

**National Institutes of Health (NIH)
National Cancer Institute (NCI) Board of Scientific Advisors (BSA)
BSA *Ad hoc* Subcommittee Meeting on Human Immunodeficiency Virus (HIV) and
Acquired Immune Deficiency Syndrome (AIDS) Malignancy**

Pooks Hill Marriott Hotel
5151 Pooks Hill Road
Bethesda, MD
June 21, 2017
1:00 – 7:00 p.m. EDT

SUMMARY

Participants

Subcommittee Members

Dr. Blossom Damania, Chair (The University of North Carolina, Chapel Hill)
Dr. Robert Yarchoan, Subcommittee Executive Secretary (NCI)
Dr. Yuan Chang (University of Pittsburgh Cancer Institute)
Dr. Elizabeth Chiao (Baylor College of Medicine)
Dr. Karen Emmons (Harvard T.H. Chan School of Public Health)
Dr. Carol Ferrans (University of Illinois at Chicago)
Dr. Denise Galloway (University of Washington)
Dr. Chanita Hughes-Halbert (Medical University of South Carolina)
Dr. Amy C. Justice (Yale University School of Public Health)
Dr. Jeffrey Martin (University of California, San Francisco)
Dr. Joel Palefsky (University of California, San Francisco)
Dr. Michael Saag (The University of Alabama at Birmingham)
Dr. Joseph Spornano (Albert Einstein College of Medicine)
Dr. Ren Sun (University of California, Los Angeles)

Other Participants

Dr. Douglas Lowy (NCI, Acting Director)
Dr. Maureen Goodenow (NIH, Office of AIDS Research, Director)
Dr. Peter Kim (NIH, Office of AIDS Research, Deputy Director)
Dr. Deborah Bruner (Emory University)
Dr. Stacy Carrington-Lawrence (NIH, Office of AIDS Research)
Dr. Elizabeth Church (NIH, Office of Aids Research)
Dr. Geraldina Dominguez (NCI, Office of HIV and AIDS Malignancy)
Dr. Gary Ellison (NCI, Division of Cancer Control and Population Sciences)
Ms. Claire Harris (NCI, Committee Management Officer)
Dr. Rebecca Huppi (NCI, Office of HIV and AIDS Malignancy)
Dr. Johnan Kaleeba (NCI, Office of HIV and AIDS Malignancy)
Dr. Wlodzimierz Lopaczynski (NCI, Division of Extramural Activities)
Dr. Mostafa Nokta (NCI, Office of HIV and AIDS Malignancy)
Dr. Elizabeth (“Betsy”) Read-Connole (NCI, Division of Cancer Biology)
Dr. Vikrant Sahasrabudde (NCI, Division of Cancer Prevention)
Dr. Lisa Stevens (NCI, Office of Science Planning and Assessment)
Dr. Glendie Marcelin (The Scientific Consulting Group, Inc., Rapporteur)

Welcome and Introduction of Attendees—Drs. Blossom Damania and Robert Yarchoan

Dr. Robert Yarchoan welcomed BSA Subcommittee members, NCI staff, and public participants and expressed appreciation for the Subcommittee members' time and contributed expertise to the meeting.

The NCI is seeking guidance from the Subcommittee regarding the best allocation of HIV/AIDS research funding. The Subcommittee is tasked with (1) identifying the highest priority HIV/AIDS research that meet the OAR's definition of "high" or "medium" priority, and also and (2) determining other worthwhile areas that should be funded but that may not fall under the Office of AIDS Research (OAR) "high" or "medium" priority list. Reaching consensus is not compulsory for the Subcommittee meeting; it is important that members provide their opinions during open discussions.

Review of NCI Research in HIV and AIDS Malignancy—Dr. Robert Yarchoan

Dr. Yarchoan provided an overview of the current NCI and NCI-funded research and also described currently proposed research projects. He also provided a brief history of NCI's involvement in AIDS research. AIDS research is now embedded in most of the various Divisions, Offices, and Centers throughout the NCI. Some pioneering advancements made through the NCI Intramural Program included the development of the first blood test for HIV infection; the first sequence determination of HIV, and the development of the first approved HIV drugs, including azidothymidine (AZT) and didanosine (ddI). HIV-infected persons are at a high risk of developing AIDS-defining cancers, such as Kaposi sarcoma (KS), aggressive non-Hodgkin lymphoma (NHL), and cervical cancers. In addition, they are at increased risk of developing other cancers, including lung cancer, anal cancer, liver cancer, Hodgkin lymphoma, and oropharyngeal cancer. AIDS-related KS is now the most common cancer in men in some countries in sub-Saharan Africa with the highest HIV burden. Yarchoan explained that since the development of effective combination antiretroviral therapy in the mid 1990s, the lifespan of persons living with HIV has increased, the average age of AIDS patients has increased, and the overall number of persons living with AIDS in the United States has approximately doubled. While the introduction of cART was associated with an initial decline in the number of AIDS-defining cancers that occur with low CD4 counts, this number has stabilized and we are now also seeing an increase in the incidence of non-AIDS defining cancers. Collectively, these data provide rationale for more research directed at understanding, preventing, and treating cancer in HIV-infected individuals.

Dr. Yarchoan described the spectrum of AIDS funding in the NCI. The amount of NCI AIDS funding has remained relatively steady over the past several years, and is now approximately 9 percent of the total NIH AIDS budget. The focused research areas span etiology, pathogenesis, and therapeutics; approximately 75 percent of funding supports HIV/AIDS malignancy research. Essentially all the extramural NCI research is focused on HIV malignancy, while the intramural divisions and Frederick conduct both research in HIV-associated malignancies and basic HIV biology not directly related to malignancies. The division with the most HIV/AIDS funding in the NCI is the Center for Cancer Research (CCR) Intramural Division.

The Office of HIV and AIDS Malignancy (OHAM) works with NCI leadership and coordinates and manages the portfolio of HIV/AIDS and AIDS malignancy research. OHAM also manages certain research programs directly and interfaces with OAR and other Institutes and Centers (ICs). A variety of programs exist with the OHAM structure, such as the AIDS Malignancy Clinical Trials Consortium (AMC). Through this consortium, the Anal Cancer High-Grade Squamous Intraepithelial Lesion Outcomes Research (ANCHOR) clinical trial is determining whether treatment of anal high-grade lesions will reduce the incidence of anal cancer among HIV-infected individuals and also is establishing a biorepository of samples to support correlative studies of pathogenesis and biomarkers of anal cancer. An

important resource funded by OHAM is the AIDS and Cancer Specimen Resource (ACSR), whose goal is to biobank samples from patients with HIV-associated cancers. This effort will, in turn, facilitate current and future research into cancers developing in people living with HIV/AIDS.

Because sub-Saharan Africa has the highest number of HIV cases and is an important region for HIV-associated cancers, the NCI U54 collaborative HIV and Cancer Consortia was developed as an interdisciplinary initiative in Uganda, Rwanda, Kenya, Tanzania, Botswana, and Malawi. This effort is designed to establish scientific leadership in Africa and enhance the research capacity at several African institutions. In addition to projects in which the NCI is the lead IC, the NCI has embarked on a number of important collaborative partnerships. For example, the NCI has partnerships with other trans-NIH HIV/AIDS initiatives that include the Centers for AIDS Research (CFAR) and Fogarty International Center. Also, there are bilateral programs, such as between the United States and Russia, and the United States and South Africa.

