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Carl Dieffenbach, PhD
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Dear Carl,

On behalf of AVAC and our partners in the US and globally, we are pleased to provide input on the re-competition of the NIAID HIV/AIDS Clinical Trials Networks. This pivotal moment comes amid significant shifts in the global funding and political landscape, as well as the recent FDA approval and CDC and WHO recommendations of six-monthly injectable lenacapavir for PrEP. These developments are collectively reshaping the future of HIV prevention research, and DAIDS, NIAID and the networks of the future need to be adaptive, responsive, focused and nimble now and for the next seven years.

The context for HIV prevention R&D in 2025 has fundamentally changed. Unprecedented funding cuts and competing global health priorities mean that HIV prevention research no longer benefits from the resources and momentum it once had. This new reality requires sharper prioritization, innovative trial designs, and more efficient use of limited resources—while ensuring that community voices remain central in setting priorities and driving accountability. Our recommendations reflect this changed landscape and emphasize the need for the next generation of networks to deliver more results with fewer resources.

Our recommendations are informed by the *People's Research Agenda (PRA)*, a comprehensive framework developed through consultations with over 130 community representatives across 23 countries to outline community priorities for the HIV prevention pipeline, including early development, efficacy trials, implementation science, and wide-scale rollout.

We submit the following recommendations, each described in more detail below:

1. Balance the research portfolio by ensuring that investments are distributed strategically across implementation science, clinical trials, and basic research to maximize impact and ensure a comprehensive toolkit.
2. Sustain strategic and focused investments in early-phase trials for vaccines and next-generation PrEP.
3. Invest in HIV prevention implementation science to address evidence gaps.
4. Retain a strong commitment to community engagement and coordination in clinical trials and basic science.
5. Design clinical trials for relevance.

1. Ensure Balance in the Research Portfolio for a Comprehensive Toolkit

The portfolio of research under the NIAID networks should accurately reflect outstanding gaps and the scientific priorities necessary to end the epidemic in the US and globally. In the context

of shrinking budgets, NIAID should re-strategize around the science. This should include a review of upstream pipelines, drug discovery, novel testing and basic immunology (vaccines, broadly neutralizing antibodies and next-generation ARVs) to eliminate duplication within and outside of NIAID-supported efforts, establish cross-field consensus on the use-case and target product profiles for all interventions in the pipeline, and outline clear milestones against which ongoing funding decisions would be based.

Continued support for the current upstream pipeline is critical to protect and build upon existing investments. However, the research agenda must also prioritize candidate products in alignment with user preferences and real-world implementation needs and realities. While additional prevention options, including an HIV vaccine, remain urgently needed, any new product under development must meet a distinct and clearly defined need relative to existing options. This includes added value in terms of:

- Duration and durability
- Delivery system, ease of use and efficacy
- Affordability (both product and programmatic costs)
- Side effect profile
- Desirability and User appeal
- Indications (including potential for dual or multipurpose prevention)

Future investments must avoid duplicating existing options and instead focus on innovation that meaningfully expands the range of effective, acceptable, and accessible prevention options. This approach ensures new products are developed as part of a balanced HIV prevention R&D portfolio that can serve diverse needs and ultimately end the epidemic – and reflects a diminishing funding landscape.

We also call on NIAID to balance ongoing R&D of new options with implementation of existing and emerging ones. While the range of PrEP options has expanded over the past decade – thanks to critical NIH investments – no single product will end the HIV epidemic. Diverse tools tailored to diverse needs remain essential to reach populations who are most at risk and often left behind. We, therefore, continue to call for *choice* in HIV prevention trials and product roll out, and urge NIAID-funded networks to appropriately balance the urgent implementation science agenda for the options now available with a robust R&D agenda for the options still needed.

In light of the need to balance, streamline, and eliminate duplication, AVAC and partners recommend an agenda that prioritizes the development of vaccines and novel prevention options; the development of novel treatment options; and implementation science to ensure that new and emerging options are delivered with speed, scale, equity and impact.

2. Sustain Investments in Early-Phase Trials for Innovative, Next-Generation Products

Building on the point above, we urge NIAID to maintain a balanced portfolio of prevention trials and research agendas, a core component of which is an early-phase pipeline for next-generation products.

We acknowledge the current fiscal constraints but underscore that early-phase trials are the foundation upon which later-stage innovations are built. Without investment in basic science and exploratory research, the pipeline will stagnate and opportunities to develop the next generation of HIV prevention tools will be lost.

Given the likely decreased funding envelope across the networks, this pipeline needs critical review. We urge a thorough review of the upstream portfolio and that investments only be made towards products that fill a gap in the prevention toolkit, and avoid simply resuscitating past programs without strategic focus.

The NIH has a longstanding mandate to advance fundamental scientific knowledge. Many of the most transformative innovations in HIV prevention and treatment are the direct result of decades of basic research supported by NIH and others. This mandate must be protected and strategically resourced, even amid broader funding pressures. We therefore recommend:

- Strategic investment in early-phase trials for multipurpose prevention technologies (MPTs) that combine HIV prevention with contraception and/or STI prevention.
- A streamlined discovery medicine agenda for HIV vaccines, addressing cellular- and antibody-based approaches both independently and in combination.
- Vaccine clinical trial network activities to be seamlessly linked with reinstated funding for the CHAVDs, which remain the engine for advancing new vaccine insights and concepts.
- Ongoing support for platform development, including mRNA and vaccine platforms, antibody engineering and testing technology, as these are critical to long-term R&D impact.
- A clear case for bNAbs, including their potential role to inform vaccine development and in cure research. Any product development of bNAbs should advance only where there is a clear path to global access to a feasibly delivered product.

