THE FORUM FOR COLLABORATIVE RESEARCH

HIV CURE: CLINICAL RESEARCH CONSIDERATIONS AND STRATEGIES WORKSHOP

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CONTENTS

INTRODUCTION

Although antiretroviral therapy (ART) has transformed HIV from a fatal disease into a manageable chronic condition, achieving durable, ART-free remission remains a top global priority. On July 30, 2025, the Forum for Collaborative Research convened the "HIV Cure: Clinical Research Considerations and Strategies Workshop" in Washington, D.C., bringing together 149 participants (in-person and remote) from five continents, including scientists, clinicians, regulators, ethicists, community advocates, and funders. Conducted in a closed, non-attribution format, the workshop facilitated candid dialogue on the scientific, ethical, operational, and regulatory dimensions of HIV cure research.

Over the past decade, proof-of-concept studies, including post-treatment control and targeted reservoir interventions have demonstrated the feasibility of sustained ART-free remission. Existing strategies, such as latency-reversing agents, intensive immunotherapies, and stem cell–based approaches, are technically complex, resource-intensive, and largely non-scalable. Concurrently, novel interventions are entering or approaching clinical evaluation, including broadly neutralizing antibodies (bNAbs), engineered T-cell therapies, CRISPR-based gene editing, therapeutic vaccines, latency-modifying agents, and long-acting ART delivery platforms. These approaches offer opportunities to improve efficacy, durability, and accessibility of potential cures.

The workshop critically examined these scientific advances in conjunction with ethical, operational, regulatory, and equity considerations, emphasizing the translation of research into globally relevant interventions. This report synthesizes key discussions and outcomes from the workshop, highlighting key challenges identified and collaborative strategies proposed to advance HIV cure research.

THE RATIONALE FOR HIV CURE

Despite the transformative impact of antiretroviral therapy (ART), a definitive cure remains a critical global priority. ART effectively suppresses viral replication, but lifelong treatment imposes persistent physical, psychological, and social burdens. People living with HIV (PWH) face daily medication adherence, long-term drug toxicities, and the ongoing stigma associated with the disease. A curative intervention would provide durable ART-free remission, alleviate these burdens and potentially restore a profound sense of autonomy and normalcy.

The economic imperative for a cure is equally compelling. Lifetime ART management for a child with HIV in the United States is estimated at approximately $1.5 million[1]. Beyond individual savings, a scalable cure would relieve financial and logistical pressures on health systems, particularly in low-

[1] Cohen, J.P., Anupindi, V.R., Doshi, R. *et al.* Estimation of Lifetime Costs Among Insured Persons with HIV in the United States. *PharmacoEconomics Open* (2025). https://doi.org/10.1007/s41669-025-00584-0

and middle-income countries (LMICs) that depend on external funding and face rising challenges from drug resistance.

Global equity further underscores the rationale for a cure. Viral and host diversity across regions necessitates research that includes populations most affected by HIV to ensure interventions are both scientifically robust and universally applicable. Prioritizing equity in research design and implementation is essential to avoid a "two-tiered" system of care and to maximize the worldwide public health impact of any successful cure strategy.

Together, the personal, economic, and global considerations establish a compelling, multidimensional rationale for accelerating HIV cure research, emphasizing interventions that are effective, ethical, and accessible to all populations.

THE EVOLVING HIV CURE RESEARCH LANDSCAPE AND CHALLENGES

HIV cure research has progressed from a theoretical aspiration to a scientifically tangible goal, yet it remains one of the most complex challenges in modern medicine.

Over the past two decades, broadly neutralizing antibodies (bNAbs) have emerged as a cornerstone of cure research. Initially identified in rare individuals capable of naturally controlling HIV, bNAbs demonstrate potent antiviral activity, neutralizing diverse viral strains and targeting both free virions and infected cells. Recent advances in vectored gene delivery aim to enable sustained in vivo production of bNAbs, potentially providing long-term antiviral protection without repeated infusions. Despite these advances, the field faces persistent challenges. Viral escape variants can compromise long-term efficacy, reservoir reduction remains modest, and manufacturing, storage, and global distribution present logistical and economic obstacles, particularly in low-resource settings.

