Protecting Household On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx MDR TB: A5300B/I2003B)

PHOENIx Site RFA dated May 17, 2022

The AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) Networks invite applications from Clinical Research Sites (CRSs) with experience of multidrug-resistant tuberculosis (MDR-TB), pharmacokinetic (PK) studies and household (HH) tracing to participate in the PHOENIx trial (see below for complete eligibility criteria).

Please apply at https://www.surveymonkey.com/r/PHOENIx_RFA.

Deadline for Applications: May 31, 2022

Background:
The World Health Organization (WHO) estimates that there were 158,000 incident cases of MDR-TB globally in 2020 [1]. MDR-TB has been shown to be almost twice as common in TB patients living with HIV compared with TB patients without HIV infection [2]. Very high mortality rates reported among HIV-infected patients with MDR or extensively drug-resistant tuberculosis (XDR-TB) are also a major concern [3]. Of the MDR-TB cases reported globally in 2019, 80% received appropriate treatment, a reversal in progress from prior years due to the COVID pandemic. For those who started treatment in 2018, only 59% had documented successful treatment outcomes [1]. Even with under-reporting because of COVID, with the rollout of rapid molecular diagnostic tools, including Xpert MTB/RIF (Cepheid), the number of adult MDR-TB cases diagnosed is growing, with an associated increase in the numbers of child and adult household contacts (HHCs) identified. For every case of MDR-TB, the majority of HHCs are likely to become infected [4, 5, 6]. HHCs of MDR-TB patients who become infected have a high risk of progressing to active disease, and in the absence of effective therapy, possibly death). While precise data are not available, HIV-infected HHCs are likely to be at much higher risk of TB disease progression, based on their known susceptibility to TB infection, reinfection, and reactivation [7].

Among HHCs in high-burden settings, the vast majority of MDR-TB in children arises from transmission within the HH, whereas TB among adolescents and adults is equally likely to be from infections acquired within the HH or in the community. No randomized controlled trials have been conducted to guide the management of adults or children exposed to MDR-TB. As a result, there are inconsistent international guidelines for the management of MDR-TB contacts. The US Centers for Disease Control and Prevention (CDC) 2000 guidelines recommend pyrazinamide and ethambutol or pyrazinamide plus a fluoroquinolone for persons at high risk of developing TB [8]. As it is not clear how these infected individuals should be managed, the WHO 2015 guidelines [10] recommend not treating MDR-TB-exposed contacts for presumed latent TB infection (LTBI) with MDR-TB, to follow contacts for up to 2 years, and to only treat those who progress to disease [9]. Some high-burden countries have local guidelines for treating young and HIV-infected child contacts of MDR-TB cases, including using INH (up to 20 mg/kg/day) in combination with a fluoroquinolone and ethambutol [11]. However, none of these guidelines are based on high-quality evidence.

Despite newly updated WHO treatment guidelines in 2016 allowing for certain MDR-TB cases to be treated for 9-12 months, this shortened regimen still includes 4-6 months of highly toxic injectable drugs (e.g., amikacin), and this regimen does not apply to all MDR-TB cases (http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/). Many people who develop MDR-TB disease still require treatment for up to 24 months with existing second-line TB therapies that are often poorly tolerated, highly toxic, poorly efficacious, frequently require hospital admission for administration, and carry a high risk of mortality, particularly in persons who are HIV-infected or malnourished. Under these uncertain and unacceptable circumstances, it is essential to re-examine the current strategy for MDR-TB

prevention in high-risk contacts [12]. There have never been randomized controlled trials in this population for MDR-TB prevention. A WHO expert committee recently identified treatment of MDR-TB contacts as an important policy gap that urgently requires randomized controlled trials to inform policy [10].

The PHOENIx trial is enrolling adult and child HH members who are HHCs of adult MDR-TB index cases and HHs are randomized to either delamanid (DLM) or isoniazid (INH) for 24 weeks. The study design involves a unique approach for the National Institute of Allergy and Infectious Diseases (NIAID) funded HIV/AIDS therapeutic network trials in that enrolment and follow-up may be conducted at participants' homes, mobile clinics, the CRS, or other settings.

