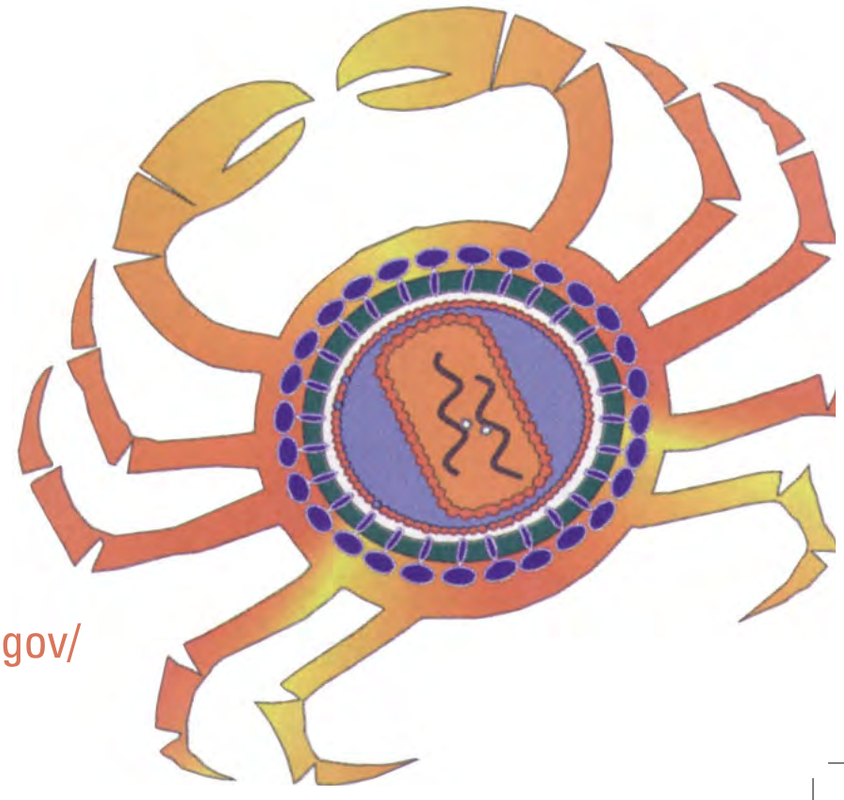
National Cancer Institute

Office of HIV and AIDS Malignancy

13th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies

November 7-8, 2011

Lister Hill Auditorium
NIH Main Campus
Bethesda, Maryland



http://oham.cancer.gov/

U.S DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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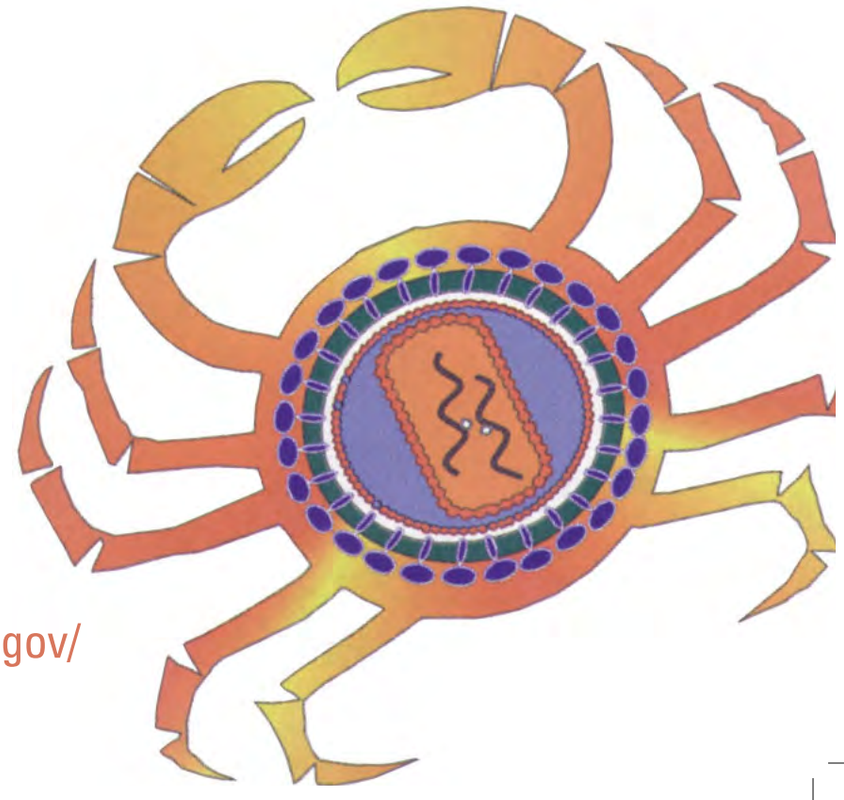

http://oham.cancer.gov/

U.S DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Accreditation Statement:

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The George Washington University School of Medicine and Health Sciences and the National Institutes of Health. The George Washington University School of Medicine and Health Sciences is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement:

The George Washington University School of Medicine and Health Sciences designates this educational activity for a maximum of 3.5 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Policy on Speaker and Provider Disclosure:

The George Washington University School of Medicine and Health Sciences has a disclosure policy whereby everyone in a position to control the content of an educational activity must disclose all relevant financial relationships with commercial interests. In addition, speakers must also disclose any unlabled/unapproved uses of drugs or devices that they plan to discuss in their presentation(s). Individuals who fail to disclose potential conflicts of interest are disqualified from participation in planning or implementing this CME activity. Potential conflicts of interest are resolved and documented.

Learning Objectives:

At the end of this activity, attendees should be able to:

1. Propose trends of specific malignancies that may occur in the context of HIV infection (AIDS defining and non-AIDS defining) and other acquired immunodeficiencies, and identify cofactors (i.e., environmental, viral, and behavioral) that may be associated with the development of these malignancies, if known. Describe which populations (geographic, ethnic, racial, sex, age, etc.) may be predisposed to developing specific malignancies.

2. Describe how the use of state-of-the-science information in the epidemiology, pathogenesis, and clinical aspects of malignancies in HIV positive and other immunocompromised patients can lead to more effective prevention, diagnosis, and treatment in those who are susceptible to these malignancies.

3. Describe how chronic immunosuppression (either in transplant recipients or HIV positive individuals on HAART) impacts the incidence and types of cancer, and the choice of therapies in those patients who develop malignancies.

Evaluating and Claiming Credits:

At the conclusion of this activity all participants will receive an evaluation sent to the email used at the time of registration. Once the evaluation is submitted, participants will be directed to a web page where they will be asked to either claim CME Credits or request a certificate of attendance. Certificates will be mailed three weeks after the conclusion of the program.

13th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies
Lister Hill Auditorium, NIH, Bethesda, Maryland
November 7-8, 2011

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- Celgene: Negotiating CRADA with group at NCI
- NIH: Patent Holder
- NIH: Patent Holder

Geraldina Dominguez, Ph.D.
Upon disclosure no commercial relationships were made.

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Upon disclosure no commercial relationships were made.

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*The program chairs and committee were tasked with identifying program content and speakers. The course director conducted the meeting with the best interest of the learning needs in mind. Both chairs and all committee members completed disclosure documents. Any potential conflicts that arose were mitigated by either (1) self-recusal or (2) concurrence by the committee that the content identified was scientifically sound and without bias and that the speakers identified would deliver balanced scientific presentations on raw data and sound evidence and make no commercial recommendations. It has been determined that no conflicts of interest exist in this role.

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Erle S. Robertson, Ph.D.
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The nature of the disclosure made is not germane to the topic presented.

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Upon disclosure no commercial relationships were made.

Robert Yarchoan, M.D.
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- Celgene: Negotiating CRADA with group at NCI
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Program

Day 1: Monday, November 7

8:00 a.m. — **Poster Setup** (posters will stay up for the entire meeting)

8:40 a.m. - 9:00 a.m. — **Opening Remarks and Welcome**
Robert Yarchoan, M.D.
Office of HIV and AIDS Malignancy
National Cancer Institute, NIH, USA

Meeting Logistics
Geraldina Dominguez, Ph.D.
Office of HIV and AIDS Malignancy
National Cancer Institute, NIH, USA

9:00 a.m. - 10:30 a.m. — **Session 1: KSHV-Associated Multicentric Castleman's Disease (MCD)**
Moderator: Richard F. Ambinder, M.D., Ph.D.
Johns Hopkins University School of Medicine, USA

9:00 a.m. - 9:20 a.m. — ***Plenary: KSHV and Multicentric Castleman's Disease: Role of vFLIP***
Ethel Cesarman, M.D., Ph.D.
Weil Cornell Medical College, USA

9:20 a.m. - 9:40 a.m. — ***Plenary: Multicentric Castleman's Disease (MCD) and Other Related KSHV Lymphoproliferations in East Africa***
Leona W. Ayers, M.D.
Ohio State University, USA

9:40 a.m. - 10:00 a.m. — ***Plenary: KSHV-Related Multicentric Castleman's Disease (MCD): Advances in Pathogenesis and Treatment***
Robert Yarchoan, M.D.
National Cancer Institute, USA

10:00 a.m. - 10:30 a.m. — **Questions and Answers** (directed at all speakers)

10:30 a.m. - 11:00 a.m. — **Break: Coffee and Poster Viewing**

11:00 a.m. - 12:15 p.m. — **Session 2: Gammaherpesvirus Genomic and Transcriptional Regulation**
Moderator: Elliott D. Kieff, M.D., Ph.D.
Harvard Medical School, USA

11:00 a.m - 11:15 a.m. — ***The Genetic Landscape of Immune-Competent and HIV Lymphoma***
Sandeep S. Dave, M.D.
Duke University Medical Center, USA

11:15 a.m. - 11:30 a.m. — ***Analysis of the miRNA Targetome in EBV-Infected B cells***
Rebecca L. Skalsky, Ph.D.
Duke University, USA

11:30 a.m. - 11:45 a.m. ***EBV-Regulated Global Changes in mRNA Isoform Usage***
Nicholas Homa
Duke University, USA

11:45 a.m. - 12 noon ***Comprehensive Analysis of the KSHV MiRNA Targetome by Ago-HITS-CLIP***
Rolf Renne, Ph.D.
University of Florida, USA

12 noon - 12:15 p.m. ***Genetic Variation in KSHV-Encoded microRNAs Affects microRNA Expression and Is Associated With Multicentric Castleman's Disease Risk***
Denise Whitby, Ph.D.
National Cancer Institute, NIH, USA

12:15 p.m. - 1:15 p.m. **Lunch** (on your own or pre-ordered lunch boxes)

1:15 p.m. - 2:15 p.m. **Poster Viewing** (Day 1 presenters stand by their posters)

2:15 p.m. - 3:15 p.m. **Session 3: Gammaherpesvirus-Host Interactions**
Moderator: Erle S. Robertson, Ph.D.
University of Pennsylvania Medical School, USA

2:15 p.m. - 2:30 p.m. ***KSHV Infection of Endothelial Cells Manipulates CXCR7-Mediated Signaling: Implications for Kaposi's Sarcoma Progression and Intervention***
Jennifer Vomaske, Ph.D.
Oregon Health & Science University, USA

2:30 p.m. - 2:45 p.m. ***Efficacy of a Latency- and Productive Infection-Deficient Gammaherpesvirus as a Vaccine Strategy***
Ting-Ting Wu, Ph.D.
University of California, Los Angeles, USA

2:45 p.m. - 3:00 p.m. ***Herpesviruses Control the DNA Damage Response Through TIP60***
Renfeng Li, Ph.D.
Johns Hopkins University, USA

3:00 p.m. - 3:15 p.m. ***Determinants of mTOR Inhibitor Therapy in AIDS-Associated Malignancies***
Dirk P. Dittmer, Ph.D.
University of North Carolina, Chapel Hill, USA

3:15 p.m. - 3:45 p.m. **Break: Coffee and Poster Viewing**

3:45 p.m. - 5:15 p.m. **Session 4: HPV-Associated Diseases**

Moderator: Joel Palefsky, M.D.
University of California, San Francisco, USA

3:45 p.m. - 4:15 p.m. ***Plenary: Development of Preclinical Models for Human Anal Cancer and Their Use in Testing Novel Therapeutic Strategies***
Paul Lambert, Ph.D.
University of Wisconsin, Madison, USA

4:15 p.m. - 4:30 p.m. ***The Impact of the HIV Epidemic on U.S. Anal Cancer Rates, 1980-2007***
Meredith S. Shiels, Ph.D., M.H.S.
National Cancer Institute, NIH, USA

4:30 p.m. - 4:45 p.m. ***Differential Modulation of Human Beta-Defensin-3 Expression in Human Oral Epithelial Cells by HPV Oncoproteins E6 and E7: Potential Implication in Oral Cancer***
Ge Jin, Ph.D.
Case Western Reserve University, USA

4:45 p.m. - 5:00 p.m. ***Human Papillomavirus Prevalence in Invasive Cervical Carcinoma by HIV Status***
Hugo De Vuyst, M.D.
International Agency for Research on Cancer, France

5:00 p.m. - 5:15 p.m. ***Prevalence of Cervical and Anal Warts Among HIV Patients on ARV Nigerian Special Treatment Center***
Modupe Onigbogi, Ph.D.
University of Lagos, Nigeria

5:15 p.m. **End of Day 1**

Day 2: Tuesday, November 8

7:30 a.m. - 8:15 a.m. **Poster Viewing** (coffee available)

8:15 a.m. - 8:30 a.m. **Introductory Remarks**
Geraldina Dominguez, Ph.D.
National Cancer Institute, NIH, USA

8:30 a.m. - 10:15 a.m. **Session 5: Clinical and Translational Research**
Moderator: Alexandra M. Levine, M.D.
City of Hope National Medical Center, USA

8:30 a.m. - 9:00 a.m. ***Plenary: Cancer and Inflammation: The Role of Gut Commensal Flora on Local and Distant Carcinogenesis and Tumor Immunity***
Giorgio Trinchieri, M.D.
National Cancer Institute, NIH, USA

9:00 a.m. - 9:15 a.m. ***Modified Dose Intensive R- CODOX-M/IVAC for HIV-Associated Burkitt (BL) (AMC 048) Shows Efficacy and Tolerability, and Predictive Potential of IRF4/MUM1 Expression***
Ariela Noy, M.D.
Memorial Sloan-Kettering Cancer Center, USA

9:15 a.m. - 9:30 a.m. ***A Phase 1/PK Study of Sunitinib With Highly Active Antiretroviral Therapy (HAART) in HIV+ Patients With Solid Tumors: AIDS Malignancy Consortium (AMC) Study 061***
John F. Deeken, M.D.
Georgetown University, USA

9:30 a.m. - 9:45 a.m. ***Serum Levels of Several Molecules That Are Associated With B Cell Activation and Inflammation Are Elevated in AIDS-Associated Non-Hodgkin's Lymphoma (AIDS-NHL) and Predict Response to Treatment***
Marta Epeldegui, Ph.D.
University of California, Los Angeles, USA

9:45 a.m. - 10:00 a.m. ***CD4 Regulatory T Cells Control CD8 T Cell Responses to Human Herpesvirus 8 Lytic and Latency Proteins***
Lauren Lepone
University of Pittsburgh, USA

10:00 a.m. - 10:15 a.m. ***Risk Factors for Death and Temporal Trends in Overall Survival in Patients With AIDS-Associated Primary Central Nervous System Lymphoma (AIDS-PCNSL)***
Thomas S. Uldrick, M.D., M.S.
National Cancer Institute, NIH, USA

10:15 a.m. - 10:45 a.m. **Break: Coffee and Poster Viewing**

10:45 a.m. - 11:45 a.m. **Session 6: Comorbidities in the Era of Antiretroviral Therapy**
Moderator: Eric A. Engels, M.D. M.P.H.
National Cancer Institute, NIH, USA

10:45 a.m. - 11:15 a.m. ***Plenary: Opportunistic Infections and Neoplasms Following Liver and Kidney Transplantation in the HIV-Infected Recipient***
Peter Stock, M.D., Ph.D.
University of California, USA

11:15 a.m. - 11:45 a.m. ***Plenary: Multimorbidity, Cancer, and Aging: An Individualized Approach to Cancer Screening***
Amy Justice, M.D., Ph.D.
Yale University, USA

11:45 a.m. - 12:45 p.m. **Lunch** (on your own or pre-ordered lunch boxes)

12:45 p.m. - 1:45 p.m. **Poster Viewing** (presenters stand by their posters)

1:45 p.m. - 3:30 p.m. **Session 7: HIV, Co-infections, and Cancer: Studies From International Settings**
Moderator: Sam M. Mbulaiteye, M.D.
National Cancer Institute, NIH, USA

1:45 p.m. - 2:00 p.m. ***Incidence of Kaposi Sarcoma in HIV-Infected Patients - A Prospective Multi-Cohort Study From Southern Africa***
Mhairi Maskew, Ph.D.
University of Bern, Switzerland

2:00 p.m. - 2:15 p.m. ***Prospective Evaluation of the Impact of Potent Antiretroviral Therapy on the Incidence of Kaposi's Sarcoma in East Africa: Findings From the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Consortium***
Jeffrey R. Martin, Ph.D.
University of California, San Francisco, USA

2:15 p.m. - 2:30 p.m. ***Gene Expression Profiling Using Formalin-Fixed Paraffin-Embedded Primary Specimens of AIDS-Related Lymphomas***
Ethel Cesarman, M.D., Ph.D.
Weill Cornell Medical College, USA

2:30 p.m. - 2:45 p.m. ***Decline in EBV-Specific IFN T Cell Responses in Kenyan Infants From a Malaria Holoendemic Region of Kenya***
Rosemary Rochford, Ph.D.
State University of New York

2:45 p.m - 3:00 p.m. ***Identifying Predictors of Increased Quantities of Human Herpesvirus 8 DNA Detection at Oropharyngeal and Plasma Sites Among Ugandan Adults With and Without HIV and Kaposi Sarcoma***
Warren Phipps, M.D.
University of Washington, USA

3:00 p.m. - 3:30 p.m. ***Plenary: Estimating the Impact of the HIV Pandemic on the Spectrum, Incidence, and Natural History of Cancer in Sub-Saharan Africa***
Corey Casper, M.D., M.P.H.
Fred Hutchinson Cancer Research Center, USA

3:30 p.m. - 4:00 p.m. **Break: Coffee and Poster Viewing**

4:00 p.m. - 5:00 p.m. **Session 8: Trends and Risk Factors in Non-AIDS Defining Malignancies**
Moderator: Michael J. Silverberg, Ph.D., M.P.H.
Kaiser Permanente, USA

4:00 p.m. - 4:15 p.m. ***Lung Cancer in the Swiss HIV Cohort Study: Role of Smoking, Immunodeficiency, and Pulmonary Infection***
Hugo De Vuyst, M.D.
International Agency for Research on Cancer, France

4:15 p.m. - 4:30 p.m. ***Incidence and Risk Factors for Lung Cancer Among Women in the Women's Interagency HIV Study (WIHS) and Men in the Multicenter AIDS Cohort Study (MACS)***
Nancy A. Hessol, M.S.P.H.
University of California, San Francisco, USA

4:30 p.m. - 4:45 p.m. ***Hepatobiliary Cancers in Persons With HIV/AIDS in the United States***
Vikrant V. Sahasrabuddhe, Dr.P.H., M.B.B.S., M.P.H.
National Cancer Institute, NIH, USA

4:45 p.m. - 5:00 p.m. ***Risk Factors for Squamous Cell Skin Cancer in HIV***
Shehnaz K. Hussain, Ph.D.
University of California, Los Angeles, USA

5:00 p.m. **End of Day 2**

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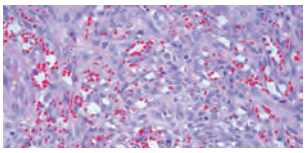
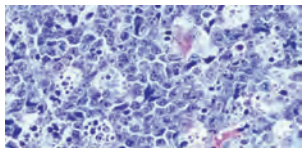
ACSR AIDS and Cancer Specimen Resource

Examples of Specimens:

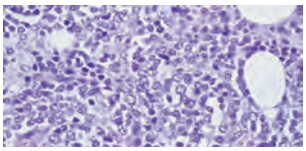
- Kaposi's sarcoma
- Non-Hodgkin's lymphoma
- Hodgkin's lymphoma
- Genito-urinary system dysplasia
- Non-HIV malignancy controls



Kaposi's Sarcoma



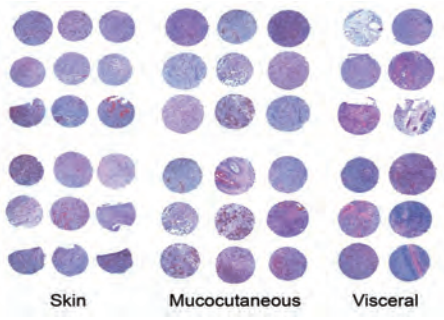
Burkitt' s Lymphoma



Large Cell L ymphoma

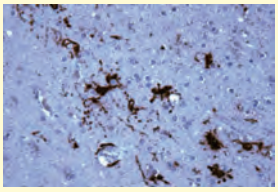
The ACSR Offers Tissue Micro-Arrays (TMA)

- Hundreds of tissue samples can be assembled into a single TMA
- HIV infected tissues and related malignancies along with non-HIV related controls
- TMA's available include Kaposi's sarcoma and AIDS lymphoma

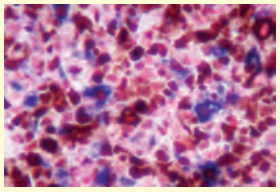


Kaposi's Sarcoma TMA, H&E stain

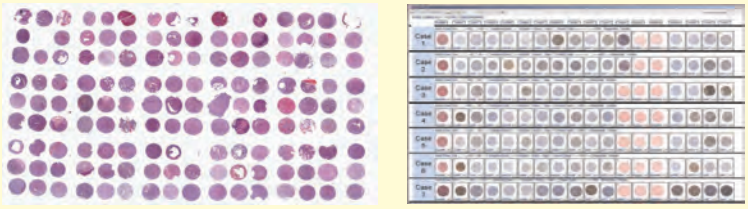
High Quality Specimens Produce Results for Your Research



Frontal cortex with HIV-encephalitis stained with HIV p24



Large cell lymphoma stained with CD68 (blue) and PCNA (brown)



Annotated HIV+ DLBCL TMA

http://acsr.ucsf.edu

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Plenary Speaker Abstracts

P1. KSHV and Multicentric Castleman's Disease: Role of vFLIP

Gianna Ballon, Ethel Cesarman

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Castleman's disease is a poorly understood atypical lymphoproliferative disorder. Two distinct histopathologic subtypes had been reported before the identification of KSHV, the more common hyaline vascular type and the plasma cell type. Clinically, Castleman's disease can be localized, or the patient may have multiple enlarged lymph nodes, therefore called "multicentric" Castleman's disease (MCD) [1]. The majority of patients with MCD have the plasma cell type morphology. While approximately half of MCD cases from immunocompetent individuals are associated with KSHV infection, this number is much higher in individuals with HIV, approaching 100%, and the presence of a single lymph node containing KS and Castleman's disease is not uncommon in HIV-positive patients. It now appears that the KSHV-positive cases represent a distinct morphologic variant, resembling more the plasma cell type but in addition to the rich interfollicular plasma cell infiltrate, these cases have larger cells, called plasmablasts, that contain KSHV and can be detected with monoclonal antibodies to the latent KSHV protein LANA1 [2,3]. KSHV-infected plasmablasts are B cells that are monotypic but polyclonal, almost invariably expressing IgMlambda [4].

Several KSHV-encoded proteins are thought to be associated with MCD pathogenesis, including a homologue of IL-6, called viral IL-6 (vIL-6), which is likely contribute to the symptoms [5], and lytic antigens that are expressed in some KSHV-infected cells in MCD. One of the latent viral genes that seems to be expressed in every infected B cell is vFLIP. This viral protein can activate the NF-kB signaling pathway, and prevent both apoptosis and autophagy. Conditional knock-in mice showed that expression of vFLIP in all B-cells, or restrictedly in germinal center (GC) cells, results in splenomegaly, lack of GC and impaired class-switch recombination with generation of increased numbers of lambda-expressing plasmablasts, reminiscent of MCD [6]. This provides evidence that vFLIP is one of the viral genes that can contribute to the pathogenesis of MCD, likely through activation of NF-kB and impairment of terminal differentiation of KSHV-infected B cells.

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P2. Multicentric Castleman's Disease (MCD) and Other Related KSHV Lymphoproliferations in East Africa

Leona W. Ayers[1], Robert Lukande[2], Joseph R. NDung'u[3], David K. Chumba[4], Lynnette K. Tumwine[2]

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Background: East Africa has among the highest seropositive rates for HHV-8 in the world (~56%) with Kaposi's sarcoma (KS) as the most visible HHV-8 related disease. HIV/AIDS infection in this region is associated with epidemic increases of KS but reports of the other known HHV-8 disease associations have not been forthcoming. The Sub-Saharan Africa Lymphoma Consortium (SSALC) with pathologist collaborators in East Africa sought out the non-KS but HHV-8 related diseases.

Materials and Methods: Lymphoma tissues collected through the SSALC were supplemented by lymph nodes originally thought to represent hyperplasia. Suspect Castleman's disease (CD) lymph nodes, all plasma cell proliferations and lymphomas were examined for LANA antigen using a tissue microarray (TMA) platform.

Results: HHV-8/HIV negative Hyaline vascular CD and HHV-8/HIV+ plasma cell variant CD, multicentric Castleman's disease (MCD) with hemophagocytic syndrome, MCD with plasma cell proliferations including plasmablastic lymphoma and plasma cell proliferative disorders with HHV-8 in the plasma cells or in the background were identified (Figure 1).

Conclusions: East Africa has HHV-8 related diseases of the types described in the world literature. While the incidence of these diseases does not appear to be high, prevalence and HHV-8 disease type distribution are not known but are likely less that KS. Also likely is that the HHV-8 diseases manifest together in some patients. Education of clinicians to the presentations of diverse HHV-8 disease and pathologists to histopathology are required.

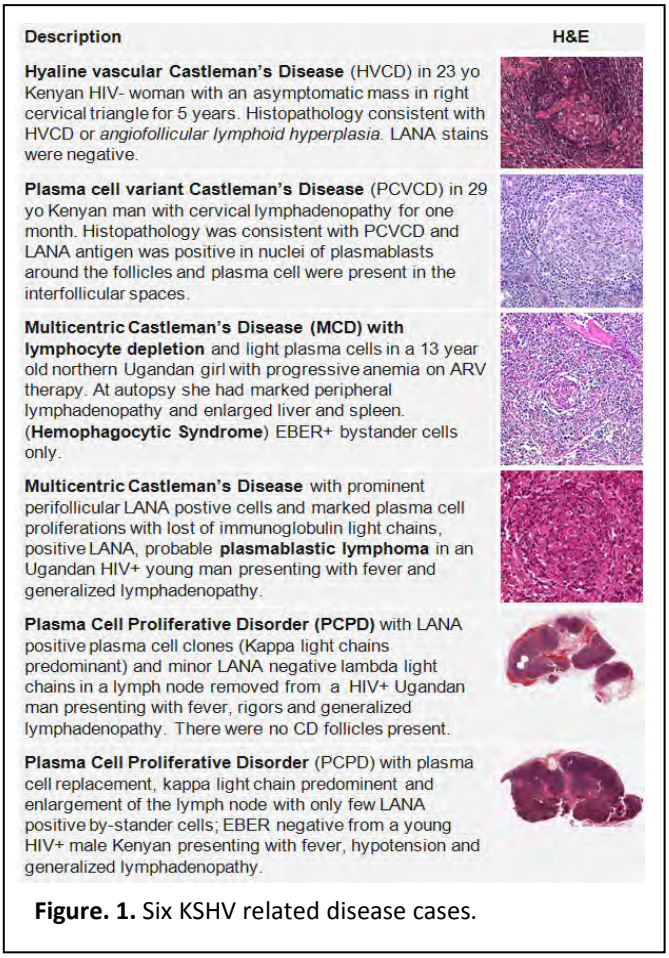

Figure. 1. Six KSHV related disease cases.

Acknowledgements: AIDS and Cancer Specimen Resource (ACSR/NCI) U01-CA66531-s, Sub-Saharan Africa Lymphoma Consortium (SSALC).

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1. Sub-Saharan Africa Lymphoma Consortium (SSALC) Facebook page [http://www.facebook.com]

P3. KSHV-Related Multricentric Castleman's Disease (MCD): Advances in Pathogenesis and Treatment

Robert Yarchoan[1], Thomas Uldrick[1], Mark Polizzoto[1], Richard F. Little, Karen A. Aleman[1], Kathy M. Wyvill[1], Denise Whitby[2], Giovanna Tosato[3], Stefania Pittaluga[4], David A. Davis[1], Victoria Wang[1]

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There are two major forms of multicentric Castleman's disease (MCD); one is idiopathic and the other caused by Kaposi's sarcoma-associated herpesvirus (KSHV). In both, the principal clinical manifestations are fevers, fatigue, weight loss, edema, lymphadenopathy, splenomegaly, cytopenias, low albumin, elevated C-reactive protein, and hyponatremia. KSHV-MCD accounts for almost all cases in HIV infected patients. MCD diagnosis is based on pathological findings including the presence of plasmablasts in an affected lymph node or spleen; in KSHV-MCD, a subset of these plasmablasts are infected with KSHV and express latency associated nuclear antigen (LANA). Overproduction of human interleukin-6 (hIL-6) as well as other cytokines is believed to cause the systemic symptoms of MCD. KSHV encodes a viral analog of human IL-6, viral IL-6 (vIL-6), that can signal through gp130 without a need for the IL-6 receptor, and the plasmablasts in KSHV-MCD express vIL-6 and sometimes other KSHV lytic genes. Overexpression of vIL-6 is believed to be central in the pathogenesis of KSHV-MCD.

In order to better understand the role of vIL-6 and other cytokines in the pathogenesis of KSHV-MCD, we studied 34 flares in 21patients with MCD. 13 of the flares were associated with an increase in both hIL-6 and vIL-6, 17 with hIL-6 only, 2 with vIL-6 only, and in 2 flares, neither were elevated at the onset. Flares were also associated with elevations of interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and the viral load of KSHV in circulating peripheral blood mononuclear cells. Thus, flares of KSHV-MCD can be associated with increases in vIL-6, hIL-6, or both, and this complexity should be considered as therapeutic strategies are developed. Looking back on our patients with other KSHV-associated conditions, we identified 6 patients with systemic symptoms and laboratory abnormalities consistent with MCD, including elevations in vIL-6 and KSHV viral loads, but in whom we could not make a diagnosis of MCD in biopsies of lymph nodes. We propose that some KSHV-infected patients may overproduce sufficient vIL-6 to cause cytokine-related symptoms without having KSHV-MCD, and have termed this condition KSHV-associated inflammatory cytokine syndrome (KICS). We have recently initiated a protocol to further study this condition.

