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

Office of AIDS Research Advisory Council
Forty-Ninth Meeting

November 15, 2018
5601 Fishers Lane, Room 1D13
Rockville, Maryland

Draft Meeting Minutes

Council Members Present: Dr. Charles Wira (Chair), Dr. Jay Radke (Executive Secretary), Dr. David Celentano,* Dr. John J. Chin, Dr. Elizabeth Connick, Dr. Scott D. Rhodes

***Ad Hoc* Members Present:** Dr. Ingrid V. Bassett, Dr. Margaret L. Brandeau, Dr. Tricia H. Burdo, Dr. Heidi M. Crane, Ms. Linda M. Dee, Dr. Maureen M. Goodenow (OAR Director), Dr. William G. Powderly, Dr. Kimberly K. Scarsi, Dr. Bruce R. Schackman, Dr. David M. Smith, Dr. Babafemi Taiwo

***Ex Officio* Members Present:** Dr. Julie Ake,* Dr. John Brooks, Dr. Victoria Davey, Dr. Carl Dieffenbach, Dr. Roy M. Gulick

Advisory Council Representatives Present: Dr. Alan E. Greenberg, Dr. Nancy Raab-Traub

Invited Speakers and Guests: Dr. Stacy Carrington-Lawrence, Dr. Nahida Chakhtoura, Dr. Rohan Hazra, Dr. Sheri Hild, Dr. Mackiewicz, Dr. Alice Pau, Dr. Yvette Edghill Spano, Dr. Carolyn Williams

Council Members Absent: Ms. Dázon Dixon Diallo, Dr. Jennifer Kates, Dr. Lynne M. Mofenson Dr. Jonah B. Sacha, Dr. Blanton S. Tolbert

*Participated remotely.

Welcome and Meeting Overview
Charles Wira, Ph.D., Geisel School of Medicine at Dartmouth

Dr. Charles Wira welcomed participants to the forty-ninth meeting of the National Institutes of Health (NIH) Office of AIDS Research Advisory Council (OARAC). Meeting materials provided to council members included the agenda, a conflict-of-interest form, and minutes from the forty-eighth OARAC meeting, held on July 12, 2018. Dr. Elizabeth Connick moved to accept the draft minutes from the forty-eighth OARAC meeting; the motion was seconded by Dr. John Chin. Members of the council voted to approve the minutes. Dr. Wira reviewed the forty-ninth meeting agenda, noting the inclusion of time for public comments.

Report of the Office of AIDS Research (OAR) Director
Maureen M. Goodenow, Ph.D., OAR, NIH

Dr. Maureen Goodenow welcomed the attendees and confirmed the next OARAC meetings on March 28, June 27, and November 7, 2019. The half-day orientation, held for the first time the

day prior, will be an annual occurrence prior to the autumn meeting. Dr. Goodenow updated the attendees on changes to OAR's staff since the previous meeting, including new staff members Drs. Brenda Frederickson and Colleen Choi, and noted that the OAR continues to recruit for several positions, including the deputy director.

This year, Congress passed its funding authorization at the beginning of FY 2019; the authorization includes an overall increase for the NIH, continued funding for the 21st Century Cures Act, and HIV/AIDS research funding at the same level as the FY 2018 enacted budget.

The NIH Strategic Plan for HIV and HIV-Related Research for fiscal years (FYs) 2019–2020 was posted recently. Dr. Goodenow explained that in 2018, the OAR restructured the NIH HIV/AIDS research planning and budget processes to support the transition from annual toward a 5-year strategic plan, which will allow the strategic plan to serve as a guiding document for the Congressional Justification and Professional Judgment budget documents.

The NIH FY 2019–2020 Strategic Plan outlines NIH's role in developing impactful research for HIV and addresses the complex and evolving dynamics of the epidemic and needs of people with HIV. A recent presentation by the OAR to the Office of Management and Budget outlined the harmonious relationship between the National HIV/AIDS Strategy, developed by the U.S. Department of Health and Human Services (HHS), and the NIH Strategic Plan for HIV/AIDS Research. The new NIH strategic plan timeframe will align with that of the next National HIV/AIDS Strategy, allowing the NIH and HHS to work together more effectively.

The next plan will cover 5 years, from FY 2021 through FY 2025. The FY 2021–2025 Strategic Plan will be the first to cover a period of 5 years. The OAR will assess progress on the plan annually, but eliminating the need for annual rewrites will allow OAR staff more time to focus on achieving the mission. Dr. Goodenow emphasized that many in the HIV/AIDS field have a high level of confidence in the current priorities as the appropriate framework for the research, supporting both continuity for ongoing efforts and flexibility to address emerging issues.

Dr. Goodenow pointed out some of the high priorities and emerging needs the OAR has addressed and supported in 2018. Funding for dolutegravir research was increased to address emerging data that suggested a possible connection to birth defects. The Multicenter AIDS Cohort Study and Women's Interagency HIV Study (MACS-WIHS) cohort is in the final stage of transitioning its primary control to the National Heart, Lung, and Blood Institute, but integration with multiple NIH Institutes, Centers, and Offices (ICOs) will be maintained. The U=U policy, which emphasizes that people who take treatment as prescribed and maintain an undetectable viral load have effectively no risk of transmitting the virus to an HIV-negative partner, has relieved a significant amount of stigma associated with HIV.

