U.S. Department of Health and Human Services
National Institutes of Health
Office of AIDS Research

Office of AIDS Research Advisory Council
62nd Meeting
March 2, 2023

Virtual
https://videocast.nih.gov/watch=48729

Meeting Minutes

Council Members Present: Dr. Blanton S. Tolbert (Chair), Dr. Tabia K. Henry Akintobi, Dr. Margaret L. Brandeau, Dr. Kathleen L. Collins, Dr. Heidi M. Crane, Dr. Shruti H. Mehta, Dr. Veronica Miller, Dr. Ricardo Rivero, Dr. John W. Sleasman, Dr. Ivy E. Turnbull

***Ad Hoc* Member Present:** Dr. Luis Montaner

***Ex Officio* Members Present:** Dr. Carl Dieffenbach, Dr. Rohan Hazra, RADM Jonathan Mermin

Advisory Council Representatives Present: Dr. Monica Gandhi, Dr. Marguerita Lightfoot, Dr. Melanie Ott

Office of AIDS Research Leadership Present: Dr. Maureen M. Goodenow, Director, Office of AIDS Research (OAR); RADM Timothy Holtz, Deputy Director, OAR; CAPT Mary T. Glenshaw, OAR Advisory Council (OARAC) Designated Federal Official and Supervisory Senior Science Advisor; Dr. Geetanjali Bansal, Health Scientist Administrator and Senior Science Advisor

Invited Speakers and Guests Present: Dr. Stacy Carrington-Lawrence, Dr. Basil Eldadah, Dr. Roy Gulick, Dr. Richard Hodes, Dr. Judy Levinson, Dr. Henry Masur, Dr. Theodore Ruel, Dr. Renee Wegrzyn, Mr. Timothy Westmoreland

Welcome and Introductions

Blanton S. Tolbert, Ph.D., OARAC Chair and Professor, Case Western Reserve University
CAPT Mary Glenshaw, Ph.D., M.P.H., OARAC Designated Federal Official and Supervisory Senior Science Advisor OAR, National Institutes of Health

Dr. Blanton S. Tolbert welcomed participants to the 62nd meeting of the National Institutes of Health (NIH) OARAC. A quorum was present. Meeting materials provided to Council members included the agenda, presentations, member information, a conflict-of-interest form, and minutes from the 61st OARAC meeting, held on October 22, 2022.

A motion to accept the minutes of the 61st OARAC meeting was approved unanimously.

Dr. Tolbert reviewed the 62nd meeting agenda, noting the inclusion of time for public comments.

Report from the OAR Director

Maureen M. Goodenow, Ph.D., OAR, NIH

Timothy Westmoreland, J.D., Professor Emeritus, Georgetown Law Center

Dr. Maureen M. Goodenow welcomed attendees and noted that several crucial HIV organizations will recognize milestone anniversaries this year. In addition to the 35th anniversary of NIH OAR, the President's Emergency Plan for AIDS Relief (PEPFAR) marks its 20th anniversary, while the Conference on Retroviruses and Opportunistic Infections (CROI) and the Ryan White HIV/AIDS Program (RWHAP) both celebrate their 30th anniversaries. Dr. Goodenow thanked Dr. Tolbert for his service as OARAC Chair, acknowledged the members who will complete their terms at the end of the month (Drs. Blanton Tolbert, Margaret Brandeau, Heidi Crane, and Jonah Sacha). She introduced Dr. Ivy Turnbull as the incoming Acting OARAC Chair. Dr. Goodenow thanked members who participated in the OARAC Orientation session, which was held on March 1, 2023.

Dr. Goodenow pointed out that the fiscal year (FY) 2023 omnibus bill includes an increase of $100 million above the FY 2022 enacted level for research related to HIV/AIDS across NIH. This amount is 3.1 percent greater than the FY 2022 NIH HIV budget, which included an increase of $104 million, the highest single-year increase since FY 2014. Overall, the NIH HIV research budget has increased by $299 million overall since 2018 after years of flat funding. The increases were deployed across the NIH HIV research program in collaboration with the NIH Office of the Director. The FY 2022 increase was primarily allocated to research associated with two of NIH's HIV-related research priorities: (1) addressing HIV-associated comorbidities, coinfections, and complications; and (2) cross-cutting research priorities. The FY 2023 increase is being deployed across nine institutes to support projects that align with the areas of emphasis outlined in the FY23 NIH HIV/AIDS Professional Judgment Budget.

The Professional Judgment Budget is a legislatively mandated annual document that highlights accomplishments in HIV/AIDS research during the prior year and estimates the amount of additional funding needed to advance priority areas of science, as outlined in the *FY 2021–2025 NIH Strategic Plan for HIV and HIV-Related Research*. The FY24 NIH HIV/AIDS Professional Judgment Budget requests $3.673 billion for NIH HIV/AIDS research, an increase of $479 million, or 15 percent, above the FY 2022 enacted budget of $3.194 billion. Scientific opportunities highlighted in the FY 2024 Professional Judgment Budget include 1) expanding basic biomedical and behavioral research; 2) the need to understand the biological, behavioral, and social conditions associated with effects of HIV across the lifespan; and 3) strengthening the capacity and diversity of the HIV/AIDS research workforce. Workforce support includes by expanding the number and diversity of early-career HIV investigators and improving infrastructure and equipment at institutions conducting HIV/AIDS research, particularly those with limited resources. The full FY 2024 Professional Judgment Budget is available on the OAR website. Dr. Goodenow noted that development cycle for the Professional Judgment Budget has been adjusted to align with U.S. government budget processes; the FY 2025 Professional Judgment Budget currently is in development.