A Request for Applications (RFA) that focused on certain “provocative questions” (i.e., non-obvious or understudied questions) that met the OAR criteria for “high” or “medium” priority research included (1) the possible effect of HIV-associated inflammation on cancer incidence or outcome, (2) the mechanisms that contribute to differential cancer risk in people with well-treated infection, and (3) the interaction of aging and HIV infection on cancer development.

Intramural HIV/AIDS activities span a variety of specific research branches; among the activities are basic HIV research, vaccine and drug development, and the study and development of effective therapy for HIV-related malignancies. In addition to the CCR, the intramural Division of Cancer Epidemiology and Genetics focuses on the epidemiology of infections, immunity, and cancer. Frederick’s AIDS and Cancer Virus Program is focused on pathogenesis, on Kaposi’s sarcoma-associated herpesvirus (KSHV) research, and on novel HIV prevention treatment approaches using non-human primate (NHP) models.

Recommendations from previous BSA Subcommittee meetings that have already been pursued (or are now in the pipeline) include the following:

- Identify prevention for KSHV infection and KSHV-related diseases and therapies for these diseases.
- Develop therapies using NHPs in sub-Saharan Africa.
- Create an Epstein-Barr virus (EBV) vaccine (NIAID is taking the lead in this effort).
- Establish a study of HPV-associated tumors.
- Analyze the interactions between aging and HIV-associated tumors.
- Study checkpoint inhibitor therapy for HIV-associated lung cancer.
- Encourage research in provocative questions (i.e., RFA).
- Develop clinical and epidemiologic research in resource-limited countries, especially in sub-Saharan Africa
- Initiate a clinical trial to determine if treatment of anal high grade intraepithelial lesions (HSIL) can effectively prevent anal cancer.

New initiatives planned for Fiscal Year (FY) 2017 and FY 2018 include the following:

- Develop an RFA to assess the interplay between tobacco use, HIV, and tuberculosis.
- Create an RFA to assess the role of HIV in regulating tumor microenvironments.
- Expand the AMC and possibly the ACSR into Latin America.

- Study HPV-related diseases in HIV-infected persons in Latin America.
- Understand the transmission of Kaposi's sarcoma-associated herpesvirus (KSHV).
- Study tobacco use and its prevention in HIV-infected U.S. populations.

In the summer of 2015, OAR and the NIH initiated a number of new processes for the management of HIV/AIDS research and articulated new priorities. The processes include the future revision of Center for Scientific Review Referral Guidelines and a possible restructuring of the AIDS Integrated Review Groups study section. Overall, the OAR considers the reduction of incidence, next-generation HIV-therapies, and research toward a cure and HIV-associated comorbidities as priorities. Some cross-cutting areas are basic research, health disparities, and training. Within these, they spelled out criteria for “high priority”, “medium priority” and “low priority” research, and stated that moving forward, AIDS funds could only be used to support “high” or “medium” priority research.

The following are “high” priority research areas:

- Develop and test AIDS vaccine candidates and microbicides.
- Develop and test HIV treatments.
- Create novel strategies for research toward a cure.
- Identify prevention and treatment strategies for HIV-associated comorbidities.
- Support basic research on HIV transmission.
- Research on reducing health disparities in incidence and treatment.
- Support training to conduct high-priority research.

“Medium” priority research areas include projects that address people who are living with, at risk for, or exposed to HIV, as part of a broader sample or comparative cohort. The desired result is advancing HIV treatment or prevention and providing tools beneficial for HIV research.

The OAR has stated that research areas that are deemed “low” priority are not considered for funding, per OAR guidelines. Of particular importance to the NCI, these include basic virology studies on herpesviruses, HPV, HBV, and HCV. However, after some discussion, research on KSHV will for the moment be considered “medium” or “high” priority. Because tumors caused by EBV and HPV occur disproportionately in HIV patients, the NCI has ongoing discussions with the OAR and the NIH Leadership about the designation of EBV and HPV research as “low priority” AIDS research. Another important research area that they consider “low priority” is cancer immunology research that is not in the context of HIV infection).

Each year, the OAR is reviewing all projects of each Institute or Center (IC) that is ending that year for their priority using the new definitions. They have said that funds for any project being used for “low priority” AIDS research will be removed from the ICs budget the following year and that this project cannot henceforth be funded with AIDS funds. The ICs will each year be given the opportunity to compete for this pool of funds that have been removed from the ICs. As a result of the 2015 portfolio review, the NCI lost \$1.2 million of AIDS funds, and as a result of the 2016 portfolio review, the NCI lost \$18.7 million. In the 2017 portfolio review, approximately \$8.2 million of “low” priority NCI projects were identified, which we have been informed will be removed from the FY 2018 budget.

The current charge to the BSA Subcommittee on HIV and AIDS malignancy is to identify opportunities and provide recommendations for the most important NCI research area in HIV/AIDS and HIV-associated malignancies, along with how to best address these priorities in the upcoming fiscal years. Because the overarching goal is to move the field of HIV and cancer forward, it is important that the committee not be constrained by the OAR definition of “high” or “medium” priority AIDS research in

making these recommendations – recommendations can include both projects that are likely to be considered “high” or “medium” priority by the OAR, as well as projects that may be considered “low priority” and would have to be funded with funds other than those managed by the OAR.

Questions and Discussion—Members

In response to Dr. Jeffrey Martin’s question, a Division of Extramural Activities (DEA) member clarified BSA’s role—BSA examines extramural initiatives and concepts across all of the NCI. Dr. Yarchoan added essentially all the extramural NCI supported HIV/AIDS funding is cancer related. (Note: Later in the meeting, it was clarified by a DEA member that the subcommittee could review and comment on the totality of NCI’s HIV and AIDS malignancy research.)

Dr. Deborah Bruner asked about the inclusion of symptom management, behavioral science, and adherence to the discussion of priority research. These issues are pertinent to the aging HIV-infected population who often face challenges with adherence to new immunotherapies. Dr. Betsy Read-Connole stated that she is part of a symptom-management working group that addresses these issues; there is also a RFA Moonshot Initiative. Dr. Yarchoan added that a high percentage of HIV-infected persons have difficulty adhering to treatment; adherence may be an area of focus in the future.

Regarding clinical trials to assess the efficacy of checkpoint inhibitor drugs in HIV-infected persons, Dr. Yarchoan confirmed that pomalidomide, lenalidomide, and checkpoint inhibitor drugs are being investigated in both intramural and extramural clinical trials.

General Discussion—Dr. Blossom Damania

Dr. Blossom Damania introduced a discussion among Subcommittee members to identify various research topics that needed to be discussed for prioritization.

Topic 1: KSHV-Associated Diseases

Dr. Damania emphasized the importance of prioritizing future research linked to KSHV-related cancers (KS, primary effusion lymphoma, and others) which are most prevalent in the HIV-infected population including in the US, where KS develops in a range of HIV infected individuals, including those with a successfully suppressed HIV viral load. Dr. Damania stated that new drugs and therapies for KSHV associated cancers are needed.

Dr. Martin expressed his concern for the relative lack of global research efforts and resources in Africa, which has the highest prevalence of KS in HIV-infected persons. Cervical cancer is another area of interest.

Dr. Yarchoan asked the Subcommittee in which specific areas these resources should be applied. Dr. Yuan Chang added that not enough efforts toward KSHV vaccine development have been undertaken. The immunological parameters for vaccine development require exploration. Dr. Yarchoan noted that KSHV vaccines should be scientifically feasible because of its lowered rates of transmission compared to other herpesviruses; however, there are substantial concerns about the economic feasibility of implementing such a vaccine even if developed. Philanthropic organizations have so far not expressed interest, but they could be queried again. Dr. Peter Kim asked about the public health impact and importance of developing a KSHV vaccine for a population that has lowered CD4-positive T-cell counts (end-stage AIDS). Dr. Kim asserted that vaccine administration may be too late for these individuals. Dr. Yarchoan responded that the optimal strategy would be to vaccinate persons before they were infected with HIV and developed AIDS, perhaps when they were children.

