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

Office of AIDS Research Advisory Council
44th Meeting

April 6, 2017
5635 Fishers Lane, Terrace Level Conference Center
Rockville, Maryland

Draft Meeting Minutes

Council Members Present: Dr. Monica Gandhi (Chair), Dr. Elizabeth Church (Executive Secretary), Mr. Moisés Agosto-Rosario, Dr. Ralph J. DiClemente, Dr. Priscilla Hsue, Dr. Daniel R. Kuritzkes, Dr. Justin C. McArthur, Dr. Lynne M. Mofenson, Dr. Scott D. Rhodes

Ad Hoc Members Present: Dr. Richard E. Chaisson, Dr. John J. Chin, Dr. Elizabeth Connick, Dr. Maureen M. Goodenow (Director of the Office of AIDS Research), Dr. Alan E. Greenberg, Dr. Roy M. (Trip) Gulick, Dr. Jennifer Kates, Dr. Michael M. Lederman, Dr. Steffanie A. Strathdee, Dr. Charles Wira

Ex Officio Member Designee Present: Dr. Julie Ake

Invited Speakers and Guests: Dr. Frederic Bushman, Dr. Janice E. Clements, Dr. Nakela L. Cook, Dr. Kristina De Paris, Dr. J. Victor Garcia-Martinez, Dr. David C. Goff, Dr. Rohan Hazra, Dr. Betsy Herold, Dr. Lita Proctor, Dr. Jacques Ravel, Dr. Ivan Vujkovic-Cvijin

Council Member Absent: Dr. Ronald T. Mitsuyasu

Welcome and Meeting Overview
Monica Gandhi, M.D., M.P.H., University of California, San Francisco

Dr. Monica Gandhi welcomed participants to the 44th 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 of the 43rd OARAC meeting on November 17, 2016. Members of the Council motioned and voted to accept the minutes from the 43rd OARAC as written. Dr. Gandhi then briefed the Council on the agenda for the day, 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 meeting members of the Council, representatives from the NIH and other government agencies, and guests from professional and lay organizations whose interests and activities align with the OAR. She particularly welcomed five new ad hoc members to the Council. Dr.

Goodenow covered key appointments in the government and gave an update on OAR personnel, including the recent appointment of Dr. Peter Kim as the deputy director.

Dr. Goodenow then provided an overview of the OARAC's organizational structure. The OARAC is chartered to contain 18 voting members comprised of 12 scientists and 6 members from the public. There are 10 non-voting members comprised of 6 Ex Officio members and representatives from the advisory committees of 4 NIH Institutes.

Highlighted activities of the OAR in this presentation included a Listening Day on February 1, 2017, meetings with advocacy and community groups at the Conference on Retroviruses and Opportunistic Infections (CROI) held February 13–16, 2017, in Seattle, Washington, and meetings with community that were hosted by the International AIDS Society and the Kaiser Family Foundation. Dr. Goodenow informed the Council that she was privileged and honored to receive the 24th Annual Herman and Gertrude Silver Lecture Award that is given to individuals who have contributed significantly to the field of pediatric HIV/AIDS. She updated the Council on the third NIH HIV/AIDS portfolio review, the OAR strategic fund, the OAR Innovation Fund, and the recently published fiscal year (FY) 2018 Trans-NIH HIV-Related Research Plan that can be accessed from the OAR website. Dr. Goodenow explained the OAR has a request for information for the FY 2019 Trans-NIH HIV-Related Research Plan that is open until May 15, 2017.

Dr. Goodenow reminded the Council that the objectives of the OAR are to foster collaborations, align research with the epidemic's emerging demographics, think globally, and plan for success. She emphasized that individuals across the lifespan are at risk for HIV and noted that appropriate treatments and preventions are needed throughout the lifespan. She shared data from the Centers of Disease Control that indicated the demographics of the HIV epidemic will change dramatically over the next 10 years. In the U.S., the largest shift will be in young persons between 15 and 29 years of age and the aging population (over 50 years of age). To develop the appropriate policies for the changing landscape, the OAR will establish new *ad hoc* working groups or task forces. Topics for upcoming task forces will include implementation research, economic issues, and HIV comorbidities, coinfections, and complications.

Update from OARAC Working Groups for the DHHS Treatment and Prevention Guidelines
Roy M. (Trip) Gulick, M.D., M.P.H., Weill Medical College of Cornell University
Rohan Hazra, M.D., Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH

Dr. Roy (Trip) Gulick reviewed the Adult and Adolescent Antiretroviral Therapy (ART) guidelines. He noted that on May 9, 2017, the panel will discuss if one or both forms of tenofovir (e.g. tenofovir disoproxil fumarate and tenofovir alafenamide) will be considered as first-line treatment, the association between boosted darunavir and cardiovascular disease, the emerging central nervous system (CNS) side effects of dolutegravir, and new drugs in the pipeline. A new edition of the guidelines is expected in the fall of 2017. Dr. Gulick announced new members of the working group and thanked the outgoing members for their service.