Dr. Goodenow introduced Mr. Timothy Westmoreland, worked for the U.S. House of Representatives Subcommittee on Health and the Environment, and coauthored the legislation that created OAR in 1988. Mr. Westmoreland reflected on the small size of the HIV research community when he began working on HIV-related issues in 1981, the prejudices against gay men expressed by members of Congress, and the political challenges to funding HIV research in the early days of the pandemic. He noted that professional judgment and expert recommendations became important for funding success; as public opinion shifted, a stronger

response was demanded. Eventually, bipartisan funding was secured, to enable HIV/AIDS research at nearly every NIH institute and center (IC), although prioritization and coordination were difficult. Legislation passed in 1988 was designed to create a federal grants program and improve research authorities; the latter was the legislation that codified OAR, but most debate surrounded the first program. The structure of OAR was incorporated into the NIH Revitalization Act, which was difficult to pass because it lifted the moratorium on fetal tissue experimentation. When the act passed, it included strengthening OAR with budget authority. Mr. Westmoreland remarked that although the HIV research field has changed, the organizational paradoxes—how to coordinate work across ICs, how to serve multiple constituencies, and how to make scientific progress amid political controversy—remain the same.

Following Mr. Westmoreland's remarks, Dr. Goodenow discussed how OAR's listening sessions are critical to accomplishing the office's mission. Sessions with community partners provide information that OAR uses to ensure that the NIH HIV research program is flexible and that research priorities are responsive to emerging challenges and needs. OAR's third listening session report, which will cover sessions held between August 2021 and December 2022, is being finalized. A major theme that emerged during these sessions—support and expansion of the HIV research workforce, infrastructure, and resources—is directly within the NIH purview. Other major themes were relevant to the entire HIV response, including HIV across the life span, sociostructural factors that affect HIV risk and uptake of services, cultural competence and community engagement in HIV research, dissemination of health education information and research findings, and effects of the COVID-19 pandemic on the HIV response.

Listening sessions with federal, academic, and community partners inform OAR's focus on specific areas of interest and the current NIH priorities for HIV and HIV-related research. These multidisciplinary areas, designated as Signature Programs, guide current and future OAR activities and include agency-wide participation from NIH institutes, centers, and offices (ICOs).

The HIV and Aging Signature Program aims to catalyze collaborations to address research gaps and opportunities at the intersection of HIV and aging. The number of In FY22, this multifaceted portfolio was supported by 17 ICOs and an estimated $119 million. In the FY 2023 omnibus bill report, Congress encouraged OAR to fund interdisciplinary research and training programs in HIV and aging. This year, OAR and the National Institute on Aging (NIA) formed the NIH HIV and Aging Working Group, with representation from ICOs that support this research. The working group plans to link strategic partners across government agencies, academia, and community organizations to ensure that NIH research is aligned with community needs and cultural preferences.

Dr. Goodenow reviewed additional topics on the meeting agenda, including more details regarding HIV and Aging activities from NIA and OAR, new recommendations on infant feeding for individuals with HIV in the United States, a presentation on expanding inclusion in HIV treatment trials, and an update on the Advanced Research Projects Agency for Health (ARPA-H). The presentation on ARPA-H is part of OAR's ongoing series to highlight existing NIH resources that can be leveraged to advance HIV research.

Dr. Goodenow commented that OAR has coordinated NIH's HIV research agenda for 35 years, convening partners to catalyze interdisciplinary efforts. OAR's goal remains the same: to end the HIV pandemic and improve the health of people with HIV. Dr. Goodenow encouraged attendees to focus on actions to prevent, treat, and cure HIV, noting that these goals will require continued commitment, innovation, and creativity. She emphasized that any reduction in effort now would lead to a resurgence of HIV worldwide, compromising global health, and stressed

the need to remain nimble to respond to new challenges, leverage new and existing partnerships, and ensure all voices can contribute. Dr. Goodenow commented on the need to build a robust repertoire of options that can improve prevention and treatment strategies. The scientific agenda will continue to support innovative research in immunology, virology, behavioral and social sciences, and implementation science research, which is key for disseminating research discoveries to the communities that would benefit the most. Dr. Goodenow emphasized that ending the HIV pandemic is an ambitious, but feasible goal.

Discussion Highlights

When asked about parallels between the HIV/AIDS pandemic and the current COVID-19 pandemic, Mr. Westmoreland noted that there is overall less stigma and ignorance regarding COVID-19 than HIV. He stressed that Congress could learn to value the importance of professional judgment in supporting HIV/AIDS research and the need for politicians to listen to scientific experts and not question recommendations or try to develop their own theories.

In response to a question about how community listening sessions have been translated into action, Dr. Goodenow commented that the four OAR Signature Programs were developed based on recurring themes in listening sessions, particularly aging and early career investigator support. Dr. Luis Montaner commented on his participation in listening sessions; he and other OARAC members commended OAR for sponsoring these impactful and productive activities.

OARAC members pointed out that engaging stakeholders in the research agenda is critical to developing OAR activities and the NIH HIV research agenda. The OARAC recommended that OAR should continue to be involved with community groups in the future.

Mr. Westmoreland agreed with a comment about the importance of bipartisan support to securing HIV/AIDS research funding and the lack of bipartisan understanding on COVID-19, noting that the moderate viewpoints present in Congress during his tenure are less prevalent; he posited that significant breakthroughs in legislation are unlikely without bipartisan agreement.

When asked whether the Signature Program for HIV and Aging applies to infants born with HIV who now are adults, Dr. Goodenow pointed out that many such individuals were able to start antiretroviral therapy (ART) early in life, and some now are parents of children without HIV. The HIV and Aging Signature Program is intended to address HIV across the lifespan; the program is flexible enough to address different features of the life span for different groups of people. Dr. Goodenow added that including individuals born with HIV in listening sessions is also important.

In response to a question about incentives to retain early career investigators and postdoctoral researchers in academia, Dr. Goodenow noted that one approach is to work with subgroups to identify specific nuances and challenges. Postdoctoral researchers may be reluctant to comment on difficulties when faculty are present. OAR's programs have focused mostly on challenges faced by early career investigators seeking their first research grants, but Dr. Goodenow commented that the entire pipeline for developing scientific investigators needs to be examined for constrictions and solutions.

