National Cancer Institute

11th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI):

Basic, Epidemiologic, and Clinical Research

Presented by the Office of HIV and AIDS Malignancy, National Cancer Institute

October
6 – 7, 2008

Lister Hill Center Auditorium
NIH Main Campus, Building 38A
8600 Rockville Pike
Bethesda, MD

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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11th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies: Basic, Epidemiologic and Clinical Research

Presented by the Office of AIDS Malignancy Program

October 6-7, 2008

Lister Hill Center Auditorium, National Library of Medicine
National Institutes of Health
Bethesda, Maryland

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MONDAY, OCTOBER 6

8:00 a.m.	**Poster Setup** (posters will stay up for the entire meeting)
8:30 a.m.	**Opening Remarks and Welcome** *Robert Yarchoan, M.D.* *Director, Office of HIV and AIDS Malignancy, National Cancer Institute*
9:00 a.m.	**Session 1: Immunosuppression and Non-AIDS Defining Cancers and the Role of Screening** *Chair: Eric Engels, M.D., M.P.H., National Cancer Institute*
9:00 a.m.	P1: Epidemiology of Non-AIDS Defining Cancers in the HAART Era: What Can We Learn from Transplant Recipients? Andrew Grulich, Ph.D. University of South Wales, Sydney, Australia
9:30 a.m.	P2: HPV, HIV, and Head and Neck Cancer: Should We Expect to See More Head and Neck Cancers in HIV-Infected Individuals? Maura Gillison, M.D., Ph.D. Johns Hopkins School of Medicine, Baltimore, USA
10:00 a.m.	P3: Anal Cancer Screening: Current Perspectives Joel Palefsky, M.D., FRCP(C) University of California, San Francisco, San Francisco, USA
10:30 a.m.	**Break: Coffee and Poster Viewing**
11:00 a.m.–12:15 p.m.	**Session 2: Global Cancer Trends in HIV-Infected Persons** *Chair: Sam Mbulaiteye, M.D., National Cancer Institute*
11:00 a.m.	Abstract O27: Epidemiology of Non-Keratinocytic Skin Cancers Among Persons With AIDS in the United States Eric Engels, National Cancer Institute, USA
11:15 a.m.	Abstract O42: Distribution, Characteristics, and Prognostic of AIDS and Non-AIDS Cancers in HIV-Infected Patients: The ONCOVIH Study Emilie Lanoy, INSERM, France
11:30 a.m.	Abstract O73: Trends in Cancer Incidence Among HIV-Infected Persons in California, 1996–2006 Michael Silverberg, Kaiser Permanente Northern California, USA

Session 2, cont.

11:45 a.m.	Abstract O47: Preliminary Findings on Cancer Incidence in HIV-Infected Persons from Six Countries in Central and South America and the Caribbean Daniel Masys, Vanderbilt University, USA
12:00 p.m.	Abstract O86: Risk of Death Among Italian AIDS Cases With AIDS-Defining Cancers in the Post-HAART Era Diego Serraino, IRCCS Centro di Riferimento Oncologico, Italy
12:15 p.m.	**Lunch** (lunch on your own)
1:00 p.m.	**Poster Viewing** (Presenters stand by your poster)
2:00 p.m.–3:15 p.m.	**Session 3: Clinical Outcomes for AIDS-Related Haematologic Malignancies** *Chair: Alexandra Levine, M.D., City of Hope Medical Center*
2:00 p.m.	Abstract O41: Autologous Stem Cell Transplant (ASCT) for AIDS-Related Lymphoma (ARL) Amrita Krishnan, City of Hope National Medical Center, USA
2:15 p.m.	P4: Rituximab Plus Concurrent Infusional EPOCH Chemotherapy Is Highly Effective Without Excessive Toxicity in HIV-Associated, B-cell Non-Hodgkin's Lymphoma Joseph Sparano, M.D., Montefiore-Einstein Cancer Center, Albert Einstein College of Medicine, New York City, USA
2:45 p.m.	Abstract O26: Good Outcome of AIDS-Related Burkitt Lymphoma (BL) and Diffuse Large B-Cell Lymphoma (DLBCL) With Abbreviated Cycles of EPOCH-Rituximab Kieron Dunleavy, National Cancer Institute, USA
3:00 p.m.	Abstract O59: Interim Results of a Clinical Trial Using Oncolytic Virotherapy in Kaposi's Sarcoma-Associated Herpesvirus (KSHV) Associated-Multicentric Castleman's Disease (MCD) Robert Yarchoan, National Cancer Institute, USA
3:15 p.m.	**Break: Coffee and Poster Viewing**

3:30 p.m.–5:00 p.m.	**Session 4: International Studies** *Chair: Richard Ambinder, M.D., Ph.D., Johns Hopkins University*
3:30 p.m.	P5: 50th Anniversary of the Discovery of Burkitt's Lymphoma: Contributions to Epidemiology, Pathogenesis, and Treatment Ian Magrath, M.D., International Network for Cancer Treatment and Research, Brussels, Belgium
4:00 p.m.	Abstract O46: Kaposi's Sarcoma-Associated Immune Reconstitution Inflammatory Syndrome (KS-IRIS) in Africa: Initial Findings From a Prospective Evaluation Jeffrey Martin, University of California San Francisco, USA
4:15 p.m.	Abstract O18: AIDS-Associated Kaposi Sarcoma in Uganda: Response to Treatment with Highly Active Antiretroviral Therapy and Chemotherapy Corey Casper, University of Washington, USA
4:30 p.m.	Abstract O16: A Population-Based Study of How Children Are Exposed to Saliva in Africa: Implications for KSHV Transmission Lisa Butler, University of California San Francisco, USA
4:45 p.m.	Abstract O64: Implementation of a "See and Treat" Cervical Cancer Prevention Program Linked To HIV Care in Zambia Krista Pfaendler, Center for Infectious Disease Research in Zambia, Zambia
5:00 p.m.	**End of Day One**

TUESDAY, OCTOBER 7

8:15 a.m.	R1: AIDS Cancer Specimen Resource (ACSR): Role in Supporting HIV-Associated Cancer Research Michael McGrath, M.D., Ph.D., University of California, San Francisco, San Francisco, USA
8:30 a.m.–10:00 a.m.	**Session 5: KSHV Basic Biology** Chair: *Scott Wong, Ph.D. Oregon Health & Science University*
8:30 a.m.	P6: KSHV-Encoded Micro-RNAs and Their Potential Role in Viral Biology and Pathogenesis Rolf Renne, Ph.D., University of Florida, Gainesville, USA
9:00 a.m.	Abstract O58: Profiling of Cellular and Viral MicroRNAs in Kaposi Sarcoma and Viral-Associated Lymphoma Dirk Dittmer, University of North Carolina at Chapel Hill, Chapel Hill, USA
9:15 a.m.	Abstract O82: Profiling Viral and Host MicroRNA Expression in Cells Infected With KSHV and EBV Denise Whitby, National Cancer Institute, USA
9:30 a.m.	Abstract O31: Rapamycin Reduces Primary Effusion Lymphoma Progression by Targeting VEGF Production and VEGF Responses Paola Gasperini, National Cancer Institute, USA
9:45 a.m.	Abstract O22: Targeting the PI3K/Akt/MTOR Pathway in KSHV-Associated Cancers Blossom Damania, University of North Carolina at Chapel Hill, Chapel Hill, USA
10:00 a.m.	**Break: Coffee and Poster Viewing**
10:30 a.m.–11:30 a.m.	**Session 6: AIDS-Associated Lymphoma** *Chair: Elliott Kieff, M.D., Ph.D., Harvard Medical School*
10:30 a.m.	Abstract O23: High-Resolution Profiling of DNA Copy Number and Gene Expression Changes in AIDS-Related Lymphoma Karen Deffenbacher, University of Nebraska Medical Center, USA
10:45 a.m.	Abstract O28: HIV Induces the Expression of Activation Induced Cytidine Deaminase (AICDA) in B Cells through a Direct Interaction between Virion-Associated CD40L and CD40 Marta Epeldegui, University of California, Los Angeles, Los Angeles, USA

Session 6, cont.

