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

Office of AIDS Research Advisory Council
Forty-Third Meeting

November 17, 2016
5635 Fishers Lane, Terrace Level Conference Center
Rockville, Maryland

Meeting Minutes

Members Present: Dr. Roy M. (Trip) Gulick (Chair), Dr. Bonnie J. Mathieson (Executive Secretary), Mr. Moisés Agosto-Rosario, Dr. Elizabeth Connick, Dr. Ralph J. DiClemente, Ms. Dázon Dixon Diallo, Dr. Monica Gandhi, Dr. Priscilla Hsue, Dr. Daniel R. Kuritzkes, Dr. Michael M. Lederman, Dr. Ronald T. Mitsuyasu, Dr. Lynne M. Mofenson, Dr. Charles Wira

Ex Officio Members Present: Dr. Victoria J. Davey, Office of Public Health and Environmental Hazards, U.S. Department of Veterans Affairs; Dr. Carl Dieffenbach, Division of AIDS, National Institute of Allergy and Infectious Diseases

Invited Speakers and Guests: Dr. Dan H. Barouch, Dr. Janice E. Clements, Dr. Liza Dawson, Dr. Lynda M. Dee, Dr. Steven G. Deeks, Dr. Anthony S. Fauci, Dr. Maureen M. Goodenow, Dr. Rohan Hazra, Dr. Keith R. Jerome, Dr. Jeffrey D. Lifson, Dr. Ruth Macklin, Dr. David Margolis, Dr. Douglas F. Nixon, Dr. James L. Riley

RESEARCH TOWARDS A CURE

Welcome and Meeting Overview
Roy M. (Trip) Gulick, M.D., M.P.H., Weill Medical College of Cornell University

Dr. Roy Gulick welcomed the participants to the forty-third meeting of the National Institutes of Health (NIH) Office of AIDS Research Advisory Council (OARAC) and asked them to introduce themselves. Meeting materials provided to the participants included the agenda, a conflict-of-interest form, a schedule with dates for the two upcoming OARAC meetings, materials to frame the discussions, and minutes of the April 7, 2016 meeting. The OARAC approved the motion to accept the minutes from the previous council as written.

Dr. Gulick then briefed the Council on the agenda for the day, noting the inclusion of time at the end of the meeting for formal public comments.

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

Dr. Maureen Goodenow welcomed all participants to the meeting, thanking both continuing and new Council members. She noted recent staff changes at OAR and updated the audience on OAR's status. The first 15 years of OAR's existence, 1985 to 2000, were focused on determining what the AIDS epidemic was and how to begin managing it, and the next 15 years included significant progress in the implementation of treatment, prevention, and international programs. The basic research done by the NIH

in drug development and prevention methods enabled the implementation of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) in 2003. OAR now is at the beginning of a new 15-year period, which aligns with the goal of achieving an AIDS-free generation by 2030.

Dr. Goodenow emphasized the amount of work and planning needed to reach an AIDS-free generation by 2030. She pointed out the plateau in funding after the first 15 years, noting that because the amount is not adjusted for inflation, flat funding is actually a decline in buying power. This funding plateau has applied across HIV-related U.S. Government agencies and programs, including PEPFAR. Dr. Goodenow displayed some of the accomplishments driven by NIH research and asked for advice on how best to articulate this progress to stakeholders and funders. The overarching success of the past NIH investments and accomplishments in HIV-related research and care have turned a previously fatal disease into a chronic, treatable disorder with a nearly normal life expectancy.

Despite this progress, nearly 40,000 new cases of HIV are diagnosed each year in the United States, largely among youth, and more than 2 million cases are diagnosed worldwide, with millions of deaths. Long-term comorbidities are poorly understood, and with flat funding, no vaccine, and no cure, the challenges remain significant. OAR has been working on meeting the NIH HIV/AIDS research priorities defined by the Director of the NIH Dr. Francis Collins in 2015, by aligning new funding to projects focused on these new research priorities: reducing incidence; developing therapies; accelerating research toward a cure; and expanding research on comorbidities, complications, and coinfections.

The Joint United Nations Program on HIV/AIDS has published a model predicting that unless new infections are brought under control, costs for treating the disease will be unsustainable in the United States and across the world. Advances in multiple disciplines recently have increased optimism about research toward a cure and development of a successful vaccine strategy. Dr. Goodenow stressed that the urgency of the United Nation's AIDS goals should be transmitted to NIH stakeholders to accelerate the pathway from discovery to implementation. Researchers have the opportunity to help change the trajectory of the epidemic with simple, safe, and sustainable strategies for prevention, treatment, and care.

OAR plans to provide incentives for collaborations and partnerships across NIH Institutes and Centers and with other organizations to reduce comorbidities, align research objectives with the current demographics of the epidemic, and to think globally—not just around the world, but across the spectrum of HIV/AIDS. Strategies for treatment are more promising than ever, and if they are to bear fruit over the next few years, appropriate infrastructure and organization to test and implement them are required for success. Dr. Goodenow emphasized that our current actions set the course for 2030.

Update on OARAC Working Groups for 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)*

Drs. Roy Gulick and Rohan Hazra provided an update on the AIDS information guidelines. Dr. Gulick explained that the adult antiretroviral guidelines were accessed at AIDSinfo.nih.gov 700,000 times during the last fiscal year; the adult opportunistic infection guidelines were accessed 300,000 times. The most recent update to the adult antiretroviral guidelines, in July 2016, included guidance for the use of the new formulation of tenofovir alafenamide (TAF) approved by the U.S. Food and Drug Administration (FDA) in April 2016. TAF now is recommended as a first-line therapy, based on clinical trials showing efficacy and suggesting less bone and renal toxicity than the previous formulation, tenofovir disoproxil fumarate (TDF). Other updates include additional options for regimen switching, more data on drug interactions with oral contraceptives, inclusion of TAF in the hepatitis B treatment section, changes to the regimens in the hepatitis C treatment section, and new recommendations for the treatment of latent tuberculosis. Sections on adverse effects and drug interactions also have been updated.

The opportunistic infection guidelines have been updated multiple times over the last year. Dr. Gulick noted that although the incidence of opportunistic infections in the United States has declined significantly, the demand for opportunistic infection guidelines has increased over time. He theorized that clinicians may be less familiar with opportunistic infections and more in need of guidance. Sections of the opportunistic infection guidelines updated in the past 6 months include those on syphilis, cytomegalovirus (CMV), toxoplasmosis, Chagas disease, herpes simplex, cryptococcosis, and enteric bacteria, and further updates are pending. Evidence supporting the opportunistic infection guidelines was gathered primarily in large, randomized clinical trials during the 1990s, when many people had opportunistic infections. Recent data for the updates are primarily based on observational or cohort data, because now large trials on individuals with opportunistic infections are conducted only in some resource-limited settings.

Dr. Rohan Hazra discussed the pediatric guidelines, published in March 2016. An online update in April 2016 included the new TAF approval, and the fixed-dose combinations (FDCs) were updated to include approved pediatric strengths and consistent formatting for FDCs throughout the drug sections. Another update in September introduced newly approved pediatric strengths of dolutegravir. Dr. Hazra noted that the working group carefully evaluated the actual methods practitioners must use to access pediatric formulations, explaining that pharmacies are required to contact GlaxoSmithKline directly to access these drugs but physicians in the field report this as an efficient and rapid system.

The pediatric guidelines group recently held a call for new members and applications currently are under review. The group plans to update the guidelines every year and is on track for an update in February or March of 2017. These updates are mainly to simplify and streamline the document and improve alignment with other guidelines in areas of overlap. The pediatric opportunistic infection guidelines are planned for updates every 2 years in a rolling cycle. Dr. Hazra described a change in the process and format of the update cycle in which they use a modified GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach.