In response to Dr. Yarchoan's suggested strategy of vaccinating children, Dr. Denise Galloway said that the cost, manufacture, and dissemination of the vaccine are factors to consider. She wondered whether there is an effective method of predicting responders to the vaccine and ways to identify those who would require more intervention than just antiretroviral therapy to treat KS. Dr. Martin added that there are platforms and trials to address predicting responders and agreed with prioritizing African children for vaccination. Dr. Galloway agreed that a KSHV vaccine is a long-term goal and expressed hope for the development of an EBV vaccine. Understanding the immune responses and viral lytic components is important for the development of therapeutic and preventative vaccines.

Dr. Ren Sun stressed that now is the time to create a plan to move KSHV vaccine development forward. Immune regulation and therapy to treat infected people is a good approach. Dr. Carol Ferrans supports the creation of a vaccine and noted that global systems are in place for development and dissemination. Dr. Joel Palefsky stated that resources should be allocated to therapeutic vaccine.

In response to Dr. Karen Emmons' question regarding the impact of race on KSHV-related disease, Dr. Yarchoan alluded to a recent article stating that African-American men who have sex with men (MSM) in the southern United States have high incidences of HIV infection and are at risk for developing KS. Dr. Huppi stated that NIH has modified what is considered a minority population to include MSM. Dr. Chiao added that in her oncology practice, she has observed an increase in KSHV among 19- to 25-year-old minority populations in Houston, Texas and sees new KS patients every month. There is also an increase in KS incidence in individuals 65 and older. This may be due to HIV-infected individuals living longer and therefore having a higher risk of developing more KS. Dr. Michael Saag said that the frequency and route of transmission, as well as immune mechanisms, will determine which vaccine is made. Dr. Yarchoan noted that the greatest need for a KSHV vaccine would probably be in sub-Saharan Africa, but that barriers exist to implementation there even if one were developed. Philanthropic support will potentially be significant to this effort.

Dr. Galloway mentioned that new approaches and platforms, such as nanoparticles and therapeutic monoclonal antibodies, can be considered for vaccine development. Protection against disease is an important selling point when seeking funding support. Dr. Martin clarified that the efficacy of a KSHV vaccine could be determined in an individual before adulthood; the goal is to prevent KSHV infection, rather than to treat KS disease.

Everyone was in agreement with the fact that in order to develop a KSHV vaccine it was necessary to understand KSHV transmission. Thus, investigating mechanisms of KSHV transmission is central to understanding immune responses to KSHV infection and to the potential development of a KSHV vaccine.

Summary of Discussion on KSHV-Associated Diseases

- More KSHV research in Africa is required.
- Novel therapies are needed for KSHV-associated cancers
- Improved therapy, especially therapy that is appropriate for sub-Saharan Africa, is needed.
- It will be important to know more about the means of spread of KSHV in various populations. This research can help identify public health measures to reduce KSHV spread and will also be important for subsequent vaccine development.
- It is important to understand how KSHV is transmitted and the immune responses to KSHV infection

- Predicting immunologic responders and also utilizing immune responses (i.e., antibodies to viral proteins) to KSHV can be used either to inform efforts to prevent disease or transmission or to help develop a therapeutic vaccine.
- The established methods used for HPV could potentially be leveraged for the development of KSHV vaccines.
- The impact of race and other factors on KSHV should be explored—for example why the virus is suppressed in some individuals, but not in others.
- Solicit philanthropic organizations for funding support of a vaccine if there is interest in moving forward in this area.
- Identifying the best initial target population for a KSHV vaccine and determine whether a preventive or therapeutic vaccine may be appropriate.

Topic 2: EBV-Associated Cancers

Regarding the types of cancers prevalent in the HIV-infected population, Dr. Damania reiterated that 39 percent of NHL in this population is linked to EBV infection. She posed to the Subcommittee whether EBV should be considered a high-priority tumor-causing virus in HIV-infected persons; several members agreed with this consideration.

Dr. Saag speculated that comparing lymphoma rates in HIV-negative and HIV-positive individuals may lend important insight into pathogenesis. Dr. Kim indicated that studying the interaction of EBV and HIV and how it may predispose an individual to developing cancers is a high priority of OAR. Dr. Amy Justice recommended having a comparative group (HIV negative) when assessing an interaction with EBV in HIV-infected persons.

Dr. Yarchoan mentioned that there are challenges when determining the causative agents of the disproportionate rates of cancers in HIV-infected individuals and separating out the relative contributions of various causes.

Dr. Sun commented that there is a “synergy” between development of an EBV and a KSHV vaccine. He added that the Subcommittee can recommend the formation a working group to devise a clear plan that can be presented to philanthropic entities.

Dr. Yarchoan explained that the next step to consider may be to form a working group to have more detailed discussion and develop ideas, reporting back to the Subcommittee, which then will formulate recommendations and identify priority areas. Dr. Palefsky agreed with this approach, but suggested creating a smaller working group to discuss prevention and therapeutic vaccines for a broader range of herpesviruses.

Drs. Chang, Chiao, Galloway, Sun, and Palefsky expressed interest in participating in the working group to address all virus-mediated cancers. Dr. Chang later suggested that Dr. Patrick Moore may be a more appropriate member of this working group than her and she proposed that she be part of another working group (see below). The members agreed that the working group’s focus would be at least in part based on immune-based treatments.

Summary of Discussion on EBV-Associated Cancers

- The Subcommittee agreed that research in EBV and EBV-related tumors continues to be a high priority HIV/AIDS research area for the NCI.

- Linkage of EBV and KSHV vaccine development should be considered. Potentially partner with philanthropic organizations to fund vaccine development.
- Compare and contrast EBV cancer incidence between HIV and non-HIV infected individuals
- Consider forming a working group to analyze the immune approaches to viruses associated with cancer (in the context of HIV infection).
- Consider forming a working group to assess treatments and interactions between virus-associated cancer, therapies, and HIV drugs in minority populations (disparities).

Topic 3: Other NHL/HL

Dr. Damania stated that other NHL/HL cancers (e.g., non-EBV lymphomas) are elevated in HIV-infected individuals. She asked whether AIDS funds could be used to study a comparative group (HIV negative) which could then be used to address the question of why HIV-positive individuals have higher cancer rates compared to uninfected individuals. Dr. Martin said that utilizing a comparative group as part of determining the mechanism through which HIV causes HL is important.

Dr. Justice added that inflammation or environmental exposure were factors potentially contributing to the elevated cancer rates. Dr. Yarchoan mentioned that it is important to understand how EBV-negative NHL tumors are increased in HIV-infected persons, especially as the data to date suggest that the increase is largely not related to environmental or viral factors.

Dr. Justice agreed with having an appropriately controlled comparative group and described the importance of understanding the mechanisms in the 65-and-older age group. Dr. Chiao added that the treatment outcomes of cancers in HIV-infected persons are often poorer than in HIV-uninfected persons and that this is an area that may benefit from further study. Dr. Justice suggested that the priority areas should include addressing the problem that in HIV-infected people, the drug interactions and toxicity from taking multiple medications may affect outcome, irrespective of age.

Dr. Yarchoan commented that a teleconference call among members is useful to discuss recommendations and identify those that are high priority. Determining the efficacy of immune-based therapeutics for cancers in HIV-infected individuals is another high-priority topic to consider.