Cell and gene therapies present a transformative frontier, demonstrating unequivocally that viral eradication is achievable. The historic cases of the "Berlin Patient" (Timothy Ray Brown) and the "London Patient" (Adam Castillejo), who achieved complete viral clearance following allogeneic hematopoietic stem cell transplantation from CCR5Δ32 homozygous donors, serve as proof-of-concept milestones. These outcomes validated the principle that HIV can be eliminated from the human body, but the procedures are invasive, carry significant morbidity and mortality risk, and are not scalable. To overcome these limitations, investigators are exploring engineered T cells, chimeric antigen receptor (CAR) T-cell therapies, and CRISPR-based proviral excision. These approaches aim to either directly remove integrated viral DNA or enhance immune-mediated clearance of infected cells. However, they face certain barriers, including long term safety concerns and complex manufacturing requirements.

Immunotherapy and combination approaches are increasingly recognized as necessary to target both actively replicating and latent viral reservoirs. Therapeutic vaccines, checkpoint inhibitors, latency-reversing agents, and immunomodulatory molecules, when used in combination with bNAbs or engineered cells, show potential to enhance reservoir clearance. Clinical studies presented at the workshop include the e-CLEAR trial which showed sustained viral suppression during a 12-week analytical treatment interruption (ATI) in 20 participants who received a combination of Romidepsin (A latency reversing agent) and 3BNC117 (a broadly neutralizing antibody) at the initiation of ART therapy.[2] Preclinical studies have demonstrated synergistic effects of combining latency reversal with immune activation, yet clinical translation remains challenging. Optimizing timing, dosing, and sequencing of these interventions is critical to balancing efficacy with safety, while operational complexity and high costs further complicate trial implementation.

Analytical treatment interruptions (ATIs) remain an indispensable tool for assessing the durability of candidate cure strategies. Updated guidance from the 2024 ATI Workshop in Nairobi emphasized ethical design, inclusivity, and robust participant protections. Despite this, ATIs carry inherent risks, including rapid viral rebound, potential clinical complications, and psychosocial stress. Patient advocates at the workshop highlighted their concerns regarding the risks of temporarily stopping ART, considering sensitization messages from HIV awareness campaigns on the importance of treatment adherence.

Across all strategies, broader structural and operational challenges persist. The global clinical trial pipeline has experienced a decline in new study registrations since 2017, and reductions in funding for NIH-supported trial networks have constrained the scale and diversity of ongoing research. Combination therapy trials, while scientifically promising, are especially costly and operationally complex, requiring sophisticated laboratory infrastructure, multidisciplinary coordination, and intensive patient monitoring. Deconvoluting the relative contribution of each agent in the combination is complex and requires larger and more complex study designs. Achieving meaningful reductions in viral reservoirs across diverse populations, while ensuring safety and tolerability, remains a central and unresolved challenge.

The current landscape of HIV cure research reflects a dynamic interplay of scientific breakthroughs, historical milestones, and ongoing challenges. From the first identification of elite controllers and the landmark CCR5Δ32 stem cell transplant cases to the ongoing clinical evaluation of bNAbs, engineered cells, immunotherapies, and combination regimens, the field has made remarkable strides. Yet each

[2] Gunst JD, Pahus MH, Rosás-Umbert M, Lu IN, Benfield T, Nielsen H, Johansen IS, Mohey R, Østergaard L, Klastrup V, Khan M, Schleimann MH, Olesen R, Støvring H, Denton PW, Kinloch NN, Copertino DC, Ward AR, Alberto WDC, Nielsen SD, Puertas MC, Ramos V, Reeves JD, Petropoulos CJ, Martinez-Picado J, Brumme ZL, Jones RB, Fox J, Tolstrup M, Nussenzweig MC, Caskey M, Fidler S, Søgaard OS. Early intervention with 3BNC117 and romidepsin at antiretroviral treatment initiation in people with HIV-1: a phase 1b/2a, randomized trial. Nat Med. 2022 Nov;28(11):2424-2435. doi: 10.1038/s41591-022-02023-7. Epub 2022 Oct 17. PMID: 36253609; PMCID: PMC10189540.

strategy carries intrinsic limitations ranging from incomplete reservoir clearance and viral escape to technical, ethical, and operational barriers, that must be navigated to advance toward a globally applicable cure.