The perinatal guidelines update was published on October 26, 2016; these guidelines will require regular updates of the individual drug sections as more data are collected about the use of antiretrovirals (ARV) in pregnancy. There were many updates to the current perinatal guidelines due to the rapid evolution of the field, including recommendations for antiretroviral therapy early in pregnancy, reclassification of several therapies as "alternative," and alignment of recommendations for testing women who present in labor with unknown HIV status with current Centers for Disease Control and Prevention (CDC) algorithms. Other updates include recommendations for counseling women regarding intimate partner violence and supportive care and referral of partners for HIV testing. Dr. Hazra thanked the staff and volunteers who support the guidelines, noting that views of each section of the guidelines have increased since the prior year.

Questions

Dr. Hazra was asked how a pregnant woman should interpret some of the language used in the perinatal guidelines. He indicated that conversations between providers and individual patients generally are more nuanced than language in the guidelines and that the data behind the recommendations for new regimens are promising.

An attendee commended the addition of counseling on intimate partner violence. Dr. Hazra clarified that updates are intended to reflect what is happening in care and provide reminders or guidance for providers who do not usually give such counsel.

Dr. Goodenow was asked how the incoming administration might change funding for AIDS issues, and she responded that the NIH always has had broad support across party lines for its research.

An attendee asked whether the guidelines include pricing information. Dr. Gulick explained that a table of average wholesale prices for various regimens has been added to the adult antiretroviral guidelines and that the working groups plan to expand pricing information to the other guidelines.

Introduction to OARAC Session Scientific Theme
Paul A. Sato, M.D., OAR, NIH

Dr. Paul Sato reminded the Council of the challenges experienced in attempting to replicate viral eradication secondarily achieved through the hematopoietic stem cell transplantations Timothy Ray Brown received in 2007 and 2008 as part of therapy for leukemia. Much remains unknown about the way HIV remains latent in hidden reservoirs within the body. Further basic and preclinical research will help develop therapeutic strategies for sustained viral remission, also called a functional cure, and advance the long-term goal of viral eradication.

One major research priority is the study of biomarkers for viral remission or reactivation. Dr. Sato emphasized that OAR would continue to support studies of innovative cure interventions, whether new or relying on combinations of existing therapies. The aim is to achieve sustained viral remission or long-term viral eradication through the development of interventions that are at least as safe as current antiretroviral therapy (ART), do not require tertiary care infrastructure, and are rapidly scalable for use in diverse populations and locations. Dr. Sato reiterated the high priority of identifying and validating novel biomarkers, assays, and imaging techniques using basic, translational, and clinical research. The current research portfolio consists of basic or preclinical, and translational and clinical research testing novel therapies around viral and host mechanisms of latency and reservoir formation.

In the fiscal year 2017 operational budget for OAR, 6 percent of the budget has been allocated to research towards a cure. Although 6 percent may seem small, Dr. Sato noted that only a few years ago there was no budget specifically for cure research. Within the 6 percent allocation, translational research is approximately 50 percent of the funds, basic research about 35 percent, and clinical research 13 percent. Behavioral and social sciences research relevant to a cure accounts for the remaining 2 percent. Dr. Sato invited the council to comment on the portfolio allocation.

Overview of NIAID Strategies for an HIV Cure 2016 Workshop
Daniel R. Kuritzkes, M.D., AIDS Clinical Trials Group/Harvard Medical School

Dr. Daniel Kuritzkes described the 2016 Strategies for an HIV Cure Workshop, organized by the National Institute of Allergy and Infectious Diseases (NIAID), highlighting the accomplishments and challenges in cure clinical research. The central principle that governs HIV cure research is the ability of therapies to either activate expression of HIV for targeted cell death (reactivation) or carry out immune destruction of cells that are expressing HIV proteins (elimination).

Dr. Kuritzkes detailed the approaches to curing HIV, the lessons learned, and the path forward in HIV research. Stem cell transplantation has led to one successful long-term remission and potential cure, in the case of Timothy Ray Brown of the Berlin, Germany case report. Other discoveries have provided insight into ways to reduce the latent HIV reservoir, thus prolonging the time to viral rebound. This latency is maintained in the absence of measurable HIV-specific cellular immunity, but the reduction in reservoir appears to be mediated by immunological mechanisms, such as graft-versus-host disease (GVHD). In addition, the virus has been shown to persist in reservoirs that are inaccessible to clinical sampling. Reactivation of rare, latently-infected cells was sufficient to cause a viral rebound.

Gene therapy approaches in HIV infection have been generally safe, particularly when modified peripheral CD4 T cells were used; genetically modified cells have been shown to persist, and HIV-resistant cells were enriched during a treatment interruption. Achieving consistent and high proportions of a gene knockout (of CCR5) in these cells is challenging, and it is unclear how the genetically modified cells eradicate the latent reservoir. Future directions for stem cell and gene therapy approaches are to confirm the results of the Berlin stem cell transplant patient; validate gene therapy results using

genetically engineered autologous cells; and determine whether introducing a population of HIV-1-resistant cells can adequately eliminate latent infected cells compared to use of gene editing. Efforts also will investigate the immunological mechanisms associated with the reduction of the latent HIV reservoir and whether those mechanisms can be harnessed to target cells harboring replication-competent HIV-1 provirus.

Dr. Kuritzkes pointed out that currently identified latency reactivating agents (LRAs, e.g., histone deacetylase inhibitors and disulfram) are only modestly effective in reactivating latent HIV-1 at their current dosing regimens. The challenge will lie in reactivating the entire reservoir *in vivo,* when observations to date indicate that maximal *in vitro* stimulation reactivates only a fraction of intact proviruses. Given these observations, it is unlikely that reactivation alone will be sufficient to deplete the latent HIV-1 reservoir. The next round of research needs to address the following: identification of safer, more effective approaches to reactivate latent provirus; determination of the number of cycles of reactivation necessary to involve the entire reservoir; and investigation of the optimal timing of latency reactivation relative to the administration of immunologically targeted interventions.

The use of cytokines, immune checkpoint inhibitors, and other immune modulators has provided encouraging data from nonhuman primate (NHP) studies, but limited human clinical trials have been completed to date. Some evidence indicates a modest impact of interferon alpha (IFN-α); however, toxicity profiles of checkpoint inhibitors continue to be a growing concern in the oncology community. Therefore, regulatory agencies have shown considerable caution in approaching clinical trials with these agents in healthy HIV-infected persons, whose virus is well controlled by current ARV regimens, primarily due to the as-yet-undefined risk-to-benefit ratio for these "immune-based" treatment approaches. The HIV research community and patients are showing continued interest in exploring the role of immunomodulatory therapies in pilot studies both as single agents and in combination with therapeutic vaccines. Safety will remain a primary endpoint and a priority into the next generation of such studies.

Therapeutic vaccines for HIV have been studied for more than 20 years, and nearly all candidate vaccines have shown some immunogenicity in Phase 1 and Phase 2 clinical trials. Encouraging results also have been reported from some preclinical NHP studies, but those have not translated readily to clinical studies. Post-vaccine control of viremia in clinical trials has been modest, with minimal statistically significant differences between the control and vaccine arms of the trials. In addition, little to no consensus exists on correlates of vaccine efficacy, and a systematic approach for building on the results of prior studies is yet to be determined. In addressing these challenges, there is a clear need to define endpoints for clinical trials, correlates of activity, long-term objectives, and criteria on the decision to discontinue novel candidate investigations, as well as to maintain a sustained focus on the most promising candidate vaccines.

There is strong interest in using HIV broadly neutralizing antibodies (bNAbs), bifunctional antibodies, and chimeric antigen receptor (CAR) T cells for HIV therapy. Studies conducted within the AIDS Clinical Trials Group (ACTG), at the NIH, and at Rockefeller University utilizing bNAbs revealed modest delays in the time to virologic rebound, but no demonstrated effect has been seen, to date, on the viral reservoir. Preexisting resistant minority variants have emerged at the time of rebound, suggesting that combination bNAb therapy will be required to maintain viral suppression. Future research efforts will focus on determining whether bNAbs or bifunctional antibodies can direct innate immunity against latently infected cells, against productively infected cells, or are accelerating immune-mediated clearance of plasma virus. It also will be necessary to determine whether bNAbs will work as a once time therapy or are most likely to succeed as long-acting maintenance agents. CAR T cells directed against malignant cells have been shown to induce a cytokine storm, a potentially fatal immune reaction. Improved immune cell engineering to minimize this risk will need to be investigated to determine whether HIV-directed CAR T cells can be safely harnessed to eradicate the viral reservoir. The potential risks for developing immune-mediated encephalitis will need to be monitored if interventions target virus resident in the central nervous system (CNS).