The sections for Coccidiomycosis and Leishmaniasis and the Drug Interaction and Adverse Drug Reaction Tables were updated in the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Evidence to support these guidelines has changed to rely on observational and cohort data rather than on randomized clinical trials due to the rare occurrence of opportunistic infections in the US.

Dr. Rohan Hazra informed the Council that the panel on the Use of Antiretroviral Agents in Pediatric HIV Infection has a new name, HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. The updated guidelines include people-first language (people living with HIV rather than HIV-infected), a clarified testing schedule for infants based on transmission risk, guidance for weight-band dosing rather than age-band dosing when appropriate, updated preferred antiretrovirals for children between 3 and 12 years of age, guidance for the use of maraviroc down to 2 years of age, and an investigational dose of raltegravir in neonates. These guidelines rely on small phase I safety and pharmacokinetic studies and observational experience from clinicians. Dr. Hazra presented the new members of the working group and thanked the outgoing members for their service.

The Pediatric Opportunistic Infections Working Group has moved to a modified-grade approach. The Perinatal guidelines were updated and released in October 2016 and future updates will incorporate people-first language. Dr. Hazra affirmed that the perinatal guidelines and the Pediatric ARV Guidelines will contain identical sections for maternal HIV testing and prevention of MTCT, diagnosis of HIV infection in infants and children, and ARV management of the HIV-exposed neonate to ensure that the recommendations are aligned and the content is readably accessible. Dr. Hazra thanked the leadership of the panels, AIDSinfo, and the volunteers.

Discussion Highlights from the Update from OARAC Working Groups for the DHHS Treatment and Prevention Guidelines

Dr. Gandhi asked about the length of service time for members of the Adult Opportunistic Panel. Dr. Alice Pau, a member of the leadership group for the panel on Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, emphasized that historical expertise is important and responded that the group is also looking for junior experts to join the working group.

Dr. Richard Chaisson asked how the Adult Opportunistic Infections panel is approaching known drug-drug interactions for the many patients worldwide who have tuberculosis (TB) and HIV. Dr. Gulick responded that the guidelines' mandate is for U.S. health care practitioners. He acknowledged that the rest of the world reads the U.S. guidelines and that developing countries are looking to these guidelines for information to treat their patients. Dr. Pau added that there needs to be additional drug-drug interaction studies for HIV and TB infection to resolve issues that remain regarding the combination of certain drugs.

Dr. Gandhi asked the attendees for a motion to accept the plans for the guidelines. The Council motioned and voted to accept the plans as presented.

Readout from the 2017 Workshop on Macrophage Infection by HIV: Implications for Pathogenesis and Cure, a Follow-up to the November 2016 OARAC
Janice E. Clements, Ph.D., Johns Hopkins University School of Medicine
J. Victor Garcia-Martinez, Ph.D., The University of North Carolina, Chapel Hill

Dr. Janice Clements explained that the introductory session of the Macrophage Workshop featured data that resident macrophages in tissues are derived from self-renewing embryonic precursors. This concept has not yet been incorporated into HIV research. This session also included an overview of the clinical trials, therapeutic strategies, and basic science for HIV cure research and highlighted that macrophages, to date, have not been specifically included in this research agenda.

The workshop also focused on the in vitro and in vivo establishment of HIV infection in macrophages. Topics covered in the workshop included macrophage reservoirs, mechanisms that contribute to macrophage infection, methods to inhibit HIV replication in macrophages, and the need for strategies to maximally reactivate infected macrophages. There were presentations on the immune response to infected

macrophages, and workshop participants discussed the essential need to understand signatures of inflammation and strategies to control HIV-associated inflammation. Single cell technologies and a quantitative viral outgrowth assay for macrophage cells are needed to characterize the macrophage reservoir in humans.

The concluding session of the workshop identified gaps in research for macrophage biology, HIV pathogenesis, the HIV/SIV reservoir, HIV eradication, and model systems: Is HIV infection and latency distinct for different types of macrophages or for the same type of macrophage in different tissues? How is viral transcription regulated in the infected macrophage? Can the macrophage reservoir re-seed the T cell reservoir? Does combination ART (cART) contribute to persistent inflammation in people living with HIV and AIDS (PLWHA)? Can new therapeutics be developed to decrease macrophage driven inflammation? Do macrophages contribute to the latent or persistent viral reservoir? What is the half-life of infected macrophages for a person suppressed on cART? How do viral sequences differ for macrophages in different tissues and in circulation? Can macrophages be better targeted by the immune system? Do we need to eradicate all reservoirs or can we reach a functional cure by combination therapy that combats inflammation? Which model systems are best to explore the role of tissue macrophages for latency?