CLINICAL, ETHICAL, AND REGULATORY CONSIDERATIONS

The design and conduct of HIV cure trials sit at the intersection of clinical innovation, ethical responsibility, and regulatory complexity. As novel interventions progress from the laboratory into human studies, the field is confronted with the challenge of creating trials that not only generate rigorous data but also safeguard participants, sustain community trust, and meet diverse regulatory standards across jurisdictions. Central to this effort is the question of how efficacy should be measured. Analytical treatment interruption (ATI) remains the primary method for determining whether an intervention can maintain viral control in the absence of ART, yet ATIs carry potential risks: viral rebound, immune decline, and the potential for onward transmission. Recent refinements in ATI protocols including broadened eligibility criteria, structured partner protections, and psychosocial support mechanisms represent important progress, but inconsistencies remain. Monitoring schedules, restart thresholds, and safety triggers vary significantly between trials, undermining comparability and slowing the accumulation of generalizable knowledge. Without harmonized definitions of “success”, whether measured by time to rebound, post-rebound viral setpoint, reservoir reduction, or the proportion achieving sustained remission, the field risks fragmenting into studies that cannot be meaningfully compared or aggregated. The absence of predictive or monitoring biomarkers further compounds this challenge, leaving the scientific community reliant on ATIs despite their inherent burdens. Standardizing study endpoints and measurements would greatly facilitate discovery of biomarkers through pooled data or federated/standardized analysis of sufficient sample size.

Safety concerns are heightened as the pipeline of interventions increasingly includes high-risk modalities such as gene editing, CAR-T cell therapies, and engineered immune modulators. These strategies may induce permanent or irreversible biological changes, with effects that could emerge years or even decades after initial administration. To address this uncertainty, workshop participants emphasized the necessity of embedding long-term follow-up into the design of every high-risk trial, supported by secured funding commitments and surveillance infrastructure capable of tracking delayed adverse events. Independent safety monitoring boards, inclusive of community voices, were viewed as essential, ensuring that oversight extends beyond scientific and clinical expertise to incorporate the perspectives of those most directly affected. Reproductive safety represents an additional layer of complexity, particularly given the theoretical possibility of germline involvement. Protocols must therefore incorporate counseling, contraception support, and registries to monitor pregnancy outcomes and intergenerational effects.

Ethical considerations cut across every stage of trial design and conduct, shaping both scientific choices and community perceptions. The very language of “cure” remains contested: while it inspires hope and mobilizes resources, it also risks raising unrealistic expectations. Terms such as “remission”

or “durable ART-free control” may more accurately reflect current realities and facilitate clearer communication with participants. Informed consent, too, must be reconceptualized. Standard documents laden with technical jargon are ill-suited for interventions whose risks are uncertain, complex, and potentially irreversible. Consent in this context should be treated not as a single transaction but as an ongoing dialogue, supported by decision aids, plain-language explanations, and regular comprehension checks. Placebo-controlled designs, long considered the gold standard for scientific rigor, introduce further ethical dilemmas in the setting of ATIs, where risks of viral rebound and transmission are non-trivial. While some argue placebo arms remain essential in certain contexts, others advocate for adaptive or alternative trial designs that minimize participant exposure to risk while preserving scientific validity.

Equally unresolved is the question of what happens once a trial ends. If a participant derives clear benefit from an experimental intervention such as extended remission or measurable reductions in reservoir size; what obligations exist to ensure continued access? Many interventions under investigation are complex, resource-intensive, and unlikely to be widely available in the near term. Communities have stressed that participants should not be left without support at the point of trial conclusion, and that sponsors and funders must address post-trial access and care obligations transparently from the outset.

