Treatment Action Group

**TAG HIV Research Network Statements: HIV Vaccine Trials Network (HVTN)**

**Background and Achievements**

The development of an effective HIV vaccine remains both a critical priority and one of the most significant challenges faced by scientists. Unlike most pathogens, HIV infects CD4 T cells, a central coordinator of the immune response, meaning that vaccination must equip the immune system with the ability to fend off an infection of itself (not an infection of the liver or the lung, as is the case for hepatitis B or SARS-CoV-2, for example). HIV integrates its DNA into the genetic code of infected CD4 T cells, making elimination of the virus extremely difficult once established.

The mutability of HIV — which is vastly greater than for influenza virus — adds yet another layer of difficulty: the virus' outer envelope is a constantly evolving moving target cloaked in decoy sugar molecules called glycans, making it highly resistant to neutralization by antibodies (typically a key contributor to immune protection). The surface of HIV is also sparsely populated with the viral spikes that antibodies must bind to achieve neutralization. The constant mutation of the virus impedes recognition not only by antibodies, but other types of immune responses including those mediated by CD4 and CD8 T cells.

The approval of several antiretrovirals for pre-exposure prophylaxis (PrEP) to prevent HIV acquisition, including the latest twice-yearly option lenacapavir, is a very welcome development but cannot fill the vaccine gap for multiple reasons including costs, drug interactions, side effects, and a prerequisite to recognize the need for PrEP. Approximately half of all new cases of HIV in the United States occur in people who wouldn't be identified as candidates for PrEP, and in some areas of the world this proportion reaches 75%. A major and unique advantage of vaccines is the potential to offer broad population coverage regardless of self-assessment of HIV exposure risk.

The HVTN has led efforts to translate the best available evidence from laboratory and pre-clinical animal research into clinical testing of experimental HIV vaccine candidates in people, conducting more than 200 studies to date involving 28,000 volunteers globally (nearly 10,000 Americans).

Additionally, the network is making critical contributions to the development of a broadly effective vaccine against tuberculosis, which remains a global scourge and the leading cause of death among people with HIV. The HVTN will remain instrumental in efforts to

study the safety and immunogenicity of TB vaccines in PLHIV so that they can be included in phase III efficacy trials and are eligible to benefit if the vaccines achieve licensure. Together with the other HIV research networks, the HVTN was instrumental in developing a series of consensus statements on studying TB vaccines in PLHIV and will be critical to ensuring its recommendations are followed.

Efficacy trials of HIV vaccine candidates that failed to demonstrate sufficient protection against HIV acquisition are sometimes cited in an attempt to cast the field in a poor light, but these were carefully conducted studies based on the evidence available at the time and the urgency of the need. The lessons from this research continue to inform the design of potentially superior candidates, and have focused attention on the importance of solving the stern scientific problem of inducing broadly neutralizing antibody responses (bNAbs) against HIV. Collaborative work between the HVTN and HIV Prevention Trials Network (HPTN) to conduct the Antibody-Mediated Prevention (AMP) trials has formally demonstrated that bNAbs can prevent HIV if present in sufficient amounts and correctly targeted against circulating viral strains.

The HVTN has also led the way in promoting community education and involvement, creating the Red Ribbon Registry for people interested in volunteering for studies and significantly increasing the diversity of participation across demographic groups. The term diversity has recently been targeted for specious political reasons, but broad representation in clinical trials is essential for ensuring interventions are efficacious and can be implemented in diverse populations. This work was foundational to the successful development of COVID-19 vaccines when HVTN and other HIV research networks supported by the National Institutes of Health stepped up to form the COVID-19 Prevention Trials Network (CoVPN) in order to successfully evaluate the vaccine candidates which, despite the avalanche of politically motivated misinformation that has since surrounded them, have saved vast numbers of lives in the U.S. and globally.

TAG's recently published annual HIV Vaccines and Passive Immunization Pipeline Report lists 30 clinical trials, 15 of which are sponsored by HVTN (in one case, in partnership with the HIV Prevention Trials Network). Our 2024 Tuberculosis Vaccines Pipeline Report shows 17 candidates under clinical development with HVTN participating in trials of MTBVAC and ID93/GLA-SE and poised to contribute to the development of newer candidates such as the novel subunit vaccine H107e/CAF10b.

As HIV vaccine scientist Glenda Gray has stated: "*We can't stop now*." Technological advances are facilitating great progress in understanding how effective antibody responses are generated, bringing scientists ever closer to the development of HIV vaccine candidates with the potential to be broadly effective. This work also has the clear potential to inform vaccine development for multiple other diseases. It's important to remember that the goal of investing in HIV vaccine research is to not only avert the human cost of the condition, but also the financial burden of lifelong care and treatment.

**TAG Recommendations on Research Priorities**

We will not be able to completely end the HIV pandemic without a safe, effective, universally accessible and affordable HIV vaccine. Achieving this demands the following:

- Research into strategies for inducing bNAbs in both adult and pediatric populations internationally, including the iterative testing of germline targeting candidates designed to guide B-cells along the pathway to generating effective antibody responses (using mRNA or other appropriate technologies based on science, not mythology and conspiracy theories). Funding should be restored for the HIV vaccine consortia at Duke University and Scripps that were making significant progress in identifying vaccine constructs for clinical testing by HVTN.

- Development and assessment of preventive vaccines for tuberculosis. Continuation of support for international research sites is essential for this work given the epidemiology and global distribution of the TB epidemic.

- Continued collaborative research with other NIH-supported networks and external stakeholders to advance clinical trials of TB vaccine candidates with a focus on generating the evidence required to include PLHIV (of all ages) in TB vaccine prevention-of-disease efficacy trials. Priority candidates positioned for phase II and III trials over the next funding period, and for which data in PLHIV will need to be generated, include live-attenuated vaccines (MTBVAC), protein/adjuvant subunit vaccines (H107e/CAF10b, ID93/GLA-SE), and the first mRNA TB vaccine constructs.

- Continued support of translational science to maximize the value of clinical trial results including participation in discovery of TB vaccine correlates of risk and protection. This should include efforts to develop scientific tools and approaches for facilitating TB vaccine clinical trials such as novel immune assays or frameworks for addressing asymptomatic TB.

- The HVTN should consider adding hepatitis C vaccines to their portfolio when they become available for clinical testing.

- Continued international engagement with communities about vaccine science and trial participation, to ensure the research is conducted in partnership with directly affected and highly affected communities, and to garner information vital to effective implementation of successful HIV and TB vaccines (including maintenance of the Red Ribbon Registry).

- Continued collaborative research with other NIH-supported networks e.g. to assess bNAb-based candidates in people living with HIV, pediatric populations.

- Preservation of HVTN’s vaccine-specific infrastructure and expertise.