



Treatment Action Group

May 13, 2024

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Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Re: Request for Information (RFI): Inviting Comments and Suggestions on NIAID's Strategic Plan

Dear Dr. Marrazzo,

On behalf of Treatment Action Group, we thank you for the opportunity to submit the below response to the Request for Information (RFI): Inviting Comments and Suggestions on NIAID's Strategic Plan. TAG is an independent, activist and community-based research and policy think tank fighting for better treatment, prevention, a vaccine, and a cure for HIV, tuberculosis (TB), and hepatitis C virus (HCV).

Priority 1: Advance foundational research on the immune system, host-pathogen interactions, and pathogen biology.

Increase knowledge into mechanisms of infection, transmission, pathogenicity, virulence, host-pathogen interactions, and development of drug resistance.

- NIAID should direct increased investment toward identifying and evaluating the accuracy of host-response TB biomarkers to support the development of new TB drugs and regimens as well as treatment monitoring diagnostics for clinical use. Such biomarkers should be evaluated across a range of populations and geographies to support more robust data sets to determine potential for broad applicability, including for children and PLHIV with lower bacillary loads. Focus should be on an end-of-treatment biomarker as a test of cure, to reduce the risk of relapse and retreatment.
- NIAID should also direct increased investment toward the more rapid development of companion diagnostics for drug-susceptibility (DST) for new TB drugs. This includes the rapid identification of critical concentrations for culture-based phenotypic DST as well as the rapid identification of genetic mutations associated with resistance for molecular genotypic DST, so that DST is rolled out alongside new TB drugs. This is necessary to ensure people with TB receive effective regimens and to reduce further development of drug resistance. In addition to direct investments, NIAID should include conditionalities on all NIAID investments in the development of new TB drugs that require the development of companion DST. This is necessary to both reduce the lag time between the roll out of new TB drugs and DST, and to conserve the efficacy of new TB drugs – an obligation under the human right to science.

Support the development of animal models and non-animal alternate methods for basic and translational research within the NIAID mission space.

- NIAID should increase its investments in hepatitis C virus vaccine research and development both domestically and through partnerships with research institutions



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abroad, taking into account all possible alternate methods for basic and translational research, particularly the growing mRNA technology platform.

- In addition, NIAID should work with FDA to expedite the approval of the Xpert® HCV VL Fingerstick test developed by Cepheid, and already approved for use in Europe, that can diagnose HCV within one hour. This will enable the decentralization of HCV care, implementation of point-of-care HCV RNA testing in less than an hour during a single visit, thereby making it possible for people who are viremic to be initiated on treatment on the same day.

Priority 2: Apply foundational knowledge of the complex interactions between microbes and the immune system to develop and test medical countermeasures against known infectious diseases (non-HIV/AIDS).

Discover unique characteristics to advance specific and sensitive diagnostic technologies for infectious diseases.

- Diagnosing TB in children and people living with HIV remains an ongoing challenge given limitations of available tests in detecting paucibacillary TB using accessible non-sputum samples. The result is that more than 70% of young children with TB are never diagnosed and TB remains the leading infectious disease killer of people living with HIV. NIAID should increase investments in the development of specific and sensitive diagnostics for paucibacillary TB appropriate for routine clinical use. This includes research to advance host response biomarker research among these specific populations and increase the limit of detection for molecular and antigen-based tests. NIAID should invest in addressing these gaps in TB diagnostics R&D to ensure that the science and test development is advanced for these populations and keeps pace with programmatic efforts to reach more children and people living with HIV with accurate, lifesaving diagnosis.

Design and assess new or improved therapeutic and prophylactic vaccines, including identifying promising new vaccine targets and vaccine adjuvants, for infectious diseases.

- NIAID should direct funding to accelerate the development of new TB vaccines by building on and bringing previous investments in immunology (e.g., IMPAc-TB), adjuvant development (e.g., AVAR-T), clinical research (e.g., clinical trials planned by the ACTG, HVTN, and IMPAACT networks), and correlates of protection (e.g. the M72 and BCG Correlates Studies) into a purposive, mission-driven program in TB vaccinology that spans lab, clinic, and community. As part of a NIAID "TB Vaccine Mission," NIAID should provide funding for socio-behavioral science to understand vaccine acceptability and hesitancy; implementation science to prepare for vaccine introduction; and community engagement to ensure TB vaccine science reflects community needs and aspirations for improved TB prevention tools. Diversifying the pipeline of candidate TB vaccines in terms of vaccine platforms, antigenic targets, routes of administration, and other vaccine characteristics stands out as an urgent priority. NIAID has an irreplaceable role in funding clinical work to study existing TB vaccine candidates in priority populations not included in efficacy trials led by outside sponsors. For example, generating data on the safety and immunogenicity of M72/AS01E in children, pre-adolescents, and pregnant and lactating people, or studying MTBVAC in PLHIV, people without TB infection (IGRA-negative individuals), and lactating persons. A NIAID-led "TB Vaccine Mission" could resemble similar initiatives to accelerate development and introduction of new TB drugs (FAST-TB).



