NIH Workshop on HIV-associated Comorbidities, Co-infections and Complications (HIV ACTION Workshop)

September 19-20, 2019

Bethesda, MD

Executive Summary

The face of the HIV pandemic has changed dramatically since the 1980s. With potent antiretroviral therapy (ART) and simplified regimens, progression of HIV infection to acquired immunodeficiency syndrome (AIDS) may be significantly delayed or avoided, and people living with HIV are achieving near-normal lifespans. However, many are suffering from HIV-associated comorbidities, co-infections, and complications (HIV-associated CCCs), often against a background of multiple complicating factors such as stigma, isolation, and socio-economic challenges.

To gain a better understanding of HIV-associated CCCs, and to foster cross-disciplinary collaborations in future research, 21 Institutes, Centers and Offices (ICOs) at the National Institutes of Health (NIH) jointly convened a workshop on September 19-20, 2019. The ICOs invited 96 experts and community representatives to prepare for the workshop by forming five working groups (WGs) and an international panel. More than 40 representatives from the 21 sponsoring NIH ICOs also joined one or more of the five WGs on the following topics: epidemiology and population science, pathogenesis and basic science, clinical research, implementation science, and syndemics (for instance, disease interactions and social, cultural, environmental, political, and economical factors that influence or exacerbate diseases or conditions). The five WGs assembled in November 2018 and worked via multiple teleconferences to identify research gaps and opportunities for further discussion at the September 2019 workshop.

More than 400 participants attended the two-day workshop onsite and remotely. During the meeting, the five WGs and the international panel posed key questions to stimulate discussion on research priorities in their fields. Attendees also heard the unique perspective of a member of the HIV community who has long lived, and is now aging, with HIV. Such broad representation ensured that all relevant views were reflected; it also provided opportunities for investigators in different disciplines and fields to communicate with each other and exchange ideas and perspectives.

From the discussion, it became clear that it is unlikely one discipline alone can advance the HIV research field, as multiple organ systems are impacted by chronic HIV infection, comorbidities (HIV-associated and not), and drug toxicities and interactions related to treatment of both HIV infection and the comorbidities. Because of this complexity, many scientific questions remain unanswered. A major challenge of such research is its high cost, which is why a more coordinated, cross-disciplinary research approach is needed. These more cost-effective efforts could focus on investigating mechanisms of

pathogenesis and testing prevention or clinical management interventions for multiple HIV-associated CCCs. This report details the priorities and opportunities identified during the workshop.

The workshop discussion encompassed several main themes:

- HIV-associated CCCs affect multiple organ systems and result in a broad range of health consequences and outcomes affecting morbidity and mortality. They negatively impact the quality of life and healthspan of people living with HIV, even in the presence of ART and in spite of improved lifespan.
- Underlying pathogenic mechanisms may be shared among HIV-associated CCCs that involve multiple systems and manifest as various concurrent conditions in people living with HIV. These may be fundamentally different from those that result in the same “diagnosis” in people living without HIV.
- The appropriate phenotypes, indicators and indices/biomarkers for research on HIV-associated CCCs will likely prove to be distinct among people living with HIV.
- Several overlapping etiologies and mechanisms contribute to the development of HIV-associated CCCs. These include factors and shared pathways that drive chronic immune activation and dysfunction in treated HIV infection and mechanisms that drive accentuated aging.
- New research methods and technologies, including appropriate animal models, are needed to study HIV-associated CCCs across the lifespan.
- Research related to the prevention and management of HIV-associated CCCs is complicated because intervention strategies must consider drug-drug interactions with ART and therefore may need to be tailored to people living with HIV. Since people living with HIV may also have multiple comorbidities, research may also need to target these complexities.
- Multiple factors likely contribute to health in aging people living with HIV, including the direct impacts of HIV on multiple organ systems, toxicity of ART, polypharmacy, social isolation, stigma and likely many other still poorly defined risk factors. Notably, most of these factors are known to affect aging in the general population, but are over represented or more pronounced in people living with HIV.
- The impacts of social, cultural, economic, political and other factors on the susceptibility to and treatment of HIV infection and other co-occuring conditions are not fully understood. Questions related to how these factors differ within and among at-risk populations, as well as the best ways to study them, remain largely unanswered.
- Syndemics research could help characterize various comorbid diseases/disorders and their synergistic effects in the context of socio-economic, political, and ecological factors in people living with HIV. As such, syndemics research can help us gain a deeper understanding of the interplay of these factors and their role in promoting disease clustering at the population level, and the impact they have on disease pathologies at the individual level. Findings of such research will encourage more holistic approaches in the clinical management of people living with HIV.

- Because implementation science is a relatively new area of research, coordinated support is needed not only to develop implementation research studies, but also to train scientists in implementation science, which could include leveraging existing training opportunities and resources. Implementation science strategies are needed to address barriers that impede the scale-up and application of scientifically proven interventions in community and clinical settings. These interventions must focus on the prevention, control, and treatment of HIV-associated CCCs in people living with HIV.

Opportunities identified include:

- ***A coordinated NIH-wide research strategy.*** This would be optimal for addressing HIV-associated CCCs, since they involve multiple organ systems and concurrent conditions. A coordinated strategy would complement efforts targeting specific research priorities within the mission of each ICO.
- ***Multidisciplinary strategies.*** These would address the common research themes, which require fostering a non-siloed, collaborative approach and encouraging further investigation across multiple areas: basic mechanisms of pathogenesis that contribute to the development of HIV-associated comorbidities, the safety and effectiveness of interventions to control inflammation and mitigate chronic immune activation in people living with HIV, syndemics, and implementation science.
- ***Innovative models.*** These would more effectively support future research on HIV-associated CCCs. Research support models should allow researchers to address the complexities of multiple comorbidities and influential factors, including socio-economic factors, and encourage collaboration. For example, multi-omics approaches and large cohorts require collaboration across ICOs. Workshop participants encouraged NIH-wide discussions on how to facilitate and fund such collaborative research.

Now more than ever, there is an urgent need for a coordinated research effort to address HIV-associated CCCs and the impact of aging. Increasing numbers of people living with HIV are expected to enter into care as a result of the President's initiative to end the HIV epidemic in the United States in 10 years. Called "*Ending the HIV Epidemic: A Plan for America*," the initiative was announced in 2019. The research priorities identified during the workshop and outlined in this document may prove vital in any optimized system of HIV care or treatment cascade designed to prevent and manage HIV-associated CCCs and ultimately improve the quality of life of people living with HIV.

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Summary

The Changing HIV Pandemic and the Need for a Coordinated Response

The success of antiretroviral therapy (ART) has ushered in a new era for the HIV pandemic. People living with HIV are living longer and healthier lives and can even achieve nearly normal lifespans if treated with effective ART. Despite these advances, multiple studies have found that people living with HIV are more likely to suffer from chronic HIV-associated comorbidities, co-infections and complications (CCCs) than their age-matched uninfected peers (Smit et al., 2015; Legarth et al., 2016; Wong et al., 2018). This has led to the concern that "healthspan" (a measure of how long a person remains healthy) has not kept pace with improvements in lifespan for those aging with HIV.

Nearly all organ systems seem to be affected by HIV and/or its treatment. The mechanism(s) that contribute to this increased risk of physiologic injury have not been fully explained. Multiple factors associated with aging – including polypharmacy, social isolation and stigma – almost certainly affect the health of individuals as they age. Chronic immune dysfunction and inflammation that persists indefinitely during ART has also been implicated.

The impact of HIV, its treatment, chronic immune activation, and immune suppression still needs to be understood to improve the health of people living with HIV. HIV-associated CCCs—malignancies; tuberculosis; cardiovascular disease; pulmonary, neurological, hematologic conditions; and metabolic and sleep disorders—as well as premature frailty associated with long-term HIV infection and ART, have been high-priority topics of research supported by the NIH (NOT-OD-15-137; https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-137.html; https://www.oar.nih.gov/hiv-policy-and-research/strategic-plan). Many Institutes, Centers and Offices (ICOs) of the NIH support research on HIV-associated CCCs. However, efforts at NIH thus far have mostly targeted specific disease areas, with few initiatives that encompass the impact of HIV on multiple organ systems or the complex interactions between multiple conditions and polypharmacy.

HIV-associated CCCs involving multiple organ systems and conditions may share underlying pathogenesis and mechanisms. Tackling this multi-layered complexity will require NIH-wide scientific discussions that fully identify gaps and opportunities for research in HIV-associated CCCs and that also foster cross-disciplinary collaboration. Findings from such consultations should help facilitate a coordinated NIH response to the growing need for research on HIV-associated CCCs, and in a way that targets the highest research prioritiesand avoids duplication of efforts and investments by the different NIH ICOs.

Planning for the NIH Workshop on HIV-associated Comorbidities, Co-infections and Complications Workshop

The planning effort for the NIH Workshop on HIV-associated Comorbidities, Co-infections and Complications was led by the National Heart, Lung, and Blood Institute (NHLBI) and the Office of AIDS Research (OAR), in collaboration with 19 other NIH ICOs (see below). Representatives of all participating ICOs formed the NIH Planning Committee, which first met on September 21, 2018.

The Planning Committee invited **Dr. Steven Deeks** from University of California at San Francisco (UCSF) and **Dr. Savita Pahwa** from University of Miami to serve as co-chairs for the workshop.

The meeting's objectives were envisioned as follows: 1) to foster discussion among experts from different fields and disciplines to gain a better understanding of HIV-associated CCCs, 2) to identify research gaps and opportunities for research in HIV-associated CCCs, and 3) to provide the research community with coordinated and consolidated recommendations for future research effortsin the United States and abroad.

The NIH workshop co-leads Shimian Zou (NHLBI) and Natalie Tomitch (OAR), the workshop organizer Leia Novak (NHLBI and later NIAID), and the workshop co-chairs Deeks and Pahwa, formed the executive team and managed the day-to-day operations of the workshop planning process.

Table 1: ICO representatives of the NIH Planning Committee

NHLBI	Sean Altekruse, Cheryl Boyce, Lis Caler, Katharine Cooper-Arnold, Helen Cox, Tony Creazzo, Fassil Ketema, Catherine Levy, Yingying Li-Smerin		
OAR	Mary Glenshaw	NIDDK	Peter Perrin, Aynur Unalp-Arida
FIC	Geetha Bansal, Susan Vorkoper, Linda Kupfer	NIMH	Pim Brouwers, Holly Campbell-Rosen, Deborah Colosi, Greg Greenwood, Amber Linde, Vasudev Rao
NCI	Geraldina Dominguez	NIMHD	Rick Berzon
NIA	Basil Eldadah, Melissa Gerald, Miroslaw Mackiewicz	NINDS	May Wong
NIAAA	Kendall Bryant	NINR	Rebecca Henry
NIAID	Robert Palmer, Joana Roe, Carolyn Williams	NLM	Milton Corn

NIDA	Vasundhara Varthakavi	ODP	David Tilley
NIDCD	Howard Hoffman	ORIP	Ronald Adkins
NIDCR	Gallya Gannot	ORWH	David Thomas, Victoria Cargill*

FIC - Fogarty International Center, NCI - National Cancer Institute, NIA - National Institute on Aging, NIAAA - National Institute on Alcohol Abuse and Alcoholism, NIAID - National Institute of Allergy and Infectious Diseases, NICHD - *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIDA - National Institute on Drug Abuse, NIDCD - National Institute on Deafness and Other Communication Disorders, NIDCR - National Institute of Dental and Craniofacial Research, NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases, NIMH - National Institute of Mental Health, NIMHD - National Institute on Minority Health and Health Disparities, NINDS - National Institute of Neurological Disorders and Stroke, NINR - National Institute of Nursing Research, NLM - National Library of Medicine, OBSSR - Office of Behavioral and Social Sciences Research, ODP - Office of Disease Prevention, ORIP - Office of Research Infrastructure Programs, and ORWH - Office of Research on Women's Health.

*Current affiliation: Baltimore City Health Department

Formation of Working Groups and Discussions prior to the Workshop

A total of 96 experts and community representatives were nominated by all participating NIH ICOs to ensure representation from all relevant disciplines and perspectives. Five Working Groups (WGs) were formed around five research fields, consisting of invited experts and community representatives, as well as more thanr 40 representatives from 21 participating NIH ICOs. The group discussed issues in five broad categories.

1. Epidemiologic and Population Research, including analysis of current burden of diseases (Epi WG)
2. Pathogenesis Research, including basic and preclinical research (Basic WG)
3. Clinical Research (Clinical WG)
4. Implementation Science Research (Implementation Science WG)
5. Syndemics, which are disease interactions and social, cultural, environmental, political, and economic factors that influence or exacerbate CCCs (Syndemics WG).

A cross-cutting panel was also formed to discuss research on HIV-associated CCCs in international settings (International Panel).

Table 2: WGs and the International Panel

Working Group or Panel	Co-chairs	No. Members
Epidemiologic and population research	Amy Justice & Ned Sacktor	26
Pathogenesis research	Dana Gabuzda & Peter Hunt	21
Clinical research	Todd Brown & Ann Kurth	26
Implementation Science research	Stefan Baral & Michael Mugavero	23
Syndemics	Ken Mayer & Emily Mendenhall	24
International research	Roger Detels & Vincent Mutabazi	14

See Annex 1 for rosters of all WGs and the international panel.