In terms of future OAR projects, Dr. Goodenow explained that World AIDS Day would occur on November 30, 2018, and would focus on celebrating the impact of basic science research on public health in the HIV/AIDS area and ensuring that research support continues. The OAR has increased its focus on data analytics, which will help OAR staff assess how HIV/AIDS research in a variety of areas is organized across ICOs and identify opportunities for increased investment, such as knowledge gaps and developing projects to which resources can be transferred.

Dr. Goodenow recommended further assessment of the use of nonhuman primates (NHPs) and increased attention to rural health in relation to the HIV epidemic. OAR staff will identify potential

big-data projects across the HIV portfolio and inventory the existing data associated with HIV research to determine how to harmonize the data with NIH's other high-priority initiatives.

Future activities mandated by the OAR's authorization include the FY 2020 budget planning process and harmonization with the National HIV/AIDS Strategy. OAR staff will assess the HIV/AIDS research priorities as defined in OAR's initial authorization and ensure that current efforts maintain ideal trajectories.

Dr. Goodenow commented on the need to track the epidemic closer to real-time. The expanded use of electronic medical records and the need to track adverse events related to the opioid epidemic have improved data collection times. Dr. Goodenow noted that most new HIV diagnoses as of 2016 occurred in synchrony with locations where greater numbers of people with HIV live. Although a majority of new diagnoses still occur during the middle of the lifespan, significant percentages of new diagnoses occur in youth and people older than 50 years of age.

Dr. Goodenow noted that more than half of the new diagnoses are occurring in the South. The locations and numbers of new diagnoses remained similar between 2010 and 2016; Dr. Goodenow emphasized that although the lack of increase is encouraging, it suggests that lowering the numbers will be difficult. Disaggregating the data, such as assessing differences between rates of new infection in men and women, will help illuminate the complexities of the epidemic. The OAR is assessing how the HIV research investment aligns with the actual progress of the epidemic; a resource distribution analysis shows concentrations in the Southeast and the North and on the West Coast.

Dr. Goodenow commented on some of the challenges, including the difficulty of reducing new infection rates and balancing flat research funding with rising costs. Additionally, complexities of demographics and co-occurring medical conditions require nuanced and creative strategies. Dr. Goodenow emphasized that data can identify opportunities and gaps, which will help to focus the research to reach the desired outcomes and improve public health.

Discussion Highlights

In response to a comment about older populations with HIV, Dr. Goodenow reflected on partnerships with the National Institute on Aging (NIA) that support creative research on the intersections of HIV with Alzheimer's disease and other neurodegenerative conditions. Cardiovascular comorbidity research can be studied more comprehensively following the reorganization of the MACS-WIHS.

Attendees commented on the historic tendency to emphasize the NIH's role in discovery research and the need to emphasize translational research equally to improve population health. Antiretroviral therapy (ART) is an effective treatment developed with taxpayer investment, but large percentages of the global population with HIV are not receiving treatment that controls the virus. Dr. Goodenow emphasized that although the NIH's focus is on research, ensuring that the research is implemented remains a high priority. Dr. John Brooks added that living well with HIV is an issue that is important to multiple agencies and jurisdictions; he suggested a future effort to identify areas of crossover between agencies, including the Health Resources and Services Administration (HRSA).

When asked about the intersection between HIV and the opioid epidemic, Dr. Goodenow clarified that the high rates of HIV infection in the South overlap with hot spots of the opioid crisis; 10 percent of the new HIV diagnoses in the United States are thought to be associated

with injection drug use, possibly because of the opioid crisis. She emphasized the opportunity to collaborate with the National Institute on Drug Abuse (NIDA).

Updates to the HHS HIV/AIDS Treatment and Prevention Guidelines from the Working Groups of the OARAC

Roy (Trip) Gulick, M.D., M.P.H., Weill Medical College of Cornell University
Nahida Chakhtoura, M.D., Eunice Kennedy Shriver *National Institute of Child Health and Human Development (NICHD), NIH*
John Brooks, M.D., Centers for Disease Control and Prevention (CDC), HHS

Dr. Trip Gulick demonstrated that a significant number of people consult the treatment and prevention guidelines; the rates of use are increasing. Although the download rates for the guidelines are decreasing, use of the guidelines app has increased, reducing the number of downloads required for the entire file. The guidelines now can be searched, allowing the working groups to identify the most popular search terms. Brief versions of the guidelines have been released, so users can find information without navigating the entire guidelines document. The brief guidelines combine the recommendations and tables, which are the most frequently consulted sections, and use the same content as the full guidelines.

In 2018, all five panels convened to update existing guidance for non-HIV-specialized providers caring for people with HIV who have been displaced by disaster events; advice for caring for people who are on methadone maintenance therapy, regardless of whether they have HIV, was a key addition.

The adult ART guidelines were updated on October 15, 2018, including reactions to the recent information about dolutegravir's potential association with neural tube defects, information about three ART drugs newly approved by the U.S. Food and Drug Administration, and comments on newly approved fixed-dose combinations. Updates to a number of sections and tables were made to better reflect current data. The guidelines now recommend proviral DNA genotypic testing as an alternative to the phenotypic test to identify those who might have CCR5-using virus.

