We have carried tuberculosis (TB) for far too long, a disease that has been around for generations and still kills more than 4,000 people per day.

IMPAACT4TB is a four-year project introducing a new way to tackle latent TB infection—the seed bed of TB—in order to slow and ultimately stop the flood of new TB cases occurring every year. We’re doing this by identifying and providing new, shorter treatment options for people with latent TB infection.

3HP is a short-course TB preventive therapy regimen that combines two TB drugs—isoniazid and rifapentine—weekly for three months. The World Health Organization (WHO) recently released consolidated guidelines for the treatment of latent TB infection that recommends the use of 3HP for people living with HIV and contacts of TB cases of any age.

The project will initially prioritize short-course TB preventive therapy for people living with HIV and children under five in 12 high-burden countries that represent 50 percent of the global TB burden. Subsequently, all those in close contact with TB patients will be targeted.

Our consortium members include the Aurum Institute, KNCV Tuberculosis Foundation, Clinton Health Access Initiative (CHAI), John Hopkins University and the Treatment Action Group (TAG). The project will run from September 1, 2017 to August 31, 2021.

The IMPAACT4TB project is being implemented in three distinct phases. During phase 1 [September 2017-April 2018], the project established management structures, started engaging with suppliers and embarked on a safety and pharmacokinetics study of interaction between 3HP and dolutegravir (more below). During phase 2 [May 2018-December 2018], consortium members will carry out market intelligence and cost of good analysis, as well as begin 3HP price negotiations. Finally, phase 3 [January 2019-August 2021] will involve procurement of 3HP and implementation, as well as ongoing research and learning.

For more information about the project, please refer to our brochure.
Key Project Updates – Phase 1

1. Safety and pharmacokinetics study
Dolutegravir-based regimens are now recommended by WHO as the first-line antiretroviral regimens for people living with HIV, and several countries with high HIV prevalence have adopted the new regimens. A small drug-drug interaction study of dolutegravir and rifapentine + isoniazid (3HP) among healthy volunteers reported hypersensitivity reactions in two of four participants [CROI 2017, poster 409A].

This safety concern led to our execution of a study to assess the safety and evaluate the pharmacokinetics of administering 3HP to people living with HIV on a dolutegravir-based regimen. During the first phase, we enrolled the first group of 12 participants and reviewed preliminary safety data. The safety data has been assessed and the review of the pharmacokinetic and viral load data from the first 12 participants is still in process for this group. This will determine the optimal dose of dolutegravir with 3HP for the remainder of participants to be enrolled. The final study results will be available in February 2019. Final approval for the project to move forward with enrollment and delivery of 3HP for people living with HIV and children under the age of five is contingent on these results.

2. Engagement with suppliers
Consortium partners are working with the 12 participating countries to complete a survey of the market size for TB prevention therapy, including 3HP, and determine market strategies for penetration in each country. This will ultimately guide discussions with Sanofi, currently the only manufacturer of rifapentine, and with potential future generic manufacturers—making the case that there is a market and demand for 3HP and seeking to lower the drug price.

CHAI has initiated work to inform supplier decisions on product development (including dosing, formulation, packaging, target pricing and demand forecasting), which will ultimately determine the availability and affordability of 3HP among the vulnerable population of children and other household contacts.

In parallel, the Global Drug Facility concluded 2018 RPT price negotiations outside of the project, finalized at 36 EUR (45 USD) per patient course.
3. Evidence generation

The correct dose of rifapentine to use in children less than two years of age is unknown. As the IMPAACT4TB consortium is targeting child contacts under the age of five, it is essential that we determine the correct dose of rifapentine for children as soon as possible.

The IMPAACT4TB is supporting a Phase I/II dosing and safety study of rifapentine in HIV-infected and HIV-uninfected children with latent TB infection (TBTC35: Tuberculosis Trials Consortium [TBTC] Study 35 [S35]). The study is being supported by the U.S. Centers for Disease Control and Prevention (CDC)—with one site at Desmond Tutu TB Centre at Stellenbosch University. To help accelerate the completion of the trial, IMPAACT4TB will be supporting an additional site at Perinatal HIV Research Unit (PHRU), in Soweto, South Africa. The study will also evaluate the pharmacokinetics, safety and tolerability of the water-dispersible rifapentine tablet and the isoniazid-rifapentine fixed dose combination tablet for children.

4. Global advocacy and communications

In March 2018, Aurum and its consortium members welcomed the release of updated guidelines for programmatic management of latent TB infection by the World Health Organization (WHO). The updated guidelines now recommend 3HP as a suitable regimen for use in countries with high TB incidence and recommend preventive TB treatment for all household contacts of people with TB.

In February 2018, TAG published its popular ‘Know your rights guide’, which contains a standalone chapter on rights related to TB prevention, and features 3HP.

This year’s TB Prevention Pipeline report chapter focuses on the availability, accessibility, acceptability and quality of rifapentine for TB prevention and includes tables giving a comprehensive overview of TB preventive therapy trials. This report will be available at the International Aids Conference and on TAG’s website.

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Related News

Risk of birth defects in infants born to women taking dolutegravir (DTG) at the time of conception

An independent NIH-funded study found that women taking DTG when they became pregnant appeared to be more likely to have babies with an abnormality called a neural tube defect than women who were taking other ARVs when they became pregnant. In light of this finding, Aurum is informing patients enrolled in the IMPAACT4TB safety and pharmacokinetics study of this risk. Women can start taking DTG once they complete a pregnancy test to ensure the participant is not pregnant, and participants will be encouraged to continue to use contraception to protect against pregnancy. For future study groups, we will ensure that contraception is being used per protocol and that participants avoid becoming pregnant while taking DTG. The WHO’s statement on the study findings and its implication can be found here.

CDC releases updated recommendations for use of 3HP

On June 28, 2018, the U.S. Centers for Disease Control and Prevention released updated recommendations for use of 3HP for treatment of latent TB infection. The updated recommendations, published in CDC’s Morbidity and Mortality Weekly Report (MMWR), support expanded use of an effective, shorter treatment regimen to reach even more people with latent TB infection.

1HP study outcomes announced at CROI in March 2018

A multicenter, randomized, open-label, phase 3 trial among HIV-infected individuals found that a four-week, once-daily regimen of rifapentine and isoniazid (1HP) was non-inferior to nine months of daily isoniazid, had fewer adverse events and was more likely to be completed in HIV-infected adults and adolescents. These results may potentially influence how rifapentine enters countries’ TB regimens and may influence the generic market. The 1HP regimen may provide a highly-effective, ultra-short course regimen for the prevention of TB in people with HIV and could contribute to improvements in global control of TB. Read more here.