Treatment Action Group

National Institute of Allergy and Infectious Diseases (NIAID)
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Response to NOT-AI-18-043: Request for Information (RFI): Inviting Comments and Suggestions on a Framework for the NIAID Tuberculosis Strategic Plan

We welcome the development of a Tuberculosis Strategic Plan by NIAID, and the opportunity to provide input. Overall, we find the areas sketched out by the Plan comprehensive and appropriately ambitious, and look forward to the inclusion of the following additional recommendations.

1. **Significant research gaps and/or barriers not identified in the framework above**

Treatment Action Group (TAG) advocates for the inclusion of vulnerable populations in TB research. Pregnant women are at high risk of TB, and their families are at high risk of poor outcomes from it. Yet pregnant women are routinely excluded from clinical trials. Without proper data and guidance resulting from research, these women are either denied access to treatment or prevention, or treated in the absence of data. Both situations pose a risk of a poor outcome for the mother and her pregnancy. As women are of child-bearing potential for the majority of their life course, a drug is truly safe only if it can be administered to women, including those who are already and/or have the potential to become pregnant.

We urge NIAID to include pregnant women and women of child-bearing potential in all research capacities within the Tuberculosis Strategic Plan. NIAID should work with NIH to establish a mandate for research networks, institutions, and independent investigators that receive funding from the NIH to institute a standing protocol to allow for the enrollment of pregnant women in the studies they conduct, or provide a justification for the exclusion of these women as part of their funding proposal (i.e., the default should be to safely include pregnant and post-partum women, making inclusion of pregnant and postpartum women opt-out, as opposed to opt-in).

We welcome the efforts NIAID has taken to appropriately include children and adolescents in research, and to ensure people with HIV (PLHIV) are included in TB clinical trials. We appreciate the inclusive nature of NIAID's stated intent in the Strategic Plan to "improve/develop accurate and rapid diagnostics for all forms of TB, in all age groups," and recommend this be furthered by explicitly including all age groups, as well as PLHIV and pregnant women, in the preceding point, "discover novel biomarkers or biosignatures for TB diagnosis and prediction of treatment outcomes," as well as inclusion of children and people with HIV in the section on vaccines, as presentation and progression of disease, and immune response, may differ in these populations.

Finally, while we commend NIAID's efforts to include PLHIV in TB clinical trials, NIAID must also use this plan to increase efforts to include people with TB in HIV clinical trials. Critical safety and dosing information on drug-drug interactions come far too late, as evidenced by the widespread roll out of dolutegravir in advance of understanding of how it could be delivered with rifamycin-based TB therapy. As HIV trials are usually larger and better resourced, NIAID's leadership in getting them to include people with TB to answer these important questions could avoid the current common situation of scrambling to catch up to ensure that innovations for preventing and treating HIV can work on the sizable number of people with both HIV and TB. NIAID should continue to support pharmacokinetic work to define drug-drug interactions between TB drugs and antiretroviral agents. It is also important to establish the safety of co-administering TB medicines with hormone-based contraception and opioid substitution therapies.

2. **Resources required or lacking that may be critical to advancing the areas of research opportunity**

NIAID is the world's leading funder of TB research and development (R&D), playing a historically crucial leadership role in spurring life-saving innovations, as well as leveraging additional investments from other donors. Yet resources for TB research — which hover at about one-third of the global projected need— still fall short of sums needed to close the deadly gaps in TB prevention, diagnosis, and treatment.

Even NIAID, and the U.S. government more broadly, are in a position to do more. TAG's fair-share methodology projects that if each country dedicates less than 0.1% of its gross annual expenditure on all forms of R&D to TB, we can effectively close the vast global TB research funding gap. According to this methodology, total U.S. government contributions to TB R&D annually should be $444,500,000. However, U.S. government investments in TB research in 2016 have totaled $316,471,566 – leaving tremendous potential for the government to build on its leadership and contribute additional resources to advance research. We recommend that NIAID, as the leading U.S. agency funding TB research, be empowered to substantially increase its annual investments in TB R&D, both to close this gap and to meet all the priorities detailed in the Tuberculosis Strategic Plan. Expanded contributions through NIAID also ensures fulfillment of our nation's ambitious vision in the National Action Plan to Combat Multidrug-Resistant TB by funding the research strategy necessary to give public health the new tools needed to eliminate this deadly disease.

In addition to fiscal resources, NIAID can leverage other resources vital to efficient, collaborative research by continuing to forge strategic partnerships with other research networks and agencies involved in TB research, such as the U.S. Centers for Disease Control and Prevention's Tuberculosis Trials Consortium, and the U.S. Agency for International Development. NIAID should explore ways of supporting and synergizing on TB research efforts funded by other U.S. government agencies, such as the Biomedical Advanced Research Development Authority, the Department of Defense (including its Congressionally-directed Medical Research Program), and the National Science Foundation.

A sorely lacking resource in TB research is clinical trial capacity. This point is noted in relation to vaccine research, but lack of trial capacity is a problem for TB drug trials as well. This had led to slow enrollment and lengthy trial timelines, with ethical implications as results are delayed and new standards of care emerge, which can complicate ongoing trials. Investments in building site capacity for TB vaccine and drug/drug regimen candidates are critical.

Another vital resource NIAID should include is its knowledge on engagement of affected communities in research design and implementation. NIAID has been a leader in ensuring effective engagement of communities in HIV research and has mobilized its network of community representatives for TB research. More can be done to ensure that representatives are aware of the unique challenges and opportunities in TB research, to work with other research sponsors to support their community engagement work, and build communities of practice across clinical trial sites and networks.

3. **Emerging scientific advances or techniques in basic, diagnostic, therapeutic, or vaccine research that may accelerate NIAID research priorities detailed in the framework above**

Whole genome sequencing (WGS) presents a major scientific advance with great opportunity for applicability for TB, particularly if more cost-effective and less resource-intensive tools for it can be developed. NIAID should include WGS in its priorities for TB diagnosis to ensure the rapid developments in WGS are applicable to TB and readily adoptable in countries where TB has the highest burden.

4. **Other comments**

In keeping with the need to ensure applicability and accessibility of innovations, and human rights principles, we also urge NIAID to make an explicit part of its Tuberculosis Strategic Plan a commitment to ensuring the availability, affordability, accessibility, and acceptability of interventions resulting from research funded by NIAID (and therefore, ultimately, the public). Products of publicly -funded research

should be considered public goods. This includes NIAD leveraging its investments to secure commitments to data sharing, collaboration, appropriate pre-approval access (also called “compassionate use” or “expanded access”), product registrations in trial-site and high TB burden countries, and affordable pricing.

We thank NIAID and its leadership for the remarkable investments and stewardship of them to date which have enabled high quality, high impact research, and look forward to more.

In collaboration,

Treatment Action Group