The consensus of the Macrophage Workshop was that infected macrophages likely persist in the setting of cART to drive inflammation and contribute to the viral reservoir. Participants agreed that macrophages need to be incorporated into the HIV cure research agenda.

Dr. Gandhi recognized Dr. Dianne Rausch, Director of the Division of AIDS Research for the National Institute of Mental Health (NIMH), who reviewed the NIMH research portfolio related to HIV, the central nervous system (CNS), and macrophages. Dr. Rausch informed Council participants that NIMH also co-sponsors efforts with the National Institute of Neurological Disorders and Stroke, the National Institute on Drug Abuse, NICHD, the National Institute of Allergy and Infectious Diseases (NIAID), and the Military HIV Research Program (MHRP). For co-sponsored clinical trials in adults and children, NIMH includes, whenever reasonable, a neuro-AIDS component to advance knowledge of the impact of HIV on the CNS and to determine whether therapeutic regimens protect the CNS.

Discussion Highlights from the Readout from the 2017 Workshop on Macrophage Infection by HIV: Implications for Pathogenesis and Cure, a Follow-up to the November 2016 OARAC

Dr. Justin McArthur asked whether the Macrophage Workshop included discussion of macrophage imaging or novel forms of therapy. Dr. Clements responded that the workshop did not include intranasal insulin as a neuroprotective therapy or human imaging. Dr. Gandhi asked Dr. McArthur what intranasal insulin would do to macrophages. Dr. McArthur explained that delivery of small doses of intranasal insulin could enter the brain and have an impact on macrophages.

Dr. Michael Lederman asked if there are models for *in vitro* induction of latency for primary monocyte-derived macrophages. Dr. Clements explained that systems are in development. Dr. Lederman commented that inflammation attributed to monocytes can have many sources. Dr. J. Victor Garcia-Martinez responded that understanding macrophage biology will require both the development of new technology and a focus on tissues. Dr. Clements added that SIV studies in the U.S. should include cerebrospinal fluid taps to study CNS effects of vaccines and other treatments.

Dr. Charles Wira complimented the Macrophage Workshop as a long overdue conversation on an underappreciated topic. Dr. Wira acknowledged the importance of the nonhuman primate model, and articulated the need to keep model systems relevant to the human. Dr. Wira suggested studies on resident

macrophages in humans at different compartmentalized mucosal sites to determine subtle differences in phenotype and function.

Dr. Gandhi asked if there was any reason to think that latency reversal agents that work on CD4 T-cells will not be effective on macrophages. Dr. Clements referred to published work that macrophages reactivate differently than T cells (via NFkappaB) and theorized that reactivation via epigenetic pathways would be similar for both cell types. Dr. Garcia-Martinez added that it is not certain whether activation in the brain would be productive or counter-productive, and that even in tissues it is difficult to assess the macrophage due to the small proportion of cells compared to the prevalence of CD4 T cells.

Report on Continued Stakeholder Engagement
Gina Brown, M.D., OAR, NIH

Dr. Gina Brown summarized the OAR sponsored Community Listening Day on February 1, 2017. The purpose of Listening Day was for the Office of AIDS Research to listen to the community perspective on HIV and HIV-related research and community engagement. Dr. Brown highlighted that Listening Day was a multi-staff event that included individuals from every area of the OAR as well as external input for participant inclusion. The Listening Day was a conversation structured around research gaps and opportunities, concerns around HIV, best practices for community engagement, and productive information dissemination. A panoply of organizations and PLWHA participated, including 28 in-person attendees, 63 live online participants, and 34 individuals who viewed the archived event.

For research gaps and opportunities, Listening Day participants agreed that research in specific populations is needed. Many participants voiced the need for trans-NIH involvement to look at the different comorbidities and coinfections; frailty; accelerated morbidity and mortality; issues of polypharmacy; and the meaningful differences related to ethnicity, sex, gender, HIV, and antiretroviral treatment for aging PLWHA. The community strongly supported inclusion of women and the most at-risk populations (youth, black men who have sex with men, and disparate ethnic populations) in research.

Community participants conveyed the need to understand how the intersection of hepatitis C and HIV affects the epidemic and how mental health issues affect enrollment in HIV research trials and interventions, follow-up studies, and a wide-range of health outcomes. Community spoke about the need for a wide range of prevention choices and the need to better understand the prevention cascade. The interest in long-acting antiretroviral therapy was mentioned in the context of prevention and treatment. Additional needs identified included alternative therapies, alternative ways to administer care that improve quality of life for PLWHA, and enhanced provider communication and cultural competency.

Participants communicated the need for the NIH to foster better inter- and intra-agency collaboration, improve support of social sciences research, maintain important basic science research, cultivate inclusion of the most affected communities in research, and embrace implementation science. The community urged the NIH to facilitate collaboration between community and academia to incorporate community feedback early in research design; provide easy-to-understand and informative consistent messaging; capitalize on successful models, understand the social and structural factors that apply, and acknowledge the Good Participatory Practice framework for community engagement; and document the success and crossover benefits for NIH supported HIV research. The community participants recommended the OAR continue to engage with the community at additional Listening Days, open forums, and scientific conferences.

