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Dear Carl,

On behalf of AVAC, I am writing to provide our thoughts on the priorities for the upcoming refining and reorganization of the DAIDS clinical trial networks. This process comes at a unique and productive time in HIV prevention research and provides an opportunity to reconsider the structure and agenda of individual networks as well as the entire DAIDS clinical trial network structure. For the past seven years, three networks have shared responsibility for HIV prevention research at the NIH. In proposing to combine the microbicide and prevention networks into one network, this consolidation has been linked to changes in the direction of the DAIDS scientific agenda for 2021-2027. Although this proposed consolidation could reduce costs and inefficiencies in structure and operating procedures, the paramount concern must be its impact of these changes on the future of HIV prevention research and its translation to impact. Irrespective of the number of networks in the end, we offer these comments about the overall research agenda.

1. Further Research is Needed on User Preferences

   We believe it is too early to contract the scientific agenda of the networks based on our current knowledge of user preferences for HIV prevention options. There is merit to making HIV prevention options that are both long-acting and systemic. These products could potentially protect against transmission and all routes of infection like through the vagina, rectum, blood and breast milk. Data from some, but not all, of the prevention trials completed so far have suggested to some that people don't want HIV prevention products that they have to take every day or even every month. It has been suggested that the data from some microbicide and oral PrEP trials show that women will not take these products. There is also data from HPTN 076 and the Partners PrEP trial that suggest that women will adhere to PrEP. Results from Phase III efficacy trials have provided important insights, but these findings may say more about trial participation than about actual product use in the real world. Men and women, inclusive of transgender individuals, deserve safe and effective HIV prevention options that provide easy, efficient protection, enabling all to lead vital, healthy lives. Those same individuals have numerous and diverse sexual health needs, beyond protection from HIV, that include protection from other sexually transmitted infections and – for many women – unintended pregnancies. A decision about the scientific agenda for the networks based about the kinds of products that men and women want based on microbicide and oral PrEP trials is premature.

   There are scientific reasons why a long-acting product could be very effective against HIV. But there are reasons why some people might <u>not</u> want or have ready access to an HIV prevention injection even if it existed. Similarly, people might prefer daily oral PrEP or a microbicide ring

(or another topical product) to a long-acting product at different times in their lives. There is a need for research that can tell us what people do and don't want outside of the clinical trials, but that research has not been done.

2. A New Prevention Network Must Retain Strengths of the MTN

The Microbicides Trials Network (MTN) is a network with an explicit focus on the prevention and treatment needs of cisgender women and adolescent girls. The HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN) both have significant investments in efficacy trials in women, particularly in sub-Saharan Africa, but have not advanced these trials under an over-arching women's prevention agenda. This focus should be incorporated into any new prevention network. In addition, explicit steps should be taken to incorporate the strengths of MTN into the new structure, including:

- Community and stakeholder engagement and "broad" (above site and trial level) Good Participatory Practice as implemented by the MTN.
- An explicit focus on the needs of cis-gendered girls and women, and of all people who engage in anal sex, as articulated by the MTN.
- Engagement of stakeholders, including civil society and other key decision makers above the site and trial community level, to ensure that new trials and interventions are understood and adjusted based on real-life country contexts and community concerns.

3. Toward a Cross-Network Coordination Mechanism

The DAIDS clinical trial networks as they currently exist have shown highly variable capacity and interest across networks in different aspects of their operation and scientific focus. The existing structure does not have a way to correct for this heterogeneity, which includes different policies with respect to trial conduct and standard of prevention, community and stakeholder engagement at the site and above site level and incorporation of behavioral and social science research into trials. The new structure must explicitly incorporate mechanisms including dedicated budget lines, cross-cutting research agendas, and cross-network coordinating mechanisms that focus on:

- Behavioral and social science research.
- Market research with potential users early in the research life-cycle to understand potential product preferences, barriers and facilitators of future uptake, etc.
- Product introduction and implementation science, providing a framework for identifying and advancing products people will use and for handing off products with clinical efficacy to mechanisms suited for implementation science.
- Research on women in all their diversities.
- Research on infants, children and young people.
- Community and stakeholder engagement and implementation of Good Participatory Practice beyond the trial and trial site.

To act on these recommendations, DAIDS must adopt a more transparent cross-network decision-making structure than exists today. There is no cross-network coordination mechanism with the authority and transparency to make sure that a comprehensive portfolio of products is developed, informed by clinical evidence and insights from user-centered

behavioral and social science research. The Office of HIV/AIDS Network Coordination (HANC) has portions of this mandate in its mission statement, but is not driving product portfolio decisions or comprehensive agendas. NIAID itself has to impose transparency and coordination for these networks, perhaps using HANC and the Office of AIDS Research as models for a cross-network coordinating structure.

4. A Translational Agenda for the Networks

   It is essential that DAIDS stay true to its accurate assessment of its strengths and weaknesses and take concrete steps to avert the "innovation pile-up" that might emerge if some or all of the slew of injectable (or future implantable) products entering efficacy trials show benefit. High efficacy won't mean high impact unless there are programs, providers and health systems that can deliver these products and people willing to use them. As a first step, product introduction plans should be incorporated into the protocols for all products in clinical trials—an approach already used by the Wellcome Trust with its research awards. A fast-track, "hand-off" oriented approach to implementation research on interventions, with an emphasis on efficiency, engagement with country government and integration into combination prevention packages will help ensure NIH prevention research achieves impact.

Finally, the Funding Opportunity Announcement (FOA) articulates the research priorities for the network and the requirements for that network's leadership group vis a vis the "research agenda" and "collaborative responsibilities." FOAs set the tone, priorities and parameters for the applications that research networks submit. Therefore, it's critical that the language be consistent, clear and inclusive in these documents.

Thank you for providing this opportunity to comment. Please do let me know if you have any questions or if there is anything AVAC or I can assist with during this process.

Sincerely,

Mitchell Warren
Executive Director