Prior to the meeting, the WGs were charged with the following:

1. Discuss the state of the research, the remaining gaps, the challenges and opportunities, as well as future research priorities.
2. Select the top 3-5 topics and speakers for high-level presentations at the workshop.
3. Prepare one-page summaries of the 3-5 topics to be posted on the website.

The Working Group chairs moderated the sessions at the meeting and led efforts to summarize the discussions at the final consensus-building session.

Each working group began their discussions in November 2018 through conference calls and email communications and identified 3-5 priority topics for their respective fields.

Each WG prepared a summary highlighting key questions, rationale, and feasibility, along with supporting references for each of the priority topics. A website was set up, and the summaries were uploaded there prior to the workshop for registered workshop participants and members of the public interested in attending the workshop remotely through videocasting.

The following NHLBI staff facilitated the discussions within each of the WGs:

- Epi WG: Sean Altekruse, Tony Creazzo
- Basic WG: Lis Caler, Leia Novak
- Clinical WG: Katharine Cooper-Arnold, Catherine Levy, Yingying Li-Smerin
- Implementation Science WG: Cheryl Boyce, Helen Cox
- Syndemics WG: Fassil Ketema, Lis Caler

Geetha Bansal of FIC organized the International Panel and facilitated discussions within the group.

To maximize participation from as many investigators and interested individuals as possible, a coordinated effort was made to reach out to the broad research community, as well as to the public. This effort was led by the Office of Science Policy, Engagement, Education, and Communications (OSPEEC) of NHLBI, in collaboration with communication offices of all collaborating NIH ICOs.

The Workshop on September 19-20, 2019

A total of 287 individuals pre-registered for the workshop by September 6 when the web-based registration was closed. An additional 16 people registratered onsite. The number of people who registratered for each WG breakout session was as follows:

Working Group	No. of registrations
Epi WG	49
Basic WG	61
Clinical WG	60
Implementation Science WG	41
Syndemics WG	49
No breakout indicated	43
Total	303

A Web-based Zoom call was also set up to allow a limited number of working group members to participate in the workshop remotely, with three participating in the event on Day 1 and two participating on Day 2.

Further, a total of 424 viewers watched the videocast live on Day 1 of the workshop, including five from Kenya, two from Vietnam, one from Guatemala, and one from Iran; 112 viewers watched the videocast live on Day 2, all from the United States. Considering that these people could have beenpart of a group, the actual number of viewers might have been higher than 424.

Day 1: September 19, 2019

Day 1 of the workshop began with opening remarks by leadership from NHLBI and OAR, an introduction by Dr. Savita Pahwa, one of the workshop co-chairs, , and keynote talks by Dr. Anthony Fauci, director of NIAID, and Dr. Keri Althoff, of Johns Hopkins University. (See Annex 2 for the agenda.)

Dr. Keith Hoots, director of the Division of Blood Diseases and Resources at NHLBI, reflected on what we have learned and accomplished since the HIV epidemic began. He shared his personal experience in caring for three teenage girls who suffered from hemophilia and subsequently were infected with HIV in the 1980s. He highlighted the neurocognitive impact that was documented in patients with hemophilia and HIV, as well as potential risk posed by false HIV elite controllers (HIV antibody-positive RNA-negative individuals found to be on ART) to blood safety. Hoots added that we must continue to be vigilant because vulnerabilities can appear where they did not seem to exist.

Dr. Timothy Holtz, deputy director of NIH OAR, indicated that the topic of HIV-associated CCCs is among the five overarching HIV-related research priorities established in 2015 for the NIH.

Dr. Pahwa then presented the objectives of this workshop. Four overall objectives were discussed.

1. Foster cross-disciplinary discussions among experts from different fields.
2. Gain better understanding of HIV-associated CCCs and intersecting epidemics.
3. Identify research gaps, priorities, opportunities and emerging research methodologies.
4. Recommend strategies to stimulate, facilitate and support future research.

Dr. Fauci gave a keynote speech entitled “HIV in 2019 – Successes of ART and Challenges of Comorbidities.” Dr. Fauci called ART one of the greatest achievements of modern medicine and highlighted remaining challenges, both in the implementation of existing treatment and prevention modalities and of comorbidities in ART-treated people living with HIV. He also discussed multiple factors that play a role in the pathogenesis of HIV-associated comorbidities, including chronic immune activation, co-infections, ART drug toxicity and higher burden of tobacco, drug, and alcohol use. For example, chronic immune activation is considered a common pathogenic mechanism in many comorbidities affecting people living with HIV, such as cardiovascular disease, neurocognitive disease, renal disease, osteoporosis, hepatic disease and cancers.

Dr. Althoff ended the first session with a presentation documenting the high burden of morbidity among people living with HIV. She noted the disease’sphysical toll (cardiovascular disease, malignancy, liver disease, metabolic syndromes, lung function problems, renal impairment, low bone mineral density, vision loss, hearing loss, and sleep disturbance) and its mental toll (neurocognitive disorders, including mental health conditions and substance use). She talked about co-infections (tuberculosis, viral hepatitis, and sexually transmitted infections) and syndromes (frailty, decreased mobility, falls, and polypharmacy). Althoff then discussed factors that may influence the burden of morbidity in the future: changing age distribution and the changing risk profiles among sub-groups of people living with HIV; prior exposure to early, more toxic ART drugs; the irreversible effects of untreated HIV infection; and secular changes in substance use.

The remainder of the agenda for Day 1 was devoted to reports by each of the five WGs, who presented the outcomes of their pre-workshop discussions on the research gaps, opportunities, and in particular, the key priority topics for discussion and commentary by all participants.

Day 2: September 20, 2019

Day 2 began with a recap of Day 1 by Workshop Co-chair Dr. Steven Deeks, a talk by Dr. Jamie Justice of Wake Forest School of Medicine on leveraging what has been learned from geroscience, and a discussion by the panel on international research.

In his recap of Day 1, Dr. Deeks noted that while the lifespan for people living with HIV may be approaching normal,the “healthspan” is not. He said this reflects the limited capacity of the healthcare system to care for aging people living with HIV, particularly those with multimorbidity. Deeks then discuused several questions raised during the first day: Does HIV infection and/or ART cause excess comorbidities, and if so, are these due to standard or distinct mechanisms? Does HIV and/or ART accelerate the process of aging?

After reviewing priority topics discussed by each of the five WGs, Deeks summarized the emerging perspectives shared by the assembled group:

- More patient-centered study approaches need to be developed.
- The social determinants of HIV will need to be fully quantified and integrated in larger cohorts and clinical trials.
- The study of healthy aging will require multidisciplinary teams.
- More synergy between behavioral/social and biomedical sciences should be encouraged.
- People living with HIV urgently need to be included in non-HIV-focused studies.

Dr. Justice shared her experience in the TAME trial – a clinical trial targeting aging to extend healthspan – and discussed how geroscience interventions can affect the biological aging process (“inflammaging”) and multiple age-related diseases. She then suggested the following for consideration in the study of HIV and aging:

- Stimulate research collaborations across disciplines, communities and stakeholders.
- Conduct clinical trials with age-related multimorbidity as an outcome.
- Identify and characterize the shared drivers of biological aging in people living with HIV, with the goal of disentangling the impacts of combined effects of aging, treatment toxicities, and a variety of disease-specific issues.

The international panel highlighted the increasing importance of HIV-associated comorbidities in low- and middle-income countries (LMICs), even though the first priority in most LMICs remains detection and effective treatment of HIV infection. In addition to larger proportions of morbidity, there are many barriers to identifying and treating HIV-associated comorbidities in LMICs. Future research targeting comorbidities should focus on strengthening capacity (investigators, infrastructure); defining the problem; setting priorities; learning more about diseases and their unique presentations in each region; developing novel scalable interventional strategies; improving integration of care; and developing implementation strategies. A critical need in LMICs is training in HIV-associated comorbidities, with a focus on improving knowledge and its exchange among both HIV and primary health care providers, increasing the capacity to provide evidence-based interventions and conduct research, and building greater regulatory capacity. Panelists emphasized the importance of considering the cultural and geographic context when conducting research and managing health care.

After listening to the reports of the international panel and all the other WGs, as well as the discussions related to those reports, each of the WGs met in breakout sessions to discuss potential revisions to their priority topics.

- The Epi WG breakout session examined how observational research in clinical and population settings can address problems of aging with HIV infection (e.g. polypharmacy, multimorbidity, falls, frailty, mental health conditions, and neurocognitive function). The session focused on determining the most important questions and how best to address them with observational data.
- The Basic WG breakout session examined the factors that drive chronic inflammation and immune dysregulation in treated HIV infection, changes in the microbiome and microbiome-host interactions, and how these events influence multiple end-organ diseases. The group also discussed the biological mechanisms that may drive accentuated aging and impact age-related comorbidities in treated HIV infection.
- The Clinical WG breakout session focused on optimizing clinical research across the lifespan to address screening, prevention, and management of HIV co-morbidities. The group discussed clinical trial designs that prioritize participant engagement and perspective, surrogate markers, and disparities.
- The Implementation Science breakout session focused on prioritizing training and research into optimal strategies for implementing clinical services and public health programs focused on addressing HIV-related comorbidities.
- The Syndemics WG breakout session examined how social, cultural, environmental, political, and economic factors produce vulnerability for HIV and co-conditions; how these factors differ within and between populations; how they may simultaneously affect HIV non-communicable as well as communicable (co-infection) disease risks; and how syndemics mediated by social and structural factors affects behavioral outcomes. The group also discussed the methodology needed to address syndemic interactions.

Following each WG's report to the full group, participants further discussed the reported priority topics.

After the breakout sessions, Mr. Jules Levin of the National AIDS Treatment Advocacy Project (NATAP) presented his perspective on aging with HIV in the United States, specifically focusing on unmet needs such as those related to clinical care, community care and services. He proposed an implementation study to evaluate a new care model which includes longer visit times with the clinician, geriatric care in the clinic, IT/telemedicine visits for patients, better communication and coordination among primary care providers, specialists and people living with HIV, and other elements.

Priorities Identified

Priorities Identified by each WG are listed below, along with the key questions related to each priority topic, and the discussions that followed.

Epidemiologic and Population Research Working Group

The Epidemiologic and Population Research Working Group identified three priority topics:

- Patient-reported outcomes that are most valuable for gauging quality of life and prognosis
- Neurobehavioral complications of HIV
- Impact of HIV, risk behaviors, and ART on falls, polypharmacy, and frailty

The Epidemiologic and Population Research Working Group raised questions about the differences in aging with and without HIV infection. They asked what tools could help identify common pathways for multimorbidity, emphasizing the need for clinical phenotype definitions and practical guidance for clinical management. The group noted that the topic of frailty comes up often, but said it may be time to reconsider the measures of frailty that have been adapted from geriatrics. The group also highlighted the importance and complexity of studying neurocognition in those aging with HIV, and it underscored the importance of understanding the roles of polypharmacy and substance use in neurocognitive compromise.

What Patient-salient Outcomes Are Most Useful to Gauge Health-related Quality of Life and Prognoses?

The following key questions were proposed:

1. What are the most accurate and generalizable risk indices for mortality, hospitalization, and common comorbid diseases for those aging with HIV infection?
2. What are the most valid and reproducible measures to study aging with HIV?
3. Is frailty a useful, independent concept in the study of aging with HIV?
4. Do appropriate measures of frailty differ from those aging without HIV?
5. How can useful indices of prognosis, quality of life, and frailty be integrated into routine clinical care and research?

Neurobehavioral Complications of HIV in the Modern Treatment Era: Challenges and Priorities for the Future

The following key questions were proposed:

1. What are the incidence and prevalence of neurobehavioral impairment in people living with HIV on ART with and without viral suppression?

2. What is the impact of demographic factors such as age, sex, education, race or ethnicity, and socioeconomic status on the epidemiology of cognitive impairment and mental health conditions in people living with HIV?
3. What impact do specific comorbidities, such as mood disorders, drug addiction, and co-infections, have on cognitive and mental health in people living with HIV? Does treatment of such comorbidities improve cognitive function?
4. How can we systematically differentiate between cognitive impairment that is due to HIV or immune suppression, and cognitive impairment that is due to age-related conditions, such as cerebrovascular disease, or age-related neurodegenerative conditions?
5. How can we delineate phenotypes of HIV-associated cognitive impairment that have value in predicting outcomes, and relate to developing specific prevention and intervention strategies?
6. What are the factors that promote neurocognitive health and resiliency among people living with HIV?
7. What are the optimal methods to screen for and confirm cognitive impairment and mental health complications in research and clinical settings for both the United States and resource-limited countries?
8. How does cognitive and mental health affect the behavior of people living with HIV, including medical adherence, self-efficacy, and risk behavior?
9. How can we improve our ability to assess, monitor, and intervene on neurocognitive impairment and mental health "in the field" (i.e., outside of clinical and research settings)? What are the opportunities using mobile technology?

How do HIV, risk behaviors, and ART influence aging syndromes, particularly falls, frailty, and polypharmacy?