Overlaying these clinical and ethical challenges is a fragmented regulatory environment. Jurisdictions differ in their expectations for gene and cell therapies, with some prioritizing long-term safety surveillance and others focusing on manufacturing standards or risk management. This variability complicates multi-country studies and creates uncertainty for sponsors seeking to advance candidates across diverse regulatory landscapes. Early and sustained dialogue with regulators was identified as essential, not only to align expectations but also to ensure preparedness for managing adverse events. The need for harmonization was repeatedly underscored, with calls for pre-competitive forums that would allow regulators, sponsors, and researchers to align approaches and accelerate responsible progress.

These discussions highlighted that the future of HIV cure research cannot be separated into discrete clinical, ethical, or regulatory domains. The three are deeply intertwined, and progress depends on addressing them in concert. Trials must be designed with clear, comparable endpoints, robust safety frameworks, and transparent consent processes. They must anticipate not only the immediate risks of ATI and experimental interventions but also the long-term obligations to participants and their communities. And they must navigate a regulatory landscape that is still adapting to the unprecedented challenges posed by cure research. Only by integrating these considerations can the field advance responsibly, ensuring that scientific breakthroughs translate into meaningful and ethically sound outcomes for people living with HIV worldwide.

PEDIATRIC CONSIDERATIONS

Children, and particularly infants who initiate therapy very early in life, occupy a distinctive and often underrecognized space in the HIV cure landscape. Biologically, they present a unique opportunity: early treated infants frequently harbor markedly smaller and more homogeneous viral reservoirs than adults, suggesting a potentially greater likelihood of achieving durable remission and position pediatric populations as one of the most promising potential populations for evaluating curative strategies. Given the complexity and risk of studies, infants are among the least represented populations in cure trials.

The barriers are not scientific, but structural and ethical. Current regulatory frameworks and research norms overwhelmingly prioritize an “adult-first” model, requiring safety and efficacy data in older populations before pediatric studies can proceed. While intended as a safeguard, this approach often delays or even prevents the inclusion of infants, precisely the group in whom curative interventions may be most effective. As a result, the very window of opportunity presented by early life biology is frequently missed.

Discussions during the workshop highlighted several paths forward to address these challenges. One central proposal was the development of master protocols with age de-escalation, allowing parallel progress across adult and pediatric cohorts while ensuring stepwise safety evaluation. Participants stressed that such designs could prevent years of delay and provide a framework for systematic, ethically sound inclusion of younger populations.

Technical innovation was also recognized as critical. Children, particularly infants, cannot safely undergo the same intensive sampling as adults, making sample-sparing assays a necessary component of pediatric trial design. The advancement of ultrasensitive virological and immunological assays that require minimal blood volumes was identified as key to generating robust data without undue burden.

Equally emphasized was the need for pediatric-specific target product profiles (TPPs) that reflect the developmental, immunological, and social contexts of children. Tailoring product goals for pediatric use would not only improve trial design but also strengthen the translational pipeline toward interventions that are feasible and acceptable in real-world pediatric care settings.

Finally, participants underscored that the success of pediatric cure research cannot rest solely on science and trial design. Family engagement and support structures ranging from counseling services to community-based education are essential for ethical recruitment and sustained participation. Without such infrastructure, even the most scientifically promising studies risk faltering in practice.

These discussions framed pediatric HIV cure research as both a profound scientific opportunity and a persistent ethical challenge. Infants and children offer a biologically compelling pathway to remission, but realizing this potential will require deliberate strategies that balance innovation with protection, accelerate inclusion without compromising safety, and engage families as partners in the research process.

CENTERING COMMUNITIES AND ENSURING EQUITY

At the heart of HIV cure research lies the recognition that communities are not passive subjects but critical collaborators whose engagement shapes both scientific validity and ethical integrity. Workshop participants repeatedly emphasized that the inclusion of people living with HIV (PLHIV), community advocates, and affected populations is essential at all stages of the research lifecycle, from trial design and implementation to dissemination. Communities were described as “powerful champions who can influence policy,” underscoring that their insights are indispensable for ensuring research addresses real-world needs and mitigates potential harms. Historical mistrust of biomedical research, pervasive misinformation, and the difficulty of translating complex immunological and virological concepts into accessible language are some of the challenges facing HIV cure research.