11:00 a.m.	Abstract O83: Expression and Function of the Chemokine, CXCL13, and its Receptor, CXCR5, in AIDS-Associated Non-Hodgkin's Lymphoma Daniel Widney, University of California, Los Angeles, Los Angeles, USA
11:15 a.m.	Abstract O12: Incidence and Risk Factors and Survival and Prognosis of HIV-Associated Non-Hodgkin Lymphoma in the Era of Combined Antiretroviral Therapy: A European Multi-Cohort Study Julia Bohlius, University of Bern, Switzerland
11:30 a.m.	**Lunch** (lunch on your own)
12:00 p.m.	**Poster Viewing**
1:00 p.m.	**Session 7: New Viruses and Viral Mechanisms** *Chair: Douglas Lowy, M.D., National Cancer Institute*
1:00 p.m.	P7: New Human Polyomavirus Associated With Merkel Cell Carcinoma Yuan Chang, M.D. University of Pittsburgh School of Medicine, Pittsburgh, USA
1:30 p.m.	Abstract O11: Development and Application of Real Time PCR Assay for Detection and Quantification of Merkel Cell Virus (MCV) in Archived Formalin Fixed Paraffin Embedded Tissue Samples of Merkel Cell Carcinoma and Other Cancers Kishor Bhatia, National Cancer Institute, USA
1:45 p.m.	Abstract O37: An Invasion Mechanism for Human Papillomavirus Related Cancers: HPV 16 E6 Degrades PTPN13 Allowing Enhanced MAP Kinase Signaling Andrew Hoover, University of Iowa, USA
2:00 p.m.	Abstract O10: Generation of vFLIP Transgenic Mice: A Model to Study KSHV-Associated Lymphomagenesis Gianna Ballon, Weil Cornell Medical College, USA
2:15 p.m.	P8: HAART Rollout in AFRICA: Possible Impact on Cancer/New HTLV Viruses William Blattner, M.D., Institute of Human Virology, University of Maryland School of Medicine, Baltimore, USA
2:45 p.m.	**Break: Coffee and Poster Viewing**

3:15 p.m.–4:30 p.m.	**Session 8: Non-AIDS Defining Cancers** *Chair: Richard Little, M.D., National Cancer Institute*
3:15 p.m.	P9: Lung Cancer in the HIV Patient Malcolm Brock, M.D. Johns Hopkins University School of Medicine, Baltimore, USA
3:45 p.m.	Abstract O14: Immunodeficiency, HIV RNA Plasma Viral Load and Risk of AIDS-Defining and Non-AIDS-Defining Neoplasia, ANRS CO3 Aquitaine Cohort (1998–2006) Mathias Bruyand, INSERM, France
4:00 p.m.	Abstract O21: Influence of HIV-Related Immunodeficiency on the Risk of Hepatocellular Carcinoma Gary Clifford, International Agency for Research on Cancer, France
4:15 p.m.	Abstract O44: Cisplatin and Radiation Therapy Induces an Immunologic Clearance of HPV+ Head and Neck Cancer John Lee, University of Iowa
4:30 p.m.	**Meeting Adjourned**

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PLENARY SPEAKER ABSTRACTS

(Listed in Order of Presentation)

P1

EPIDEMIOLOGY OF NON-AIDS DEFINING CANCERS IN THE HAART ERA: WHAT CAN WE LEARN FROM TRANSPLANT RECIPIENTS?

GRULICH AE[1]
[1]National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, NSW, Australia

The long-term iatrogenic immune suppression that is necessary after organ transplantation creates a state of moderate to severe acquired immune deficiency. There are increased rates of a range of opportunistic infections, but thus far, there has been relatively limited epidemiological investigation of cancer occurrence.

We conducted a retrospective cohort study of 28,855 end stage renal disease (ESRD) patients with 273,407 person-years of follow-up. Incident cancers (excluding non-melanocytic skin cancers) diagnosed between 1982 and 2003 were ascertained by probabilistic record linkage between two population-based national registers, the Australian and New Zealand Kidney Dialysis and Transplant Register and the National Cancer Statistics Clearing House. The expected numbers of cancers up to 5 years prior to treatment were adjusted by site-specific relative survival rates. Standardized incidence ratios (SIRs) were calculated using age, sex, calendar year, and state and territory-specific population cancer incidence rates. We then conducted a meta-analysis comparing data on published cancer rates in solid organ transplant recipients with rates of cancer in people with HIV infection.

The incidence of all non-skin, non-ESRD related (myeloma, kidney, urinary tract) cancer was increased slightly in the 5 years prior to treatment (SIR 1.17, 95% CI 1.08-1.26), modestly during dialysis (SIR 1.36, 95% CI 1.27-1.45) and strikingly after transplantation (SIR 3.26, 95% CI 3.09-3.45). Rates increased after transplantation for almost all infection-related cancers, including those related to EBV (non-Hodgkin lymphoma, Hodgkin lymphoma); HPV (anogenital cancers and head and neck cancers); HBV and HCV (liver cancer) and *helicobacter pylori* (stomach cancer). Rates did not increase for most epithelial cancers common in the general population, including cancer of the breast, prostate and ovary. The meta-analysis revealed, with few exceptions, the pattern of increased cancer incidence was strikingly similar in people with HIV to transplant recipients, and thus suggest that is the shared risk factor of immune deficiency that is responsible for the increased cancer rates. These data challenge the prevailing view that only a few cancers are associated with immune deficiency in people with HIV, and strongly suggest that a wide range of mainly infection-associated cancer occurs at increased rates related to immune deficiency in people with HIV.

A key question of current interest is whether reversal of immune deficiency in HIV infection can reduce cancer risk. Further study of cancer in kidney transplant recipients has the potential to contribute to our understanding of the reversibility of increased cancer risk. Unlike other solid organ transplant recipients, where failure of the transplanted graft results in death or re-transplantation, when kidney grafts fail, it is usual for the person to cease immune suppression and go back onto dialysis for a period of time. Our preliminary analysis of cancer risk in these people suggests that cancer risk rapidly returns to baseline on cessation of immune suppression. Whether or not this can be translated to chronic HIV disease, where reversal of immune suppression is often more gradual and less complete, is uncertain. Describing cancer rates by current level of immune function is an important research priority among people with HIV. If cancer incidence is raised even in the modestly immune deficient, cancer risk may become an important consideration in deciding when to start HIV therapy, and in setting goals for optimal immune recovery in people receiving HIV therapy.

P2

HPV, HIV, AND HEAD AND NECK CANCER: SHOULD WE EXPECT TO SEE MORE HEAD AND NECK CANCERS IN HIV-INFECTED INDIVIDUALS?

GILLISON ML
Johns Hopkins Medical Institutions, Baltimore, Maryland, USA

Head and neck squamous cell carcinoma (HNSCC) is a major cause of morbidity and mortality worldwide, with more than 560,000 new cancers diagnosed annually. In 2007, 42,000 Americans were diagnosed with HNSCC. HNSCC are etiologically heterogeneous, with one major subset attributable to tobacco, alcohol use and poor oral hygiene and another to oral, high-risk, human papillomavirus (HPV) infection. HNSCC associated with HPV, overwhelmingly (~90 to 95%) type HPV16, arise predominantly from the lingual and palatine tonsils of the oropharynx, have risk factors related to sexual behavior and marijuana use and occur four times more frequently among men than women in the United States.