The following key questions were proposed:

1. What frailty instruments are most valid in people living with HIV?
2. What nondrug interventions, such as exercise, have the biggest effect on reducing frailty in HIV?
3. How does ART modify risk of falls among people living with HIV?
4. How does alcohol, analgesics, and medication-assisted treatment (MAT) affect falls risk?
5. How should interventions for falls and fractures be modified to maximize their beneficial effects among those with HIV?
6. What are the most important mechanisms of antiretroviral (ARV)/non-ARV drug–drug interactions in terms of actual clinical practice?
7. What are polypharmacy's effects on comorbidities in people living with HIV?
8. What is the impact of deprescribing non-ART medications among people living with HIV?

Discussion Themes and Opportunities

Catalog available tools. Few people in the community appear to be familiar with all of the available tools, so publishing a list is a priority. In a forthcoming paper, the group aims to publish a summary table of measures and identify those that have been validated in populations of people living with HIV. It is feasible to validate scales to measure comorbidities in people living with HIV within the next five years. Tools developed by NIH, including those in the Patient-Reported Outcomes Measurement Information System (PROMIS) program and the NIH Toolbox®, were evaluated in a general population. Verifying that they are equally useful for populations of people living with HIV could be a future priority for research.

Consider multiple comparator groups. If we want to better understand how aging with HIV is like and unlike aging without HIV, we need to include people who do not have HIV, people who have unsuppressed virus, and those who have long-term viral suppression. It is also important to consider whether individuals received optimal ART initially and what co-infections—including tuberculosis, viral hepatitis (B and C), and cytomegalovirus (CMV)—they are likely to carry. Predictors of illness or adverse outcomes may differ by group. In addition, keeping results relevant for global settings is a priority. Developing improved definitions of subgroups and phenotypes using a precision-medicine approach is a research priority.

Develop tools to assess exercise and functional status. Physical activity is another important area where assessment tools are underdeveloped. We need to understand what components of functional performance and sarcopenia are most important.

Develop tools to assess fall risk, capturing behavior as a factor. Many priority research questions regarding falls risk have yet to be answered. How does ART modify falls risk among people living with HIV? How do alcohol and medications influence the risk of falling, and how does this differ by HIV status? How does HIV interact with interventions to reduce the risk of falls and fractures? Determining how best to measure falls is another priority. Radiologic exam results coupled with a machine learning algorithm could identify falls that have occurred, but measures to predict future falls still need to be developed. Finally, are the same tests appropriate for resource-rich and resource-limited settings?

Define frailty in HIV. Recognizing that the optimal measures of frailty for those with HIV may differ from geriatrics, the group identified a need to develop and validate instruments among those aging with HIV. The group recognized that different components of frailty may be salient for different populations and noted that what drives frailty for those with HIV may be different than among uninfected individuals. Frailty assessments should look at factors strongly associated with health-related quality of life rather than solely focusing on quantity of life. Even if life expectancy has increased, the critical question is how we live our lives. Frailty measures should also keep racial and geographic variation in mind; measuring frailty in diverse populations may require multiple scores or thresholds. In examinations of cohort data, most people living with HIV fall in a pre-frailty category, but it is not clear whether pre-frailty and frailty are

separate concepts. As new frailty indexes are proposed for HIV, they should be compared with existing measures such as those previously collected in the Multicenter AIDS Cohort Study/Women's Interagency HIV Study (MACS/WIHS) and data from HIV– groups.

Advance frailty research priorities. Research priorities include understanding the underpinnings of frailty in HIV and determining whether there is a single type of frailty in HIV. Aggregate measures may better capture this complicated state. At the same time, it might be valuable to trace individual components to determine which ones track with people living with HIV and other factors, such as drug use, functional and cognitive decline, and co-infections. In addition, more work relating frailty to disease outcomes would be beneficial. Researchers and those who fund research are showing growing interest in investigating the use of machine learning to enhance clinical prediction. To what extent should frailty be defined by its association with frailty-related outcomes such as poor health-related quality of life, inability to live independently, pneumonia, falls, dementia, hospitalization, and mortality?

Capture social factors with qualitative research. More qualitative research and mixed methods studies need to be done. This would entail going into communities to better understand patient perspectives and what outcomes they consider important. How can indices capture factors like marginalization or social isolation and assess how they shape outcomes? Being able to quantify barriers such as stigma will be valuable and is possible only through qualitative studies. This kind of research could also identify barriers that interventions could alter.

Explore machine learning. It would be valuable to explore using computer learning approaches on large data sets, such as those from Veterans Aging Cohort Study, Kaizer Permanente, or MACS/WIHS, to identify psychosocial and clinical variables contributing to neurobehavioral complications in HIV. Patients' diagnostic images may change subtly over time in ways that are difficult for the human eye to detect. Massive computing power can help detect these signals if applied to very large samples, such as might be available in health systems like Kaiser Permanente and Veterans Healthcare Administration. Of note, changes in neurocognition over time may be related to other factors, such as isolation or frailty. For example, changes in physical function may precipitate changes in mental function.

Find better ways to assess brain health and cognitive decline. Coming to an agreement on standardized measures for neurocognitive dysfunction is a priority. Other priority questions include what the phenotypes of neurocognitive dysfunction are and what factors promote neurocognitive health. There are many important factors that should be explored to better understand mechanisms, including mental health, suicidality, substance use, social determinants of health, isolation, and social support.

Clarify what is unique about neurocognitive decline in HIV. It is not yet clear how much aging-associated neurocognitive decline in people living with HIV might differ from

neurocognitive decline in the general population It is important to avoid duplicating what we know from aging studies, but evidence shows that the biology in HIV comorbidities may differ from the biology in the general population. For example, a definition of sarcopenia developed from HIV populations had no predictive value in the MACS/WIHS study for decreased mobility or falls.

Characterize emerging neurocognitive disease. The basic science of neurological outcomes needs focused attention. One priority for the HIV research community is to understand how pathogenesis in the context of aging with HIV may lead to a new type of neurocognitive dysfunction since other conditions may synergize with neurological comorbidities. How do different levels of comorbidity and polypharmacy contribute to dementia? What are the mechanisms that drive pathogenesis? Understanding the impact of long-acting ART and its interactions with other medications on neurocognitive function is also a priority. Neurocognitive impairment is dependent on adherence to ART and viral suppression. Because earlier medications may have had more adverse effects, impairment may also depend on treatment used.

Encourage collaboration across existing studies. The group felt strongly that research on neurocognitive dysfunction in HIV is an opportunity for cross-cohort collaboration—for example, through the International epidemiology Databases to Evaluate AIDS (IeDEA) network.

Think creatively about screening tools. It can be difficult to identify neurocognitive disease without screening, and physicians seem to have less time to evaluate patients. Having annual neurocognitive screening data available would be ideal. However, standard neuropsychological tests are not part of routine clinical care. Studies that have tried to identify the ideal screening instrument have concluded that it varies from clinic to clinic. No single tool works everywhere. One reason screening methods fail may be due to differences in individual clinic populations. Study analysis should be designed to account for these differences. Using digital platforms, it may be feasible to present a primary screening tool to all participants, with additional screens for specific populations (e.g., differing by age, site, or other factors). A response-driven algorithm that alters questions based on previous responses is shorter and more accurate and looks like a promising solution.

Characterize links between mental health and inflammation in HIV. Key gaps in the field deserve attention, such as potential links between inflammation and stressors like cortisol or conditions like depression or PTSD. Similarly, a higher risk of domestic and sexual violence exists among people living with HIV, and its effects on inflammation should be considered.

Advance polypharmacy research priorities. It will be important to think carefully about medications, given the many complicating factors that present when people living with HIV take five or more medications daily. What are the best ways to capture the range of medications someone is taking? Research on polypharmacy must not focus

solely on prescription drugs. Other substances that patients are using, including alcohol, cocaine, marijuana, dietary supplements, herbs, and over-the-counter medications should be considered. The research community needs to develop new methods to identify and meaningfully group drug–drug interactions and their outcomes. Drug metabolism differs by age, race, sex, weight, and physiologic injury. How do these factors modify the risk of toxicity? Other priorities include investigating the impact of polypharmacy on the progression of chronic liver disease, kidney disease, cardiovascular disease, and other comorbidities and understanding the possible effect of deprescribing drugs on important patient outcomes.

Account for the complexity of substance use. As in polypharmacy, there are many types of substance use, and these substances can interact with other medications. Disentangling the effects of different substances from each other will be essential, and different approaches can be taken to do this. For example, association studies look for signals for various outcomes from different interactions and then look at specific outcomes and specific drugs. Two of the most important and potentially modifiable factors in most comorbidities are alcohol and tobacco use. Focusing on these is of high priority.

Incorporate objective measures of substance use. Researchers are finding that self-reporting for substance use is not reliable. In one example, half of the study participants who said they were not using alcohol were using it. In planning research, it is important to think about testing as well as asking patients. Special considerations for direct measures of alcohol use in older populations may be needed.

Include health care quality as a factor in research comparing people living with HIV to those living without HIV. When comparing cohorts of people living with and without HIV, researchers must not forget to account for the quality of existing care. Many people living with HIV have access to comprehensive clinic care that is not accessible to people living without HIV, especially vulnerable ones. Adherence and access to health care are important factors to keep in mind regarding at-risk people living without HIV. Often individuals in those groups do not do as well as predicted. Should research be incorporating assessments of at-risk groups?

Pathogenesis and Basic Science Research Working Group

The Pathogenesis and Basic Science Research Working Group focused on three priority topics:

- Immunopathogenesis
- The microbiome and virome
- Aging and senescence

The Pathogenesis and Basic Science Research Working Group raised questions about where it is best to intervene in treated HIV. The immune system affects all organ systems, so it is important to delineate where on mechanistic pathways to intervene. A key goal is to go after root causes of inflammation and immune activation, and to understand the contribution of ongoing virus production in the reservoir to immunopathogenesis and associated comorbidities. Understanding mechanistic pathways and drivers is a key part of a future research agenda and is also potentially actionable. In addition, because this concept is not unique to HIV, the HIV research community has the capacity to teach the rest of the medical community about chronic inflammation, immune activation and immune dysfunction for its role in comorbidities. The group also considered the roles of the microbiome, fungome, and virome, among others, and the complexity of big data. Ultimately, interventional studies will be needed, using knowledge gained from basic research.

Immunopathogenesis

The following key questions were proposed:

1. Do all “root drivers” contribute equally to inflammation and immune activation?
2. Do some inflammatory pathways (“branches” of the “tree”) drive some diseases more than others and are they different in people living with HIV from HIV uninfected?
3. Do inflammation, immune activation and immune dysfunction in HIV differ across the lifespan?
4. Will intervening on some inflammatory pathways have adverse consequences (e.g., infections, cancer)?
5. Can systems biology approaches help us prioritize interventions?
6. Can we improve our understanding of systems biology from clinical trials and animal models?
7. Can we use novel inflammatory indices and imaging to stratify risk and monitor treatment response?
8. Is there need for a tailored approach to decrease inflammation?

Microbiome and Virome

The following key questions were proposed:

1. What are the mechanisms of host-HIV-microbiome interactions and do they differ based on age of the host?
2. Does the microbiome play a causal or contributory role in HIV comorbidities?
3. How do other cofactors interact with HIV infection to affect the microbiome and downstream comorbidities?
4. If the microbiome is causal or contributory to HIV-related comorbidities, rather than just a consequence or association, can it be manipulated to modify these pathways?

Aging and Senescence

The following key questions were proposed:

1. Have we overlooked important drivers or mechanisms?
2. How do markers and drivers of senescence including immune senescence change with advancing age?
3. Which are the most critical drivers or mechanisms to target, and how do we target them?
4. Can we identify overlapping or intercepting pathways to disrupt, or are we doomed to address each driver or mechanism separately?
5. Which are the best models to use to carry out both mechanistic and treatment studies of aging with HIV infection?

Discussion Themes and Opportunities

Distinguish effects of specific immune pathways. Expanding research on inflammation is a priority. What do we know about the different "flavors" (patterns) of inflammation and how these different inflammatory pathways define associated comorbidities? It is likely that different inflammatory pathways will drive different effects on end-organs. Residual inflammation is related to development of comorbidity, and may affect renal, cognitive, cardiovascular, and other systems. Research should also consider tissue-specific immune dysfunction and alterations in phenotype and function of immune cell subsets in the context of comorbidities and inflammation. Researchers will need to use systems biology approaches to characterize these processes, as well as the different patterns of inflammation that can occur in HIV infection, in order to identify biomarker clusters and their relationship to distinct patterns of inflammation and multimorbidity.

Investigate drivers of inflammation. The impact of inflammation on disease may reflect the initial drivers of inflammation. How does the size of virus reservoir affect inflammation? In addition to ongoing low-level virus production, researchers should also consider possible effects of viral proteins, such as HIV Tat and Nef, as potential drivers of inflammation. How much of a role ongoing production of HIV virions or proteins might play in triggering innate immune responses, chronic inflammation, and associated comorbidities in an ART-suppressed person is an important question. Another priority:discovering interventions that can block other root drivers of inflammation, such as microbial translocation. The sources of inflammatory mediators in blood should be investigated. It is important to keep in mind, however, that what leaks into the blood is distinct from what is happening in end organs. How should cells and responses to inflammatory mediators be evaluated, and what are the appropriate controls?

