Board of Scientific Advisors (BSA)
BSA *ad hoc* Subcommittee Meeting on Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) Malignancy

Teleconference
August 8, 2013
10:30 a.m. – 12:00 p.m. EDT

DRAFT SUMMARY

Participants

Subcommittee Members
Dr. Lawrence Corey, Chair (Fred Hutchinson Cancer Research Center)
Dr. Richard Ambinder (Johns Hopkins University)
Dr. Stanton Gerson (Case Western Reserve University, University Hospitals Case Medical Center)
Dr. Chanita Hughes-Halbert (Medical University of South Carolina)
Dr. Amy Justice (Yale University School of Medicine)
Dr. Elliot Kieff (Harvard Medical School, Brigham and Women's Hospital)
Dr. Ronald Mitsuyasu (University of California, Los Angeles)
Dr. Joel Palefsky (University of California, San Francisco)
Dr. David Scadden (Harvard University, Massachusetts General Hospital)
Dr. Ren Sun (University of California, Los Angeles)
Mr. Jeff Taylor, Advocate

NCI Staff
Dr. Geraldina Dominguez (NCI, Office of HIV and AIDS Malignancy)
Ms. Claire Harris (NCI, Committee Management Officer)
Dr. Rebecca Huppi (NCI, Office of HIV and AIDS Malignancy)
Ms. Denise Jenkins (NCI, Office of HIV and AIDS Malignancy)
Dr. Mostafa Nokta (NCI, Office of HIV and AIDS Malignancy)
Mr. Ricardo Rawle (NCI, BSA Executive Secretary *pro tempore*)
Dr. Robert Yarchoan (NCI, Subcommittee Executive Secretary)
Ms. Darlene Summers (The Scientific Consulting Group, Inc., Rapporteur)

Other Participants
Dr. Karen Mowrer (Lewis-Burke Associates LLC)

Action Items

- No action items were raised.

Call to Order and Welcoming Remarks—Dr. Lawrence Corey

Dr. Lawrence Corey welcomed members of the BSA Subcommittee, NCI staff, and members of the public and thanked participants for attending via teleconference. Roll call was taken.

Dr. Corey said that the Subcommittee's meeting in February yielded useful suggestions to the NCI regarding its ongoing and future support of HIV/AIDS malignancy research. Because of budget restrictions faced by the NCI, the Subcommittee's principal task today is to prioritize its

recommendations and provide an overall message on the most important topics in this area that the NCI should support.

Update on HIV/AIDS Research in the NCI—Dr. Robert Yarchoan

Dr. Robert Yarchoan expressed appreciation to the Subcommittee members for their time and noted that their guidance has already been quite helpful. He stated that the Subcommittee's recommendations from the February 14, 2013, meeting have been shared with the BSA, the NCI Scientific Program Leaders (SPL), and the Office of AIDS Research (OAR), as well as specific NCI Divisions interested in the topics. In addition, the African Research Consortia Request for Applications (RFA) has been approved as a U54 mechanism, and a preliminary notice has been disseminated. External review of the Anal Cancer Host Trial to determine whether the treatment of high-grade squamous intraepithelial lesion (HSIL) will prevent anal cancer has been completed; the next step is review by the SPL and National Cancer Advisory Board (NCAB). The OAR, which is impressed with the trial and the Office of HIV and AIDS Malignancy's (OHAM) efforts to prioritize research activities, said that it would provide supplemental support to OHAM to advance this work.

Dr. Yarchoan said that the NCI is starting the process of developing a Provocative Questions exercise. A brainstorming workshop is planned for January or February 2014 to identify understudied areas for RFA research studies. He asked members to send him names of appropriate experts including individuals knowledgeable about AIDS malignancy as well as general cancer research experts who might participate in the workshop.