Healthy Aging with HIV: Advancing HIV Research at NIA

Richard J. Hodes, M.D., Director, NIA, NIH

Dr. Richard Hodes provided an overview of NIA's wide scope of research and its interests in HIV research and training. The FY 2023 appropriation included a specific increase for Alzheimer's disease (AD) and Alzheimer's disease–related dementias (ADRD) research. The NIA budget has risen steadily, and the AD/ADRD budget has risen very quickly. Recruiting from diverse backgrounds to supply this growing AD/ADRD research workforce is critical. From FY 2015 through FY 2022, about one-third of NIA's AD/ADRD awardees were new or early-stage investigators; about one-fifth of these investigators were new to the field. Several tools are available to help investigators recruit diverse study participants for AD/ADRD clinical trials, tailor recruitment strategies, and access real-time enrollment and inclusion data.

NIA has been working with OAR to promote healthy aging among people with HIV. About half of all people with HIV in the United States are age 50 or older, with about 17 percent of new HIV infections each year occurring in this age group. The field of geroscience links the studies of aging and chronic disease, investigating the genetic, molecular, and cellular mechanisms that make aging a major risk factor and driver of chronic conditions in older people. Expanding the current understanding of geroscience will help identify how HIV interacts with the aging process and accelerates aging-related changes. Priority areas of HIV and aging research within NIA include the interaction between HIV and aging-related genetic, molecular, and cellular changes and physiological outcomes; understanding molecular mechanisms common to multiple conditions comorbid with HIV; the contributions of individual, interpersonal, social, structural, and institutional factors to the well-being of persons aging with HIV and to social inequalities and health disparities; identifying relationships between HIV infection and cognitive decline; and enhancing the assessment and treatment of older individuals with HIV and comorbidities, polypharmacy, disability, or disparities in health outcomes.

Dr. Hodes pointed out that the N committee in the NIH UNITE Initiative—which focuses on new research on health disparities, minority health, and health equities—is most relevant to HIV and aging. NIA's Healthy Aging Start-Up Challenge, which aims to foster diversity and accelerate innovation in aging research, was launched in 2022. Dr. Hodes noted that many groups underrepresented in biomedical research have even less representation in entrepreneurial areas. The challenge winners were selected from 20 finalists; each received a $60,000 prize to begin development of a small-business application with continued mentoring. The Butler-Williams Scholars Program, a weeklong immersion program for junior faculty and researchers new to the field of aging, will be held virtually in August. Dr. Hodes noted upcoming virtual conferences, including an annual research summit on AD with a focus on care, services, and supports for people with dementia and their care partners and caregivers—which will include some overlap on challenges faced by individuals with HIV—and a summit on geroscience.

Discussion Highlights

When asked about promising intervention trials that could benefit people with HIV, Dr. Hodes pointed out that the longest-standing aging intervention generally is caloric restriction. Recent progress in identifying and eliminating senescent cells, which have adverse effects in many domains, has led to upcoming clinical trials of conditions in which senescent cells accumulate. Although the science is not yet applicable to HIV, Dr. Hodes commented that future impacts on eliminating chronic infection could be imagined.

Dr. Hodes noted that NIA's efforts to recruit investigators new to the field are relatively novel; the initiatives were well received when first presented, but other parts of NIH have not yet implemented similar programs.

HIV and Aging at NIH

Stacy Carrington-Lawrence, Ph.D., Division of Aging Biology, NIA, NIH
Basil Eldadah, M.D., Ph.D., Division of Geriatrics and Clinical Gerontology, NIA, NIH

Dr. Stacy Carrington-Lawrence explained that NIA's Division of Aging Biology promotes and supports research on HIV and aging to understand HIV infection and pathogenesis in the context of aging-related genetic, molecular, and cellular changes and physiological outcomes and works to understand molecular mechanisms common to multiple states comorbid with HIV. Many studies supported by the division focus on the hallmarks of aging and inter-organ communication, both affected by HIV infection. Hallmarks of aging are biochemical changes that lead to loss of functionality; and inter-organ communication is the gateway to metabolic health and whole-body homeostasis. The division supports geroscience research, focusing on the discovery and translation of biological targets for interventions on aging-related deficits, including interventions that affect both longevity and health span. Recent studies supported by the division have provided evidence of accelerated epigenetic aging from the time of initial HIV infection.

NIA's Division of Neuroscience supports HIV research focused on relationships between HIV infection and cognitive decline, especially in AD/ADRD and other neurological impairments in people with HIV and advancing age. The portfolio includes several collaborations between OAR and NIA to assess similarities in HIV-associated neurological complications and AD. Six studies have been supported through the NIA–OAR Pathogenesis of Age-Related HIV Neurodegeneration Request For Applications so far, with several important discoveries resulting. One study found that HIV infection does not increase the abnormal deposition of amyloid beta that is characteristic of AD, but longer HIV disease duration replaces chronological age as a risk factor for amyloid beta deposition.

Dr. Basil Eldadah explained that NIA's Division of Geriatrics and Clinical Gerontology supports clinical and translational research focused on assessing and treating older individuals with HIV and comorbidities, polypharmacy, disability, or disparities in health outcomes. Clinical aging research often uses a multimorbidity framework to describe an individual with multiple chronic conditions, recognizing that people's lives may be affected by conditions or syndromes in addition to their diagnosed co-occurring diseases, such as disability, falls, or hearing or visual impairments. Dr. Eldadah emphasized that the field needs to shift from treating each condition separately to understanding how multiple conditions interact with one another, focusing on the patient as an individual affected by multiple contexts. One study currently supported by NIA developed a model of multimorbidity for people aging with HIV that could project long-term clinical outcomes and compare strategies for prevention, diagnosis, and treatment of multiple co-occurring conditions. NIA's Grants for Early Medical/Surgical Specialists' Transition to Aging Research (GEMSSTAR) program provides research support for early medical and surgical specialists who transition to aging research and has supported eight awardees focused specifically on HIV and aging projects since its start in 2011.