According to Surveillance Epidemiology and End Results (SEER) data, incidence rates for HPV-related oral cancers (e.g., base of tongue and tonsil) steadily increased from 1973 through 2004 in the United States (particularly among men under age 60 years), in contrast to a decline in incidence rates for oral cancers not associated with HPV. Age-period-cohort analysis of incidence trends for HPV-related and unrelated HNSCC revealed a strong birth cohort effect, consistent with changes in sexual behavior, tobacco, and alcohol use during the last 50 years in the United States. The annual number of HPV-associated HNSCC diagnosed in the United States from 1998 to 2003 prior to FDA approval of Gardasil® in 2006 was second only to cervical cancer (~10,800 cervical versus ~5,600 HNSCC) and exceeded the number for all other HPV-associated non-cervical cancers combined (e.g., anal, penile, vulvar and vaginal). Data to date indicate that HIV-infected individuals are at increased risk for all HPV-associated cancers, including head and neck cancers. Data on the associations among oral HPV infection, HIV and HPV-associated oral cancers will be presented.

P3

ANAL CANCER SCREENING

PALEFSKY JM
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Similar to cervical cancer, a high proportion of anal cancers are associated with human papillomavirus (HPV) infection, primarily HPV 16. The incidence of anal cancer has been rising every year in the general population among both men and women, but the increase has been most marked among HIV-positive individuals. Several recent publications have highlighted the increasing incidence of anal cancer since antiretroviral therapy (ART) has become available, indicating that ART has had little or no impact on reducing the incidence of anal cancer. As in the cervix, the entire spectrum of anal intraepithelial neoplasia (AIN) can be found, and both the prevalence and incidence of high-grade AIN (HGAIN) are increased among HIV-positive men and women compared with HIV-negative men and women. Several prevalence and incidence studies show that about half of all HIV-positive men who have sex with men (MSM) have HGAIN. Combined with mounting evidence that HGAIN represents a true anal cancer precursor, the absence of routine screening and treatment of HGAIN along with increased longevity due to ART suggests that the incidence of anal cancer may continue to increase in the future.

Screening for and treatment of the cervical cancer precursor lesion, high-grade cervical intraepithelial neoplasia, has led to a substantial reduction in the incidence of cervical cancer. Although AIN screening programs are being increasingly implemented on an ad hoc basis nationally and internationally, to date, a program analogous to the cervical screening program has been adopted for high-risk individuals by only one official governmental body, the New York State Department of Public Health. Current IDSA/USPHS guidelines do not call for routine screening but acknowledge that some experts recommend it. The principal reasons for this are: 1) uncertainty about optimal screening strategies, including the best use of anal cytology, high resolution anoscopy (HRA)-guided biopsy and anal HPV testing; 2) paucity of clinicians skilled in HRA and treating HGAIN; 3) few data on efficacy of current treatment modalities for HGAIN; and 4) absence of data demonstrating that treatment of HGAIN will reduce the incidence of anal cancer. There are now increasing data on screening and treatment strategies, and increasing numbers of clinicians are being trained. Randomized controlled trials utilizing this information are now needed to determine whether screening for and treating HGAIN should become standard of care for high-risk individuals.

P4

RITUXIMAB PLUS CONCURRENT INFUSIONAL EPOCH CHEMOTHERAPY IS HIGHLY EFFECTIVE WITHOUT EXCESSIVE TOXICITY IN HIV-ASSOCIATED, B-CELL NON-HODGKIN'S LYMPHOMA

SPARANO JA[1,2], LEE J[2], KAPLAN LD[2]
[1]Montefiore Medical Center-Weiler Division Department of Oncology, Bronx, New York, New York USA
[2]AIDS Malignancy Consortium

Background: The anti-CD20 antibody rituximab plus intravenous bolus chemotherapy is a standard treatment regimen for immunocompetent patients with B-cell lymphoma. Some studies have suggested that rituximab is associated with excessive toxicity in HIV-associated lymphoma, and that infusional chemotherapy may be more effective for this condition. We sought to determine the safety and efficacy of infusional chemotherapy, given either concurrent with rituximab or sequentially prior to rituximab, in patients with HIV-associated B-cell Non-Hodgkin's lymphoma.

Methods: Patients were randomized to receive rituximab (375 mg/m2) given intravenously either concurrently just prior to each infusional EPOCH chemotherapy cycle (N=51) for up to 6 cycles, or weekly for up to 6 consecutive weeks following completion of 4-6 cycles of EPOCH (N=55). EPOCH consisted of a 96-hour intravenous (IV) infusion of etoposide (60 mg/m2/day), doxorubicin (10 mg/m2/day), and vincristine (0.4 mg/m2/day) plus oral prednisone (60 mg/m2/day for 5 days) followed by IV bolus cyclophosphamide (187.5-375 mg/m2 or higher).

Results: The complete response (CR) rate was 69 percent (95% confidence intervals [CI] 56%, 79%) in the concurrent arm and 53 percent (95% CI 41%, 64%) in the sequential arm. The null hypothesis that the CR rate is 50 percent was rejected for the concurrent arm (P=0.005) in favor of the alternative that it is 75 percent, but not for the sequential arm (P=0.39). Features significantly associated with CR included the concurrent treatment arm (odds ratio 2.41; p=0.041) and stage III-IV disease (odds ratio 0.28; p=0.041). There was no significant difference between arms in the incidence of grade 3–5 adverse events.

Conclusions: Concurrent administration of rituximab with infusional EPOCH chemotherapy was not associated with increased risk toxicity compared with EPOCH followed sequentially by rituximab, and resulted in a CR rate that is higher than previous trials evaluating standard therapies.

Trial Registration: Clinical Trials.gov identifier NCT00049036

P5

FIFTIETH ANNIVERSARY OF THE DISCOVERY OF BURKITT LYMPHOMA: CONTRIBUTIONS TO EPIDEMIOLOGY, PATHOGENESIS AND TREATMENT

MAGRATH I[1]
[1]International Network for Cancer Treatment and Research, Brussels, Belgium

Burkitt lymphoma (BL) was discovered 50 years ago when there was limited understanding of the immune system, no comprehension of the molecular mechanisms of disease and few tools available for studying the biology of cancer. Since then, research into BL has contributed to the evolution of treatment as well as to the understanding of the epidemiology and pathogenesis of lymphomas. BL was literally "put on the map" by Burkitt and colleagues in the late 1950s and 1960s. It has provided a valuable paradigm for the understanding of environmental and genetic factors in lymphomagenesis. Burkitt described a clinical syndrome, but based only on children with jaw tumors. Subsequently, O'Conor and Davis from the pathology department reviewed all childhood cancers in the registry and recognized the very high percentage of lymphomas among them, some of which did not involve the jaw.

Through primitive but effective epidemiological studies, Burkitt and colleagues showed the distribution of the tumor to be limited by temperature and rainfall, similar to several insect-vectored infectious diseases, suggesting that the disease may be caused by a virus. This led to the discovery of the first human tumor virus, Epstein-Barr virus (EBV), in 1964, in cell lines derived from tumor samples sent to London from Kampala. The Henle's subsequently demonstrated by serology that EBV infection is highly prevalent, but patients with BL have higher antibody titres to "lytic" EBV antigens (the expression of which results in cell death) than control populations, indicating that EBV may be of pathogenetic relevance but is not a sufficient cause. Dalldorf's alternative proposal, that malaria predisposes to BL, is now well supported, although still indirectly, by epidemiological studies. HIV also predisposes to BL, but the fraction of HIV-positive cases in children is very low, while there is limited data regarding HIV-positive BL in adults, in part because of inadequate diagnosis. Whether malaria, EBV and HIV act together in predisposing to BL is an interesting question that remains to be answered—more studies regarding EBV association in HIV-associated lymphomas in Africa are needed.