Dr. Martin mentioned that survivorship is an understudied area and should be looked at for all of the tumors seen commonly in HIV-infected patients.

Summary of Discussion on Other NHL/HL

- A high-priority research area will be the study of the development of NHL/HL in the presence or absence of HIV (with comparative groups).
- Research should address the role of HIV in inflammation and immune senescence in the development of HL.
- A high-priority research area for all cancers in the HIV-positive population is understanding the treatment interactions between cancer therapies and combined antiretroviral drugs.
- A high-priority research area for all cancers in the HIV-positive population is assessing immune-based therapies (e.g., checkpoint inhibitors, antibodies, etc.) in HIV-infected persons.
- Research should address survivorship of all forms of cancers in HIV-infected versus HIV-negative individuals.

- Research should address the interaction of aging and HIV infection on immune function in the context of cancer.

Topic 4: HPV-Associated Cancers

Dr. Palefsky commented that issues relating to HPV include the effect of aging and role of HIV in the pathogenesis of HPV-related tumors, which are provocative questions (PQ) from a previously submitted RFA. Dr. Yarchoan responded that another RFA to address this could possibly be through a PQ mechanism. He also encouraged the Subcommittee to consider the key questions and research areas and not necessarily be constrained by the “high” or “medium” OAR priority criteria. Dr. Geraldina Dominguez added that addressing HIV and aging is a trans-NIH area of interest across several ICs. From her perspective, however, cancer researchers are generally not interested in this issue. Dr. Read-Connole agreed with that comment; she has attempted to discuss this issue with cancer researchers and the CFARs. Dr. Chang noted that the lack of interest for these topics may be because the questions the Subcommittee are discussing currently do not focus on one research discipline, but rather overlap the areas of infectious diseases and cancer biology. Dr. Martin agreed with Dr. Chang’s assessment; he suggested that an infrastructure where basic scientists can collaborate with clinicians is needed.

Dr. Justice added that hospital networks, Kaiser Permanente, and other organizations can potentially be solicited for facilitation of basic science research, collaborations, and resources (e.g., clinical specimen sharing). Dr. Dominguez indicated that collecting prospective samples at the time of cancer development may be another suitable approach. Dr. Chiao suggested creating a working group to identify the best methods to obtain clinical specimens, such as those from Africa. Dr. Damania suggested that discussions be initiated with the ACSR working group regarding specimens. Dr. Yarchoan added that the annotation of high-quality samples is critical for this endeavor. According to Dr. Joseph Sparano, samples may be obtained from the National Clinical Trials Network (NCTN). Concerning specimen collection, Dr. Sparano suggested the formation of a registry to identify HIV-positive patients in NCI-sponsored trials. Dr. Palefsky added that understanding how HIV causes anal cancer (pathogenesis) independent of HPV infection is important. This may be addressed through the ANCHOR study; this study may identify prognostic factors that can determine the progression of these tumors to cancers.

Dr. Galloway observed that prophylactic vaccines to prevent HPV infection are important to stimulate a more robust immune response in the context of HIV infection.

Dr. Palefsky noted that another important topic is determining at the molecular level what HIV does to increase the risk of HPV-mediated lesions.

Dr. Damania opened a discussion regarding penile and vulvar cancers in HIV-infected persons. Dr. Chiao said that vulvar and penile cancer is elevated in infected individuals and that vulvar cancer is associated with perianal and anal cancer in women. Both these ailments are important HIV-associated diseases. Dr. Sparano added that the National Clinical Trials Network has a focus on penile cancer and may, therefore, be a source of collaboration.

Estimating the implementation of cancer screening for HIV-infected persons is important according to Dr. Chiao. She added that screening is important to implement even before ANCHOR completes its effort. Dr. Martin added that cervical cancer screening in Africa is vital for survivorship among HIV-infected women. Dr. Palefsky said that the challenge to screening in Africa is related to the overall poor health care delivery infrastructure. The infrastructure requires better HPV testing to optimize the screening approach.

Summary of Discussion on HPV-Associated Cancers

- A high-priority area is obtaining access to clinical specimens from various cohorts, especially those preceding cancer development; working with ACSR will be important in this effort.
- Immune-based therapies for not just HPV-related cancers, but for all cancers in the HIV-positive population are important.
- Research should address the development of prognostic factors to define which anal lesions will lead to anal cancer. Developing virus-specific treatment options for anal cancer is important
- Research should address the development of prophylactic vaccines to prevent HPV infection and related disease in the HIV infected population.
- Research should address understanding the effect of HIV on HPV acquisition.
- Optimizing screening for cervical cancer in HIV-positive individuals in Africa is needed.

Topic 5: Liver Cancer, Including Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV)-Related Cancers

Liver cancer rates are elevated among the persons infected with HIV. To start the discussion on liver cancer-related recommendations, Dr. Yarchoan reviewed the recommendations from previous BSA Subcommittee meetings, including those addressing screening approaches, pathogenesis, improved therapies, studies curing latent HBV infection, and studies on antiretroviral therapies.

Dr. Saag suggested studying people who are co-infected with HIV and HBV and are taking tenofovir therapy, as well as a matched cohort of HIV-negative individuals who are not on tenofovir. Dr. Justice added that co-infected people have more rapid progression of HCV disease than HIV-negative individuals; treatment of HIV reduces this progression. Therefore, studying chronic virus infection is important.

Dr. Ferrans said that the Subcommittee should consider prioritizing identifying the relevant health disparity (race, economic status) questions regarding all of the recommended topics.

Dr. Chanita Hughes-Halbert mentioned that incorporating questions from a population and behavioral science perspective is important for this discussion. Such questions relate to lowering the rates of new infections (which may lower the rates of HIV-related cancers) and to identifying the biological mechanisms contributing to increased rates of cancer. Additionally, efforts should focus on how to prevent the onset of HIV-related cancer in HIV-infected people and how to address the role of social determinants in disease onset.

Dr. Emmons said that addressing adherence is important and agreed with developing strategies focused on social determinants.

Summary of Discussion on Liver Cancer, Including HCV/HBV-Related Cancers

- Research should further the understanding of coinfection of HIV and HBV in people on therapy and to compare these to HIV-negative individuals not on therapy.
- Research should address understanding HCV-related cancer and cirrhosis development in response to treatment in both HIV-positive and -negative people.
- The Subcommittee agreed not to diverge from recommendations made in previous meetings.

Topic 6: Addressing disparities in the HIV-infected population related to social determinants of health

Drs. Carol Ferrans, Dr. Chanita Hughes-Halbert, and Dr. Karen Emmons wanted to highlight issues in behavioral sciences in the HIV infected population. The discussion centered around symptom management, behavioral science and adherence. Older HIV+ patients get more cancer and more severe symptoms. There is a need to assess and improve the quality of life in these cancer patients who are HIV infected. There is substantial evidence that HIV-infected patients with cancer fare worse than HIV-uninfected patients with the same tumor types. Part of this is due the presence of the HIV-infection, but not all. Social determinants of health also contribute to poorer outcomes in HIV-infected individuals with cancer, which are poorly understood, and make effective and equal care challenging. Issues include different access to cancer care, differences in adherence, and reluctance of physicians to utilize appropriate cancer therapy in HIV-infected patients. The question also arose as to how we could lower HIV infection rates.

