs). This positive finding raises the need to conduct additional studies to assess whether 1HP is safe and effective in other populations, including HIV-negative people, children, and pregnant women.

The **TBTC** is housed at the U.S. Centers for Disease Control and Prevention (CDC) Division of TB Elimination. More information on the TBTC can be found here.

While most ongoing trials are assessing HP given for different durations and on different dosing schedules, one upcoming study will examine whether rifapentine can prevent TB when taken alone (without isoniazid). The Tuberculosis Trials Consortium (**TBTC**) is preparing to launch a phase III pragmatic trial of the safety, tolerability, and effectiveness

of six weeks of daily rifapentine (6P) in preventing TB (TBTC Study 37/ASTERoiD).[51] In contrast to BRIEF-TB, this trial will take place among primarily HIV-negative individuals living in settings with low TB incidence (the United States and the United Kingdom). The trial will enroll 3,400 participants aged 12 and above who have a positive TST or IGRA or are otherwise deemed at high risk (e.g., household contacts of someone with TB or recently arrived immigrants to the United States or United Kingdom from high-TB-burden countries).[52] If successful, this study would offer a short-course prevention option that does not include isoniazid, and therefore one that might spare patients from isoniazid-related hepatotoxicity.

The phase III clinical trial that established the safety and efficacy of 3HP (TBTC Study 26/PREVENT-TB) took place in countries with low or moderate TB incidence. The WHIP3TB trial, funded by the U.S. Agency for International Development, is studying the safety and effectiveness of 3HP in high-burden settings.[53] The trial is enrolling 4,000 participants with HIV two years of age and older. Participants are randomized to receive a single round of IPT (6H), a single round of 3HP, or 3HP given once a year for two years (referred to as periodic 3HP, or p3HP). Individuals receiving 6H will be followed for one year and those in the 3HP and p3HP arms for two years. The trial has two parts. Part A is an observational, randomized comparison of 3HP to 6H (combining data from the 3HP and p3HP arms for the first year of follow-up). The primary objective in this stage is to compare treatment completion between individuals taking 3HP versus IPT for six months; secondary objectives include assessing TB incidence, all-cause mortality, and discontinuation due to adverse events.[54] Part B will compare the effectiveness of a single round of 3HP to that of p3HP in preventing TB disease at two years of follow-up. The pulsing strategy seeks to determine the durability of protection offered by 3HP in settings of high TB incidence.

Accessibility of rifapentine-based TB preventive therapy

The 3AQ framework defines accessibility in terms of four dimensions. Foremost, health facilities, goods, and services must be accessible to all without discrimination "in law and in fact."[55] Accessibility also includes physical accessibility, affordability, and the ability to seek and impart health-related information. Each of these dimensions has become a flashpoint for TB programs and patients seeking access to rifapentine, which is manufactured by a single quality-assured supplier (Sanofi).

Conversations about rifapentine so often focus on its inaccessibility that it could be easily mistaken for a kind of global health contraband. Approved for the treatment of MTB infection in just four countries (the United States, Taiwan, Hong Kong, SAR, and the Philippines), with registration pending in several others, rifapentine remains inaccessible to most who need it. That is changing, thanks in large part to a long-awaited agreement between the Global Drug Facility (GDF) and Sanofi to list rifapentine on the GDF product catalog.[56] While the price of $15/24-tablet blister pack ($45 for the rifapentine component of a full 3HP course) is 40% lower than the price charged in the United States ($24 per pack), it is significantly higher than the average cost of 6H ($4–6).

Crucially, the rifapentine price provided to GDF is volume dependent. Implicit in this agreement is a challenge to the global health community: if total procurement volumes over the next year (the period ending March 2019) fall short of expectations, Sanofi may settle on a higher price in future years. If volumes reach certain thresholds, however, the price may come down significantly.[57] Is this a threat or an incentive? It feels like both—and that should come as no surprise. In 2013, TAG's Erica Lessem wrote about Sanofi's "double-edged sword."[58] On one side, Lessem acknowledged that Sanofi has contributed to the development of rifapentine by supporting investigator-initiated studies and clinical trials conducted by the TBTC and ACTG. On the other side, **Sanofi** initially priced rifapentine beyond the reach of TB programs in the United States, sparking a successful campaign by civil society to lower the price of the drug for the U.S. public health market.[59] The global situation is now recapitulating the double-edged dynamic seen in the United States in that Sanofi's agreement for global distribution holds both risk and reward. Sanofi has priced rifapentine at a level most public health programs cannot long afford, but within this same arrangement lies the potential to reach a more sustainable price point if purchase volumes rise.