The discovery of Ig-*MYC* translocations in BL led to the recognition of the central role of deregulated *MYC* in promoting cell proliferation. Recently published gene expression profiling has provided a new, objective definition of BL and clarified the indistinct morphological boundary between BL and diffuse large B cell lymphoma (DLBCL). Morphologically intermediate lymphomas, referred to as atypical BL, and some DLBCL, have the molecular profile of BL (mBL), whereas genetically intermediate lymphomas predominantly have the morphology of DLBCL. Interestingly, some mBLs have non-Ig translocations and some no myc translocation at all, indicating that multiple pathogenetic pathways can lead to BL. These recent finding raise many questions about the molecular lesions of HIV-associated BL in Africa.

Finally, BL was one of the first tumors to be shown to be curable by chemotherapy—in a small fraction of cases, even by a single dose of, for example, cyclophosphamide. Burkitt, Clifford, and Ngu were the pioneers, but NCI played an important role in demonstrating the value of combination chemotherapy and the need for CNS therapy. Recently, INCTR initiated a treatment program for African BL in several centers in East Africa and Nigeria, which will be expanded to HIV-positive patients and adult patients with BL in these same countries. Unfortunately, in spite of progress made in the United States and Europe, and the foundation provided by African studies, the majority of patients with BL in Africa die.

R1

AIDS CANCER SPECIMEN RESOURCE (ACSR): ROLE IN SUPPORTING HIV-ASSOCIATED CANCER RESEARCH

MCGRATH, M
University of California, San Francisco, San Francisco, USA

Background

The AIDS Cancer and Specimen Resource (ACSR) supports scientific discovery in the area of HIV/AIDS-associated malignancies. The ACSR was established as a cooperative agreement between the NCI (Office of the Director, Office of HIV and AIDS Malignancy) and regional biorepositories, University of California, San Francisco (West Coast), George Washington University (East Coast) and Ohio State University (Mid-Region) to collect, preserve and disperse HIV-related tissues and biologic fluids and controls along with clinical data to qualified investigators. The available biological samples with clinical data and the application process are described on the ACSR Web site at http://acsr.ucsf.edu.

Results

The ACSR tissue bank has more than 100,000 human HIV positive specimens that represent different processing (43), specimen (15), and anatomical site (50) types. The ACSR provides special biospecimen collections and prepares specialty items, e.g., tissue microarrays (TMA), DNA libraries. Requests have been greatest for Kaposi's sarcoma (32%) and non-Hodgkin's lymphoma (26%). Dispersed requests include 83% tissue (frozen and paraffin embedded), 18 percent plasma/serum and 9 percent other. ACSR also provides tissue microarrays of, e.g., Kaposi's sarcoma and non-Hodgkin's lymphoma, for biomarker assays. ACSR has developed collaborations with other groups that provide access to additional AIDS-related malignancy specimens.

Conclusions

The ACSR promotes the scientific exploration of the relationship between HIV/AIDS and malignancy by participation at national and international scientific meetings, contact with investigators who have productive research in this area and identifying, collecting, preserving, enhancing, and dispersing HIV/AIDS-related malignancy specimens to funded, approved researchers at no fee. Scientific discovery has been advanced by this unique biorepository. Investigators are encouraged to browse the ACSR Internet site for materials to enhance their own scientific initiatives.

P6

KSHV-ENCODED MICRO-RNAS AND THEIR POTENTIAL ROLE IN VIRAL BIOLOGY AND PATHOGENESIS

ROLF R[1]
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MicroRNAs are small, non-coding RNAs that post-transcriptionally regulate gene expression by binding to 3' UTRs of target mRNAs. Kaposi's sarcoma-associated herpesvirus (KSHV), a virus linked to malignancies including KS and primary effusion lymphoma (PEL), encodes 12 miRNA genes but only a few regulatory targets are currently known. Using ectopic expression of viral miRNAs in combination with gene expression profiling, we identified miRNA targets, including THBS, a strong anti-angiogenic factor, and several genes involved in regulation of apoptosis and proliferation.

In addition, we found that KSHV-miR-K12-11 shares 100 percent seed-sequence homology with hsa-miR-155, a miRNA frequently found up-regulated in lymphomas and critically important for B-cell development. Based on this seed-sequence homology, we hypothesized that both miRNAs regulate genes that are essential for terminal B-cell differentiation and as a result, KSHV-miR-K12-11 may mimic hsa-miR-155. Previously, our lab and others have published that ectopic expression of either miRNA inhibited expression of a BACH-1 3' UTR luciferase reporter, indicating that both miRNAs can indeed regulate identical gene targets (1, 2).

Using bioinformatic approaches in combination with 3' UTR reporter assays, we found that CEBP/β and PU.1 are both targets for miR-K12-11 and miR-155. Because CEBP/β and Pu.1 have been shown to play essential roles in terminal B-cell differentiation, we suggest that viral miRNA mimics miR-155 in order to regulate post-germinal center differentiation of B-cells. Ongoing experiments to directly evaluate the effects of KSHV-miR-K12-11 expression on B-cell differentiation, as well as miRNA profiling studies in endothelial cells, will also be discussed.

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P7

NEW HUMAN POLYOMAVIRUS ASSOCIATED WITH MERKEL CELL CARCINOMA

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Merkel cell polyomavirus (MCV) is a novel human virus recently identified by digital transcriptome subtraction and is found in ~70% of Merkel cell carcinomas (MCC). MCC is one of the most aggressive forms of skin cancer; about 50% of advance MCC patients live 9 months or less. MCC occurs more frequently than expected among immunosuppressed transplant and AIDS patients. Although rare, its incidence has tripled over the past two decades in the United States to 1500 cases per year.

MCV has a circular genome of 5387 nucleotides which is monoclonally integrated into the host genome in the majority of MCC tumors. The MCV genome encodes typical features of a polyomavirus, including an earlyT antigen region. Mapping of this early region shows that MCV expresses transcripts in MCCs similar to large T (LT), small T (ST), and 17kT transcripts of SV40. We examined nine MCC tumor-derived LT genomic sequences, and all were found to harbor mutations prematurely truncating the MV LT helicase. In contrast, four presumed episomal viruses from non-tumor sources did not possess this T antigen signature mutation. Using coimmunoprecipitation and origin replication assays, we find that tumor-derived virus mutations do not affect retinoblastoma protein (pRB) binding by LT but do eliminate viral DNA replication capacity. These results demonstrate that MCC-derived T antigens acquire mutations ablating MCV replication capacity while retaining its ability to interact with tumor suppressor proteins. These mutations preclude such replication deficient viruses to be merely passenger viruses found in tumors as a result of secondary infection. The evidence of MCV clonal integration and loss of replicative ability independently suggest a causal association between this newly identified human polyomavirus and MCC.