Summary of Discussion on addressing disparities in the HIV-infected population related to social determinants of health

- Need to identify the strategies and models that can be used to address social determinants in accessing care and increasing adherence rates in HIV positive cancer patients.
- Need to lower rates of new HIV infections
- Need to prevent or lower the onset of cancer in the HIV-positive population
- Need to study and address the poorer outcomes of cancer in HIV-infected patients as compared to HIV-uninfected patients.
- The issue of disparities across all of the proposed recommendations/study areas is important.
- Need to address disparities in all the work that is being done on HIV malignancies.

Topic 6: Non-AIDS-Defining Cancers, Including Lung Cancer

To start the discussion on non-AIDS-defining cancers, Dr. Yarchoan reviewed the suggestions from previous BSA Subcommittee meetings. The main recommendations were to: (1) Dissect the roles of HIV and other factors in the high incidences of lung cancer in HIV-infected populations, (2) identify the best screening and diagnosis approaches in HIV-infected and lung cancer populations, and (3) develop clinical trials to test the efficacy of antibodies to checkpoint inhibitors to treat lung cancer in HIV-infected persons.

Dr. Yarchoan indicated that no reports suggest that HIV directly causes lung cancer. Dr. Justice stated that an important question is whether cancer occurs more in HIV-infected individuals after other risk factors are taken into account.

Dr. Chiao commented that it is important to address the impact of smoking and smoking cessation on head and neck cancers in the HIV-positive population. Dr. Palefsky added that assessing a potential difference between the different types of oropharyngeal cancers in HIV-infected populations is important.

Regarding causality, Dr. Martin expressed that there is still insufficient knowledge of which cancers are linked to HIV and which just occur more often in HIV-infected populations because they have higher exposure to other cancer risk factors. Dr. Justice advised that there should be criteria (i.e., dose response) or causality applied in determining this linkage.

There was general agreement that understanding the pathogenesis of non-AIDS cancers and treatment options for these cancers are important. Dr. Emmons wondered if there is an interaction between the time of treatment for HIV versus cessation treatment for tobacco use. The Subcommittee agreed to prioritize

researching smoking cessation in HIV-positive individuals with lung cancer. There was also discussion of the fact that HIV-infected patients with cancer have poorer outcomes than HIV-uninfected patients. Some of the reasons identified included lack of knowledge of optimal treatment cancer in HIV-infected patients and lack of knowledge about drug-drug interactions.

Dr. Justice added that another area of interest is the population of HIV-infected people who have recurrent bacterial infections, which increases lung cancer rates.

Summary of Discussion on Non-AIDS defining cancers

- Evaluate stage or grade of cancer and how they differ between HIV positive and HIV negative individuals
- Evaluate impact of smoking and smoking cessation on head and neck and lung cancer in HIV positive population
- Evaluate progression of cancer and how they differ between HIV positive and HIV negative individuals
- Study drug-drug interactions that may impact treatment of cancers in HIV-infected populations
- Study treatment of NADC in HIV positive versus HIV negative population with the aim of improving the outcome in HIV-infected patients so that they approach or equal that in HIV-uninfected patients.

Topic 7: International Efforts

Dr. Yarchoan said that two areas of current research focus discussed in the previous committee were enhancing the international infrastructure to conduct HIV-associated research and also to understand the epidemiology of the pediatric HIV-positive population in Africa.

Dr. Martin suggested that the Subcommittee's international public health recommendations be based on scientific data and public health findings. Related to the topic of infrastructure, Dr. Palefsky said that one recommendation should be to increase funding support for the importation of medication into low-resourced countries. Dr. Yarchoan agreed and said that BSA has discussed this issue before.

The discussion then turned to a discussion of the Provocative Questions (PQ) RFA in HIV malignancy and whether the Subcommittee felt that some sort of extension, follow-up, or other approach to focusing research on questions of importance should be considered. Dr. Yarchoan stated that the funding mechanism should not be through the general NCI PQ (which is not focused on HIV malignancies) and noted that if a PQ-like mechanism is not utilized, the RFA should be on a focused area. Dr. Chiao recommended that the RFA be broadened, while Dr. Palefsky cautioned that this approach might hinder the support for and funding of this RFA. Dr. Sun added that a clear path toward developing this RFA is required. Dr. Damania indicated that some of the priorities should be a stand-alone RFA since an RFA is broader than a PQ and may elicit more applications. Dr. Justice suggested developing two RFAs: one targeted toward epidemiology and database analysis and the other focused on basic laboratory science. Drs. Saag and Kim indicated that the six priority questions raised during previous BSA Subcommittee meetings remain valid and important.

Dr. Damania commented that NCI is currently doing a great job with twinning U.S. Institutions (e.g. NCI designated cancer centers) with universities in Africa to further develop pathology and diagnostics in Africa. It was felt that this should be continued in the future.

Summary of Discussion on International Efforts

- Good support for import of drugs
- General infrastructure is needed
- Good cancer registries in sub-Saharan Africa are needed.
- Continue twinning of NCI designated cancer centers and African institutions to further develop pathology and diagnostic capabilities in country.

There was some discussion of a working group to prioritize the important questions related to international efforts. Support for the international efforts may fall outside of OAR's "high" and "medium" priority criteria and may be supported by non-AIDS funding.

Topic 8: General Infrastructure and Research Areas

Dr. Yarchoan introduced the priority area of developing an infrastructure to support HIV malignancy research, including help for basic scientists in addressing clinically relevant questions regarding cancers in the HIV-infected population. Dr. Palefsky explained the importance of international cancer registries that not only provide valuable access to specimens, but also are a vital aspect of infrastructure. Dr. Martin said that a highly functioning health care system, which is critical for the development of registries, is lacking in several regions of Africa. However, the NCI has a HIV Primary Care System Network that may provide insight. Dr. Saag recommended establishing international partnerships (e.g., in South Africa). Dr. Damania said that the NCI has training programs and partnerships with institutions in South Africa, Zambia, and Malawi.

Dr. Chang commented on the importance of basic virology, such as the basic molecular biology of KSHV in KS-affected HIV-positive populations. In response to a discussion regarding the importance of funding AIDS associated malignancy research, Dr. Damania said that for the review of these types of grants, a study section comprising cancer biologists, infectious diseases experts and immunologists, is critical. She said the field needs a study section that has cancer biologists, infectious diseases and immunologists all together. Otherwise AIDS malignancy research grants fall through the cracks if the study sections are only comprised of either cancer biologists or infectious disease experts.

Dr. Justice explained the significance of better collaborations and of ensuring that the quality of data generated from research meets the requirement of the research question. Funding mechanisms for ongoing cohorts are needed.

Dr. Martin mentioned that a re-evaluation of a comorbidity basic science infrastructure correlated to clinical outcomes is necessary to prevent disease and morbidity.

Dr. Yarchoan queried the Subcommittee on their thoughts on the importance of two previous recommendations: (1) Investment in infrastructure in the developing world to enhance research internationally and (2) A search for new infectious agents that may cause cancers in HIV-positive persons. Dr. Sporano said conducting therapeutic cancer trials in areas that have a more established infrastructure is a better approach than targeting low-resource regions. Dr. Sun agreed with this assertion and suggested partnering with China because of its health care system (e.g., advanced medical record-keeping system) and stable economy.

In reply to Dr. Palefsky's suggestion about international cancer registries, Dr. Justice indicated that creating a specimen collection and analysis network is needed to address the issue of strengthening

infrastructures. Dr. Chiao added that there are opportunities to obtain well-annotated samples from consortia that are conducting longitudinal prospective cohorts of individuals with cancer.

Dr. Martin suggested a focus on training international investigators. Regarding prioritization efforts in low-resource regions, such as Africa, he stated that focusing on prevention and screening is a better approach than conducting difficult treatment studies.