KSHV-encoded lytic enzymes can activate both zidovudine (AZT) and gancyclovir to toxic tri-phosphate moieties, and we have found that the combination of AZT and ganciclovir can kill PEL cells in the laboratory. Based on this, we initiated a protocol of high dose AZT and valganciclovir (VGC), a prodrug of ganciclovir, in 14 patients with KSHV-MCD. 86% achieved a major clinical response, based on predetermined criteria, and median progression-free survival was 6 months. We are also exploring other approaches such as a combination of rituximab and liposomal anthracyclines. Finally, given the major role of hIL-6 in MCD pathogenesis, targeting hIL-6 may be worthwhile, and we have recently initiated a trial of toclizumab (antibody to the IL-6 receptor).

KSHV-MCD is considered to be a rare condition. However, it is not tracked on tumor registries, and data on its incidence are incomplete. There is some evidence that its incidence may be increasing with widespread use of combination anti-HIV therapy. Our experience is that the diagnosis is missed in many cases, and clinicians should be alert for KSHV-MCD in HIV-infected patients with fevers, edema, anemia, lymphadenopathy, or other cytopenias, especially if they have Kaposi's sarcoma or other evidence of KSHV infection. It has been asked whether some cases of KICS may be a variant of MCD, but if so, may suggest that the incidence of KSHV-MCD may be substantially higher than has been generally appreciated. Furthermore, we have seen a number of cases of KSHV-MCD in African immigrants to the United States in our clinic, suggesting that this disease is substantially more common in Africa than has been recognized.

P4. Development of Preclinical Models for Human Anal Cancer and Their Use in Testing Novel Therapeutic Strategies

Paul.F. Lambert, M.S. Thomas, R. Yang, P. Menden, Amy Liem, Henry C. Pitot, Gregory Kennedy

University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

The incidence of anal cancer in HIV-infected patients has risen dramatically since the introduction of HAART, particularly among men who have sex with men. Anal cancer is primarily caused by the same sexually transmitted, high-risk, human papillomaviruses (HPVs) that cause cervical and other genital (i.e. of the vagina, vulva, and penis) cancers as well as a growing fraction of head and neck cancers. As in these other cancers, two HPV genes, E6 and E7, are selectively expressed in anal cancers. These viral genes encode highly oncogenic proteins best known for their abilities to inactivate the cellular tumor suppressors p53 and pRb, respectively. We recently established a preclinical model for human anal cancer making use of genetically engineered mice that express in their anal epithelium the E6 and E7 oncogenes of the most common high risk HPV, HPV16. When treated topically with a chemical carcinogen, these HPV transgenic mice rapidly and selectively developed progressive neoplastic disease culminating in squamous cell carcinoma of the anus (SCCA) akin to that seen in humans. Using these mice we dissected the individual contributions of HPV E6 and E7 in anal cancer. E7 was found to be the more potent oncogene in causing anal cancer, similar to what we have observed previously in mouse models for HPV-associated human cervical and head/neck cancers.

The standard of care therapy for treating human anal cancer, a combination of chemo (5-FU + mitomycin C) and radiotherapy has remained static for over two decades, can be associated with severe morbidity, and is poorly effective in treating recurrent/metastatic disease. We discovered that in human anal cancer, as in some other human cancers, the cellular mTOR pathway is highly activated. This was also seen in the anal cancers arising in the HPV16 transgenic mice, leading us to use this mouse model to investigate the use of rapamycin, a drug that inhibits this pathway, in treating anal cancer. Rapamycin was highly effective in slowing the growth of mouse anal cancers.

To assess whether rapamycin was also effective in treating human anal cancer we established human anal cancer-derived tumor grafts in mice. These tumor grafts bore remarkable similarity histopathologically to the primary cancer, are HPV16-positive and can be passaged in mice allowing one to evaluate their response to various therapeutic treatment strategies. When treated with rapamycin human anal cancer tumor grafts were reduced dramatically in their growth. However, as in other human cancers, rapamycin treatment led to the undesired activation of the MEK/ERK pathway. Not surprisingly, combinatorial treatment with rapamycin and a MEK inhibitor, AZD6244, led to a more favorable therapeutic response. Current studies evaluating the use of these two drugs in combination with radiation as an alternative to the standard of care chemoradiotherapy will also be described.

P5. Cancer and Inflammation: The Role of Gut Commensal Flora on Local and Distant Carcinogenesis and Tumor Immunity

Giorgio Trinchieri, Amiran K. Dzutsev, Rosealba Salcedo, Noriho Iida., C. Andrew Stewart, Romina Goldszmid

Cancer and Inflammation Program, National Cancer Institute, National Institutes of Health, Frederick, MD, USA

Alteration of the response to the commensal flora in several models of genetic immunoalteration is responsible for enhanced susceptibility to colon carcinogenesis. For example, the enhanced susceptibility of MyD88, inflammasome, or IL-18 deficient mice to colon chemical carcinogenesis is associated to changes in the gut commensal flora composition. Interesting, induction of colitis in MyD88 deficient mice with Dextran Sulphate Sodium (DSS) is also associated with the emergency of thymic lymphomas in a proportion of mice suggesting a distant effect of alteration of mucosal permeability and interaction with the commensal flora. Also, depletion of the commensal flora with antibiotics or in germ free mice determines changes in the inflammatory component in subcutaneous tumor stroma that are associated with decreased efficacy of immune therapy and chemotherapy in these animals. These animal models could provide relevant information on the effect of mucosal microbial translocation on systemic inflammation and immunity in HIV-infected individuals.

P6. Opportunistic Infections and Neoplasms Following Liver and Kidney Transplantation in the HIV-Infected Recipient

Peter Stock

University of California, San Francisco, San Francisco, CA, USA

Background: Chronic exposure with HIV and co-pathogens as well as prolonged antiretroviral therapy has resulted in increased morbidity and mortality rates from end-stage liver and kidney disease in the HIV infected population. We performed a prospective, nonrandomized multicenter trial (NIH AI052748) to determine the safety and efficacy of kidney and liver transplantation in people with HIV. This analysis examines the impact of immunosuppression on the development of post-transplant malignancies in this group.

Methods: Participants required CD4+ T-cell counts of at least 200/µL (kidney) and 100/ µL (liver) and undetectable plasma HIV-1 RNA levels while being treated with a stable anti-retroviral regimen. A detectable HIV-1 RNA was permitted in liver recipients if ARV therapy had to be held secondary to hepatotoxcity. Post-tx management included protocol acceptable prophylaxis against opportunistic infections, immunosuppression, management of rejection, and antiretroviral therapy.

Results: Between November 2003 and February 2010, 275 HIV infected patients underwent transplantation. Of the 150 kidney recipients, median (IQR) CD4 cell count at transplant was 471 (274-663) and 37 (25%) had a history of OIs prior to transplant. Of the 125 liver recipients, median (IQR) CD4 cell count at transplant was 179 (74-320) and 15 (12%) had history of OIs prior to transplant. Survival for kidney and liver recipients was followed for a median of 3.6 (2.8-5.0) and 4.0 (2.6-5) years, respectively. There were 14 cancers in kidney recipients post-tx: 5 skin cancers, 3 *de novo* cutaneous *Kaposi* sarcoma (KS) lesions, 1 penis squamous cancer, 3 head and neck cancers, and 2 renal cell cancers. KS did not reoccur in any of these patients who had pre-transplant KS. There were 3 CA related deaths in the kidney tx recipients; 2 secondary to metastatic renal cell CA and 1 metastatic oral squamous cell CA. There were 14 cancers in liver tx recipients post-tx: 9 skin cancers, 3 liver CA, 1 *de novo* KS, and one lymphoma. Of note, 45 (36%) of the liver transplant recipients had HCC within Milan criteria at the time of transplant, and three recurrent CAs as above. There were 4 cancer related deaths in the liver transplant recipients; 2 recurrent HCC, 1 recurrent cholangioCA, and 1 lymphoma. Since Human papilloma virus (HPV) mediated anal lesions are a concern in people with HIV, a subset of 89 HIV infected transplant recipients were followed for anal cytology. Pre-transplant, 15% were diagnosed with atypia, 27% with low-grade (LSIL) and 2% with high-grade (HSIL) anal cytologic abnormalities. Following transplantation for a median follow-up of 26 weeks, 13% were diagnosed with atypia, 25% with LSIL and 19% with HSIL. In a multivariable analysis, there was evidence for the association of tx with HSIL (p=0.019), but little evidence for a role for CD4+ T-cells, HIV-1 plasma RNA, use of T-cell depleting agents, or type of organ transplanted.

Conclusions: Despite the necessity for chronic immunosuppression, there has not been an increased risk of malignancies associated with chronic HIV infection. There were no cases of EBV-mediated lymphoproliferative disease, and one death secondary to lymphoma. Although HHV-8 mediated cutaneous KS occurred in 4/275 recipients, all lesions were easily treated with sirolimus. Even though 45/125 (36%) of the liver transplant recipients had viral induced (hepatitis B or C coinfection) HCC at the time of transplant, only 2 had recurrent HCC post-tx. The incidence of skin cancers is not greater than in the HIV negative cohort of transplant recipients. HPV mediated disease may be problematic in people infected with HIV undergoing transplant and immunosuppression, and will require longer term rigorous follow-up. The protocol and associated manuscripts from the NIH multicenter trial are available at www.hivtransplant.com.

P7. Multimorbidity, Cancer, and Aging: An Individualized Approach to Cancer Screening

Amy C. Justice

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VA Connecticut Healthcare System, West Haven, CT, USA

Dr. Justice will begin with a review of the epidemiology and emerging multimorbidity among those aging with HIV infection. She will consider important issues surrounding the comparison of cancer events among those with and without HIV infection including competing risk of death, differences in age distributions, and differences in established risk factors. Finally, she will use the Veterans Aging Cohort Study Index (VACS Index) to illustrate how a clinical index which accounts for organ system injury from multimorbidity and treatment toxicity can be used to individually tailor screening and treatment.

P8. Estimating the Impact of the HIV Pandemic on the Spectrum, Incidence, and Natural History of Cancer in Sub-Saharan Africa

Corey Casper

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After three decades of careful research in the United States, epidemiologic trends in the incidence of HIV-associated malignancies (HIVAM) and estimates of survival after cancer diagnosis have led to important scientific understandings related to disease pathogenesis and improved therapies. Measuring the impact of the HIV epidemic on cancer incidence and survival in resource-limited settings has been more challenging, however, for several reasons. First, in settings were resources are limited, there are very few comprehensive, population-based cancer registries from which trends in cancer incidence can be deciphered. Second, in the absence of nationalized personal identification systems, it is very difficult to link cancer registries with information on HIV status, or determine with accuracy mortality among registered cancer cases. Third, data on cancer incidence and survival are only now starting to be prospectively collected among large cohorts of HIV-infected individuals under care in resource-limited areas. Despite the challenges, emerging data from sub-Saharan Africa are showing many similarities, but also important differences, in the epidemiology of cancers among persons with HIV. Data will be presented which highlights those cancers which appear to be more common among HIV-infected individuals in the region, outlines unique predictors of cancer incidence and survival, and raises a number of important questions about strategies to ameliorate the burden of HIVAM in sub-Saharan Africa in the coming years.

Oral Speaker Abstracts

O1. The Genetic Landscape of Immune-Competent and HIV Lymphoma

Jenny Zhang[1], Vladimir Grubor[1], Cassandra L. Love[1], Anjishnu Banerjee[2], Kristy L. Richards[3], Piotr Miezcowski[3], Cherie H. Dunphy[3], William W.L. Choi[4], Wing-Yan Auv, Gopesh Srivastava[4], Patricia L. Lugar[5], David A. Rizzieri[5], Anand S. Lagoo[5], Leon Bernal-Mizrachi[6], Karen P. Mann[6], Christopher R. Flowers[6], Kikkeri N. Naresh[7], Andrew M. Evens[8], Leo I. Gordon[9], Magdalena B. Czader[10], Javed I. Gill[11], Eric D. Hsi[12], Qingquan Liu[1], Alice Fan[1], Katherine Walsh[1], Dereje D. Jima[1], Micah Luftig[5], Ting Ni[13], Jun Zhu[13], Amy Chadburn[9], Shawn Levy[14], David B. Dunson[2], Sandeep S. Dave[1,5]

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Burkitt lymphoma (BL) and diffuse large B cell lymphoma (DLBCL) are aggressive forms of lymphoma in adults and demonstrate overlapping morphology, immunophenotype and clinical behavior. The risk of developing these tumors increases ten to hundred-fold in the setting of HIV infection. The genetic causes and the role of specific mutations, especially in the setting of HIV, are largely unknown.

The decoding of the human genome and the advent of high-throughput sequencing have provided rich opportunities for the comprehensive identification of the genetic causes of cancer. In order to comprehensively identify genes that are recurrently mutated in immune-competent DLBCL and BL, we obtained a total of 92 cases of DLBCLs and 40 cases of BL. These cases were compared to a set of 5 DLBCLs and BL tumors derived from patients with HIV. The DLBCL cases were divided into a discovery set (N=34) and a prevalence set (N=61). The Burkitt cases were also divided into discovery and prevalence sets (N=15, N=45 respectively). For each of the discovery set cases we also obtained paired normal tissue. We performed whole-exome sequencing for all of these using the Agilent solution-based system of exon capture, which uses RNA baits to target all protein coding genes (CCDS database), as well as ~700 human miRNAs from miRBase (v13). In all, we generated over 6 GB of sequencing data using high throughput sequencing on the Illumina platform.

We identified a total of 432 genes that were recurrently mutated in DLBCL and BL. We found that each tumor had an average of 20 gene alterations, which is fewer than most other solid tumors sequenced to date. Commonly implicated biological processes comprising these genes included signal transduction (e.g. PIK3CD, PDGFRA), immune response (e.g. B2M, CD83, IRF8) and chromatin modification (e.g. MLL3, SETD2). We found that lymphomas that arose in the setting of HIV had fewer mutations overall and had a paucity of mutations related to immune response.

These data implicate the depressed immune response by HIV as a contributing risk factor for the development of lymphomas and suggest that HIV lymphomas are genetically less complex than their immune competent counterparts. This study represents one of the largest applications of exome sequencing in cancer, and provides early clues to the genetic causes of HIV-lymphomas.

O2. Analysis of the miRNA Targetome in EBV-Infected B Cells

Rebecca L. Skalsky[1], David L. Corcoran[2], Eva Gottwein[3], Christopher L. Frank[1], Markus Hafner[4], Jeffrey D. Nusbaum[4], Regina Feederle[5], Henri-Jacques Delecluse[5], Micah Luftig[1], Thomas Tuschl[4], Uwe Ohler[2,6], Bryan R. Cullen[1]

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microRNAs (miRNAs) are ~22 nt, non-coding regulatory RNAs expressed by all metazoans and several viruses. During latent infection, Epstein-Barr virus (EBV) expresses 25 pre-miRNAs and influences the expression of cellular miRNAs, such as miR-155 and miR-21, all of which potentially have roles in viral oncogenesis. To date, only a limited number of EBV miRNA targets have been identified; thus, the role of viral miRNAs in viral pathogenesis and/or oncogenesis is not well defined. Using photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP) [1] combined with high-throughput sequencing and computational analysis [2], we interrogated the miRNA targetome in EBV-infected B cells. We identified miRNA binding sites in over 5,700 cellular 3' untranslated regions (UTRs), 25% of which contained sites for EBV miRNAs. miRNA binding sites were also identified at a lower frequency in coding regions. Our results reveal that EBV miRNAs predominantly target host cellular transcripts, thereby reshaping the host environment. Furthermore, viral miRNA targets are involved in multiple biological processes that are directly relevant to EBV infection, including modulation of immune responses, cell proliferation, and cell survival. Finally, we identified a number of viral transcripts that contained conserved binding sites for cellular miRNAs, including members of the myc-regulated miR-17/92 cluster. This comprehensive survey of the miRNA targetome in EBV-infected B cells is a positive step towards identifying novel therapeutic targets for EBV-associated malignancies.

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O3. EBV-Regulated Global Changes in mRNA Isoform Usage

Nicholas Homa, Raul Salinas, Eleonora Forte, Timothy Robinson, Mariano Garcia-Blanco, Micah Luftig

Department of Molecular Genetics and Microbiology, Duke University, Durham, NC, USA

Approximately 90% of the global adult population is latently infected with Epstein-Barr Virus (EBV). Latent EBV infections are normally asymptomatic due to a robust cytotoxic T cell response. However, in the event of immunosuppression, as observed in HIV/AIDS patients, these latent infections can lead to B-cell lymphomas. *In vitro* EBV has the capacity to transform primary B-cells into immortalized Lymphoblastoid Cell Lines (LCLs). In order to assess changes in both overall mRNA abundance and mRNA isoform usage, we queried resting, primary human B cells and LCLs using Human Exon (HuEx) and conventional Affymetrix U133 arrays. Using a novel computational algorithm, SplicerEX, we identified 433 genes whose mRNAs undergo changes in alternative isoform usage during the transformation from primary B-cells to LCLs. Isoform changes were largely orthogonal from expression changes as only ~1/3 of mRNA isoform changes were also changed at the level of overall abundance. Isoform changes were classified into alternative 5' initiation, internal exclusion/inclusion of exons, 3' terminal exon choice, and 3'UTR alterations. The most striking mRNA isoform change was 3'UTR shortening, accounting for ~25% of all changes. Gene ontology analysis of mRNA isoform changes revealed a strong enrichment for nucleic acid binding proteins, including splicing and transcription factors. We have confirmed a subset of the predictions made by SplicerEX using isoform-specific RT-PCR. Importantly, many mRNA isoform changes observed were in fact regulated by EBV latent infection, not just proliferation per se, as they were also observed in the conversion of EBV-negative Burkitt's lymphoma cells (BL41) to latency III expressing BL41/B95-8 cells. Our preliminary results further indicate that two transcription factors, the E2 family member TCF4 and the plasma cell differentiation factor XBP1, are both regulated by EBV at the level of alternative isoform usage. These proteins both impact activation of the BZLF1 lytic promoter and our data thus suggest a novel mechanism by which EBV maintains latent infection in immortalized B cells. These data may point to new approaches in regulating the latent/lytic switch crucial to the pathogenesis of EBV-associated AIDS lymphomas.

04. Comprehensive Analysis of the KSHV MiRNA Targetome by Ago-HITS-CLIP

Irina Haecker, Lauren Gay, Alison Morse, Marty McCrory, Yajie Yang, Jianhong Hu, Lauren McIntyre, Rolf Renne

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The gamma-herpesvirus Kaposi's Sarcoma-associated Herpesvirus (KSHV) is the etiological agent of Kaposi's Sarcoma (KS), Primary Effusion Lymphoma (PEL) and a subset of Multicentric Castleman's Disease (MCD) in immunocompromised individuals. As all herpesviruses KSHV has a latent and a lytic life cycle. Malignant cells in KS, PEL, and MCD are latently infected with KSHV. Interestingly, the virus encodes 12 miRNA genes giving rise to 25 mature miRNAs that are predominantly expressed during latency, i.e. in malignant cells. This, together with the increasing evidence for the involvement of miRNAs in cancer, suggests a potential role for the KSHV miRNAs in viral tumorigenesis. However, to date, very little is known about the function of these viral miRNAs. To address the question we performed Ago-HITS-CLIP (1) using the anti-Ago antibody 2A8 (2) to isolate RISC complexes from KSHV-infected lymphoma cells (BCBL1, BC3). RNAs extracted from these complexes were analyzed by Illumina sequencing to identify viral and cellular miRNAs and their target genes. The search for canonical seed sequence matches (nt 2-7) of the KSHV miRNAs within the mRNA-derived sequencing tags revealed more than 1000 cellular targets. Gene ontology analysis revealed that KSHV miRNA targets are enriched in genes involved in apoptosis, lymphocyte activation, cell cycle regulation, and transcriptional control. Importantly, we reproducibly obtained clusters of reads on experimentally confirmed KSHV miRNA target sites in several known target genes (e.g. Bach1, BCLAF1, and THBS1). New target genes are in the process of experimental validation, with 4 confirmed targets so far: TP53INP1, TPD52, ANXA2, C/EBPB. Target analysis for non-canonical seeds as well as for cellular miRNAs is currently ongoing.

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O5. Genetic Variation in KSHV Encoded microRNAs Affects microRNA Expression and Is Associated With Multicentric Castleman's Disease Risk

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Kaposi sarcoma-associated herpesvirus (KSHV) encodes 12 pre-microRNAs which potentially yield 25 mature microRNAs and have been shown to play prominent roles in the viral lifecycle including maintaining viral latency, evading the host immune response, and controlling lytic replication. We previously reported phylogenetic analysis of the microRNA-coding region of KSHV from Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD) patients. We showed a high level of conservation for most sequences, but also a divergent cluster of 5 KSHV sequences including 2 from MCD patients [1]. We additionally observed single nucleotide polymorphisms (SNP) in the sequence of KSHV encoded mature and pre-miRNAs from clinical samples including a SNP in mir-K12-5 reported to result in increased expression of the mature miRNA [2].

To determine whether SNPs in other KSHV encoded miRNAs resulted in differences in miRNA processing and expression we used four complimentary approaches. Analysis of KSHV miRNA expression levels in PEL cell lines using custom ABI real time qPCR assays showed differential expression that correlates with sequence. Lentiviral vectors constructed to express wild type and variant pre-miRNAs were transduced into 293T cells to make stably expressing cell lines. miRNA expression was assessed using custom ABI real time qPCR assays. Luciferase reporter assays were performed following transient transfections of each miRNA. In addition, *in vitro* maturation assays were performed to assess differences in Drosha/DGCR8 and Dicer cleavage between wild type and variant pre-miRNAs. Our results indicate that polymorphisms within the pre-miRNA sequence can cause subtle expression differences as in the case of KSHV miR-K12-6 or more profound changes as observed in miR-K12-5. Our data clearly shows that SNPs can affect pre-miRNA processing resulting in changes in mature miRNA expression levels.

To extend our studies on miRNA variation in MCD patients, KSHV miRNA sequences from 23 MCD patients and 7 patients with a newly described KSHV-associated inflammatory cytokine syndrome (KICS) were examined by amplification, cloning, and sequencing of a 646-bp fragment of K12/T0.7 encoding miRNA-K12-10 and miRNA-K12-12 and a 2.8-kbp fragment containing the remaining 10 pre-microRNAs. Phylogenetic analysis showed a distinct variant cluster consisting exclusively of MCD and KICS patients in all trees. Pearson's chi-squared analysis revealed 40 single nucleotide polymorphisms (SNPs) at various loci were significantly associated with MCD and KICS risk. Additionally, cluster analysis of these SNPs generated several combinations of three SNPs as putative indicators of MCD and KICS risk. Taken together, these findings show that MCD and KICS patients frequently have unusual KSHV microRNA sequences and suggest association between the observed sequence variation and risk of MCD and KICS.

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O6. KSHV Infection of Endothelial Cells Manipulates CXCR7-Mediated Signaling: Implications for Kaposi's Sarcoma Progression and Intervention

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CXCR7 was recently characterized as an alternative receptor for the chemokine CXCL12/SDF-1, previously thought to bind and signal exclusively through CXCR4. We recently identified CXCR7 as a key cellular factor in the endothelial cell (EC) dysfunction associated with KSHV infection. CXCL12 signaling is critically associated with tumor growth, angiogenesis and metastasis in several diverse tumors and is one of the most studied chemokine/chemokine receptor interactions in cancer systems. The tumorigenic activity of the CXCL12 signaling axis offers an attractive target for therapeutic intervention in multiple cancers including Kaposi's Sarcoma (KS). However, most of the research to date was based on the assumption that CXCR4 was the sole CXCL12 receptor, and thus focused on the development of CXCR4-targeted treatments. CXCR4 participates in important homeostatic functions including hematopoiesis and mucosal immunity, while CXCR7 is rarely expressed in normal adult cells. As a result, CXCR7 may be a more specific chemotherapeutic target for tumor cells and tumor-associated vasculature with fewer adverse effects than treatments targeting CXCR4. CXCR7 is poorly studied throughout the cancer literature and although CXCR7 expression has been found in tumor-associated vasculature, no studies comprehensively examine the biology of CXCR7 in EC and its implications for tumor biology. We seek to define the role of CXCR7-mediated CXCL12 signaling in EC biology, and in the context of KSHV infection, in order to determine potential contributions of CXCR7 signaling to KSHV-mediated EC transformation and KS tumorigenesis. We demonstrate that CXCR7 is strongly expressed on LANA+ spindle cells in KS biopsy tissue at all stages of tumor progression. We further demonstrate that CXCR7 induction by KSHV *in vitro* is specific to lymphatic EC lineages and occurs coincident with the acquisition of spindle morphology. Detailed examination of CXCR7 functions in EC biology reveals multiple roles for CXCR7 that could impact KS tumorigenesis, including effects on cellular proliferation, junctional integrity, cell survival and metastatic capacity. Specifically, we determine that CXCR7 expression results in a loss of PECAM/CD31 expression, perturbing the formation and maintenance of EC monolayers. Moreover, CXCR7+ EC display significant SDF-1 dependent hypermotility, as measured via Electrical Cell-Substrate Impedence Sensing (ECIS). We also demonstrate that SDF-1 signaling through CXCR7 expression is enhanced in EC undergoing anchorage-deprivation, affecting EC cell survival and invasion into SDF-1 rich niches. Taken together, these results demonstrate that CXCR7 is a novel KSHV-induced oncogene with the capacity to influence multiple aspects of KS pathogenesis including tumor growth, seeding and metastasis.

O7. Efficacy of a Latency- and Productive Infection-Deficient Gammaherpesvirus as a Vaccine Strategy

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Background: Human gamma-herpesviruses, Epstein-Barr virus (EBV or HHV-4) and Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8), are associated with several malignancies, especially in AIDS patients. Although highly active antiretroviral therapy (HARRT) has significantly reduced the incidence of EBV- and KSHV-associated tumors, it does not eliminate EBV or KSHV infection, and the tumor risk remains high for HIV-1-infected individuals who are also carriers for EBV and KSHV. Tumorigenesis of gamma-herpesviruses is associated with the persistence of infection. Thus, vaccination to elicit protective immunity that inhibits the establishment of viral persistence will prevent the occurrence of virus-associated cancers. However, currently there are no effective vaccines available for KSHV or EBV.

Materials and Methods: For proof of concept vaccination experiments, we utilize a mouse gamma-herpesvirus infection model. Previously, we have shown that vaccination with a non-persistent highly lytic live attenuated virus (AC-RTA) provides effective protection against a challenge infection by the wild type virus. To increase the safety of vaccination, the *in vivo* lytic replication capacity of a live gamma-herpesvirus needs to be significantly weakened without losing immunogenicity. We hypothesize that removal of the viral genes that inhibit the host immune responses will reduce the fitness of the virus but potentially increase its immunogenicity. For this purpose, we have removed immune evasion genes from AC-RTA along with other modifications.

Results: The resultant virus named DIP (**D**eficient in **I**mmune evasion and **P**ersistence), replicates in cell culture but is severely attenuated in mice, deficient in acute productive infection and latency. However, immunization of the DIP virus prevents latency establishment by the challenge wild type virus. Next, we aim to test strategies to improve the immunogenicity in immunocompetent and CD4-deficient hosts by incorporating expression of co-stimulatory molecules into the DIP virus.

Conclusions: The non-persistent DIP virus that undergoes limited *in vivo* viral replication provides us a novel vaccine strategy for preventing infection of human gammaherpesviruses. The "proof of concept" study in the mouse infection model is necessary to provide fundamental insights into the development of vaccines for the tumor-associated human herpesviruses.

O8. Herpesviruses Control the DNA Damage Response Through TIP60

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Background and Results: Herpesviruses establish life-long persistent infections that result in clinical manifestations ranging from mild cold sores, to pneumonitis and cancers. Immunosuppressed populations, including AIDS patients, are at risk for more serious disease outcomes. Although the -, -, and -herpesviruses infect different tissues and cause distinct diseases, they confront many of the same challenges in producing new virions and spreading infection. The herpesvirus families each encode a conserved serine/threonine kinase that plays an important role in virus replication and spread. Despite the potential of these kinases as pharmacological targets, the extent of substrate conservation and the key common cell signalling pathways targeted by these enzymes are unknown. We applied a human protein microarray, high-throughput approach to identifying shared substrates of the conserved kinases from herpes simplex virus, human cytomegalovirus, Epstein-Barr virus (EBV) and Kaposi's sarcoma associated herpesvirus. We identified 110 shared host substrates targeted by at least three conserved viral kinases. Bioinformatics analyses revealed that proteins involved in the DNA damage response (DDR) were statistically enriched and further orthogonal analysis led to an in-depth characterization of a histone acetyltransferase, TIP60, as a master regulator that is exploited by these viruses. In EBV replication, TIP60 acts both by triggering the EBV-induced DDR and by regulating expression of viral lytic genes (see Figure 1).

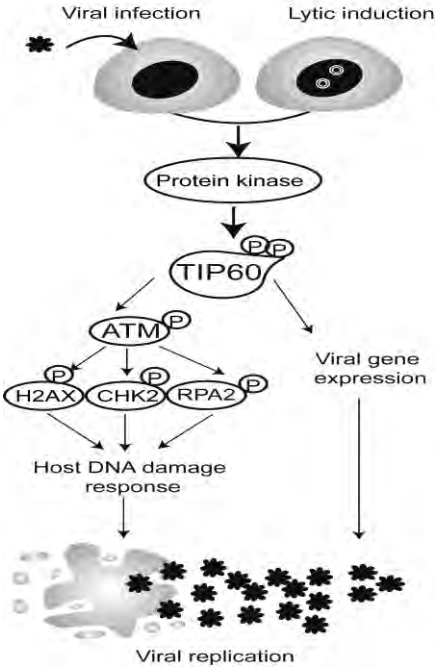

Figure 1.

Conclusions:

1. The conserved herpesvirus kinases target the DNA damage response (DDR) pathway.
2. The EBV kinase BGLF4 induces the DDR and regulates key lytic viral genes through TIP60.
3. TIP60 knockdown impairs and herpesvirus replication.
4. Identification of key cellular targets of the conserved herpesvirus kinases will facilitate the development of broadly effective anti-viral strategies.