Dr. Yarchoan added that Dr. Varmus was pleased with the Subcommittee's recommendations but would now like the group to prioritize recommendations and to share their thoughts about the overall level of funding in the AIDS malignancy area. Consensus by the Subcommittee on the highest priority areas would be helpful as well as pointing out any ongoing projects for which members are less enthusiastic. Is NCI's current funding level for HIV malignancy-related research adequate, too much, or too little?

Dr. Corey suggested that the Subcommittee rank its recommendations into three categories—highest, middle, and low priority—rather than by numerical order. Dr. Yarchoan thought this approach adequate, and members agreed.

Discussion on Prioritization of HIV/AIDS and HIV/AIDS Malignancy Research in the NCI—Members

Dr. Corey informed the members that he and Dr. Yarchoan distilled 16 recommendations from the Subcommittee's discussions at the February 2013 meeting. These have been shared with the Subcommittee and Dr. Varmus, and the purpose of this meeting is to discuss and prioritize the recommendations.

Dr. Joel Palefsky noted that the recommendations cover new/potential and ongoing activities. He asked if the prioritization is to help the NCI decide how to handle an infusion of new funds into the area or simply to prioritize the topics in general. Dr. Corey replied that members should consider the topics in general. For example, if a research activity is ongoing, should it continue and/or be expanded?

Dr. Amy Justice suggested that Recommendations 8, 9, and 10 appear to be closely related and might be consolidated into one recommendation.

Dr. Corey said that some of the recommendations (e.g., Recommendations 1 and 2) might be associated with the Provocative Questions exercise. Dr. Yarchoan clarified that the purpose of the Provocative

Workshop is to fund studies in important cancer research areas that have not been addressed. He added that the Provocative Questions Initiative is one area that could receive new funds.

Dr. Chanita Hughes-Halbert recalled that Dr. Yarchoan had mentioned about progress underway regarding Provocative Questions on HIV-related malignancies. Based on sentiments expressed at the Subcommittee's February meeting, which articulated this as a high priority, his office has already started the administrative process to tentatively convene a meeting.

Recommendation 1: Surveillance and epidemiologic studies of HIV malignancies in low and middle income countries (LMIC), including enhanced pathologic assessment of tumors.

Dr. Corey noted that nothing is ever simple. He noted that various ideas were presented in February regarding how this might be leveraged or funded, and he asked members where this idea ranks in importance based on policy and funding.

Dr. Ronald Mitsuyasu observed that the NCI already is participating in large, epidemiological studies, including malignancies in HIV epidemiologic assessments throughout the world. The overall concept is a high priority as all diseases should be characterized, including differences based on locations. The pathology assessment is critical but would be challenging to conduct as it would require central reviews from various countries to authorize the export of specimen collections. In the practical context, the process would need to be completed for each country.

Dr. Ren Sun suggested that telepathology—that is, sharing and reviewing samples digitally—might be an option, and he described work conducted effectively in China through a digital network sharing of images. He noted that accuracy in reading digital slides has improved significantly in China.

Dr. Justice said that another option is to collaborate with the International Epidemiologic Databases to Evaluate AIDS (IeDEA) network. Many of the IeDEA groups have some infrastructure in place that this proposal could support or expand.

Dr. Mitsuyasu commented that much of the pathology currently conducted in certain malignancies requires fairly sophisticated work (e.g., immunohistochemistry, molecular assessment of tumors). To standardize this is quite challenging. Telemedicine might facilitate some of this work, such as histological assessments.

Another participant pointed out that infrastructure for the collection of clinical and correlative data will need to be bolstered in many of the locations as well.

Dr. Justice suggested that this work would be essential for many of the other goals. If the incidence and prevalence in the developing world (or other settings) are unknown, how can one determine whether the pathology in specimens from various locations is alike or different?

Dr. Corey summarized the group's sentiment that this is a basic area that needs strengthening and could be advanced by leveraging other resources and collaboration. In addition, a strategic plan might be needed, perhaps one that emphasizes selective surveillance rather than every country.