P8

HAART ROLLOUT IN AFRICA – POSSIBLE IMPACT ON CANCER/NEW HTLV VIRUSES

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The President's Emergency Plan for AIDS Relief (PEPAR) has finished its first $15 billion funding cycle, and the 5-year renewal for $48 billion has been approved. Already 2 million persons have been placed on HAART therapy representing the largest public health clinical program ever implemented. In the target countries—mainly in sub-Saharan Africa, where 75 percent of the 33 million persons with HIV reside—the impact of HIV on rates of malignancy is poorly understood, but data from selected countries show that AIDS defining cancers occur in excess as well as excesses of some non AIDS defining cancers. Given that key oncogenic viruses [herpes virus 4 (lymphomas), herpes virus 8 (Kaposi sarcoma and lymphomas), HPV (cervical cancer, penile cancer, anal cancer), hepatitis C (hepatocellular and lymphoma) and hepatitis B (hepatocellular) are prevalent in these hard-hit areas, the large size of the PEPFAR cohort provides a rich opportunity to investigate patterns and incidence of HIV and malignany and study the impact of HAART on cancer rates including the emergence of unrecognized malignancies. Given the strong association between known oncogenic viruses and HIV-associated malignancies, studies of these non AIDS defining malignancies may reveal new linkages of known viruses to malignancies as well as promote the discovery of yet to be recognized etiologic agents. For example, HTLV-1 and -2, which are prevalent in West Africa, are closely related to non-human primate STLV and their transmission into human populations has been demonstrated. Such investigations have led to the discovery of two new members of this family of PTLV, HTLV-3 and HTLV-4, and their STLV homologues. Given the close interactions between human and non-human primates study of HIV-associated malignancy may inform the relationship of this new class of viruses as well as other examples of non-human primate oncogenic viruses that may be linked to HIV-associated malignancies. Systematic studies of HIV-associated malignancies in the context of the PEPFAR program are feasible because of its scope and infrastructure and a modest cancer research investment can provide the evidence base for integrating cancer care and prevention into the PEPFAR mandate.

P9

LUNG CANCER IN THE HIV PATIENT

BROCK, MV

Over the last several years, it has become increasingly clear that there is an increased risk of lung cancer in HIV-infected patients and lung cancer has become an important cause of death in HIV-infected patients. In urban Baltimore at the Johns Hopkins Hospital, we have identified more than 100 HIV-positive patients with lung cancer. HIV lung cancer patients are younger than HIV indeterminate patients with lung cancer (median age 46 vs. 63 years, p=0.001). Both groups are majority male, but differ by race with the HIV cohort being more likely to be African-American. HIV patients also more frequently present with adenocarcinoma. No patient in our cohort has developed lung cancer before HIV diagnosis and the median interval between HIV diagnosis and lung cancer is 5 years. Although all except one patient are either current or former smokers, the HIV-positive patients have a lower average pack-years of smoking observed than the HIV-indeterminate lung cancer patients (35 versus 53 pack-years, p=0.001), despite the fact that the prevalence of smoking is higher in the HIV patients (99% vs. 88%). Even when adjusted for smoking, the incidence ratios are still elevated for lung cancer in HIV-infected patients. Together with other recent studies on this urban cohort, the risk of lung cancer in this population seems higher than can be explained by smoking alone suggesting that although smoking is permissive other co-factors such as an oncogenic virus, chronic pulmonary infections or HIV infection itself may be implicated. The prognosis of these patients is worse than similar age-matched controls (unadjusted hazard ratio 1.57, 95%CI 1.25-1.96) with 92 percent of deaths in this population due to lung cancer. CD4 counts and HIV-1 RNA levels indicate preserved immune function and worse survival is mainly due to the patients being diagnosed at a very advanced cancer stage partly as a result of low clinical suspicion in these young patients. Preliminary data interrogating the tumor biology of these HIV-infected patients reveal an aggressive malignancy with a high prevalence of genomic and epigenetic alterations. Current standards of care regarding diagnostics and treatment are identical to HIV-indeterminate patients despite some evidence that the efficacy and toxicity of chemotherapeutic agents and even the ability to tolerate surgical procedures may be different in these patients. Strategies of early detection with molecular analyses of blood and sputum and the use of CT screening in this defined population may also be critical in optimizing therapy.

ORAL SPEAKER ABSTRACTS
(Listed in Order of Presentation)

Abstract O27

EPIDEMIOLOGY OF NON-KERATINOCYTIC SKIN CANCERS AMONG PERSONS WITH AIDS IN THE UNITED STATES

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Background: Immunosuppression may increase the risk for some skin cancers. Solid organ transplant recipients have an elevated risk for melanoma and, to a greater extent, squamous and basal cell carcinomas (two skin cancers derived from keratinocytes). The frequency and patterns of occurrence of skin cancers in HIV-infected persons have not been well documented. Ultraviolet radiation is an established risk factor for the various types of skin cancer. In the present study, we used linked AIDS and cancer registry data to examine skin cancer epidemiology among persons with AIDS. Cancer registries in the United States do not collect information on the occurrence of the two most common types of skin cancer, squamous cell and basal cell skin carcinomas, so these outcomes could not be included. Thus, our study focuses on the occurrence of melanoma, Merkel cell carcinoma, and appendageal carcinomas among persons with AIDS.

Methods: The HIV/AIDS Cancer Match Study links population-based HIV and AIDS and cancer registry databases in nine states and five metropolitan areas of the United States. We evaluated risk of the major non-keratinocytic skin cancers (melanoma, Merkel cell carcinoma, and appendageal carcinomas, including sebaceous carcinoma) for the period from 60 months before until 60 months after AIDS onset. Standardized incidence ratios (SIRs) were calculated to relate skin cancer risk in people with AIDS to that in the general population. We also used logistic regression to compare risk according to demographic factors, CD4 count, and a geographic index of ultraviolet radiation exposure.

Results: The study included 497,142 people with AIDS diagnosed from 1980 through 2004. From 60 months before to 60 months after AIDS onset, persons with AIDS had elevated risks of melanoma (SIR=1.3, 95%CI 1.1-1.4, n=292 cases) and, more strongly, of Merkel cell carcinoma (SIR=11, 95%CI 6.3-17, n=17), appendageal carcinomas (SIR=4.2, 95%CI 2.5-6.7, n=17), and specifically sebaceous carcinoma (SIR=8.1, 95%CI 3.2-17, n=7). Risk for appendageal carcinomas increased with progressive time relative to AIDS onset (p-trend=0.03), but this trend was not significant for melanoma (p=0.10) or Merkel cell carcinoma (p=0.66). Based on data for 308,152 subjects, melanoma risk was unrelated to CD4 count at AIDS onset (p-trend=0.32). Risk of each of these skin cancers was higher in males than females and higher in non-Hispanic whites compared with other racial and ethnic groups. Across HIV risk groups, only men who had sex with men manifested an elevated risk for melanoma (SIR=1.6). Risks for melanoma and appendageal carcinomas rose with increasing ultraviolet radiation exposure (p-trend$<10^{-4}$ and p-trend$=10^{-3}$, respectively).

Conclusion: Among persons with AIDS, there is a modest excess risk of melanoma that is not strongly related to immunosuppression and may instead relate to ultraviolet radiation exposure. In contrast, the greatly increased risks for Merkel cell carcinoma and sebaceous carcinoma in people with AIDS suggest an etiologic role for immunosuppression and the possibility that these cancers arise, at least in part, from loss of immune control of oncogenic viruses. The recent discovery of a novel polyomavirus in Merkel cell carcinoma tumors is consistent with this hypothesis. The modestly elevated risk of a common skin cancer (melanoma) and the greatly elevated risk of two rare non-keratinocytic skin cancers (as well as reports of aggressive squamous cell skin cancers in HIV-infected persons) suggest a need for guidelines aimed at prevention and early detection of skin cancers in HIV-infected individuals.