Criteria for Participating in the PHOENIx Trial:

Required Criteria

- Prior National Institute of Health (NIH)/US Food and Drug Administration (FDA) interventional trial with study drug experience
- A functional grants and financial management system that will enable the ACTG Leadership and Operations Center to contract with the sites for their services
- Access to an institutional review board or ethics committee with a federal-wide assurance number (FWA)
- Have an existing community advisory board (CAB) or ability to develop one
- Study pharmacy in place
- No significant geographic overlap with other sites participating in the PHOENIx trial
- Local epidemiology supports potential to enroll 50 index MDR-TB cases/yr with ability to enroll at least 100 HHCs per year
- Ability to describe the epidemiology of MDR-TB in proposed trial sites, including sites of care, case load by age group (0-5, 6-17, >17 years), MDR-TB diagnostic algorithms, drug-susceptibility testing patterns, and treatment approaches for prevention and treatment
- Access to an established laboratory approved to support the PHOENIX study and/or an accredited laboratory with capacity to support safety testing and diagnosis of pulmonary and extrapulmonary TB in adults and children
- Access to molecular TB methods including Xpert Ultra and line probe assays (LPA) as per the study protocol
- Access to automated MGIT culture, first and second line drug susceptibility testing (DST)
- Willingness to participate in periodic DAIDS Good Clinical Laboratory Practice (GCLP) audits
- Laboratory participation in an External Quality Assurance (EQA) program for protocol required tests and willingness to participate in existing DAIDS EQA programs as needed (The ACTG Lab Center will work with selected sites to choose an appropriate lab if necessary)
- Ability to receive and ship samples to and from international partners
- Local specimen storage capacity and TB isolate biobanking capabilities (access to Laboratory Data Management System (LDMS) barcoded labelling will be provided if site is selected)
- Trained clinical research staff and outreach team
- Delamanid must have in-country regulatory approval
- 6 months or less turnaround time for regulatory approvals
- Prior TB treatment or clinical trial experience
- Availability of a pediatrician with experience in the management of TB and/or MDR-TB in children, including children <5 years of age

Preferred Criteria

- Have a TB infection control plan that at least meets local standards

- Availability of a pediatrician or clinician with experience in the management of TB and/or MDR-TB in children, including children <5 years of age
- Prior MDR-TB treatment or clinical trial experience
- Existing strong linkages with MDR diagnosis and care centers
- HHC/community based interventional trial experience, with ability to perform pre-screening, screening, and follow up investigations in the HH or elsewhere as required
- Have transportation to do HH visits (for transporting site staff to HHs, and participants to the sites)
- Prior experience enrolling children into trials
- Experience with digital chest radiograph/X-ray (CXR) and access to reader

Application Process:
Evidence of ALL these criteria should be included in the application and/or supportive documentation provided with the application to address these items. After review by an independent committee, final scores and subsequent selection decisions will reflect evidence of addressing all these criteria. CRSs that meet the selection criteria, but are not currently funded for ACTG/IMPAACT Network will be considered protocol specific PHOENIx trial sites. Preference will be given to sites demonstrating capacity to enroll large numbers of participants, including HHCs<5 years of age and people living with HIV. Preference will also be given to otherwise capable "qualified reserve" sites not funded for the ACTG/IMPAACT networks.

Interested sites should complete the application form at https://www.surveymonkey.com/r/PHOENIx_RFA.

After site selection, all sites will be required to provide an acceptable protocol-specific Site Implementation Plan (SIP), detailing how the protocol will be implemented, and sites must successfully meet all protocol activation requirements prior to protocol activation. If after selection it is determined that a particular site cannot meet the activation or other requirements, the site may be replaced.

References:

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3. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006;368:1575-80.
4. Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Infect Dis 2008;8:359-68.
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