Dr. Gulick reminded attendees of the data gathered in May 2018 that suggested dolutegravir use in pregnant women may be related to birth defects. In collaboration with the perinatal guidelines working group, each mention of dolutegravir was updated to reiterate the new data. A pregnancy test now is recommended prior to dolutegravir initiation for those with childbearing potential; the guidelines recommend that providers discuss the risks and benefits with the patient. New recommendations advise against dolutegravir for persons who are pregnant or might become pregnant if other ART options are available.

The current "Where to Start" section recommends integrase inhibitor–based regimens for most people, with newer options added and less effective options removed. Additionally, the recommendations have been updated to address the most current information on certain clinical situations that require treatment regimens that are less common, including guidance for dolutegravir use. A newer, expanded section provides recommendations for optimizing ART in the setting of virologic suppression and emphasizes the importance of using cumulative resistance testing and proviral genotypic testing.

Dr. Brooks explained that members of the adult opportunistic infection guidelines' leadership group represent the NIH, Infectious Disease Society of America, HIV Medical Association, and CDC. Subject-matter experts are appointed for 3-year terms, with consideration of diversity and

succession planning, which is particularly important for maintaining up-to-date information on diseases that have become rarer. The lead for each subject group distributes a quarterly literature review, and then the group discusses how to update the guidelines. Each section is labeled with the date of the last update and revised on a schedule appropriate to the clinical impact of the change.

Dr. Brooks reviewed changes to individual chapters of the adult opportunistic infection guidelines. Guidance on herpes viruses was updated to address diagnostic tests, ophthalmologic complications, and new drugs. Updated information on therapy and immunizations for hepatitis B was added in November 2018. The sections on progressive multifocal leukoencephalopathy and mycobacterium avium complex were updated to align with current recommendations. Recommendations for Gardasil 9 use for individuals 25–45 years of age were added to the section on human papillomavirus (HPV). Additional data were added regarding drug interactions for hepatitis C, as well as information on hepatitis B activation after initiation of hepatitis C therapy. Sections on immunizations and tuberculosis have been expanded and updated to reflect current practice.

Dr. Nahida Chakhtoura reviewed the updates to the perinatal, pediatric ART, and pediatric opportunistic infection guidelines. She reminded attendees of the statement regarding the use of dolutegravir that was released in May 2018 and noted that sections were updated where relevant to provide detailed information and recommendations related to dolutegravir. All sections of the perinatal guidelines were reviewed and updated where appropriate. Guidance for women living with HIV who want to breastfeed was published on March 27, 2018, and linked within the guidelines. An overview of considerations for ART use in pregnant women was added, as was an update to guidelines for identification of perinatal HIV exposure.

Other updates were consistent with those made to the adult ART guidelines. A specific recommendation related to fertility counseling for men without HIV who have female partners with HIV was added. Additional recommendations were added related to the use of ART in pregnancy to align with current data. Information about hepatitis C testing for exposed infants now recommends that providers counsel patients about the importance of pediatric followup. Postpartum follow-up recommendations were aligned with the new American College of Obstetrics and Gynecology guidelines.

Dr. Chakhtoura explained that the pediatric guidelines were updated in May 2018. A pediatric drug information appendix was published in November 2018. The review for the next update will be completed early in 2019. Section reviews and revisions for the next update are anticipated for completion in early 2019.

The pediatric opportunistic infection guidelines are updated by topic, similar to the adult opportunistic infection guidelines. Updated sections include a new evidence rating for herpes simplex virus and changes to influenza recommendations. Updates related to *Candida* and *Giardia* will be published soon.

Discussion Highlights

In response to a question, Dr. Gulick clarified that not enough information is available to recommend bictegravir use in pregnancy.

Dr. Brooks was asked to elaborate on succession planning for experts who have served on the opportunistic infections panel for many years; he explained that the succession mechanism is

similar to the mechanism for the ART guidelines committees. One potential succession planning strategy involves managing topics related to rare diseases in a way that reduces the burden on the process. Some of these topics may not require further updating because of the ongoing lack of substantive new knowledge.

When asked about generic ART medications, Dr. Gulick pointed out that the section of the guidelines addressing cost is relatively new. Guidance for generic medication is under discussion.

A participant asked about the rationale for maintaining separate guidelines for treatment and prevention, particularly related to pre-exposure prophylaxis (PrEP). Dr. Brooks and Dr. Gulick acknowledged the overlap between guidelines and noted that Dr. Brooks' presence on both panels ensures coordination. Dr. Chakhtoura added that PrEP is addressed in the perinatal guidelines where appropriate.

When asked where a physician could turn for guidance about a particularly complicated situation, Dr. Brooks noted that the CDC and HRSA support the National Clinical Consultation Center, a hotline for clinicians to consult an expert on particularly difficult cases. Callers can be referred to local clinicians when necessary and offered emergency support to address post-exposure prophylaxis. Dr. Chakhtoura added that a similar perinatal guidance hotline is listed in the guidelines.

In response to a question about the difference between these guidelines and other available guidelines, Dr. Gulick explained that these guidelines focus on an audience of U.S. providers, although they are consulted by people around the world.