NIA's Division of Behavioral and Social Research supports social, behavioral, psychological, and economic research and training to understand the contributions of individual, interpersonal, social, structural, and institutional factors to the physical, psychological, and economic well-

being of persons aging with HIV. This division supports both basic and intervention research focused on a broad range of topic areas. One example is a study of the effects of structural racism and discrimination on older men's health inequities, which aims to examine how layered stigma affects health outcomes for older gay men in four racial and ethnic groups and across HIV status.

NIH OAR HIV and Aging Signature Program

Geetanjali Bansal, Ph.D., Senior Science Advisor, OAR, NIH

Dr. Geetanjali Bansal provided an overview of the OAR HIV and Aging Signature Program and research portfolio. Some of the epigenetic changes associated with aging have been seen in younger people with HIV, but older adults with HIV face the same aging challenges as their peers without HIV, as well as some additional challenges. This group is more likely to experience such comorbidities as neurocognitive impairment, bone and muscle disorders, frailty, and cardiovascular disease. Polypharmacy and drug–drug interactions have become major issues. People aging with HIV face multiple intersectional stigmas, so this age group requires complex care and support services.

Aging with HIV requires a multidimensional response—the current HIV and aging portfolio is supported by 17 ICOs at a level of $119 million, or about 5 percent of the total HIV research budget. Over the past 5 years, five ICs have increased their HIV and aging research funding by 50 percent or more. HIV and aging research is conducted under all NIH research priorities, with the majority of the investment focused on crosscutting research and addressing treatments for HIV-associated comorbidities and coinfections. NIH funding in this area also helps expand the pool of clinicians trained in HIV and other relevant disciplines; two HIV and aging funding opportunity announcements are active.

OAR's HIV and Aging Signature Program aims to catalyze collaborations to address research at the intersection of HIV and aging. To further this goal, OAR has partnered with NIA to fund 1-year administrative supplements. The robust response to this program has resulted in 17 awards. OAR is collaborating with multiple other ICs to identify additional opportunities for supplements. NIA and OAR have formed a think tank to discuss research questions, community needs, and strategies to facilitate interdisciplinary research and acceleration of research results. Based on the think tank's recommendations, a multi-IC working group was launched. The group endeavors to link the community, researchers and relevant USG partners to foster collaborations, to identify research gaps and opportunities, and facilitate integrative research and training.

Discussion Highlights

In response to a question about the involvement of the AIDS Clinical Trials Group (ACTG) in NIA activities, Dr. Eldadah confirmed that NIA has ongoing conversations with ACTG leadership about aging questions and plans to continue this relationship.

Dr. Montaner encouraged OAR to discuss collaborations with the Martin Delaney Collaboratory for HIV Cure Research regarding long-term ART.

Dr. Monica Gandhi pointed out that the University of California, San Francisco (UCSF), has a GEMSSTAR program that supports comprehensive care for older people living with HIV. She commented on the need for more implementation science studies to accelerate care for people

with HIV who are aging. Dr. Bansal responded that NIA has and OAR have been discussing how to facilitate faster implementation of research results. One goal of the NIH HIV and Aging working group is to link relevant partners and discuss how to address those needs.

Dr. Melanie Ott noted that many clear molecular links with aging pathways have been discovered, but better molecular and mechanistic insights are needed to illuminate interactions that may have clinical applications.

Update: Infant Feeding for Individuals with HIV in the United States

Judy Levison, M.D., M.P.H., Professor of Obstetrics & Gynecology and Family and Community Medicine, Baylor College of Medicine; Member, Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission

Theodore Ruel, M.D., Professor of Pediatrics, Chief, Division of Pediatric Infectious Diseases and Global Health, Director, Pediatric Infectious Diseases Fellowship, UCSF Benioff Children's Hospitals; Co-Chair, Panel on ART and Medical Management of Children Living with HIV

Dr. Judy Levison outlined the changes to recommendations for infant feeding in the Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal Transmission in the United States, which were updated on January 31, 2023. In the past, the Guidelines advised against breastfeeding by mothers with HIV. With the most recent update, the Guidelines now support parental choice through shared decision-making with providers rather than a specific infant feeding method. Considerations include the health benefits associated with breastfeeding for both infants and parents, equity concerns, and cultural sensitivities. Without maternal ART or infant ART prophylaxis, the risk of the infant acquiring HIV through breastfeeding is estimated to be 15 to 20 percent over 2 years. Maintaining viral suppression through ART during pregnancy and postpartum decreases the breastfeeding transmission risk to less than 1 percent, although not zero.

Dr. Theodore Ruel reviewed the new perinatal HIV guidelines content. For people with HIV who are not on ART or do not have a suppressed viral load at the time of delivery, the guidance has not changed—replacement feeding with formula or banked pasteurized donor human milk is recommended to eliminate the risk of HIV transmission. The new content addresses individuals with HIV on treatment who have a consistently suppressed viral load during pregnancy (at a minimum throughout the third trimester), as well as at the time of delivery. The Guidelines recommend that such individuals be counseled openly on different options for infant feeding. This counseling should center on two points: (1) infant feeding options that eliminate the risk of transmission are formula and pasteurized human donor milk, and (2) fully suppressive ART during pregnancy and breastfeeding decreases breastfeeding transmission risk to less than 1 percent, but not zero. The updated guidance outlines situations in which stopping or modifying breastfeeding are recommended. In the case of a detectable viral load, breastfeeding should be temporarily stopped. If a repeat viral load is detected, the Panels advise immediate cessation of breastfeeding.