O9. Determinants of mTOR Inhibitor Therapy in AIDS-Associated Malignancies

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Rapamycin/Sirolimus™ leads to the regression of transplant-associated Kaposi sarcoma (KS). It also leads to disease stabilization in HIV-associated KS. Case reports and a wealth of preclinical studies support rapamycin's efficacy also in AIDS associated lymphoma, such as primary effusion lymphoma (PEL). Rapamycin inhibits the mammalian target of rapamycin (mTOR) and papamycin derivatives are approved for the treatment of mantle cell lymphoma and other cancers. It is not universally effective against all solid tumors. Even within this group of clinically responsive cancers, there are exceptions of cases or cell models in which this drug or its derivatives (rapalogs) fail.

We hypothesized that genetic alterations of the tumor will determine the response to rapalogs. We used a novel KS TMA (from the AIDS cancer specimen resource (ACSR) to evaluate the PI3K/Akt/mTOR pathway in KS and identified a unique pattern of protein activation that is associated with sustained expression and phosphorylation of the PTEN tumor suppressor protein. We used Affymetrix array-based comparative genome hybridization (CGH) and targeted sequencing to query genomic loci of members of the mTOR pathway, which confirmed the absence of genetic alterations, which in other cancers have been associated with mTOR pathway activation. We conclude that in KS, PEL and perhaps other virus-associated cancer the mTOR pathway is activated post-translationally, which is not as permanent and does not have the same impact as for instance a deletion in PTEN. This may explain the unique sensitivity of these tumor types to rapalogs.

We established a novel animal model of KS (L1T2 cells), which develops tumors with short latency and in which the KS associated herpesvirus (KSHV) is maintained in each tumor cell. We evaluated multiple rapalogs (Sirolimus™, Temsirolimus™, Everolimus™), Tacrolimus/FK506 and Doxil™ in this model. We found sustained, but reversible tumor suppression by the rapalogs, which was associated (a) with inhibition of mTOR activity and (b) with reduced neo-angiogensis. In this model rapalogs outperformed Doxil™, presumably because of a combined effect on endothelial lineage KS tumor cells and endothelia lineage tumor vasculature. This represents the first animal test of rapalogs in a human KS tumor model, it validates novel biomarkers and provides a strong rational for further clinical development and testing of rapalogs in AIDS-associated Kaposi sarcoma.

As rapamycin has recently become affordable and is available in developing countries, where the majority of KS-associated mortality occurs, it is one of the few new anti-cancer drugs with a cost/benefit profile that is affordable for global cancer treatment.

O10. The Impact of the HIV Epidemic on U.S. Anal Cancer Rates, 1980-2007

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Background: U.S. incidence rates of anal cancer have increased steadily over time, and are generally higher in women than men. It has been proposed that the HIV epidemic may have influenced U.S. anal cancer trends. Compared to the general population, anal cancer rates are strongly elevated in HIV-infected individuals. Anal cancer rates in HIV-infected individuals have also increased over time. We estimated the impact of the HIV epidemic on U.S. anal cancer trends during 1980-2007.

Methods: Data on anal cancer incidence rates were obtained from the HIV/AIDS Cancer Match Study, which links 14 U.S. HIV/AIDS and cancer registries. We estimated incidence rates with anal cancer cases and person-years for the general population, and then subtracted 2 groups of cases in people with AIDS: cases that occurred after AIDS diagnosis (incident) and within 5 years prior to AIDS (prevalent). All rates were standardized to the 2000 U.S. population by age, sex and race. Poisson regression was used to estimate changes in rates over time.

Results: During 1980-2007, a total of 25,011 anal cancers occurred in 2.1 billion person-years of follow-up. Of these, 1087 were incident and 456 were prevalent cases in people with AIDS. Among men, the anal cancer rate increased 2.0% per year from 0.69 to 1.06/100,000 during 1980-2007 (Figure 1A). Excluding cases in people with AIDS, the rate only increased 0.77% per year to 0.77/100,000 in 2007. Among women, the anal cancer rate increased 2.1% per year from 1.09 to 1.71/100,000 during 1980-2007 (Figure 1B). Removal of cases with AIDS changed the trends very little (increase of 2.1% per year). Among 20-49 year olds, AIDS cases strongly influenced trends in men. Overall rates increased 4.0% per year, but rates excluding AIDS cases increased only 0.72% per year. In contrast, among women aged 20-49 years, AIDS had little impact on annual anal cancer rates (3.7% overall vs. 3.4% excluding AIDS cases). In 70+ year olds, the age group with the highest anal cancer incidence, AIDS had a small effect on male and no effect on female trends. During 2003-2007, 24.2% of anal cancers among men and 1.6% among women occurred in people with AIDS.

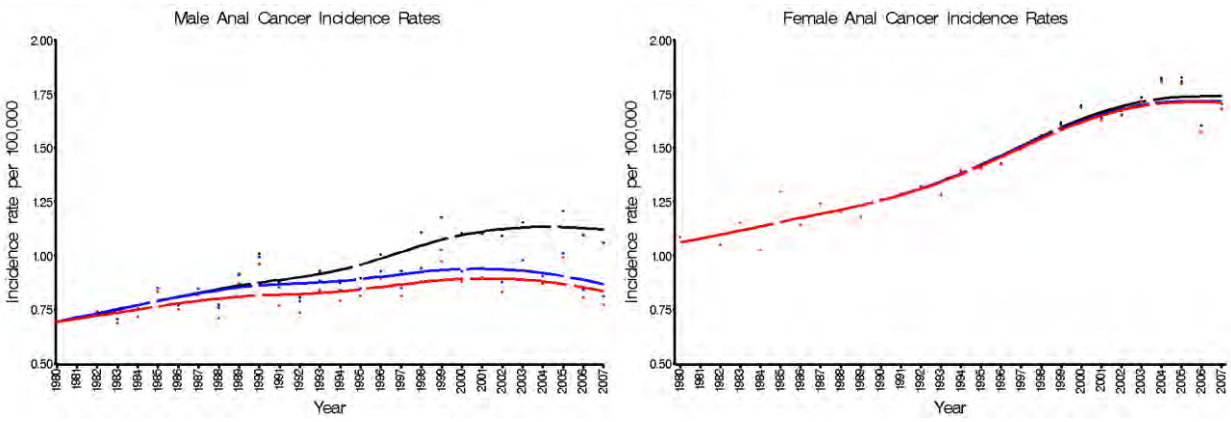

Figure 1. Male (A) and female (B) anal cancer incidence rates in overall (black line), excluding incident cases in people with AIDS (blue line), and excluding incident and prevalent cases in people with AIDS (red line), 1980-2007.

Conclusions: During 1980-2007, the U.S. anal cancer epidemic in young men was strongly influenced by the HIV epidemic; however, among women, the anal cancer epidemic was independent of HIV. Effective anal cancer prevention in HIV-infected men would have a substantial impact on U.S. anal cancer rates.

O11. Differential Modulation of Human Beta-Defensin-3 Expression in Human Oral Epithelial Cells by HPV Oncoproteins E6 and E7: Potential Implication in Oral Cancer

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Background: Human papillomaviruses (HPVs) are small, non-enveloped DNA viruses that infect stratified squamous mucosal and cutaneous epithelia, causing diseases ranging from benign warts to invasive tumors. Failure of the immune system to detect and clear persistent HPV infections frequently leads to the development of oral warts and cancer. HPV infection has been etiologically linked with oral warts and a subset of oral squamous cell carcinoma, particularly in HIV infected patients. The incidence of HPV-related oral lesions is increased in HIV+ subjects on highly active antiretroviral therapy (HAART). We previously showed that tumor cells in oral carcinoma in situ (CIS) lesions overexpress human beta-defensin-3 (hBD-3), an antimicrobial peptide with immunomodulatory capabilities. Expression of hBD-3 in CIS contributes to the local pro-tumor immune response by selectively chemoattracting tumor-associated macrophages and by enhancing tumor development and progression.

Results: To elucidate mechanisms by which high-risk HPV could evade immune detection and clearing via infected epithelial cells, we investigated if oncoproteins E6 and E7 derived from high-risk HPV-16 modulate the innate immune response of infected epithelial cells and the role of HPV-induced gene expression in orchestrating local immunity. We have found that cancer cells of HPV-related oral and oropharyngeal squamous cell carcinoma biopsies overproduce hBD-3. Introduction of an expression vector producing HPV-16 E6 or E7 oncogene into oral squamous cancer cell lines or primary oral epithelial cells increases the levels of hBD-3 mRNA and peptide. However, E6 derived from the low-risk HPV-11 is significantly less potent in promoting hBD-3 expression. Combination of oncogenic E6 and E7 in oral epithelial cells also shows reduced induction of hBD-3. Furthermore, the transactivity of an hBD-3 luciferase promoter construct is differentially stimulated by oncogenic E6 and E7 compared with MEKK1, a known inducer of hBD-3 expression. Although the pharmacological inhibitors for MAPK and PI3K reduce the transactivity of a 2.5 kb hBD-3 promoter reporter, they do not exhibit the inhibitory effect on the promoter reporter containing a 450 bp 3'-regulatory region. These data suggest that high-risk and low-risk early genes of HPV differentially modulate hBD-3 expression in oral epithelial cells.

Conclusion: Our results suggest that oncoproteins of high-risk HPV strains induce higher levels of hBD-3 expression compared with early genes of low-risk HPV. The oncogenic E6 and E7 genes may contribute to overexpression of hBD-3 in the early oral lesion, which then leads to recruitment of tumor-associated macrophages to further develop and promote the progression of cancer.

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012. Human Papillomavirus Prevalence in Invasive Cervical Carcinoma by HIV Status

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Background: Data on the prevalence of human papillomavirus (HPV) types in invasive cervical carcinoma (ICC) in women with HIV are scarce but are essential to elucidate the influence of immunity on the carcinogenicity of different HPV types, and the potential impact of prophylactic HPV vaccines in populations with high HIV prevalence.

Objectives: To compare the prevalence of HPV types in ICC by HIV status.

Methods: From 2007 to 2009, a multicentre case-case study was conducted at two referral hospitals in Nairobi, Kenya, and in Durban, South Africa. Women over 18 years of age presenting with ICC were recruited, and frozen biopsies were obtained and tested for HPV DNA using GP5+/6+-PCR methodology. The present analysis was limited to the 235 squamous cell cancers (SCC) detected.

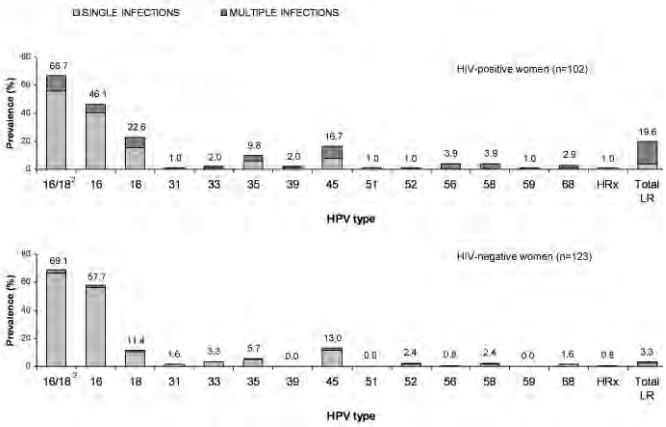

Figure 1. Prevalence of human papillomavirus (HPV) in 225 women with cervical squamous cell carcinoma by HIV status and multiplicity of HPV infection[1]

Results: We included 106 HIV-positive (mean age 40.8 years) and 129 HIV-negative women (mean age 45.7) with SCC. Among HIV-positive women, the mean CD4 count was 334 cells/μL and 48.1% were on combined antiretroviral therapy. HIV-positive women had many more multiple HPV infections (21.6% of HPV-positive carcinomas) compared to HIV-negative women (3.3%) ($p < 0.001$) and the proportion of multiple infections was inversely related to CD4 level. An excess of HPV18 of borderline statistical significance was found in HIV-positive compared to HIV-negative women (Prevalence ratio (PR) = 1.9, 95% confidence interval (CI): 1.0-3.7, adjusted for centre, age and multiplicity of infection). HPV16 and/or 18 prevalence combined, however, was similar in HIV-positive (66.7%) and HIV-negative women (69.1%) (PR = 1.0, 95% CI: 0.9-1.2). No significant difference was found for other HPV types (Figure 1).

[1]10 HPV-negative women were excluded; [2]Either 16 or 18 as single infection or in combination with any type as multiple type infection; HPV: human papillomavirus; HRX: uncharacterized high-risk type; LR: low-risk.

Conclusions
Overall, our data suggest that current prophylactic HPV vaccines against HPV16 and 18 may prevent similar proportions of cervical SCC in HIV-positive as in HIV-negative women provided that vaccine-related protection is sustained after HIV infection.

O13. Prevalence of Cervical and Anal Warts Among HIV Patients on ARV Nigerian Special Treatment Center

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Background: With the introduction of HAART in many HIV treatment centers in Nigeria, there has been a decreased incidence of AIDS-related mortality and growing concern about the incidence of AIDS specific and non-AIDS specific cancers. This study thus sought to investigate patterns and incidence of cervical and anal warts among patients in a Special Treatment Center (SPC) before being diagnosed of having HIV and after starting ARVs.

Materials and Methods: We linked results from a population-based HIV registry in our SPC with that of two cancer registries and evaluated the risk of developing anal or cervical warts a year prior to onset of ARV and a year after commencement of HAART. Standardized incidence ratios (SIRs) were calculated to relate presence of cervical and anal warts in people with AIDS to that in the general population. We also used logistic regression with 95% confidential interval to compare risk according to demographic factors and CD4 count.

Results: The study involved 542 patients diagnosed with HIV within the two years of the study. Persons with AIDS had elevated risks of cervical warts (SIR=11.7, 95% CI 6.2-14.4, n=52) and anal warts (SIR=1.8, 95% CI 1.3-2.7, n=13). Risk for cervical warts increased with increasing time relative to AIDS onset (p=0.02), this trend was not significant for anal warts (p=0.12). Risk of developing both warts was unrelated to CD4 count at onset of treatment (p=0.43).

Conclusions: There is a modest excess risk of developing cervical and anal warts among this group of patients. The risk seems to increase with increasing years on ARVs. This is not related to the immune state of the patients. There is a need to pay attention to patients on ARV therapy as they advance in years with ARV medication.

O14. Modified Dose Intensive R- CODOX-M/IVAC for HIV-Associated Burkitt (BL) (AMC 048) Shows Efficacy and Tolerability, and Predictive Potential of IRF4/MUM1 Expression

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Background: HIV associated BL remains of concern for toxicity of dose-intensive regimens used in HIV negative patients (pts). Less intensive regimens have a high relapse rate. We modified CODOX-M/IVAC hoping to preserve efficacy while improving tolerability, particularly treatment related mortality (TRM). Primary object: improving 1 year overall survival (OS) from the historical 65 to 85%.

Methods: Modifications of the US NCI regimen include rituximab (R), cyclophosphamide reduction [800 mg/m2 x 2 days], vincristine 2 mg cap, methotrexate (mtx) 3000 mg/m2, dual chemotherapy lumbar punctures and IVAC infusion (high risk pts). Antibiotic prophylaxis & growth factor support specified, 100% grade IV hematopoietic toxicities in the original regimen. HAART therapy at the discretion of the local MD. Pathology review included CD20, CD10, BCL2, BCL6, p53, Ki67, BLIMP1, IRF4/MUM1 and EBV EBER.

Results: Accrual of 33 planned pts by April 2010. Baseline: Classical Burkitt, 97%; Low/High Risk, 9/91%; Median (range) Age 42 (19 – 55); CD4 count 195 (0 - 721), CD4 <100, [5] (27%); HIV viral load 1819 (Undetectable – 1,187,968). Median follow up (fu) is 9 mos for surviving pt. Number of pts with gr3/4 toxicity: any 20 (61%), 13 (39%) hematologic, 16 (48%) infection including 7 febrile neutropenia, 6 metabolic with 1 tumor lysis syndrome, 4 neurologic, 2 thrombotic and 1 each coagulation, GI or pain. Only 2 gr 1/2 stomatitis/mucositis; 0 had gr 3/4. Six deaths: encephalopathy with hepatic failure, hepatitis B and pneumonia (1), disease progression (3) including 1 in the CNS; fungal infection (1); HIV. Median 1 year OS (n=34) was 81.7% (61.0%, 92.1%) with a 35 mo median survival. OS by non-BL defining proteins: EBER +/- (8/16) and p53 +/- (10/10) were not predictive. IRF4/MUM1 +/- (8/15) highly predictive in overall pts, but not in the confirmed Burkitt +/- (6/14) with only 1 IRF4/MUM1 neg pt dying of BL.

Conclusions: AMC 048 with a median fu of 9 mos has a 1 yr OS of 82% in BL. Relapses after 1 year are rare. TRM was zero. R did not appear to increase toxicity. Only 5 pts withdrew due to AEs. Grade 3/4 toxicities were markedly reduced. Results compare favorably with 2 studies of HIV neg pts. Magrath (1995) reported 100% grade 4 hematologic and 20% grade 4 mucositis in 39 adults, 33 children (92% 2 yr EFS). MRC/NCRI LY10 trial (Mead 2008) reduced mtx (3gr/m2), but reported 9% TRM (64% 2 yr OS). IRF4/MUM1 deserves further study in BL.

Acknowledgements: This study is presented on behalf of the AIDS Malignancy Consortium

Status	N (%)
Treatment Completed per protocol	21 (62%)
Disease Progression	3 (9%)
Early termination due to adverse event*	5 (15%)
Early termination due to patient withdrawal**	2 (6%)
Early termination – counts did not recover within time frame to begin cycle 4	1 (3%)
Treatment ongoing	2 (6%)

*1 pt with grade (gr) 4 thrombocytopenia and gr 3 infection; 1 pt with gr 3 left hemiparesis; 1 pt with gr 3 confusion unrelated to treatment; 1 pt with prior hepatitis B and cirrohosis had gr 3 encephalopathy and pulmonary infiltrates; 1 pt with gr 4 neutropenia and gr4 thrombocytopenia.
**1 CR 2 yrs post treatment.

O15. A Phase 1/PK study of Sunitinib With Highly Active Antiretroviral Therapy (HAART) in HIV+ Patients With Solid Tumors: AIDS Malignancy Consortium Study 061

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Background: In developed counties the rates of non-AIDS defining cancers (NADCs) now exceed those of AIDS-defining cancers in HIV-positive patients. Drug-drug interactions between HAART and chemotherapy may complicate the treatment of patients with NADCs. In order to determine the proper dosing of new targeted chemotherapies in patients with NADCs who are also on HAART, the AMC is performing a series of phase I/pharmacokinetic (PK) studies to determine the proper dosing of these agents in HIV+ cancer patients. We present the results of the first such study which investigated sunitinib, an oral multiple tyrosine kinase inhibitor.

Methods: Patients with HIV and cancers refractory to standard therapy were stratified into two arms: (1) non-ritonavir based HAART or (2) ritonavir-based HAART. Six patients were to be enrolled on arm 1 and receive the standard dose of sunitinib (50mg po qd). Arm 2 used a phase I, 3+3 dose escalation design (25, 37.5, and 50mg po qd). Cycles were 4 weeks on/2 weeks off. PK monitoring of sunitinb and its active metabolite (S-M) were performed throughout cycle one, and normalized based on dose level, to calculate $AUC_{0\text{-}24}$, C_{max}, and trough level.

Results: Between 8/09 and 4/11, 19 patients were enrolled and completed cycle 1 (10 on arm 1, 9 on arm 2). Cancer types included Kaposi's Sarcoma (7), lung (2), anal (2), head and neck (2), NHL (1), and other solid tumors (5). Median cycles was 2 (range 1-7). Following enrollment of the first 6 patients to Arm 1, that arm was expanded to include 3 additional patients on efavirenz, a potent inducer of CYP3A4, to better characterize sunitinb-efavirenz interactions. Patients on arm 1 tolerated standard treatment of 50mg with no dose limiting toxicities (DLTs). In the ritonavir arm, three patients tolerated 25mg with no DLTs. At the 37.5mg level, one patient had a DLT (wound dehiscence) and another three of five patients experienced Grade 3 neutropenia. With 4 of 6 patients experiencing grade 3/4 toxicity, enrollment was stopped, and no further dose escalation was attempted. No patient had a CR or PR, but five patients (26%) had stable disease for >4 cycles. Grade 3/4 toxicities during cycle 1 were: neutropenia (16%), leukopenia (16%), wound complications (5%), and abdominal pain (5%). PK analysis showed significant inter-patient variability of sunitinib and S-M. There were no PK alterations of sunitinib between the arms, but there were significant alterations in the PK of S-M. Efavirenz resulted in a 220% increase, whereas ritonavir caused a 69% decrease in the AUC of S-M, respectively.

Conclusion: The recommended dose of suninitib for patients on ritonavir is 37.5mg, whereas patients on NNRTI-based therapy can be treated with the standard dose of 50mg per day.

O16. Serum Levels of Several Molecules That Are Associated With B Cell Activation and Inflammation Are Elevated in AIDS-Associated Non-Hodgkin's Lymphoma (AIDS-NHL) and Predict Response to Treatment

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Background: B cell hyperactivation, as well as loss of immunoregulation of Epstein-Barr virus (EBV) infection, are believed to contribute to AIDS-NHL. Elevated serum levels of several cytokines and immune activation molecules are seen prior to the diagnosis of AIDS-NHL [1]. In this study, we quantified plasma levels of B cell activation-associated molecules (sCD23, sCD27, sCD30, IgE), cytokines (IL-6, IL-10, CXCL13), and *AICDA* expression, prior to and after the initiation of treatment in persons with AIDS-NHL in the AIDS Malignancies Consortium (AMC) 034 study.

Materials and Methods: Plasma and PBMC were obtained from AIDS-NHL patients (n=70) in the AMC 034 study, which evaluated treatment of AIDS-NHL with EPOCH chemotherapy and rituximab. Plasma was collected prior to the initiation of therapy, and post-treatment, after the first cycle of chemotherapy, and at 6 and 12 months following completion of treatment. Biomarkers were quantified by ELISA, *AICDA* expression by qPCR.

Results: Higher pre-treatment plasma levels of most of these B cell activation-associated molecules (IL-6, IL-10, CXCL13, sCD27, sCD30) were seen in AIDS-NHL patients, when compared to HIV+ and HIV-negative reference groups. However, sCD23 levels were lower post-AIDS-NHL than typically seen in the years preceding NHL diagnosis. Additionally, *AICDA* expression in PBMC was not detected in specimens collected after AIDS-NHL diagnosis. Treatment of NHL was seen to result in decreased plasma levels of these molecules, with decreased levels persisting for one year following the completion of treatment. CXCL13 and sCD27 decreased the most after treatment (mean levels went from 487 pg/ml to 310 pg/ml, and 1,080 units/ml to 330 units/ml, respectively) and remained low at one year following initiation of treatment (86.6 pg/ml and 362 units/ml, respectively). Pre-treatment levels of some of these molecules (IL6, IL10, CXCL13) were associated with subsequent response to lymphoma therapy, as were LDH levels and IPI scores. Using a normalizing transformation on CXCL13, CD27 and LDH, logistic regression analysis showed that the only factor significantly correlated with response was CXCL13.

Conclusions: Biomarkers for AIDS-NHL identified in prior epidemiologic studies were often further elevated post-AIDS-NHL diagnosis, and decreased with treatment for NHL. Importantly, elevated pre-treatment CXCL13 was associated with a poorer subsequent response to treatment, and was a better predictor of response than LDH levels and IPI scores.

Reference:

Breen EC et al. B cell-stimulatory cytokines and markers of immune activation are elevated several years prior to the diagnosis of systemic AIDS-associated non-Hodgkin's lymphoma. Cancer Epi Biomarkers Prev 2011, 20:1303-1314.

O17. CD4 Regulatory T Cells Control CD8 T Cell Responses to Human Herpesvirus 8 Lytic and Latency Proteins

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Objectives: CD8 T cells are considered to play an important role in controlling human herpesvirus 8 (HHV-8/KSHV) infection. However, these T cell responses are non-robust compared to other herpesviruses, suggesting that they are under tight regulatory control.

Methods: Longitudinal PBMC samples were obtained from subjects with various outcomes of HHV-8 infection over many years in the Multicenter AIDS Cohort Study. The PBMC were tested by HLA A*0201 multimer staining specific for memory CD8 T cell epitopes of viral lytic and latency proteins, and polyfunctional flow cytometry to detect HHV8-specific, polyfunctional CD8 T cell populations. The effect of Treg was examined by depleting $CD4^{+}CD25^{Hi}$ cells.

Results: Direct staining of PBMC with multimer MHC I complexes showed a relatively high frequency of circulating, HHV-8 lytic and latency antigen-specific CD8 T cells, but low anti-HHV-8 T cell polyfunctional reactivity. Removal of Treg enhanced T cell responses to these HHV-8 epitopes. The frequency of T cells specific for HHV-8 lytic antigens was greater than for latent antigens, and this effect was greater when Treg were removed. Numbers of HHV-8 specific effector memory CD8 T cells increased and terminally differentiated memory CD8 T cells decreased over many years of HHV-8 infection. We are currently assessing anti-HHV-8 T cell and Treg activity in relation to development of KS.

Conclusions: We show for the first time that Treg suppress CD8 T cell responses to HHV-8 lytic and latency antigens, effectively masking more robust, underlying anti-HHV-8 T cell responses. The involvement of CD8 T cells and Treg in control of HHV-8 infection has important implications for development of vaccines to prevent KS.

O18. Risk Factors for Death and Temporal Trends in Overall Survival in Patients With AIDS-Associated Primary Central Nervous System Lymphoma (AIDS-PCNSL)

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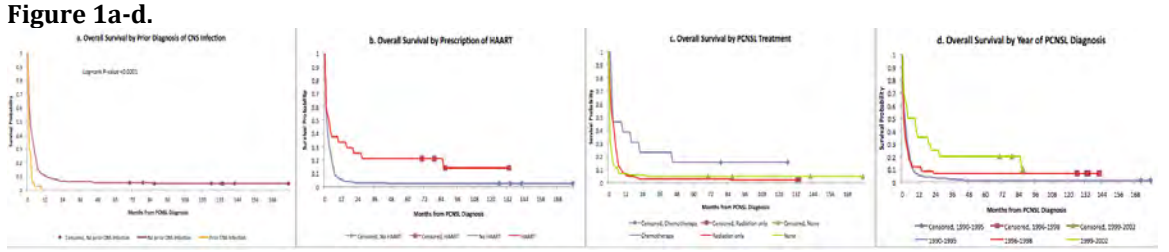
Background: AIDS-PCNSL is a rare EBV-associated B-cell neoplasm that continues to carry a poor prognosis, even in the highly active antiretroviral therapy (HAART) era. We hypothesized that overall survival (OS) is affected by prior diagnosis of central nervous system (CNS) infections as well as treatment approaches to both HIV and AIDS-PCNSL. We evaluated risk factors and temporal trends for OS in patients with AIDS-PCNSL.

Methods: Adults with AIDS-PCNSL were identified through a computer linkage that matched AIDS case diagnosed between 1990-2000 from the San Francisco adult AIDS case registry with the California Cancer Registry (1985-2002), with mortality follow-up through 12/31/2007. Patients with non-B-cell histology or history of systemic non-Hodkgin lymphoma diagnosed within 2 years prior to AIDS-PCNSL diagnosis were excluded. Prognostic factors evaluated include: diagnosis of CNS infection prior to AIDS-PCNSL, diagnosis of other common opportunistic infection (OI) prior to AIDS-PCNSL (pneumocystis pneumonia [PCP] or mycobacterium avium complex [MAI]), pathologic versus clinical diagnosis, receipt of cancer therapy, HAART prescribed prior to or within 30 days of AIDS-PCNSL diagnosis, and year of diagnosis (1990-1995, 1996-1998, 1999-2002). Survival analyses employed Kaplan-Meier methodology.

Results: A total of 207 patients were identified, 96% male and 4% female. Median age 39 (IQR 35-46), 68% white, 21% black, 20% Hispanic, 2% Asian. Median CD4 20 cells/uL (IQR 6-53). HIV risk group: 79% MSM, 8% IDU, 9% MSM/IDU. CNS infections prior to AIDS-PCNSL: toxoplasmosis 8%, cryptococcus 9%, histoplasmosis 1%, extrapulmonary tuberculosis 1%. Treatment category: none 42%, radiation only 52%, chemotherapy 6% (5/13 chemotherapy only, 6/13 chemotherapy and radiation, 2/13 chemotherapy and immunotherapy). Risk factors for OS included prior CNS infection (p<0.0001), HAART (p=0.0023), AIDS-PCNSL treatment (p<0.0001), and calendar period of AIDS-PCNSL diagnosis (0.001), but not prior PCP or MAC (p= 0.23). (Figures 1a-d.) OS was improved by HAART across treatment groups (p<0.0001).

Figure 1a-d.



Conclusions: Prior diagnosis of CNS infection, HAART, and cancer treatment are strong predictors of OS. OS improved over time in these patients. Earlier diagnosis of AIDS-PCNSL and/or CNS infection, treatment of CNS infections, and cancer treatment that includes HAART and concomitant chemotherapy may increase AIDS-PCNSL survival. Prospective evaluation of curative-intent chemotherapy-based approaches to AIDS-PCNSL is urgently needed. Additional analyses are ongoing.

O19. Prospective Evaluation of the Impact of Potent Antiretroviral Therapy on the Incidence of Kaposi's Sarcoma in East Africa: Findings from the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Consortium

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Background: Prior to the rollout of potent antiretroviral therapy (ART), Kaposi's sarcoma (KS) was the most commonly reported malignancy in many resource-limited settings, such as most of sub-Saharan Africa. In resource-replete settings (e.g., U.S. or Europe), the advent of ART—and the availability of established research networks—resulted in documentation of a marked decrease in KS incidence. In contrast, in resource-limiting settings like Africa, the heretofore lack of epidemiologic infrastructure has limited our knowledge about the effect of ART on KS incidence.

Methods: We prospectively followed HIV-infected adults, without prior KS, attending 26 HIV/AIDS clinics at the Mbarara (Uganda) or AMPATH (Kenya) sites of East Africa IeDEA. Time zero was October 2008, when we introduced skin punch biopsy for KS diagnosis, which was available same-day free of charge. Biopsies were adjudicated by board-certified UCSF dermatopathologists. Patients were followed until they developed KS, death, loss-to-follow-up, or administrative closure. Once started on ART, patients were considered on ART irrespective of adherence/interruptions. Incident KS was defined as any new occurrence of KS 30 days after clinic enrollment that was documented either pathologically or by clinical diagnosis in the absence of pathology.