The motion to approve the guidelines was forwarded by Dr. Elizabeth Connick and seconded by Dr. Scott Rhodes. The motion passed with no abstentions.

Update from the NICHD on HIV/AIDS Research Activities—Dolutegravir
Rohan Hazra, M.D., NICHD, NIH

Dr. Rohan Hazra presented an update on dolutegravir research activities. He reviewed the study data in Botswana that indicated that dolutegravir use by pregnant women in the first trimester may increase the risk of neural tube defects in infants. Updated data decreased the rate of defects from 1 percent to 0.7 percent, but the confidence interval does not cross any other groups. Dr. Hazra stressed that although many actions were taken in response to these data, the information is very preliminary. Using the OAR's strategic innovation funds, multiple ICOs were able to address the issue promptly. The NICHD supplemented the study in Botswana to expand its reach to more than 70 percent of births in Botswana, which should produce a more robust data set. Using the IMPAACT network, a pilot project will use electronic health records to review pregnancies in women with HIV from 2003 through 2017.

Two additional projects use mouse models. One has a well-established model looking at *in utero* exposure to antiretrovirals; strategic innovation funds will allow the principal investigator to investigate the link between dolutegravir and neural tube defects and, if confirmed, the mechanisms. Another project is an existing P01 funded by NIDA showing how dolutegravir causes oxidative stress in the brain. The researchers plan to evaluate whether translocated dolutegravir accumulates in the fetal developing brain at high concentrations.

Several other possibilities for study might be available with existing collaboration projects across ICOs. The IMPAACT 2010 trial compares dolutegravir-containing regimens with efavirenz. The study team has added testing for glucose, whole blood folate, and hemoglobin A1C, factors that are known to be associated with neural tube defects. The Pediatric HIV/AIDS Cohort Study studies *in utero* ART exposure. The definition of "neurologic condition" used in the study is very broad, but the case definition is very carefully phenotyped. The study shows a small but notable percentage of children with neurologic conditions. These data are preliminary; enrollment is ongoing. Another study takes advantage of the International Epidemiologic Database to Evaluate AIDS (IeDEA) cohort to examine dolutegravir experience among pregnant women in Brazil; the pediatric working group within IeDEA is developing additional ideas based on the protocol. Dr. Hazra emphasized that all the data are preliminary—efavirenz and dolutegravir might have other impacts.

Dr. Hazra stressed the importance of the strategic innovation funds in allowing investigators already doing related work to quickly add a component to study an emerging issue. Research networks are another significant contributor to enabling rapid response.

Dr. Hazra provided general NICHD updates. The data set effort established in 2015 has grown to include more than 100 studies, 58 of which are related to HIV/AIDS. Another recent initiative was a request for applications (RFA) to utilize existing data and specimens to answer questions in maternal and pediatric HIV. The NICHD produced a report, in response to a mandate in the 21st Century Cures Act, on medication effects in pregnant and lactating women. Additionally, NICHD's strategic plan will be updated for the first time since 2000. A request for information (RFI) will be released in January, with a final plan anticipated around the summer of 2019. An additional project suggested by the 21st Century Cures Act is the NIH Pediatric Research Consortium (N-PeRC), which convenes 38 representatives across ICOs to coordinate pediatric research networks across the NIH.

Discussion Highlights

Dr. Wira asked whether evidence of neural tube defects had been seen in early dolutegravir studies; Dr. Hazra clarified that the link to defects is not yet proven, nor is any other neurologic effect dolutegravir might have. He commented on the difficulty of identifying the correct numerator and denominator to study such a complex issue and noted that although the current recommendations are based on neural tube defects, many other outcomes are possible. Researchers must thoroughly understand the situation before definitive public health recommendations are made.

Attendees urged Dr. Hazra to utilize existing clinical data research networks to query large numbers of electronic medical records across many different vendors. Dr. Hazra commented on potential data linkage challenges, such as ensuring that records of a mother and her child are linked.

Dr. Hazra further explained the report on medications in pregnant and lactating women. As the age of women becoming pregnant increases in the United States, the number of women with comorbidities, including those that require medication maintenance, increases. Additionally, medications for pregnancy-related conditions must be studied further. Dr. Hazra emphasized that pregnant women no longer should be considered vulnerable subjects according to research guidelines.

In response to a clarification about the four neural tube defects seen in the Botswana study, Dr. Hazra explained that although each neural defect was different, a study that provided folate supplements to pregnant women in China (not in the context of HIV and dolutegravir) reduced the rate of all defects, suggesting that they are related. He noted that HIV research can contribute to general research in such a case, because if the causal pathway for these defects is confirmed through research prompted by the dolutegravir study, it can inform a general model for defects.

Updates from NIH Advisory Council Representatives

AIDS Research Advisory Committee (ARAC)
Carl Dieffenbach, Ph.D., National Institute of Allergy and Infectious Diseases (NIAID), NIH

Dr. Carl Dieffenbach updated the attendees on a study supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) that concluded that treatment as prevention is necessary, but it is not sufficient to control the global HIV pandemic. The study continues to assess how to use PrEP on an ongoing basis. Dr. Dieffenbach noted that additional data have expanded the support for U=U, showing effectively no linked transmissions for men who have sex with men in the presence of effective therapy.