Discussion Highlights from the Report on Continued Stakeholder Engagement

Dr. McArthur asked if the reproducibility of research results was mentioned by participants. Dr. Brown responded that this topic was not specifically discussed.

Dr. Gandhi asked about the OAR economics task force and recommended that all issues related to HIV be included in the economic analysis. Dr. Goodenow acknowledged the multi-factorial aspects of the economics task force and communicated the need to provide focused and discrete outcomes.

Dr. Alan Greenberg commented that the same themes discussed at the Listening Day were also discussed at community meetings of the District of Columbia (D.C.) Center for AIDS Research (CFAR). He asked if the OAR staff heard any themes that were surprising. Dr. Brown replied that she was surprised that community endorsed basic science research and understood how government agencies can work together.

Dr. Wira asked if there was discussion about care for elderly PLWHA and acquisition of HIV in the elderly population. Dr. Brown responded that this was in the broader discussion that included the need to understand how HIV affects different age groups, particularly regarding issues of frailty and morbidity.

Dr. Chaisson asked how community advisory boards (CABs) could be more efficient or involve new members to reduce the burden on participants. Dr. Brown responded that Listening Day included new community members and postulated that new individuals might participate in conversations held in different geographical locations and styles. Dr. Goodenow commented that she was impressed by the number of vocal, educated younger people at CROI and at a recent UNAIDS community event. Mr. Moises Agosto-Rosario noted that the paradigm of HIV has changed, and he recommended an intentional process be brought to community engagement that communicates how community engagement is expected to benefit scientific outcomes.

Update on the NIH AIDS Executive Committee and the Trans-NIH Plan for HIV-Related Research (Fiscal Year 2018/2019)
Peter Kim, Ph.D., OAR, NIH

Dr. Peter Kim explained that the OAR is working to increase communication, coordination, and collaboration not only among the NIH Institutes and Centers (ICs), but also with other U.S. agencies and non-U.S. government collaborators. The OAR is actively working to facilitate stronger connection between the OAR, the OARAC, and other OAR-sponsored working groups. One important OAR working group is the NIH AIDS Executive Committee (NAEC) that is comprised of representatives from every NIH IC and Office involved in HIV/AIDS research. The NAEC facilitates information dissemination from the OAR to the appropriate NIH ICs and Offices and will now facilitate the flow of information from the NIH ICs to the OAR and from one NIH IC to the other. To broaden the conversation, the NAEC will include discussion of funding opportunities and key initiatives from representative ICs as well as new approaches and scientific advances that are of interest to multiple NIH ICs and Offices.

The FY 2018 Trans-NIH plan for HIV-Related Research was recently released and represents a delineation of the overarching high-priority research areas: reducing the incidence of HIV/AIDS; next-generation therapies; research towards a cure; and co-infections, comorbidities, and other complications. The FY 2019 Trans-NIH plan for HIV-Related Research will consider input from multiple stakeholders. Dr. Kim encouraged everyone to respond to the request for information by May 15, 2017. Input from NIH Coordinating Committees that are focused on the specific high-priority research areas, the NAEC, and the OARAC will also be considered in finalizing the FY 2019 plan.

Discussion Highlights from the Update on the NIH AIDS Executive Committee and the Trans-NIH Plan for HIV-Related Research (Fiscal Year 2018/2019)

Dr. Kuritzkes commented that the AIDS Clinical Trials Group has collaborated with many of the NIH ICs, but some remain recalcitrant to collaboration. He urged the OAR to consider how collaboration within the Networks could be improved. Dr. Kim commented that the networks will be discussed at the NAEC meeting on April 18, 2017, and called for ICs and Offices to participate.

Update on HIV/AIDS Research Activities, National Heart, Lung, and Blood Institute
David Goff, M.D., Ph.D., National Heart, Lung, and Blood Institute (NHLBI), NIH
Nakela Cook, M.D., M.P.H., NHLBI, NIH

Dr. David Goff explained that two goals of the NHLBI are to mitigate comorbidities and accelerate cures for PLWHA. He presented data for PLWHA to support improved survival and longevity as well as the increased burden of comorbid conditions in recent decades. Dr. Goff explained that PLWHA have a significantly increased chance of a cardiovascular or pulmonary comorbid condition as compared to the uninfected population, and that chronic immune activation and inflammation play an important role.