3. Invest in HIV Prevention Implementation Science to Address Evidence Gaps

In July 2025, the World Health Organization released guidelines recommending that long-acting injectable lenacapavir be offered as an additional HIV prevention option as part of a comprehensive combination prevention approach. The guidelines also highlight critical evidence gaps that must be addressed through implementation science to support roll-out and scale-up. Key evidence gaps include:

- Data on alternative injection sites and dosing regimens.
- Differentiated service delivery models for lenacapavir, including task-sharing with various cadres of providers and provision in community-based and virtual settings.
- Models of self-care and preferences for service delivery.
- Patterns of use, persistence, and strategies to support on-time injections.
- Tailored delivery approaches for adolescents, key populations, and vulnerable groups, including displaced individuals.
- Evidence on HIV testing approaches specific to injectable long-acting PrEP.

NIAID network investment in implementation science should play a leadership role in answering these questions, particularly those related to user preferences, choice, and access to ensure that lenacapavir and other emerging options can be delivered effectively, safely, and in ways that meet the diverse needs of populations at risk of HIV. NIAID and future network leadership will need to tightly coordinate these efforts with the pharmaceutical companies that developed these PrEP options, the CDC, State Department and WHO to ensure implementation science questions are answered and operationalized in the most efficient and effective manner possible, and to avoid duplication of effort.

We underscore the importance of research that goes beyond biomedical innovation to examine real-world implementation—how products are accessed, adopted, and used across diverse populations. This requires intentional investment in studies that explore the why and how of service uptake, persistence, and discontinuation. Social and behavioral research should remain an integral component of the network's agenda, ensuring that the HIV prevention pipeline is not only scientifically advanced but also people-centered and grounded in lived realities.

4. Retain Strong Commitment to Community Engagement and Coordination in Clinical Trials

Even as resources become increasingly constrained – and especially as they do – we call on NIAID to ensure that its clinical trials networks retain their commitment to meaningful community engagement throughout the research enterprise. Especially as the prevention pipeline must become more streamlined, community input will be core to ensuring research can be translated to the real world through strategic, objective-focused engagement at all relevant stages, especially once products get to development stages.

We recommend that NIAID continue support for HANC as a dedicated structure to provide leadership and coordination of community engagement efforts across networks. This body should work in close partnership with network-level Community Working Groups as well as external research advocacy and engagement efforts to ensure consistent input into decision-making at all levels, including executive and leadership committees.

Further specific recommendations include:

- Sustained investment in leadership and dedicated staff responsible for community engagement at network and site levels;
- Clear and adequate budgeting for robust stakeholder and community engagement activities;
- Strengthened funding and infrastructure for local, regional or global community advisory/accountability mechanisms across trials and networks; and
- Embedding Good Participatory Practices (GPP) across all stages, from research agenda-setting to protocol design and implementation to results dissemination.

5. Design Trials for Relevance

In an ever-evolving clinical trial landscape, ongoing and future trials must adapt to both constrained funding realities and the rapidly advancing HIV prevention pipeline. As new products emerge and existing ones improve, trials must be designed for relevance while remaining responsive to this shifting context. With fewer resources available for HIV prevention R&D, there is an urgent need to adopt more resource-efficient trial designs, co-developed with communities and responsive to the landscape. Community perspectives—such as those that informed the design of recently launched efficacy trials of Merck's monthly PrEP pill, MK-8527, in alignment with GPP—are essential to ensure trials reflect real-world needs and priorities.

We also note that while artificial intelligence (AI) holds promise for modeling and streamlining research processes, its use must be rooted in community ethics, transparency, and inclusivity. We urge the field to co-create a framework for the responsible application of AI in HIV prevention trials—one that safeguards equity, data privacy, and human-centered values.

We further make the following recommendations on designing trials for relevance:

- Control groups in efficacy trials be designed with careful ethical consideration in contexts where effective prevention options already exist.
- Trials include diverse geographies and populations, such as people who inject drugs, pregnant and lactating people, and trans communities, to ensure that findings are broadly applicable as we have learnt from recent PURPOSE trials.
- No product should begin efficacy trials without a clear, transparent commitment to access planning, including regulatory approvals, manufacturing, licensing, and country and global coordination, particularly with regard to participating trial countries and across low- and middle-income countries.
- Pharmacokinetic and bridging studies should explore protection onset, forgiveness, and drug tail effects to understand the full spectrum of a product's impact. Stakeholders, including community and civil society, should have a full understanding of the role of PK studies, especially in cases where they provide licensure data.

Thank you for considering these priorities. We welcome the opportunity to discuss them further and explore ways to integrate these recommendations into the re-competition process. We also remain committed to our partnership with DAIDS and all research networks. Please do not hesitate to reach out if additional input or collaboration would be helpful.

Yours sincerely,

Mitchell Warren, on behalf of AVAC, and
Julie Patterson, Advocate & Partner
Adaobi Olisa, Root to Rise
Ntando Yola, Advocacy for Prevention of HIV &AIDS (APHA)