Assess the relative importance of biological drivers of aging. Priority research questions include identifying the critical drivers and mechanisms to prioritize, which pillars of aging are key to driving multiple comorbidities, and which are easiest to tackle. Epigenetic aging of host cells is also important. Cellular senescence can have a key role in the immune system and adipose tissue, among others. Immune senescence can affect response to vaccines and lead to development of co-infections and comorbidities.

The biology of resilience is also important to study. Animal models will be useful for studies on aging and senescence during HIV/SIV infection and ART exposure.

Advance genetic research. Studying host genetics has the advantage of creating opportunities for Mendelian randomization and enabling researchers to start to infer causality and determine where in the host to intervene. The analysis of host genetics may also help identify causal mechanisms, as well as patient subgroups (clusters) and their associated biomarkers that relate to increased risk for end-organ dysfunction and comorbidities. This work will require the integration of large research teams and cohorts.

Dive deeper into infection-related comorbidities. The role of co-infections is understudied in the context of HIV infection. Even in people who start ART early, there is increased risk for infectious complications such as tuberculosis, and the biological mechanisms are likely distinct and are likely to be impacted by age of the host. The increased risk of infection-related cancers also deserves more attention. Parasitic co-infections in resource-limited settings might alter vaccine or treatment outcomes and are also worth investigating.

Investigate animal models. How can research best use animal models? They offer access to tissues where the immune response resides and the possibility of investigating high-risk interventions. Animal models that include substance use and other exposures are needed to more closely mimic humans. Research should address what is unique in HIV compared to other diseases. Research using animal models of aging can provide insight into comorbidities and co-infections as well as drivers of inflammation. Animal models such as aging non-human primates are currently understudied in the HIV field.

Integrate people living with HIV into clinical trials. This is a research priority. It would be valuable to leverage ongoing large cohort studies of aging and age-related comorbidities, such as Targeting Aging with Metformin (TAME), either by not excluding people living with HIV or by doing parallel studies of people living with HIV so large data sets and specimens can be analyzed to understand biological drivers and pathways of aging and comorbidities. Even if there are not enough people living with HIV in these studies to make definitive conclusions, there is value in collecting samples and preliminary data. Such data can point the field toward a preliminary understanding of the biology and help research move forward in important ways. Clinical studies should also incorporate basic science questions.

Capture more biological complexity. It is typical to study only one organ system at a time, but researchers need to look at the interaction of organ systems. Organ systems are interconnected, so integrating organ systems by examining interactions such as the neuro-gut axis or neuro-–immune axis, for example, is important. What research designs can look at groups of diseases? Investigators should think about mechanisms of cell and tissue injury and study sets of diseases related to those mechanisms. Collaboration and interdisciplinary research is necessary to make that possible. A focus

on dissecting immune system alterations using novel technologies and approaches to probe the immune system—for example, by evaluating immune response to vaccines—is needed.

Compile research resources. One priority involves infrastructure development around data sets. For large longitudinal or intervention studies of people living with HIV, make cohort characteristics and data dictionaries publicly available to facilitate new collaborations and analyses will be valuable. Making specimens and data more readily available to other investigators will also facilitate key research on complex biological mechanisms driving comorbidities. Understanding what clinical samples are available would make the process easier for basic scientists and others who are not part of the clinical research community. Another need: to develop an atlas of molecular and cellular changes that predict multimorbidity in HIV. Atlases from the TAME trial, the Molecular Transducers of Physical Activity Consortium (MoTrPAC), and Trans-omics for Precision Medicine (TOPMed) could offer fruitful comparisons. Similar atlases on aging consist of linked multi-omic data. Basic scientists should take part in discussions about the collection of samples at an early stage, so that investigators collect the appropriate samples using the proper methods. There should be guidelines not only for the types of specimen collected, but also for specimen processing and storage. Researchers in both primary and add-on studies need to think about the use of samples collectively, and set research priorities in advance.

Expand research approaches and interdisciplinary collaborations. Integrating multiple disciplines in crosscutting studies and genotyping of large cohorts are research priorities. NIAID is tackling big data science questions by working on common data standards, bringing large data sets together, and ensuring greater access. Studying the microbiome offers opportunities for targeted therapy and chances to develop drugs in a different way. Microbiome metabolites represent an important focus of this research. Advancing microbiome research will also require more people with necessary expertise to analyze the microbiome. More people need to be trained in data science to analyze complex big data and provide support mechanisms to analyze these types of data.

Support collaboration. An important structural issue involves the need for support from multiple NIH institutes. Multi-omics approaches and interdisciplinary research in large cohorts will require collaboration across institutes. There should be better mechanisms for ancillary studies than R01s. One idea is to develop support mechanisms for “add-on” studies and new analyses of existing cohort data or samples to enable analysis of more than one comorbidity. Basic science often encounters difficulty in getting support for crosscutting multimorbidity research. Having trans-institute discussions on how to do research that cross disciplines and diseases, including multimorbidity, is a priority. Doing this is likely to advance the discovery of prognostic biomarkers and patient clusters with similar phenotypes.

Clinical Research Working Group

The Clinical Research Working Group prioritized three topics:

- Prevention as treatment
- Comorbidity management in HIV
- Patient-reported outcomes and biomarkers

The Clinical Research Working Group raised some of the bigger issues that will emerge over the next decade.

Regarding comorbidity prevention and treatment, the group asked how people living with HIV are different and whether they should be screened differently. Should doctors be more aggressive with blood pressure or cholesterol management? Why are the outcomes of treatment different with people who have HIV?

As research moves forward, patient-reported outcomes will need to be measured more carefully. Unique clinical trials that are not limited to specific diseases will also be needed. It will be important to think more broadly and more holistically. Results showing that blocking abnormal inflammation helps across many diseases suggest that is a direction should be pursued, and the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) is a good example of moving in that direction.

The working group's discussions highlighted several principles, including the importance of addressing a life course perspective, disparities, and age, sex, gender, and orientation issues. Importantly, support calls developed out of this discussion should solicit applications from both international and domestic perspectives.

Prevention as Treatment: Clinical and Translational Studies to Prevent Comorbidities

The following key questions were proposed:

1. What are the best ways to screen for, identify, and prevent comorbidities in research and clinical settings for both the United States and resource-limited countries?
2. What are the high-priority screening and prevention guidelines (across the age spectrum) that need to incorporate HIV as an additional risk factor?
3. Are there high-priority prevention strategies that need to be employed or targeted in individuals with HIV across the age spectrum?
4. Are standard prevention strategies, such as diet and exercise, as effective in people living with HIV?
5. Are there modeling strategies that can assist in delineating the risk, benefit, and cost savings of implementing screening and prevention strategies among people living with HIV?

Comorbidity Management in HIV: Should It Be the Same as in the General Population or Tailored?

The following key questions were proposed:

1. How should clinical practice guidelines and standards of care for different comorbidities be tailored to older people living with HIV, including those with multimorbidity?
2. How do interventions aimed at decreasing inflammation and immune activation in older people living with HIV affect risk and progression of individual comorbidities, as well as multimorbidity?
3. How should treatment of comorbidities be prioritized among older people living with HIV who have multimorbidity? Should frailty and measures of physical function be used to prioritize and tailor therapies?

Patient-Reported Outcomes and Biomarkers

The following key questions were proposed:

1. How do comorbidities affect different understudied patient populations, including older people living with HIV (e.g., age 65 years or older), gender (male, female, transgender/non-binary), racial and ethnic minorities in the United States, and people in low-resource settings?
2. What patient-reported outcomes and biomarkers are most useful for prevention, early detection, and management of common comorbidities in people living with HIV?
3. What are mechanisms by which HIV may accelerate aging processes and increase the risk for comorbidities, and how can patient-reported outcomes and biomarkers help explicate these?
4. How can patient-reported outcomes and biomarker studies in comorbidity clinical trials be used to optimize HIV care across the lifespan?
5. How can new technologies facilitate efficient assessment of patient-reported outcomes and biomarkers?

Discussion Themes and Opportunities

Share the fruits of HIV research with other fields. HIV research can offer valuable information to other fields, such as how comorbidities and patient-reported outcomes group together. Studies that compare SF-12 scores between cohorts with and without comorbidities are one example.

Make HIV clinics a model for integrated mental health care. Evidence shows that psychological interventions can be just as effective among people living with HIV as among those without HIV. Integrating mental health care is a challenge for a general HIV practice. Providers know that mental health conditions are elevated in people living with HIV, are aware that there is a better cost benefit to integrating mental health care into HIV care, and have screening tools that work for mental health and cognitive deficits. However, the question of optimal follow-up care remains. Advocating for the integration of mental health treatment in HIV primary care could lead the way for other primary care centers. Studies that show cost-effectiveness will be important. Doctors

often need to adjust medications after the initial prescription, even when they are effective. In HIV populations, it may take 12 to 20 sessions with a qualified therapist to show effectiveness. Research should examine approaches for integrating treatment for trauma and other factors that increase risk for mental health issues in clinical care.

Explore other care models. Providing clinic-based services, as in the Ryan White era, is no longer working. People over age 60 are isolated and invisible; many are so disabled they cannot travel. Existing care and services are not meeting their needs, and this argues for a restructuring of clinics and services. The field of geriatrics has models of care that could be informative for people living with HIV. For example, some models focus on how best to preserve what matters most to the patient, such as mental capacity, mobility, and medications. Finding a geriatric model that every HIV clinic can follow should be front and center. Integrated geriatric care may be an appropriate approach. At some level, integration has to happen because of comorbidities, but it is unclear whether this needs to come earlier in the care process for people living with HIV. In the United States, an HIV patient's first referral is to an HIV physician. Other countries have more integrated health care systems that treat patients in a more coordinated fashion and more successfully. How does the United Kingdom or Sweden, for example, structure its subspecialty care with a smaller number of subspecialists? How are these kinds of issues managed within the Department of Veterans Affairs (VA), Kaiser Permanente, and other systems? Some prioritize efficiency of screening and referral to subspecialty care and are doing a good job. Experimentation around models of care delivery is a priority. Is there a role for centers of excellence in HIV-related comorbidities in investigating telemedicine delivery, reimbursement, and related issues? Telemedicine is one example of a different model of care. What are ways to conduct e-consults for patients who cannot visit a center? For example, the VA consultation and health care delivery model uses telehealth. The discussion of telemedicine must include the question of how to monitor people in their homes. The accessibility of telehealth is also relevant for low-income countries. Experts need tools that can help teach patients and physicians what to do.

Improve patient education. Patient education is another essential element. People may feel uncomfortable going to the doctor. When discussing research, that often gets pushed to the side, but it must come first. Some patients are able to understand what their bodies are going through, and it is important to have providers who can explain these things in lay terms. People may feel that doctors are talking over their heads or may be unsure how to ask doctors to explain their results. In addition, patients have a lifetime of dealing with different care institutions and may have a history of negative associations with care. Can doctors help circumvent other uncertainties that come with comorbidities? Common messages about healthy living are appropriate for both people living with and without HIV, but HIV still increases the risk for certain comorbidities. What needs to be prioritized to generate guidelines for this community? Doctors have an opportunity to ask about vitamin D and diet, exercise, and other components in the context of discussing comorbidities like osteoporosis. Patients may not connect

comorbidities to their HIV status, so it is important to educate both physicians and patients. Establishing a consultation service would be helpful so specialists can access and understand what is known about people living with HIV. As perinatally diagnosed patients get older, their providers may not emphasize information about diet, smoking, and possible complications such as diabetes or hypertension.

Test new tools to measure morbidity. Better tools and measurements to assess health-related quality of life, stigma, and other elements are needed. How should these tools be used to measure morbidity and mortality? How can morbidity be captured better? These questions need to be a focus of research. Quality of life research is its own field and offers many findings and resources that could be leveraged in HIV/AIDS research. Mental health status may be reflected in different ways; do the tools reflect that (e.g., reactions expressed as sadness vs. anger), and have they been tested in different populations?

Study applicability of general treatment guidelines. When treating people living with HIV, doctors often follow the guidelines developed for people living without HIV because that is what is available. However, it is not always clear how to tailor treatment for people living with HIV. Experts need to study how traditional interventions should be applied to people living with HIV. This was the purpose of REPRIEVE. Is this needed for other interventions? For the general population, guidelines for aspirin are shifting. What should HIV/AIDS care providers know about these and other interventions? Making sure all general practice guidelines mention care of people living with HIV should be a priorty, because general practitioners will not look up HIV-specific guidelines. Social determinants of health also affect a patient's experience. Treatment must be effective, but it should not add to a patient's burden. Making sure that the part of subspecialty guidelines addressing people living with HIV is correct is important. Primary care guidelines are based on evidence, which needs to be updated regularly. This group needs to prioritize where gaps in the evidence base exist and clarify the best ways to fill them. Should the evidence come from observational studies or other kinds of research? Researchers can leverage data from different cohorts. Some data could come from clinical trials, and modeling can also be used. Does the guideline also address cost (e.g., of medicine to prevent osteoporosis vs. treatment for a fracture)? Some conditions come with overwhelming amounts of guidance, so it is important to prioritize what guidance to enforce and to distinguish between what can be done and what should be done.