KS Incidence During Non-ART Use and ART Use in East African HIV-infected Adults

	During Time of No ART Use			During ART Use		
CD4+ T cell count (cells/mm^3)	No. KS cases	Person-years	Rate (95% CI)*	No. KS cases	Person-years	Rate (95% CI)*
0-50	19	645	2943 (1877, 4615)	62	4070	1523 (1187, 1954)
51-100	2	613	326 (81, 1304)	37	5166	716 (518, 988)
101-200	8	1682	475 (237, 951)	45	15651	287 (214, 385)
201-350	27	6383	423 (290, 616)	40	27035	147 (108, 201)
>350	23	13926	165 (109, 248)	31	37804	82 (57, 116)

* per 100,000 person-years

Results: We followed 98,024 HIV-infected adults: 31% men, 66% ever on ART, and median values at study enrollment of 35 years old (IQR: 29-43) and 277 CD4+ T-cells/mm^3 (IQR: 137-453). Patients were followed for 144,182 person-years (median 1.8 years/patient) for 499 incident KS diagnoses, 43% of which were pathologically confirmed. KS incidence during non-ART use was 1876 cases/100,000-person-years in Uganda and 596 in Kenya; incidence during ART use was 201/100,000-person-years in Uganda and 270 in Kenya. After adjustment for age and gender, ART-users had a substantially reduced rate of KS compared to non-users: 88% reduction in Uganda ($p<0.001$), and 50% in Kenya ($p<0.001$). Further adjustment by CD4+ count showed a persistent ART effect, suggesting ART benefits for KS prevention above and beyond CD4 restoration (Table). In ART-users who achieved a CD4+ count of >350 cells/mm^3, KS incidence declined to 18/100,000-person-years in Uganda and 93/100,000-person-years in Kenya.

Conclusions: In a prospective study in East Africa, KS incidence was very high in untreated HIV-infected adults but was substantially reduced by ART — similar to that observed in resource-replete settings. Despite ART, absolute rates of KS remained considerable until a CD4+ count of >350 was achieved, suggesting the need for earlier ART initiation. The IeDEA platform provides unique opportunities for prospective African KS research.

O20. Incidence of Kaposi Sarcoma in HIV-Infected Patients – A Prospective Multi-Cohort Study From Southern Africa

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Background: The incidence of Kaposi Sarcoma (KS) is high in sub-Saharan Africa. Data on KS among HIV-infected patients receiving and not yet receiving antiretroviral therapy (ART) are, however, scarce in Africa. Within the framework of a large multi-cohort project, the International epidemiologic Database to Evaluate AIDS (IeDEA), we estimate the incidence and risk factors for the development of KS in HIV-infected patients in Southern Africa.

Methods: We analyzed prospectively collected data of HIV-infected children and adults participating in IeDEA-SA. We included all patients who were ART naive at start of observation, regardless of cancer history, with at least 30 days follow up. Prevalent KS cases were also excluded. Incidence rates and 95% confidence intervals (CI) were calculated based on the Poisson distribution; risk factors were estimated using crude and adjusted Cox proportional hazard models. Hazard ratios (HR) with 95% CI and medians with interquartile ranges (IQR) are presented.

Results: We included 184,592 patients from 10 cohort studies in Botswana, Mozambique, South Africa, Zambia and Zimbabwe. The median age was 34 years (IQR 28–41), the median CD4 cell count at first contact was 152 cells/µl (IQR 75-252) and 146 cells/µl (IQR 74-226) at start of ART. 61% of patients were female. During a total follow-time of 391,852 person-years, 349 patients developed KS before starting ART, 585 developed KS after starting ART and 183,658 remained KS-free. In patients not receiving ART the KS incidence rate was 624 (95% CI 562–692) per 100,000 person-years and in patients receiving ART the KS incidence rate was 174 (95% CI 161-189) per 100,000 person-years, rate ratio for ART versus no ART = 0.28 (95% CI 0.24 - 0.32). Univariate and multivariate analyses showed that men were more likely than women to develop KS and that the incidence rate for KS increased with increasing age and with decreasing CD4 cell counts. These effects were more pronounced in patients not receiving ART than in patients receiving ART.

Conclusions: In Southern African countries with a high prevalence of HHV-8 the risk of developing KS in HIV infected patients receiving ART increases steeply with age and immune-suppression. ART reduced the incidence of KS substantially.

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O21. Gene Expression Profiling Using Formalin-Fixed Paraffin-Embedded Primary Specimens of AIDS-Related Lymphomas

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Background: Gene expression profiling has been useful for classification and prognostication of a variety of hematologic neoplasms occurring in the general population. This type of analysis of AIDS related lymphomas (ARLs) has been limited because of their rarity, heterogeneity and lack of frozen tissue for analysis, with the largest studies including 25 cases (Klein et al., Blood 2003, Deffenbacher et al., J AIDS 2010). To overcome this limitation, we employed a *cDNA-based microarray technology, DNA-mediated Annealing, Selection, Ligation and Extension (DASL) for the analysis of* formalin-fixed paraffin-embedded (FFPE) *archival samples,* allowing us to perform gene expression analysis of the largest cohort of ARLs thus far.

Materials and Methods: We performed expression profiling from FFPE samples of AIDS related lymphoma for using DASL (Illumina®), with modification of the cDNA and quality control (QC) steps. The following cases of ARL with confirmed diagnosis and sufficient RNA were used for evaluation in duplicate: Weill Cornell Medical College in New York, USA (36 cases), the AIDS Malignancy Consortium (AMC) (24 cases), University of Siena, Italy (20 cases), Italy (21 cases), Tata Memorial Hospital in Mumbai, India (35 cases), University of Ibadan, Nigeria (1 case). Non-AIDS lymphomas were included as controls (15 cases from India and 13 cases from Weill Cornell). A 1mm diameter core was obtained from each block and RNA extracted. Tissue microarrays were also prepared of the available specimens, and characterization of viral status and lymphoma subtype were determined by immunohistochemistry and *in situ* hybridization for Epstein-Barr encoded RNA (EBER). Fluorescent in situ hybridization (FISH) was used to evaluate for genomic deletions in A20, and translocations of cMYC, BCL-2 and BCL-6.

Results: Gene expression profiling of 126 cases was initially performed using DASL. Quality control assessment and data analysis revealed poor predictive ability of the QC method and poor quality of the cDNA resulting in data variability and lack of reproducibility. Therefore, we developed alternative methodologies for cDNA preparation and assessment of quality of the RNA, resulting in more than double the number of genes detected and good reproducibility in the majority of the samples. Analysis of gene expression profiling of 116 cases of ARL and 28 matched non-AIDS lymphomas will be presented.

Conclusions: We have developed methods that allow gene expression analysis of large numbers of ARLs, which will pave the way of determining whether subtype specific signatures resemble those of lymphomas in immunocompetent individuals, and eventually if these have clinical implications.

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O22. Decline in EBV-Specific IFN T Cell Responses in Kenyan Infants From a Malaria Holoendemic Region of Kenya

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Background: Endemic Burkitt's lymphoma, the most prevalent childhood cancer in Equatorial Africa, is a rapidly growing B-cell malignancy that is ultimately fatal if untreated. Two co-factors are linked to the etiology of this pediatric cancer: Epstein-Barr virus (EBV) infection, and sustained and intense exposure to *Plasmodium falciparum* malaria (holoendemic malaria). In this study, we wanted to test the hypothesis that *P. falciparum* infections during early infancy results in elevated EBV viral load which results in diminished EBV-specific T-cell immune responses over time.

Methods: Infants were enrolled from two rural sites in Kenya: Kisumu District where malaria transmission is holoendemic and risk for eBL is high and Nandi District where malaria transmission is limited and the risk for eBL is low. Finger prick blood samples were taken through 2 years of age to measure EBV viral load, EBV antibodies, and malaria parasitemia. Venous blood samples were collected at 12, 18 and 24 months of age and PBMC were isolated and stimulated with peptides for both EBV lytic and latent antigens. After 2.5 days of stimulation, IFN ELISPOTS enumerated EBV-specific T cell responses, and the number of SFU/10^6 PBMC was determined by scanning with ImmunoSpot Reader and Software.

Results: When we compared EBV lytic and latent IFN T cell responses at 12, 18 and 24 months of age, we saw that although children in Kisumu were able to mount an IFN response against EBV lytic peptides, the magnitude of that response declined significantly by 24 months of age. In contrast, the magnitude of the response did not decline in the Nandi cohort. We also observed higher overall viral loads in infants from Kisumu suggesting that the apparent loss of EBV-specific IFN response to lytic antigens in the Kisumu children may be associated with these higher viral loads.

Conclusions: We found that by 2 years of age, there was a significant difference in the capacity of children living in a malaria holoendemic region compared to malaria sporadic region to maintain a T cell response to EBV lytic antigens. This suggests that *P. falciparum* malaria contributes to loss of EBV-specific immunity by inducing the collapse of an antiviral IFN- mediated CD8+ T cell response.

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O23. Identifying Predictors of Increased Quantities of Human Herpesvirus 8 DNA Detection at Oropharyngeal and Plasma Sites Among Ugandan Adults With and Without HIV and Kaposi Sarcoma

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Background: Persons with KS and uncontrolled HIV infection have HHV-8 DNA detected more frequently at mucosal sites and plasma [1], but it remains unknown whether the quantity of HHV-8 detected is associated with KS development or HHV-8 transmission. We sought to characterize and determine the correlates of elevated HHV-8 DNA copy number in the oropharynx and plasma of Ugandan adults with and without HIV and KS.

Methods: Participants collected daily oral swabs and weekly plasma samples over 4 weeks to quantify HHV-8 DNA by polymerase chain reaction.

Results: 297 participants collected a total of 8,045 oral swabs and 1,392 plasma samples. HHV-8 DNA was detected in 1,561 (19%) oral swabs and 419 (30%) plasma samples. The frequency of detecting any HHV-8 differed by KS status. HHV-8 was detected in the oropharynx of 70% (64/92) persons with KS vs. 27% (52/194) without KS (p<0.001), and in the plasma of 96% (88/92) persons with KS vs. 20% (38/194) without KS (p<0.001). The median amount of HHV-8 DNA detected in oral swabs was significantly lower in persons with KS (3.2 log copies/ml) than those without KS (3.8 log copies/ml, p<0.001) (Figure 1). HHV-8 quantities in the oropharynx did not differ by participants' HIV status (p=0.13), but elevated HHV-8 quantities were associated with CD4 counts >500 (coef 0.59, CI 0.16-1.03, p=0.007). In multivariate analysis, factors associated with higher oral HHV-8 copy number included absence of KS (coef 0.45, CI 0.14-0.75, p=0.004) and poor dentition (coef 0.37, CI 0.08-0.65, p=0.01). The median amount of HHV-8 DNA in plasma was significantly higher in persons with KS (3.6 log copies/ml) than those without KS (2.4 log copies/ml, p<0.001). In contrast to oral detection, higher plasma HHV-8 quantities were associated with CD4 counts <500 (coef 0.73, CI 0.40-1.05, p<0.001). In multivariate analysis, higher plasma HHV-8 copy number was associated with KS (coef 0.99, CI 0.80-1.17, p<0.001) and HIV infection (coef 0.39, CI 0.15-0.63, p=0.002).

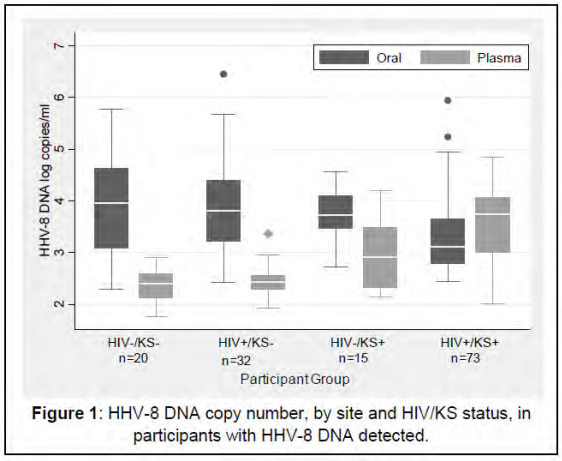

Figure 1: HHV-8 DNA copy number, by site and HIV/KS status, in participants with HHV-8 DNA detected.

Conclusions: Increased quantities of HHV-8 DNA were detected in the oropharynx of persons without KS and those with poor dentition. The latter observation may be explained if higher CD4 counts allow for increased inflammation in the oropharynx, in turn leading to greater HHV-8 replication. Quantities of HHV-8 are higher in the plasma of persons with either HIV infection or KS, perhaps representing the propensity of HHV-8 to disseminate systemically in the absence of effective immune control or from foci of replication in KS tumors.

Reference:

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O24. Lung Cancer in the Swiss HIV Cohort Study: Role of Smoking, Immunodeficiency, and Pulmonary Infection

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[15]HUG, Geneva, Switzerland
[16]Coordination and Data Center, Swiss HIV Cohort Study, Lausanne, Switzerland.

Background: We undertook a matched case-control study nested in the Swiss HIV Cohort Study (SHCS) to investigate HIV-related immunodeficiency, smoking and AIDS-related pulmonary infections as causes of lung cancer among HIV-infected persons.

Patients and Methods: 68 lung cancer cases were identified in the SHCS or through linkage with Swiss Cancer Registries and were individually matched to 337 controls by SHCS centre, gender, HIV-transmission category, age and calendar period. Odds ratios (OR) and corresponding confidence intervals (CI) were estimated by conditional logistic regression.

Results: 96.1% of lung cancer cases and 72.9% of controls were ever smokers, confirming the high prevalence of smoking in this population and its strong association with lung cancer (OR for current *versus* never=14.4, 95% CI 3.36-62.1). However, no significant associations were observed between CD4+ cell count and lung cancer, neither when measured within 1 year (OR for <200 *versus* >500=1.21, 95% CI 0.49-2.96), 1-2 years (OR=0.96, 95% CI 0.41-2.24), or further back in time, prior to lung cancer diagnosis. Use of combined antiretroviral therapy was not significantly associated with lung cancer risk (OR for ever *versus* never=0.67, 95% CI: 0.29-1.52). History of AIDS-related disease, whether with pulmonary involvement (OR=0.49, 95% CI 0.19-1.28) or not (OR=0.53, 95% CI 0.24-1.18), was under-represented in lung cancer cases. Controlling for smoking status did not materially affect findings.

Conclusions: Lung cancer in the SHCS appears not to be significantly associated with immunodeficiency or with a history of AIDS or AIDS-related pulmonary disease, but to be almost entirely driven by heavy tobacco smoking.

O25. Incidence and Risk Factors for Lung Cancer Among Women in the Women's Interagency HIV Study (WIHS) and Men in the Multicenter AIDS Cohort Study (MACS)

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Background: Studies have reported an increased incidence of lung cancer among people with HIV/AIDS as compared to population estimates [1], but it is unclear whether this increase is due to HIV or to other lung cancer risk factors such as cigarette smoking. One study found that HIV-infected adults with preexisting lung disease displayed trends for increased lung cancer risk [2]. Another study of people with AIDS reported that individuals with recurrent pneumonia were at significantly higher lung cancer risk than those without [3]. Our aims were to determine the incidence and risk factors for lung cancer among the participants in two longitudinal studies of HIV infection in United States women and men.

Methods: Data from 3763 women in the WIHS and 6972 men in the MACS were analyzed and incidence rates (IR) per 100,000 person-years and rate ratios (IRR) were calculated.

Results: We identified 44 lung cancer cases (33 HIV+ and 11 HIV-), 25 in the WIHS and 19 in the MACS, all with a history of smoking cigarettes. Among current and former smokers, the IR was significantly higher in the WIHS than in the MACS (WIHS IR=110.4 and MACS IR=35.8, $p<0.001$) but did not differ by HIV status. In multivariable analyses of the MACS participants, >30 pack-years of smoking (IRR=10.2) and a prior AIDS diagnosis (IRR=4.9) were significantly associated with an increased lung cancer rate. In multivariable analyses of the WIHS participants, age >49 (IRR=2.9 for 50-59; IRR=10.1 for 60+), Black race (IRR=4.6), >9 pack-years of smoking (IRR=14.7 for 10-30 pack-years; IRR=20.7 for >30 pack-years), and prior AIDS pneumonia (IRR=7.5) were significantly associated with and increased rate of lung cancer while more recent year of cohort enrollment (IRR=0.4 for 2001-2002) was associated with a lower rate.

Conclusions: HIV infection was not associated with lung cancer in the WIHS and was no longer significant in the MACS after adjustment for a prior AIDS diagnosis. A prior diagnosis of AIDS pneumonia was a risk factor for lung cancer in the WIHS. Pack-years of smoking was a strong risk factors for lung cancer in both cohorts but was twice as strong in the WIHS. A better understanding of the effect of HIV on lung cancer is needed but cessation of smoking is an ideal goal for HIV-infected individuals.

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O26. Hepatobiliary Cancers in Persons With HIV/AIDS in the United States

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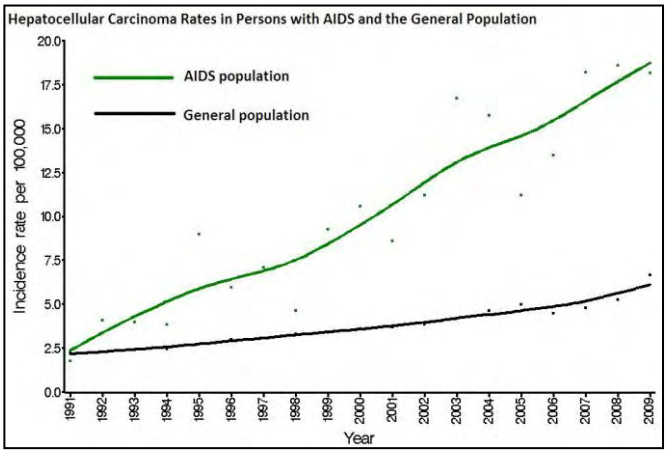
Background: Cancers of the hepatobiliary tract (liver, bile duct and gall bladder) are characterized by relatively infrequent occurrence, aggressive growth, and recurrences after treatment. Hepatocellular carcinoma (HCC) is of special concern in the context of HIV/AIDS due to substantial associated morbidity and mortality. The overall burden of liver cancer may increase in people with AIDS as the combined effects of alcohol use, coinfection with hepatitis C virus (HCV) and hepatitis B virus (HBV), and other risk factors manifest as chronic liver disease.

Methods: Registry linkage data from the U.S. HIV/AIDS Cancer Match Study were used to estimate standardized incidence ratios (SIRs) to compare the risk of hepatobiliary cancers in people with HIV/AIDS to the general population. We also estimated rate ratios (RRs) of HCC by HIV risk group, calendar period and AIDS status. HIV risk groups were categorized by HCV prevalence [high prevalence: hemophiliacs, injection drug users (IDUs), and IDU-men who had sex with men (MSM); and low prevalence: heterosexuals, non-IDU MSM, and others].

Results: Compared to the general population, people with AIDS had higher risk for HCC (366 observed cases, SIR: 3.85; 95%CI: 3.47-4.27). SIRs were also elevated for other liver and intrahepatic bile duct tumors (27 cases, SIR: 3.26; 95%CI: 2.15-4.75), but not for cholangiocarcinomas (22 cases, SIR: 1.36; 95%CI: 0.85-2.05) or gallbladder tumors (11 cases, SIR: 1.39; 95%CI: 0.70-2.49). Adjusted for sex and age, people with high HCV prevalence were at higher risk for HCC than people with lower HCV prevalence (RR: 2.12; 95%CI: 1.72-2.60). SIRs were elevated for all HIV risk groups, with the highest SIRs among hemophiliacs (40.4), IDUs (5.59), and IDU-MSM (4.39). Steadily increasing risk among persons with AIDS was observed across calendar time, including during the HAART era (Figure). In an analysis limited to registry areas with data on HIV-infected people without AIDS), persons with AIDS had higher HCC risk than persons with HIV-only (RR: 2.59; 95% CI: 1.71-3.91).



Conclusion: This study reinforces the primary role of HCV coinfection in HCC pathogenesis in persons with AIDS in the United States. HCC risk is higher in people with AIDS than people with HIV infection without AIDS, consistent with a contribution from prolonged immunosuppression. Rising HCC incidence in the era of HAART suggests that HAART itself does not fully correct the negative impact of HIV on HCV-related cirrhosis, and that access to appropriate anti-HCV therapies in HIV-infected individuals is critical for prevention of progression to HCC.

O27. Risk Factors for Squamous Cell Skin Cancer in HIV

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Introduction: Squamous cell skin cancer (SCSC) risk is increased in the setting of HIV making it one of the most common non-AIDS defining cancers. However, very few studies have examined individual level risk factors for SCSC in the setting of HIV.

Methods: The Multicenter AIDS Cohort Study, which includes 6,973 adult homosexual and bisexual men from four metropolitan areas in the U.S., was the study population used to address our aims. Incident SCSC diagnoses were initially captured through self-report on the biannual study visit questionnaire, and verified by review of pathology reports. Age-standardized incidence ratio was calculated to compare SCSC risk in HIV positive study participants to risk in HIV negatives. Multivariate Cox proportional hazards regression models were used to obtain hazard ratios (HR) and 95% confidence intervals (CIs) for the association between exposures of interest and SCSC risk. HIV positive participants entered the analysis on the date of their first HIV positive study visit and were followed until an SCSC diagnosis, death, or loss to follow-up.

Results: We identified 55 pathologically confirmed SCSC cases, 39 in HIV positive participants and 16 in HIV negative participants. In the HIV positive population, all cases occurred among white, non-Hispanics, and 18 (46%) were HAART exposed prior to cancer diagnosis. HIV positive men were more than four times as likely as HIV negative men to be diagnosed with SCSC (SIR=4.64, 95% CI=3.15-6.83). In multivariate models including only white, non-Hispanic, HIV positive participants, SCSC risk increased with increasing age (HR=1.12, 95% CI=1.07-1.17 per year) and HIV load (HR=1.38, 95% CI=1.19-1.56 per log unit increase). SCSC risk decreased with increasing CD4+ T cell number (HR=0.45, 95% CI=0.34-0.59 per log unit). Adjustment for MACS study site and HAART exposure did not strongly influence these associations.

Conclusions: Increasing age and HIV load, and decreasing CD4+T cell count, all suggesting decreased immunologic competence, were significantly associated with SCSC risk in the HIV-infected study population.

Poster Abstracts – Day 1

1. AIDS-Related Lymphoma at the University of Calabar Teaching Hospital (Nigeria): A Seven Year Review

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Background: With the use of HAART and effective treatment, prolongation of life of persons living with HIV, there has been a steady increase in cases of AIDS-related lymphoma (ARL). The number keeps increasing. The complexity of managing patients with ARL in a resource limited setting needs to be evaluated in view of the diagnostic and managerial challenges.

Objectives: To determine the prevalence of ARL in our hospital. To evaluate the outcome of patients management.

Subjects and Methods: Hospital records of patients with tissue diagnosis of lymphoma from January 2005-June 2011 were examined. Those with retroviral positive results were further followed up to treatment centre at the Presidential Emergency Programme for AIDS Relief (PEPFAR) clinic. Records were also reviewed at the Calabar Cancer Registry.

Results: Fifty-four patients with lymphoma were seen within the period (2005-2011).Non-Hodgkin's lymphoma (NHL) was the most frequent 35(63%) Hodgkin's lymphoma (HL) 8(18.2%), Burkitt's lymphoma(BL) 7(15.9%) and nasopharyngeal lymphoma(NL) 1(2.3%). ARL was 12(18.2%) with NHL, HL, and NL contributing 9(62%), 2(25%), 1(12.5%) respectively. Mortality was significantly higher in the ARL than in the non-ARL group.

Conclusions: ARL is not a rarity in our environment. A survey of all the HIV treatment centres will reveal a larger statistics. A greater understanding of the biology of this complex is needed. Training of `all care providers to effectively manage the disease is highly recommended. The cost of drugs for the treatment of the lymphoma is prohibitive to most of the indigent patients who present to our centre.

2. Changes in Incidence and Prognosis of Malignancies in Children With HIV

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Aim: The aim of this study was to analyze the differences in patient demographics as well as in the relative incidence and outcome of childhood cancers, associated with the HIV infection.

Materials and Methods: A retrospective comparative study of two series of children with malignant disease, one with HIV one without, was carried out. The former series consisted of 99 African children with cancer and HIV, consecutively admitted at Tygerberg Children's Hospital, Cape Town and Universitas Hospital, Bloemfontein, from 1995 to 2010. The latter series was formed of 570 African children with malignant diseases, not infected with HIV, consecutively admitted at the 2 hospitals, from January 2002 to December 2010. Variables studied were age, sex ratio, distribution of various malignancies, length of follow-up, treatment abandonment and mortality.

Results: The HIV positive children tended to be younger at diagnosis. The male/female ratio was slightly over 2 to 1 in the HIV positive group, while in the control group the sex ratio approached 1:1. Kaposi sarcoma was seen exclusively in the HIV positive series.

The death rate was 50.5% in the HIV positive children (versus 40.8% in HIV negative) but the difference is not significant.

When subgroups with matched cancers were compared, children infected with HIV had a significantly higher risk to die of drug-induced toxicity (relative risk 29.2, 95% confidence interval 3.7-225.8); only 26% of the HIV-positive children survived, compared with 51.2% in those not HIV infected (p=0.02).

Conclusions: The infection with HIV increases the risk for Kaposi sarcoma, for death due to cytostatic toxicity as well as the overall risk of death in children with cancer.

3. Malignancies in HIV-Positive Children in South Africa

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[2]Epidemiology and Genetic Unit, York University, York, United Kingdom

Background: The aim of the study was to review the epidemiology, management and chemotherapy response of HIV-positive South African children presenting with malignancy.

Procedure: A retrospective analysis was performed by examining the medical records of all HIV-positive children diagnosed with malignancy at seven participating centres. Variables studied were age, sex ratio and distribution of various malignancies, length of follow-up, treatment abandonment and mortality, HIV treatment, survival, modalities of treatment.

Results: Three hundred and two HIV-positive children were diagnosed with malignancy between 1990 and 2009. Age at diagnosis ranged from 17 days to 18.64 years. Of the 222 with HIV-associated malignancy, 108 (37.4%) presented with B-cell lymphoma (61 Burkitt lymphomas and 47 other B-cell lymphomas including two primary CNS lymphomas), 97 (33.6%) with Kaposi sarcoma, 12 with Hodgkin's Lymphoma and four with Leiomyosarcoma. Eighty-two patients presented with incidental malignancies. Average annual incidence increased from seven per year prior to 2003 to 34 per year in the subsequent seven years. The highest annual incidence was 55 in 2008.

Most patients (77.5%) were naïve to antiretroviral therapy (ART) at diagnosis. Many (33.6%) did not receive ART which only became available in 2003. One hundred and ninety eight cases were treated with chemotherapy and 90 were palliated due to advanced malignancy and /or advanced HIV disease.

Overall survival for the whole group was 29.0%. Considering only those treated with intention to ART and chemotherapy it was 57.4%; 71.4% for Hodgkin lymphoma, 58.2% for Kaposi sarcoma, 54.6% for Burkitt lymphoma, 40.6% for non-Burkitt B-cell lymphoma and 73.0% for incidental malignancies.

Conclusions: All patients diagnosed with Kaposi's sarcoma were HIV positive. A high frequency of non Burkitt cell lymphoma was found with relatively less primary CNS lymphoma present.

Most patients were naïve to antiretroviral therapy at diagnosis which could explain the poor survival rate of the group.

Acknowledgements: Data are presented on behalf of ACCESS South Africa.

4. Creating a Nationwide Cancer Registration System to Support AIDS-Cancer Match Studies in Nigeria

Clement Adebamowo, Elima Jedy-Agba, Emmanuel Oga, Peju Osinubi, Festus Igbinoba, Gloria Osubor, Theresa Otu, Henry Kumai, Michael Okobia, Prince Ejiroghene, Ahmed Mayun, James Abdulazeez, O. Erinomo, Adebayo Ojo, Cornelius Uka, Gloria Oyeoka

Nigerian National Cancer Registry System

Background: Cancer registration started in Nigeria in 1962 but after a very promising start, the momentum was lost.[1] [2] Since 2009, Nigerian Health Ministry, IARC and IPRI, have given training, troubleshooting and mentoring.

Materials and Methods: 20 cancer registries were trained and 5 have met criteria for population based cancer registries. Data for 2009 are presented in this report.

Results: The commonest cancer at all sites is Prostate in men and Breast in women. There was a gradient in the incidence that paralleled the socio-economic development of the regions of the country. The ASR for breast cancer ranged from 101.1 in Abuja to 7.5 in less cosmopolitan areas. For Prostate the ASR ranged from 73 in Abuja to 1.7. The other common cancers were Kaposi Sarcoma and Colo-Rectal in men, and cervix in women. Additional data collection and analysis is ongoing.

Conclusions: This study showed that breast and cervical cancer are the commonest in women while prostate is the commonest cancer in men.

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5. Anal HIV DNA Is Associated With High-Risk HPV Genotypes in Anal Cytology Specimens Obtained for Anal Neoplasia Screening

Bruce Shiramizu[1], Chin-Yuan Liang[1], Xumei Zhu[2], Melissa Agsalada[1], Ian Nagata[1], Kellie Kitamura[1], Jeffrey Killeen[3], J. Michael Berry[4], Marc Goodman[2]

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Purpose: High-grade anal neoplasia (AN) is associated with high-risk human papillomavirus (HPV) genotypes and is the precursor to anal cancer. Individuals infected with human immunodeficiency virus type 1 (HIV) continue to be at increased risk for AN even while on effective antiretroviral therapy (ART) with undetectable HIV RNA levels. The study was undertaken to assess HIV DNA from anal cytology specimens to determine if HIV DNA copy number was a factor for presence of high risk HPV genotypes.

Materials and Methods: Anal cytology specimens were obtained as part of an AN study according to guidelines approved by the local institutional review board. Anal HPV genotype, HIV DNA copy numbers, and cytology were obtained for each specimen. High-risk HPV genotypes included 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Analysis was performed by logistic regression model with high HPV risk as the response and HIV DNA copy numbers, anal Pap cytology results, and nadir CD4 cell counts as predictors. Lemeshow goodness-of-fit test was then performed to check model fit. Similar procedure was performed in sub-cohort of undetectable HIV RNA patients.

Results: 46 specimens were available from 38 males and 8 females. 52.2% of the specimens were negative for any HPV with 52.6% of males being HPV-positive compared to 25% of females. Of 46 specimens, 42 patients had undetectable HIV RNA level. The odds of having high-risk HPV genotypes among subjects with (x+100) copies of HIV DNA was 1.161 times the odds among subjects with x copies of HIV DNA (p=0.013). Inclusion of nadir CD4 count in the logistic regression model did not predict HPV risk. Distributions of HIV DNA were statistically different between normal and abnormal anal cytologies (p=0.009); median and interquartile HIV DNA copy numbers for abnormal and normal cytologies 792 (38-2100) and 27.5 (10-225), respectively, Figure 1. Anal cytology results were also associated with HPV risk (p=0.034). Patients with undetectable HIV RNA (n=42) had similar findings.