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Priority 3: Apply knowledge of HIV/AIDS to reduce HIV incidence through the development of safe and effective prevention, treatment, and cure strategies.

Explore interventions to prevent and treat HIV coinfections and comorbidities.

- As antiretroviral treatment for HIV introduces new agents available in long-acting formulations it will be important for NIAID to support work to establish the safety, pharmacokinetics/pharmacodynamics, and other drug-drug interaction concerns with drugs used in TB preventive treatment and treatment of TB disease. Over the next strategic plan period, the TB treatment pipeline is expected to introduce new, shorter regimens for treating and preventing TB that make use of new compounds with novel mechanisms of action. Work is also underway to develop long-acting formulations of existing TB drugs (e.g., rifapentine, isoniazid, bedaquiline). NIAID is uniquely positioned to ensure that developments in HIV and TB drug development run in parallel and in such a way that people with HIV/TB are not left behind the state of science for lack of timely drug-drug interaction data.
- In addition, we encourage NIAID to expand clinical trial capacity to address TB and other leading HIV coinfections and comorbidities. One concrete opportunity would involve funding and capacitating RePORT International sites to participate in clinical trials of new TB interventions (drugs, diagnostics, vaccines). Past investments in RePORT International have created a solid foundation of TB research infrastructure and experience on which complex clinical trials can be built, including sites with diverse epidemiology, extensive detailing of local epidemiology, and biobanking capacity. TAG notes that expanding RePORT to undertake clinical trials and interventional studies would be consistent with the original vision of the program when it was established in 2012 to "[increase] clinical research capacity in high-burden settings, enabling rigorous multicenter clinical trials for drugs, diagnostics, and vaccines to proceed with greater speed and efficiency" (Hamilton et al, 2015 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4583572/>).
- We also recommend that NIAID fund and capacitate sites at research institutions in high TB burden settings, even where rates of TB and HIV co-infection are relatively low (e.g. in countries in the Asia-Pacific Region), to become clinical trial units that can contribute to studies sponsored by the four federally funded HIV/AIDS clinical trials networks. This additional research capacity is important for more expeditiously completing TB clinical trials, especially those conducted in populations historically under-represented within TB research initiatives such as children and pregnant women. It currently takes the IMPAACT network over six years to enroll phase I/II pediatric pharmacokinetic and safety studies of new TB drugs in children, with sample sizes of just 48-84 children. Timely completion of these smaller phase I/II studies as well as larger phase III trials designed to evaluate the efficacy and safety of novel regimens and/or treatment strategies in these populations will require the engagement and participation of more sites in high TB burden settings.

Foster partnerships to determine how best to implement effective interventions at scale to maximize impact.

- Recent investments in TB drug and regimen development have upended standards of TB care in place for decades -- we now have one month or once weekly TB preventive treatment (TPT) regimens, and can cure drug-sensitive TB in just four months and drug-resistant TB in just six months (1/4/6 regimens). The landmark studies behind these regimens and the corresponding updates to the World Health Organization (WHO) guidelines were supported by NIAID (ACTG A5279 [1HP], ACTG A5259 [3HP], ACTG A5349 [4HPMZ]). Despite the strong evidence base



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from these phase III trials, adoption of and access to these novel regimens has been limited. This is in part due to a lack of complimentary investments made in social and behavioral sciences necessary to inform and support the introduction and adoption of new TB regimens and other innovations. In addition to considering the evidence (i.e., the benefits vs. harms of an intervention) and the quality of the evidence emerging from clinical trials, the WHO GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) Evidence to Decision framework also takes into consideration other criteria, including the acceptability and feasibility of the intervention. Limited data to inform Guideline Development Group discussions about the acceptability and feasibility of an intervention often weakens the overall strength of the WHO's recommendation, affecting the speed and enthusiasm with which country programs translate WHO guidance into national policies and programs. Over the next strategic plan period, NIAID should require and fund socio-behavioral science work as a core component of all clinical trials it supports.

Additional Themes

Diversity, equity, inclusion, and accessibility (DEIA)

- NIAID should integrate Historically Black Colleges and Universities (HBCUs) into potential clinical trial sites and research to foster greater diversity and inclusion, particularly in addressing the HIV epidemic. By partnering with HBCUs, we can engage marginalized communities that are disproportionately affected by HIV, ensuring that clinical trials reflect the demographics most impacted by the disease. This approach not only enhances the ethical conduct of research but also strengthens trust within these communities, ultimately leading to more effective interventions and treatments.