Studies using dolutegravir were modified to increase the level and intensity of coverage for prevention of pregnancy. Guidelines for contraception were modified for a study of cabotegravir. Updated data from Botswana are expected in spring of 2019.

The clinical trials network recompetition is on schedule to complete its activities as previously outlined. Additional concepts presented at the ARAC meeting are related to biomarker discovery for tuberculosis- and HIV-infected and exposed children and long-acting ART. A series of initiatives for HPV co-infection with HIV is planned, as well as collaborative biomedical research programs between the United States and Brazil and the United States and South Africa, for which ARAC is seeking continued permission.

National Cancer Advisory Board (NCAB)
Nancy Raab-Traub, Ph.D., Lineberger Cancer Center, The University of North Carolina at Chapel Hill

Dr. Nancy Raab-Traub focused on interesting results from the Cancer Moonshot℠. Recommended areas for research included immunotherapy, high-risk cancers, and prevention and screening. She explained several initiatives, including an immuno-oncology translation in which new antigens might be accessible as immunotherapy targets. Another effort will explore data from the Human Tumor Atlas Network.

Dr. Raab-Traub reviewed several current immunotherapy approaches. One uses nanoparticles to reduce the need for repeated harvest of donor dendritic cells. Another with the possibility of becoming broadly useful uses a sponge that can be implanted and infused with a broadly specific presenter cell with multiple antigens, which can be matched by T-cells as they pass through the sponge. Dr. Raab-Traub emphasized the need to work with interdisciplinary groups—such as viral engineers, biologists, and immunologists—to develop the implantable sponges. She commented on the difficulty of procuring funding for new approaches that might not have preliminary data. Dr. Raab-Traub noted plans to build a three-dimensional network, rather than a database of sequences to help address epigenetic regulation.

The NCAB participates in global oncology research, much of which is conducted in Africa with people with HIV. Many of the cancers seen in these populations are caused by viruses, but the global oncology research community needs more direction and more coordination with other institutions. Internal and external advisory boards are recommended.

National Advisory Mental Health Council (NAMHC)
Alan Greenberg, M.D., M.P.H., Milken Institute School of Public Health, The George Washington University

Dr. Alan Greenberg noted that only one of the six divisions of the National Institute of Mental Health (NIMH) is focused on HIV. He added that NIMH's Division of AIDS Research is merging with the Office for Research on Disparities in Global Mental Health, which will allow new possibilities for collaboration in line with the cost-sharing plan.

The recent meeting of the NAMHC included a report from the Research Domain Criteria (RDoC) Workgroup, concept clearances, and a closed session with council grant review. Dr. Greenberg presented the RDoC report, which addresses a possible new approach to access the effects of HIV on cognition and other mental health domains. Two concept clearances were relevant to HIV. One relates to the neuropsychiatric side effects and neurologic toxicities of ART. The other concept outlines implementation research to inform PEPFAR's PrEP delivery platform, which Dr. Greenberg emphasized is a particular priority for the Division. The grant review included a broad range of applications from basic neuro-HIV to behavioral and social science.

Discussion Highlights

In response to a question about the sponge concept, Dr. Raab-Traub clarified that it is theoretical at this point but would be applicable for HIV. Dr. Dieffenbach emphasized the importance of engineers to such a project, noting a recent meeting cosponsored by NIAID and the National Institute of Biomedical Imaging and Bioengineering that convened biomedical engineers and vaccinologists to discuss such innovations.

When asked about the global health focus at various ICOs, Dr. Dieffenbach commented that the NIH funds HIV research in a way that encourages collaboration, so global health considerations are integrated into the networks. Dr. Dianne Rausch from the NIMH added that NIMH's global mental health program has expanded during the past few years; the impact of impaired mental health on both prevention and treatment has become very apparent. Merging the global mental health program with the Division of AIDS Research will allow further integration and progress on international work related to mental health.

Dr. Raab-Traub clarified that HIV was not discussed specifically at the last NCAB meeting, but the meeting focused on global health issues, in which HIV plays a role. Dr. Dieffenbach emphasized the existing integration across basic science areas. He noted that although council meetings often focus on problem areas, many ongoing efforts are proceeding well.

When asked which ICO leads studies of HPV infection in HIV-infected women, particularly in sub-Saharan Africa, Dr. Raab-Traub commented on efforts to increase the use of the HPV vaccine in children in the United States. Dr. Dieffenbach noted that the major emphasis for the NCI AIDS program is the Anal Cancer High-Grade Squamous Intraepithelial Lesion Outcomes Research (ANCHOR) Study, which is a large multicenter study on men who have sex with men across the United States.

In response to a question about shifting emphasis in the clinical trials network, Dr. Dieffenbach noted that the network is moving from a single prevention network to separate networks for pediatric therapeutics, adult therapeutics, and HIV vaccine.

When asked about research into why people do not take certain medications or why research does not translate to implementation, Dr. Greenberg clarified that implementation is a focus of NIMH's Division of AIDS Research, so identifying the facilitators and barriers to PrEP use is important to the Division. Dr. Rausch agreed that adherence to PrEP was a major focus of the grant session.