Panelists' opinions differed on antiretroviral (ARV) prophylaxis for infants of individuals with sustained viral suppression who are breastfed. Dr. Ruel pointed out that this update includes significant amounts of new content about management; much of this content is based on expert opinion. Dr. Ruel emphasized that engaging Child Protective Services or similar agencies is not an appropriate response to the infant feeding choices of an individual with HIV; such engagements can be extremely harmful to families, exacerbate the stigma and discrimination experienced by people with HIV, and be disproportionately applied to minoritized individuals.

The updated Guidelines include community input, input from lactation specialists at the Centers for Disease Control and Prevention (CDC), and collaboration between the Perinatal and Pediatric Guidelines Panels. Dr. Ruel pointed out that CDC now refers queries about infant feeding in the United States to the Perinatal Guidelines rather than maintaining its own recommendations. Interest in this issue has been increasing among providers across the country; surveys show that providers are uncomfortable with this issue and the lack of institutional guidance. Patients also struggle to navigate infant feeding in the absence of more guidance, leading to mistrust of health care providers. The updates restore trust and leave space for open discussion and patient choice. Dr. Ruel encouraged attendees to consult the Guidelines website and the National Clinician Consultation Center.

Expanding Inclusion in HIV Treatment Trials Workshop

Veronica Miller, Ph.D., Executive Director, Forum of Collaborative Research, University of California, Berkeley

Dr. Veronica Miller reported on a workshop on expanding inclusion in HIV treatment trials, with the goal of improving access to long-acting ART for people who most need such therapies, including people with challenges adhering to a daily oral regimen and people who are historically underrepresented in research. Access includes factors beyond the ability to acquire the treatment, such as existence of evidence-based recommendations for safe and effective use, availability and administration of treatment, and reimbursement options.

Many people who could benefit from new therapeutic interventions are excluded from early clinical research for safety concerns, including those designated “special populations,” such as people who inject drugs or experience mental health challenges or other comorbidities. Patients in rural settings far from traditional clinical trial centers often cannot participate in trials and may have different issues from people living in urban centers. Although there are reasons to be cautious about safety in early trials, researchers need to plan to include more people in clinical trials as early as possible. Information on the safety and efficacy of new therapies in real-world patients often is lacking at the time of marketing approval. Currently, only one long-acting injectable regimen, cabotegravir-rilpivirine, is approved for treatment. It is indicated only for people who are already virologically suppressed, with no previous treatment failures and no relevant resistance mutations. Lessons from the first iteration of long-acting ART should be applied to future developments, including planning ahead for a seamless transition to diverse populations before the time of approval.

The workshop aimed to discuss challenges in clinical trials assessing long-acting ART for populations most at need for such therapies and to recommend solutions. Participants learned that hepatitis C virus pre-approval trials included people who are actively injecting drugs, demonstrating that they can be involved successfully, including before marketing approval. Dr. Miller commented that the message of this session is to be brave and plan carefully and inclusively. One presentation demonstrated the cost-effectiveness of long-acting psychiatric therapies and implementation within communities, showing that cost-benefit ratios improve over time and that an initial investment in long-acting therapies pays off. She added that researchers should consider the community outreach implementation model and co-implementation programs.

The patient perspective session described long-acting therapies as “life changing.” Reasons for preferring long-acting therapy were as diverse and heterogenous as patients. Workshop presentations emphasized that investigators need to respect the communities they serve,

including the real or perceived threats under which some populations operate. Dr. Miller emphasized that patients need to be recognized in research and policy discussions and that long-acting ART should be available to all. A session on research opportunities in rural America touched on the Institutional Developmental Awards (IDeA) States Consortium for clinical Research (ISCORE) Network, which builds capacity for clinical research, and the fact that rural areas are hot spots for HIV incidence despite the paucity of clinical trials. ISCORE's contributions to COVID-19 research show that rural and other nontraditional research centers have the capacity, patients, and resources to participate in trials and that nontraditional sites should be considered for publicly and privately funded HIV research.

Dr. Miller noted the need to balance standard trial designs for efficient approval with earlier inclusion of adherence-challenged patients. When drugs are known to be effective, trials are needed in specific populations to assuage any concerns about safety issues. These studies can focus on safety monitoring in single-arm studies in relevant populations; some post-approval opportunities for trials exist as well.

The key take-home points from the workshop were that engaging individuals from populations historically underrepresented in long-acting ART clinical trials with high levels of success is possible; although safety is a concern, long-acting ART can be lifesaving for patients at the end of oral treatment options. Dr. Miller outlined the recommendations generated by the workshop. Researchers should work collaboratively to generate useful data for treatment Guideline Panels and regulatory authorities. Multiple avenues for data should be used to ensure that all options are explored. Approaches should combine the drug regimen and behavioral support. Research should be inclusive. Researchers should learn from existing proof-of-concept clinics, such as UCSF affiliated HIV clinic Ward 86, to find implementable options. Low- and middle-income countries should be considered.

Discussion Highlights

Dr. John Sleasman recommended publicizing the new infant feeding recommendations broadly outside the Guidelines and website, engaging other groups for endorsement, and providing granular information to reduce the confusion and pushback that could occur.

When asked about engaging people with lived experience in the development of studies, Dr. Miller agreed that such inclusion will be important to recognizing the full experience of the people clinical trials are serving.

Dr. Gandhi commended the Guidelines Panels for the infant feeding update and noted that ACTG has requested a study on long-acting ART.

ARPA-H: The Mission

Renee Wegrzyn, Ph.D., Director, ARPA-H

Dr. Wegrzyn provided an overview of ARPA-H, which aims to accelerate better health outcomes for everyone. ARPA-H focuses on supporting the exploration of audacious ideas through a model that differs from how research and commercial products usually are supported in the United States. ARPA-H is situated within the U.S. Department of Health and Human Services (HHS) and is intended to catalyze the entire HHS system. It is not an ICO, but it is located within NIH, which allows the organization to begin its work quickly and access support systems, such as payroll and benefits, as well as subject matter experts when programs begin operation.