Dr. Yarchoan reviewed the ideas of forming two working groups: (1) a general, broad-focused group to discuss the efforts of the Subcommittee moving forward and (2) a group focused on the immunological aspects of developing therapeutic and preventative vaccines and on creating other immunological therapies. The recommendations and summary of the meeting will be sent to all members, followed by a teleconference among the Subcommittee to identify high-priority focus areas from the recommendations. Dr. Sporano suggested developing a mechanism to foster communication between different NIH programs (e.g., AMC) for the coordination or harmonization of their efforts. Dr. Palefsky wondered whether AMC members should be included in study sections for clinical trials on HIV-infected persons.

Dr. Justice proposed creating a working group to foster basic science research that incorporates the appropriate cohorts and access to vital specimens. A basic scientist may encounter challenges addressing PQs because of a lack of support. Dr. Palefsky suggested that this working group be focused on building infrastructure.

Dr. Yarchoan summarized the Subcommittee's assertion that various aspects of research infrastructure must be improved, such as access to annotated tumor specimens for use in a laboratory setting. The infrastructure working group should establish solutions and focus on creating a resource of high-annotated clinical specimens, including those collected prior to cancer diagnosis. Obtaining prospective samples will require a clinic-based cohort. Those who expressed interest in joining this working group were Drs. Chang, Chiao, Justice, Palefsky, and Sporano. Dr. Chang suggested incorporating a bioinformatics group to assist with sample annotation.

Dr. Sun recommended that the Subcommittee identify methods to enhance the use of the Tissue Bank for AIDS Research, which may be a source of specimens. He added that adding the platform for vaccine development to the infrastructure building recommendation is a valuable approach.

Summary of Discussion on Infrastructure

- Good support for import of drugs
- Need funding mechanisms to fund ongoing cohorts to collect specimens and store them and standardize specimens.
- Recommendation to keep AOIC study section for the review of all grants related to malignancies in the HIV positive population
- Need to develop mechanisms to coordinate cancer trials in the HIV positive in the AMC with those being done outside the AMC.

Summary of Priority Areas for Future Studies—Dr. Blossom Damania

Dr. Damania reiterated the statistics regarding cancers in HIV-positive persons and presented to the Subcommittee a summary of the discussed priority activities for addressing malignancies in the HIV-infected population:

- Develop new drug therapies for KSHV, EBV and HPV-associated cancers.

- Develop immunotherapies (e.g., checkpoint inhibitors, chimeric antigen receptor [CAR] T cell therapy, and antibodies) against cancers in the HIV-positive population.
- Study the interactions (toxicity) of combined HIV antiviral therapies with cancer therapeutic drugs, which may induce non-adherence.
- Continue basic research into the pathogenesis and immunology of cancers in the HIV positive.
- Determine the mechanisms contributing to an increase in cancer rates in the aging HIV-infected population.
- Address cancer care disparities between HIV-positive and HIV-negative individuals.
- Create EBV, KSHV, and HCV vaccines for high risk populations. Understanding virus transmission is critical for this effort.
- Reviewed what was learned from studies on cancer biology and its impact on HIV treatment (e.g., histone deacetylase inhibitors to treat HIV-positive individuals in a “shock and kill” approach to cure HIV).
- Elucidate how aging affects the immune system and cancer development in the HIV-positive population. Strengthen the research infrastructure to address this effort.
- Discover novel oncogenic agents.

Dr. Damania restated the recommendation to have a separate AIDS malignancy study section like the AIDS-Associated Opportunistic Infections and Cancer (AOIC)—with expertise in cancer biology, immunology, and infectious diseases—to review these types of AIDS cancer-related grants.

Dr. Palefsky suggested including on this list the previously discussed recommendation of cancer prevention (e.g., smoking cessation to prevent lung cancer).

In response to a discussion regarding surveying the basic science community to determine what kind of infrastructure is critical for HIV/AIDS malignancy, Dr. Read-Connole mentioned that this survey must be conducted in the least burdensome way; DEA may provide input. Dr. Yarchoan said that informal surveys may be accomplished by informally addressing colleagues. Several members discussed alternative approaches, such as an RFI (Request for Information).

Briefing of Dr. Douglas Lowy, NCI Acting Director, on Subcommittee Deliberations

Dr. Douglas Lowy expressed his interest in being informed of the Subcommittee discussions and thanked them for their efforts. Dr. Yarchoan summarized the goal of forming two working groups focusing on: (1) immunology-related issues, such as understanding the immunological responses to KSHV and the development of preventative and also therapeutic vaccines against cancer-causing viruses (i.e., KSHV, EBV, HPV), and (2) infrastructure improvement that will allow basic scientists to gain access to reagents, such as annotated specimens. A document summarizing the deliberations will be circulated to the Subcommittee, which then will prioritize these discussions during a teleconference.

Dr. Damania briefed Dr. Lowy on the specific focus areas discussed during the meeting—the route of transmission of KSHV and vaccine development for KSHV. Dr. Lowy provided his comments regarding KSHV vaccine efforts. He recommended that for KSHV, the vaccine must be formulated as a subunit, rather than a live vaccine, since a subunit vaccine will presumably face fewer hurdles from regulatory authorities. He stated that he is unaware of any effective subunit vaccine formulations for herpesvirus infection. Mimicking protective immune responses in other virus models is important for the KSHV vaccine effort. Commercial partners or philanthropic organizations are most suitable for regional manufacturing. He proposed that OAR may support research looking at KSHV disease as a comorbidity of HIV infection.

Dr. Sun reiterated that a clear plan is required for support from commercial partners and philanthropic organizations. He suggested that developing vaccines that undergo a single round of virus replication is suitable for identifying mechanisms of protective immunity and also will face fewer regulatory barriers. Dr. Lowy speculated that a vaccine manufactured overseas (e.g., China) can be used in trials in the United States. Dr. Chang commented that there is sufficient information to begin the KSHV vaccine effort; she acknowledged, however, that more information is needed to understand the transmission and immunology of the virus.

In response to Dr. Kim's question regarding using a KSHV vaccine in younger recipients, Dr. Lowy said that because there is a long time interval between KSHV infection and disease progression, protection against infection may be a surrogate for protection against disease. Dr. Chang said that there is a KSHV-related disease endpoint in children; discovering the outcomes of disease does not take a long time (i.e., 30 years). Dr. Martin added that the incidence of KS in children in Africa is probably too low to use this as an endpoint for vaccine trial. However, he noted that when assessing KSHV acquisition in Africa, the rate in children younger than 4 years old is 30 to 40 percent, so relatively few subjects would be needed if this could be used as an endpoint. Prevention of infection probably would also involve follow-up to assess for the development of KS.

Dr. Sun said an immediate goal is immune reconstitution in KS patients to reverse or prevent this disease using a therapeutic vaccine. Dr. Lowy agreed that in some instances a therapeutic vaccine is more suitable because of the long timeframe required for observing the efficacy of preventative vaccines.