Abstract O42

DISTRIBUTION, CHARACTERISTICS, AND PROGNOSTIC OF AIDS AND NON-AIDS CANCERS IN HIV-INFECTED PATIENTS, THE ONCOVIH STUDY

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Background: With the advent of combined antiretroviral therapy (cART) in 1996 and the decreased incidence of AIDS and death, growing concerns about cancer and in particular non-AIDS-defining cancers have emerged. For instance, in a mortality study conducted in France in 2005, AIDS malignancies including Non-Hodgkin lymphomas (NHL), Kaposi sarcoma and cervical cancer still represented 14 percent of the causes of death among HIV-infected persons and the part of non-AIDS-defining cancers rose from 13 percent in 2000 to 21 percent in 2005. ONCOVIH is a cross-sectional study based on the prospective reporting of new cases of malignant tumors occurring in patients with HIV infection, observed in France, during a 12-month period, year 2006.

Methods: The main objectives of ONCOVIH were:

- To prospectively record all the new cases of malignancies in HIV-infected patients in 2006 in France
- To describe the main characteristics of HIV infection (CD4 cell count and nadir, history of antiretroviral therapy, plasma HIV-RNA, AIDS stage), cancer (personal and family history of cancer, viral co-infections, histology and staging of the tumor), and of therapeutic management of the cancer
- To evaluate the prognosis of HIV-infected patients with malignancies

The data were collected from more than 300 different care centers involved in the management of patients with either HIV or malignancies. Duplicate records of the same patient from different centers were reconciled for the HIV- and tumor-associated data. Clinical follow-up, antiretroviral therapy and characteristics of HIV infection, therapeutic cancer management including chemotherapy, radiotherapy, or immunotherapy and occurrence of death and cause of death were collected every three months during the first year following the diagnosis. Centralized review of diagnoses and classification of the cause of death were done by a team of clinicians and epidemiologists. Data from HIV patients in care in 2006 in France were extracted from the French Hospital database on HIV (ANRS CO4 FHDH).

Results: In the ONCOVIH study, 694 tumors were reported in 690 patients by 116 clinical centers for an estimated 83,000 HIV infected patients in care. Of those, the case report forms were completed for 673 tumors in 669 patients. Most common cancers were NHL (21.5%, n=145), Kaposi sarcoma (15.9%, n=107), lung cancer (9.4%, n=63), anal cancer (8.2%, n=55), Hodgkin lymphoma (7.6%, n=51), cutaneous non-melanoma (5.8%, n=49) and liver cancers (5.6%, n=38). Cervix cancer was diagnosed in 10 women. For AIDS and non-AIDS-defining cancers, median ages at diagnosis were 44 years (IQR=38-51) and 49 years (IQR=42-57). Twenty percent and 21% of diagnosed patients were women. For AIDS-defining cancers, the median CD4 cell count at the time of cancer was 194/mm^3 (IQR=67-359) and the nadir CD4 cell count was 135/mm^3 (IQR=47-263). For non-AIDS-defining cancers, the corresponding figures were 330/mm^3 (IQR=192-503) and 147/mm^3 (IQR=51-258). The diagnosis of cancer revealed HIV infection in 28 percent and 5 percent of cases. Twenty-three percent and 62 percent were receiving cART and had plasma HIV-RNA<500 copies/ml, respectively. In FHDH at the same period, the median age of HIV patients in care was 43 years (IQR=37-49) with 33% women. The median CD4 cell count was 454 (IQR=312-634), and 67 percent received cART with plasma HIV-RNA<500 copies/ml. In the general population, the mean age at diagnosis of cancer was 66 years of age in 2005.

The overall 1-year survival rate was 72% (n=185, 95% CI: 68-75%). Prognosis after a diagnosis of lung cancer (1-year survival rate: 35%) hepatocarcinoma (47%) and NHL (65%) were the worst. Most common causes of death were NHL (45), lung cancer (35) and liver diseases (hepatocarcinoma or cirrhosis or hepatic failure, n=18).

Conclusion: NHL and Kaposi sarcoma remain the most frequent cancers diagnosed in 2006 in France in HIV-infected people despite the widespread use of cART. However, non-AIDS-defining cancers including lung cancer, anal cancer and Hodgkin lymphoma represent 62% of diagnosed cancers. Diagnosis of cancer occurred at much younger age than in the general population, in patients with a lower CD4 cell count and more often with detectable plasma HIV RNA than in HIV-infected patients not diagnosed with cancer, suggesting that a better control of HIV and its induced immunodeficiency is required to prevent AIDS and non-AIDS cancer in HIV infected patients in addition to the control of other usual risk factors for cancer.

Abstract O73

TRENDS IN CANCER INCIDENCE AMONG HIV-INFECTED PERSONS IN CALIFORNIA, 1996–2006

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Background: Population-based surveillance for malignancies in HIV-infected patients in the antiretroviral therapy (ART) era is warranted given the aging population of patients and the high prevalence of risk factors in this population including tobacco use and viral co-infections.

Methods: We identified all adult HIV-infected persons enrolled in Kaiser Permanente (KP), an integrated health care system providing care to ~25 percent of all Californians in the most populated areas. Subjects at least 18 years of age at first enrollment after 1996 were included and followed until the earliest of an incident cancer diagnosis, last health plan enrollment, or the end of the study period (December 31, 2006). Incident AIDS-defining and non-AIDS-defining cancers were ascertained from the KP cancer registries, which participate in the California SEER program. Poisson regression was used to obtain age-adjusted calendar trends in cancer incidence from 1996 to 2006. Results are presented for KP Northern California only, but will be updated with additional data from KP Southern California.

Results: Between 1996 and 2006, 10,366 eligible HIV-infected persons were identified contributing 46,114 person-years. Subjects were mostly male (90.2%), with mean age 40 years and mean years known HIV+ of 4.1 years at study enrollment. Subjects were 59 percent Caucasian, 17 percent African-American, and 13 percent Latino. HIV exposure risk factor was 65 percent men who have sex with men, 15 percent heterosexual transmission, and 8 percent injection drug use. A total of 394 AIDS-defining cancers were identified consisting of 212 Kaposi's sarcomas (KS), 180 Non-Hodgkin's lymphomas (NHL), and two invasive cervical cancers. A total of 380 non-AIDS-defining cancers were identified. The most common non-AIDS-defining cancers were digestive and gastrointestinal (141), consisting primarily of anal (99), colorectal (22) and liver (12) cancers; genitourinary (54), consisting primarily of prostate (29) and kidney (9) cancers; head and neck cancers (24); gynecologic cancers other than cervix (18); Hodgkin's lymphoma (29); lung (43); and, melanoma (32). The AIDS-defining cancer rate/10,000 person-years declined from 128.7 in 1996-99 to 53.9 in 2004-06, corresponding to a relative rate (RR) per calendar year of 0.88 (95% CI: 0.85, 0.92). KS and NHL showed similar declines. The non-AIDS-defining cancer rate increased from 78.9 percent in 1996 to 1999 to 97.3 percent in 2004 to 2006, corresponding to a RR per calendar year of 1.01 (95% CI: 0.98, 1.04). Most individual non-AIDS-defining cancers showed a similar lack of a calendar trend in incidence. However, there was a suggestion of an increase during the ART era in colorectal cancers (RR=1.15; 95% CI=0.99, 1.35) and genitourinary cancers (RR=1.10; 95% CI=1.00, 1.21).

Conclusion: In the ART era, AIDS-defining cancers have declined and non-AIDS-defining cancer rates have generally remained stable. However, surveillance for non-AIDS-defining cancers should continue given the introduction of new therapeutic classes with the potential for oncogenic side effects, and the fact that HIV-infected patients continue to have increased rates of many cancers compared to the general population.