In 2014, **Sanofi** lowered the price of rifapentine in the United States from its original $75 per 32-tablet blister pack to $32 per 32-tablet blister pack, a historic 57% reduction.

National TB programs must act without delay to scale up rifapentine-based TB preventive therapy. And they have few excuses for inaction. On paper, almost everything required for access appears to be in place: rifapentine has been approved by a stringent regulatory authority, pre-qualified by the World Health Organization (WHO), listed on the WHO model lists of essential medicines for adults and children, endorsed for TB prevention as part of the 3HP regimen in WHO guidelines, and included in the GDF catalog. Post-marketing evaluations and phase IV studies conducted by the U.S. CDC and the governments of Australia and Taiwan also indicate that 3HP is safe to use in programmatic settings, has higher completion rates than IPT, and is cost-effective.[60,61,62]

So, issuing a challenge to the global health community to embrace 3HP is warranted. But this challenge should be accompanied by setting some expectations—and delivering a reminder—for Sanofi. First, the expectations: Sanofi must negotiate in good faith by lowering the price of rifapentine as volumes rise and by committing to registering the drug with regulatory authorities in both high- and low-TB-burden countries. The company must become more forthcoming with information and engage honestly with multilateral institutions, country governments, civil society, and TB-affected communities.

Second, the reminder: Sanofi inherited rifapentine when it acquired the pharmaceutical company Aventis in 2004. Aventis, in turn, obtained rifapentine in 1999 through the acquisition of Hoechst Marion Roussell, the corporate child of a merger between Hoechst AG and Marion-Merrell-Dow, which itself came into possession of rifapentine when its forbears Merrell-Dow and Dow Chemical purchased a major stake in Lepetit Labs.[63] It was there, in northern Italy in the 1950s, where the rifamycin compounds were first synthesized.[64] Rifapentine has a complex parentage. It has had many private owners and mostly **public benefactors**, and it has taken four decades to get from the initial patent filings on rifapentine by Lepetit Labs in 1976 to where we are now, with rifapentine poised to make a major contribution to the TB elimination agenda.[65] Sanofi can fulfill the promise of its inheritance by working with the TB community to ensure that rifapentine is accessible to all who need it.

Major public funders of rifapentine development efforts include the U.S. CDC, National Institutes of Health, USAID, Unitaid, and the European and Developing Countries Clinical Trials Partnership.

Acceptability of rifapentine-based TB preventive therapy

The acceptability plank of the 3AQ framework requires governments to ensure that health facilities, goods, and services respond to the biological, social, and cultural needs of those concerned.[66] Acceptability is of paramount importance for preventive medicine. People who take TB prophylaxis may be at risk, but they are not, by definition, sick. At most, individuals eligible for TB preventive therapy might be considered pre-symptomatically ill, although the absence of diagnostics that can reliably predict which people with MTB infection will develop active TB disease makes even this label difficult to apply at present.[67] Consequently, regimens to prevent TB must be safe, simple to take, and easy to complete. Some of the most pressing acceptability issues concern the compatibility of TB drugs with ART and the high pill burden associated with TB regimens.

One of the most urgent acceptability questions is whether rifapentine can safely be given with dolutegravir, which is purported to be the most widely prescribed integrase inhibitor in the world and a key component of WHO-recommended first-line regimens for HIV.[68,69] A small study looking at drug-drug interactions between 3HP and dolutegravir in HIV-negative, MTB-uninfected adult volunteers stopped early when two out of four enrolled participants developed serious adverse reactions (flu-like hypersensitivity syndrome) following the third 3HP dose.[70] The cause remains unclear; rifapentine has been associated with flu-like hypersensitivity reactions in previous studies, and some evidence suggests these events are more common when rifapentine is dosed intermittently (as in the 3HP regimen).[71] In the small healthy volunteer study, investigators observed a temporal relationship between hypersensitivity symptoms and plasma concentrations of certain **cytokines**, particularly interferon-gamma. Intriguingly, the two participants who developed flu-like syndrome had isoniazid concentrations that were "markedly higher" than expected but normal concentrations of rifapentine.[72] This points to the need to better understand the role of isoniazid in flu-like events, which have previously been thought to be solely rifapentine associated.