Update on IeDEA
Carolyn Williams, Ph.D., M.P.H., NIAID, NIH

Dr. Carolyn Williams presented an overview of IeDEA. She explained that when IeDEA was awarded in 2006, many people who had not been a part of clinical trials were starting ART in the international setting, so outcomes and medications in these environments were unknown. IeDEA was designed to coordinate the wealth of data in others' data sets and build strong data systems that could serve as a foundation for answering local questions in the clinic. IeDEA's specific missions include improving data quality through such methods as refining statistical methods and analytical approaches and identifying and filling data gaps. Dr. Williams noted that researchers and clinicians in the field can help IeDEA improve its data quality by requesting answers to their most important questions.

IeDEA has funded seven regions in the world, with 1.7 million people with HIV entering data. IeDEA includes a large cohort of children, not all of whom are HIV-positive, promising a significant opportunity to address pediatric care questions. The consortium has been very stable, maintaining most of its founding PIs and investigative teams. Many regions pair an investigator from the United States or Europe with one from the local region. Some studies are large, representative populations of Americans with HIV; others are looking at how people who are HIV negative are moved through testing and treatment. Dr. Williams emphasized the focus on supporting a culture of trust to ensure effective collaboration. Sites are able to collect their own data, with flexibility at the site level and support from the larger consortium when needed. Sites own their data, which is transferred to IeDEA only after the sites approve each concept.

To ensure data quality, coordinating work is conducted by the regions, which was found to be more efficient than an overarching coordinating center. A program called Harmonist is improving the quality of data within the program substantially. Each working group is led by a member from the region; members from all regions participate. IeDEA harmonizes the many forms of data gathered at the sites as the data are organized into regional and intermediate databases. As the data become more organized, tools can be implemented to investigate quality, make corrections, create visualizations, and share the data across the consortium. Dr. Williams noted that investigators are incentivized to collect data in the ideal format, leading to an increase in data quality over time. She added that IeDEA is the only global source of such high-quality patient-level data, which are necessary to evaluate outcomes.

The first two iterations of IeDEA published 365 papers; the consortium now has 2 years remaining in its third iteration, with more than 450 papers already published across the regions. The breadth of the data set enables interrogation on a range of issues, including assessments of the impact of ART, ways to enhance the quality of inferences about guidelines and statistics, and issues related to treatment regimen durability and tolerability. IeDEA provides advice to

regions on how to improve efforts along the care cascade, compares effectiveness across care delivery settings, and serves as a resource for those conducting implementation science.

IeDEA collaborates with other large consortia to address more complex questions, such as the relationship of CD4 counts to income level and the proportion of people starting ART at a low immune state. In addition, IeDEA allows inquiries into specific populations that are relatively small. IeDEA's data can be used for global cancer studies, including those of outcomes and comorbidities and coinfections; the data set has been used to show that ART reduces the risk of non-Hodgkin's lymphoma. Regions use the data to study substance abuse and mental health as well. Another effort is related to issues around disclosure to children—one significant risk factor to loss of care is the number of children who reach adolescence without having their HIV-positive status disclosed to them by their family. Stigma is another complex and significant issue worldwide that can be assessed using IeDEA's data.

Future questions to be addressed as the data set becomes more robust include the decline in patients taking CD4s and increase in distributed care, necessitating systems to track patients between care facilities. Dr. Williams suggested that IeDEA's abilities could be improved with additional K awards, more specific engagement in the collection of site-level and supplemental data, increased ability to correct data, increased links to a wider variety of data types, and expansion into other settings where patients are known to be receiving care.

Discussion Highlights

When asked about proudest accomplishments and lingering concerns, Dr. Williams noted that because the program relies on the quality of the data, data degradation is a significant worry. Many associated programs depend on funding to keep their data available, so if funding is lost, the data are lost. As for accomplishments, Dr. Williams commended a paper on how to sample people who have become lost to followup and a paper addressing the "when to start" issue that was produced by the North American region. Dr. Williams clarified that some cultural practices contribute to whether people are lost to followup, such as a tradition of returning home when ill. Some countries have death registries that can be consulted to clarify data. Dr. Williams emphasized that prioritizing data quality could limit data degradation.

In response to a question about training opportunities, Dr. Williams commented on a recent Fogarty International Center training award now available to international investigators. She added that as the NIH expands its data science programs, IeDEA can contribute its high-quality data sets to attract researchers to the field and support investigators working in statistics and data science.

Dr. Williams clarified that IeDEA does not collect data itself, but harmonizes data from other studies across common domains. Intensive site assessment surveys have been illuminating and have informed knowledge of care delivery. Dr. Williams noted that IeDEA's data exchange standard was developed in collaboration with the European cohort consortium, so although many regions collect different kinds of data and the breadth of data cannot be harmonized worldwide, the areas in which data have been harmonized have been reviewed very closely.

When asked about data on neurologic impairment, Dr. Williams explained that data vary by site, but because NIMH is one of IeDEA's funders, neurologic complications are a focus.