Dr. Nakela Cook summarized how NHLBI reorganized in 2012 to enhance the coherence, coordination, and outreach for the intersection of HIV research and the emerging public health needs for PLWHA. NHLBI convened a working group that brought together researchers from the infectious disease, HIV, cardiovascular, pulmonary, and hematologic communities to discuss potential overlapping research gaps and priority areas. Many basic and clinical research initiatives on epidemiology, pathophysiology, treatment opportunities, and management strategies deemed important for comorbid conditions were developed. In 2015, NHLBI convened a working group to review progress and identify additional gaps. This workshop revealed the opportunity to focus on specific areas of HIV-related heart, lung, blood, and sleep research including implementation science.

Dr. Cook reported the progress from the NHLBI working groups including NHLBI investment in a largest clinical trial focused on an intervention to prevent cardiovascular disease among PLWHA. Currently, NHLBI is interested in leveraging extant cohorts to facilitate comorbidities research to understand cardiovascular disease, pulmonary disease, sleep disorders, and implementation science. NHLBI is collaborating with NIAID on the Beyond Heart initiative to support cure research focused on key elements of hematopoietic stem cells. Dr Cook summarized that NHLBI is charting an integrated portfolio of research strategies across a broad spectrum of diseases that have an increased burden among PLWHA and these strategies are aligned with the areas outlined in the NHLBI strategic vision.

Discussion Highlights from the Update on HIV/AIDS Research Activities, National Heart, Lung, and Blood Institute

Dr. Gulick asked if Drs. Goff and Cook could speak to the research agenda on underlying traditional risk factors that may play a role in comorbid conditions. Dr. Goff replied that the REPRIEVE study is doing exactly that and is conducting research to understand heightened risk factors for cardiovascular health of PLWHA. Dr. Gandhi added that smoking, diabetes, and hypertension significantly contribute beyond inflammation in PLWHA and research should focus on these factors as well. Dr. Goff responded that implementation science would be important for these other factors. Dr. Priscilla Hsue commented that a study published the day prior indicated risk factors among PLWHA are more complicated than the traditional risk factors. Dr. Lederman added that the accelerated morbidity of smoking among HIV-infected patients compared to smoking in uninfected persons suggests that an aspect of HIV, possibly inflammation, contributes.

Dr. Lynne Mofenson asked about the research agenda for the HIV-infected children and HIV-exposed uninfected children. Dr. Cook acknowledged that NHLBI has focused heavily on the adult domestic population and pointed out that this gives NHLBI the opportunity to think about ways to support research in the areas pointed out by Dr. Mofenson.

Mr. Agosto-Rosario asked about specific approaches to address the needs of aging PLWHA in the context of health disparities and existing comorbidities. Dr. Cook replied that this is an area of interest to NHLBI and could be supported in the initiative focused on implementation science. NHLBI will consider opening this initiative to international participants. Mr. Agosto-Rosario agreed that looking at the intersection of issues facing this population is important for implementation science and expressed that he was glad to hear NHLBI is thinking along these lines.

Dr. Julie Ake asked about NHLBI's interest in comorbidities in international resource-limited settings, particularly sub-Saharan Africa. Dr. Cook responded that NHLBI would like to explore a more global focus and recognized a natural alignment between global health research and implementation science in areas of research covered by the Institute.

Introduction: The Impact of the Microbiome in HIV Prevention and Pathogenesis
Stacy Carrington-Lawrence, Ph.D., OAR, NIH

Dr. Stacy Carrington-Lawrence introduced the microbiome and explained that components of the microbiome can be beneficial. The microbiome refers to the aggregate of microorganisms residing on and within the body and includes bacteria, fungi, archaea, and viruses. Dr. Carrington-Lawrence explained the relationship between the human microbiome, metabolism, and the immune system.

The NIH's Human Microbiome Project (HMP), established in 2008, first provided resources for the comprehensive characterization of the human microbiota and then, in the second phase, created integrated datasets from the microbiome and host over time for specific microbiome-associated diseases. In addition to the NIH effort, the National Microbiome Initiative was developed to foster the integrated study of microbiomes across different ecosystems. The NIH committed $20 million to the combined investment of $121 million in the National Microbiome Initiative in FYs 2016 and 2017. Goals for this initiative were to support interdisciplinary research, develop platform technologies, and expand the workforce working on the microbiome.

Dr. Carrington-Lawrence reviewed the timeline of the OAR's interest in research related to the microbiome which began in 2007 and continues today. She explained that the OAR added a microbiome focus to the FY 2010 Trans-NIH plan for HIV-Related Research, HIV-related microbiome research began to expand around 2012, and there is currently at least one active funding opportunity that includes HIV.

In 2012, the NIH invested $13.5 million in microbiome research. The NIH investment in this topic has increased to $38.5 million in 2016. Dr. Carrington-Lawrence presented support for microbiome research by NIH IC, and noted that most of the microbiome research today is investigator initiated. She emphasized that the presentations on the microbiome during this session will identify gaps and high-priority opportunities for HIV microbiome research and summarized the afternoon agenda.