Lastly, the results from the use of early ART initiation in the Virological and Immunological Studies in Controllers after Treatment Interruption (VISCONTI) trial in France have stimulated the interest of other groups to participate in these type of studies. Investigators have been able to show that very early initiation of ART post-infection limits, but does not prevent, seeding of the HIV reservoir. The importance of the use of proper controls after treatment interruption trials was emphasized. Both virological and immunological mechanisms are likely to contribute to the post-treatment control of HIV, but it remains unclear how these findings can be translated to chronic infection. The VISCONTI data provide evidence that acute infection is an informative model system, but only a stepping stone towards a cure.

Dr. Kuritzkes reported briefly on the work of the ACTG and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network. The ACTG is investigating interventions to reduce or control replication-competent HIV using various treatment modalities, including a long-term study of ART in HIV controllers. A portfolio of studies is being conducted within the IMPAACT Network, including very early ART in newborns, studies with bNAbs, and other interventions in older children. In closing, Dr. Kuritzkes remarked on the importance of correlates and surrogates markers for an HIV cure, the need to rethink post-treatment interruption, and unanswered questions in HIV cure research.

Questions

A participant pointed out that follicular dendritic cells (FDCs) contain extracellular virus in the untreated state that could play a role in relapse and asked whether studies to investigate the non-cellular reservoir would be included in future research. Dr. Kuritzkes acknowledged the importance of deciphering the role of the non-cellular reservoir in patient relapse, but the delay in patient relapse would be hard to explain given the considerable amount of virus that normally binds to the FDCs. Another participant described current work being performed to investigate the infectious virus in immune complexes on the FDC network in response to ART, which might address this issue.

In response to a question about natural killer (NK) cells serving as surrogate markers, Dr. Kuritzkes replied that the objective is to have dynamic markers that respond quickly and are capable of reducing the viral reservoirs. Whether NK cells (or another cell subset) will have these properties is yet to be determined.

A participant commented that the monocyte/macrophage has not been well studied as a potential reservoir. An opportunity exists to leverage the many ongoing NHP studies in HIV research to investigate the virus in the cerebrospinal fluid (CSF). The virus has been shown to have persistent effects on the brain, and CSF specimens could provide additional insights into treatments. Dr. Kuritzkes noted that ACTG's long-term follow-up study collects CSF from patients.

General Discussion

Dr. Gulick invited attendees to comment on any of the preceding presentations.

An attendee commented that in light of Dr. Sato's emphasis on both remission and eradication, the Mississippi child should be considered the best example to date of remission after treatment with an intervention. Dr. Gulick and others discussed the ability of patients to remain on antiretroviral therapy for many years, noting that location, life events, and resource limitations can affect access to therapy. It was generally agreed that long-lasting agents are the future of antiretroviral therapy. .A meeting participant noted the added importance of long-acting therapies in reducing stigma; even the promise of a cure conveys a large benefit on the community in further reduction of stigma. Dr. Kuritzkes added that defining the parameters of remission is important—remission is very different than a cure, and a strategy that requires periodic boosting is not a cure but rather another form of intermittent therapy. Another participant pointed out that it is a false dichotomy to talk about a short-term goal of remission and a long-term goal of a cure; the scientific efforts to reach either overlap significantly, and researchers have little

understanding of how either will work. He expressed concern about how to direct the research if it is defined that one goal should come first and one second.

An attendee asked whether it would be fruitful to have a discussion about how participants are recruited to cure research. In many locations, individuals who have access to the least toxic therapies are leading healthier lives, whereas low-income groups using older therapies have had less success. She recommended that research for remission and cure strategies focus on those who cannot maintain their current therapies.

In closing this discussion, Dr. Gulick identified the two main points of debate: (1) the importance of viral reservoirs beyond the blood and lymph nodes (e.g. central nervous system), and (2) remission versus eradication.

Addressing HIV Persistence: A Novel Approach Involving α4β7 Integrin
Anthony S. Fauci, M.D., NIAID, NIH

Dr. Anthony Fauci described approaches to address HIV persistence, including recent findings using α4β7 integrin. The first study of the effects of the discontinuation of therapy, published in 1999, showed that HIV-1 viral loads inevitably rebounded in patients with sustained viral suppression after cessation of highly active antiretroviral therapy.

HIV persistence can be addressed either by eradicating the reservoir or controlling viral rebound to produce sustained virologic remission. Sustained virologic remission may be best achieved by commencing ART as early as possible in the infection. Following early suppression, the following three approaches are considered: (1) take advantage of natural, HIV-specific immunity; (2) develop a therapeutic vaccine to enhance or broaden the immune response; or (3) control the infection via passive transfer of HIV-specific antibodies. More than 300 neutralizing antibodies have been described; HIV-1 antibodies 3BNC117 and VRC01, which interact with the CD4 binding site of the virus, have been shown to delay viral rebound after interruption of ART, but they do not eradicate the virus.

The role of integrin α4β7 in HIV/simian immunodeficiency virus (SIV) disease pathogenesis has been explored. Integrin α4β7, the gut mucosal homing receptor for peripheral T cells, is a receptor to which the HIV-1 envelope protein binds, producing aberrant signaling. The natural ligands of α4β7 are MadCAM, VCAM, and fibronectin, and its principal function is to mediate migration to and retention of leukocytes in the gut. On the surface of CD4+ T cells, α4β7 binds to the cell envelope close to CD4. The population of CD4+ T cells on whose cell surface integrin α4β7 forms a complex with CD4 were found to be highly susceptible to HIV-1 infection. Founder viruses involved in early transmission of HIV were discovered to bind preferentially to α4β7, revealing that α4β7+/CD4+ T cells are key targets in mucosal transmission. In a rhesus macaque model, blocking α4β7 decreased plasma and gastrointestinal tissue viral loads in SIV-infected animals.

These results suggest that a monoclonal antibody directed against α4β7 might protect against mucosal transmission of SIV/HIV. A rhesus adapted anti-α4β7 antibody has been made that has very similar binding characteristics to the human antibody, vedolizumab, which is used to treat ulcerative colitis and Crohn's disease. Targeting α4β7 with an anti-α4β7 antibody was found to reduce SIV transmission from low-dose vaginal challenge in NHP. The viral load in gut biopsies of the antibody-treated animals that became infected was lower than in controls. The proviral load in gut-associated lymphatic tissue and other peripheral lymphoid tissues following termination of anti-α4β7 treatment remained lower than in controls.

Because the anti-α4β7 antibody was able to prevent transmission, they tested whether it would, induce sustained virologic remission following interruption of ART in animals already infected with SIV. NHPs were treated with ART plus anti-α4β7 (test cases) or immunoglobulin G (IgG) controls and the plasma viral loads were measured following cessation of treatment over a period of 30 weeks. Animals that received anti-α4β7 antibody settled into chronic suppression after brief increases in viral load, whereas the viral loads of IgG controls rebounded and stayed relatively high. The geometric means of plasma

viremia levels of the two study arms following treatment cessation were significantly different ($p < 0.0001$). The mechanism by which this suppression was achieved, however, is not known. An antibody response against variable region 2 of envelope glycoprotein 120 (gp120 V2) was observed in all of the test cases but in only three of seven controls. Study RV144 has shown the first signal of efficacy in an HIV vaccine clinical trial, and the vaccine targets an area on gp120 V2 that aligns with HIV/SIV peptide 43.