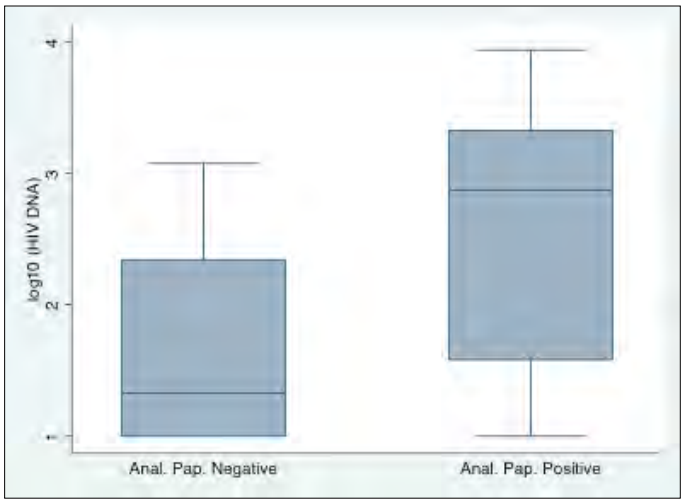

Figure 1. Differences in HIV DNA distributions between normal and atypical anal Pap groups (p=0.011).

Conclusions: Individuals with higher HIV DNA copies in anal specimens were more likely to have high-risk HPV genotypes independent of nadir CD4 cell count. Abnormal anal cytologies were also associated with high-risk HPV. The association of HIV DNA copy number in anal specimens needs validation in future studies to determine the role in the pathogenesis of AN and high risk HPV. Grant support: RR011091, RR026136, CA121947, CA143727, CA096254

6. Curation and Semantic Modeling of Unstructured AIDS-Related Malignancy Data

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Background: The increased longevity of HIV/AIDS patients due to the successful application of antiretroviral therapy has also come with an increase in rates of cancer, which presents researchers with unique data integration and analysis challenges. We report our current work on the applicability of data curation and semantic modeling to create a workflow infrastructure that builds blocks of interoperable information that allow unstructured data to be curated, modeled, accessed and rendered online.

Method: Our approach involved semantic modeling and integration of unstructured data available, rendering of integrated data, and access to statistical analysis tools to fit particular research questions using, e.g., survival or logistic regression analyses (see Figure 1). We leveraged data modeling concepts from caBIG's Cancer Common Ontological Representation Environment, defined relevant informatics requirements and how these requirements can be addressed to model the relevant cancer and HIV data of interest. We report here our work with cancer data from Grady Health System's Ponce de Leon Clinic and one specific AIDS-related malignancy, Hodgkin's Lymphoma.

Results: We develop secure Grid services to access the data and build a user interface that includes tools for statistical analysis. For the purposes of this study, we consider the factors that affect survival in cancers to include age, socioeconomic, race, gender, HIV status, performance score, stage of cancer at diagnosis, smoking status, alcohol use, co-morbidities and if HIV+ (e.g., CD4 counts at cancer diagnosis, duration of CD4 levels, ARV use or not, ARV interruption or not). We only look at the "final" outcome (either survival time or death status), i.e. one outcome per patient, but also included longitudinal CD4 and ARV data at each of the time points when CD4 and ARV were measured, men versus women, at 1 year, 2 years, 5 years survival.

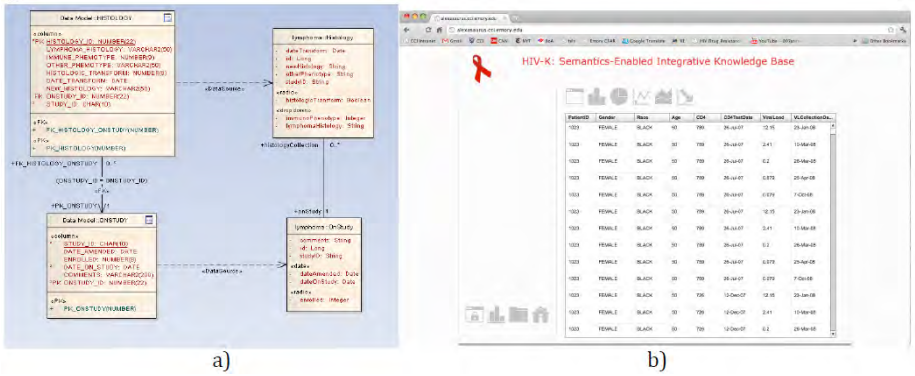

Figure 1. a) Relevant relationships between attributes are used to determine logical data constructs and their associations; b) Curated data is made accessible to a secure web interface and analysis tools.

Conclusion: We identified relevant data sources, created a process for modeling the data and logical models, implemented the infrastructure required to access the data based on caBIG standards, and prepared the groundwork for future work to characterize the relationship of multiple factors connecting HIV/AIDS and malignancies, in hope of identifying and characterizing relevant biomarkers contributing to this link.

Reference:

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7. Demographics and Survival of AIDS Cases With Cancer, Washington, DC, 1996-2006

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Background: Washington, DC (DC) has one of the highest HIV/AIDS rates in the U.S and cancer is the second leading cause of death among DC residents. This study sought to examine the demographic characteristics and survival of persons with AIDS defining cancers (ADCs) compared to those with non-AIDS defining cancers (NADCs) between the early HAART era (1996-2001) and the late HAART era (2002-2006) in DC.

Methods: Cases reported from 1996-2006 to the DC Cancer Registry and the AIDS Surveillance Registry were linked using a probabilistic matching algorithm. Cases were included if the cancer occurred from 4 months to 60 months post-AIDS diagnosis and were stratified into ADCs and NADCs for analyses. Cancer diagnoses were stratified into the early and late HAART eras to compare the availability of HAART on the distribution of cancer type. Kaplan-Meier survival analysis and adjusted Cox proportional hazards regression were used to assess survival time and risk of death by cancer type.

Results: From 1996-2006, among 8,800 AIDS cases, 300 (3.4%) cases had a cancer diagnosis. NADCs accounted for 51% of cancers and were significantly more likely to be diagnosed with AIDS ($p<0.0001$) and cancer ($p<0.0001$) at 40 years or older and had a significantly longer median time from AIDS to cancer diagnosis (2.46 vs. 1.75 years, $p=0.01$) compared to ADCs. The most common ADCs were Kaposi sarcoma (40%) and non-Hodgkin lymphoma (NHL) (44%); the most common NADC cases were lung (20%), Hodgkin lymphoma (8%) and anal (8%) cancer. ADCs accounted for 56% of cancer cases in the late-HAART as compared to the early-HAART period (45%). Mortality within the first year of cancer diagnosis was similar (ADC 41% vs. NADC 37%) and no statistical difference in survival time was observed. In the adjusted model, NHL and lung cases were significantly more likely to die as compared to other cancers (NHL HR=3.06; Lung HR=3.44).

Conclusions: In DC, despite high HIV/AIDS and cancer prevalence, only a small proportion of AIDS cases also develop cancer with ADCs and NADCs being equally common. HAART availability does not seem to have altered survival among ADCs and NADCs. Survival among NHL cases was relatively low reflecting the need for increased access to care among HIV+ persons. NADC cases are most likely developing cancers related to advancing age with higher proportions of lung cancers being observed. Public health efforts should focus on lung cancer prevention and continued monitoring of HIV-infected persons for cancers.

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8. Diagnosing Kaposi's Sarcoma (KS) in East Africa: How Accurate Are Clinicians and Pathologists?

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Background: HIV-associated KS is the most common reported malignancy in sub-Saharan Africa, and appropriate therapy of KS requires accurate diagnosis. In much of the region, however, KS diagnosis is limited to clinical suspicion without pathologic confirmation. Where pathology is available, specific anti-KSHV stains are rarely available and overall pathologic accuracy for KS has not been evaluated.

Methods: We introduced skin punch biopsy for KS at HIV/AIDS care clinics in Uganda and Kenya within the East Africa IeDEA Consortium. Clinicians suspecting KS could obtain a biopsy same day without charge. After interpretation by local African pathologists who only had access to routine H&E staining, biopsies were read by dermatopathologists at UCSF who could, at their discretion, recut and restain specimens or stain against latency-associated nuclear antigen (LANA) of KSHV. The interpretation by the U.S. dermatopathologists, who serve a large base of HIV-infected patients, was considered the gold standard.

Results: Clinicians at 26 HIV/AIDS clinics in Uganda and Kenya referred 739 patients with clinically suspected KS for skin biopsy. Overall, 77% (95% CI: 74%--80%) of these clinically suspected cases were determined pathologically to be KS after U.S. review; 19% had another diagnosis and 4% were indeterminate. There was no significant difference in the percentage found to be KS between countries (p=0.20) or over time (p=0.11). When KS was not found, a wide variety of other diagnoses, both clinically significant and insignificant, were made by the U.S. dermatopathologists (Table). Two different pathology services, one in Uganda one in Kenya, submitted biopsies for review by U.S. dermatopathologists. Overall concordance between African and U.S. interpretations was 71% (95% CI: 68%--74%). When the U.S. interpretation was considered gold standard, sensitivity of the African pathologic interpretation for KS was 72% and specificity 84%. Over time, sensitivity increased at one African center (p=0.04) but decreased in another (p<0.001); specificity increased at one center (p=0.001) and was unchanged in another (p=0.68).

Sample of pathologic diagnoses made by U.S. dermatopathologists when KS was not present

Scar (n=9)	Post-inflammatory pigmentation (9)	Psoriasis (8)	Lymphoma (5)
Wart (5)	Bacillary angiomatosis (4)	Morphea (4)	Sarcoidosis (2)
Polyarteritis nodosa (2)	Pyogenic granuloma (2)	Mycobacterial dermatitis (2)	Lichen planus (2)
Dermatofibroma (2)	Castleman's Disease (1)	Squamous cell carcinoma (1)	Deep fungal infection (1)
Secondary syphilis (1)	Erythema multiforme (1)	Eccrine poroma (1)	Xanthoma (1)

Conclusions: Amongst clinicians at HIV/AIDS clinics in East Africa, clinical suspicion of KS alone is not optimally specific for KS diagnosis. Clinical suspicion alone often either misdiagnoses conditions which are less concerning than KS or misses other serious conditions that require different therapy than KS. Assuming the U.S. interpretation is the gold standard, pathologic determination of KS in East Africa is specific but not optimally sensitive. The findings urge for increased availability of skin punch biopsies for KS diagnosis in Africa and augmentation of pathology services.

9. Poor Immune Status and Systemic Disease Are Independently Associated With Mortality in AIDS-Related Kaposi Sarcoma in Nigeria

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Background: AIDS-related Kaposi's sarcoma (AIDS-KS) is the most common AIDS-associated malignancy and remains a significant cause of morbidity and mortality in sub-Saharan Africa. We describe the determinants of mortality among patients with AIDS-KS in a comprehensive HIV care and treatment program in Jos, Nigeria.

Materials and Methods: We collected epidemiologic, clinical, staging and survival data for 357 patients with a diagnosis of AIDS-KS enrolling for HIV-care at the Jos University Teaching Hospital. Patients were staged according to the AIDS Clinical Trials Group (ACTG) criteria, which are based on the evaluation of tumor extension (T), CD4+ cell count (I), and patient's systemic status (S), stratified by good (0) versus poor (1) risk. Information on survival was obtained through an active follow-up on verification of vital status of the patients. Survival analysis was computed by the Kaplan-Meier method, and the log-rank test was used to test the difference between subgroups.

Results: During the period of the study (2004-2008), there were 197 women (55.2%) and 160 (44.8%) men with AIDS-related Kaposi Sarcoma. Their mean age was 37±8 years and the median follow-up was 15 months (1-49 months). The median CD4+ and viral load were 107cells/mm^3 and 58,561copies/ml respectively at baseline. Only 42 (11.8%) were on HAART at KS diagnosis, however all patients were commenced on HAART in line with existing national guidelines subsequently. 262(74.4%) had poor immune system status (I1: CD4+<200cells/mm^3), 77.5% had widespread tumor extension (T1) and 80.2% had systemic disease (S1). Poor immune system (I1) status (AOR 2.07, CI 1.25-3.42, p=0.002) and presence of systemic disease (S1) (AOR 2.10, CI 1.03-4.28, p=0.004) were independently associated with mortality.

Regarding ACTG classification, the 4-year survival rate was 67% for I0 vs 46% for I1 (p=0.05), 58% for S0 vs 49% for S1 (p=0.41), 60% for T0 vs 46% for T1 (p=0.19).

Conclusion: Poor immune status and systemic disease are independent predictors of mortality in patients with AIDS-KS in Nigeria.

10. Evaluation of the AIDS Clinical Trials Group Staging Criteria for Kaposi Sarcoma in a Resource Limited Setting

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Background: Kaposi sarcoma (KS) is commonly staged using by the AIDS Clinical Trials Group (ACTG) criteria. The three variables of the ACTG are dichotomized as good risk (0) and poor risk (1).Good risk immune status (I0) is defined as CD4 T-cell count ≥200cells/µl, and poor risk (I1) as CD4 < 200cells/µl. Although validated in the US and Europe, no evaluation has been done in resource-limited settings during the HAART era. We sought to determine whether the ACTG staging criteria is predictive of overall survival among Ugandan patients with HIV-associated KS.

Methods: Data were abstracted from medical records of adult patients with HIV-associated KS seen at the Uganda Cancer Institute (UCI) from 2000-2006.The primary outcome was 2-year overall survival. Vital status at 2 years was determined from the medical chart, or by contacting the patient or next of kin using the phone contact provided in the chart or ART clinic. Survival was modeled using Kaplan-Meier methods. Factors associated with survival were evaluated using Cox proportional hazards.

Results: The median survival time was 468 days (range 0, 5411). At 2 years following KS diagnosis, 165 (40.8%) of participants were alive and 166 (41.1%) had died, while 73(18.1%) were lost to follow-up. Factors associated with death before 2 years from KS diagnosis included T1 tumor stage, S1 stage, nodular lesion morphotype, and trunk edema (Table 1). Baseline CD4 count under 100 cells/µl was associated with decreased survival (HR 1.7, 95%CI 1.26-2.39 and p= 0.001), but ACTG immune status criteria (CD4 under 200 cells/µl) was not.

Table 1: Factors associated with death before 2 years from KS diagnosis

	Univariate			Multivariate		
FACTOR	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
T1 VS T0	4.13	2.18-7.81	<0.001	4.33	2.36-8.77	<0.001
I1 VS I0	1.25	0.64-2.44	0.52	……..	……	……..
S1VS S0	1.71	1.13-2.57	0.01	1.69	1.12-2.53	<0.01
Age (yrs)	0.98	0.96-1.00	0.05	0.98	0.96-1.00	0.01
Nodular KS morphotype	1.50	0.97-2.32	0.07	1.34	0.84-2.15	0.22
Trunk edema	2.91	1.53-5.53	<0.001	2.45	1.27-4.75	0.01
On HAART at diagnosis	0.75	0.54-1.02	0.07	0.62	0.45-0.87	0.01
Receipt of chemotherapy	0.46	0.33-0.65	<0.001	0.29	0.20-0.42	<0.001

* Multivariate analysis adjusted for T, S, age, nodular morphotype, trunk edema, HAART, and chemotherapy.

Conclusions: ACTG criteria Tumor extent (T) and Systemic symptoms (S) were associated with survival; Immune status (I) was not. Factors associated with decreased survival included: baseline CD4 counts <100, age, trunk edema, while receipt of HAART and chemotherapy were associated with increased survival. Studies are needed to validate ACTG staging criteria in sub-Saharan Africa and to identify additional prognostic factors.

References available upon request.

11. Factors Associated With Cancer Pathogenesis Among Patients Attending Oncology Clinic at Kamuzu Central Hospital in Malawi

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Introduction: Cancer is the cause of 13% of total worldwide mortality, and was the leading cause of in 2010 according to the World Health Organization. HIV prevalence in urban Malawi is approximately 20% and contributes to the pathogenesis of cancers, particularly AIDS-defining cancers. To evaluate risk factors for specific malignancies in Malawians, we designed an observational study to collect clinical data for cancer patients presenting at Kamuzu Central Hospital (KCH) in Lilongwe, Malawi.

Methods: This was an observational study enrolled patients with suspected or confirmed malignancies presenting to Kamuzu Central Hospital (KCH) in Lilongwe, Malawi. From June 2010 to July, 2011, patients underwent interviews and medical chart reviews to complete database questionnaires. The questionnaire data were entered into a Web-based database and extracted into Microsoft Excel. Descriptive statistics were performed.

Results: From June 2010 to July 2011 317 patients were enrolled into the study, 123 (39.3%) were male and 190 (60.7%) were female 4 had missing information. Age ranged from 18 to 86. 227 (70.9%) tested negative for HIV and 90 (28.3%) tested negative for HIV. 3 (.94%) had missing HIV test results. 38 (11.9%) had Kaposi's sarcoma, 12 (7.74%) had lymphoma, 71 (22.4%) had cervical cancer, 26 (8.2%) had breast cancer, 96 (30.2%) had esophageal cancer and the other cancers were smaller categories. 232 (76.32%) and 216 (71%) had never taken alcohol. Only 8.5% had family history of primary cancers. On past medical history, only 1.5% never had malaria, and 295 (93 %) reported to have past or present infection with malaria, TB, or schistosomiasis. Of note is that 89% of Kaposi's sarcoma patients had concurrent HIV infection. Excluding the patients with KS, only 56 of the total were HIV positive.

Conclusions: AIDS related malignancies are common in Malawi. However, HIV rates in traditionally non-AIDS related malignancies appear to match general population HIV prevalence rates.

12. Gender Differences in HIV-Infected and HIV-Uninfected Patients With Lung Cancer

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Clinical Background: Lung cancer (LC) is the leading cause of cancer-related death among people living with HIV (PLWH)(1). In the general population, adenocarcinoma is more common in women with LC, while squamous cell carcinoma (SqCC) is more common in men. Survival after lung cancer is worse among PLWHA. We explore potential gender-related difference in lung cancer in HIV+ and HIV- patients.

Methods: A retrospective review of the hospital cancer registry from 2000-2010 was performed. HIV status of identified lung cancer patients was assessed. Demographics, stage of cancer, and outcome were recorded for HIV+ and HIV- patients. Data were analyzed using SAS 9.1.

Results: Over the 10-year period, 1250 lung cancer cases were identified (75HIV+, 205 HIV-, and 970 unknown HIV status. There were 20 women (W+) and 55 men (M+) with HIV, and 85 women (W-) and 120 men (M-) who are HIV-. There were significantly more men tested for HIV at cancer diagnosis than women (p=0.0001). The distribution of lung cancer type is similar among the HIV+ and HIV-. Median age at cancer diagnosis is not significantly different with W+(50 years old), W-(55) , M+(55) and M-(58). Presentation at stage IIIB or IV occurred in 69%W+, 67% W, 68%M+ and 73%M-. There is no difference of median CD4 (W+=233, M+=159, p=0.1) or HAART use at cancer diagnosis among M+(53%) or W+(63%) , p=0.4. The median survival time for W+(386 days), M+(192 days), W-(475 day) and M-(247 days) . There is trend for longer survival for W+ versus M+ (log rank p=0.07), as well as W- versus M- (log rank p=0.06), but no difference for W+ vsW- (LR p=0.7) or M+ vs M- (LR p=0.8).

Conclusion: The experience in our hospital reveals that in the HAART era, there does not seem to be a difference in lung cancer presentation among HIV+ or HIV- patients, and that there is a trend for better survival among women compared to men.whether HIV+ or HIV-. Further studies are needed to explain this gender difference.

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13. HIV/AIDS-Related Non-Hodgkin's Lymphomas and Confounders: Preliminary Report of the Sub-Saharan Africa Lymphoma Consortium (SSALC)

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Background: SSALC was established to characterize HIV/AIDS-related lymphoma and the indigenous background of malignant lymphomas (ML) in sub-Saharan Africa. Because WHO classified lymphoma subgroups can vary in prevalence African, Asian or European ancestry, we surveyed lymphoma heterogeneity in geographically diverse East, South and West sub-Saharan populations, particularly for HIV/AIDS associated immunophenotypes.

Methods: A consortium of African pathologists, hematologist/oncologists and oncologic surgeons contributed ML cases and participated in sub-grouping according to WHO classification criteria after appropriate Institutional Review Board (IRB) approvals, Memoranda of Understanding and Material Transfer Agreements were obtained. Paraffin blocks were examined for tissue morphology (H&E), immunophenotype (34 antibodies IHC), EBER, *kappa* and *lambda* light chains (CISH) and c-myc and bcl2 translocations (FISH). HIV/AIDS diversity controls were contributed from Europe by consortium and USA by ACSR.

Results: Consortium members contributed 46 - 368 cases each with 1408 total cases to date: 246 diffuse large B-cell lymphoma (DLBCL), 296 Burkitt lymphoma, 163 Hodgkin disease, 69 plasma cell proliferative disorders and 644 others. Aggressive DLBCL, plasmacytoma/plasmablastic lymphoma, KSHV disease and lymphoid hyperplasia will be highlighted.

Conclusions: Sub-Saharan Africa has a variety of ML subgroups; true incidence altered by: 1) Aspiration vs. biopsy for diagnosis; 2) HIV status not communicated to pathologist; 3) known HIV/AIDS patients not biopsied; 4) initial diagnosis by morphology alone, 5) tissue preservation/processing variable.. General observations: HIV/AIDS-related lymphoma is more likely EBER+, has higher cell proliferation rates, and unfavorable immunophenotypes; regions differ in HIV clades with South (clade C) having the most "immunosuppression" associated lymphoma subgroups; East region has more pre-T lymphoblastic lymphomas and West region has more follicular lymphomas. Confounders: infectious lymphadenopathies (EBV+ lymphoproliferations), undifferentiated neuroblastomas, neuroectodermal tumors (PNETs), poorly differentiated, metastatic carcinomas and malignant melanoma (amelanotic).

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14. HIV-Associated Non-Hodgkin's Lymphoma - Experience From a Tertiary Referral Cancer Center

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Background: Infection with human immunodeficiency virus infection (HIV) is associated with an increased risk of Non Hodgkin's lymphoma (NHL). There is limited data on the treatment and outcome of these lymphomas in India. We describe a retrospective study of 277 HIV infected patients with NHL at a tertiary referral cancer center in Mumbai.

Materials and Methods: All patients included in this study were registered at the HIV cancer clinic of the hospital during 2001-2010. All patients were diagnosed to have NHL by tissue biopsy and were confirmed by immunohistochemical tests. Patients were staged with the Ann Arbor staging system. Data of their demographic profiles, immune status, NHL stage, treatment received, response and outcomes were analyzed. We used the gender and age-specific proportion of NHL of the year 2002 that was recorded in the Hospital Cancer Registry to estimate an expected number of NHL among HIV positive cancer patients during the period 2001-2010 (n=770) and the proportional incidence ratio (PIR) was calculated

Results: There were 277 patients during the ten year study period. In males the PIR for NHL was 12.6 (95% CI 1.2-14.6) and in females it was 22.1 (95%CI 17.1-28.3) .Among the 277 patients there were 69 females (24.9%) and 208 males (75.1%). The mean age of males was 38 years and median age was 38 years. In females the mean age was 36 years and the median age was 37 years.100 Patients (36.1%) were previously known to be HIV positive(range 6 mths-15 years).The CD4 count was less than 200 per cumm in 127/192 (66.14%) patients.76/277 (27.43%) had current or past history of tuberculosis. 172/277 (62%) patients had extranodal involvement.

168/277 (60.64%) received cancer directed treatment .The data of the 168 patients who received treatment was analyzed. 91/134 (67.91%) had CD4 counts less than 200. 115/168 (68.45%) received antiretroviral therapy. 60% had extranodal involvement.72 (42.9%) had DLCL, 42 (25%) plasmablastic, 21(12.5%) Burkitt's type and 31 (18.5%) others.90/168 (53.6%) had advanced disease at presentation. All patients were treated with chemotherapy. 54 patients also received RT. The response was evaluated in 96 patients. There was complete response in 46 (47.9%), partial in 15 (15.6%), stable in 6 (6.3%) and 29 (30.2%) patients had progressive disease. The median survival was 25.3 months (range 0-56 months). ART affected survival significantly; however age, sex, CD4 counts at presentation, histopathology, and presence of extranodal involvement and stage of disease did not affect the survival.

Conclusions: In our study the PIR for NHL was high in HIV-infected patients. The proportion of plasmablastic lymphomas is high. The use of antiretroviral therapy has impacted the overall survival.

15. Making the Case for Better Integration of Cervical Cancer Screening and Treatment for HIV-Infected Women Attending Care and Treatment Clinics in Dar es Salaam, Tanzania

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Background: HIV infected women are more likely to have persistent oncogenic human papillomavirus infections that lead to precancerous cervical lesions and cervical cancer [1-4]. Of the incident cases of cervical cancer in Africa, 40% occur in East Africa [5]. Tanzanian women bear the highest burden of cervical cancer in the region with age adjusted standardized incidence and mortality rates of 50.9 and 37.5 cases per 100,000 women [5]. Cervical cytology was performed to estimate the prevalence of squamous intraepithelial lesions (SIL) and determine patient follow up for treatment of histologically confirmed SIL.

Methods: Between December 2006 and August 2009, physicians in HIV care and treatment clinics in Dar es Salaam, Tanzania performed conventional PAP smears on 1440 women who voluntarily accepted a cervical screening. Slides were prepared and sent to the histopathology lab at the Muhimbili National Hospital, Dar es Salaam, for examination. Positive smears included the detection of low-grade SIL (LSIL) and high-grade SIL (HSIL). Negative smears were defined by the detection of atypical squamous cells of undetermined significance and normal results.

Results: A total of 1440 smears were examined, and 124 (8.61%) of women had SIL. On cytology, 72 (5%) had LSIL and 49 (3.4%) had HSIL. On histology, 889 (61.74%) of all women screened had cervicitis or inflammation. Of those who were positive for SIL, 95 (76.61%) had cervicitis or inflammation. None of the women were found to have invasive cancer. Of the 124 women with SIL, 5 (4%) presented for follow up and treatment at the national cancer center in Dar es Salaam. The remaining 119 women had to be tracked using a district tracking mechanism comprised of trained lay health workers.

Conclusion: The findings indicate a need for better integration of cervical cancer prevention for women attending HIV care and treatment clinics. Even in highly efficient HIV clinics with good health services, cervical screening programs based on cytology do not provide adequate screening coverage and timely access to treatment. *Single visit* models including immediate treatment with cryotherapy are more effective and context appropriate. However, innovative patient retention approaches will likely be necessary for treatment procedures that do not meet the criteria for cryotherapy and require follow up at the national cancer center. Implementation research will be needed to identify novel and sustainable approaches for comprehensive service delivery of cervical cancer screening and treatment in the context of HIV care and treatment clinics.

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References available on request.

16. Digital Cervicography and Cold Coagulation for Cervical Cancer Screening in Nigeria

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Background: Cervical cancer (CC) is most common cancer among women in Africa and in women living with HIV.[1, 2] Its prevalence has remained stable or increasing with introduction of HAART suggesting complex interactions with HIV.[3, 4] Current screening programs can substantially reduce all-cause mortality of CC but implementation in LMIC is hobbled by poor infrastructure, cost and lack of personnel. Nurse provider led, minimal visit, screen and treat programs offer an opportunity to reduce CC morbidity and mortality in LMIC.[5] In this study we evaluate the implementation of cervical cancer screen and treat programs at 2 HIV treatment and prevention sites in Nigeria

Materials and Methods: CC screening programs using nurse providers, VIA, off the shelf camera for digital cervicography, treatment of eligible lesions by cold coagulation and referral as required was implemented at 2 PEPFAR supported sites in Abuja, Central Nigeria. QA was provided by Gynecologist and based on weekly review of digital cervicographs and client recall as required.

Results: From July 2010 to July 2011, 2002 HIV+ women had been screened for CC at the 2 sites, but only data on 925 is reported in this abstract. Mean (SD) age was 35.2 (7.0) years; mean (sd) age at sexual debut was 19.0 (3.9) years; range, mean, sd of pregnancies was 0 – 16, 3.4, 2.5; range, mean, sd of pregnancies was 0 – 12, 1.6, 1.8; range, mean, sd of most recent cd4 count before screening was 11 – 1197, 466.7, 239.0; 6.8% were VIA positive; 0.2% had invasive CC and 0.2% were uncertain. Concordance between the clinical review and nursing diagnosis was 65% at the beginning of the program but reached 100% after 3 months.

Conclusions: This study showed nurse provider led CC screening and treatment program is a viable public health intervention among PLWHIV in Nigeria.

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17. HPV Monitoring in Kidney Transplanted Patients

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Background: Renal allograft recipients, as for HIV/AIDS patients, have a well-documented increased incidence of human papillomavirus (HPV)-related malignancies and preventive strategies should be specifically implemented. While in females the use of the Papanicolau test and HPV detection assay are used currently as a screening test for cervical cancer, no diagnostic procedures have been implemented to monitor HPV infection in males. The aim of this study was to test for HPV infection and to determine the spectrum of viral genotypes in urine samples of men with renal transplants.

Material and Methods: The study included 103 patients who underwent kidney transplantation between 1999 and 2008. HPV sequences were detected by nested PCR, using the broad-spectrum consensus- primer pairs MY09/MY11 and the new MGP system, and characterized by nucleotide sequence analysis.

Results: Overall, 49 (47.5%) samples were found positive for HPV sequences and the most common genotypes were HPV 16 (51.0%) and HPV 54 (10.2%) followed by HPV6, 53, 56, 58, 66, 11, 12, 20, 45, 62, and 71, in descending order of prevalence (Table 1). The majority of HPV 16 isolates were classified as European and only two as African-1 variant on the basis of nucleotide signature present within the MGP L1 region.

Conclusion: The high prevalence of HPV 16 among renal allograft recipients suggests that an HPV-16-based preventive or therapeutic vaccine may be effective for prevention or treatment of HPV-related neoplasia in this group of immune compromised patients.