Introduction to the Human Microbiome
Lita Proctor, Ph.D., National Human Genome Research Institute, NIH

Dr. Lita Proctor, program director of the HMP, explained that microbes associated with healthy human tissues have been found all over the human body. She noted that the term "microbe" refers to all

microbial life—including bacteria, eukaryotic viruses, bacteriophages, archaea, and fungi—and the term "microbiome" refers to all microbial life, along with its genomic and metabolic capabilities.

Dr. Proctor presented a natural history of the microbiome, noting that microbiota are acquired anew each generation. The initial inoculum in a new born baby is low in diversity, and succession of microbial communities colonize the body over the next 1.5 to 2 years to become adult-like. Interactions of the microbiota and host impact the immune system, digestion, drug metabolism, and brain function. Some important modern practices—including sanitation, antibiotic use, Cesarean birth, formula feeding, mercury amalgams, and diet changes—may result in an unhealthy microbiota that is postulated to be associated with chronic low-level inflammation, which could lead to human disease.

The HMP at the NIH began 10 years ago when antibiotics, vaccines, and public health practices had reduced the incidence of many kinds of infectious diseases, but many autoimmune diseases had become more common. The first phase of the HMP invested $1.85 million to survey the microbiome in humans and showed that microbial composition of healthy adult microbiomes is highly variable and unique in each part of the body. In phase two, The Integrative HMP (iHMP), $35 million was invested to analyze the biological properties of both the microbiome and the host over time to look for biomarkers of health and disease for (1) pregnancy and preterm birth, (2) inflammatory bowel disease, and (3) onset of type 2 diabetes.

Dr. Proctor noted efforts on the microbiome include activities of The Trans-NIH Microbiome Working Group, a Workshop between the NIH and the National Institute of Standards and Technology on standards for microbiome measurements (August 2017), and the 16-agency Microbiome Interagency Working Group that is developing a Federal strategic plan.

Interrogating the Microbiome: A Systems Biology Approach
Frederic Bushman, Ph.D., University of Pennsylvania

Dr. Frederic Bushman stated that, in recent years, the term "microbiome research" has come to mean comprehensive studies of microbe communities using deep sequencing methods. From studies in the SIV model, no effects of SIV on the gut microbiota were detected, and researchers concluded that the gut microbiome among SIV-infected primates is fairly robust. At the time of the SIV publications, numerous papers suggested HIV influenced the human gut microbiome. Dr. Bushman gave an example of the back-and-forth in the literature that currently goes on as to whether HIV infection affects the gut microbiota and proposed HIV and SIV might have a larger effect on the virome.

Dr. Bushman described the Lung HIV Microbiome Project, a multicenter study of HIV-positive subjects and healthy controls. The lung microbiome is challenging to sample and this study has not yet identified if changes in the microbiota from this compartment are specific to HIV. He moved on to talk about the association of HIV and the vaginal microbiome and advocated for the need to understand the cause of persistent bacterial vaginosis in women who are living with HIV. Studies of the influence of the microbiome on health through the production of small molecules are underway and the next step is to screen purified metabolites and determine function in diverse biological settings. Dr. Bushman suggested that a possible future direction is to study the microbiome and HIV infection in global populations, which would allow the opportunity to understand the microbiome, inflammation, and HIV disease progression or cardiovascular disease; the role of the microbiome in shaping immune responses to lentivirus infection; and HIV infection, alterations in the microbiome, and alterations to the metabolome.

How Biologic Sex Influences the Microbiome
Jacques Ravel, Ph.D., University of Maryland

Dr. Jacques Ravel introduced the concept of the microgenderome, the microbiome unique to each gender, which to date, is relevant only for autoimmune and neuroimmune conditions. Dr. Ravel made the case for future applied and mechanistic research to consider the effect of sex differences on the microbiota and all influenced functions.

Dr. Ravel noted the concept of the estrobolome, the aggregate of enteric bacteria whose products are capable of metabolizing estrogens and change the amount of estrogen in the body in a highly sex-specific manner, which leads to effects on many organs. Dr. Ravel reviewed the vaginal microbiome at each stage of the life cycle, and outlined the potential gut-vagina axis mediated by sex hormones. He highlighted that the rate of change in the vaginal microbiota might mean that healthy asymptomatic women could potentially be at an increased risk of STIs or other adverse outcomes and commented on the need to review the management of asymptomatic conditions and explore ways to restore healthy microbiota.

For the male microbiome, Dr. Ravel discussed the effect of male circumcision on the penile microbiome, noting the effect of circumcision on HIV acquisition. Male circumcision alters the penile microbiome, decreases HIV target cell activation and recruitment, and decreases HIV susceptibility. In a study of penile microbiota and female partner bacterial vaginosis, men with a greater abundance of microbes were significantly more likely to have a female partner with microbial imbalance. There is a possibility that dysbiosis is bidirectionally sexually transmissible, which ultimately can affect HIV susceptibility.