A participant commented that having access to substantial specimen collections from different sites to compare diseases at various sites and studying potentially novel aspects (e.g., lymphoma) in certain situations is a high-priority research issue. It is inadvisable, however, to invest in all possible sites as the research novelty would be limited. An ideal approach might be to select approximately six sites with an established presence to allow the likelihood of in-depth analysis at those sites. Dr. David Scadden agreed,

pointing out that this could be a very broad initiative unless it is highly targeted. Dr. Elliot Kieff added that a strategic review might reveal that some sites might need more basic infrastructure. Dr. Justice commented that a strategic review should encompass a training component for standardization as well. It was noted that the NIH is heavily invested in at least six sites in criteria of this Recommendation, and leveraging that investment would be helpful.

The group agreed that Recommendation 1 is a high priority.

Recommendation 2: Provocative Questions RFA focused on HIV malignancies.

Dr. Corey said that he saw this as one of the highest priorities for the Institutes as it is a way to bring new funding into this topic and will support riskier and edgier research than in standard RFA study sections.

Dr. Justice agreed and observed that it is important for the right person(s) to attend the brainstorming workshop in early 2014 to ensure a broad array of perspectives is discussed.

Dr. Corey said that the Subcommittee could suggest separate provocative questions on the biology and on the epidemiology. Separate review committees are used for the provocative questions. The Subcommittee should recommend that the provocative questions encompass all the general subjects included on this list.

Dr. Kieff asked whether the provocative questions are targeted to R01 investigators. Dr. Yarchoan responded that these grants are funded through the R01 and R21 mechanisms; applications must be submitted specifically for the Provocative Questions RFA, not a general R01 submission.

Dr. Stan Gerson said that the provocative questions effort has been productive within the NCI leadership to spawn new ideas and focus via an iterative process. He suggested that the Subcommittee should participate in some fashion as the provocative questions are being refined. Dr. Yarchoan reiterated his request for names of people who might be interested in participating at the Provocative Questions workshop that will develop the questions to be addressed.

Dr. Corey summarized the group's concurrence with Recommendation 2 as a very high priority.

Recommendation 3: Genotypic typing of HIV-associated malignancies and other malignancies arising in HIV-infected patients (in addition to effort on DLBCL, lung, and cervical now underway).

Dr. Yarchoan stated that the NCI's Office of Cancer Genomics (OCG) currently is supporting sequencing work at the University of Vancouver. OCG is working with OHAM to collect samples of B-cell lymphoma, lung, and cervical cancers to sequence and compare those tumors arising in HIV-infected individuals with those arising in non-HIV infected individuals. A big challenge has been to collect adequate samples. The aim is to sequence the genotype from the tumor sequence. In the February 2013 meeting, the proposal was to include HIV-associated malignancies in other general ongoing sequencing efforts and to support a focused effort on other HIV-related malignancies.

Dr. Corey asked whether other funded efforts were underway regarding Burkitt's lymphoma and Kaposi sarcoma (KS). Dr. Yarchoan responded that studies of Burkitt's lymphoma are ongoing in partnership with a private consortium; KS, however, was deemed to be technically not feasible because there are so many different cells in the tumors that they could not sequence the tumors.

Dr. Mitsuyasu commented that for this recommendation to be successful, investment in appropriate specimen collection and processing at the site of collection is needed. In Africa, central biorepositories

could accomplish this, but the cooperation of local oncologic surgeons would be needed at other collection sites.

Dr. Corey said that the Subcommittee should assume that collection or implementation activities would be conducted properly. Dr. Yarchoan clarified that part of the recommendation is to include tumors from HIV-infected individuals in the broad sequencing efforts—specifically, do not exclude these individuals, but try to include some of them. Participants agreed that this made sense and noted that studies should be sufficiently powered to elucidate differences.

Dr. Corey summarized the Subcommittee's advocacy for increased resources, ensuring that follow-on programs for specific tumors include adequate samples of HIV-associated malignancies, including non-AIDS defining cancers among HIV-positive persons, that would allow genotyping of similarities and differences. In addition, programs could target those with substantially increased risk (e.g., anal cancers) among those HIV-infected after adjusting for routine risk factors.