The ARPA-H ecosystem will be led by program managers as decision-makers shepherding the projects. Funding will use cooperative agreements and Other Transaction Authority mechanisms to ensure ARPA-H remains engaged in the project. Because ARPA-H is intended to be a catalyst for the health ecosystem and is strictly a funding agency, it has no internal research laboratories. Congress has capped its workforce at 210 federal employees, including 100 program managers, but ARPA-H will supplement this level with a flexible contractor workforce to maintain adequate support for the current projects. ARPA-H will update its partners on progress regularly to ensure that projects are on track to serve the American people.

Program managers will be appointed for a 3-year term, with an optional 3-year extension; programs are expected to last between 2 and 4 years. The ARPA-H portfolio will be dynamic and a reflection of the program managers, who will be the nucleus of the organization, with high levels of autonomy that allow them to take risks. Only projects with the potential for radical change will be supported.

Dr. Wegrzyn emphasized that the programs will be well resourced but very focused on achieving the goal. Transition is a key element of ARPA-H—programs must be able to graduate from ARPA-H and exist in the real world. The private sector is necessary to support these transitions, with program partners involved from the start and able to scale the solution for large, diverse communities everywhere.

Multiple programs will run simultaneously and can be at different stages of the life cycle between design and transition. Insights from experts will help program managers understand the marketplace for solutions to difficult and well-defined health problems Initial mission focus areas will include health science futures, scalable solutions, proactive health, and resilient systems. ARPA-H's Project Accelerator Transition Innovation Office (PATIO) will work from the beginning of a program to ensure that solutions can be transitioned to real-world use at the end of the program life cycle.

Discussion Highlights

When asked how to balance equity and inclusion with high-risk projects and frequent turnover, Dr. Wegrzyn emphasized that program managers must outline a clear plan for equity before their program is approved.

When asked whether transformational goals are achievable in such a short time frame, Dr. Wegrzyn explained that the final status of each program is not restricted to a particular technology level—not every program will end with a fully developed technology, but the risk of the solution must be reduced. She clarified that ARPA-H is not meant to fund the entire development process but only the spark.

In response to a question about network bias, Dr. Wegrzyn pointed out that PATIO will work to reduce bias by working proactively to fund outside the usual networks, ensuring stakeholder involvement, and publicizing announcements widely to reach new people.

Updates from the NIH Advisory Council Representatives

National Advisory Mental Health Council (NAMHC)

Marguerita Lightfoot, Ph.D., Associate Dean for Research, Oregon Health & Science University and Portland State University School of Public Health

Dr. Marguerita Lightfoot provided updates from the recent NAMHC meeting. The National Institute of Mental Health (NIMH) director reported on the record $2.3 billion NIMH budget, which includes $25 million to expand research on COVID-19 and mental health. New NIMH initiatives include involvement in the Roadmap for Behavioral Health Integration released by HHS; support for new data-sharing requirements; and participation in administrative supplements for Diversity, Equity, Inclusion and Accessibility mentorship (NOT-OD-23-022) and research opportunities for new and "at-risk" investigators to promote workforce diversity (PAR-22-181). In addition, NIMH released a *Strategic Framework for Addressing Youth Mental Health.*

The NAMHC received an update on global mental health research from the director of the NIMH Center for Global Mental Health Research, which aims to strengthen the research capacity in global mental health and increase the body of evidence related to mental health interventions in low- and middle-income countries (LMICs). The power of cross-group learning and reciprocal learning between LMICs to scale up interventions effectively was emphasized.

Dr. Lightfoot reviewed a Division of AIDS Research concept titled "Mechanisms of Reciprocal Interactions Between HIV-Associated Neuroinflammation and Central Nervous System (CNS) Persistence: Implications in HIV Neuropathogenesis and Cure" that was cleared by the NAMHC. The goal of the concept is to encourage research using novel CNS cell systems, brain organoids, and single-cell technologies to examine mechanisms of reciprocal interactions between HIV-associated neuroinflammation and HIV persistence in the CNS despite effective ART.

National Advisory Council on Drug Abuse (NACDA)

Melanie Ott, M.D., Ph.D., Director, Senior Investigator, Gladstone Institute of Virology and Immunology; Professor of Medicine, UCSF

At the request of the NACDA, Dr. Ott shared two scientific articles. She highlighted one study published in *Molecular Cell* showing that 3-D genome remodeling in microglia represses neural genes in HIV and HIV encephalitis. HIV is actively transcribed in a subset of highly active microglia and targets genomic regions that switch to a more open state during HIV infection. The second article, which was published in *PLOS Pathogens*, focused on a CRISPR screen to identify epigenetic pathways contributing to HIV latency. The screen identified the inhibitor of growth family member 3 gene as a novel epigenetic factor involved in maintaining latency.

The National Institute on Drug Abuse (NIDA) concepts for fiscal year 2024 have been finalized. The concepts include "The Neuro-Immune Axis: Therapeutic Approaches in the Context of HIV and Addictive Drugs," which aims to support research identifying biological targets and pathways that regulate neuroimmune interactions at the intersection of HIV and substance use, and "Microglial Pathophysiology in Comorbid HIV and Substance Use Disorder (SUD)," which aims to generate microglial profiles of various brain regions and cell types in the context of HIV and SUD.