Table 1. Prevalence of HPV Genotypes in Renal Transplant Patients

HPV genotype[a]	HPV positive, n (%)
HPV positive	49 (47.5)
HPV negative	54 (52.4)
Single infections	
16	25 (51.0)
56	2 (4.0)
58	1 (2.0)
54	5 (10.2)
6	2 (4.0)
11	1 (2.0)
12	1 (2.0)
20	1 (2.0)
53	1 (2.0)
62	1 (2.0)
66	1 (2.0)
71	1 (2.0)
Total single infections	42 (85.7)
Total multiple infections	4 (8.2)
Undetermined	3 (6.1)

[a]Gray shadow indicates HPV genotypes defined by IARC working group as class I carcinogens for humans [Bouvard et al., Lancet Oncol 10:321–322, 2009]

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18. Knowledge Attitude and Practice of Malignancies Among PLWHIV in Nigeria

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Background: HIV+ individuals are at increased risk of cancers.[1] Data suggest active surveillance and screening are required otherwise cancers in this population will present in advanced stages.[2] Early diagnosis depends on increased awareness. Previous studies noted low levels of awareness of cancers in LMIC and there is need to provide contextual, culturally appropriate health education.[3] We elucidate knowledge, practice and attitude (KAP) of PLWHIV in Nigeria to provide foundation for client education.

Materials and Methods: Random sample of HIV+ and HIV- persons in Nigeria, were consented, and asked to participate in FGD on AIDS Associated Malignancies. Each FGD consisted of 10 persons, managed by a researcher and a note-taker using a discussion guide. FGD was recorded, transcribed and analyzed.

Results: Most participants had heard about cancer and considered it a fatal disease, but they had poor knowledge of the causes. *None had heard of any of the common cancers that occur in PLWHIV.* When asked about specific cancer like Kaposi Sarcoma, Lymphoma and Cervical Cancer, only cervical cancer was mentioned and while they know that it occurs in female reproductive tract, they did not associate it with HIV.

Most respondents did not believe that it is possible to have HIV and cancer though some opined that it may be possible since both are caused by viruses.

Most respondents think that cancer is incurable or treatable by traditional means only.

Participants emphasized use of mass media, community engagement, pre-test counseling and confidentiality as issues that need to be attended to in order to have successful screening program.

Conclusions: This study showed low levels of awareness of cancer among PLWHIV

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19. Malignancies in AIDS Patients: The Experience of a Tertiary Hospital in a High Prevalence Zone

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Background: Both AIDS defining malignancies and non AIDS defining malignancies occurring in HIV infected persons are poorly documented in Nigeria. Our hospital is a reference centre located in one of the South –south states,which has a HIV sero prevalence of 8%[1{]http/www.unaids.org/en/dataanalysis/monitoringcountryprogress/2010progressreportsubmittedbycountries/nigeria_2010_country_progress_report},with a low antiretroviral coverage[1].

Materials and Methods: A five year retrospective study was carried out to review the frequency of diagnosis of three tumours classified as AIDS defining malignancies(Kaposi sarcoma,Non Hodgkin Lymphoma,Cervical cancer)and one non AIDS defining malignancy(squamous cell carcinoma of the conjunctiva),also commonly diagnosed in these patients. Records of the patients which are histologically confirmed and diagnosed between 1st January 2005 and 31st January 2009 were sorted out and their retroviral status classified.

Results: A total of 4123 histologically confirmed biopsies were received, 852 (21%) were cancers, 24 (2.8%) were Kaposi sarcoma (KS), 8 (33%) KS occurred in females, range 21-60 years (y), 16 (67%) in males, range 19-60 y and 17 (71%) of KS were AIDS associated, 6 (35%) females and 11 (65%) males. Thirty five 35 (4.1%) of cancers were Non Hodgkin lymphomas including Burkitt's lymphomas, 8 (23%) in females, range 6-60 y and males 27 (77%), range 6-71 y.Two 2 (5.7%) were AIDS associated 2 (100%) were males on long standing antiretroviral treatment. Cervical cancers accounted for 84 (9.9%) all cancers and 14 (17%) occurred in HIV positive patients age range. Conjunctival squamous cell carcinomas were 13 (1.5%) of all cancers, 6 (46%) females 7 (54%) males. Two 2 (15%) occurred in HIV positive patients.

Conclusion: AIDS associated malignancies appear to be very common in this environment and perhaps non AIDS associated malignancies may be on the increase. Under-reporting and lack of capacity may account for the fewer numbers reported in this environment.

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20. Pap Testing Among Newly Diagnosed Women Living with HIV/AIDS (WLWHA) in South Carolina (SC): Routine Screening and Abnormal Follow-Up Behaviors of HIV-Positive Female SC Medicaid Recipients 18-64 Years Between 2005-2009

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Background: Oncogenic human papillomavirus (HPV) infection is a main cause of cervical cancer. HIV-positive women are at an increased risk of becoming infected with high risk HPV (hrHPV) types that can lead to cervical cancer. Unlike other AIDS defining cancers, such as Kaposi's sarcoma and Hodgkin's lymphoma, the incidence of invasive cervical cancer among WLWHA has not decreased with the arrival of highly active antiretroviral therapies (HAART).[1-2] Annual Pap tests are recommended for WLWHA because the risk of developing cervical cancer, an AIDS defining illness, is increased in this group.[3] Early detection of abnormal, precancerous cells and following up on abnormal cytology results is essential to the prevention and control of cervical cancer among WLHWA.

Materials and Methods: Approval was obtained from USC and SCDHEC's institutional review boards (IRBs) to link the SC Medicaid and HIV/AIDS Reporting System (HARS) databases. A purposive sample of 1,183 HIV-positive females 18-64 years old who had an initial HIV-positive diagnosis, and were enrolled in the SC Medicaid database between January 1, 2005 and December 31, 2009 was obtained. Routine Pap testing and abnormal cytology follow-up behaviors are described. Frequencies and proportions are reported.

Results: Among our sample of WLWHA, 18% (216 of 1,183) had a Pap test during the same year of their initial HIV-positive diagnosis. Over the 5-year period, 45% (532 of 1,183) did not have a Pap test. An abnormal Pap test diagnosis was found in 21% (250 of 1,183) of our sample. Of the 250 WLWHA who had an abnormal Pap test diagnosis between 2005-2009, 42% (105 of 250) had a follow-up Pap test within one year. Only 34% (36 of 105) of those who had a follow-up Pap test within the past year did so within four months of the initial abnormal Pap test diagnosis.

Conclusions: Adherence to recommended cervical cancer screening guidelines among our sample of WLWHA was suboptimal. Our study's findings highlight failures across the cancer care continuum despite the increased prevalence, incidence, and persistence of hrHPV infection among WLWHA. These data are especially alarming given challenges with linking and retaining newly diagnosed WLWHA into HIV treatment care. Prevention and control efforts are needed to improve adherence to cervical cancer screening among this high risk group of WLWHA. This includes multi-level interventions that address system-level factors, as well as patient-provider communication. It is our recommendation that these prevention and control efforts target providers and WLWHA independently.

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21. Penile Cancers Without the AIDS Epidemic in Cameroon

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Background: Cancer of the penis is an uncommon malignancy in developed countries, But the incidence is as high as 17% of all male cancers in some undeveloped countries. The most important aetiologic factor is the presence of an intact foreskin but this is still unknown.

Cameroon is a blank area on the world cancer map because medical facilities necessary for recording cancer cases and the population data necessary for the calculation of rate are scarce or inexistent. Only 10% of malignant neoplasms are confirmed by histology.

Methods: We described the pathological aspects of 10 cases of penile cancers observed in Cameroon, a developing country of 20.000.000 inhabitants, within a period of twenty seven years (1984-2011). Human Immunodeficient Virus (HIV) serology test was done for nine patients of this series. Human Papilloma Virus (HPV) DNA detection and typing were carried out on paraffin-embedded specimens of our cases by Polymerase Chain Reaction.

Results: The patients aged 43 to 75 years and were circumcised. Four of the ten cases were diagnosed in 2004. HIV serology test done on 3 cases before 2004 were negative. After 2004, six patients were registered and out of these six, three came down with HIV-AIDS.

One patient has type II diabetes mellitus. All patients consulted late with metastatic disease. The pathological type was squamous cell carcinoma for nine patients while one other has a Diffuse large B cell lymphoma. HPV DNA was detected in six cases.

Conclusion: Ten cases of penile cancer were observed in Cameroon within the AIDS epidemic. These are cases which are confirmed by histology as only 10% of the patients with cancer can have histology performed. The aetiology is unclear. The HIV should be investigated as an etiologic factor.

22. Multicentric Castleman's Disease in HIV/AIDS Patients at an Urban HIV Clinic in Atlanta, Georgia, in the Combined Antiretroviral Therapy Era

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Background: Multicentric Castleman's disease (MCD), which has been associated with human herpesvirus-8 (HHV-8), is a lymphoproliferative disorder with an increased prevalence in HIV positive patients [1]. We describe our experience with MCD in a group of patients with HIV/AIDS in an urban HIV clinic.

Methods: Our clinic serves annually 5,000 patients diagnosed with AIDS. Patients with a diagnosis of multicentric Castleman's disease between 2006 and 2010 were identified from the pathology database at Grady Memorial Hospital or referrals to the clinic. Clinic charts and medical records were abstracted. Patients' demographics, CD4 counts, HIV viral load, HIV and MCD treatment and outcomes were recorded.

Results: Nine patients diagnosed with MCD were identified in our HIV/AIDS population. All patients were male and reported sex with men (MSM) as their risk for HIV infection. The mean age at MCD diagnosis was 39.22 ± 11.40; the mean CD4 cell count nadir was 68.33 ± 62.2 cells/mm^3. 85% (7/9) were on cART (combined antiretroviral therapy) at the time of MCD diagnosis with a mean CD4 count of 233.67±157.44 cells/mm^3. MCD was of the hyaline vascular variant in 3 patients, plasma cell variant in 2, transitional in 1 patient, and unspecified in 2 patients. Systemic symptoms were present in three patients. Five patients had both Kaposi sarcoma (KS) and MCD (2 with KS occurring after MCD diagnosis, 1 with KS before MCD, 2 with KS and MCD diagnosed simultaneously). Most of the patients were anemic with mean hemoglobin of 8.99±4.04 g/dL and hypoalbuminemic (2.31±0.96). 85% had anemia, hepatosplenomegaly, and low albumin at diagnosis. Treatment consisted of valgancyclovir, chemotherapy and/or rituximab. In the 5 patients who died, the mean time from MCD diagnosis was 425.2±447 days.

Conclusions: HIV-associated MCD is characterized by lymphadenopathy, splenomegaly, anemia and hypoalbuminemia. Among the diseases associated with HHV8 (KS, primary effusion lymphoma, and MCD), MCD appears to be the least affected by cART use or degree of immunosuppression [2]. In our cohort, 85% of patients had a CD4 count above 200 at MCD diagnosis.The survival with cART is still dismal, with one year survival of 50%. Larger multicenter study is needed to better understand the pathogenesis of HIV-associated MCD and its treatment.

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23. Prevalence of HIV in Medicare Beneficiaries With Lung Cancer

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Background: Human immunodeficiency virus (HIV) patients are at higher risk for lung cancer than the general population (1). The impact of HIV on the lung cancer population is unclear. In this study, we estimate the prevalence of HIV among Medicare beneficiaries diagnosed with lung cancer.

Material and Methods: This study used the SEER-Medicare database which links Medicare claims data with patients identified through cancer registries as part of the Surveillance Epidemiology and End Results (SEER) program. There were 250,500 patients who were diagnosed with malignant lung cancer between 1998 and 2007: 225,233 qualified for Medicare based on age and were 65 years or older at diagnosis and 25,267 qualified for Medicare based on disability and were less than 65 years old at diagnosis. Demographic information was taken at the time of the initial lung cancer diagnosis. Patients were classified as prevalent HIV cases if their first Medicare claim with a diagnosis of HIV preceded the diagnosis of lung cancer or occurred within one year after lung cancer was diagnosed. Relative risk (RR) was used to assess risk factors.

Results: The prevalence of HIV in lung cancer cases was 180.6 (95% CI: 163.8 to 199.0) and 1,646.0 (95% CI: 1,495.1 to 1,812.3) per 100,000 among elderly and disabled beneficiaries, respectively. It doubled from 1998 to 2007 for elderly beneficiaries and increased by 35% for disabled beneficiaries. Risk factors for HIV were male gender, non-white race, never having been married, and residence in a metropolitan area (Table 1).

Elderly HIV and non-HIV patients were comparable with respect to stage of lung cancer at diagnosis, but HIV-infected disabled beneficiaries were more likely to present with distant metastases than their non-HIV counterparts.

Table 1.

	Elderly Beneficiaries RR	Disabled Beneficiaries RR
Male vs. Female	1.9*	3.5*
African-American vs. White	6.4*	3.1*
Other race vs. White	2.0*	0.7
Never married vs. Other (Men)	4.8*	7.3*
Never married vs. Other (Women)	2.2*	4.6*
Big Metro vs Other	5.5*	5.2*
Metro vs. Other	2.9*	2.9*

*RR significantly > 1.0

Conclusions: The prevalence of HIV among elderly Medicare beneficiaries with lung cancer was 2.6 higher than in the general population 65 years and older (2). For disabled beneficiaries, the prevalence of HIV among lung cancer cases was higher than for those without lung cancer (3). The increasing prevalence of HIV in lung cancer cases may result in a commensurate increase in demand for health care services for Medicare beneficiaries.

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24. R-CHOP Versus CHOP in HIV-Associated Lymphoma: A Meta-Analysis of Prospective Studies

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Introduction: Several recent trials have demonstrated superiority with the addition of rituximab to traditional chemotherapeutic regimens in HIV-negative non-Hodgkin lymphoma (NHL) patients. In HIV-positive patients, the benefit of adding rituximab is less clear. In a randomized controlled trial, the addition of rituximab to CHOP showed no survival advantage. We performed a study-level meta-analysis of prospective studies to ascertain outcomes in HIV+ NHL patients treated with CHOP vs. R-CHOP.

Methods: We performed a Pubmed/MEDLINE literature search from January 1990 through June 2011, with search terms "(HIV OR AIDS) AND lymphoma AND rituximab" and limited our results to English language prospective trials with either CHOP or R-CHOP in HIV+ NHL. Characteristics and outcomes were collected from published data. Chi-square was used to compare the characteristics between groups. The main outcomes were overall response rate (ORR), complete response (CR) rate and 2-year overall survival (OS) and will be reported as odds ratio (OR).

Results: We identified 3 studies on HIV+ NHL patients treated with R-CHOP and 9 with CHOP from a total of 119 publications. Nine studies (75%) administered *Pneumocytis jirovecci* pneumonia prophylaxis. Four studies (33%) administered prophylactic intrathecal chemotherapy, and in 3 (25%) it was optional. Four studies (33%) administered G-CSF routinely, and 3 studies (25%) only if grade 3/4 neutropenia occurred. A total of 810 patients were studied, 569 treated with CHOP and 241 with R-CHOP. The median age was 38 and 43 years for CHOP and R-CHOP, respectively, with 86% and 85% of male patients, respectively (p=0.98). With regard to HAART, 68% of patients treated with CHOP and 92% with R-CHOP were on HAART prior to lymphoma diagnosis (p<0.0001). The median CD4 count was 109 and 136 cells/mm^3 in CHOP and R-CHOP patients, respectively. Clinically, 65% and 54% of CHOP patients presented with advanced stage and age-adjusted International Prognostic Index (aaIPI) score 2-3, while the proportion was 74% and 45% in R-CHOP, respectively (p=0.02 for stage and p=0.03 for aaIPI scores). The OR for ORR, CR and 2-year OS in patients treated with R-CHOP vs. CHOP was 1.05 (95% CI 0.71-1.55; p=0.81), 1.42 (95% CI 1.04-1.93; p=0.03) and 2.37 (95% CI 1.73-3.25; p<0.0001), respectively

Conclusions: HIV+ NHL patients treated with R-CHOP had higher odds for CR and 2-year OS (42% and 137%, respectively) when compared to CHOP. However, patients treated with R-CHOP also had higher rates of HAART administration, higher CD4 counts and lower aaIPI scores.

25. Sarcomas Other Than Kaposi's Sarcoma in Immunodeficiency

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Background: Individuals with acquired immunodeficiency are at heightened risk for multiple subtypes of cancer. Among sarcomas, increased risk in both adults and children has been identified only for Kaposi's sarcoma (KS), and in HIV-infected children for leiomyosarcoma. In contrast, broader diversity in subtypes of lymphomas and carcinomas has been reported. Sarcomas constitute <1% of all incident cancers in the general population. Modest increases in risk of rare sarcoma categories in the immunocompromised may thus be difficult to capture. We therefore reviewed published data from case reports/series to describe sarcoma subtypes in HIV-infected individuals and solid organ transplant recipients.

Methods: Literature review of sarcoma case reports in people with HIV and recipients of organ transplants were conducted using PubMed and citation searches. Surveillance Epidemiology and End Results (SEER) data (1974-2008) were queried to obtain counts of each type of sarcoma, and the age distribution of leiomyosarcomas.

Results: A total of 152 cases of sarcomas (other than KS) were identified in people with HIV/AIDS (n=62) and in recipients of solid organ transplants (n=90). Leiomyosarcomas represented the bulk of all sarcomas (98/152), followed by angiosarcoma (16/152) and fibrohistiocytic tumors (15/152). Compared to the distribution of sarcomas in SEER, leiomyosarcoma was overrepresented by 4-fold (16.9% in SEER; 64.4% in immunodeficiency). Ages of HIV-related leiomyosarcoma cases suggested a bimodal distribution with an early peak among 0-9 year olds (36%) and later among 30-39 year olds (34%). More than 80% of immunodeficiency-related leiomyosarcomas were Epstein-Barr virus (EBV)-positive. Most HIV-related leiomyosarcomas (>93%) were in people with AIDS diagnoses and the majority of transplant-related leiomyosarcomas (>62%) were reported in renal transplant recipients. Leiomyomas were also reported in people with immunodeficiency (n=37), and >65% of leiomyomas and leiomyosarcomas reported in people with HIV infection occurred with CD4 counts of <50 cells/mm^3. All 14 cases of transplant-related angiosaromas were in renal transplants. Ninety three percent (13) occurred in males. Half of transplant-related angiosarcomas occurred at the site of an arteriovenous fistula.

Conclusions: EBV-positive smooth muscle tumors are frequently reported in people with immunosupression. Both children and adults are at risk for leiomyosarcomas. Leiomyomas and leiomyosarcomas occurred with the same propensity in people with CD4 counts below 50. Angiosarcomas occurred specifically in males in renal transplant recipients and may be related to an arteriovenous fistula.

26. The AIDS Malignancy Clinical Trials Consortium (AMC) Patient Navigator (PN) Initiative

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Clinical Background: Cancer remains a major health concern in the management of HIV infection in areas of the world with and without access to highly active antiretroviral therapy. In the USA alone, approximately 56,000 people were newly diagnosed with HIV infection in 2006; 53% of these new diagnosis occurred in gay and bisexual men but Black/African American men (45%) ,women (27%) , and Hispanics (17%) were also strongly affected [1]. Recruitment of members of these groups into cancer clinical trials has traditionally been challenging [2]. Among domestic AMC studies, a relatively small percentage of all participants have included women (8%), African-Americans (29%), and Hispanics (21%). Patient Navigation has been identified as an effective strategy to reduce barriers to care as well as to increase access to cancer clinical trials [3]. In an effort to bolster opportunities for HIV-infected minorities, women, and medically underserved populations to become involved in AMC clinical trials, a PN initiative was implemented in seven AMC sites located in Boston, Los Angeles, San Diego, Houston, Columbus, and Honolulu. The main objectives of the PN initiative were to provide greater opportunity for minority groups and women to participate in AMC-sponsored cancer trials and to increase awareness of HIV/AIDS malignancies in the local communities where the PNs worked. From January 2010 to April 2011, PNs implemented multi-strategy activities to increase the enrollment of women and minorities in AMC trials. PNs reported 466 activities in the programmatic areas of recruitment and retention, community outreach and education and awareness. Recruitment and retention refers activities to recruit new participants and increase retention in AMC trials. Community outreach was targeted to the medical community or the general population to increase their awareness of AIDS-related malignancies. Education and awareness were activities to educate the community on HIV-related malignancies in general and AMC-sponsored clinical trials in specific. PNs efforts were concentrated on community outreach (54%, n=251), followed by recruitment and retention (28%, n=129) and education and awareness 18% (n=86).

Conclusion: AMC-PNs conducted activities that raised awareness in their local communities of AIDS-related malignancies, developed partnerships with local health community organizations and identified areas where further communication was needed. PNs took the lead in developing a PN brochure and in the design of several tailored recruitment strategies. The PN program is making important inroads into behavioral interventions to increase participation of minorities and underserved populations in AMC trials.

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27. Ultraviolet Radiation Exposure and HIV-Associated Non-Hodgkin Lymphoma Risk

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Introduction: Although the role of sun exposure to risk of non-Hodgkin lymphoma (NHL) has been controversial, recent studies have suggested a protective effect rather than a promotive effect. The impact of HIV infection on this relationship is unknown, thus we sought to explore the association between sun exposure and sun sensitivity and NHL in the setting of HIV.

Methods: The study population consisted of a subset of the Multicenter AIDS Cohort Study; 573 HIV+ men who responded to a special ultraviolet radiation exposure questionnaire administered between October 1993 and April 1994, including 33 men who were subsequently diagnosed with pathologically confirmed NHL. The questionnaire elicited information on skin color, natural hair color, eye color, sunburn tendency, average daily sun exposure, occupational sun exposure, recreational sun seeking behaviors, vacationing in sunny locations, sun screen usage, and use of sun lamps or light therapy. Cox proportional hazards regression models were used to obtain hazard ratios (HR) and 95% confidence intervals (CIs) for the association between exposures of interest and NHL risk. HIV positive participants entered the analysis on the date of their UVE questionnaire and were followed until an NHL diagnosis, death, or loss to follow-up. Models were adjusted for race, MACS study site, and CD4+ T cell count.

Results: Men who reported a high frequency of going to the beach or pool on summer weekends over the last five years had a significantly reduced risk of NHL: HR=0.31 (95% CI =0.15-0.86) for ≥5 times versus never, and HR=0.45 (95% CI=0.20-1.0) for 1-4 times versus never. Compared to men who have rarely taken a beach vacation in the last five years, men who occasionally have were at a significantly reduced risk of NHL (HR = 0.36, 95% CI=0.15-0.86). With respect to sunburn tendency, men who never blister were at reduced risk of NHL compared to men who occasionally blister, although this did not reach statistical significance (HR=0.45, 95% CI=0.19-1.06). Men with green or hazel eyes were at reduced risk of NHL compared to men with blue eyes, although this did not reach statistical significance (HR=0.38, 95% CI= 0.14-1.05).

Conclusions: Consistent with the NHL literature on HIV uninfected populations, we found that a high level of recreational sun exposure and a low level of sun sensitivity are associated with a decreased risk of NHL in the setting of HIV. Studies are currently underway to elucidate possible mechanisms for these associations, including a possible role of vitamin D.

28. Hodgkin's Lymphoma Characteristics in HIV-Infected and Uninfected Patients at an Urban Hospital in the Late Combined Antiretroviral Era

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Background: As combined antiretroviral therapy has allowed patients infected with HIV to survive longer due to improved immunity, increasing incidences of non-AIDS associated malignancies as well as chronic comorbidities are reported. One of the more commonly reported non-AIDS associated cancers is Hodgkin's lymphoma (HL)(1). We report our experience of HL among HIV-infected and uninfected patients.

Methods: Grady Health System (GHS) provides care to the majority of the urban indigent population of Atlanta. Patients who were diagnosed with HL between January 2000 and June 2011were identified from the GHS pathology records and the GHS cancer registry. Clinic charts and medical records were reviewed. Patients' demographics, CD4 counts, HIV viral load, HIV and HL treatment and outcomes were recorded.

Results: During the study period, 95 patients were diagnosed with HL (26% HIV-, 30% HIV+ and 43% HIV status unknown). The characteristics are displayed in Table 1.

Table1. Characteristics of HL in HIV- and HIV + patients

	HIV-	HIV+
N	25	29
M:F	16:9	22:7
Race (Black :other)	20:5	25:4
Median age (range)	33(19-52)	40(22-54)
Stage (I-II versus III-IV)	5:9	2:19
B symptoms	4	5
Diagnosis made solely by bone marrow biopsy	0	3
Morphology NS/LR versus MC/LD	12:5	9:2
One year survival	76%	45%

Among the HIV+ patients, at time of HL diagnosis, the median Cd4 at time of HL diagnosis was 95(8-865)cells/mm^3, and 3 (10%) are on cART .The median time from HIV diagnosis to HL diagnosis is 2 years (0-20).

Conclusions: In the current cART era, in our institution, HL in HIV+ patients is more likely to present with advanced disease (65% with stage III/IV). Interestingly, in 3 HIV+ patients, HL was diagnosed solely by bone marrow biopsy. Despite the availability of cART, patients are not accessing care. This may account for the poor one-year survival among HIV+ patients with HL.

Acknowledgement: This work was facilitated by the Center for AIDS Research at Emory University (P30 AI050409).

Reference:

1. Spina M, Carbone A, Gloghini A, Serraino D, Berretta M, Tirelli U. Hodgkin's Disease in Patients with HIV Infection. Adv Hematol. 2011;2011. pii: 402682. Epub 2010 Sep 23.

Poster Abstracts – Day 2

29. A Core Laboratory for the Generation of Quality-Controlled g-Herpesvirus Bacmids: Generation of KSHV MicroRNA Mutants

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Kaposi's sarcoma-associated herpesvirus (KSHV) encodes 12 viral microRNAs that are expressed during latency. Research into the function of these microRNAs has suffered from the lack of an experimental system that allows for the systematic removal of individual microRNAs. Here we have used the *E. coli* Red recombination system in conjunction with a new bacmid background, 219BAC, generated in the Jung Lab to create mutants for every known KSHV microRNA. The specific microRNA deletions or mutations and the integrity of the viruses has been strictly quality controlled using PCR, restriction digestion and sequencing based assays. In addition, stable viral producer cell lines for wildtype, ΔmiR-K12-1, ΔmiR-K12-3, and ΔmiR-K12-11 have been created in iSLK cells generously provided by Don Ganem. Deep sequencing was employed to sequence verify all of the current producer cell line mutants and a qPCR assay was used to verify the expression of the remaining viral microRNAs. Creation of producer cell lines for all of the microRNA mutants is ongoing and these viruses will be made available to the research community for further study.

This project was funded by ARRA RC2CA148407 to RR.

30. A Regulatory Circuit Between Kaposi Sarcoma-Associated Herpesvirus and Host Innate Immune System

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Kaposi sarcoma-associated herpesvirus (KSHV) is a human γ-herpesvirus associated with several human malignancies. The replication and transcription activator (RTA) is necessary and sufficient for the switch from KSHV latency to lytic replication. Toll-interleukin-1 receptor (TIR) domain-containing adaptor-inducing β-interferon (TRIF, also called TIR-domain-containing adaptor molecule-1 (TICAM-1)) is a signaling adaptor molecule that is critically involved in the Toll-like receptor 3 (TLR-3) and TLR-4 signaling pathways for type I interferon (IFN) production, a key component of innate immunity against microbial infection. Previously we have identified that RTA blocks TLR3 signaling activation by degrading cellular TRIF, and this RTA-mediated degradation is at least partially mediated through the ubiquitin-proteasome pathway. In this report, we have identified a new mechanism that innate immunity regulates KSHV replication. We find that TRIF increases the expression of KSHV RTA. The enhancement of RTA expression and the degradation of TRIF are two independent pathways. TRIF specifically enhances the translation efficiency of RTA mRNA. Because RTA may not directly interact with TRIF, the functional interactions between TRIF and RTA may be indirect through unknown mediators.Taken together, these data suggest that KSHV employs a novel mechanism to block the innate immunity by degrading TRIF protein, and at the same time, use the innate immune system to boost viral replication by increasing the expression of KSHV RTA. This regulatory circuit may be an important part of the KSHV-host interactions for the initial infections. This work may contribute to our understandings on how KSHV interacts with the host immune system for its survival in vivo.

31. CpG Methylation as a Tool to Characterize Cell-Free Epstein-Barr Virus DNA

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Background: In order to differentiate Epstein-Barr virus (EBV) virion DNA versus viral DNA released from tumor cells, we have taken advantage of the observation that viral episomal genomes of herpesviruses are methylated in latently infected cells whereas un-methylated genomes are synthesized and packaged into virions during the lytic phase. We used paramagnetic beads linked to methylCpG binding protein to separate virion and cell-derived viral DNA.

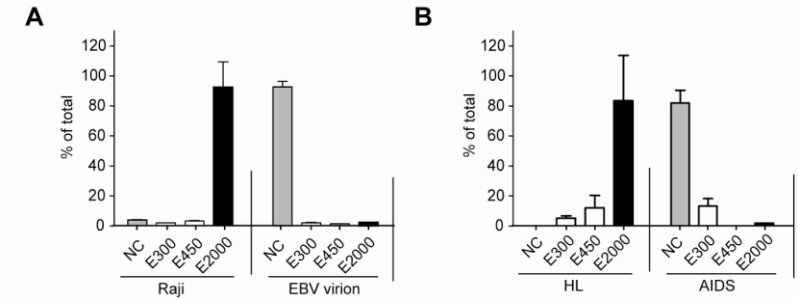

Figure 1: (A) DNA isolated from purified EBV virions or from latently infected Raji cells were subjected to binding to paramagnetic beads linked to methylCpG binding protein. DNA isolated from the non-captured fraction (NC), washes (300mM and 400mM) and the elution (2000mM) was subjected to real-time PCR with primers that amplify a region in EBV BamW. (B) DNA isolated from the plasma of an AIDS patient and the plasma of a patient with EBV(+) Hodgkin lymphoma was subjected to binding to paramagnetic beads linked to methylCpG binding protein. DNA isolated from the different fractions was amplified as in B.

DNA isolated from EBV (Figure 1A) virions failed to bind to the methylCpG binding protein and were detected only in the non-captured (NC) fractions, while DNA isolated from latently infected cell lines were detected predominantly in the bound fractions (E2000, high salt elute). Unmethylated EBV DNA, presumably virion DNA, was detected in the plasma of 3 AIDS patients without lymphoma, while methylated DNA was detected in the blood of 3 patients with EBV-associated Hodgkin lymphoma (HL) (without HIV infection) (Figure 1B).

Conclusions: Tumor derived viral DNA can be distinguished from virion associated viral DNA based on preferential binding to methylCpG binding protein. Tumor derived viral DNA was predominantly present in the blood from patients with Hodgkin-Lymphoma, but not in patients without EBV associated malignancy. This technique may be applied to detect tumor derived viral DNA in the blood of patients with EBV associated malignancies.