Cytokines are small proteins that act as cell-signaling molecules. They play an important role in immunity by calling and directing the behavior of various immune cells.

To further investigate the safety of coadministering 3HP and dolutegravir, the Unitaid-funded IMPAACT4TB consortium, led by the Aurum Institute and Johns Hopkins University, is conducting the DOLPHIN trial. This single-arm safety and pharmacokinetic (PK) study is evaluating the safety of 3HP given with dolutegravir-based ART in adults with HIV.[73] The trial will enroll 60 participants; an interim analysis will assess safety in the first 12 and determine whether the dose of dolutegravir needs to be adjusted when administered with 3HP. Unitaid has made the absence of a 3HP/dolutegravir safety signal a condition of its continued support for IMPAACT4TB—a short-sighted stance since people with HIV constitute just one piece of a much larger market for 3HP now that WHO guidelines recommend preventive therapy for all household contacts regardless of HIV status or age.[74] The DOPHIN study is ongoing and is expected to provide final results by January 2019.[75]

TAF stands for tenofovir alafenamide, an oral prodrug form of tenofovir disoproxil fumarate (TDF).

The DOLPHIN trial will answer just one of many questions about the compatibility of rifapentine-based TB preventive therapy with HIV treatment. **Box 2** outlines other acceptability issues that will need to be resolved to improve TB prevention among people with HIV in the era of newer ARVs such as dolutegravir and **TAF**.

Box 2: Using rifapentine-based TB preventive therapy with newer ARVs—many needs, few of them fulfilled

Acceptability is all about making sure that interventions work for the people who need them. Here are some key knowledge gaps regarding the acceptability of rifapentine-based TB preventive therapy for people with HIV taking ART.[76]

3HP:

- **Is 3HP safe to use with dolutegravir in people with HIV and MTB infection? If yes, does the dose of dolutegravir need to be adjusted?**
  - The DOLPHIN study is investigating these questions.
- **Can 3HP and TAF be given together safely and without TAF dose adjustment?**
- **Can 3HP be used safely in pregnant women with HIV?**
  - The International Maternal, Pediatric, Adolescent AIDS Clinical Trials Network is conducting a study (P2001) to answer this question. Additionally, a retrospective analysis of women who became pregnant during the TBTC Prevent-TB and iAdhere trials did not find an unexpected number of adverse pregnancy outcomes (e.g., fetal loss, congenital anomalies) compared with rates seen in the general U.S. population.[77]
- **Can 3HP be used safely in children with HIV?**
  - TBTC Study 35 will evaluate the safety of 3HP in children with and without HIV using a child-friendly, water-dispersible fixed-dose combination of rifapentine and isoniazid developed by Sanofi.

1HP:

- Is 1HP safe to use with dolutegravir in people with HIV and MTB infection? If yes, does the dose of dolutegravir need to be adjusted?
- Can 1HP and TAF be given together safely and without TAF dose adjustment?
- Can 1HP be used safely in pregnant women with HIV? (There is also a need to study 1HP in HIV-negative pregnant women.)
- Can 1HP be used safely in children with HIV? (There is also a need to study 1HP in HIV-negative children.)

The high pill burden associated with 1HP and 3HP is another major acceptability concern. **Table 3** shows the pill burden of each regimen based on currently available and possible formulations of rifapentine and isoniazid. Patients taking 3HP must take nine pills at a time, and those on 1HP must take five. In the United States, where rifapentine has been

indicated for treating MTB infection since 2014, TB programs have cited pill burden as the second biggest barrier to programmatic implementation of 3HP, following concerns about cost.[78] Different formulations of rifapentine (e.g., a 300 mg standalone tablet) would alleviate pill burden somewhat, but the development of a fixed-dose combination (FDC) of rifapentine and isoniazid would offer an even bigger improvement. Sanofi has developed a child-friendly, water-dispersible 3HP FDC (slated for use in a safety/pharmacokinetic study among infants and children aged 0–12 in South Africa sponsored by the TBTC and IMPAACT4TB). Sanofi has also spoken of plans to develop a 3HP FDC for adults, although the project is in a nascent stage.[79]

Table 3. Per-Dose Pill Burden of Rifapentine-Based Preventive Regimens by Possible Rifapentine Formulations