Dr. Fauci summarized by saying that combining anti-α4β7 infusions with ART induced long-term virologic suppression following discontinuation of all therapy. These treatments restored CD4+ T cells in the gut, blood, and certain peripheral lymphoid tissue. Most important, although the mechanisms of this effect are unknown, it was correlated with an increase in cytokine-synthesizing NK cells, an increase in NKp44+ innate lymphoid cells, and a skewing of the antibody response toward the gp120 V2 domain. The studies described might point to mechanisms that could be pursued for HIV prevention and/or remission maintenance. Dr. Fauci noted that NIAID currently is involved in an exploratory clinical trial of the efficacy of vedolizumab in inducing sustained viral remission following an intensively monitored antiretroviral therapy pause for analytical purposes.

Questions

Participants questioned whether short-term increases in viral loads might be occurring in the anti-α4β7 antibody test cases. Dr. Fauci responded that measurements occurred monthly or bimonthly, not weekly, so he cannot be certain that no short-term signals are occurring.

The protocol of the human clinical trial was discussed. The timing of administering the antibody relative to ART in the NHP study of the anti-α4β7 antibody was intended to mimic as closely as possible the protocol of the human clinical trial. The animals were treated with ART until they were aviremic and then were administered the antibody. The human trial involves recruiting stable subjects who have a CD4 count greater than 450 cells/mm^3 and a viral load well-controlled by ART. The subjects will be given an infusion of antibody, ART will be stopped, and then two more infusions will be given.

Dr. Fauci indicated that the effect of the anti-α4β7 antibody likely was not on lymphocyte trafficking. Instead, the effect is more likely a direct interaction with the α4β7+/CD4+ T cells to induce a new type of immune response. In response to a related question, Dr. Fauci stated that as the virus buds, it can have high levels of α4β7 binding sites.

An attendee suggested that in the animal study, bNAbs produced after treatment might have led to the sustained remission. Dr. Fauci responded that in earlier studies, removing the bNAbs led to viral rebound, sooner or later. In this study, however, the virus did not rebound, implying that the remission is the result of an immunological response because the virus is present and replication-competent but does not rebound. A current area of investigation is whether depleting CD8+ T cells might lead to viral rebound.

Highlights of the NIAID Strategies for an HIV Cure 2016 Workshop: Basic/Preclinical Research
Janice E. Clements, Ph.D., Johns Hopkins University School of Medicine

Dr. Janice Clements explained that a barrier to eradicating HIV is the existence of a latent reservoir of cells that resists drug intensification and does not appear to evolve over time. Only 11.7 percent of the reservoir has an intact genome, and only a very small fraction of those genetically intact cells are capable of being reactivated. For reasons that are poorly understood, this functional reservoir of HIV-1 viruses, defined as cells that can make new virus, requires many rounds of reactivation to begin to replicate virus. The origin of the reservoir is not well understood. Although patients have a high diversity of virus, a large number of identical, independent clones are consistently present in plasma. The viruses are not just replicating themselves; rather, infected T cells that carry HIV-1 provirus can undergo clonal expansion, accounting for the majority—57 percent—of the HIV reservoir.

HIV integration sites have been studied under the National Cancer Institute's (NCI) HIV Dynamics and Replication Program. Clones of HIV-infected cells have been found to arise early during infection and have been documented to persist as long as 10 years. Among individuals on ART, more than 40 percent of all infected cells are clonal in origin. Clones can carry infectious proviruses and release these proviruses into the blood. Only a small fraction of the clonal cells produce viral RNA, and only some infected clones grow large enough to be detected. Clones do not arise as a consequence of ART; they also are found in HIV-infected self-controllers. Low levels of virus are found in the lymph nodes and other tissues of HIV controllers.

Another recent advance is the development of new approaches to imaging HIV reservoirs. Whole-animal positron emission tomography (PET) scans conducted before and after ART reveal changes in infection. In addition, recent work (RNAscope and DNAscope) has led to the ability to visualize viral RNA and DNA in tissues, allowing determination of which genes are being expressed actively. These highly sensitive *in situ* hybridization techniques enable enumeration of latent cells.

Existing data that indicated resistance of HIV-infected macrophages to CD8+ cytotoxic T lymphocyte (CTL) killing have been reanalyzed, revealing that HIV-infected macrophages resist CTL-induced necrosis, stimulate pro-inflammatory and chemokine expression, and contribute to chronic inflammation and maintenance of viral reservoirs.

In closing, Dr. Clements indicated that the source of a stable viral CD4+ T cell reservoir now is better understood, as are the molecular forms of defective HIV and its role in persistence. Next steps include studying what occurs in a single latent cell using such new technologies as microfluidic and single-cell analysis; searching for long-lived latent HIV reservoirs other than CD4+ T cells; and taking advantage of opportunities offered by the SIV model, including the ability to obtain tissue specimens not readily available in humans.

DARE Martin Delaney Collaboratory
Steven G. Deeks, M.D., University of California, San Francisco

Dr. Steven Deeks explained that what underlies the efforts of the Delaney AIDS Research Enterprise (DARE) Collaboratory is that virus-producing cells persist during ART. Enhanced killing strategies are needed to reduce the reservoir, because even a single virus can cause major clinical consequences. Likely, a sustained host response will be needed that will involve T cells. An ideal intervention would generate activated effector memory CD8+ T cells that localize to where the virus resides, respond rapidly, target conserved epitopes, and are maintained indefinitely. Achieving a cure or lasting remission will require detailed knowledge of the mechanism for virus persistence and a way to measure HIV in the target tissues for use in clinical trials.

The DARE Collaboratory has four research foci. The first is disruption of the B cell follicle, which has been found to serve as a sanctuary for SIV infection in elite controllers. This leads to the questions of whether B cell follicle disruption will lead to reduction of SIV during ART, whether it will enhance the efficacy of a therapeutic vaccine, whether it will enhance the efficacy of other interventions, and what will be the ideal combination therapy. The second focus is on lymphoid tissue biology. Evidence exists that the virus in blood and lymph nodes differs significantly, with virus in blood often being clonal and archival whereas the virus in lymph nodes is replicating actively. The key questions regarding the biology and anatomy of the persistent viral reservoir are where replication-competent HIV resides during short-term ART, long-term ART, and among those initiating therapy soon after HIV infection versus those starting ART months to years later, as well as how the reservoir can be measured using PET-based imaging. The third focus is on characterization of immune checkpoint receptors in ARV-treated HIV disease. Initial studies showed that latent HIV is enriched in CD4+ T cells that express programmed cell death protein 1 (PD-1), TIGIT, and lymphocyte-activation gene 3 (LAG-3). Other results suggest that inhibition of immunoregulatory pathways might contribute to SIV/HIV control and enhance therapeutic vaccine efficacy. Collaborations with the NCI to recruit cancer patients who are HIV positive are planned, as are NHP studies. The fourth focus is testing the safety and immunogenicity of the CMV vector

engineered as a replication-deficient HIV/SIV vaccine. Initial studies involving treatment of SIV from established low-inoculum infections showed virus eradication in approximately 50 percent of the test subjects. Safety and immunogenicity studies are planned using various cohorts to determine the lowest effective dose, as well as outcomes in acute versus chronic cases. After being proved safe as a monotherapy, the vaccine will be tested in combination with other therapeutics. Combination strategies to create an environment that will make the vaccine more efficacious likely will be needed to achieve a durable remission; therefore, the DARE program will leverage work by partner institutions.

Questions

The rationale for follicle disruption, given that B cell follicles reconstitute after disruption ceases, was discussed. Dr. Deeks responded that the researchers hypothesize that after disruption, the reservoir will be smaller, allowing the immune system to gain advantage. A participant added that multiple disruption cycles are likely to have cumulative effects. Other possible approaches include engineering follicular helper T (Tfh) cells, as well as producing cytokines and immunomodulators.