Dr. Corey summarized the Subcommittee's consensus of Recommendation 3 as a high priority, although not as high as Recommendations 1 and 2. The NCI should be selective and leverage current resources and ongoing efforts as well.

Recommendation 4: Using transplantation and other expertise at the NCI and NCI-funded researchers and Centers to eradicate ("cure") HIV in patients.

Dr. Scadden said that this is an opportunity for the NCI to have a major impact on HIV infection by leveraging expertise within the NCI. Because this offers a potential to cure HIV, it seems a very worthwhile use of resources. It could fundamentally change the way one looks at HIV infection. This recommendation involves applying techniques that already are used at the NCI for the goal of curing people with HIV infections (e.g., transplantation, some oncologic drugs to kill cells, other cancer drugs that may activate the virus).

The Subcommittee discussed the possibility of a joint RFA, sponsored by the NCI (e.g., Cancer Centers), National Institute of Allergy and Infectious Diseases (NIAID), and National Heart, Lung, and Blood Institute (NHLBI) to support research on using transplantation to help with finding a cure. It was pointed out that the NCI is currently working with NHLBI currently on this issue.

Dr. Justice asked whether a Provocative Question venue could help flesh out this area; there are many other approaches beyond transplantation: Which approaches should be included? Dr. Yarchoan said that a meeting could be held on this topic to brainstorm for ideas and that this was a good suggestion. Dr. Kieff thought that this is an area of truly novel, clinical investigation that is proceeding simultaneously in multiple directions and might be worthy of consideration in a Provocative Question approach.

Discussion on this topic is ongoing, but few with cancer training are engaged in the conversations. Many of the drugs that could be evaluated are oncologic agents or immune modifiers that are used in cancer treatment and/or transplantation biology in transplantation and gene therapy approaches. It is important to involve cancer investigators, and a brainstorming session might be helpful.

Dr. Corey observed that the Subcommittee has significant enthusiasm for this topic and it should be a high priority.

Recommendation 5: Using the enhanced development of tumors in HIV-infected patients as an "experiment of nature" to understand cancer in general.

a. Includes studies of enhanced aging in HIV disease and role in oncogenesis.

b. **Includes an analysis of why certain tumors not caused by infectious agents or other known factors (such as cigarette smoke) are increased.**
c. **Includes a study of the interplay between chronic inflammation, immune suppression, and immune dysregulation in oncogenesis.**
d. **Research into how HIV and HIV-encoded proteins may directly or indirectly enhance tumor development through mechanisms other than immunodeficiency or immunodysregulation.**
e. **Study of how the tumor microenvironment of HIV patients differs from that in other patients.**

Dr. Corey observed that this recommendation focuses on understanding the biology of tumors, and the Subcommittee should consider (1) the packaging and (2) how much to foster this area.

Dr. Gerson commented that this area was discussed actively by the Subcommittee during the February meeting. These elements are speculative. The challenge is to determine how to advance these into a Provocative Question discussion for better refinement as some will progress and others will not. It is a unique opportunity as none of this is understood, and a Provocative Question dialogue would be helpful.

Dr. Justice said that because many of these factors pertain to a number of other viral infections, the language should not exclusively refer to "HIV" but rather "HIV and other viral infections." Better insight might be gained by comparing and contrasting HIV with other virus areas. Dr. Kieff noted that the factors also apply to other immunosuppressed states. This population has so much co-infection, that it would be an interesting domain to compare/contrast people with a single viral infection or multiple infections. Dr. Yarchoan agreed, noting that this would include the oncogenic viruses like the Epstein-Barr virus (EBV) and hepatitis C virus (HCV), and that the NCI would not exclude other viruses. Studies of other immunosuppressed states are difficult to fund with AIDS money, but studying them as controls for AIDS might be funded.