Dr. Damania resumed her summation of the discussed priorities:

- Compare and contrast EBV-related cancers in the HIV-positive and -negative populations.
- Develop an EBV vaccine.
- Research EBV-negative NHLs that are elevated in HIV-positive populations.
- Determine how immune status (inflammation) relates to a susceptibility to NHL/HL.
- Explore the development of effective immunotherapy (e.g., checkpoint inhibitors, CAR T cell therapies, and antibodies) for all cancers in HIV-positive individuals.
- Create a cohort and enable access to specimens to study HPV-related tumors.
- Explore the development of immunotherapies to treat HPV-positive cancers.
- Elucidate the role of HIV in the development of anal cancer.
- Identify prognostic factors for high-grade anal lesions that become malignant.
- Identify treatment strategies for the early onset of anal cancer.
- Create guidelines and implement screening for anal cancer in the United States and cervical cancer in Africa.
- Develop prophylactic vaccines to prevent disease or infection in the context of HIV infection.
- Determine the effects of HIV infection on HPV acquisition.
- Regarding liver cancers, compare individuals who are coinfecting with HBV and HIV and are on tenofovir with HBV-negative/HIV-positive people who are not on tenofovir.
- Concerning HCV, understand the differences in development of hepatocellular carcinoma and cirrhosis between HIV-positive and -negative people.
- Assess health disparities in all discussed cancers and work toward preventing the onset of HIV-related cancers in the population.
- Determine how social determinants affect accessibility of care and the adherence rates in HIV-infected population.
- Study non-AIDS-defining cancers, such as lung cancer and even those not known to be caused by HIV, such as prostate cancer, in HIV-infected persons; determine if the stage or grade of lung cancer differs between HIV-positive and -negative individuals

- Elucidate the effect of tobacco use, or cessation of smoking, on lung or head and neck cancer development in HIV-positive people.
- Use modern definitions of causality to help the NCI define what cancers are caused by HIV.
- Continue current international efforts, such as research training grants (i.e., D43), U54 grants, and domestic and international partnerships.
- Study KS in HIV-positive children internationally.
- Provide support for importing medicines into low-resource regions (i.e., Africa).
- Develop stronger infrastructures and registries in sub-Saharan Africa.
- Continue programs between U.S. cancer centers and African institutions.
- Identify funding mechanisms to create a cohort to collect stored annotated specimens.
- Develop a study section mirroring AOIC to review AIDS malignancy-related grants.
- Coordinate communication regarding all the cancer trials that the AMC is conducting under OHAM.
- Develop an infrastructure allowing basic scientists to gain access to reagents, such as annotated specimens.
- Because of the elevated cancer rates in elderly, understand the interaction between HIV and aging in cancer development.

Dr. Lowy provided insight regarding the discussed priorities. He speculated that a single dose of an HPV vaccine may not be sufficient for protection in HIV-positive people. He advised that one area of emphasis should be on vaccine uptake in the general population (HIV negative) and that this will decrease the likelihood of HPV exposure in HIV-positive individuals (“herd immunity”). Dr. Lowy agreed with the usefulness of studying liver cancers in the United States; within the next 15 years, the mortality rates are predicted to double. Establishing a NIH Consensus Conference might help define the cancers caused, at least in part, by HIV. Dr. Lowy suggested that the Subcommittee rank the priority list and identify a limited number (e.g. three) emphasized areas.

It was agreed that a preliminary summary of the Committees initial recommendations would be developed by Dr. Damania at the end of the meeting. This summary follows at the end of these minutes.

Adjournment

Dr. Yarchoan reiterated that the Subcommittee will review the meeting summary followed by a teleconference to refine the discussed priority areas. Consideration will be given to forming working groups to address the areas regarding immunological correlates of transmission, vaccine development, and infrastructure building. The Subcommittee meeting was adjourned at 7:09 p.m.

B. Damania 9/29/2017
 Dr. Blossom Damania Date
 Chair

Robert Yarchoan 9/29/17
 Dr. Robert Yarchoan Date
 Executive Secretary

**Preliminary Recommendations from the June 21, 2017 Meeting of the NCI BSA
Subcommittee on HIV and AIDS Malignancy**

Charge to the Committee by NCI leadership

The NCI BSA Subcommittee on HIV and AIDS Malignancy committee was given the charge to define research priorities for cancers that occur in HIV-infected individuals. The committee was briefed on the definitions of “high”, “medium”, and “low” priority AIDS research that were recently established by the NIH Office of AIDS Research (OAR), but told to not be constrained by these definitions as they established the highest priorities for NCI HIV/AIDS malignancy research.

Overarching themes across all cancers in the HIV-infected population

The committee was provided with information on the current NCI portfolio of research in HIV malignancy. They broadly endorsed the current efforts and expressed the view that the NCI should continue to fund research on the gamut of HIV malignancies as they are now doing, including research on epidemiology, basic science, translational science, and clinical science (including behavioral issues). They also identified a number of high priority areas that they felt were worthy of particular focus.

Overall common themes:

Common areas felt to be of particular importance to the AIDS-associated malignancy research agenda were:

- Understanding the treatment interactions between cancer therapies and combined antiretroviral drugs in HIV-positive cancer patients.
- Developing and assessing the utility of novel therapies for cancers in HIV-infected persons (including immunotherapies).
- Addressing the interaction of aging and HIV infection in cancer development, including studies of how they interact in affecting immune function.
- There was agreement that soliciting focused research addressing certain areas or questions related to HIV malignancies would be of value. The committee felt that the questions articulated in the HIV-focused Provocative Question (PQ) Request for Proposals (RFP) were good, but that they could perhaps be expanded and might benefit from facilitated collaboration between those with access to large patient and data samples and early translational investigators.
- Understanding the causes of reduced survival of HIV-infected cancer patients as compared to patients without HIV infection and reducing cancer disparities in minority populations of HIV-infected patients.

These themes relate to and will inform all the specific research areas and topics.

Specific recommendations for research on malignancies in the HIV-infected population:

The committee examined a number of topics of AIDS-associated malignancy research in order to define the key issues. These topics are listed below:

- 1) Kaposi sarcoma associated herpesvirus (KSHV)-associated cancers
- 2) Non-Hodgkin lymphoma (NHL), Hodgkin disease (HD), and EBV-associated cancers
- 3) Human papillomavirus (HPV)-associated cancers
- 4) Liver Cancer including hepatitis C (HCV) and hepatitis B (HBV)-related cancers
- 5) Non-AIDS defining cancers (NADC)
- 6) Addressing disparities in the HIV-infected population related to social determinants of health
- 7) International Efforts

8) General Infrastructure

For these topics, the research areas described below were deemed to be of particular high priority.

1) KSHV-associated cancers

KSHV-related cancers (Kaposi's sarcoma, primary effusion lymphoma, multicentric Castleman's disease) are among the most common cancers in HIV-infected patients. This is true globally as well as in the U.S. Kaposi's sarcoma develops in a range of HIV-infected individuals, including those with a successfully suppressed HIV viral load.

Areas felt to be of particular priority were:

- Development of novel therapies, including immune-based therapies, for KSHV-associated cancers. Furthermore, therapies that are appropriate for sub-Saharan Africa and other resource-limited regions are particularly needed.
- Understanding the mechanism of KSHV transmission as well as immune responses to KSHV infection.
- Developing strategies to prevent KSHV disease and/or transmission. There was interest in exploring the development of a therapeutic vaccine. There was also considerable interest in exploring the feasibility of developing a preventive vaccine, although there were also some concerns about its practicality and the likelihood of success (it was felt that an attenuated vaccine might be most feasible but that it was unlikely to be approved).

2) NHL/HL and other EBV-associated cancers

NHL is one of the most common AIDS-defining cancers in the United States, and there is also an increased incidence of HD and other EBV-associated cancers. Approximately 39% of NHL in HIV-infected individuals are EBV positive. Additionally, most cases of HD in the context of HIV infection are caused by EBV. There is a very high incidence of NHL, HD, and other EBV-associated cancers in HIV-infected persons throughout the world.