Women's Health

- Despite increased risk of TB and poor outcomes, pregnant women are routinely excluded from TB research initiatives. The IMPAACT network, established to conduct research in this and other populations underrepresented in research, has demonstrated the feasibility and importance of studying new TB regimens in pregnant and postpartum populations. IMPAACT P1078 evaluated isoniazid preventive therapy (IPT) in pregnant and postpartum women 60 years after its initial introduction into TB programs, revealing that prior assumptions about the safety of IPT during pregnancy and the postpartum period were wrong. In fact, IPT increased the risk of adverse pregnancy outcomes, and postpartum women on IPT were more likely to experience liver toxicity. The IMPAACT network supported a PK study of a novel short-course TB preventive treatment regimen (3HP) during pregnancy and the postpartum period (P2001) but left studies powered for safety and to evaluate another novel, short-course TB preventive treatment regimen (1HP) in this population to the Unitaid-funded IMPAACT4TB Project to address. As a result, NIAID isn't currently supporting any TB prevention or treatment studies in pregnant or postpartum women (with the exception of P2026, which is an opportunistic PK study). This absence of investment isn't for lack of work to be done -- there are critical data gaps in pregnant women for the four-month rifapentine- and moxifloxacin-containing regimen for drug-sensitive TB, and the six-month bedaquiline- and pretomanid-containing regimen for drug-resistant TB. These PK and safety data gaps prevent pregnant women from accessing the benefits of scientific advancements in TB treatment. In the meantime, pregnant women around



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the world are relegated to TB prevention and treatment regimens that are longer, more toxic, less tolerable, and less efficacious, likely contributing to excess morbidity and mortality. Over the next strategic plan period, NIAID should invest in clinical trials that address data gaps for new TB drugs and regimens in pregnant women.

Research inclusivity

- The meaningful engagement and participation of individuals and communities most affected by a particular disease or condition is a human right and essential for ensuring non-discrimination in accessing and enjoying scientific benefits. Citing the experience of TB and HIV research, a recent UN report recognized that "Participation in science is also a prerequisite for access to the benefits of scientific progress, ensuring that it is applicable and relevant to specific groups of people" (A/HRC/55/44).
- As such, we think it's important that representatives of affected communities be more meaningfully engaged in NIAID decision making and priority setting moving forward. Building the research literacy and capacity of a new generation of people with lived experiences with HIV and/or TB to engage with NIAID and the federally funded trials networks will help to ensure that research funded by NIAID is needs-driven, has social value, and is translated into policies and programs that benefit affected communities. Facilitating this level of community engagement requires partnership, power sharing, and acknowledgement, including by establishing policies that fairly compensate community representatives making contributions to research networks and initiatives for their time and expertise.

Data science and sharing

- NIAID should continue to support data sharing and Open Science approaches to ensure equitable access to research resources. Open Science programs should be designed to support the goals of other "additional themes" listed in this RFI – including DEIA, research inclusivity, and global health – by ensuring scientists from all backgrounds, including from low- and middle-income countries, can contribute to and access such resources. Good examples of work in this area include the TB Portals Program and TB ReFLECT (TB Reanalysis of Fluoroquinolone Clinical Trials). NIAID should consider developing an Open Science strategy that goes beyond the emphasis on scholarly publication policies in the NIH Public Access Policy to outline actions on Open Science themes such as increasing collaboration between scientists, promoting the community engagement in scientific activities, and building public trust and understanding in science. The 2021 UNESCO Recommendation on Open Science, endorsed by the United States government and 192 other UN member states, includes recommended Open Science activities that NIAID should consider, including establishing funding mechanisms to support open science.
- NIAID should increase investment to support research coordination and global systems for data sharing on TB drug resistance, and should require data sharing on TB drug resistance as a condition of NIAID funding. The lack of rapid identification and data sharing of genetic mutations associated with phenotypic drug resistance results in delayed compilation and availability of these mutations for diagnostics developers. Emblematic of this delay is the recommendation of Cepheid's Xpert MTB/XDR after the regimen it was developed for was already obsolete. Current challenges with increasing bedaquiline resistance alongside insufficient knowledge of resistance mutations for molecular drug-susceptibility testing poses significant



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threat of treatment failure for people on bedaquiline-based DR-TB regimens as well as the continued development of resistance in the absence of effective molecular drug-susceptibility testing. Considering these significant risks and challenges NIAID should prioritize investments that facilitate data sharing on TB drug resistance.

Workforce training

- NIAID should prioritize comprehensive protections for biomedical science doctoral students and early career investigators within its strategic plan. This entails investing in robust HR policies safeguarding their well-being, implementing measures to enhance diversity and inclusion, and establishing protocols to combat harassment and bullying. Additionally, offering adequate time off and salaries that reflect the cost of living is crucial for ensuring a supportive environment conducive to their success and holistic development.

We thank you for the opportunity to submit our response to this RFI, and we look forward to continued engagement on NIAID's Strategic Plan. Please do not hesitate to contact Elizabeth (Lizzy) Lovinger, US and Global Health Policy Director, at Elizabeth.lovinger@treatmentactiongroup.org with any questions.

Sincerely,

A handwritten signature in black ink, appearing to read 'EL', is positioned above the typed name.

Elizabeth Lovinger
US and Global Health Policy Director
Treatment Action Group