A participant asked whether, in the vaccine study in which 55 percent of the animals were protected, the virus differed between those who were cured and those whose viral load rebounded. Dr. Jeff Lifson, a collaborator, responded that no obvious differences were found.

A participant pointed out that in autopsy samples from patients who had been on long-term therapy, exceptionally good mixing between the lymph nodes and blood has been observed, indicating that virus migrated freely in and out of the lymph nodes. Dr. Deeks noted that this finding would need to be reconciled against findings by others that the cell types enriched in lymph nodes differ from that in blood.

CARE Martin Delaney Collaboratory
David Margolis, M.D., University of North Carolina at Chapel Hill

The mission of the Collaboratory of AIDS Researchers for Eradication (CARE) is to pursue a goal of eradication of HIV infection through an accessible, interactive, and coordinated program. Dr. David Margolis indicated that CARE has focused on the development and discovery of agents and targets for latency reversal, including identifying proteins and antigens that reveal which cells to clear. Initial discovery efforts focused on a high-throughput approach, which revealed relatively few latency reversal agents (LRAs), approximately 4,500 out of 3 million candidates. Two-thirds of these LRAs were compounds with an unknown mechanism of action. CARE, on the other hand, is targeting agents by focusing on agents with latency reversal activity early in the disease. CARE is focusing on cell types and compartments with LRA activity, addressing pharmacokinetics, and conducting repeat dosing and combination studies. The hits with unknown mechanisms were tested in *ex vivo* models, revealing that most were inactive. Even when active, results for a given compound and model frequently varied. Primary T-cell analysis of hits with unknown mechanisms was conducted, resulting in 18 hits with activity in three or more models but many compounds that were inactive.

CARE is now focusing on retargeting antibodies to bind to HIV-infected cells. Antibody-like dual-affinity re-targeting (DART) proteins have been constructed from antibodies to create agents that bind to HIV-infected cells at two distinct sites. DARTs are new tools to clear infected cells from HIV-infected individuals. Two DARTs are available for testing, and four more are under development. Two studies of DARTs have been conducted in human cells *ex vivo*, which showed that DARTs together with CD8+ CTL eliminated HIV-infected CD4+ T cells. Combination therapy likely will be necessary to target all of the reservoir. New DARTs are being constructed with monoclonal antibodies to bind to HIV-infected cells with the goal of promoting CD8-mediated T cell killing of HIV-infected cells after administration of a latency reactivating agent.

CARE is conducting assay validation and development studies to support *in vitro, ex vivo,* and *in vivo* studies. Metrics are needed for envelope expression so that infected cells can be quantified upon latency reactivation. Quantification methods evaluated include Quantum Simply Cellular beads and Quantrix

SIMOA™ technology. Dr. Margolis provided examples of data obtained by SIMOA™ from a clinical study of the effects of dosing with the LRA vorinostat.

Candidate *in vivo* models to test latency reversal and clearance include human clinical trials, NHPs infected with SIV and simian/human immunodeficiency virus (SHIV), and humanized mice. The primary outcome will be quantifying the functional viral reservoir. The first clinical trial protocol proposed for a combination latency reversal and clearance trial involves alternate dosing with vorinostat and vaccine (Argos dendritic cell therapy). The second protocol involves dosing with a vorinostat series and infusions of HIV-1 specific T cells.

Dr. Margolis shared the 5-year timeline for CARE. Milestones included new LRA discovery, LRA testing in animal models, DART development, combination trials of LRAs, and DARTs in animal models, and safety and efficacy testing of single arms in humans. CARE is working toward improved community engagement for education and information transfer.

Questions

A participant asked whether the clinical trials have received FDA approval; Dr. Margolis responded that the trials were approved by the FDA and have enrolled several patients. The cell-based study protocol is awaiting final approval by clinical and community groups.

defeatHIV Martin Delaney Collaboratory
Keith R. Jerome, M.D., Ph.D., Fred Hutchinson Cancer Research Center, University of Washington

Dr. Keith Jerome described the primary strategy that the defeatHIV Collaboratory intends to pursue is to effect a sterilizing cure for HIV. He presented the initial goals of defeatHIV, which will focus on the use of cell and gene therapy approaches, including the establishment of robust NHP models for gene therapy. One gene therapy approach would enable efficient disruption of CCR5 expression and the overall evaluation of the immune control of HIV after transplantation of hematopoietic cells first, followed by genetically modified cells. He described the experimental design of transplantation studies conducted during the first iteration of this collaboratory. Studies were performed that exhibited durable suppression of viremia using combinatorial antiretroviral therapy. Experimentally, effective anti-retroviral therapy (three-drug regiment, cART) was administered to animals several weeks post SHIV challenge (virus suppression), then cART removal caused characteristic viremia rebound. Animals displayed HIV pathology—T cell depletion with multiple reservoir sites throughout tissues. CCR5-modified transplanted stem cells led to long-term multi-lineage engraftment and restoration of a functional immune system. Dr. Jerome explained that the findings demonstrated that the first iteration of defeatHIV established a valuable animal HIV model, which provided key insights into the challenges of translating cell and gene therapy research for an HIV cure. Identifying cell and gene therapy strategies, which can be tested in this NHP model and affect the HIV reservoir in human trials, must be explored.

Dr. Jerome stated that three strategies will be tested in established models for the next 5 years. He presented a schematic of the proposed experimental approach using cell and gene therapy strategies. Under the first strategy, chimeric antigen receptor (CAR) T cells containing a targeting element (e.g., broadly reactive antibody) fused to a signaling component will induce cell co-stimulation and signaling. Dr. Jerome hypothesized that the efficacy of CAR-based therapy requires recognition of reservoir HIV-infected cells by CAR T cells, which may be established through latency reversal. The second strategy involves the passive or vectored delivery of the synthetic HIV-neutralizing bispecific molecule eCD4-Ig with an incorporated peptide domain. The hypothesis is that virus replication from reactivated reservoir cells will be reduced through neutralization by eCD4-Ig. The third approach, gene protection of T cells, builds upon the first two strategies. The goal is to enhance an orchestrated immune response to HIV by protecting uninfected T cells, increasing their activation and frequencies. They have proposed that the efficacy of gene-protected T cells will be maximized when combined with therapeutic vaccination.

Dr. Jerome noted that with the NHP studies, all of the approaches and each experimental animal group will be compared with a common control cohort, allowing the most efficient use of animals. Results will aid in the development of combination approaches in animals and ultimately human trials. He concluded that the cell and gene therapy approaches are expanding, and combined approaches are most likely to be successful clinically. NHP models will continue to be informative and the model for choosing strategies to use in clinical studies. Dr. Jerome stressed the importance of strong collaboratories and inter-collaboratory interactions.

General Discussion

The DARE Collaboratory's protocol involving the CMV vaccine was discussed. A participant clarified that the anticipated outcome of the vaccine is viral control, rather than eradication. Dr. Deeks agreed that eradication is not a feasible outcome of the interventions being tested, and anecdotal cases of complete eradication of the virus in humans treated with highly complex, high-risk, interventions (e.g. bone marrow transplant) are not generalizable at this time. The new interventions currently being tested might reduce the viral reservoir substantially, but are unlikely to be curative.

A participant made the point that cells infected with HIV or SIV that have a single integration site might develop different immune phenotypes depending on their developmental environment. Dr. Deeks responded that clones exist in multiple T cell subsets, indicating that different types of cells can be infected and that a total analysis by integration site is needed to understand the targets of integration.