Abstract O47

PRELIMINARY FINDINGS ON CANCER INCIDENCE IN HIV-INFECTED PERSONS FROM SIX COUNTRIES IN CENTRAL AND SOUTH AMERICA AND THE CARIBBEAN

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Background: The Caribbean, Central and South America network (CCASAnet) is one of seven regions funded by the International Epidemiologic Databases to Evaluate AIDS (IeDEA) program sponsored by the National Institute of Allergy & Infectious Diseases and National Cancer Institute[1]. CCASAnet performs analyses using HIV epidemiology data from clinical care sites in Argentina, Brazil, Chile, Haiti, Honduras, Mexico and Peru. In August of 2007, with a funding supplement provided by NCI, six participating sites in the network began a project to determine the incidence, treatment and outcomes of cancer occurring in HIV-infected individuals in the region.

METHODS: A total of approximately 13,000 HIV-positive individuals followed at the participating sites formed the study cohort. Chart reviews began in fall 2007 and are continuing at present. A standardized cancer case abstract form was developed by the Vanderbilt data coordination center and its use was validated by Fundación Huésped in Buenos Aires. English and Spanish language versions of the case report form and instructions for its use were created, along with a secure online Web interface for capturing data in computerized format.

PRELIMINARY RESULTS*

Site– Country	FH – Argentina	UFRJ – Brazil	FA – Chile	GHESKIO – Haiti	IHSS – Honduras
Total adult patients	2000	2800	2400	4000	1000
Adult patients reviewed to date for cancer diagnoses	1200	620	2400	450	946
Cancer cases identified as of May, 2008	107	36	125	27	51
Current cancer incidence estimate in HIV cohort	8.90%	5.80%	5.20%	6%	5.40%
Method of diagnosis (Clinical/Histopathological)	Histopathological 90% Clinical 10%	Histopathological 100%	Histopathological 100%	Histopathological 40% Clinical 60%	Histopathological 80% Clinical 20%
Cancer types found to date	71 KS 22 NHL 2 HL 1 breast 1 cervix	TBD	70 KS 28 NHL 6 HL 13 solid tumors: 3 anorectal, 4 in situ cervical neoplasias (CIN), 1 non KS sarcoma, 1 basal cell Ca 3 testicle, 1 prostate, 1 colon	9 KS 5 Cervical Cancer 2 Lymphoma 2 Hodgkin 1 Ovarian 2 Breast 1 Colon 2 Oro-pharyngeal 1 Right eye 1 Liver 1 Pancreas	Case reviews and confirmations in progress. To date, 5 NHL cases found (2 Burkitt, 1 small cell, 2 NHL not otherwise specified)

*Updated incidence figures and characterization of cases will be presented at the conference.

CONCLUSION: The preliminary incidence and cancer types occurring in selected cohorts in the Caribbean, Central and South America are consistent with previously reported cancer findings in HIV-infected populations.

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Abstract O86

RISK OF DEATH AMONG ITALIAN AIDS CASES WITH AIDS-DEFINING CANCERS IN THE POST-HAART ERA

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This study intended to quantify the impact of AIDS-defining cancers on the risk of death in the post-HAART era. With this aim in mind, data regarding all Italian AIDS cases reported to the National AIDS Registry were analyzed.

Between 1999 and 2005, a total of 12,433 individuals were diagnosed with AIDS in Italy. Specifically excluded from this analysis were people with AIDS who were: 1) not-Italian citizen (n=1918); 2) resident in Italian areas where individual information on death was not available (n=108); 3) resident in unknown areas (n=119); 4) pediatric or vertical transmission cases (n=50); 5) diagnosed solely at autopsy (n=576). The presence of AIDS-defining cancers (i.e., Kaposi's sarcoma–KS, non-Hodgkin lymphoma–NHL, and invasive cervical cancer–ICC) at AIDS diagnosis is routinely ascertained at the National AIDS Registry, together with some other information, including age, sex, date of AIDS diagnosis, HIV transmission category, CD4+ cells count. Information on vital status of AIDS cases, as of December 2006, was assessed through a semi-automated linkage procedure, ensuring confidentiality of individual data, with the national death certificates database. Survival function was estimated by the Kaplan-Meier method; Cox regression model was used to estimate death hazard ratios (HR), and corresponding 95% confidence intervals (CI), associated to the presence of AIDS-defining cancers at diagnosis, adjusted for age at AIDS diagnosis, sex, HIV transmission category, and CD4+ cells count at diagnosis.

Of the 9,662 AIDS cases included in the present study, 478 had KS, 429 immunoblastic NHL, 158 Burkitt's lymphoma, 69 ICC, and 58 NHL of the central nervous system (CNS). As of December 2006, 3,096 deaths were registered: of these deaths, 505 occurred among cases with AIDS-defining cancers. The proportion of AIDS cases still alive 5 years after AIDS diagnosis was 66.6 percent. The shortest survival period was seen among individuals diagnosed with CNS NHL (median survival = 4 months), followed by those with immunoblastic NHL or Burkitt's lymphoma (median survival = 16 and 38 months, respectively), whereas the longest ones were recorded among cases with ICC or KS (median not reached). In comparison with AIDS cases without AIDS-defining cancers, those with a CNS NHL had a 4.7-fold higher risk of death (95% CI: 3.5-6.4), those with immunoblastic NHL or Burkitt's lymphoma had more than twice the risk (HR=2.6, 95% CI: 2.2-2.9; and HR=2.3, 95% CI: 1.8-2.8, respectively), and, among women, those with ICC had a 1.8-fold elevated risk (95% CI: 1.2-2.7). Conversely, among individuals with KS (HR=0.7, 95% CI: 0.6-0.9) the risk of death was lower than that of cases without AIDS-defining cancers.

In conclusion, this exhaustive survival analysis of Italian AIDS cases in the post-HAART era highlighted the persisting lethality of NHL and the long survival of cases with KS and ICC.

Abstract O41

AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) FOR AIDS-RELATED LYMPHOMA (ARL)

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High-dose therapy with ASCT is an established therapy for relapsed Non-Hodgkins (NHL) and Hodgkin's lymphoma (HL). Randomized trials have shown a benefit for this approach when compared to standard dose salvage therapy for HIV-negative NHL. Since these first trials, transplant-related mortality (TRM) has decreased due to the use of peripheral stem cells and improved supportive care. Concomitantly, the treatment of HIV infection has also improved. Highly active antiretroviral therapy (HAART) has improved hematologic and immune function in HIV positive patients. In addition, with the use of HAART and prophylactic antibiotics, the incidence of opportunistic infections has greatly decreased. This improvement in control of OIs and immunologic function in HIV infected patients due to HAART set the platform for the use of ASCT in patients with high-risk ARL.

Herein we report the long-term follow-up of 32 patients with ARL who underwent ASCT at the City of Hope Cancer Center between 1998 and 2007. Median age at ASCT was 42 years. Histologies included Diffuse large cell n=16, Burkitts n=9, Anaplastic large cell n=2, HL n=5. The conditioning regimen consisted of CBV (carmustine 450mg/m2, cyclophosphamide (CY) 100mg/kg, VP16 60mg/kg) in 28 patients and FTBI 1200 cGY/CY 100 mg/kg/VP16 60mg/kg in 4 patients, All patients engrafted at a median of 10 days to an ANC >500 (range 5-19 days). One patient died of regimen-related cardiac toxicity. Other regimen-related toxicities included grade 3-4 hepatic toxicity n=3, interstitial pneumonitis n=2. OI's included PCP pneumonia in 2 patients who were not compliant with prophylaxis, CMV infection n=3, VZV n=2. One case of treatment related myelodysplasia was seen and the patient ultimately died of myelodysplasia while in remission from his ARL. Median HIV viral load at ASCT was 5726 copies/ml, with 25 patients having an undetectable viral load. Median CD4 count at ASCT was 156 (range 25–1064), which rose to 420 (range 95–1164) at 2-year follow-up. Only 10 patients had an undetectable VL at 2 years. Three patients who were in remission were lost to follow-up after 4 years. Median f/u for the entire group is 47 (range 0.7–104) months. Two-year overall survival is 80 percent (95% CI 66–89) and progression-free survival (PFS) is 81 percent (95% CI 67–90). In conclusion, this large single institution series of ASCT in ARL demonstrates that the procedure has low transplant-related mortality and can lead to long-term remission without deleterious effects on the underlying HIV infection.