Where will screening have the greatest impact? There is a consensus that early screening and identification of comorbidities is a priority. Given that people living with HIV often have multiple comorbidities, how should the field prioritize screening for these conditions? Is it the same for everyone? How strong does the evidence need to be to recommend screening people living with HIV earlier for comorbidities? Identifying conditions associated with HIV infection that warrant alternative screening guidelines and conditions for which screening data is still needed in the context of HIV infection

should be research priorities. Data will show where screening is not indicated. It will be important to weigh the benefits and costs of screening. Some decisions will be based on priority outcomes, and function should be one of these. Screening and early diagnosis must be linked to rapid intervention. Studies can help find effective strategies for early identification. Clinic structures that will aid early diagnosis and rapid treatment should also be identified. Deprescribing also deserves attention: At what point can screening be stopped? This research may present opportunities for analytics, data mining, and artificial intelligence (AI). It will be important to take into account differences across the lifespan and in different clinical contexts. Finally, it is vital to think through the implications of a positive screen and know what the clinical response will be. The algorithm proposed for primary prevention in Australia incorporates guidance for what to do whether the test is positive or negative and includes a timeline for when to reassess people. It is also important to consider how easily providers can apply screening management guidelines in low-resource countries. MACS/WIHS has been phenomenal for people living with HIV because it offers the options to have a range of screening tests. How can support be made available for other organizations to offer patients the same benefits?

Decide on a framework for ranking priorities. A potential framework for priorities is a net clinical benefit. In many cases, it is not clear what has absolute benefit or risk. However, it is possible to assess where immediate implementation is feasible and should be prioritized. The clinical benefit framework helps clarify where to focus the research. Modeling can help determine how benefits change over time.

Tailor recommendations to the patient population. People living with HIV are often all lumped together, but subgroups differ in important ways. This population should be stratified, and the target group clearly defined. For example, people who were diagnosed and started treatment many years ago have fared differently from individuals who fell through the cracks in the system, remained untreated for many years, and are more susceptible to comorbidities. In many people living with HIV and comorbidities, the comorbidity preceded HIV infection. In addition, CVD and its complications are shifting, as in the general population, from an atherosclerosis-focused condition to one in which heart failure predominates. Understanding how these complications interact with substance use is important.

Explore a precision medicine approach. It is not financially responsible to screen everyone; there may be value in screening just those with a genetic predisposition to certain conditions. One priority may be to focus on a precision health approach. There should be alternative screening guidelines in the context of HIV infection to help clinics further risk stratify (e.g., considerpostmenopausal women and men over age 50 as candidates for osteoporosis screening). For some comorbidities, such as COPD, it may be more appropriate to focus on finding cases based on symptoms than screening everyone who meets very general criteria. For example, it is easy to identify smokers with a cough as a priority for screening. One of this working group's priorities was to

look at the prevalence of various diseases, but understanding how incidence changes as people get older also emerged as a real need.

Improve exchange of information between specialist and primary care. Academic centers with multiple specialties need to identify a better referral process, as patients are often referred to clinics that do not know how to treat them. Specialists whose expertise does not extend to HIV and its comorbidities need to be better trained. Practitioners outside of HIV care need to understand the issues that are unique to HIV. They often face challenges working in collaboration with people in HIV clinics, and they often lack guidance around which screening guidelines are appropriate. Possible solutions include remote consultation with experts, centers of excellence of care, and dialogue between HIV specialties. Generally, information does not get adequately disseminated to HIV providers and subspecialists. Screening practices used in the general population are not necessarily known to HIV providers, and those used for patients who are living with HIV may not be known to subspecialists. Raising this issue at provider meetings is a priority. In addition, the challenges of the consolidation of patient care to a few centers in each city must be addressed. Clinic providers want to be good internists for all patients, but this becomes more challenging as the complexity of patients' health issues grows. It is a priority to define when providers can refer patients receiving specialty treatment back to primary care. For patients whose virus has been suppressed for a long time, is there a Veterans Aging Cohort Study (VACS) index score to which they can be referred?

Advance research on preventive interventions. When screening for traditional risk factors, interventions like statins or aspirin are used for prevention. Where are HIV-specific interventions? Even with viral suppression, inflammation is still occurring. There is a gap between the basic and clinical groups in identifying contributing factors and translating those to targetable interventions that needs to be addressed with research. Where would researchers find samples to study tissue before the development of lung cancer or a heart attack? What study design would allow researchers to find biomarkers for predictive or causal determinants? Preventive interventions, such as smoking cessation and exercise, are thought to have a big impact on health, although research is scarce. Priorities include better understanding the use of medications specific to certain diseases—such as statins—in people living with HIV and identifying effective interventions for patients with multiple morbidities. Research can also help the community understand the risks and benefits of screening and interventions over time and how best to balance those interventions against the geriatric principle of deprescribing. It is crucial to keep in mind patients' perspectives on what is important.

Prioritize research on secondary prevention. We do not fully understandwhether people living with HIV who develop a secondary health incident responddifferently to prevention and treatment than do those without HIV. For each comorbidity, there are secondary prevention questions, such as what the relapse rate for depression medications is. Risk factors for incident disease have been studied, but there is value in

looking into recurrence. Adherence and access to medications affect secondary prevention, and differences in the underlying disease process could, too.

Prioritize research on interventions for social factors. People living with HIV or who are vulnerable to acquiring it deal with stigma and many other vulnerabilities, which can affect biological substrates. Research priorities include studying ways to ameliorate social conditions and improve quality of life. Drivers of disease, such as poverty, loneliness, and access to care, may drive comorbidities, and drug treatment will not change these factors, which should be included in baseline data.

Provide wraparound care to support tobacco cessation. Smoking is a root cause of many comorbidities, but MACS/WIHS data show that even repeated attempts to quit may not be successful. Particularly for patients who are living with HIV, it is important to provide wraparound mental health care to support their cessation attempts. The reason it is more difficult for people living with HIV or those on ART to quit may be at the interface of biology and behavior. HIV may affect patients' metabolic rate. Figuring out how to make cessation successful is particularly important, given the increase in young adults who are addicted to e-cigarettes.

Consider the level of resources available in the community. In low- and middle-income countries, HIV programs have been aggressively decentralized and moved to primary health care settings, and comorbidities have become the new face of the HIV epidemic. In this context, it is crucial to consider the resources available to manage this. Are sufficient human resources and lab infrastructure available? Are those primary health care facilities ready to deal with this new challenge? It is important to pay attention to resource-limited communities, as well as resource-limited countries. Resource-limited communities, including everyone with HIV, need more attention. The system of care needs to be restructured to address problems of an aging population. We should have access to real-time data that quantifies the number of people who are able to visit the doctor, cook, leave their apartment, or do other daily activities, to help define specific functional disabilities.

Assess the level of comorbidity in research and care. Being cognizant of gradients of comorbidity is important. A blood pressure reading of 160/110 mmHg is different from 132/84 mmHg, and these values interact differently with HIV. Much work needs to be done to understand the clinical course of individual comorbidities in the context of HIV. In addition, filling the gaps in clinical data on mortality related to various comorbidities, as well asreal-time outcome data for specific interventions, is a priority.

Consider patient perspectives. It is crucial to think of outcomes from the patient's perspective. How do patients define outcomes and benefits? It is not clear what healthspan means for individuals. Study measures may not align with patients' priorities. For example, researchers may design a trial to benefit mobility, but the patient may be interested in pain relief. Studying patient-caregiver dyads and how they affect treatment and management strategies will require a different methodology. It is important for

research to account for the bidirectional relationship between chronic pain and depression in patient-reported outcomes. Research on perceptions that affect adherence is another unmet need. Patients often do not have a good understanding of the importance of medicines other than those to treat their HIV. The patient perspective regarding what treatments are important (i.e., prioritizing HIV medications over high blood pressure medicine) deserves more attention.

Validate and use patient-reported outcomes. Consider using patient-reported outcomes as key stratification variables and predictors of outcomes. For example, statins can worsen pain. Do people with pain have a different response to statin treatment? When considering patient-reported outcomes, assessing the validity of the measures being used and considering which populations have validated them becomes important. Focus on best practices does, too, because literature reviews on patient-reported outcomes may reference high-quality and low-quality studies together. Finally, it is critical to understand, from the patient perspective and through validated instruments, the similarities and differences between symptom profiles and biomarkers for people with conditions such as insomnia or neuropathy. For example, is nausea the same in the context of antiretroviral treatment vs. chemotherapy? Researchers also need to harmonize patient-reported outcomes and clinical endpoints. Currently, it is difficult to compare outcomes from HIV/AIDS studies with other studies, and being able to do so is important.

Identify outcome biomarkers from existing study data. To assess multimorbidity properly, developing indices, such as VACS, that capture the pathophysiology of patients is necessary. It is time to talk about identifying biomarkers. There is value in coming up with predictive indices that are responsive and could be followed as an outcome. For biomarker discovery, repositories must be established. MACS/WIHS is relatively small, but there are other sources for doing this kind of research, such as the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Research has generated a great deal of biomarker data, but in many cases, it is in silos. It would be valuable for some tech-savvy people to identify biomarkers that are relevant to outcomes for some or many diseases.

Use biomarkers for eligibility, phenotyping. Biomarkers should be used as eligibility criteria. Biomarkers can offer promising opportunities for phenotyping patients and stratifying them for inclusion criteria and outcomes. REPRIEVE is an opportunity to include biomarkers. Discussion of the TAME study raised questions such as the value of a metformin treatment study on prediabetes patients. In the TAME trial, the effects of metformin will be investigated for people without diabetes. Biomarkers might be helpful in examining the heterogeneity of effects—for example, would people with insulin resistance be more responsive? However, researchers would need a large enough group to study, and it is not clear what support mechanisms would apply. Biomarkers can help with deeper phenotyping for interventions. Tight, comprehensive phenotyping, which is an essential first step, is needed.

Incorporate people living with HIV in clinical trials. The inclusion of people living with HIV in large trials is a priority. Historically, trials have excluded this population categorically, and this needs to change. Integrating people living with HIV in general studies is critical because of potential differences in pathogenesis. Including people living with HIV and cognitive impairment in a dementia trial may reveal different pathological paths. It is important to evaluate where including people living with HIV in general trials makes scientific sense. There should be rules for including people whose HIV is under control or is undetectable and has been for years. There may be lessons to learn from cancer research, where the consensus has moved toward inclusion, unless there is a good scientific reason to exclude. One concern about including people living with HIV revolves around the feasibility of enrolling adequate numbers. New statistical methods could make enrollment estimates more precise. In addition, clinical trial investigators and networks could be encouraged to invite ancillary studies on HIV comorbidities.

Leverage opportunities for collaboration. The TAME trial presents an opportunity for the HIV research community to collect comparable samples. This could help researchers understand whether patterns of biological changes seen in people living with HIV are a form of accelerated aging or a unique pattern. The HIV research community is welcome to use the biorepository as a platform. As the biorepository will not be enriched for HIV, TAME offers an opportunity for HIV/AIDS researchers to run parallel trials. For example, the HIV community could do a cross-sectional biomarker study to address fundamental questions, such as HIV patterns associated with other signs of aging. Other large biorepositories, such as the Collaborating Consortium of Cohorts Producing NIDA Opportunities (C3PNO), exist.

Define strategies for evaluating multiple endpoints. The AIDS Clinical Trials Group (ACTG) has done a good job of sharing endpoints for intervention, and many are linked. One of the opportunities coming out of this conference should be to work out how to look at multiple endpoints. How should these endpoints be funded and considered?

Reassess NIH models for research support. Interventions on CCCs aim to decrease the risk of multiple diseases, but it can be a challenge to secure funding for multiple disease endpoints, given the diverse mission areas of NIH ICOs. Moreover, as people living with HIV agechronic disease is gaining increasing focus, but HIV research has not had a history of geriatric specialization. Support models may have to change to accommodate this. A shift in support of comorbidity research is now occurring: It used to be that this support came from NIAID, but other institutes are taking on more of this responsibility. Concern about the future of comorbidity researchis emerging, tooFor example, support from NHLBI for cardiovascular comoboridies is part of a large portfolio of research designed to understand, prevent and treat cardiovascular disease among many vulnerable groups, including older men and women, people of color, and people with risk factors such as obesity or diabetes. NHLBI, NIAID and other ICOs will need to find ways to maintain a portfolio balance while investing appropriately in HIV

comorbidities research. Efficient study design and shorter times to outcomes might require a paradigm shift at NIH. A supplement mechanism to study comorbidities specifically would be helpful. Research could also be supported by a new type of supplement with a longer follow-up. Within the limits of some support structures, there may be insufficient time to look at the data or include an ancillary study. NHLBI supports approximately 25% of the MACS/WIHS Combined Cohort Study as part of a combined NIH effort. This is a successful cross-NIH collaboration and could be a model for similar efforts. Possible additional funders include the Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI). Support should encompass domestic and international studies.