FY 2019–2020 NIH Strategic Plan for HIV and HIV-Related Research, RFI for FY 2021–2025, RFI for NIH Research Priorities
Yvette Edghill Spano, Ph.D., OAR, NIH

Dr. Yvette Edghill Spano explained the OAR's need to ensure that NIH's HIV research funding is directed at the highest priority research areas and facilitate maximum return on investment. To accomplish this, the annual strategic plan process is being adjusted to cover 5 years (FY2021-FY2025). A Notice (NOT-OD-15-137) was issued in August 2015 to outline priorities. The RFI in Summer 2018 serves for the development of the FY2021-2025 Strategic Plan. Although 177 total responses were received, many of these addressed several of the questions; an extensive analysis of these responses will serve as the basis for the next strategic plan for FY2021-FY2025. Dr. Edghill Spano reviewed the most common topics addressed, including gaps and opportunities, emerging areas, and scientific developments. She noted that the low percentage of responses related to major accomplishments was a surprise.

Responses were coded using the OAR's overarching priorities. Dr. Edghill Spano commented that the many thoughtful responses included suggestions for how to take advantage of technology, improve basic research translation, and consider implementation science. Although few comments offered suggestions for how to shift investments to support new initiatives, many new and expanded research areas were identified.

Discussion Highlights

Dr. Edghill Spano clarified that although the responses to the RFI mentioned some activities that would incorporate adolescents and young adults or older adults, gender disparities and the life cycle were not specifically addressed. She stated that the affiliation of each respondent was self-identified and categories were not specifically defined.

Dr. Edghill Spano explained that in accordance with the Legislative Mandate Section 2353 of the Public Health Service Act, the OAR coordinates the scientific, budgetary, legislative, and policy elements for the NIH HIV research portfolio. She outlined OAR's three congressionally mandated documents: the Strategic Plan for HIV and HIV-related Research, the Congressional Budget Justification, and the Professional Judgment Budget.

When asked how the new and emerging areas suggested by the RFI dovetail with existing areas, Dr. Edghill Spano clarified that the office will work with ICOs and stakeholders to determine how to move new projects forward in alignment with existing initiatives. She reminded attendees that this strategic plan looks forward several years, so although the state of the science at that time cannot be predicted, the OAR can lay a foundation for efficient allocation of HIV research funds.

Update from the NIA on HIV/AIDS Research Activities and Cost Sharing
Miroslaw "Mack" Mackiewicz, Ph.D., NIA, NIH
Stacy Carrington-Lawrence, Ph.D., OAR, NIH

Dr. Mack Mackiewicz reported on the collaborative effort between the OAR and the NIA. He noted the overlap between the HIV-related research priorities identified by each division in the NIA and elaborated on the studies produced within his division, the Division of Neuroscience. Dr. Mackiewicz explained that as the population of people with HIV ages, it is important to understand how people with HIV age differently. Aging is understood to include macromolecule

damage, changes in the epigenetic landscape, decreased stem cell activity, and problems with proteostasis and inflammation; some indications suggest that people with HIV age prematurely. Typically, studies of Alzheimer's disease look for amyloid beta accumulation in the brain; however, amyloid plaques are a common pathological feature in HIV as well. Dr. Mackiewicz explained some potential differences and noted that researchers may need to reassess how amyloid beta is measured or imaged in people with HIV. Differences in tau deposition have been shown as well, but results are highly variable.

Dr. Mackiewicz reviewed additional new and unsettled research related to HIV and aging, particularly mechanisms of neurodegeneration in HIV compared with those in Alzheimer's disease. He recommended that neuro-HIV be considered as a distinct category of dementia. The collaboration between the OAR and the NIA was prompted by similarities in the brain pathologies of people with HIV and people with Alzheimer's disease and Alzheimer's-related dementia.

Dr. Stacy Carrington-Lawrence explained that the cost-sharing strategy encourages basic research to compare molecular and cellular mechanisms underpinning neurodegeneration in Alzheimer's disease and HIV. The RFA for the collaboration had a total cost of about $5 million shared equally between HIV and Alzheimer's disease funds, with diverse related research areas included. Eight applications were funded based on score, breadth of research, cross-discipline aspects, use of existing databases and samples, and potential impact. Funded projects range from basic mechanisms of neurodegenerative processes, Alzheimer's disease, and HIV to more clinical projects. Next steps include an annual workshop to bring together investigators and the potential for additional RFAs to address HIV-related comorbidities across the life course.

Discussion Highlights

Attendees commended the collaboration and encouraged consideration of clinical and epidemiological studies. People with HIV may have increased rates of vascular dementia related to their increased cardiovascular and atherosclerotic risk, so understanding differences in expression and clinical behavior will be important for determining mitigation strategies. Attendees further commended investigators' willingness to collaborate with the HIV community.

In response to a question about neuroimaging, Dr. Mackiewicz explained that secondary data analysis includes neuroimaging analysis, but large-scale neuroimaging studies are beyond the budget of this RFA. He added that any results of the first round of projects that suggest further neuroimaging studies could be used to engage other ICs in participating in further research.

Dr. Mackiewicz acknowledged his interest in supporting additional applications related to HIV and Alzheimer's disease at the NIH. He confirmed that many aspects of neurodegenerative diseases suggest impaired immunity, which is an overlap with HIV.