AIDS Research Advisory Committee (ARAC)

Monica Gandhi, M.D., M.P.H., Professor of Medicine and Associate Chief, Division of HIV, Infectious Diseases, School of Medicine, UCSF; Global Medicine Director, UCSF-Gladstone Center for AIDS Research; Medical Director, "Ward 86" HIV Clinic, San Francisco General Hospital

Dr. Gandhi provided updates from the recent ARAC meeting, including remarks on the National Institute of Allergy and Infectious Diseases (NIAID) budget and paylines. The ARAC discussed how NIAID funding could contribute to pandemic preparedness after Congress did not approve funding for the pandemic preparedness initiative. The group emphasized the significant but underappreciated contributions to public health that NIH provided during the COVID-19 pandemic, including research and clinical trials related to COVID-19 vaccines and therapeutics through the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) network. The ARAC reviewed factors that contributed to successful outcomes during the COVID-19 pandemic (e.g., ACTG expertise, Division of AIDS [DAIDS] expertise, ACTIV framework for agent selection, broad enrollment and use of existing resources) and areas for improvement (e.g., study delays because of international regulatory timelines, time required to build new infrastructure, inability to pivot quickly because of complex trial designs, inefficient leveraging of real-world evidence).

The ARAC discussed several DAIDS research programs. Under the umbrella of the DAIDS Vaccine Research Program, results from the "Mosaico" Phase 3 clinical trial conducted by the HIV Vaccine Trials Network showed that an experimental HIV vaccine regimen was safe but ineffective. The study will be discontinued. Much more promising is the use of mRNA delivery for an HIV vaccine, which results in broadly neutralizing antibody precursors in humans. The Therapeutic Research Program at DAIDS is weighted toward clinical trials related to cures and treatments for HIV, COVID-19, and other infections. Goals for the next phase of HIV treatment include new long-acting treatments and associated strategies. The Prevention Science Program (PSP) at DAIDS prioritizes diverse goals, including the development of HIV prevention products; improved engagement of key populations; and optimized strategies to diagnose, treat, and prevent tuberculosis in maternal and pediatric populations. Highlighted PSP accomplishments in 2022 included regulatory approval of long-acting injectable cabotegravir for pre-exposure prophylaxis in South Africa, Zimbabwe, and Australia; regulatory approval of Triumeq for pediatric patients with HIV; ongoing trials of HIV monoclonal antibody combinations; and promising results from studies of the dapivirine ring in breastfeeding mothers. PSP soon will release the request for proposals (RFP) relating to Resources to Advance Pediatrics and HIV Prevention Science contract and discussed establishment of international collaborations on pediatric HIV treatments.

NIH HIV/AIDS Executive Committee

Geetanjali Bansal, Ph.D., Senior Science Advisor, OAR, NIH

Dr. Bansal reviewed concepts and funding opportunity announcements related to HIV cleared by IC advisory councils and published since the previous OARAC meeting. Between October 2022 and February 2023, 29 HIV-related concepts were cleared by the advisory councils of NIAID, NIDA, NIMH, NICHD NIAMS, NIDCR, NIAAA, NIMH, and ORIP, comprising 17 new concepts and 12 reissues.

HIV Clinical Guidelines Working Groups of OARAC Updates

Overview of HIV Clinical Practice Guidelines Processes

Roy M. Gulick, M.D., M.P.H., Professor in Medicine, Chief of the Division of Infectious Diseases, Weill Medical College of Cornell University; Panel Co-Chair, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

Dr. Roy M. Gulick provided an overview of processes related to the HIV Clinical Practice Guidelines, which are managed by five OARAC Working Groups. Dr. Gulick described the history of the *Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV* (Adult and Adolescent ARV Guidelines). The HHS Adult and Adolescent ARV Guidelines Panel was first convened in 1996 to provide evidence-based guidance on safe and effective use of ART after regulatory approval of the first HIV protease inhibitors. The first Guidelines were published in 1998. In 2005, the Guidelines Panel formally became an OARAC Working Group. The Panel structure of the Adult and Adolescent ARV Guidelines comprises 1 Executive Secretary, 2 Co-chairs, 5 HHS members, 38 clinical or scientific members, and 5 community members. Non-HHS members are selected through open applications. The Panel oversees 21 writing teams, each of which consists of 1 or 2 lead authors and 4 to 12 members.

The development or revision of the Guidelines begins with a review of the relevant literature and identification of gaps for updating. Initial section drafts are reviewed by the full Panel via conference call after being finalized by the writing team. Feedback from the Panel is used to revise each section as needed. The Panel votes on each new recommendation and provides final approval of all sections. After Panel approval, the sections are submitted to HIVinfo for editing. Sections are published after being reviewed and finalized by the Executive Secretary, Chairs, and editors. Completion of section revisions requires 4 to 9 months of effort. All writing teams work simultaneously; updates to the Guidelines generally are released annually. Specific guidance can be released when new issues (e.g., the COVID-19 pandemic) warrant rapid communication.

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Henry Masur, M.D., Senior Investigator, Critical Care Medicine Department, NIH; Panel Lead, Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Dr. Henry Masur presented on the *Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV* (Adult OI Guidelines). Dr. Masur noted that the Adult OI Guidelines received 483,748 page views in 2022, making them the second-most accessed HIV Clinical Practice Guidelines. The Pneumocystis Pneumonia section was the most commonly viewed section of the Adult OI Guidelines in both 2021 and 2022. The sections, including those that are infrequently accessed, are updated on an *ad hoc* basis. Most recently, treatment recommendations and a drug interaction table in the Hepatitis C Virus section were updated. Updates to the roster, Table 2 (on treatment of HIV-associated OIs), and the Cryptosporidiosis section recently were published, and other section updates are coming soon. Tables are being simplified to improve readability. Person-first language is being implemented in all sections. The Adult OI Guidelines are written in partnership with the CDC, HIV Medicine Association, and Infectious Diseases Society of America. All three organizations review changes to the recommendations.

Discussion Highlights

OARAC members asked whether guidance on caring for people with HIV during clinical trials will be published, noting that providers must be educated on this topic to enable a diverse population of people with HIV to participate in trials. Dr. Masur pointed out the development of clinical guidelines for HIV is expensive and time consuming. He wondered whether such an effort was beyond the scope of NIH. Dr. Gulick agreed.