Implementation Science Research Working Group

The Implementation Science Research Working Group identified three priority topics:

- Identify priority implementation science HIV comorbidity research questions
- Develop novel observational and experimental implementation science research designs
- Expand training opportunities and resources to expand the implementation science research workforce

The Implementation Science Research Working Group introduced a theoretical discussion of methods. Recommendations included bringing implementation scientists to the table early to help determine which approaches have the most impact and the most effective ways forward. Several questions were addressed. For a given HIV-associated comorbidity, what can be learned from implementation science research that has been conducted outside the HIV setting? In resource-limited settings, what can we learn about screening, diagnosis, and management of HIV-related comorbidities that will be relevant to the care of people living without HIV? Should Implementation science research around screening and management of risk factors for HIV-related comorbidities (e.g., smoking, obesity) that could result in the prevention and/or earlier detection of several HIV-related comorbidities, reducing their ultimate burden? Would a better understanding of the preferences of clients, patients, and providers with respect to a given evidence-based intervention be useful to better inform the design of strategies to improve their uptake, engagement, and delivery?

Synthesizing Priority Implementation Science HIV Comorbidity Research Questions

The following key questions were proposed:

1. What combination of implementation strategies would be necessary and sufficient to increase the impact of interventions for HIV-related comorbidities?

2. Given limited resources in our jurisdiction, what implementation strategies will be most effective when implementing interventions for HIV-related comorbidities at the lowest cost?
3. How can we learn from our successes and challenges as we roll out interventions for HIV-related comorbidities over time to more expediently achieve implementation?
4. Can the cost and resources involved in a successful multicomponent implementation strategy package be reduced while maintaining its impact?
5. How can the field begin to optimize implementation during the development and testing of new interventions for HIV-related comorbidities?

Novel Observational and Experimental Implementation Science Research Designs

The following key questions were proposed:

1. How do we define program or implementation equipoise, versus clinical equipoise, and how does it influence experimental methods?
2. How can we define and measure counterfactuals in implementation science research methods?
3. How do we attribute changes in incidence of comorbidities and health outcomes to a complex system of interventions that have been adopted or implemented and adapted over time?
4. How can we characterize the context and the mechanisms by which context influences the impact of interventions?
5. How can we evaluate and assign effect size to the adaptive decision-making that health service providers make for patients?
6. How can we leverage multiple layers of routinely collected programmatic data to rapidly adapt the implementation of services to incoming data?

Training Opportunities and Resources to Expand the Implementation Science Research Workforce

The following key gaps identified and questions proposed were:

1. Investigators cannot just “do” implementation science research without training.
2. What can be easily layered onto current implementation science generalist training?
3. What can be easily layered into HIV-related research consortia and activities?
4. Almost all NIH-sponsored trainings in implementation science are targeted to a specific disease topic area; there is nothing specific to HIV.
5. There is high demand for, but a low supply of, implementation science training programs.
6. Except for larger NIH-funded training programs to a specific institution, most NIH-funded trainings target only clinician investigators.

Discussion Themes and Opportunities

Optimize by studying what to take away and what to put in place. There is a need for more de-implementation studies, which focus on the impact of taking away an intervention that might not be working. The diagnostic and treatment protocols available in public health programs for HIV are changing monthly or yearly. How do we strike a balance between bringing in new, more effective implementation science studies and de-implementing what is not effective? This is an important question to consider, because providers and clinics cannot just keep adding services. In some cases, less intervention may have the same outcomes as more. Is it possible to do more with less, or does quality of care suffer? Investigators can use natural experiments to examine situations where interventions or services have been taken away. However, the questions these studies ask are different, and that can make it hard to sell them to reviewers. The work of de-implementation has advanced the most in studies of antibiotic prescribing, and this area offers the most to learn.

Research priorities for HIV comorbidity care. Regarding comorbidities, some of the most important and interesting implementation science questions have to do with HIV specialty care and primary care. How do different types of care affect the implementation of CVD prevention or treatment of comorbidities? How can screening and documentation of HIV and comorbid diseases be optimized? Who should be screened and how? Pre-implementation studies are important for examining specific comorbid diseases and patient groups. We have a limited understanding of subpopulations and specific determinants. Regarding intervention for comorbidities, it is important to look at broader health care structures. What are the best models or strategies for evidence-based collaborative care, and how can the existing HIV infrastructures for care be used? Since sustainability is core to implementation science, it is important to examine budget implications. Can hybrid effectiveness implementation studies be used?

Make support for implementation science training a priority. A key principle for training is to involve multidisciplinary teams early on. In order to bring in implementation science researchers at the study design phase training more implementation research scientists will be essential. A concerted effort is being made to build the next generation of scientists. NHLBI has developed a K12 mechanism specifically to address this need, which has been growing quickly. Prioritizing sustained mentorship and long-term training is important, as this will be more effective for early researchers than a single class. Implementation science research can provide insight into where to focus the budget.

Focus on outcomes. With complex strategies, it is important to pay attention to implementation outcomes. Often, researchers conduct complicated interventions but do not measure the implementation outcomes and so cannot explain why they worked or failed. Measuring implementation outcomes forces researchers to explain and measure their work so they can optimize it through further studies. Implementation science can help determine what elements have to be the same and what can change over time.

Make use of innovative approaches. Researchers have opportunities to integrate implementation science into other studies. Collaboration with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) or the Health Resources and Services Administration (HRSA) could help take programs to scale. The data would be available for implementation at the next level. Modeling and simulation are tools that researchers need to look at different scenarios. Smartphones and other devices can provide data streams for research, but because of privacy concerns, access to data sets may be limited. Modeling can help researchers understand the prevalence and burden of diseases over time. It can also provide a way to look at multiple strategies to determine what the optimal set of interventions will look like, given that budgets probably will not change. There are different approaches to implementation science research, such as mixed method, regression discontinuity, or adaptive or SMART designs.

Consider context. Where the interventions will be implemented is an important consideration; for example, implementation science can help measure factors unique to an urban vs. rural context. Study design may differ depending on the population studied; for example, technology-based methods may be more appropriate for adolescent participants, and in-person models may suit older patients better.

Share tools and resources. Compiling resources for implementation science in the United States and internationally is a priority.

Identify sources of support for implementation science. Obtaining funding for implementation research may require "shopping" across multiple sources, which are growing as the field itself grows. HRSA funded a hybrid study of 10 sites that are integrating community health workers into HIV care. NIDA strongly highlighted the need for implementation science in the Helping to End Addiction Long-term℠ (HEAL) Initiative. However, even as funders are supporting implementation science, getting reviewers to accept it remains a challenge. Obtaining support for implementation science may require looking outside of NIH to pharmaceutical companies, the CDC, HRSA, or other organizations. What are models of success?

Syndemics Research Working Group

The Syndemics Research Working Group presentations focused largely on definitions. Members emphasized how local context matters and how strong the impact of social determinants of disease is. Several overall priority questions were addressed.

1. When is something syndemic and when is it not?
2. How does the syndemic approach advance our understanding of mitigating upstream or clinically to make the biggest impact?
3. Why does syndemic thinking matter for HIV?

Syndemic Methods

The following key questions were proposed:

1. On a theoretical level, what does it mean when we assert that epidemics are "working together" within populations or when we assert that diseases are "working together" within individuals?
2. Do the competing theoretical models yield differing programmatic, clinical, and/or policy recommendations?
3. Are there settings in which co-occurring epidemics do not need to be characterized as a syndemic, when a more parsimonious appeal to social determinants of health would suffice?
4. On an empirical level, how do epidemics interact at the level of populations?
5. Which co-occurring epidemics warrant being characterized as a syndemic?
6. How does the label improve the public health response?

HIV–Infectious Disease Syndemics

The following key questions were proposed:

1. What are the optimal prophylactic regimens to decrease sexually transmitted infections, viral hepatitis, and/or tuberculosis (TB) acquisition in people living with HIV and those at greatest risk?
2. To what extent does early diagnosis and treatment of co-pathogens result in improved health?
3. What insights in mucosal biology can lead to better prophylactic approaches in the prevention of HIV and co-pathogen acquisition?
4. Which structural interventions (e.g., economic empowerment, enabling legal environments) are most effective in decreasing the spread of HIV and synergistic co-pathogens?

Discussion Themes and Opportunities

Consider local context. Diseases rarely exist in isolation. HIV infection may manifest as different diseases in different contexts. Given what is known about psychosocial context and comorbidities, how can HIV research address HIV in both the U.S. and international contexts? An appreciation of the context using a syndemics framework is essential.

Advance syndemics research priorities. Research priorities include answering questions such as what syndemic pathways interact with HIV. These could be biological, social, structural, behavioral, or psychological. For example, what are pathways to internalized stigma? There will be common features, and one syndemic can inform another, but one size does not fit all. Understanding pathways, moderators, and mediators makes important sense. What interactions produce adverse outcomes? What are the mechanisms by which factors that affect HIV-associated comorbidities (e.g., stigma, housing) affect HIV care? Figuring out how to design and test

interventions to multiple comorbidities associated with HIV is another priority. Can we define interventions with a multifactorial outcome where HIV is one of the factors? The HIV syndemic is unique because people are living longer than initially predicted, so there is a new element of rapid aging in the existing syndemic.

Improve syndemics methodology. Regarding the development of methods, multidisciplinary teams typically produce local tools. Syndemic approaches include ethnographic study of local social, psychological, and medical problems; development of tools from ethnographic or qualitative data; epidemiological study of syndemic clusters; development of quantitative methodologies to understand and interpret the interactions and pathways between syndemic drivers, clusters, and outcomes; tests of syndemic cluster complexity via ethnographic or qualitative methods; and refinement of hypotheses to test interventions. Developing a rigorous syndemics methodology is a priority. It is also important to bring in key stakeholders for every step of the research to determine how to analyze interactions critically and productively.

Involve other parties to facilitate implementation. Implementation science and syndemics findings point to solutions that the scientific and medical communities alone cannot implement. Trying to heal or cure the disease alone is not sufficient; health and social policy changes are crucial. Are all the right players at the table to affect factors like poverty or smoking? Exercise is known to be important, but many neighborhoods have no place to exercise; should the conversation include representatives of housing departments who can speak to designing neighborhoods that make it easier for people can exercise? Who else outside of NIH needs to be thinking about these issues? Multi-level interventions that address multiple comorbidities will have the most impact.

Use syndemics to explore solutions. Often, there is too much of a focus on negative outcomes; in addition to risk factors, survival and resilience factors should be examined. A syndemic approach to health should include asking people about solutions. A resiliency survey developed for reseach in Palm Springs, California is one example of a tool that could be used to conduct this research among people living with HIV.

Panel on International Research

Worldwide, 23 million people are now using ART. Although the detection and effective treatment of HIV remain the highest priorities in most low- and middle-income countries, there is a growing need to address comorbidities. The Panel on International Research identified three priority topics in low- and middle-income countries:

- Challenges and barriers to identifying and treating comorbidities
- Research needs targeting HIV/AIDS comorbidities
- Curricula for training in HIV/AIDS comorbidities

Discussion Themes and Opportunities

Convey to donors the need for fewer restrictions on support. One challenge to integrating primary care in HIV clinics in low- and middle-income countries is that donors restrict the clinics to activities that help them fundraise in the United States. It is important to raise awareness among donors who contribute to organizations that provide services along the continuum of integrated care. Donors should make it easy for countries to branch out. This could also improve care for people who do not have HIV who are alsoserved by the clinics. Support must be available to deliver effective primary care.

Improve data collection on comorbidities. Estimates of the global burden of disease rely on scant epidemiological data. Researchers are making many assumptions, so it is important to gain a better understanding. Because it is unclear which comorbidities are most common, researchers are operating in the dark. The burden of non-communicable diseases (NCDs) also differs from country to country. In addition, due to stigma, people may not seek health care for comorbidities such as diabetes, neurological disorders, or epilepsy. Part of understanding epidemiology is understanding disorders for which people do not seek care but that are still a burden. The World Health Organization has standardized its STEPwise approach to Surveillance (STEPS) methodology to understand the burden of NCDs. The IeDEA network, spanning 42 countries and hundreds of clinics, is starting to understand issues such as the capacity to screen, diagnose, and treat NCDs by using site surveys. These results help set the research agenda for the network. Support is needed to set up sentinel sites to quantify the burden of noncommunicable diseases and their risk factors for both people living with and without HIV. A network of sentinel research sites is a good idea, but its reach needs to be wider. Researchers have relied on health care systems to understand the burden of diseases or conditions, but it is not clear how reliable the data are. Nationally representative surveys of demographic health traditionally have collected information about reproductive health and infectious disease and are a potential resource for efforts to integrate NCD surveillance. Some countries are already moving in that direction. It would be valuable to bring this group to the table to help with that shift. For example, the PEPFAR Population HIV Impact Assessment (PHIA) surveys could capture the prevalence and burden of NCDs and their risk factors. It may be worth looking at STEPS or Demographic and Health Survey (DHS) Program tools and other study designs. These surveys show the same levels of chronic disease as other instruments and could be applied to people living with HIV.

Expand care for NCDs at HIV clinics. Until government ART clinics were established in low- and middle-income countries, there was often no place for sick people to get health care after they got their childhood vaccines. Now many people go for screenings even when they are not sick, and this has highlighted the burden of disease. A model for providing targeted, efficient, universal care can and should be developed. How can HIV care be integrated with comorbidity diagnosis and care in developing countries? Some people may hesitate to go to an HIV clinic to have other conditions treated because of the stigma associated with HIV.