To address these challenges, participants highlighted innovative strategies for scientific communication and engagement. Applying relatable methods such as visual storytelling, graphic novel, and art-based education can help convey the mechanistic and clinical nuances of interventions, such as latency-reversing agents and broadly neutralizing antibodies; in ways that foster community understanding and ownership. The workshop also underscored the inspirational role of high-profile cases of HIV remission, which serve not only as scientific proof-of-concept but also as narrative touchstones that can galvanize public trust and advocacy.

Equity was framed as both a moral and a scientific imperative. Women, racial and ethnic minorities, and populations in Africa, Asia, and Latin America remain underrepresented in clinical trials, despite shouldering the greatest burden of HIV infection. This underrepresentation compromises both the generalizability of trial findings and the ethical legitimacy of research. Participants emphasized that equitable inclusion requires more than broad recruitment; it necessitates structural supports that address the logistical, social, and psychosocial barriers faced by participants. Mechanisms such as transportation stipends, childcare support, culturally tailored educational materials, and access to psychosocial counseling were identified as essential to facilitate participation and retention. The need for stigma reduction and protection of confidentiality was also highlighted as a core component of ethical trial conduct.

Community advisory boards (CABs) emerged as a central mechanism for embedding equity and accountability. Engaging CABs from the earliest stages of protocol development ensures that trial design is informed by lived experience and community priorities. Dedicated budget allocations for CAB activities were emphasized to guarantee substantive, rather than tokenistic, participation. Beyond advisory roles, communities were seen as partners in co-designing trials, helping to define inclusion criteria, endpoints, and strategies for post-trial access. Psychosocial support systems, particularly surrounding ATIs, were emphasized as crucial for participant well-being, given the physical, emotional, and social risks associated with viral rebound.

The workshop underscored that meaningful community engagement extends to the reporting and interpretation of results. Public transparency regarding enrollment diversity metrics, dissemination of trial outcomes in accessible formats, and the inclusion of community voices in interpreting scientific data are critical for sustaining trust and ensuring that research outcomes are relevant to those most affected. One advocate succinctly captured the consensus: “If cure research is to have legitimacy, it must reflect the diversity of the epidemic. Otherwise, we risk producing science that does not serve those most affected.”

In summary, centering communities and ensuring equity are not optional components of HIV cure research; they are foundational to its success. By integrating community perspectives, addressing structural barriers to participation, and embedding ethical safeguards into trial design and implementation, the field can produce interventions that are scientifically robust, ethically sound, and globally relevant. Effective engagement transforms communities from passive subjects into active partners, ensuring that advances in HIV cure research translate into meaningful, inclusive, and sustainable outcomes.

FUNDING AND GLOBAL PARTNERSHIPS FOR SUSTAINABILITY

The sustainability of HIV cure research is contingent upon coordinated, long-term investment and robust global partnerships that can support the inherently high-risk, resource-intensive, and multi-phase nature of the field. Traditional grant mechanisms, structured around short-term cycles, are insufficient for interventions requiring decades-long surveillance, complex infrastructure, and longitudinal follow-up of participants. Workshop participants underscored the necessity of establishing a multi-stakeholder funding consortium that integrates public funders, philanthropic organizations, and industry partners. Such a consortium would strategically align investments across the research continuum, minimize duplication, and underwrite not only clinical trials but also ancillary infrastructure including registries, biobanks, pediatric networks, and capacity-building initiatives in under-resourced regions.

A primary rationale for the consortium model is to de-risk high-risk, high-reward interventions, such as gene and cell therapies, broadly neutralizing antibodies, and combination immunotherapies, which require sustained capital beyond conventional project timelines. Mechanisms such as milestone-based funding, public guarantees, and blended financing were proposed to attract private sector participation while maintaining ethical oversight. Humanitarian licensing provisions and cost-access commitments were highlighted as critical to ensuring that eventual curative interventions are globally scalable and equitably accessible, particularly in low- and middle-income countries where the HIV burden is greatest. Long-term funding was also emphasized as essential for sustaining longitudinal safety monitoring, post-trial follow-up, and implementation readiness, ensuring both the scientific integrity of the research and its translational relevance.