Transmission of HIV from mother to child was discussed. A few participants emphasized the need for more study of the neonatal immune system. Point-of-care testing around birth offers an opportunity to treat infection almost at inception. Currently, clinical studies on mother-to-child transmission are being conducted in Botswana, South Africa, and other international sites via the IMPAACT Network. Advances in basic science, such as those discussed at this meeting, are needed to inform these clinical studies. Studies of treatment efficacy in early infection in human subjects, versus chronic disease, are being studied in NHP models. Dr. Persaud countered that based on preliminary data from blood samples of mother-to-child transmission cases that have been treated successfully, clonal expansion does not appear to be different in individuals infected as adults and those infected by mother-to-child transmission. Another attendee pointed to clinical testing of integrase inhibitors such as raltegravir for the treatment of infants. This is particularly appealing, given that a large fraction of infants in some regions of the world have HIV that is resistant to nevirapine. Studies of the efficacy of bNAbs for reducing viral reservoirs in the first year of life also are planned. Blood volume limitations are a particular challenge in infants, which makes identification of biomarkers or better assays of HIV persistence essential in the era of triple combination therapy.

The question of active replication of the viral reservoir was discussed. Dr. Deeks asserted that more virus likely is being produced from the viral reservoir but not necessarily through replication and spread to new cells. In some individuals, up to 10 to 25 percent of the reservoir is being expressed daily. Cells are making virus but not dying. Data are convincing that sequence evolution is not occurring over time during treatment, but sequence evolution might not be sufficiently sensitive to detect low-level, sporadic, isolated replication events. The vast majority of the reservoir is likely static, but whether or not low levels of static virus can spread in some individuals is not known.

Lynda Dee, J.D., emphasized the need to better understand the degree of community engagement in research being done in the collaboratories, particularly the degree of engagement outside of community advisory boards. She requested that collaboratories provide regular updates on their community engagement strategies and advocated for partnering with the collaboratories and community-based organizations and nongovernmental organizations, as well as with the key and vulnerable populations that they represent. The effects on quality of life of whether research outcomes represent a cure, remission, or sustained suppression need to be considered.

I4C Martin Delaney Collaboratory
Dan H. Barouch, M.D., Ph.D., Beth Israel Deaconess Medical Center/Harvard Medical School

Dr. Dan Barouch presented on the combined immunologic approaches to cure HIV-1 (I4C)—a new Martin Delaney Collaboratory. The goal of the program is to evaluate active and passive immunologic strategies to target the viral reservoir in SHIV-infected rhesus monkeys and HIV-infected humans. They hypothesize that a combined immunologic approach that optimizes antiviral humoral and cellular immune responses, together with latency reversal, effectively will reduce or control the viral reservoir in ART-suppressed, SHIV-infected NHPs and in ART-suppressed HIV-1-infected humans to achieve a functional cure. Given the hypothesis, a two-fold strategy is proposed: rapid elimination of the majority of the virally-infected cells, employing use of bNAbs combined with latency reversal; and long-term immune control of residual virally-infected cells, for which the concept is to use therapeutic vaccines to augment immunity. He summarized that iterative testing of bNAbs (passive immunization) and vaccines (active immunization) is the combined immunologic approach they are employing for induction of a *functional cure* of HIV. Dr. Barouch explained that these efforts were being undertaken in collaboration with industry partners—Janssen Vaccine and Prevention and Gilead Sciences.

Dr. Barouch detailed other clinical products the group is evaluating and the preclinical and clinical studies (Phase I and Phase II) being conducted accordingly. Phase I trials testing two HIV bNAbs, designated PGT121 and PDGM1400, will be supported by the Bill and Melinda Gates Foundation, and VRC07 and N6 trials will be conducted in collaboration with the Vaccine Research Center (VRC), NIH. Current Phase I trials supported by Gilead Sciences are investigating the effects of GS-9620 on HIV-1. Regarding vaccines, the Ad26/MVA Phase I and Phase II clinical trials currently are in progress, and a Phase I trial to evaluate a dendritic cell vaccine is planned to begin in 2017 at the University of Pittsburgh. Dr. Barouch remarked on recent findings, published November 11, 2016, in *Nature* ("Ad26/MVA Therapeutic Vaccination with TLR7 Stimulation in SIV-Infected Rhesus Monkeys"), showing decreased levels of viral DNA in lymph nodes and peripheral blood, as well as improved virologic control and delayed viral rebound following discontinuation of ART. These responses correlated inversely with set-point viral loads and directly with the time to viral rebound. He summarized preclinical studies which demonstrate that PGT121 and AD26/MVA, in combination with TLR7 agent, affect viral rebound following the discontinuation of ART in NHPs. These data suggest that passive and active immunization strategies alone may be able to target the viral reservoir.

The question being addressed is whether the combination of active and passive immunization could improve therapeutic efficacy. This collaboratory has established two efforts: Focus 1, Efficiency of Combined Approaches, and Focus 2, Mechanism and Next Generation of Products. Using hypothesis-driven research and related specific aims, Focus 1 and Focus 2 will explore active and passive immunization together with latency reversal to establish virologic control without ART and facilitate development of HIV-1 cure strategies.

Questions

A participant asked about the ability of HIV bNAbs to produce sustained control post-ART and in the years beyond and whether bNAbs were known to have special effects on the immune system. Dr. Barouch replied that bNAbs administered in combination with latency reversal agents to ART-suppressed infected individuals, acute or chronic, are anticipated to produce significant log kill of virally infected cells. This will depend on the effectiveness of the compounds and the proof-of-concept studies yet to be completed. In regard to the immune system effects, Dr. Barouch noted that new data in the literature suggest an expansion of the autologous antibody response (B-memory cell response) upon administration of bNAbs.

BEAT-HIV Martin Delaney Collaboratory
James L. Riley, Ph.D., Perelman School of Medicine, University of Pennsylvania

Dr. James Riley stated that the BEAT-HIV Collaboratory's mission is to develop and test innovative combined immunotherapy strategies to either eradicate or induce remission in the absence of ART. The collaboratory is structured with an executive committee that oversees three key areas: Research Focus Groups (e.g., Working Groups), Scientific Research Supports, and Community Engagement.

One BEAT-HIV working group is addressing the challenge of the expanding reservoir by investigating the many integrations, compartments, and key biological relationships. Another is exploring how IFNα treatment leads to HIV depletion in the gastrointestinal tract. BEAT-HIV is conducting a Phase II clinical trial to investigate the effects of peg-IFN-α2b combined with bNAbs 3BN117/10-1074. One treatment arm of the study will include an intensively monitored antiretroviral pause. Study participants will be monitored for rebound time, HIV latent reservoir levels, and viral resistance. Dr. Riley touched on key data involving infusion of C-C chemokine receptor type 5 (CCR5)-modified CD4 T cells that are driving the experimental plan for the T cell therapy clinical trial that Working Group 4 is poised to do. He noted the uncertainties in the appropriate length of the treatment interruption period. Patients initially rebound but may experience a 50 percent decrease in their viral loads. Working Group 4 will engineer HIV-resistant and HIV-specific T cells and will address key questions regarding the optimal use of these cells for induction of a cure. The draft clinical design is expected to reflect the results from this exercise and forge the BEAT-HIV path forward to a cure for HIV.

Questions

A participant asked for clarification on the T cell therapy clinical trial design in terms of safety and FDA requirements. Dr. Riley replied that the FDA has not been the limiting factor thus far in developing the trial; safety issues related to continuing the treatment interruption past initial viral rebound to when the virus reaches its original set point or potentially a set point at a lower level have encountered resistance at the NIH. Specific guidelines exist for immediately restoring treatment to patients who reach their pre-treatment set points, and long-term monitoring is a requirement of any gene therapy trial.

BELIEVE Martin Delaney Collaboratory
Douglas F. Nixon, M.D., Ph.D., The George Washington University

Dr. Douglas Nixon reported on the Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication (BELIEVE) Collaboratory. The goal of the collaboratory is to enhance autologous lymphocytes *ex vivo* and infuse them in combination with latency-reversing agents to target effectors to sites where latent virus resides. BELIEVE is composed of researchers from the United States, Brazil, Canada, and Mexico, located at 18 different participating universities, medical centers, and hospitals. Dr. Nixon acknowledged the BELIEVE executive committee, community engagement group, initial research focus groups (IRFs), management and operations, support group, and corporate partners: Altor BioScience and Torque.