Dr. Corey said that this sounds like it falls into the Provocative Question area. Overall it had a high priority, but in conducting the Provocative Questions workshop, the specific questions could be prioritized further and those questions of particular interest could be selected.

Recommendation 6: Discovery of novel infectious agents causing HIV malignancies.

Members discussed if this recommendation could be grouped with another recommendation (e.g., 3 or 5). Dr. Corey observed that this recommendation was one of the originally issued Provocative Questions though in that context it was not specifically related to HIV, and could again be brought forward as an HIV-associated Provocative Question. Overall the committee had high enthusiasm for this approach.

Recommendation 7: Study of markers identified in the Early Detection Research Network (EDRN) as possible markers for HIV tumors, leading to prevention strategies.

Dr. Corey commented that a prospective cohort is implicit in this and wondered whether a cohort with high incidence malignancy exists that might be leveraged. He thought that this offers a good research opportunity if a bank of samples already existed in which incidence rates are high enough for this study; however, a cohort should not be established solely to accomplish this.

Dr. Kieff observed that this is tied to Recommendation 1 and might be conducted best in the context of administering research centers in those parts of the world where new agents might be readily detected.

Dr. Justice indicated that unless markers will be significantly different, it is not clear why this should be done in HIV *per se*.

Dr. Gerson commented that if there is a different genomics fingerprint of HIV-associated malignancies, then early detection methodologies also might be different as they would be driven genomically. This recommendation could also be linked with Recommendation #3 under the rationale that there are extensive capabilities of testing methodologies that are Clinical Laboratory Improvement Amendments (CLIA)-approved, but this population has not been assessed. In addition, many repositories of pre-tumor onset samples exist that could be utilized.

Participants agreed overall that while some aspects might be worthy of further consideration, this recommendation should be ranked as low to moderate priority.

Recommendation 8: Study of the best treatment of non-HIV-associated tumors that arise in HIV patients.

Recommendation 9: Study of pharmacokinetic interactions between cancer and anti-HIV drugs.

Recommendation 10: Study of HIV-associated tumors as a model to study roles of frailty and polypharmacy in predisposing patients to toxicity from cancer therapy.

Dr. Corey suggested discussing these three recommendations together.

Dr. Justice suggested that they be integrated into one RFA and allow scientists to bring their expertise into different areas. Pharmacokinetic interactions will depend on the number of medications patients take; both toxicity and efficacy influence decisions about the treatment for non-HIV associated tumors that arise in HIV. Tumors occur in this population and the cocktails of current chemotherapy regimens and antiretroviral and other medications that patients take make this area a pressing issue that will increase as the population ages and takes even more medications. The intent here is to ensure that cancer treatments do not interfere with antiretroviral therapies (ARTs). This domain is relevant in HIV as well, but in the HIV population, these concerns arise 20 years earlier. Another participant said that studying drug interactions is important for treatment to know what mixture(s) of antiretroviral and chemotherapy agents are inadvisable; studies addressing Recommendation #8 could examine specific cancers.

A participant indicated that he had seen only minimal pharmacological interactions of concern when treating these patients for cancer. Others responded that this area should be examined as there are many new tyrosine-kinase inhibitors and other drugs; there is a dearth of literature about this as many early trials excluded HIV-infected patients. Dr. Corey said that although this is a good opportunity, it would be challenging to dedicate resources to discover a problem.

One option is to require registries at Cancer Centers to collect data that include patients with HIV and malignancies and obtain details, such as treatment, outcomes, response, dose changes, and toxicities. This could inform relative problems that occur as well as efficacy, with standard treatments. An additional option is to capture data retrospectively from Cancer Centers, if possible. The AIDS Malignancy Consortium (AMC) is trying to do this prospectively but, with limited sites, has been unable to capture adequate information about non-AIDS defining cancer (NADC) patients and/or patients who are on novel therapies.