Parallel to financial coordination, data management and sharing were identified as central to accelerating progress. Open, interoperable platforms are indispensable for rapid cross-trial learning; however, there must be a balance in accessibility with participant privacy and adherence to local governance standards. A federated data-sharing model with standardized dictionaries, controlled access, and harmonized assay protocols was proposed as a practical framework to enable meta-analyses, comparative studies, and validation of surrogate biomarkers while safeguarding ethical and regulatory compliance.

Capacity building in high-burden regions was characterized as both a scientific necessity and an ethical obligation. Many regions lack the laboratory infrastructure, trained personnel, and technological capabilities required to participate fully in cure research. Investments in training programs, technology transfer, and infrastructure development were emphasized not as auxiliary tasks but as core components of a globally relevant research ecosystem. Strengthening local capacity ensures that research outputs are applicable across diverse epidemiological and sociocultural contexts and fosters equitable inclusion in clinical trials.

Participants concluded that the long-term viability of HIV cure research hinges on the integration of coordinated funding mechanisms, global partnerships, data harmonization, and capacity-building initiatives. Without these elements, even scientifically promising interventions risk remaining inaccessible, non-scalable, or inequitable. A dedicated multi-stakeholder consortium, coupled with federated data-sharing platforms and strategically targeted capacity-building programs, represents the most effective strategy to sustain high-risk, high-reward research, accelerate scientific discovery, and ensure global equity in access to future curative interventions.

KEY TAKEAWAYS

The need to balance innovation, safety, and ethics in HIV cure clinical trials

Trials must integrate rigorous endpoints, validated biomarkers, and standardized ATI protocols to ensure comparability and reproducibility. High-risk interventions demand long-term follow-up, independent safety oversight, and reproductive safety measures. Ethical imperatives include iterative informed consent, careful use of placebo arms, and planning for post-trial access. Regulatory variability across jurisdictions necessitates early, ongoing engagement to harmonize standards and facilitate multi-country trials.

Pediatric populations present unique opportunities for HIV cure research

Early treated infants and children present unique opportunities for durable remission due to smaller, more homogeneous reservoirs. Inclusion is delayed by adult-first regulatory models. Master protocols with age de-escalation, sample-sparing assays, pediatric-specific target product profiles, and family-centered engagement are critical to accelerate ethical pediatric participation.

Communities are equal partners in HIV cure research

Communities are essential collaborators, not passive participants. Effective engagement requires integrating community input into trial design, inclusion criteria, endpoints, and dissemination. Structural supports such as transportation, childcare, psychosocial services, and culturally tailored materials enhance participation and retention. Community advisory boards ensure accountability and equitable representation, particularly for women, racial and ethnic minorities, and populations in high-burden regions.

A multistakeholder funding consortium is necessary for sustainability of cure research

Sustained, coordinated investment is critical for high-risk, resource-intensive research. A multi-stakeholder funding consortium can align public, philanthropic, and industry resources, de-risk innovative strategies, and support trials, registries, long-term follow-up, and capacity building. Federated data-sharing platforms, humanitarian licensing, and targeted infrastructure development in under-resourced regions are essential for global scalability, equity, and scientific rigor.

Conclusion

HIV cure research is at a scientific and ethical frontier. Progress depends on integrating innovative interventions with standardized clinical frameworks, robust ethical safeguards, equitable community engagement, pediatric inclusion, harmonized regulation, and sustainable funding. Achieving a globally applicable, durable cure requires coordinated efforts across scientific, operational, and societal domains.

NEXT STEPS

The Forum plans to invite workshop participants to collaborate on a manuscript to be published in a peer-reviewed journal. The meeting closed with the appreciation of participants for their commitment to advancing HIV cure research.