According to soon-to-be-published data from the Government of the District of Columbia's Department of Health, HIV/AIDS, Hepatitis, STD and TB Administration (HAHSTA), the highest number of reported cases of HIV—epidemic levels—are seen in the southeast quadrant of Washington, D.C. The number of newly diagnosed cases has decreased, but the number of people living with HIV in the District remains high. Demographically, 4 percent of African American males and 2 percent of white males, Hispanic males, and African American females are infected with HIV. To address this problem, the D.C.-based BELIEVE Collaboratory held a kickoff meeting October 2016 with the D.C. Center for AIDS Research (CFAR).

Dr. Nixon remarked on a compound that the collaboratory is investigating. ALT-803, Altor BioScience's lead interleukin 15 (IL-15) superagonist product, is being used in clinical trials, including one HIV-related trial. ALT-803 induces cell-mediated proliferation and IFNγ production, increases serum half-life, and prolongs residence time in lymphoid tissue. In addition to its superagonistic effects, ALT-803 behaves as a latency-reversing agent. In addition, the biotechnology company Torque has developed a Backpack

Cell Therapy™ product that is designed to enhance the function of adoptively transferred immune cells and could be used to deliver latency reversing agents. BELIEVE is partnering with them to develop novel HIV immunotherapies for clinical trials.

Strong community engagement in the collaboratory focuses primarily in three areas: developing an active and representative community advisory board, providing input and feedback on clinical protocols and ethical concerns, and developing outreach and educational tools. BELIEVE has uniquely paired community advisory representatives with scientists in each of the Initial Research Foci (IRFs) to interpret scientific discoveries and progress to the community. Dr. Nixon described the major scientific objectives of the IRFs: IRF 1 will harness natural and engineered CTLs to eradicate HIV reservoirs; IRF 2 is working to combine natural killer cells with bNAbs to target antibody-dependent cell-mediated cytotoxicity against the viral reservoir; IRF 3 is focusing on directing immune effectors to viral sanctuaries in lymphoid tissue; and IRF 4 will combine T cell therapy with an IL-15 superagonist to target HIV reservoirs in trail participants.

Questions

A participant asked about the receptor chain differences between Altor's ALT-803 and heterodimeric IL-15. Dr. Nixon explained that Altor had compared them and identified some differences. Given the challenging nature of developing an effective IL-15 agonist, it is rewarding to know that others are making these efforts.

Ethical Issues in HIV Cure Studies Using Intensively Monitored ART Pauses (IMAPs)
Liza Dawson, Ph.D., National Institute of Allergy and Infectious Diseases, NIH

Dr. Liza Dawson presented on the risk of IMAPs – also referred to as analytical treatment interruptions (ATI) - and whether the risk is justified in early-phase trials. How risk analysis relates to broader ethical concerns and issues must be considered, as well as the fact that risk assessment is complicated by three factors: (1) the lack of directly applicable data to assess risk, (2) the large uncertainty about downstream effects, and (3) contravening clinical practice guidelines and standards of care. Additionally, early-phase cure studies differ from typical drug development studies, complicating the risk-benefit analysis.

Regarding the lack of applicable data, the results of the NIH-sponsored Strategies for Management of Antiretroviral Therapy (SMART) study data published in 2009 used a very low CD4 threshold for initiating therapy, the duration of treatment interruption in some cases was long (so virus replication would have been ongoing), and a large number of subjects was needed in that study to see significant differences. Given the expected hazard ratio for treatment interruption, smaller studies with less prolonged treatment interruptions would be unlikely to observe any significant differences. Therefore, SMART study data cannot be used directly to extrapolate what is occurring in current cure trials with IMAPs. It is not possible to measure the kind of clinical consequences that are important from the patient or the research subject perspective. Dr. Dawson cited a recent presentation stating that risk to third parties (e.g. those who could be infected if HIV+ individuals discontinue their ART regimens and transmit virus) is an unexplored area of research ethics, including the social and community implications of performing studies. In addition to factors that are observable in a trial, theoretical risks exist; a number of parameters could lead to downstream consequences of concern (e.g., reservoir expansion or development of drug resistance). Direct assessment would require collecting adverse clinical outcomes of interrupted versus non-interrupted patients in the same time frame; these outcomes are impossible to extrapolate in a quantitative way from the SMART or from the Strategic Timing of Antiretroviral Treatment (START) study, another study whose results are often discussed as potentially relevant in this context.

Regarding theoretical versus observable harms, the ability to predict potential harm (e.g., clinical consequences of reservoir expansion) in HIV IMAP studies is hampered by the current state of the science. Behavioral economics studies show a human preference for "ambiguity aversion"; that is, decision makers frequently prefer an unambiguous choice even when the overall odds are equal or more

favorable for the ambiguous choice. Clinical researchers and scientists are human and thus subject to decision bias such as ambiguity aversion. A high level of uncertainty, however, does not imply a high level of risk. It is rational to think that the risks of IMAPs might be low because there are no observable harms. Although previous trials do not allow direct extrapolation, they do provide an upper benchmark of the risk.

Clinical practice guidelines have been evolving rapidly in response to large randomized controlled trials and large amounts of observational data. The benefits of early and continued ART to third parties in terms of reduced transmission to partners have been documented and translated into clear and actionable public health messages. Unambiguous public health messaging assists patients with decision making but creates difficulty when discussing risks, such as limited treatment interruptions, in a more nuanced manner.

HIV cure trials must be managed (e.g., careful enrollment, risk minimization) and justified similarly to early-phase trials, which frequently lack direct clinical benefit but are justified by the scientific knowledge gained. The ethics of early-phase trials have been extensively discussed; following this model, if HIV cure trials provide reasonable assessment about risk, then the risk-benefit profile may be ethically acceptable. The ethical requirement of careful enrollment can exist in tension with other requirements, such as diversity and inclusion in selecting the trial population. In summary, Dr. Dawson noted that the pathway to assuaging these risk-complicating factors may be unclear compared to other early-phase trials. The studies must be scientifically valuable, risks must be minimized through careful management, and issues regarding participant understanding and fair inclusion must be addressed.

Interactive Discussion: Milestones and Paths for Moving Forward Research Towards a Cure
Lynda M. Dee, J.D., AIDS Action Baltimore
Roy M. (Trip) Gulick, M.D., M.P.H., Weill Medical College of Cornell University

Dr. Gulick and Ms. Dee moderated a discussion with OARAC members and invited guests about whether the goal for HIV cure research should be sustained remission, eradication, or both.

- Dr. Margolis stated that the research agendas for both outcomes likely will be similar, but the long-term health of people in remission will need to be compared to those who remain on ART. The ultimate goal, however, should be eradication.
- Dr. Deeks remarked on the similarity of many of the interventions, all with a goal of sustained virologic remission except for gene therapy, which targets a cure. He opined that remission will be easier to achieve than a universally applicable, safe, and inexpensive cure, which many believe impossible. Practically, eradication that is not completely verifiable is the same as remission. He concluded that science should drive the goal, and current research at the collaboratories is directed toward remission.
- Dr. Ronald T. Mitsuyasu compared HIV to cancer, where long-term remission is equated with a cure. Achieving a cure might be a matter of perspective. In addition, procedures that result in sustained remission could lead to a cure. Achieving a sustained remission will depend on the relapse rate. He advocated for pursuing sustained remission and a cure simultaneously.
- Dr. Kuritzkes considered the difference between remission and a cure to be semantic. Research directed toward a cure likely would be received more enthusiastically by the scientific community. Defining a cure might prove difficult. He proposed adopting a functional definition of a cure in humans—a lifetime of virologic remission without rebound—because complete necropsies cannot be conducted on living people, and testing every cell, starting with CD4+ T cells and macrophages, for virus is not practicable.
- Dr. Nixon characterized eradication as an aspirational research goal. In pursuit of this goal, major scientific gains and discoveries of new ways of attaining sustained remission are likely. He pointed out that current antiretroviral therapies generally are well tolerated, affordable, and adhered to.