Areas felt to be of particularly high priority were:

- Research on lymphoma and EBV-related tumors in HIV patients should be a high priority. Also, general research in EBV and EBV-related tumors in general should be a high priority, although this research may need to be funded using a combination of AIDS and non-AIDS funds.
- Understand the increased incidence of NHL and HD in HIV patients, especially those cases not associated with EBV. Additional epidemiologic studies comparing the development of NHL/HL in various populations of HIV patients and comparator groups may be useful.
- Address the roles of HIV, HIV-associated inflammation, and immune senescence in the development of NHL and HD.

3) HPV-associated cancers

HPV-associated cancers e.g. cervical cancer and anal cancer are substantially increased in the HIV-infected population. How HIV infection increases HPV-associated cancers is not well understood. Assessing the effectiveness of prophylactic vaccines to prevent HPV infection in HIV-infected patients is potentially important, especially if such vaccines may be found to help prevent HPV re-infection. Although there is a HPV vaccine available, it is not effective against pre-existing HPV cancers. The subcommittee was highly supportive of continuing the ANCHOR study to look at the utility of screening and treatment of anal high-grade squamous intraepithelial lesions (HSIL) to prevent of anal cancer.

Areas felt to be a priority were:

- Research should address understanding the effects of HIV on HPV acquisition and possibly of assessing the effects of HPV on HIV acquisition.
- Address prognostic factors to define which anal lesions will lead to anal cancer.
- Develop improved treatment options for anal and cervical cancer and other HPV-associated cancers and precursor lesions, especially those based on an understanding of viral pathogenesis.
- Develop optimal and cost-effective strategies to screen for cervical cancer in resource-poor countries and strategies to screen for anal-cancer (especially in high resource countries).

4) Liver Cancer including hepatitis C (HCV) and hepatitis B (HBV) related cancers

The incidence of hepatocellular carcinoma (HCC) is increased in individuals with HIV infection. This includes both HBV- and HCV-associated HCC. HIV and HCV co-infected individuals have a more rapid progression of HCV associated disease than HIV-negative individuals and cART reduces this effect.

Areas felt to be a priority were:

- Assessing how various antiretroviral therapies affect HIV/HBV coinfection and development of HCC.
- Research should address how HCV-related cancer and cirrhosis develop in response to HCV treatment in both HIV-positive as compared to HIV-negative individuals.
- Hepatocellular cancer presents with widely divergent histology. Understanding the degree to which histologic presentation is influenced by HIV, HCV, and HBV infection may identify important subtypes for treatment and prognosis.

5) Non-AIDS defining cancers (NADC)

A number of NADCs are on the rise in HIV-infected individuals and it is anticipated that these cancers will continue to rise as HIV-positive individuals live longer due to cART. In addition to cancers that are increased in HIV infection, it is expected that we will see an increase in incidental cancers (such as prostate cancer). However, treatment of such cancers in the presence of HIV infection will pose challenges, and we need to understand how to optimally prevent, screen for, and treat such cancers in HIV-infected persons.

Areas felt to be a priority were:

- Epidemiology studies to assess changes in the spectrum of HIV-associated cancers as the HIV-infected population lives longer and ages.
- Evaluating the differences in the stage, grade and progression of NADCs in HIV-positive versus HIV negative individuals. Also, assessing if there are molecular differences in the cancers of the same type that arise in HIV-infected vs. HIV-uninfected individuals.
- Understanding the ways that HIV infection may contribute to the pathogenesis of various NADC.
- Studying treatment of NADCs in HIV-positive versus HIV negative individuals with the aim of improving the outcome in HIV-infected patients so that they approach or equal that of HIV-uninfected patients. This will include exploring the use of immunotherapy in patients with HIV infection and cancer.
- Assessing the best ways to screen for lung cancer in HIV-infected patients, given their increased incidence of other lung diseases.

6) Addressing disparities in the HIV-infected population related to social determinants of health

There is substantial evidence that HIV-infected patients with cancer fare worse than HIV-uninfected patients with the same tumor types. Part of this is due the presence of the HIV-infection, but not all. Social determinants of health also contribute to poorer outcomes in HIV-infected individuals with cancer. These determinants, which are poorly understood, make effective and equal care challenging. The committee felt there was a need to investigate ways to improve the survival and quality of life in cancer patients who are HIV-infected.

Areas felt to be a priority were:

- Developing optimal strategies for smoking cessation in HIV-infected persons. Also understanding the impact of smoking and smoking cessation on head and neck and lung cancer in the HIV-positive population.
- Develop strategies and models that can be used to address social determinants in accessing care and increasing adherence rates in HIV-positive cancer patients.
- Need to study and address the poorer outcomes of cancer in HIV-infected patients as compared to HIV-uninfected patients.
- Need to address disparities in cancer incidence and outcomes in minority populations with HIV infection.
- Need to develop better quality-of-life measures for HIV malignancies, including treatment and cancer prevention efforts

7) International Efforts

HIV infection and HIV-associated cancers are an enormous burden world-wide. This is especially the case in sub-Saharan Africa, which has the highest number of cases of HIV infection and a high prevalence of infection with oncogenic viruses (such as KSHV) and other factors that promote AIDS-associated cancers. Enhancing the international infrastructure to conduct HIV-associated malignancy research in Africa is important. The committee felt that NCI's current efforts to develop HIV-associated research programs in Africa is very valuable and that enhanced efforts are needed to study HIV-associated cancers in countries in which there is an especially high incidence.

Areas felt to be a priority were:

- Good support for the importation of cancer drugs into Africa is needed to support clinical trials
- Support for strategies (such as improved cancer registries) in sub-Saharan Africa to develop a more accurate epidemiologic assessment of cancer development is needed.
- Lack of pathologic support was viewed as a major impediment to clinical research in resource-poor countries. Strategies to enhance cancer pathology are needed.
- Continue twinning of NCI-designated cancer centers and African institutions to further develop pathology and diagnostic capabilities in country.
- An understanding of the pathogenesis of HIV-associated cancers and the factors that may contribute to the particularly high incidence of such cancers (such as ocular cancer) that occur largely in sub-Saharan Africa or other less-developed regions and that are now poorly understood.
- Improved strategies to prevent and screen for HIV-associated cancers (especially cervical cancer).
- Strategies to optimally treat various HIV-associated cancers that are appropriate for resource-poor countries and middle income countries.

8) General Infrastructure

The committee identified several factors that were needed in order to support and sustain the general infrastructure for AIDS-associated malignancy research.

Areas felt to be a priority were:

- Need mechanisms to fund ongoing cohorts to collect and store specimens and to standardize specimens.
- Recommendation for the NCI to support the continued existence of AIDS-associated opportunistic infections and cancer (AOIC) study section for the review of grants related to malignancies in the HIV-positive population. It was noted that it would be optimal to have a study section with reviewers who have expertise in both HIV and viral oncology. One option that was suggested was to recommend a study section focused just on viral and HIV-associated malignancies and that adequate expertise be obtained for the role of inflammation and immune activation.
- Need to develop mechanisms to optimally coordinate cancer trials in the HIV-positive in the AIDS Malignancy Consortium (AMC) with those being conducted outside the AMC.

There was agreement that the committee would need more time to consider these areas of research and that further discussion of the Subcommittee would help in identifying those that were of highest priority. Also, members of the Subcommittee recommended that two working groups be formed as outlined below:

- 1) A working group focused on the immunological aspects of developing therapeutic and preventative therapies and vaccines and understanding transmission of oncogenic viruses that cause HIV malignancies, especially KSHV.
- 2) A working group to discuss ways that the research infrastructure for AIDS-associated malignancies could be enhanced.