Dr. Goodenow requested that OARAC members comment on the link between clinical care and the NIH mission to develop products that are implemented in clinical care. Dr. Miller noted that the Guidelines could include information about clinical trials and future treatment options. Expanded access (also known as "compassionate use") is one area where clinical care and drug development overlap. This area could be discussed in the Guidelines. Dr. Masur commented that the Panels might not have sufficient resources to perform this task effectively.

Dr. Montaner asked whether the number of international page views for particular sections of the Adult OI Guidelines had been evaluated. Dr. Gulick answered that most page views come from within the United States. Dr. Masur pointed out that intentionally promoting the Guidelines to an international audience was a complicated issue because they are published by U.S. health care providers under the auspices of a federal entity of the United States. CAPT Mary Glenshaw commented that page view metrics are collected by location and can be shared upon request. In particular, the Guidelines related to OIs have many international page views because international OI guidance is uncommon. Dr. Miller expressed interest in reviewing the page view metrics of the Guidelines.

OARAC members discussed improving access to treatment and prevention trials for people who use or inject drugs, The increasing overlap between treatment and prevention regimens should enable this population's ability to access clinical trials.

RDML Mermin asked whether OAR could support syndemic approaches to helping people with HIV. He provided an example that is currently being considered by the CDC of a high-throughput test for chronic infections to help inform patients of their coinfection status. Dr. Goodenow responded that such efforts do fall under OAR's purview. Given OAR has a finite budget, the current challenge is to prioritize areas that are intimately related to HIV research.

In response to a question regarding how the Guidelines view off-label use of HIV therapeutics (e.g., use of long-acting ART in people with HIV that is not suppressed). Dr. Gulick shared that the Guidelines consider U.S. Food and Drug Administration indications carefully but are not bound by them. Recommendations can be based on anecdotal data.

Public Comment

CAPT Mary T. Glenshaw, Ph.D., M.P.H., OAR, NIH

CAPT Glenshaw summarized a comment from Mr. Jules Levin of the National AIDS Treatment Advocacy Project, who thanked NIH for the discussion on aging with HIV but expressed concern that NIH is not meeting the needs around people with HIV and aging. People with HIV, particularly those age 65 and older, are more likely to suffer comorbidities with earlier onset and at higher prevalence than their peers without HIV. He acknowledged the broad NIH research efforts but emphasized the need to expand beyond basic and translational approaches. Mr. Levin advocated more research on HIV and aging through the ACTG network. *[The full text of this comment appears at the end of this document].*

Closing Remarks and Adjournment

Maureen M. Goodenow, Ph.D., OAR, NIH

Blanton Tolbert, Ph.D., OARAC Chair, Professor, Case Western Reserve University

CAPT Glenshaw and Dr. Goodenow thanked Dr. Tolbert for his service as chair. Dr. Goodenow thanked the Council members and speakers and reminded attendees that the June 22 meeting is scheduled to be in a hybrid format. Dr. Tolbert adjourned the meeting at 4:06 p.m. EST.

Certification

I hereby certify that, to the best of my knowledge, the foregoing summary minutes are accurate and complete.

Blanton Tolbert, Ph.D.
Chair, OARAC

7/25/23
Date

Mary Glenshaw -S Digitally signed by Mary Glenshaw -S
Date: 2023.05.26 12:06:33 -04'00'

CAPT Mary Glenshaw, Ph.D., M.P.H.
Executive Secretary, OARAC

5/26/2023
Date

Public comment received: 1:02 pm on March 2, 2023
Comment made by: Jules Levin, National AIDS Treatment Advocacy Project

Hello OARAC Members

Thanks for your discussion around aging & HIV today and thanks for hearing & listening to my concerns and from others around this problem which I and others have voiced with many of you & the OAR. But our main concerns remain unmet.

Aging with HIV is a major problem for older PLWH over 50 but much worse for many PLWH over 65. Older PLWH are suffering earlier onset for comorbidites & multicomorbidities and in higher numbers compared to people without HIV of similar age. As well mortality is higher by 9 years among PLWH according to the Kaiser Permanente Study presented by Julia Marcus at CROI & published.

Our elderly (>65) and older (>50) PLWH are all too often not receiving the care they need, their care needs are often unmet due to underfunding & insurance reimbursement restrictions at the clinic level. Geriatric screenings that should be performed are mostly not performed in HIV clinics and Geriatric Care is not provided in most HIV clinics including at major medical center hospital based large HIV clinics.

In essence again the needs of older PLWH & elderly PLWH are not being met in the clinic, and this needs change before more people decline further with severe mental & physical impairment, and suffer premature death.

Regarding aging & HIV research, despite your broad effort - it is no longer enough to conduct mostly translational & basic science aging & HIV research. The current aging & HIV research agenda needs to be updated to better address current clinical needs & developments accruing to our aging population, which require more & wider in scope new & innovative research including implementation research that includes providing opportunities to improve and help support clinical care for older and elderly PLWH and to provide the geriatric care & screenings they must receive but are not receiving.

The HIV aging advocacy community who have been having ongoing discussions around this problems need & want to and look forward to having direct discussions with the OAR and all of you around these matters of great concern. Some of us were not part of the OAR community listening sessions.

As I have said to the NIA and as Dr Gandhi mentioned today better clinical care & implementation research is needed & can be provided to improve clinical care.

Community have been left out of your Aging WG. I would like to participate in that.

The ACTG is blocked or it's been made much too difficult to get funding support for ACTG aging & HIV research. ACTG researchers have been unable to conduct aging & HV research with subsidies that require mandatory approval by every institute that is now required to be involved for each & every subsidy, this makes it impossible to conduct much aging research. The ACTG designed an aging senoylytics study that DAIDS refused to fund.

As well perinatally acquired PWH who are now young adults are experiencing increased comorbidities and this needs attention. They need good care.

By the way some HIV neurology research suggest PLWH may be at greater risk for alzheimers.

Jules Levin
National AIDS Treatment Advocacy Project