Dr. Yarchoan stated that the literature describes potential interactions between cancer and AIDS drugs, as well as cancer and tuberculosis drugs, based on looking at delivery systems. Selective studies could focus on agents where at least some interaction might be predicted but is not yet understood. He asked participants whether the NCI should continue efforts to include HIV patients on cancer trials of other agents when possible. Participants concurred that this would be a good idea, provided that planning study

discussions include people with AIDS and pharmacology expertise at the start. In addition, data should capture an appropriate staging and/or description of the patients' overall frailty; although most patients currently being treated are relatively healthy, toxicities in that population will increase as treatments are broadened.

The group's consensus was to combine Recommendations 9 and 10, with a high-priority ranking, and to give Recommendation 8 a middle ranking.

Recommendation 11: Kaposi sarcoma (KS):

a. **Studies to define people who are most at risk, especially for severe or visceral KS.**
b. **Studies of the factors affecting KSHV/HHV-8 prevalence and the risk of KS in KSHV/HHV-8-infected people.**
c. **Prevention and cost-effective therapies, especially for resource-limited regions.**

Dr. Corey stated that Recommendations 11–16 are focused on tumors previously identified by the Subcommittee as a priority.

One member stated that to address prevention of KS, data are needed: the factors of being infected must be listed first. Some data currently are being captured, and studies could examine differences in biology and/or genetics in host populations or environmental cofactors; the diseases are different. RFAs, however, are not necessarily needed for these studies. Dr. Sun suggested that parts of Recommendations 11 and 12 could be combined, specifically KS and EBV.

Dr. Yarchoan reminded participants that the Subcommittee previously had indicated that the EBV vaccine was important but not the KSHV vaccine. He asked if this recommendation should be applied universally or specifically to Africa.

Dr. Kieff stated that in some sites in Africa, because the acquisition of KSHV infection is almost linear from age 8 to age 50+, the primary question is not about preventing infection but rather committed treatment of HIV infection to prevent KS.

Participants agreed that while KS is less common in the US since the widespread use of ART, it continues to be one of the most common HIV-associated malignancies in the US. Also, KS remains a very important clinical entity in Africa, even with the use of ARTs. Dr. Yarchoan noted that the NCI's global health activities encompass KS.

Dr. Justice asked whether the issue was about targeting KS among those who have access to ARTs or trying to prevent KS for those who do not have ART access. Upon clarification that data already show that ARTs in Africa do not have the desired impact on KS, she revised the focus to ART efficacy and whether it is possible to prevent HIV patients from being infected with KSHV.

Dr. Corey summarized the group's discussion by noting that while KS was now only a medium clinical problem in the US, it continues to be a high priority in resource-challenged countries and especially in sub-Saharan Africa. It is thus important for the NCI to support research in KS, particularly defining the biology of KSHV, the biology of KS in Africa, and determining why ART is not eradicating KS there. The focus should be on preventive and cost-effective therapies. In addition, the group thinks that KS studies should be focused on addressing KS in high prevalence areas, especially in sub-Saharan Africa. There also may be efficiencies in doing clinical studies of KS in Africa, because of its high incidence.

Recommendation 12: NHL and Hodgkin Disease (HD):

a. **Biomarkers for defining and classifying the lymphomas, especially in resource-limited**

settings.

b. **Strategies to prevent and treat NHL, especially in resource-limited settings.**
c. **EBV vaccine development.**

Participants agreed that more research needs to be done on the pathogenesis, diagnosis, classification, and treatment of HIV-associated NHL and Hodgkin's disease. The consensus that an EBV vaccine would have more impact that a KS vaccine was reiterated. KSHV is seen as a more attractive vaccine target because it is less prevalent than EBV. A clinical trial conducted with a gp350 EBV vaccine showed evidence of a reduction of symptoms with mononucleosis but not effective prevention against the spread of EBV. If successful, such prevention would have broader implications than just AIDS and HIV.