32. Delayed Cell Death in Epstein-Barr Virus-Transformed B Cells Undergoing Lytic Reactivation

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Periodic reactivation of the tumorigenic herpesvirus Epstein-Barr virus (EBV) from latency results in the release of progeny virus. This lytic reactivation is important in the pathogenesis of EBV-mediated diseases such as lymphomas and lymphoproliferative diseases that arise during immunocompromise. Detection of lytic viral DNA and proteins is an important component of host innate and adaptive defense mechanisms. While on the one hand, attempts are made to stall production of infectious virus and pro-apoptotic signals are delivered within the infected cell, EBV is able to stave off apoptotic death of the host cell by expressing anti-apoptotic viral genes and inducing expression of anti-apoptotic and pro-survival cellular genes. Delay of host cell death allows for replication and release of progeny virus. The mechanisms contributing towards such delayed cell death in lytically infected cells has received little attention. Here we report studies of cell stress and activation of cell death pathways in EBV-transformed lymphoblastoid cell lines (LCL) undergoing spontaneous lytic reactivation. LCLs closely resemble the tumor cells of post-transplant lymphoproliferative disease. Propidium iodide staining of unfixed cells revealed that plasma membrane integrity began to deteriorate when infected cells expressed the early lytic protein EA-D and worsened in cells expressing the late protein gp350. LCL expressing surface gp350 had condensed nuclei consistent with cells undergoing the nuclear reactions of apoptosis. Notably, many of these intact cells appeared to have fractional nuclei when examined by immunofluorescence. Flow cytometry-based examination of DNA content confirmed that while all cells expressing EA-D contained 2N to 4N DNA, approximately 25% of live, gp350-positive late lytic cells contained less than 2N DNA. To precisely define the kinetics of cell death in relation to lytic reactivation, we developed additional methods to identify discrete sub-populations of lytic cells in different stages of the lytic life cycle by co-staining for EA-D and gp350. Simultaneous staining with Annexin V revealed a progressive increase in the fraction of Annexin V-positive lytic cells in early, intermediate lytic, and late lytic stage cells. Together, these results indicate that signs of cell stress are demonstrable upon lytic reactivation and worsen as lytic replication proceeds. Further studies in our laboratory are aimed at characterizing the cell death pathways activated by lytic replication of EBV and delineating viral mechanisms that are necessary to delay host cell death.

33. Development of Multiplex Serological Assays to Detect Oncoviral Infections

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Serological markers of infection (antibodies or antigens) of viruses that cause cancer are most often detected using ELISA-based methodologies. In many cases, multiple markers of infection must be assessed to determine a final sero-status. Volume requirements and costs of reagents for single analyte ELISAs are high and studies which include multiple viruses can require milliliters of plasma, often not available from archived cohorts. Thus, we sought to develop a Luminex® bead-based customizable panel initially including Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Epstein-Barr Virus (EBV) and often the concomitant infection, Human Immunodeficiency Virus (HIV) to reduce sample volume requirements, overall cost and increase flexibility. Peptides, antigens and antibodies were sourced from multiple manufacturers and tested for suitability in this platform. Where necessary, suitable reagents were designed and produced in-house. The HCV assay multiplexes four HCV peptides designed to detect antibodies raised to HCV Core (2), HCV NS4, HCV NS5 gene regions. The HBV assay multiplexes a HBV early antigen peptide, a recombinant HBV core protein and either a recombinant HBV surface antigen or an antibody specific for HBV surface antigen to assess HBV infection. The EBV assay multiplexes peptides specific to viral capsid antigen, EBNA-1 and early antigen (Cyto-Barr, Zuidhorn, The Netherlands). HIV-1 assay development is ongoing and the list of antigens to be included in the assay has not been finalized. These assays can be run singly or with any combination (multi-plex) of the above listed targets. Each target has been independently validated using samples of known molecular and serological status to determine specificity (false positive versus false negative) and re-evaluated under multiplex conditions to confirm assay performance. In addition, where possible, samples were assayed on commercial testing platforms as well as our multiplex assay to assess concordance (94-99%). Dependent on the panel selected and the expected antibody titers in a particular population, plasma or serum volumes in the range of 10 µL to 125 µL per subject would be required to determine the HBV, HCV, EBV and/or HIV serostatus of a subject. This assay platform is inherently flexible and the benefits include amenability to expansion to include other oncogenic viruses as well as screening large epidemiological cohorts or smaller subsets of samples in an economical and high throughput manner.

34. Epstein-Barr Virus Induces Adhesion Molecule CD226 (DNAM-1) Expression During Primary B Cell Transformation Into Lymphoblastoid Cell Lines

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Epstein-Barr virus (EBV), an oncogenic herpesvirus associated with Burkitt's lymphoma and other AIDS-related B cell malignancies, transforms primary human B cells into lymphoblastoid cell lines (LCLs) *ex vivo*. As LCLs express viral gene products similar to those found in EBV-mediated cancers, LCLs provide a practical model for tumorigenesis. Previous unpublished findings from our lab indicate that LCLs constitutively express the adhesion molecule CD226 (DNAM-1), found on virtually all peripheral blood NK cells, T cells, and monocytes, but only a small subset (~3%) of B cells. Although CD226 is known to mediate T-cell differentiation and cytotoxicity, NK cell cytotoxicity, NKT cell apoptosis, and monocyte extravasion, CD226 function in B cells remains relatively unstudied. Biochemically, CD226 functions to support the interaction between the intracellular adhesion molecules LFA-1 and ICAM-1. Here, we demonstrate that EBV specifically induces CD226 expression in primary human B cells and EBV-negative B lymphoblasts during viral-mediated proliferation and outgrowth. EBV infection of primary B cells increased CD226 surface expression 5-fold during early proliferation and approximately 30-fold upon transformation into LCLs. EBV-converted Burkitt's lymphoma cells constitutively express CD226, while EBV-negative B cell lymphomas do not. Additionally, we demonstrate that LMP-1, an EBV latency III membrane oncoprotein, induces CD226 expression in EBV-negative Burkitt's lymphoma cells. Finally, we demonstrate that the NFκB pathway regulates CD226 expression. Indeed, B cell lymphomas with high NFκB activity (activated B cell-like diffuse large B-cell lymphomas) express CD226 at higher levels than B cell lymphomas with low NFκB activity (germinal center B cell-like diffuse large B cell lymphomas). As CD226 supports the interaction between LFA-1 and ICAM-1, which is critical to maintain the constitutive aggregation of EBV-transformed B cells, we propose that EBV-mediated induction of CD226 drives cell-cell contact ensuring B cell survival. These data suggest that CD226, a newly identified EBV-induced cell adhesion molecule, may play a key role in the pathogenesis of AIDS-associated and other B cell lymphomas.

35. Epstein-Barr Virus Lytic Gene Expression Is Tightly Linked to ER Stress but not Cytotoxicity With Bortezomib or Nelfinavir

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Epstein-Barr virus (EBV) is associated with AIDS-related lymphomas and other malignancies. We have previously shown that the proteasome inhibitor bortezomib is an activator of EBV lytic gene expression and that these effects are mediated by ER stress and the unfolded protein response (UPR) [1]. We investigated the relationship between the induction of UPR and EBV lytic gene expression with a variety of UPR inducers, as well as the association of their viral and antitumor effects in a variety of tumor cell lines. Bortezomib, thapsigargin, and tunicamycin activate the UPR and EBV lytic cycle. Recently, nelfinavir has also been reported to lead to ER-stress and the UPR. We found a dose-dependent relationship with bortezomib and with nelfinavir for the induction of the UPR markers (Bip, ATF4, XBP1s, and CHOP10), EBV lytic gene expression (measured as ZTA RNA), and cell toxicity in Burkitt's lymphoma cell lines.. Blocking ER stress and UPR activation, by cycloheximide (CHX) treatment or by Bip knockdown, diminished ZTA induction but had no effect on cellular toxicity. We also studied EBV lymphoblastoid cell lines (LCLs). In contrast to the BL cell lines, bortezomib did not induce ER stress, activate the UPR or lead to EBV lytic gene expression but was nonetheless toxic to LCLs. These results indicate that bortezomib and nelfinavir both induce ER stress and UPR leading to EBV lytic reactivation in BL cells. UPR induction corresponds with EBV lytic gene induction but appears to be distinct from cellular toxicity. Our findings suggest that ER stress, UPR and viral activation are closely linked but may be separable from the cytotoxic effects of some pharmacologic inducers. Bortezomib and nelfinavir may serve as laboratory and clinical tools for manipulating viral gene expression in EBV associated malignancies.

Reference:

1. Shirley CM, Chen J, Shamay M, Li H, Zahnow CA, Hayward SD, Ambinder RF. Bortezomib induction of C/EBP mediates Epstein-Barr virus lytic activation in Burkitt lymphoma. Blood 2011, 117(23): 6297-6303

36. ER Stress Activates Lytic Gene Expression in KSHV-Associated Tumor Cell Lines

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Background: Activating the herpesvirus lytic replication cycle presents an opportunity for targeted therapy. We explored the effects of endoplasmic reticulum (ER) stress inducers on Kaposi's sarcoma herpesvirus (KSHV) lytic activation in primary effusion lymphoma (PEL) cell lines. We included nelfinavir (an HIV-1 protease inhibitor) in our investigations because it has been reported to induce ER stress in various tumor cell lines [1]. Treatment with bortezomib, thapsigargin or nelfinavir resulted in increased expression of ER stress markers such as activating transcription factor 4 (ATF-4) and the spliced form of X-box binding protein 1 (XBP-1(s) (see figure 1). Treatment was also associated with an increase in RNA expression of the KSHV immediate early "replication and transcriptional activator" (RTA) (see figure 2). To determine whether ER stress mediated KSHV lytic reactivation associated with these agents, we prepared doxycycline-activated short hairpin RNA knockdowns of ER stress genes (Grp78 and XBP-1(s)). Treatment of these knockdowns with doxycycline for 72 hours resulted in inhibition of ER stress and inhibition of viral lytic gene expression.

Conclusion: These results demonstrate that in KSHV-infected cell lines, induction of ER stress is associated with activation of KSHV lytic genes and raises the possibility that nelfinavir might be incorporated into future treatment strategies for KSHV-associated malignancies.

Figure 1

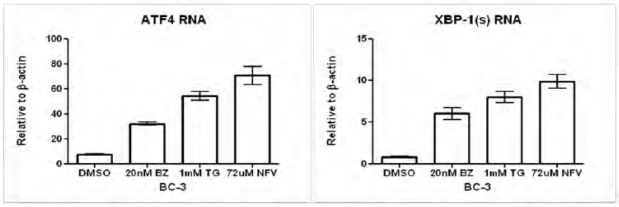

Figure 1: Treatment of BC-3 cells leads to induction of ER stress markers. KSHV⁻ PEL cells (BC-3) were treated with DMSO, 20nM bortezomib (20nm BZ), 1mM thapsigargin (1mM TG) or 72uM nelfinavir (72uM NFV). RNA was isolated and RT-PCR was performed using primers for ATF-4 and XBP-1(s). Primers for β-actin were used as an internal control. Error bars indicate SEM.

Figure 2

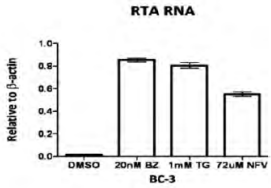

Figure 2: ER stress inducers activate KSHV lytic gene expression. KSHV⁻ BC-3 cells were treated with DMSO, 20nM bortezomib (20nm BZ), 1mM thapsigargin (1mM TG) or 72uM nelfinavir. RNA was isolated and RT-PCR was performed using primers for RTA. Primers for β-actin were used as an internal control. Error bars indicate SEM.

Reference:

1. Gills JJ, Lopiccolo J, Tsurutani J, Shoemaker RH, Best CJ, Abu-Asab MS, Borojerdi J, Warfel NA, Gardner ER, Danish M, et al. Nelfinavir, a lead HIV protease inhibitor, is a broad spectrum, anticancer agent that induces endoplasmic reticulum stress, autophagy and apoptosis in vitro and in vivo. Clin Cancer Res 2007. 13:5183-5194.

37. Global Expression Analysis of EBV-Infected B Cells Early and Late After Infection Reveals a Dynamic Interplay Between Growth and Survival Signals

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Epstein-Barr virus (EBV) is a member of the γ-herpesvirus family estimated to infect 90% of the world's adult population. Despite the high prevalence of infection, EBV-associated malignancies are largely kept in check by a strong cytotoxic T cell immune response. However, EBV causes lymphoproliferative disease in immune-deficient individuals following transplant and CNS and other lymphomas in HIV-infected individuals. EBV also plays a role in the pathogenesis of endemic African Burkitt's lymphoma, Hodgkin's disease, and nasopharyngeal carcinoma. *In vitro,* EBV infection of primary human B cells results in proliferation and outgrowth of indefinitely proliferating lymphoblastoid cell lines, or LCLs, which represent a viable model for the pathogenesis of EBV-associated malignancies.

Ongoing studies in our group have shown that the earliest EBV-infected proliferating B cells differ greatly from LCLs phenotypically. Using CFSE staining and flow cytometry-based sorting, we have isolated these early proliferating B cells and analyzed genome-wide exon level mRNA expression relative to uninfected resting B cells and LCLs. Gene ontology analysis of these expression data identified enrichment of genes associated with proliferation and the DNA damage response in early proliferation. Furthermore, c-Myc mRNA and activity, as inferred from its genome-wide expression signature, were also highly induced early.

Most interestingly, however, analysis of changes from early proliferating to final LCL outgrowth revealed striking attenuation of proliferative gene sets and c-Myc, along with delayed induction kinetics of NF B activation. Specifically, genes with NF B motifs in their promoters were highly expressed from early proliferating B cells to LCL and many canonical NF B targets and pathway components were induced at late times after infection. These results suggest a novel, dynamic EBV-driven growth pattern and expression program that relies on mutually exclusive signals from c-Myc and NF B. Furthermore, our data suggest that the earliest stages of EBV-driven B cell immortalization may provide unique insight into the pathogenesis of EBV-associated malignancies.

38. HPV+ Cancer Cell Lactate Production Attenuates Immune Response During Treatment: Lactate Production Inhibition Leads to Improved Long-Term Cures

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Background: Normal cellular metabolism is altered in cancer cells, shifting away from the TCA cycle towards glycolysis, increasing glucose consumption and lactate production. This key characteristic change in metabolism is termed the Warburg effect. Importantly, HPV 16 E7 oncoprotein alters the function pyruvate kinase type M2, increasing glucose consumption and lactate production. Clinically, increased lactate production in head and neck cancers is associated with a decreased response to therapy. Cancers with high lactate production have a poor five year survival, approximately 40% worse than similar tumors with low lactate production. Lactate has also recently been shown to disrupt functions of key immune cells (CD8 and DC's) *in vitro*. We have recently shown that an immune response is required to clear HPV+ head and neck squamous cell carcinomas (HNSCC) *in vivo*. In this project we tested the hypothesis that lactate within the tumor microenvironment inhibits immune mediated clearance of HPV+ cancers.

Materials and Methods: Experiments were completed in culture on human and mice HPV+ cancer lines, in a preclinical mouse model of HPV+ cancer and a human phase 2 clinical trial initiated.

Results: We show that human and mouse HPV+HNSCC's have enhanced lactate production. Inhibition of lactate with either Dichloroactetate (DCA) or Oxamate decreases tumor cell growth in colony forming assays. DCA-mediated lactate inhibition *in vivo* was well tolerated, decreased tumor lactate levels, increased tumor pH. DCA treatment by itself did not alter tumor growth significantly. However, to test whether it would enhance immune related clearance during cisplatin/radiation, studies in immune competent mice were completed and compared to identical studies in immune deficient (RAG1) mice. The studies show that inhibition of lactate production resulted in enhanced immune mediated clearance during treatment with cisplatin and radiation therapy. Furthermore, siRNA-mediated knock down of lactate dehydrogenase (LDH) confirmed the role of LDH and epithelial cell lactate production in this response. These findings show that altered metabolism and decreasing lactate in the tumor microenvironment not enhances immune clearance during therapy. Due to these finding a phase 2 clinical trial has been initiated which combines DCA with cisplatin/radiation. The initial results from the trial will be presented.

Conclusion: Tumor produced lactate attenuates the immune clearance of HPV+ cancers. Decreasing this lactate and thus enhancing immune clearance may be very relevant for immune suppressed HIV+ individuals during therapy.

39. Human Herpesvirus 8 Replicates in Primary B Lymphocytes and Induces Polyfunctional Cytokine and Chemokine Responses

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Objectives: We have previously shown that DC-SIGN expressing, activated B cells support human herpesvirus 8 (HHV-8; KSHV) replication. Cytokines and chemokines play an important role in KS, including tumor-cell proliferation, angiogenesis and vascular permeability. We therefore examined virus replication in relation to production of soluble immune mediators by HHV-8 infected B cells.

Methods: B cells were loaded with purified "live" HHV-8, purified UV-light inactivated HHV-8 (UV-HHV-8) or soluble HHV-8 glycoprotein B (gB). HHV-8 replication was measured by real time PCR for viral DNA and intracellular staining (ICS) and flow cytometry for the viral lytic proteins ORF59 and K8.1. ICS was used to assess cell-associated, polyfunctional cytokine-chemokine production, and B cell supernatants were tested for cytokine/chemokine secretion by Cytometric Bead Array (BD Biosciences).

Results: ORF59 and K8.1 HHV-8 lytic proteins were detected in subpopulations of B cells expressing IgM, CD19, CD20, CD23 and CD38 surface antigens. The percentage of ORF59 and K8.1 positive B cells and level of viral DNA increased over several days of infection. The lytically infected B cells were more polyfunctional and produced more cell-associated TNF-α, IL-6, IL-8, MIP-1α and MIP-1β than the uninfected cultures. Significant increases in the 5 immune mediators were also detected in the supernatant of HHV-8 treated cultures by 24 hours, which were 16-100 fold higher than in untreated B cell cultures. Treatment of the B cells with UV-HHV-8 or gB induced a similar pattern of cytokine and chemokine production in the supernatant as did live HHV-8.

Conclusions: This is the first evidence of HHV-8 replication in primary B cells by both flow cytometry and viral DNA analysis, together with polyfunctional B cells producing multiple immune mediators, over the course of in vitro HHV-8 infection. There was similar production of cytokines and chemokines induced by live HHV-8, UV-HHV-8 and HHV-8 gB, indicating virus binding via gB alone is sufficient to elicit a B cell immune response to HHV-8. We are currently delineating B cell subsets that support HHV-8 lytic infection and investigating the role of individual cytokines and chemokines on HHV-8 replication.

40. Hybrid Microarray Analysis of a Model Gammaherpesvirus Pathogen During De Novo Infection and Upon Reactivation From Latency Reveals Distinct Transcriptomes

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Background: Herpesvirus infection is comprised of periods of *de novo* infection, latency, and reactivation. Murine gammaherpesvirus 68 (MHV68), a pathogen of murid rodents is closely related to KSHV and EBV; B cells are a latency reservoir and infection of mice is associated with lymphomas. This model system has advanced our understanding of the molecular constituents of latency and reactivation, immune control and virus-associated pathologies. The identification of virus and host factors that contribute to this complex interplay have rapidly advanced in the MHV68 system, yet gene expression programs during different stages of infection remain poorly defined. We examined whether the program of gene expression during reactivation from latency mirrors the cascade of gene expression upon *de novo* infection of permissive cells.

Methods: We applied a custom microarray to compare gene expression and viral transcript structure in a timecourse of *de novo* infection of fibroblast cells and upon phorbol ester-mediated reactivation from latently-infected B cells. Our hybrid arrays consisted of ~12,000 60mer overlapping oligonucleotides that tile the MHV68 genome and probes for several thousand cellular genes. Bioinformatic analysis revealed distinct transcriptional profiles for the two types of productive infection and also defined new transcript structures. Bioinformatics was complemented by RACE, Northerns, and quantitative RT-PCR.

Results: During reactivation, nearly all ORFs were transcribed and clustered into five major temporal groups that were overlapping, yet distinct from clusters based on the *de novo* timecourse. Nearly a dozen genes were detected prior to peak RTA expression during reactivation and others had greater relative transcript abundance compared to *de novo* infection. High-density transcript analysis at two-hour intervals captured spliced structures of ORF50 and ORF57 and mapped gene boundaries with a 20nt resolution, including a previously undefined transcript for the ORF63 homolog of KSHV vNLRP1 and ORF6. The region upstream of ORF6 transcript initiation was responsive to lytic infection and RTA, identifying a novel RTA-responsive promoter. Regions consistent with previously defined noncoding RNAs were detected. For cellular genes, we observed an extensive reduction of gene expression consistent with previous reports of host shutoff. We are validating a set of cellular genes that are stably expressed across the timecourse to use for normalization and further characterization of host genes that are differentially expressed during infection.

Conclusions: The gammaherpesvirus transcriptome is dynamic and distinct during both types of productive infections. Further global analyses of the context-dependent molecular events that govern gene expression programs during chronic infection is critical to understanding the etiology of gammaherpesvirus-associated cancers and the development of novel therapeutics.

41. Induction of KSHV Latency-Associated Nuclear Antigen (LANA) by Hypoxia and Hypoxia-Inducible Factors (HIF)

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Hypoxia activates KSHV lytic replication in primary effusion lymphoma (PEL) cells. In the current study, we show that LANA mRNA levels were up regulated in BC-3 PEL cells in hypoxia. Further, the total levels of LANA protein were elevated in BC-3 PEL cells after 24 h hypoxia and increased through 72 h. Also, infection of BC3 cells with a retroviral vector encoding siRNA to HIF-2α (or HIF-1α) decreased the levels of LANA protein. By contrast, protein levels of LANA-2, which is also a latent protein, remained unchanged in hypoxia. Computer analysis of a 1.2-kb sequence upstream of the LANA translational start site revealed six potential hypoxia-responsive elements (HRE). Reporter assays in Hep3B cells utilizing this region resulted in moderate activation by hypoxia and CoCl2 (a hypoxia mimic) and greater activation by co-transfection with degradation-resistant HIF-1α or HIF-2α. Greater induction was seen with HIF-2α than HIF-1α. Sequential deletion studies revealed that much of this activity was mediated by one of these HREs (HRE 4R) oriented in the 3′ to 5′ direction located between the constitutive (LTc) and RTA-inducible (LTi) mRNA start sites. Site directed mutation of this HRE substantially reduced the response to both HIF-1α and HIF-2α in reporter assays. Electrophoretic mobility shift assays (EMSA) and chromatin immunoprecipitation (ChIP) assays demonstrated binding of both HIF-1α and HIF-2α to this region. Consistent with the reporter assays, ChIP revealed greater binding of HIF-2α than HIF-1α. These observations suggest that hypoxia induces the transcriptional activation of LANA by the interaction of HIF through at least one HRE in the LANA promoter region and that this activity is preferentially responsive to HIF-2α. Computer analysis of LTi promoter revealed the presence of RTA-responsive elements adjacent to HRE 4R and 5R. Cotransfection assays in Hep3B cells revealed that RTA cooperates with HIF to induce LTi promoter activity. Hypoxia or CoCl2 treatment of Hep3B cells transfected with RTA confirmed this cooperative effect on LTi promoter activity. Immunoprecipitation assays using the nuclear extract of PEL cells exposed to hypoxia revealed that RTA associates with HIF-1α and HIF-2α to activate the inducible LANA promoter. Taken together with previous studies, these results provide evidence that hypoxia and HIFs activate both latent and lytic KSHV replication and play a central role in the life cycle of this virus.

42. Kaposi Sarcoma Associated Herpesvirus Infection of Primary Human Endothelial Cells Activates the Proto-oncogene STAT3

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Kaposi's sarcoma associated herpesvirus (KSHV) in the etiological agent for 3 AIDS-related cancers: Kaposi's sarcoma (KS), primary effusion lymphoma, and multicentric Castleman's disease. The molecular mechanisms used by KSHV to induce cancer are incompletely understood. KS lesions harbor proliferating latently-infected endothelial cells (ECs), large numbers of inflammatory cells, and marked neoangiogenesis. Considered the major driving force in the development of KS, these KSHV-infected ECs elaborate a variety of pro-inflammatory and angiogenic factors that contribute to tumourigenesis. Considerable evidence has accumulated suggesting a critical role for activated signal transducer and activator of transcription-3 (STAT3) in malignant transformation. STAT3 is a latent transcription factor that upon activation, drives the expression of a number of genes involved in cell proliferation, survival, and immune responses. Canonical STAT3 activation occurs via phosphorylation of Y705, dimerization, and nuclear translocation, followed by phosphorylation of S727 for maximal transcriptional activity. Activated STAT3 has been observed in a variety of malignancies and has been shown to induce fibroblast transformation *in vitro* suggesting that STAT3 is a proto-oncogene. Interestingly, evidence has accumulated suggesting a role for S727 mono-phosphorylated STAT3. Here we show that latent KSHV infection of primary human endothelial cells (ECs) *in vitro* activates STAT3, and identify a key latency protein, kaposin B, that contributes to this activation. Kaposin B expression in ECs causes STAT3 phosphorylation at S727, in the absence of significant Y705 phosphorylation, and enhanced expression of a subset of STAT3 target genes including CCL5. Recent work shows that the tripartite motif-containing protein 28 (TRIM28, a.k.a. TIF-1β, KAP-1) negatively regulates STAT3 by recruiting transcriptional silencing complexes. The repressive activity of TRIM28 is mediated by post-translational modifications and a key site in the regulation of repressor activity maps to S473. Phosphorylation of this residue disrupts the recruitment of transcriptional silencing complexes effectively deactivating the co-repressive function of TRIM28. Confocal microscopy and western blot analysis demonstrate phosphorylation of TRIM28 at S473 in KSHV latently infected and kaposin B expressing ECs. Taken together, our studies suggest kaposin B may contribute to tumourigenesis via constitutive activation of STAT3.

43. Kaposi Sarcoma Herpesvirus (KSHV)-Associated Lymphomas Are Associated With Markedly Elevated Serum IL-10, Elevated IL-6, IL-17 and Circulating KSHV

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Background: KSHV, also called human herpesvirsus-8 (HHV8), is the etiologic agent of primary effusion lymphoma (PEL) (including extracavitary variant), and large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease (together, KSHV-associated non-Hodgkin lymphoma (KSHV-NHL). Additional KSHV-associated diseases include: Kaposi sarcoma (KS), a form of multicentric Castleman disease (KSHV-MCD), and a proposed KSHV-associated inflammatory cytokine syndrome (KICS). Like KSHV-MCD, inflammatory symptoms are common in KSHV-NHL. We compared an array of inflammatory and angiogenic cytokines, chemokines, growth factors, and select clinical laboratory values between HIV-infected patients with KSHV-NHL and other lymphomas (HIV-lymphoma).

Methods: Patients were enrolled in HAMB and/or NIAID protocols. Cases had KSHV-NHL; controls other HIV-lymphoma. Clonality of PEL diagnosed from effusions was confirmed by PCR for immunoglobin rearrangements. Serum was evaluated by ELISA for IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12p70, TNF-α, IL-17, VEGF-A, (Meso-Scale Discovery, Gathersberg, MD), CXCL1, VEGF-C (R&D Systems, Minneapolis, MN). In patients with KSHV-NHL, peripheral blood mononuclear cell associated KSHV viral load was measured. Clinical data included demographics, CD4 count, albumin, platelets, hemoglobin, and c-reactive protein (CRP). Comparison of each parameter between patients with KSHV-NHL and other HIV-lymphoma employed an exact form of the Wilcoxon rank-sum test. P-values are 2-sided, with $p \leq 0.01$ considered statistically significant, and $0.01 < p < 0.05$ considered strong trends.

Results: Subjects:13 KSHV-NHL cases: 12 men, 1 woman. Median age 44, (IQR 39-55). 4 white, 4 Hispanic, 3 African-American, 2 African. PEL (8), extracavitary variant PEL (3), large B-cell lymphoma arising in HHV8-associated MCD (2, both with large effusions), history pathology confirmed KSHV-MCD (4). 28 HIV-associated lymphoma controls: 23 men, 5 women. Median age 38 (IQR 35-46). 17 white, 4 Hispanic, 6 African-American, 1 African. Histologies: primary central nervous system lymphoma (13), diffuse large B-cell lymphoma (DLBCL) (10), Hodgkin disease (1), Burkitt lymphoma (2), plasmablastic lymphoma (1), EBV+ large B-cell lymphoma NOS (1). KSHV-NHL subjects had elevated KSHV viral load, [median 2812 copies/10^6 cells (IQR 186-115,789)] and CRP [median 51 mg/L (IQR 45-67)]. Compared to other HIV-lymphomas, patients with KSHV-NHL have higher CD4 counts (median CD4 133 vs. 29 cells/uL, p=0.002), hypoalbuminema (median albumin 1.9 vs. 3.5 mg/dL, p= 0.0034)), and trend towards more severe anemia, thrombocytopenia, and hyponatremia. KSHV-NHL is associated with elevated circulating KSHV, marked elevations in IL-10 (513 vs. 12.2 pg/mL, $p < 0.0001$), elevations in IL-6 (29 vs. 4.1 pg/mL, p=0.0013), IL-17 (1.6 vs. 0.5 pg/mL, p=0.0074), and trends towards increased IFN-γ and IL-1β.

Conclusions: Inflammatory cytokines are important n KSHV-NHL pathogenesis and symptomatology. Clinical and translational studies evaluating these abnormalities in KSHV-associated malignancies are ongoing.

44. KSHV Encoded miRNA Single Nucleotide Polymorphisms Identified in Clinical Samples Can Affect miRNA Processing and Level of Expression

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MiRNAs are a class of non-coding RNA molecules between 19-25 nucleotides in length that have been shown to be involved in many biological processes by post-transcriptionally regulating gene expression. Aberrant miRNA expression has recently been associated with disease including many human cancers. Kaposi's sarcoma associated herpesvirus (KSHV) encodes 12 miRNAs located within the latency associated region. We previously reported single nucleotide polymorphisms (SNP) in the sequence of KSHV encoded mature and pre-miRNAs from clinical samples [1]. An earlier report showed that a SNP in mir-K12-5 resulted in increased expression of the mature miRNA [2]. In the current study, we have analyzed three different classes of miRNA polymorphisms to determine if any affect mature miRNA processing and expression. The identified SNPs include single and multiple polymorphisms within the pre-miRNA transcript, single mutations within the terminal loop, and single sequence changes within the mature miRNA. We used four complimentary approaches to detect differences in miRNA processing and expression resulting from sequence polymorphisms. Analysis of KSHV miRNA expression levels in PEL cell lines using custom ABI real time qPCR assays showed differential expression that correlates with sequence variation. Lentiviral vectors constructed to express wild type and variant pre-miRNAs were transduced into 293T cells to make stably expressing cell lines. miRNA expression was assessed using custom ABI real time qPCR assays. Luciferase reporter assays were performed following transient transfections of each miRNA. In addition, *in vitro* maturation assays were performed to assess differences in Drosha/DGCR8 and Dicer cleavage between wild type and variant pre-miRNAs.
Our results show that polymorphisms within the pre-miRNA sequence can cause subtle expression differences as in the case of KSHV miR-K12-6 or more profound changes as observed in miR-K12-5. This is also the case with SNPs located within the terminal loop as some miRNAs exhibited no discernable change, miR-K12-7 and miR-K12-10, while others can cause a reduction in mature miRNA transcripts as noted in miR-K12-4. Mutations within the mature transcript appear to have the most potential to effect mature transcript processing and expression. The polymorphism within miR-K12-2 results in reduction of mature miRNA levels while the multiple changes in miR-K12-9 leads to complete loss of the mature transcript.