Dr. Ravel concluded that sex-specific microbiota affect the physical barriers to infection and more research is needed to resolve the mechanism by which the microbiota interact with the host in a sex-specific manner in the context of HIV. He displayed a diagram of all the interactions between the host, microbiota, environment, and HIV for each sex and noted that many questions are yet to be answered.

The Effects of the Microbiome on Physiology and ART Pharmacokinetics and Pharmacodynamics
Betsy Herold, M.D., Albert Einstein College of Medicine

Dr. Betsy Herold explained that the interaction between antiretrovirals (ARV) and the human microbiome is likely to differ in the vagina and the gut and by the route of administration for ARVs used for HIV prevention. She noted that the efficacy of pre-exposure prophylaxis (PrEP) – although highly linked to adherence- is slightly lower than the percentage of protection expected, which led researchers to ask if there is a biological reason why PrEP is not fully protective against HIV acquisition.

Research using samples from the CAPRISA 004 Tenofovir (TFV) gel Trial showed a correlation between women with increased inflammatory cytokines and increased acquisition of HIV. Dr. Herold presented two follow-up studies that also used samples from CAPRISA 004 to link the microbiome with inflammation and/or HIV acquisition. Two studies also suggested that differences in the microbiome likely affected the dose of the ARV (TFV gel and TFV film) locally. Active bacterial vaginosis (and the presence of organisms that lead to BV) seem to decrease the efficacy of 1% TFV gel applied locally, likely by direct breakdown of the gel by Gardnerella and other dysbiotic organisms. In contrast, data from one of these studies showed the same efficacy of oral PrEP regardless of the Nugent score for bacterial vaginosis. Therefore, although the efficacy of 1% TFV gel may be reduced by vaginal dysbiosis, the efficacy of PrEP does not seem to be altered by active bacterial vaginosis or the presence of dysbiotic organisms in the vagina.

Dr. Herold explained the different mechanisms of ARV (TFV, tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and dapivirine (DPV)) uptake into different cells and indicated that tenofovir enters cells by an inefficient method of endocytosis. Prodrugs of tenofovir (TDF and TAF) and DPV passively diffuse in and out of cells. Dr. Herold presented in vitro data that uptake of TFV is

effected by pH, the presence of bacteria, and products released from bacteria (adenine), and ended with a conceptual model of how TFV, TDF, TAF, and DPV enter cells.

Panel: Research Gaps and Opportunities for Future HIV Microbiome Studies
Facilitator: Monica Gandhi, M.D., M.P.H., University of California, San Francisco
Panelists: Ivan Vujkovic-Cvijin, Ph.D., Cancer Research Institute, NIH; Kristine De Paris, Ph.D. University of North Carolina, Chapel Hill; Betsy Herold, M.D., Albert Einstein College of Medicine; Jacques Ravel, Ph.D., University of Maryland

Dr. Gandhi introduced the panelists and moderated the discussion. Dr. Ivan Vujkovic-Cvijin introduced himself as presenting on behalf of Dr. Yasmine Belkaid. He described his research interests, including the relationship between the gut microbiome, the immune system, and HIV. Dr. Kristina De Paris introduced herself. She is an immunologist who worked on the vaginal transmission model of SIV and now works in the infant macaque model and immunological development in human infants.

Dr. Gulick asked Dr. Herold whether the vaginal microbiome has implications for systemic PrEP. Dr. Herold shared that the simple answer is yes, but indicated there is a debate in the field. With systemic PrEP, she speculated that protection is occurring in areas where the microbiome is not likely to play a role. In topical PrEP, the protection is local at the level of the first infected cell in the vagina so the microbiome is more likely to play a role. Dr. Gulick and Herold discussed that the amount of drug is high at the topical site of administration and low in the vagina when administered systemically. Dr. Herold advocated for the best topical drug to be one that is not affected by the microbiome or other factors.

Dr. Lederman followed-up that topical ARVs would act in the tissue in the body, and asked what is known about the levels of drugs in tissues as affected by the microbiome. Dr. Herold referred to the FAME study, which examined cervical biopsies and saw an association between drugs in the tissue and the microbiome. Dr. Herold responded that she thinks drug levels matter in the lumen and the tissue and ended by agreeing that the level of drug in tissues is important.

Dr. Gandhi added that certain drugs used for treating HIV (e.g., maraviroc) are found at high levels in cervical vaginal tissues, and asked if drugs that passively diffuse in and out of cells would be favored. Dr. Herold confirmed that Dr. Gandhi was correct and cautioned about grouping TFV and the prodrugs since they are taken up into cells by different mechanisms. She further commented that we do not know the mechanism of uptake for protease inhibitors and integrase inhibitors and talked about the problematic nature for the uptake of certain drugs. Dr. Herold concluded that the most favorable drugs will be those that are most consistently effective in a real-world setting.