A Northern European study of 20,000 people have led to the hypothesis that the prevention of adolescent mononucleosis would be followed by a reduction of adolescent Hodgkin disease. Estimations at an NCI-sponsored meeting with vaccine experts several years ago were that 200,000 patients would be needed per arm to see a significant difference. A cost-effective study via Kaiser Permanente in the 1990s concluded that developing a vaccine for adolescent mononucleosis would be cost effective; the usefulness of a vaccine in the context of AIDS and AIDS malignancies is a different question. It is estimated that a study to determine whether an EBV vaccine would prevent Burkitt's lymphoma in East Africa may require 50,000 participants. It is possible that a study on EBV acquisition in childhood could be conducted with 100 children. One participant suggested that it would be beneficial to think in terms of the developing world, not the Western world.

Dr. Sun advocated the development of a mononucleosis vaccine as the virus is becoming an increasing problem in both the developed and developing worlds and the cost of a vaccine would be shared by those interested in mononucleosis prevention. In this context, it would not be driven by HIV factors *per se*. Participants indicated that it would be worthwhile but raised concerns about vaccine and uptake, the latter because of the human papillomavirus (HPV) implementation experience: Do the technologies exist to make a mononucleosis vaccine feasible? Dr. Kieff noted that a specialty market for needed protection is transplant recipients; they need a vaccine that is both antibody and T-cell based. These remarks show the diverse interest in a EVB vaccine. It was recognized by all that a long-term commitment would be needed for such an endeavor.

Overall, the participants concluded that HIV-associated NHL and HD was a high priority area of research and that specific consideration should be given to the development of an EBV vaccine and determining its role in preventing EBV-associated tumors, especially if the vaccine did not prevent EBV infection but instead reduced symptoms of mononucleosis.

Recommendation 13: HPV-related tumors:

a. **HGAIN Outcome Study (HOST) to determine if treating anal High Grade Anal Epithelial Neoplasia (HSIL) prevents anal cancer.**
b. **Studies on how to best prevent and screen for cervical cancer, especially in resource-limited settings.**

There was clear endorsement for a trial to assess whether screening and treatment of HPV-associated anal pre-cancer will prevention anal tumors that is now under formal review in the NCI. Participants also strongly encouraged expansion of this sort of effort into other cancers, such as oropharyngeal cancer. The interaction(s) between HIV and HPV is not completely understood and provides an opportunity for study.

Dr. Yarchoan pointed out that it was somewhat unclear, from the minutes of the first meeting of this committee, whether they strongly endorsed other studies of screening and prevention of cervical cancer, and asked the committee to clarify this. Dr. Palefsky said that prevention and screening for cervical

cancer is a key issue in developing countries. A joint AMC-ACTG group has convened to develop priorities for collaborative work in Africa. The draft report recommends several high priorities for improving the see-and-treat approach as well as improving prevention, diagnostic, and treatment approaches for women in those countries. NIAID also has an interest in the area. A key area of emphasis for AMC and the NCI may be specifically in the treatment of cervical cancer in Africa; very little radiation therapy is available there, and better approaches to diagnosis and treatment of cervical cancer are needed.

Dr. Palefsky added that newer approaches and technologies (e.g., novel adjuvant therapies) are being used in the United States. More effective therapies should be moved into lower resource areas. In addition, better understanding of the impact of chemotherapy and radiation therapy of people on ART is needed. This area requires more attention to prevent premature death. It was pointed out that the NCI could bring its cancer treatment expertise to international collaborative efforts with other organizations already emphasizing this area.

The Subcommittee ranked this area overall as a high priority.

Recommendation 14: Liver cancer:

a. **Studies of pathogenesis and screening approaches.**
b. **Studies of improved therapy.**
c. **Studies of curing latent HBV infection.**
d. **Studies of ART in prevention.**

Liver cancer is a significant problem in resource-limited countries and deserves attention. In the HIV context, there is little information regarding the impact of highly active ART (HAART) except in delaying the time of tumor development. Although notable from the public health perspective, most aspects of liver cancer (e.g., curing cancer, HBV, HCV, combination effects of HAART) already are being evaluated.