Establish research priorities. Behavioral and social science agendas are important to include, because they are relevant to disease outcomes and can help in understanding stigma and health-seeking behaviors.

Be aware of unique aspects of sex and gender. Several studies show that women have worse outcomes with regard to aging, physical disability, and mental disability. Menopause could be the reason women with HIV fare worse than men. In the general population, women are at greater risk for falls and mobility issues, so it may be general epidemiology that is apparent in HIV. It is important to be aware that sex and gender can have different effects in Africa than in the United States. For example, problems with Kaposi's sarcoma-associated herpesvirus are more common in sub-Saharan Africa. Women have a lower risk of developing Kaposi's sarcoma but fare worse than men when they do. It is unclear what factors lead to that outcome. It is also worth thinking carefully about gender aspects of comorbidity care. Around the world, many women with HIV need specific attention; for example, breast and cervical cancer are significant burdens in many parts of the world. Researchers should consider when to stratify data by gender.

Investigate unique aspects of inflammation. Low-level persistent inflammation, even after viral suppression, is recognized as a root cause of elevated comorbidities in people living with HIV, and understanding that would help researchers understand comorbidities. However, infectious exposure to diseases like malaria or dengue may result in different immune profiles and effects on comorbidities. There may be other root drivers or modifiers of the inflammatory state in people living in low- and middle-income countries, so it is essential to study conditions in different settings.

Build the community of HIV researchers. Engaging translational and basic scientists in international settings makes critical sense. In the United States, we often take for granted that researchers from different specialties are all part of the same community, but this is not always the case in low- and middle-income countries. The Fogarty International Center is committed to supporting training in developing countries.

Keep care delivery in mind. It is essential to keep the implementation perspective in mind. As the basic epidemiology is worked out, it is worth thinking ahead to large-scale system changes for delivering health care. An effort is now underway to decentralize HIV services out of centers to mobile clinics, community drug distribution sites, and other settings. Fewer contacts with the system may improve adherence. How can both agendas be achieved?

HIV Community Perspective: Aging with HIV in the United States

The workshop featured the patient perspective in a presentation from Jules Levin, a long-time activist and the founder of the National AIDS Treatment Advocacy Project,

who has been living with HIV for more than 35 years. Mr. Levin highlighted three main priorities: an implementation study to address urgent needs in the community, basic research on HIV and aging, and community action to provide care services. The presentation and subsequent discussion highlighted the themes below.

Advance basic science. Researchers need to do the science to understand what HIV is and how it causes disease.

Conduct an implementation study. An implementation study could evaluate a new care model for people living with HIV and whether it improves quality of life. The new care model could include longer visit times with physicians, changes to reimbursement, more dedicated staff, improved coordination and communication among providers, education for patients, geriatric care in the clinic, telemedicine options, and home visits. Many older people are isolated and lonely, cannot leave their homes, or find it difficult to navigate the health care system. Exploring options like home monitoring visits and telemedicine is critical in order to improve services. The study could also help address the increased cost of care and answer questions about brain function, bone health, social isolation, the impact of substance abuse, and other factors. Doing this research could also help address the increased cost of care. The study could be integrated into MACS/WIHS. It is also essential to have community representation on the study.

Address barriers to implementation. Cost will be the biggest obstacle, so research should help collect data to show what cost savings will be realized if a new care model is implemented. Fragmentation of the health care system is another obstacle, and demonstrating cost savings could help break down care silos.

Address priorities that are relevant to an aging patient population. Because of aging, the patient population has changed and will continue to change, and care and research structures will need to reflect that. Priority research questions about the onset of comorbidities include the nature of aging with HIV (whether it is premature, accentuated, or accelerated); the underlying cause of comorbidity in each organ; the roles of immunosenescence and cell senescence; relative contributions of HIV, lifestyle, and behavior; the role of inflammation; what causes cognitive impairment; what happens with muscle; and the effect of changes on functional disability. Fatty liver disease is a particular concern, but it is not clear what all the risk factors are. Another gap is in the information shortage from patients over 65, whose input is not quantified and collected. Some of these patients may not share details with their doctors because they feel stigmatized, or the doctor does not take the time. Some existing studies have collected data in large age groupings but have not drilled down to those older age ranges for more details. While it is good to propose purposeful study in those who are older, it is also worth going back to existing data. Substance abuse is becoming prevalent in the context of disabling neuropathy, which is common but not widely discussed. Some patients turn to illegal drugs because they cannot endure the pain.

Common Themes that Emerged from the Discussions

From the advance work accomplished by the five WGs and the international panel, as well as the discussions during the two days of the workshop, several common themes have emerged.

- HIV-associated CCCs affect multiple systems and diverse health outcomes, negatively impacting the quality of life and healthspan of people living with HIV, even in the presence of ART and in spite of improved lifespan.
- Underlying pathogenic mechanisms may be shared among HIV-associated CCCs that involve multiple systems and manifest as various concurrent conditions in people living with HIV. These may be fundamentally different from those that result in the same “diagnosis” in people living without HIV.
- The appropriate phenotypes, indicators and indices/biomarkers for research on HIV-associated CCCs will likely prove to be distinct among people living with and without HIV.
- Factors and shared pathways that drive chronic immune activation and dysfunction in treated HIV infection and mechanisms that drive accentuated aging are among the overlapping etiologies and mechanisms that contribute to the development of HIV-associated CCCs.
- New research methods or technologies, including appropriate animal models, are needed for research of HIV-associated CCCs across the lifespan.
- Prevention and management of HIV-associated CCCs is a complicatedarea of research because intervention strategies must consider drug-drug interactions with ART and therefore may need to be tailored to people living with HIV. Targeting multiple HIV-associated comorbidities may also be necessary.
- Multiple factors likely contribute to health in aging people living with HIV, including the direct impact of HIV on multiple organ systems, toxicity of ART, polypharmacy, social isolation, stigma and likely many other still poorly defined risk factors. Notably, most of these factors are known to affect aging in the general population but are over represented or more pronounced in people living with HIV.
- The impacts of social, cultural, economic, political and other factors on the susceptibility to and treatment of HIV infection and other co-conditions are not fully understood. How these factors differ within and between at-risk populations and the best ways to study them are largely undefined.
- Syndemics research could help characterize various comorbid diseases/disorders and their synergistic effects in the context of social, political, and ecological factors in people living with HIV. As such, syndemics research can help us gain a deeper understanding of the interplay of those factors and their role in promoting disease clustering at the population level, and the impact they have on disease pathologies at the individual level. Findings of such research will encourage more holistic approaches in the clinical management of people living with HIV.
- Implementation science is a relatively new area of research and, hence, coordinated support is needed not only to develop implementation research studies but also to

train scientists in implementation science, which could include leveraging existing training opportunities and resources. Implementation science strategies are needed to address barriers that impede the scale-up and application of scientifically proven interventions in community and clinical settings for the prevention, control, and treatment of HIV-associated CCCs in people living with HIV.

Opportunities Identified

The workshop suggested the following strategies to advance research on HIV-associated CCCs.

A coordinated NIH-wide research strategy would be optimal for addressing HIV-associated CCCs, since they involve multiple organ systems and concurrent conditions. This strategy would be developed in addition to efforts targeting specific research priorities within the mission of each ICO.

Multidisciplinary strategies are needed to address the common research themes that emerged from the workshop. These strategies will require a non-siloed collaborative approach and further investigation on topics such as the following:

- Research to understand underlying pathogenesis and mechanisms that may be shared among HIV-associated CCCs, that involve multiple systems, and that manifest as various concurrent conditions in people living with HIV that may be fundamentally different from the same “diagnosis” in persons without HIV and may be affected by age.
- Syndemics research to characterize and integrate various comorbid diseases/ disorders and their synergistic effects in people living with HIV, while taking into account social, political, and ecological factors. Such research can help us gain a deeper understanding of the interplay between these factors and their role in promoting disease clustering at the population level, and the impact they have on disease pathologies at the individual level. Findings of such research will encourage more holistic approaches in the clinical management of people living with HIV.
- Implementation science research to address barriers that impede the scale-up and application of scientifically proven interventions in community and clinical settings for the prevention, control, and treatment of HIV-associated CCCs in people living with HIV.
- Prevention and management of HIV-associated comorbidities, co-infections and complications. This area of research is complicated because interventions need to be targeted, such as for hypertension, pulmonary arterial hypertension, chronic obstructive pulmonary disease and/or obstructive sleep apnea. On the other hand, current evidence points to chronic immune activation and inflammation as important drivers for multiple comorbidities or complications and residual immune deficiency in HIV. Hence, understanding basic mechanisms, as well as the safety and effectiveness of interventions to control inflammation and immune activation in

people living with HIV, should be of interest to many NIH ICOs. A major challenge of such research, however, will be its high cost. Accordingly, it would be more effective if certain coordinated research efforts could be leveraged to investigate mechanisms and test prevention or clinical management interventions that could address multiple HIV-associated CCCs.

Innovative models are needed to more effectively support future research on HIV-associated CCCs. In particular, research support models should allow multi-morbidity research and collaboration. For example, multi-omics approaches and large cohorts require collaboration across institutes, centers and offices of NIH. Fostering NIH-wide discussions on how to facilitate and fund such collaboration will be a promising way to start.

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Planning Committee members: see Table 1 above.

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Annex 1: HIV ACTION Workshop Agenda

Day 1: 9/19/2019

9:00-9:05: Welcome and acknowledgement

Dr. Shimian Zou, Ms. Natalie Tomitch and Dr. Leia Novak on behalf of NIH Planning Committee

9:05-9:20: Opening remarks

Dr. Keith Hoots (introduction by ***Dr. Shimian Zou***)

Dr. Timothy Holtz (introduction by ***Ms. Natalie Tomitch***)

9:20-10:30: Session 1: Introduction

Purpose of the Workshop (10 mins): ***Dr. Savita Pahwa***

HIV in 2019 – Successes of ART and Challenges of Comorbidities (30 mins): ***Dr. Anthony Fauci*** (introduction by ***Dr. Savita Pahwa***)

Current burdens of HIV-associated comorbidities, co-infections and complications and influences on future burden (30 mins): ***Dr. Keri Althoff*** (introduction by ***Dr. Savita Pahwa***)

10:30-10:35: Logistics: ***Dr. Leia Novak***

10:35-10:50: Break

10:50-11:50: Session 2: Epidemiologic research

Moderator: Dr. Amy Justice

What patient salient, and/or patient reported, outcomes are most useful to gauge health related quality of life and prognoses? (5 mins): ***Dr. Amy Justice***

Discussion (15 mins)

Neurobehavioral Complications of HIV in the Modern Treatment Era: Challenges and Priorities for the Future (5 mins): ***Dr. Igor Grant***

Discussion (15 mins)

How does HIV, risk behaviors, and ART influence aging syndromes, particularly falls, multimorbiditiy, polypharmacy, and frailty? (5 mins): ***Dr. Vincent Lo Re***

Discussion (15 mins)

11:50-12:45: Lunch

12:45-1:45: Session 3: Pathogenesis/Basic Science Research

Moderator: Dr. Dana Gabuzda

Immunopathogenesis overview (10 mins): ***Dr. Peter Hunt***

Discussion (10 mins)

Microbiome/Virome overview (10 mins): ***Dr. Ronald Collman***

Discussion (10 mins)

Aging and Senescence overview (10 mins): ***Dr. Beth Jamieson***

Discussion (10 mins)

1:45-2:45: Session 4: Clinical research

Moderators: Dr. Todd Brown and Dr. Ann Kurth

Overview (5 mins): ***Dr. Todd Brown***

Prevention as Treatment: Clinical and Translational Studies to Prevent Comorbidities (5 mins): ***Dr. Allison Agwu***

Discussion (10 mins)

Comorbidity Management in HIV: Should it be the same as the general population or tailored? (5 mins): ***Dr. Kristina Crothers***

Discussion (10 mins)

Patient-Reported Outcomes and Biomarkers (5 mins): ***Dr. Thomas Uldrick***

Discussion (10 mins)

Sum-up (5 mins): ***Dr. Ann Kurth***

2:45-3:00: Break

3:00-4:00: Session 5: Implementation Science research

Moderators: Dr. Stefan Baral and Dr. Michael Mugavero

Introduction to Implementation Science (IS) Research (5 mins): ***Dr. Denis Nash***

Discussion (10 mins)

Synthesizing Priority IS HIV Co-morbidity Research Questions (5 mins): ***Dr. JD Smith***

Discussion (10 mins)

Novel Observational and Experimental IS Research Designs (5 mins): ***Dr. Elvin Geng***

Discussion (10 mins)

Training Opportunities and Resources to Expand the IS Research Workforce (5 mins): ***Dr. Mari-Lynn Drainoni***

Discussion (10 mins)

4:00-5:00: Session 6: Syndemics

Moderators: Dr. Ada Adimora and Dr. Steven Safren

Introduction/Overview (5 mins): ***Dr. Ada Adimora***

HIV-NCD Syndemic Production (10 mins): ***Dr. Emily Mendenhall***

Syndemic Methods (10 mins): ***Dr. Alex Tsai***

HIV-Infectious Disease Syndemics (10 mins): ***Dr. Kenneth Mayer***

Discussion (25 mins): ***Dr. Steven Safren***

Day 2: 9/20/2019

8:45-9:00: Recap of Day 1

Dr. Steven Deeks

9:00-9:30: Session 7: Clinical trials targeting aging to extend healthy lifespan: the TAME trial: ***Dr. Jamie Justice*** (introduction by ***Dr. Steven Deeks***)