- Mr. Agosto-Rosario noted the challenge of aging with HIV. Current therapies cause known co-morbidities and may cause more undiscovered conditions. Remission studies merit continued study because they might offer long-term health advantages over drug therapy.
- Dr. Jerome added that many interventions discussed at this meeting do not fit exactly into either eradication or remission (e.g., eradicating viral reservoir, controlling reactivation). He agreed with pursuing eradication, while being alert to possible benefits from sustained remission.
- Dr. Riley emphasized the need to define and understand what a cure comprises.
- Dr. Charles Wira suggested that future funding constraints be considered. A diminishing budget might make it impossible to reach the aspirational goal of a cure.
- An attendee emphasized the need for participants in clinical trials to understand the goal of the intervention being tested, whether it be remission or a cure. He also expressed concern that overconfidence regarding the time frame for a cure might lead to a decrease in resources allocated for HIV/AIDS research.

Dr. Gulick moderated a discussion of whether the current resource allocation presented by Dr. Sato is the appropriate balance. Translational research was defined as applying results from basic research to initial phase trials, including research using animal models and *ex vivo* research. Regarding vaccine research, Dr. Sato indicated that resources have been focused recently on large-scale Phase 2b and Phase 3 trials, which require more extensive funding, but if the entire research portfolio is considered, resources have been allocated similarly to the overall HIV research effort.

- Dr. Deeks supported the current resource allocation but stated that over time, more resources will need to be devoted to clinical trials.
- Dr. Kuritzkes thought the resource allocation should reflect the current state of the science. For example, most research on cures for HIV now are at the level of basic research; no therapy has been developed yet that is ready for a large clinical trial. Hopefully, a future therapy will be promising enough to test clinically. He also suggested that research on behavioral and social sciences, which addresses such issues as community preferences and adherence, should be incorporated into other types of research in addition to translational research.
- Dr. Margolis advocated for better funding of later stage clinical and translational research. He also commented that basic HIV research is not attractive to trainees because of the perception that it is an area with a limited future.
- Ms. Dázon Dixon Diallo noted that discoveries in basic HIV research inform many other disease states; these benefits should be quantified.
- Overlap among the categories of research was discussed. Ms. Diallo suggested determining how much basic research actually is research aimed at developing a cure. Dr. Sato added that much of the high-quality work performed in vaccine research as well as pathogenesis research has implications for cure research.
- Dr. Gandhi recommended requiring that clinical study teams include experts in clinical trial design to ensure adequate sample size.
- Dr. Nixon emphasized including pediatric patients, adolescents, women, and ethnic minorities in research projects. Dr. Dee suggested requiring researchers to report the breakdown by sex in their study populations, which might encourage them to consider including more women.
- Dr. Elizabeth Connick warned of a tendency to favor mainstream ideas over novel approaches when funding increasingly is directed toward large collaboratories, rather than into R01 grant mechanisms. Dr. Wira agreed, noting that some institutions no longer apply for program project grants. He reported a general consensus among researchers from other fields (e.g., heart, lung) that such large grants do not provide the best return for resource investments. Managing successful program projects grants requires good stewardship to match the energy and desire to succeed evidenced among the collaboratory leaders who presented at this meeting.

Dr. Gulick asked the participants to discuss how to identify success, prioritize among research pathways, support the most successful investigations, and develop milestones.

- Dr. Deeks opposed using the traditional metric of publishing high-impact articles in high-impact journals. Milestones for success should depend on the group that is being evaluated and the nature of the project they are working on. He suggested that fundees seek to develop a regimen that is testable at the proof-of-concept level; some projects, however, might be ready for animal testing within the next 5 years.
- Dr. Margolis predicted that the next significant step in HIV cure research will be a study that develops a robust assay and uses it to show significant clearance of infection. Such a study would represent substantial progress towards a cure. Simultaneously, preventative vaccine and immunotherapeutic research should continue because they bring in complementary approaches to traditional antiretroviral therapy. Basic research also needs to continue because it is the source of innovative and surprising advances.
- Mr. Agosto-Rosario proposed that the OARAC establish a working group to examine the types of broad questions that Dr. Gulick had posed. Future political changes might affect investments in a cure and necessitate prioritization among research pathways. Because of limitations on available resources, Dr. Dee advocated for developing a mechanism to terminate research efforts that are not performing well either managerially or scientifically.

Public Comments session

Dr. Gulick called for public comments. An attendee expressed his appreciation of the global perspective that the United States has adopted, providing 80 to 90 percent of the funding worldwide for cure research. The attendee encouraged the United States to continue to take a global perspective when prioritizing the agenda for cure research.

Closing Comments
Roy M. (Trip) Gulick, M.D., M.P.H., Weill Medical College of Cornell University
Maureen Goodenow, Ph.D., OAR, NIH

Dr. Gulick recounted the topics addressed over the course of the meeting. Though the distinction between sustained virologic and eradication may be semantic, the consensus was that both should be pursued. Eradication is the aspirational goal, but its pursuit will necessitate assessing the difference between today's antiretroviral therapies and sustained remission and also will reap the benefits of discoveries made along the way. Both the oncology model and the hepatitis C model for HIV should be considered for investigations. Current distribution of resources seems appropriate and reflects the current state of science, though funding mechanisms for smaller, innovative programs should be considered. Attendees agreed that evaluations and milestones are important, but they would like to see these investigations lead to proof-of-concept results, at least in animal models, within the next 5 years. Specific goals include significant clearance of the reservoir and determination of measurements for immune treatment and response. It was agreed that these goals are tentative; science is unpredictable, so funding can be provided only to move goals forward, and the path will evolve naturally. It will be important to determine metrics not only for evaluating success but also for evaluating investigations that are not leading to results.

Many attendees commented on the power of the word "cure." This term has been diluted to sometimes refer to therapies that are not true cures, and it is critical to be mindful of how it is used in explanations to the community. Researchers can look to other areas, such as oncology, and other infectious diseases, such as hepatitis C, to define the concept of a cure. This OARAC meeting, and the preceding NIH-sponsored conference, also included discussion of the importance of reservoirs, which focus primarily on CD4s but also should include other areas, such as the central nervous system. Attendees discussed the benefits of clinical trials to individuals and society and how to balance those benefits with the risks. Study

populations should be diverse, reflecting those who are affected and include pediatric populations, women, and ethnic and racial minorities.

Speakers during the conference repeatedly emphasized that any interventions found to be effective should be safe, simple, and scalable and should compare favorably to the current standard of care -- lifelong antiretroviral therapy. Attendees discussed how to consider implementation as interventions move forward. Community engagement also was discussed, including how best to keep the community informed. Dr. Gulick commented on the easily overlooked importance of simply collecting all the conference participants in one place to discuss the same issues. He noted that many of the best conversations during this conference happened in hallways, at lunch, and at the poster session, because these interactions encouraged participants to reach across their boundaries and communicate with others.

Dr. Goodenow thanked the participants for their persistence. She emphasized the importance of messaging and the urgency of the OAR mission. Milestones and program evaluation have been important components of PEPFAR's success that should be translated to OAR programs. OAR currently collaborates with PEPFAR only in small ways, but Dr. Goodenow expressed her eagerness to develop relationships with other agencies and open avenues for NIH-funded investigators to collaborate across organizational boundaries. She also noted the capacity building and development that has occurred in Africa over the last 15 years of investment by PEPFAR, which can be helpful for NIH investigators. Dr. Goodenow noted that programs are being developed at the NIH that cover some of the areas of need identified during the conference, and OAR will be working with the Institutes and Centers to address suggestions from this meeting not yet under development. Dr. Goodenow anticipates asking attendees to participate in working groups as projects develop.

The meeting was adjourned at 4:15pm by the Chair of OARAC, Dr. Trip Gulick.

Bonnie J. Mathieson

Bonnie Mathieson, Ph.D., Executive Secretary

Roy M. Gulick

Roy M. Gulick, M.D., Chair