Our data clearly show that SNPs can affect pre-miRNA processing resulting in changes in mature miRNA expression levels. The biological significance of these phenotypic and genotypic variants merits further study.

References:

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45. KSHV Induces Rapid Release of Angiopoietin-2 From Endothelial Cells to Promote Angiogenesis and Inflammation

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The development of Kaposi's sarcoma (KS), the most common malignancy in AIDS patients, results from Kaposi's sarcoma-associated herpesvirus (KSHV) infection of endothelial cells and subsequent induction of proliferation, angiogenesis, and inflammation. Previously, we demonstrated that KSHV infection of human umbilical vein endothelial cells (HUVEC) induced a transcriptional induction of Angiopoietin-2 (Ang-2), a pro-angiogenic and pro-inflammatory cytokine that is highly present in KS tumors. This transcriptional up-regulation of Ang-2 started at 12 h and peaked at 54 h post-infection. In difference to our previous data, here we demonstrate that KSHV infection of HUVEC induces rapid release of Ang-2 within minutes of viral contact. Pre-made Ang-2 is stored in the Weibel-Palade body in endothelial cells and is released through regulated exocytosis. KSHV binding to HUVEC is responsible for rapid Ang-2 release because blockade of viral binding inhibits this cytokine exocytosis. We find that KSHV binding to its integrin receptors on endothelial cells activates the integrin tyrosine kinase receptors signaling pathways, including tyrosine phosphorylation of the kinases FAK and Src, and triggers rapid calcium mobilization. This mobilization likely plays a key role in mediating Ang-2 release, as its inhibition by various calcium chelators and calcium channel blockers substantially reduces Ang-2 release. We also demonstrate a direct interaction and association of the kinase Src with the alpha1C subunit of L-type calcium channel. Indeed, specific inhibitors of protein tyrosine phosphorylation not only disrupt this interaction but also abolish Ang-2 release. Finally, preliminary data from in vitro cell adhesion assays suggest that this rapidly released Ang-2 enhances migration and adhesion of monocytes to the infected endothelial cells. To our knowledge, this is the first demonstration of interaction between KSHV and its integrins receptors in regulating rapid cytokine release. This study also uncovers a novel mechanism of KSHV induction of angiogenesis and inflammation, which is much faster, and could likely play important roles in the early event of KS tumor development.

46. Sequence Analysis of KSHV microRNAs in Patients With Multicentric Castleman Disease and KSHV-Associated Inflammatory Cytokine Syndrome

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Kaposi sarcoma-associated herpesvirus (KSHV) encodes 12 pre-microRNAs which potentially yield 25 mature microRNAs and have been shown to play prominent roles in the viral lifecycle including maintaining viral latency, evading the host immune response, and controlling lytic replication. We previously reported phylogenetic analysis of the microRNA-coding region of KSHV from Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD) patients. We showed a high level of conservation for most sequences, but also a divergent cluster of 5 KSHV sequences including 2 from MCD patients [1]. To further investigate this observation, KSHV microRNA sequences from 23 MCD patients and 7 patients with a newly described KSHV-associated inflammatory cytokine syndrome (KICS) were examined by amplification, cloning, and sequencing of a 646-bp fragment of K12/T0.7 encoding miRNA-K12-10 and miRNA-K12-12 and a 2.8-kbp fragment containing the remaining 10 pre-microRNAs. Phylogenetic analysis showed a distinct variant cluster consisting exclusively of MCD and KICS patients in all trees. Pearson's chi-squared analysis revealed 40 single nucleotide polymorphisms (SNPs) at various loci were significantly associated with MCD and KICS risk. Additionally, cluster analysis of these SNPs generated several combinations of three SNPs as putative indicators of MCD and KICS risk. Taken together, these findings show that MCD and KICS patients frequently have unusual KSHV microRNA sequences and suggest association between the observed sequence variation and risk of MCD and KICS.

Reference:

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47. Signal Transducer and Activator of Transcription 3 (STAT3) Controls Susceptibility to Epstein-Barr Virus Reactivation in B cells

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Epstein-Barr Virus (EBV) is known to cause malignancies in immunocompromised individuals, including lymphomas and lymphoproliferative disorders. Reactivation of EBV from latency is important in the pathogenesis of such malignancies. Therapeutically, oncolysis of tumors harboring lytic EBV holds promise. However, exposure of latently infected cultured B cells to lytic cycle inducing stimuli results in virus reactivation within only 20% to 50% of cells. Host cell determinants, that govern this susceptibility to lytic reactivation within latently infected B cells, are not well understood. Our research has previously identified that higher levels of signal transducer and activator of transcription 3 (STAT3) within cells correlate with resistance to EBV lytic reactivation. We now investigate whether inhibiting function of STAT3 promotes susceptibility of latently infected B cells to known lytic cycle inducing stimuli or results in induction of EBV lytic cycle. We found that pharmacological inhibition of STAT3 phosphorylation by Janus Kinase 2 (JAK2) inhibitors (AG490 or WP1066) in latently infected cells (HH514-16 Burkitt lymphoma and B95-8 lymphoblastoid cells) increased lytic reactivation by chemical stimuli that function by distinct mechanisms. Moreover, functional inhibition of STAT3 alone resulted in lytic reactivation in these cells. EBV-Lymphoblastoid cell lines (LCL) newly generated from healthy individuals also demonstrated increased susceptibility to lytic cycle inducing stimuli in the presence of AG490 but variable susceptibility to lytic reactivation when exposed to AG490 alone. Since this lack of uniform response to AG490 alone could be due to inadequate functional suppression of STAT3, we examined EBV-LCLs derived from patients with Autosomal Dominant Hyperimmunoglobulin-E syndrome (AD-HIES or Job syndrome). Patients with AD-HIES carry a dominant negative mutation in their *Stat3* gene resulting in lower basal levels of functional STAT3. When LCLs from AD-HIES patients were exposed to a JAK2 inhibitor alone, we observed a strong increase in lytic reactivation by expression of early and late lytic antigens over LCLs derived from healthy individuals. Lytic reactivation in the presence of AG490 occurred in these cells despite lack of discernable increase from basal levels of expression of ZEBRA, the viral lytic switch protein, when compared to cells not exposed to AG490. Thus, STAT3 is important in determining susceptibility to EBV reactivation. Fully understanding how STAT3 governs such susceptibility can lead to novel therapeutic strategies for EBV-related diseases.

48. The Combination of Vorinostat With Bortezomib Potently Induces Lytic Gene Expression and Cell Death, Without Increased Viremia, in Gamma-Herpesvirus Related Lymphomas

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The gamma-(γ)-herpesviruses Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated human herpesvirus (KSHV) are directly associated with oncogenic transformation. Approximately, 30% of HIV-related Burkitt's lymphoma and diffuse large B-cell lymphoma cases are EBV+. Primary effusion lymphoma (PEL) is an aggressive disease with poor prognosis usually affecting HIV-infected individuals. PEL is always KSHV+ and 80% co-infected with EBV. The treatment of γ–herpesvirus-induced lymphomas can be challenging in severely immunocompromised patients, in relapsed disease, and in highly aggressive variants like PEL. The rarity of disease occurrence and scarcity of suitable animal models for these lymphomas have hindered the development of novel regimens for testing under clinical trials.

γ-herpesviruses represent ideal targets for treating malignancies harboring them as viral lytic induction can result in highly specific tumor cell death. Vorinostat, also known as suberoylanilide hydroxamic acid (SAHA), and the 26S proteasome inhibitor bortezomib (Btz) are anti-neoplastic drugs known to reactivate γ-herpesviruses. Herpesviruses depend on the proteasome for mature virion production; thus, lytic induction with concomitant inhibition of the proteasome may provide a highly targeted strategy for eradicating herpesvirus-infected cells without leading to increased viremia. Previously, we reported in a direct xenograft PEL model (UM-PEL1) that Btz enhanced the survival of tumor-bearing mice compared to doxorubicin. Consequently, we hypothesized that combining Btz with SAHA may act synergistically. We found that Btz and SAHA potently induced apoptosis in primary AIDS-related PEL and EBV+ lymphoma cell lines. With UM-PEL1, we observed *in vitro* that SAHA/Btz synergized to induce expression of the KSHV replication and transcription activator (RTA). However, expression of the late lytic gene, K8.1, was inhibited relative to SAHA induced cells, suggesting that Btz may inhibit mature virion production. This effect was confirmed by a viral infection assay. To test our hypothesis *in vivo,* we challenged our NOD/SCID xenograft model, UM-PEL1. Strikingly, mice that received SAHA/Btz survived significantly longer than mice treated with either drug alone ($p<0.001$). Intriguingly, the *in vivo* combination also led to a synergistic increase in RTA expression, but transcription of all late lytic genes tested (ORF8/gB, K8.1, ORF39/gM, ORF38, ORF67) was uniformly inhibited relative to SAHA alone, suggesting that Btz prevents completion of the full viral replicative cycle in vivo. Further, SAHA/Btz resulted in persistent inhibition of NF-κB in vivo as demonstrated by gel shift assay.

In conclusion, this study provides strong pre-clinical evidence for the combined use of FDA approved HDAC inhibitors, with clinically relevant proteasome inhibitors, like bortezomib, for treating γ-herpesvirus lymphomas.

49. The Prevalence of HIV-1 DNA in AIDS-Related Lymphoma and Kaposi Sarcoma Throughout the AIDS Epidemic

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Background: Chronic inflammation is linked to tumorigenesis for many cancer types and likely contributes to tumor development in the HIV-infected patient population. AIDS-related lymphoma (ARL) and Kaposi Sarcoma (KS), two AIDS-defining cancers, are associated with the tumor viruses EBV and KSHV, respectively. However, EBV is only detectable in ~40% of ARLs and KSHV alone is not sufficient for KS development. Recent studies have shown that HIV is localized to tumor associated macrophages (TAM), not malignant B cells, in a portion of EBV-negative ARLs suggesting, that HIV infected TAM may play a role in tumorigenesis. The goal of this research was to determine the prevalence of HIV+ ARL and KS throughout the AIDS epidemic and examine tumor associated HIV for unique genetic signatures.

Materials and Methods: Whole genomic amplified DNA from ARL and KS biopsies was used for quantitative HIV gag gene amplification. The 3' *env-LTR* segment of HIV-1 genomes from tumor and non-tumor tissues from two patients that died of ARL were sequenced and Bayesian phylogenies were inferred using BEAST. All specimens were provided by the AIDS and Cancer Specimen Resource.

Results: Of the 119 ARL and 91 KS biopsies, 45% and 40% contained detectable HIV-1 DNA, respectively. There was a significant decrease in the prevalence of HIV-1 DNA positive ARL and KS cases in the post-HAART era (after 1996; ARL=39%, KS=16.7) as compared to pre-HAART (ARL=54%, KS=45%). Our data suggest the overall amount of HIV DNA is less in tumor biopsies from the post-HAART era. A subset of ARL contained extremely high levels of HIV-1 DNA (~1 copy/cell). In addition, visceral KS had a higher prevalence of HIV-1 DNA (51.9%) as compared to skin KS (30.7%). HIV sequence evolution analysis of metastatic ARLs revealed that HIV was compartmentalized within sites of lymphoma and was distinct from HIV present in non-lymphoma sites.

Conclusions: The prevalence of HIV-1 DNA positive ARLs declined in the post-HAART era, but not to the same extent as KS, consistent with the incidence of both tumor types in the post-HAART era. Higher prevalence of HIV-1 DNA in visceral sites of KS and lymphoma specific-HIV sequences in sites of metastatic lymphoma suggests that HIV, especially HIV infected macrophages, may play a role in the pathogenesis of KS and ARL disease progression. Additionally, HIV-infected macrophages are a source of chronic inflammation that may further enhance tumorigenesis. Our data suggest a tumor specific form of HIV may be evolving within individuals who develop ARL.

50. Viral FLICE Inhibitory Protein of Rhesus Monkey Rhadinovirus Inhibits Apoptosis by Enhancing Autophagosome Formation

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Rhesus monkey rhadinovirus (RRV) is a gamma-2 herpesvirus closely related to human herpesvirus 8 (HHV8). RRV encodes viral FLICE inhibitory protein (vFLIP), which has death effector domains. Little is known about RRV vFLIP. This study intended to examine its function in apoptosis. Here we found that RRV vFLIP inhibits apoptosis induced by tumor necrosis factor-α (TNF-α) and cycloheximide. In HeLa cells with vFLIP expression, the cleavage of poly [ADP-ribose] polymerase 1 (PARP-1) and activities of caspase 3, 7, and 9 were much lower than those in controls. Cell viability of HeLa cells with vFLIP expression was significantly higher than control cells after apoptosis induction. However, RRV vFLIP appears unable to induce NF-κB signaling when tested using NF-κB reporter assay. RRV vFLIP was able to enhance cell survival under starved conditions or apoptosis induction. At early time points after apoptosis induction, autophagosome formation was enhanced and LC3-II level was elevated in cells with vFLIP and, when autophagy was blocked with chemical inhibitors, these cells underwent apoptosis. Full length of vFLIP is needed for the function against apoptosis as truncation variants of vFLIP were unable to block apoptosis induction. Moreover, RRV latent infection of BJAB B-lymphoblastoid cells protects the cells against apoptosis by enhancing autophagy to maintain cell survival. Knockdown of vFLIP expression in the RRV-infected BJAB cells with siRNA abolished the protection against apoptosis. These findings indicate that vFLIP protects cells against apoptosis by enhancing autophagosome formation to extend cell survival. The finding of vFLIP's inhibition of apoptosis via the autophagy pathway provides insights of vFLIP in RRV pathogenesis.

51. Pathogen Discovery in AIDS-Related Lymphoma by High-Throughput Sequencing

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Background: Approximately 30% of AIDS-related lymphomas (ARL) are associated with infection by the EBV, and about 4% by the KSHV/HHV-8. It is likely that if other lymphomagenic pathogens exist, these associations would occur in the context of ARL. The advent of high throughput sequencing provides a unique opportunity to address this question. High throughput sequencing, followed by computational subtraction of human sequences was used for enrichment of candidate pathogenic sequences.

Methods: Eleven primary tissues of ARL have been used to generate cDNA libraries. Out of these six were frozen specimens and five were formalin-fixed paraffin-embedded (FFPE). These libraries were subjected to high throughput Illumina sequencing to generate 30-60 million 76bp paired-end sequence reads per sample. Quality filtered reads were analyzed using our automated pipeline, *PathSeq,* which carries out several subtraction steps involving alignments to i) human genome sequence databases; ii) human transcriptome sequence databases; and iii) other vertebrate sequence databases. Residual sequence reads were then compared with microbial databases, either individually or as part of *de novo* assembled contigs.

Results: Using both frozen and formalin-fixed paraffin-embedded (FFPE) tissues, we have identified unique sequences previously unassociated with hematological cancers and inflammatory diseases. In addition, our pathogen discovery pipeline works with both transcriptome and whole genome sequencing (WGS) data, and it is applicable to data across all high throughput sequencing platforms. Most notably, we are able to detect as low as 1 viral sequence per billion total sequences for WGS data, a sign of the sensitivity of our method. Among the known pathogens, we found 12423 sequences corresponding to EBV in the one case where the presence of this virus was also documented by EBER in situ hybridization. Three additional cases that were EBER-negative revealed EBV sequences, in the range of 3 to 351 reads, suggesting that the virus was present in tumor-infiltrating cells, rather than in the lymphoma. Eight cases had HIV sequences ranging from 1 to 403 reads, and one case had a single read corresponding to KSHV.

Conclusions: We have developed an integrated pipeline, *PathSeq*, for pathogen discovery in both frozen and FFPE tissues using a high throughput sequencing-based computational subtraction process. The presence of >10,000 reads in the known EBV-positive case confirms the effectiveness of the method. Specific EBV and HIV sequences were seen emanating from tumor-infiltrating cells that will shed light on expression patterns of these viruses in this cellular compartment.

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52. Dysregulated Cytokine and Growth Factor Expression in OSSN HIV-1 Patients From Botswana With Multiple Infections

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Background: Ocular surface squamous neoplasia (OSSN) is a conjunctival or corneal neoplastic tumor that is becoming prevalent in HIV-1 infected patients. Prior to the HIV pandemic, OSSN was noted to occur predominantly in the elderly for whom it is the third most common oculoorbital tumor after melanoma and lymphoma. In Africa OSSN is becoming more common, more aggressive, and affects young people, especially females. In parallel with the dramatic increase of HIV in Africa, several countries have noted a sharp rise in the incidence of OSSN in HIV infected individuals such that OSSN is currently the most common ocular tumor among adults. The underlying cause of this cancer in HIV-infected patients from Botswana is not well defined.

Method: Diluted sera from OSSN, pterygia, and control samples were used in Ray Biotech Assay kit for determination of expression of several cytokines and growth factors. We extracted RNA from tissue samples and used designed type specific primers for cytokines and growth factors to analyze expression. The samples were further analyzed for the expression of other pathogens using pyrosequencing technology.

Results: Cytokine array results from OSSN and pterygia cases indicated expression of some inflammatory cytokines and growth factors associated with tumor development and growth. Further, quantitative RT-PCR showed the expression of similar inflammatory cytokines and growth factors by a panel of OSSN and pterygia tissues. The expression of the factors were not different in the two conditions of OSSN and pterygia respectively. Additional analysis utilizing pyrosequencing technique identified a number of bacterial, viral, parasitic, and fungal sequences in the patient samples.

Conclusion: We identified anti-inflammatory cytokines and growth factors associated with cancer pathogenesis in OSSN and pterygia tissues. We also showed sequences of bacterial, parasitic, fungal, and other viral pathogens in the samples that may contribute to immunosuppression. Further studies are necessary to characterize the molecular mechanisms associated with cytokines and growth factors elicited by oncogenic viral proteins and the development of OSSN. Studies to elucidate the significance of other infectious pathogens in OSSN pathology will be necessary.

53. Effect of Immunodeficiency and Tumor Marker Expression on HIV-Related Diffuse Large B-Cell Lymphoma Prognosis

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Background: Several tumor markers may predict survival in HIV+ patients with diffuse large B-cell lymphoma (DLBCL). Here, we evaluate the association of immunodeficiency (CD4<200) on expression of prognostic tumor markers and survival.

Methods: HIV+ DLBCL cases diagnosed between 1996-2007 within Kaiser Permanente California were identified. H&E slides were reviewed to identify representative tumor blocks for tissue microarray (TMA) construction. Immunohistochemistry staining of TMA cores was used to detect the expression of selected markers in the categories of (1) cell cycle regulators, (2) B-cell activators, (3) anti-apoptotic proteins, and (4) others, including Epstein Barr Virus (EBV). Percent of DLBCL cells with visible marker staining was scored on a scale from 0-4 (i.e., 0-9%, 10-24%, 25-49%, 50-74% and ≥75%). EBV infection was determined by in situ hybridization of EBV RNA. We also considered high vs. low expression levels based on previously established cut-offs. Of the 20 markers previously examined, three had emerged as significant predictors of survival, including EBV, cMYC and BLIMP1 [1]. Here, we evaluated the association between CD4 and expression of these three markers by t-test for mean levels and chi-square for % high levels. We also evaluated the combined effect of immunodeficiency and marker expression on 2-year survival in unadjusted Cox models.

Results: We identified 194 HIV+ DLBCL cases; 80 patients had adequate tissue for the marker analyses. Of the three markers, only EBV was associated with CD4 level (Table 1).

Table 1. Tumor marker levels by CD4

	EBV			cMYC			BLIMP1		
	CD4			CD4			CD4		
	<200	≥200	P	<200	≥200	P	<200	≥200	P
Mean levels	1.9	0.6	0.009	1.6	1.7	0.90	0.3	0.2	0.65
% high levels	45.7	16.0	0.016	68.6	64.0	0.71	11.1	8.0	0.69

Survival was lowest in cases with high levels of EBV or cMYC in combination with low CD4 (Table 2). Survival was not evaluated for BLIMP1 given the low prevalence.

Table 2. Two-year survival by CD4 and marker levels

	EBV			cMYC		
	HR	95% CI	P	HR	95% CI	P
low CD4/high marker	4.0	1.6-10.2	0.004	3.3	1.0-11.5	0.057
low CD4/low marker	1.8	0.7-4.9	0.236	1.0	0.2-4.8	0.970
high CD4/high marker	1.6	0.3-7.7	0.557	1.3	0.3-5.1	0.739

Conclusion: Immunodeficiency was associated with EBV+ DLBCL. Cases with low CD4 and high levels of EBV or cMYC had worse survival. Risk stratification may consider both CD4 and tumor marker expression, although confirmation is needed in larger studies.

54. [^{18}F]-fluoro-D-deoxyglucose Positron Emission Tomography Findings in Kaposi Sarcoma Herpes Virus Associated Multicentric Castleman Disease: Correlation With Clinical, Inflammatory, and Virologic Parameters

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Background: KSHV-associated multicentric Castleman disease (KSHV-MCD) is a lymphoproliferative disorder associated with severe inflammatory symptoms, cytopenias and biochemical abnormalities. Improved techniques to assist diagnosis and aid monitoring are required. We prospectively assessed ^{18}FDG-PET/CT findings in KSHV-MCD in relation to clinical symptoms and markers of disease activity.

Methods: Patients enrolled on a natural history study of KSHV-MCD underwent ^{18}FDG-PET/CT at disease activity, except where unstable, and at complete clinical and biochemical remission. ^{18}FDG-PET/CT was evaluated blind to clinical status. Symptoms, C-reactive protein (CRP), HIV viral load (VL) in plasma and KSHV VL in peripheral blood mononuclear cells were assessed. Associations with ^{18}FDG-PET/CT maximal standardized uptake value (SUV_{max}) were explored using Spearman correlations (CRP, symptoms, $\log_{10}$[KSHV VL]) or exact Wilcoxon rank sum (HIV VL, detectable or not).

Results: 26 patients (24 male, median age 43 [range 34-56], all with HIV) were studied. In 3, we identified intercurrent lymphoma; these were excluded from the primary analysis. The remaining 23 underwent 19 studies during disease activity (16 symptomatic, 3 with laboratory manifestations only), and 21 studies at remission.

In symptomatic patients, ^{18}FDG-PET showed symmetrical hypermetabolic adenopathy (diffuse in 15 [94%], focal in 1 [6%]) and increased splenic metabolic activity with splenomegaly (abnormal in 14 [93%] of the 15 with intact spleens). Marrow and hepatic abnormalities were less common and mild. In patients with laboratory manifestations only, 2 (66%) had mild splenomegaly and limited adenopathy and 1 (33%) isolated adenopathy.

During disease activity, median SUV_{max} was 6 (2-8), and was associated with symptom severity (R=0.61 p=0.005), CRP (R=0.54, p=0.017) and KSHV VL (R=0.56, p=0.013), but not HIV VL (p=0.69). Intercurrent lymphomas (2 PEL and 1 diffuse large B-cell) demonstrated intensely hypermetabolic abnormalities involving restricted asymmetrical sites, with median SUVmax 11 (range 7–38). At remission, 11 (53%) had normal ^{18}FDG-PET/CT; 10 (47%) had minor nodal abnormalities and 4 (19%) mildly increased splenic metabolism without splenomegaly. Intercurrent pathologies contributed to some abnormalities. One had progressive increase in splenic and nodal SUV_{max} over 3 scans (not included in primary analysis) before relapse.

Conclusion: ^{18}FDG-PET/CT demonstrated widespread nodal and splenic abnormalities during disease activity, improving with remission. Subclinical disease may also be detectable. Findings were distinguishable from suppressed HIV or intercurrent lymphoma by intermediate metabolic intensity and diffuse anatomic distribution. SUV_{max} was associated with symptom severity, systemic inflammation, and KSHV burden. ^{18}FDG-PET/CT may be a useful non-invasive adjunct in the diagnosis and monitoring of KSHV-MCD.

55. HIV-1 DNA Is Not Found in Purified CD34+ Hematopoietic Progenitor Cells in Patients on Antiretroviral Therapy

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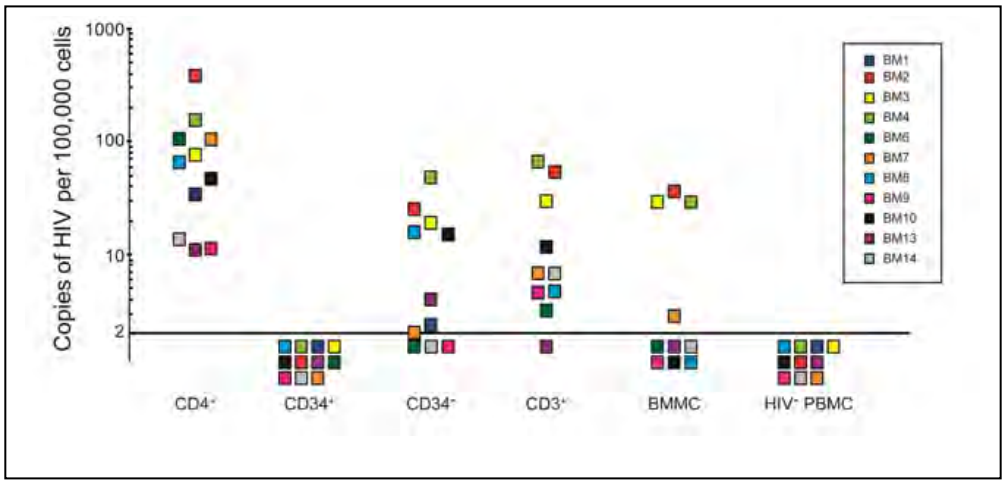
Background: Before the advent of highly active antiretroviral therapy (HAART), most studies reported that CD34+ cells were not infected by HIV-1. However a recent study in HIV-1 infected patients on HAART with undetectable plasma HIV-1 RNA reported evidence of HIV-1 in CD34+ cells in more than 40% of patients.

Materials and Methods: We obtained bone marrow from 11 patients on HAART. CD34+ cells were purified by fluorescence-activated cell-sorting (FACS). Real-time PCR was used to quantify HIV-1 DNA. In 7 patients, CD34+ cells were cultured with cytokines to promote differentiation and co-cultured with lymphocytes for 3 weeks and supernatants were assayed for HIV-1 antigen and HIV-1 RNA.

Results: The purity of the CD34+ cell populations was > 98.7% in all patients. The frequency of HIV-1 DNA per 10^5 cells in peripheral CD4+ T cells and bone marrow fractions is shown in Figure 1 with a limit of detection of 2 copies of HIV-1 DNA/10^5 cells. HIV-1 was detected in CD4+ T-cells in all patients (mean 64 copies/10^5 cells). In 11/11 patients, no HIV-1 DNA was found in CD34+ cells, with a median of 5.5 x 10^5 CD34+ cells tested per patient. HIV-1 DNA was frequently detected in bone marrow populations containing mature T-lymphocytes. In a subset of 7 patients from whom CD34+ cells were differentiated with cytokines and cultured, HIV-1 antigen and RNA were not detected.



Conclusions: We found that in patients on ART, HIV-1 DNA is not detected in bone marrow fractions but can be detected in bone marrow fractions containing mature T-lymphocytes. This suggests that in the majority of patients on HAART long-lived hematopoietic progenitor cells are not a reservoir for HIV-1.

56. Nylon-Flocked Swab Collection Method Better Predicts High-Grade AIN Than Does Dacron Swab Method

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Background: Invasive anal cancer (IAC) is a health crisis for gay, bisexual, transgender, and other men who have sex with men (MSM) who show a 20-40 fold higher risk for disease, especially if infected by HIV despite the introduction of HAART. *Human papillomaviruses* (HPV) that cause invasive cervical cancers (ICC) in women appear responsible for the majority of IACs. Although cervical cytology using Pap test has reduced ICC incidence by ~70%, anal Pap test only shows modest sensitivity and poor-to-modest specificity for detecting high-grade anal intraepithelial neoplasias (HG-AIN). Currently anal Pap testing using Dacron swab is recommended annually and biennially for HIV-infected and uninfected MSM, respectively. Swabs are inserted blindly through the anus, and ASCUS, low- and high-grade dysplasias (LG-, HG-SIL) are evaluated using high resolution anoscopy (HRA).

Materials and Methods: Dacron-swab cytology specimens were collected first using standard procedures; subsequently, Nylon Flocked (NF)-swabs were collected through an anoscope inserted just beyond the verge. Swabs were approximated to the canal, rotated slowly while withdrawn, and placed into preservatives. HRA, with medical biopsy, where indicated, was performed by experienced clinicians. Pathologists evaluated cytology using the Bethesda Classification System, and histology using the International Classification of Diseases for Oncology. HPV genotypes were assessed from cytology specimens using Linear Array (Roche Diagnostic Laboratories, Pleasanton, CA).

Results: Among 69 specimens obtained, 10 Dacron and 8 NF-specimens were inadequate for cytological evaluation: 14.5% and 11.6%. Sensitivity for HG-AIN and specificity were higher for cytology using NF- than Dacron swabs: 82% (66-98%) and 59% (44-74%), versus 55% (34-76%) and 49% (33-65%), respectively. Multivariate analyses showed NF-swab specimens more accurately predicted HG-AIN than Dacron swabs. Specimens showing either ASCUS /LG-SIL, or HG-SIL on NF-swab were 10 (1.9, 52.0) and 5.3 (0.4, 74) times more likely than unaffected specimens similarly collected to predict HG-AIN; whereas, Dacron-swab specimens using these cut-points showed no statistically greater risk for HG-AIN on histology, OR=0.4 (0.1, 2.3) and OR=4.7 (0.4, 61.5), respectively. These relationships persisted after controlling for age, HIV-infection, duration of infection, and multiple observations (n=7).

Conclusions: Cytology specimens using Dacron swab blindly inserted through the anus less often predicted HG-AIN than did NF-swab specimen used in conjunction with an anoscope to guide placement.

References available upon request.

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