Regimen	H 300 mg + P 150 mg standalone tablets	H 300 mg + P 300 mg standalone tablets	HP FDC (H 300 mg/ P 300 mg)	HP FDC (H 300 mg/ P 600 mg)*	HP FDC (H 300 mg/ P 300 mg) + P 300 mg standalone tablet
3HP (900 mg H/900 mg P weekly for three months)	9	6	3	NA	3
1HP (300 mg H/600 mg P daily for one month)	5	3	NA	1	2
6P (600 mg P daily for six weeks)	4	2	NA	NA	2

H: isoniazid; P: rifapentine; FDC: fixed-dose combination; mg: milligrams; NA: not applicable

The column in red shows pill burden based on currently available formulations of P and H.

Note: the above pill counts do not include vitamin B6, which should be given with isoniazid to prevent peripheral neuropathy.

* Manufacturers have expressed reservations about whether a single FDC tablet could accommodate 600 mg of rifapentine.

Quality of rifapentine-based TB preventive therapy

The quality element of the 3AQ framework requires that "health facilities, goods, and services be scientifically and medically appropriate and of good quality."[80] Essentially, health products must be evidence based, approved by relevant regulatory authorities, manufactured to standard, unexpired, and made of the base materials and active pharmaceutical ingredients they are advertised to contain.

Quality closely intersects with other elements of the 3AQ framework. For example, the current reliance on a single quality-assured supplier (Sanofi) is a major factor contributing to rifapentine accessibility challenges. In essence, the market for quality-assured rifapentine is a monopoly. Rifapentine is off patent, so this monopoly is not the result of strict intellectual property protections or market exclusivities. Instead, it reflects the limited commercial interest in TB prevention—something that is now changing. The entry of additional rifapentine suppliers could lower the price of 3HP by creating competition

with Sanofi. Generic manufacturers could also help to solve acceptability challenges related to pill burden by developing 3HP FDCs or standalone formulations of rifapentine at higher doses.

It is imperative that any new rifapentine suppliers obtain quality assurance by registering their products with stringent regulatory authorities or the WHO prequalification program. The global health community has made major strides in creating stable markets for quality-assured medicines through, for example, purchase requirements set by the U.S. President's Emergency Plan for AIDS Relief and the Global Fund and the technical assistance, demand generation, and centralized procurement and forecasting services offered by groups like GDF. It is thanks to this work that a global market for quality-assured rifapentine is even a possibility. The systems that promote quality medicines must be maintained. This is a shared, global responsibility and not merely a matter of national sovereignty; national and international actors each have roles to play. At the national level, governments must create policy and regulatory environments that promote access to quality medicines. On the international level, multilateral institutions such as the **Global Fund**, Unitaid, WHO, and other organizations must ensure that the billions of dollars collectively invested in strengthening incentives, systems, and safeguards to promote quality health commodities yield the assurance of quality medicines for generations to come.

As drawn, the Global Fund's sustainability, transition, and co-financing policy could have major negative ramifications for sustainable access to quality-assured medicines, and activists should watch this closely.

Table 2. Recently Completed, Ongoing, and Planned Clinical Trials of Tuberculosis Preventive Therapy

Study Name Sponsor Phase Sample Size (N =)	Status	Regimen	Population	Study Location(s)
TB APPRISE/P1078 IMPAACT Phase IV N = 956	Results presented at CROI in February 2018	Immediate (antepartum) vs. deferred (postpartum) isoniazid given daily for six months (6H)	Pregnant or postpartum women with HIV in high-TB-incidence settings	Botswana, Haiti, India, South Africa, Tanzania, Thailand, Uganda, Zimbabwe
4R vs. 9H Trial McGill University, Canadian Institutes of Health Research Phase III N = 6,031	Results expected 2018	Four months of daily rifampicin (4R) versus daily isoniazid for nine months (9H)	Adults with positive TST or IGRA, including adults with HIV on rifampicin-compatible ARVs	Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, South Korea
4R vs. 9H Pediatric Trial McGill University, Canadian Institutes of Health Research Phase III N = 844	Results expected 2018	Four months of daily rifampicin (4R) versus daily isoniazid for nine months (9H)	Children aged 0–18 years with or without HIV and with documented positive TST or IGRA	Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia
Clinical Trials of Rifapentine-Based Tuberculosis Preventive Therapy				
BRIEF-TB/A5279 ACTG Phase III N = 3,000	Results presented at CROI in February 2018	One month of daily isoniazid and rifapentine (1HP) versus 9H	People with HIV aged 13 and older living in high-TB-incidence settings or with positive TST or IGRA	Botswana, Brazil, Haiti, Kenya, Malawi, Peru, South Africa, Thailand, United States, Zimbabwe
WHIP3TB Aurum Institute, KNCV, USAID Phase III N = 4,027	Active, not enrolling	Part A: 12 weeks of once-weekly isoniazid and rifapentine (3HP) versus 6H Part B: 3HP given once versus 3HP given once a year for two years (p3HP)	People with HIV aged 2 and older living in high-TB-incidence settings	Ethiopia, Mozambique, South Africa