Update from the Office of Research Infrastructure Programs (ORIP): NHP Evaluation and Analysis of Future Demand and Supply
Sheri Hild, Ph.D., Office of Research Infrastructure Programs, NIH

Dr. Sheri Hild introduced ORIP, which builds infrastructure and resources for innovative research and collaborates frequently with the OAR. ORIP provides construction and instruments services for institutions and participates heavily in animal research. Although many species are used, Dr. Hild focused on the role of NHPs, which are important in HIV research because of their similarity to humans. Current models important to HIV research include the rhesus

macaque, the pigtail macaque, and the Mauritian cynomolgus macaque. The OAR helps support many of ORIP's colonies of specific pathogen-free macaques, which are important for vaccine trials. In addition, the OAR co-funds the National Primate Research Centers (NPRCs) and collaborates with ORIP on initiatives to support early-stage investigators working in NHP research on HIV.

ORIP recently conducted an analysis of NHP research use across the NIH to assess current and future NHP needs, how these needs are being met, the use of NIH resources, and which biomedical fields need to continue using NHPs in research. Future demand and supply was evaluated with a review of major suppliers' capabilities, a review of past NIH awardees, a survey of NIH-sponsored NHP users, and data and forecasts from service providers. An expert panel forum was convened that determined that all ICOs use NHPs; Dr. Hild reviewed the most common areas of study. She reiterated that although total use of NHPs across the NIH is not a major component of NIH awards, it is an amount critical to research. Numbers of awards for NHP studies have increased for all species, as have the numbers of animals. Use of the rhesus macaque is the biggest driver of these increases and is predicted to increase by 10 to 25 percent. Although NPRCs are a major service provider for groups that do not have NHPs at their institutions, NIH-funded centers may not be able to satisfy the predicted demand.

The expert panel was asked to assess the future use of NHPs, discuss the scientific advances driving the research, and identify relevant and emerging NHP models for NIH investment. Use of NHPs in behavioral and social sciences research and HIV/AIDS research comprises the largest projected increase. Attendees at the expert panel forum included representatives from the ICOs driving NHP research, NPRC directors, and commercial suppliers. The forum discussed NIH research priorities, scientific considerations, and factors affecting NHP supply.

The expert panel identified animal shortages driven by infrastructure and space limitations. Scientific barriers include limited high-quality reference genomes and limited availability of NHP reagents for specific species, necessary training for the next generation of researchers, the need for standardized methods of collecting and reporting phenotypic data, limitations on using emerging transgenic NHP models, lack of sufficient NHP expertise on peer review panels, and the effects of funding cuts. Dr. Hild explained that the long lifespan of many NHP species affects whether researchers can effectively study such processes as development and aging within the typical life of an award.

The expert panel recommended establishing NHP planning groups to increase communication, including a trans-NIH NHP working group and an annual NHP symposium meeting. Improvements to infrastructure are needed to support colony expansion, but existing mechanisms could be used to begin this process. The panel recommended determining the genetics of existing colonies as a way to refine the model and fully utilize existing resources, such as marmoset colonies that could provide breeding pairs to satellite colonies. Panel members expressed additional interest in establishing domestic colonies of cynomolgus macaques to ensure a supply of high-quality animals regardless of issues that might affect international supplies.

Discussion Highlights

Dr. Hild clarified that the assessment of need for NHP used NIH-sponsored grants or cooperative agreements. She offered additional comments on the potential to use K awards for NHP investigators working in the field of HIV/AIDS research. OAR's practice of ensuring that young investigators have mentors for both their clinical and NHP work could serve as a model

for other fields. Dr. Hild clarified that K01 awards are separate from pilot grants; the K01 awards provide support for the early-stage investigator and funds to develop an independent NHP program, whereas pilot grants are an ongoing program built into the support system of the NPRCs that engage investigators who have not used NHPs.

Dr. Hild clarified that some data from the NHP Evaluation and Analysis was classified using NIH grants while other data was from a survey in which investigators could self-select one or more research area of emphasis. She emphasized that the data suggest that both HIV/AIDS and behavioral and social science research would continue to be heavy users of NHPs.

Public Comments
Charles Wira, Ph.D., Geisel School of Medicine at Dartmouth

Dr. Wira invited members of the public to comment. Jules Levin, the executive director of the National AIDS Treatment Advocacy Project, emphasized the seriousness of the issue of aging with HIV and urged OARAC members to continue to support research in this area.

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

Dr. Goodenow thanked the council members, guidelines working groups, and speakers. She commended those council members who agreed to remain on the OARAC for additional time to maintain a quorum until the new members can be approved. Dr. Goodenow noted that the complexity and scope of the topics covered in this meeting reflects the complexity and scope of the HIV research agenda at the NIH. Although much progress has been made, much work remains to be done before the next OARAC meeting.

Adjournment
Charles Wira, Ph.D., Geisel School of Medicine at Dartmouth

Dr. Wira thanked the attendees and adjourned the meeting at 3:37 p.m.

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

- S -

Charles Wira, Ph.D.
Chair, Office of AIDS Research Advisory Council

2/4/2019
Date

- S -

Jay Radke, Ph.D.
Executive Secretary, Office of AIDS Research Advisory Council

2/5/2019
Date