Dr. Elizabeth Connick asked about where the field is for clinical trials regarding the use of TAF for PrEP. Dr. Herold responded that data have been collected on whether orally administered TAF is reaching the vagina, but several unanswered questions remain. She added that it is unclear whether TAF is superior to Truvada (i.e., TDF) as a topical medication. No TAF ring is available, but TAF as an implant is in preclinical development. Dr. Gandhi clarified that the DISCOVER trial, which compares the daily oral regimen of emtricitabine (FTC)/TAF (trade name Descovy) to Truvada for pre-exposure prophylaxis, is only enrolling men and transgender with no large study among females underway.

Dr. Wira asked how the virome and microbiome are similar at the mucosal surfaces or gastrointestinal tract, given the little that is known about the virome. Dr. Ravel responded that there are more data available on the gastrointestinal tract due to sample availability. There are no data regarding the virome in the vaginal tract. Dr. Wira theorized that the virome may be more important in regulating the innate immune system than the microbiome. Dr. Herold referenced data showing no difference. Dr. Gulick asked what viruses are in the virome other than herpes DNA virus. Dr. Ravel and Dr. Vujkovic-Cvijin

commented that human papilloma virus (HPV), bacteriophages and *Anelloviridae* viruses are also components of the virome.

Dr. Gandhi asked about breastmilk and how the interaction of breastmilk with the microbiome might be influencing the immune system to protect against pathogens. Dr. De Paris explained that she is new to this area and does not study the impact of breastfeeding on the microbiome. However, she also commented that her research interests focus on how the immune function changes in the first year of life and if these changes can be correlated to the microbiome. She emphasized the importance of investigating whether inflammation impacts the microbiome and affects health outcomes in HIV-positive infants and exposed uninfected infants.

Separately, Dr. De Paris advocated that the oral microbiome is understudied and reminded everyone that dental health care is not routinely included or always covered in the set of primary care services available for HIV-infected patients. She recommended looking at dental health, including changes in the microbiome in the oral cavity from birth to adulthood, to understand the stability of the oral microbiota and how it is affected by inflammation and antiretrovirals.

Dr. Lederman asked what we know about the role of fungi and yeast in the microbiome. Dr. Herold explained that most studies of these organisms in the microbiome have come from the respiratory tract; she is unaware of studies in the gastrointestinal area. Dr. Vujkovic-Cvijin added that studies of the mycobiome must be intentional due to the more difficult experimental approaches necessary to retrieve genomic material from fungi and advocated for more research to better understand the mycobiome in PLWHA.

Dr. Wira asked if research on the microbiome has been conducted collectively for the gut, rectum, and the vagina. Dr. Ravel and Dr. Vujkovic-Cvijin both agreed that they do not know of any studies that have followed vaginal, rectal, and intestinal microbiota in the same set of individuals at a resolution that allows interpretation and correlation. Dr. Ravel added that colonization of bacterial species is site specific to the different areas of the human body (e.g. rectum, vagina, and intestine). Dr. Vujkovic-Cvijin commented that there is a consistent difference seen in the microbiome in PLWHA compared to those without HIV infection that is independent of lifestyle and sexual practice.

Dr. De Paris wondered if the field should be focused on metabolomics, bacterial metabolites and byproducts, rather than specific species of the microbiome. Dr. Ravel replied that for the vaginal tract the field is moving in that direction. He commented that the metabolome may be more informative to the field, but studies need to be powered correctly to create solid data sets. Dr. Herold also advocated for mechanistic research related to the microbiome.

Dr. De Paris suggested that standardized methods of sample collection, expert data analysis, and accessible reagents and services should be made available to move microbiome research and metabolomics forward. Dr. Garcia-Martinez asked about available models for the microbiome. Dr. Ravel and Dr. Herold indicated that humans are the best model to study the microbiome since the primate model would have important differences in the microbiome from humans.

Dr. Wira commented on how microbes that are passively delivered do not colonize. He noted that an area that needs to be focused on is understanding how the field might be able to learn how to colonize human with a different microbiome or increase the diversity of the microbiome among humans. Dr. Ravel agreed that colonization is the big question and acknowledged that there is no viable product on the market or in development to truly alter the human microbiome.

Public Comments

Dr. Gandhi called for public comments; no comments were given.

Adjourn

Dr. Gandhi adjourned the meeting at 4:03 p.m. on April 6, 2017.

Certification

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

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_____ 6/27/17

Monica Gandhi, M.D., M.P.H. Date
Chair, NIH Office of AIDS Research Advisory Council
Professor, University of California, San Francisco, CA

– S –

_____ 06/27/17

Elizabeth Church, Ph.D. Date
Executive Secretary, NIH Office of AIDS Research Advisory Council
OAR, DPCPSI, OD, NIH