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P2001 IMPAACT Phase I/II N = 82	Enrolling	Safety and pharmacokinetics of 3HP in pregnant and postpartum women with and without HIV	Pregnant and postpartum women with and without HIV and with MTB infection	Haiti, Kenya, Malawi, Thailand, United States, Zimbabwe
DOLPHIN IMPAACT4TB/Aurum Institute, Unitaid Phase I/II N = 60	Enrolling	Safety and pharmacokinetics of 3HP given with dolutegravir-based ART	Adults with HIV aged 18 or over on stable dolutegravir-based ART	South Africa
TBTC Study 35[1] TBTC, Unitaid (IMPAACT4TB/Aurum Institute), Sanofi Phase I/II N = 60	Enrollment beginning late 2018	Safety and pharmacokinetics of 3HP given as a fixed-dose combination	Infants and children aged 0–12 with and without HIV	South Africa
ASTERoiD/TBTC Study 37 TBTC, TBESC, UK MRC Phase III N = 3,400	Enrollment beginning late 2018	6 weeks of daily rifapentine (6P) vs rifamycin-based standard-of-care regimens (3HP, 4R, or 3HR)	People >12 years of age with MTB infection and at high risk of disease progression	United Kingdom, United States
CORTIS Phase II/III University of Cape Town N = 3,200	Enrolling	3HP versus no intervention and active surveillance for TB	HIV-negative adults with MTB infection deemed at high risk for TB disease progression as identified by a gene-based correlate of risk (COR)	South Africa

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

TB CHAMP South African MRC, Wellcome Trust, U.K. MRC, DFID Phase III N = 1,556 children from 778 households	Active, not enrolling	6 months of daily levofloxacin vs. placebo	HIV-positive or HIV-negative infants and children aged 0–5 years who are household contacts of individuals with MDR-TB	South Africa

V-QUIN Australian NHMRC, government of Vietnam Phase III N = 2,006 participants	Enrolling	6 months of daily levofloxacin vs. placebo	Household contacts of people with MDR-TB; in the first phase, contacts must be adults aged 15 and above	Vietnam
PHOENIx/A5300B/I2003[2] ACTG, IMPAACT Phase III N = 3,452 household contacts from 1,726 households	Enrollment beginning late 2018	6 months (26 weeks) of daily delamanid vs. 6H in preventing TB among individuals exposed to MDR-TB	High-risk adult, adolescent, and child household contacts of individuals with MDR-TB	25 international ACTG and IMPAACT sites

ACTG: AIDS Clinical Trials Group, U.S. National Institutes of Health; ARV: antiretroviral CROI: Conference on Retroviruses and Opportunistic Infections; DFID: U.K. Department for International Development; IGRA: interferon gamma release assay; IMPAACT: International Maternal Pediatric Adolescent; AIDS Clinical Trials Group, U.S. National Institutes of Health; MDR-TB: multidrug-resistant tuberculosis; MTB: Mycobacterium tuberculosis; NHMRC: National Health and Medical Research Council (Australia); TB: tuberculosis; TBESC: Tuberculosis Epidemiologic Studies Consortium, U.S. Centers for Disease Control and Prevention; TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention; TST: tuberculosis skin test; UK MRC: Medical Research Council, United Kingdom; USAID: U.S. Agency for International Development

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TAG
Treatment Action Group

www.treatmentactiongroup.org

90 Broad Street, Suite 2503
New York, NY 10004
Tel 212.253.7922, Fax 212.253.7923

tag@treatmentactiongroup.org

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501(c)(3) organization.
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