9:30-10:30: Session 8: Panel on international research

Moderators: Dr. Roger Detels and Dr. Eugene Mutimura

10:30-10:45: Break

10:45-12:15: Session 9: Breakout discussion by WGs

Moderators: WG Co-chairs

12:15-1:00: Lunch

1:00-1:50: Session 10: Report from WG breakouts (10 mins each)

Moderators: Dr. Steven Deeks and Dr. Savita Pahwa

Epidemiologic research***: Dr. Amy Justice***

Pathogenesis research***: Dr. Dana Gabuzda and Dr. Peter Hunt***

Clinical research***: Dr. Ann Kurth and Dr. Todd Brown***

IS research***: Dr. Stefan Baral and Dr. Michael Mugavero***

Syndemics***: Dr. Emily Mendenhall and Dr. Ken Mayer***

1:50-2:00: Session 11: HIV Community Perspective: Aging with HIV in the US: ***Jules Levin***

2:00-2:50: Session 12: Panel Discussion for Consensus Building

Moderators: Dr. Steven Deeks and Dr. Savita Pahwa

2:50-3:00: Closing Remarks

Dr. Steven Deeks and Dr. Savita Pahwa

Annex 2: Working group rosters

Epidemiologic and Population Research Working Group Roster

Chairs:
Amy Justice, MD/PhD – Professor, Yale University
Ned Sacktor, MD – Professor, Johns Hopkins University, School of Medicine

Members:
Keri Althoff, PhD/MPH – Associate Professor, Johns Hopkins University, School of Public Health
Kathryn Anastos, MD – Professor, Albert Einstein College of Medicine
Don Des Jarlais, PhD – Professor, New York University
Roger Detels, MD – Professor, University of California, Los Angeles
Matthew Freiberg, MD – Professor, Vanderbilt University Medical Center
Igor Grant, MD – Professor, University of California, San Diego
Lisa Jacobson, ScD – Professor, Johns Hopkins University, School of Public Health
Miriam Laufer, MD – Professor, University of Maryland, School of Medicine
Vincent Lo Re, MD – Associate Professor, University of Pennsylvania, Perelman School of Medicine
Jeff Martin, MD – Professor, University of California, San Francisco
Scott McClelland, MD/MPH – Professor, University of Washington
Leah Rubin, PhD/MPH – Associate Professor, Johns Hopkins University
Kevin Robertson, PhD – Professor, University of North Carolina, Chapel Hill
Michael Silverberg, PhD/MPH – Research Scientist III, Kaiser Permanente, Northern California
Jeff Taylor – Adovcate, HIV^+ Aging Research Project, Palm Springs
Julie Womack, BSN/RN/NP/PhD – Associate Professor, Yale University, School of Nursing

NIH Representatives:
Sean Altekruse, DVM/MPH/PhD – National Heart, Lung, and Blood Institute (NHLBI)
Samantha Calabrese, MPH – National Institute of Child Health and Human Development (NICHD)
Tony Creazzo, PhD – National Heart, Lung, and Blood Institute (NHLBI)
Mary Glenshaw, PhD/MPH – Office of AIDS Research (OAR)
Howard Hoffman, MA – National Institute on Deafness and Other Communication Disorders (NIDCD)
Amber Linde, PhD – National Institute of Mental Health (NIMH)
Natalie Tomitch, MPH/MBA – Office of AIDS Research (OAR)
Carolyn Williams, MPH/PhD – National Institute of Allergy and Infectious Diseases (NIAID)

Clinical Research Working Group Roster

Chairs:

Todd Brown, MD/PhD – Professor, Johns Hopkins University
Ann Kurth, MPH/PhD – Dean, Yale University, School of Nursing

Members:

Allison Agwu, MD – Associate Professor, Johns Hopkins University, School of Medicine
Joyce Anastasi, PhD – Professor, New York University
Kristina Crothers, MD – Professor, University of Washington
Judith Currier, MD – Professor, University of California, Los Angeles
Kristine Erlandson, MD – Associate Professor, University of Colorado, Anschutz Medical Campus
Marcia Holstad, BSN/RN/NP/PhD – Professor, Emory University, School of Nursing
Priscilla Hsue, MD – Professor, University of California, San Francisco
Jules Levin – Founder, Executive Director of National AIDS Treatment Advocacy Project
David Metzger, PhD – Professor, University of Pennsylvania
Lauren Patton, DDS – Professor, University of North Carolina, Chapel Hill, Adams School of Dentistry
Robert Remien, PhD – Professor, Columbia University
Serena Spudich, MD – Professor, Yale University
Lauryn Taylor – Clinical Research Coordinator, Neurotrials Research
Emmanuel Thomas, MD/PhD – Associate Professor, University of Miami, School of Medicine
Thomas Uldrick, MD – Deputy Head, Global Oncology, Fred Hutchinson Cancer Research Center

NIH Representatives:

Deborah Colosi, PhD – National Institute of Mental Health (NIMH)
Katharine Cooper-Arnold, MPH – National Heart, Lung, and Blood Institute (NHLBI)
Geraldina Dominguez, PhD – National Cancer Institute (NCI)
Gallya Gannot, DMD/PhD – National Institute of Dental and Craniofacial Research (NIDCR)
Rebecca Henry, BSN/PhD – National Institute of Nursing Research (NINR)
Catherine Levy, MHA/BSN/RN – National Heart, Lung, and Blood Institute (NHLBI)
Yingying Li-Smerin, MD/PhD – National Heart, Lung, and Blood Institute (NHLBI)
Aynur Unalp-Arida, MD/PhD – National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Vasundhara Varthakavi, DVM/PhD – National Institute on Drug Abuse (NIDA)

Pathogenesis/Basic Science Research Working Group Roster

Chairs:

Dana Gabuzda, MD – Professor, Dana-Farber Cancer Institute
Peter Hunt, MD – Professor, University of California, San Francisco

Members:

Tricia Burdo, PhD - Associate Professor, Temple University, School of Medicine
Judith Campisi, PhD – Professor, The Buck Institute
Ronald Collman, MD – Professor, University of Pennsylvania, School of Medicine
Dirk Dittmer, PhD – Professor, University of North Carolina, Chapel Hill
Howard Fox, MD/PhD – Professor, University of Nebraska Medical Center
Nicholas Funderburg, PhD - Associate Professor, Ohio State University
Beth Jamieson, PhD – Professor, University of California, Los Angeles, David Geffen School of Medicine
Michael Lederman, MD – Professor, Case Western Reserve University
Ivona Pandrea, MD/PhD – Professor, University of Pittsburgh
Russell Tracy, PhD – Professor, University of Vermont, Larner College of Medicine
Steven Wakefield - Director, External Relations – HVTN, Fred Hutchinson Cancer Research Center
Cara Wilson, MD – Professor, University of Colorado, Anschutz Medical Campus

NIH Representatives:

Ronald Adkins, PhD – Office of Research Infrastructure Programs (ORIP)
Elisabet Caler, PhD – National Heart, Lung, and Blood Institute (NHLBI)
Leia Novak, PhD – National Institute of Allergy and Infectious Diseases (NIAID)
Peter J. Perrin, PhD – National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Vasudev Rao, MBBS/MS – National Institute of Mental Health (NIMH)
May Wong, PhD – National Institute of Neurological Disorders and Stroke (NINDS)
Shimian Zou, PhD – National Heart, Lung, and Blood Institute (NHLBI)

Implementation Science Research Working Group Roster

Chairs:

Stefan Baral, MD – Associate Professor, Johns Hopkins University, School of Public Health
Michael Mugavero, MD – Professor, University of Alabama, Birmingham

Members:

Margaret Czarnogorski, MD – Head, Innovation and Implementation Science, ViiV Healthcare
Mari-Lynn Drainoni, PhD – Professor, Boston University, School of Medicine
Carey Farquhar, MD/MPH – Professor, University of Washington
Elvin Geng, MD/MPH – Professor, Washington University, School of Medicine
Matthew Golden, MD/MPH – Professor, University of Washington
Christian Grov, PhD – Professor, City University of New York, School of Public Health and Health Policy
Lisa Hightow-Weidman, MD/MPH – Professor, University of North Carolina, Chapel Hill
Lisa Metsch, **PhD** – Professor, Columbia University
Sharmistha Mishra, MD/PhD – Assistant Professor, University of Toronto
Denis Nash, PhD/MPH – Professor, City University of New York
Wynne Norton, PhD – Program Director, National Cancer Institute
Izukanji Sikazwe, MD/MPH – CEO, Centre for Infectious Disease Research, Zambia
Justin D. Smith, PhD – Associate Professor, Northwestern University, Feinberg School of Medicine
Gail Wyatt, PhD – Professor, University of California, Los Angeles, The Semel Institute

NIH Representatives:

Cheryl Boyce, PhD – National Heart, Lung, and Blood Institute (NHLBI)
Dara Blachman-Demner, PhD – Office of Behavioral and Social Sciences Research (OBSSR)
Holly Campbell-Rosen, PhD – National Institute of Mental Health (NIMH)
Helen Cox, MHS – National Heart, Lung, and Blood Institute (NHLBI)
Linda Kupfer, PhD – Fogarty International Center (FIC)
Kathryn Morris, MPH – Office of Behavioral and Social Sciences Research (OBSSR)
Joana Roe, BA – National Institute of Allergy and Infectious Diseases (NIAID)

Syndemics Research Working Group Roster

Chairs:

Kenneth Mayer, MD – Professor, Harvard University Medical School
Emily Mendenhall, PhD – Associate Professor, Georgetown University

Members:

Ada Adimora, MD/MPH – Professor, University of North Carolina, Chapel Hill
Moises Agosto-Rosario – Director of Treatment, National Minority AIDS Council
Frederick Altice, MD – Professor, Yale University
Heidi Crane, MD/MPH – Professor, University of Washington
Wafaa el-Sadr, MD/MPH/MPA – Professor, Columbia University
Gregg Gonsalves, PhD – Assistant Professor, Yale University, School of Public Health
Sally Hodder, MD – Professor, West Virginia University, School of Medicine
Brandon Kohrt, MD/PhD – Associate Professor, George Washington University
Eugene Mutimura, PhD – Senior Lecturer, University of Rwanda
Kimberly Page, PhD – Professor, University of New Mexico, Health Sciences Center
Emmanuel Peprah, PhD – Assistant Professor, New York University, College of Global Public Health
Miriam Rabkin, MD/MPH – Associate Professor, Columbia University, Mailman School of Public Health
Steven Safren, PhD – Professor, University of Miami
Ronald Stall, PhD/MPH – Professor, University of Pittsburgh
Alex Tsai, MD – Associate Professor, Massachusetts General Hospital
Darrell Wheeler, PhD/MPH – Provost, Senior Vice President of Academic Affairs, Iona College

NIH Representatives:

Geetha Bansal, PhD – Fogarty International Center (FIC)
Rick Berzon, DrPH/PA – National Institute on Minority Health and Health Disparities (NIMHD)
Kendall Bryant, PhD – National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Elisabet Caler, PhD – National Heart, Lung, and Blood Institute (NHLBI)
Victoria Cargill, MD – Assistant Commissioner, Baltimore City Health Department
Gregory Greenwood, PhD/MPH – National Institute of Mental Health (NIMH)
Fassil Ketema, MS – National Heart, Lung, and Blood Institute (NHLBI)
David Tilley, MPH/MS/CPH – Office of Disease Prevention (ODP)
Susan Vorkoper, MPH/MSW – Fogarty International Center (FIC)

International Research Working Group Roster

Chairs:

Roger Detels, MD – Professor, University of California, Los Angeles
Vincent Mutabazi, MD, MSc – Director, Regional Alliance Sustainable Development, Rwanda

Members:

Frederick Altice, MD – Professor, Yale University
Kathryn Anastos, MD – Professor, Albert Einstein College of Medicine
Stefan Baral, MD – Associate Professor, Johns Hopkins University, School of Public Health
Dirk Dittmer, PhD – Professor, University of North Carolina, Chapel Hill
Peter Hunt, MD – Professor, University of California, San Francisco
Jules Levin – Founder, Executive Director of National AIDS Treatment Advocacy Project
Scott McClelland, MD/MPH – Professor, University of Washington
Eugene Mutimura, PhD – Senior Lecturer, University of Rwanda
Jean Nachega, MD/PhD – Associate Professor, University of Pittsburgh
Denis Nash, PhD/MPH – Professor, City University of New York
Serena Spudich, MD – Professor, Yale University
Thomas Uldrick, MD – Deputy Head, Global Oncology, Fred Hutchinson Cancer Research Center

NIH Representatives:

Geetha Bansal, PhD – Fogarty International Center (FIC)
Mary Glenshaw, PhD/MPH – Office of AIDS Research (OAR)
Denise Russo, MS/PhD - National Institute of Child Health and Human Development (NICHD)