Dr. Yarchoan asked for thoughts on priority ranking among the subtopics (A through D). Participants felt that the NCI should work on liver cancer research but not necessarily through the HIV program. Dr. Yarchoan clarified that even though liver cancer an important problem outside the setting of HIV infection, some of this work could be funded in part using AIDS dollars and asked the participants for their overall sense of priority of research in this area. Members noted that although HIV's role as a modifier is important, liver cancer is untreatable and better approaches are needed for liver cancer. In terms of viral-related malignancies, however, the area of HIV and liver cancer deserves further study. An issue that continues to arise in practical HIV diagnosis and management is how best to screen patients who are HPV- and HCV-positive for liver cancer. Dr. Yarchoan summarized the discussion. Liver cancer itself is important, especially prevention, but is not directly focused on HIV and should be examined in that context.

A majority of participants ranked this as an important area overall, but not a high-priority area for HIV malignancies, but there was not full consensus during the discussion.

Recommendation 15: Lung cancers:

a. **What is the role of HIV vs. other factors in explaining increased incidence in HIV patients.**
b. **What are the best approaches to screening and diagnosis?**
c. **Trial of antibodies to PD-1 in HIV-associated lung cancer.**

Dr. Yarchoan asked participants for their thoughts in ranking the three subtopics. Participants agreed that lung cancers are a definite priority; it is one of the more common non-AIDS associated cancers.

Participants discussed the subtopics. Regarding Subtopic C, antibodies are important for cancers but not specific to lung. In addition, PD-1 is important to call out because of its role in the future of cancer immunotherapy, but participants did not think the subtopic was a top priority as the effect of the association is not understood. Subtopics A and B present interesting issues, but testing will be challenging. One suggestion was to revise Subtopic A to the question: Is the screening test valuable in the HIV population? Regarding Subtopic A, some epidemiologic studies are trying to tease out HIV versus immunosuppression versus the extent of smoking; the discovery of infectious agent(s) or other markers would be helpful in advancing these investigations. Participants agreed that the subtopics raise important issues, but the best approach to them is unclear.

Dr. Mitsuyasu said that the AMC has targeted lung cancer as an important NADC tumor. It is overall a priority as a disease. Specific factors, such as smoking, could be targeted.

Dr. Yarchoan noted that participants felt that HIV-associated lung cancer was overall a high priority held mixed views regarding specific therapies and some uncertainty about how to approach lung cancer.

Recommendation 16: HIV-associated tumors in children:

a. Screening and treatment strategies, especially for resource-limited settings.

Dr. Yarchoan stated that the NCI has not focused on HIV-associated tumors in children, which are a problem in Africa but not in the United States. Participants agreed that this topic should be included in Recommendation #1, as we still need to gather more epidemiologic data Dr. Mitsuyasu commented that the AMC has struggled with this issue. More data are needed regarding current approaches and efficacy. He noted that treating Burkitt's lymphoma appears to make a difference. Dr. Yarchoan asked whether there were any tumors worth treating in kids in Africa beyond Burkitt's lymphoma. Participants named KS as important and indicated that more epidemiological data are needed to understand the scope of the problem.

In summary, the participants felt that the area was overall of middle priority, and that initially efforts should focus on gathering more accurate epidemiologic data about the incidence of these tumors in resource-limited regions.

Closing—Drs. Corey and Yarchoan

Dr. Yarchoan thanked participants for their comments. Drs. Corey and Yarchoan will review and disseminate the minutes from this meeting, and request further comments if more insight is needed on specific issues. The low- and high-priority rankings offered today will help advance the NCI's efforts in its malignancies research. Dr. Yarchoan added that the OAR was impressed with the efforts thus far, particularly the Subcommittee's recommendations.

Ms. Claire Harris asked that members of the public who came onto the teleconference after roll call to identify themselves.

The Subcommittee meeting adjourned at 12:15 p.m.