Abstract O26

GOOD OUTCOME OF AIDS-RELATED BURKITT LYMPHOMA (BL) AND DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) WITH ABBREVIATED CYCLES OF EPOCH-RITUXIMAB

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The addition of rituximab to CHOP chemotherapy may augment tumor response but in patients with low CD4 counts, one study suggested that this benefit may be offset by increased infectious deaths (Kaplan. Blood 2005;106:1538). We hypothesized that the addition of rituximab to EPOCH chemotherapy could improve tumor kill, allowing fewer cycles of treatment and therefore reducing toxicity.

Patients received EPOCH-R (in mg/m^2/d – etoposide 50, vincristine 0.4 and doxorubicin 10 all CIV d 1-5; cyclophosphamide 750mg IV d 5; prednisone 60 po days 1-5 and rituximab 375 IV d 1,5 and G-CSF sc d 6-15) every 21 days. Prophlactic IT methotrexate was administered and HAART was suspended during therapy. Cyclophosphamide was adjusted based on absolute neutrophil count (ANC) nadir. Response was assessed by CT and FDG-PET scan and patients received one cycle beyond CR for a minimum of three cycles. Characteristics of 40 enrolled patients are: median (range) age 42 (9-60) years; IPI 3 (0–4); ECOG PS 1 (1–4), CD4 count 222 (0–835) cells/mm^3; HIV viral load 34,766 (0–6,080000) RNA copies/mL; male sex 35 (88%); LDH > N 27 (68%); stage IV 27 (68%) and histology DLBCL 32 (80%) and BL 8 (20%). Of 38 evaluable patients (2NE), median (range) number of cycles given is three (3–5) with CR/CRu in 35 (92%) and PR in one (3%) patients.

All eight patients with Burkitt lymphoma are in continuous remission. At four years median potential follow-up, PFS and OS are 86 percent and 70 percent. For patients with CD4 > and < 100 cells/mm^3 PFS is 96 percent and 69 percent, respectively. IPI did not impact OS and PFS. Early PET scanning (after cycle 2) had a very high negative predictive value (100%) but a low positive predictive value (20%). One treatment-related death occurred (from complications of mycobacterium avium intercellulare (MAI)) and other toxicity included fever or neutropenia on 30 percent, ANC < 500/mm^3 on 40 percent, and platelets < 50,000 on 23 percent cycles. EPOCH-R was associated with less CD4 loss - median 128 cells/mm^3 (range +154 to –639) compared to EPOCH alone (median 189 cells/mm^3 (range +19 to –973). Abbreviated EPOCH-R is highly effective with acceptable tolerability in ARL and enables the administration of fewer treatment cycles (median 3 versus 6). Although patients with CD4 < 100/mm^3 have good tumor control with EPOCH-R with a PFS of 70 percent at four years, overall survival for this group was only 31 percent due mainly to later deaths from complications of advanced AIDS. In contrast, patients with high CD4 counts > 100/mm^3 have an extremely favorable outcome with and survival following EPOCH-R. The addition of rituximab did not appear to contribute to infection related complications or deaths. EPOCH-R showed excellent efficacy in eight patients with BL with an OS and PFS of 100 percent. PET scanning has a high negative but low positive predictive value for subsequent relapse. Accrual continues.

Abstract O59

INTERIM RESULTS OF A CLINICAL TRIAL USING ONCOLYTIC VIROTHERAPY IN KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS (KSHV) ASSOCIATED-MULTICENTRIC CASTLEMAN'S DISEASE (MCD)

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Kaposi's sarcoma-associated herpesvirus (KSHV), also called human herpesvirus-8 (HHV-8), is an oncogenic gammaherpesvirus associated with Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), and a form of MCD. KSHV-associated MCD (KSHV-MCD) is a rare B-cell lymphoproliferative disease almost universally found in association with HIV infection that is characterized by a recurrent systemic syndrome of fatigue, fevers, cytopenias, elevated serum C-reactive protein (CRP), and lytic KSHV replication with production of a virally-encoded interleukin-6 (vIL-6). There is no standard therapy for KSHV-MCD although there are reports of patients responding to a variety of agents including interferon alpha, cytotoxic chemotherapy, rituximab or ganciclovir. Overall, the prognosis is poor (median survival 14 months). KSHV open reading frames (ORF) 21 and 36 respectively have the ability to phosphorylate zidovudine and ganciclovir to toxic triphosphate moieties. We found that when these lytic genes are activated in PEL cell lines, as by hypoxia, the cells can be killed by concentrations of these drugs that are clinically attainable (*Cancer Res* 2007; 67:7003–10).

We have explored the translation of these observations to the clinic in MCD, taking advantage of lytic KSHV replication already present in the tumor cells. Ten patients with symptomatic biopsy-confirmed KSHV-MCD were treated with high dose oral zidovudine (HDAZT), 600 mg every 6 hours, and valganciclovir (VGCV), 900 mg every 12 hours; the protocol was approved by the NCI Institutional Review Board and all patients gave informed consent. Treatment length of the first cycle was dependent on response, and ranged from 7–21 days. Subsequent cycle length was 21 days with treatment administered during the first 7 days. Treatment was stopped when patients achieved a complete response (CR) or plateau in response. Patient characteristics were: median age 40 (range 33-56); ECOG PS 2 (1-3); median enrollment CD4 count 189 (range 19-1319 UL); median HIV viral load <50 copies/ml^3 plasma (range <50 to 27,500). All patients were on combination antiretroviral therapy; this was adjusted during the time patients were on AZT. Eight patients had a history of KS. Median duration of MCD was 3.5 months (range 0.5-45 months); seven patients had received at least one prior therapy for MCD (range 1-6). All had MCD-related constitutional symptoms and CRP above 0.8mg/dl (median 13.1, range 1.06-38.7 mg/dl) at treatment initiation. A total of 112 cycles have been administered to date, with a median of 10 (range 3-29) cycles per patient.

Nine of 10 patients had documented improvement in constitutional symptoms, C-reactive protein levels or cytopenias. Five patients achieved an objective response as defined by the protocol (two CR and three partial remissions). The median survival has not been reached; the 12 month probability of survival is 70 percent, and patients remain alive from 12.5 to 32 months. The median PFS is 5.4 months; two patients have not yet progressed after 15.5 and 27 months on study. Seven patients remain alive. Treatment was well tolerated; toxicity included two patients with fatigue (grade [gr] 3), one with nausea (gr3), one with transaminitis (gr3) and one with insomnia (gr3). Grade 3 or 4 hematologic toxicity not attributable to disease was seen in only two patients. Two patients developed KSHV-associated lymphoma. Three infectious events occurred, a staphylococcal skin abscess, streptococcal meningitis and a streptococcal pneumonia. There were no neutropenia-associated infections. In summary, this preliminary data suggests that the combination of HDAZT and VGCV is well tolerated and has activity in patients with KSHV-MCD. Accrual continues.

This research was supported by the Intramural Research Program of the NIH, NCI.

Abstract O46

KAPOSI'S SARCOMA-ASSOCIATED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (KS-IRIS) IN AFRICA: INITIAL FINDINGS FROM A PROSPECTIVE EVALUATION

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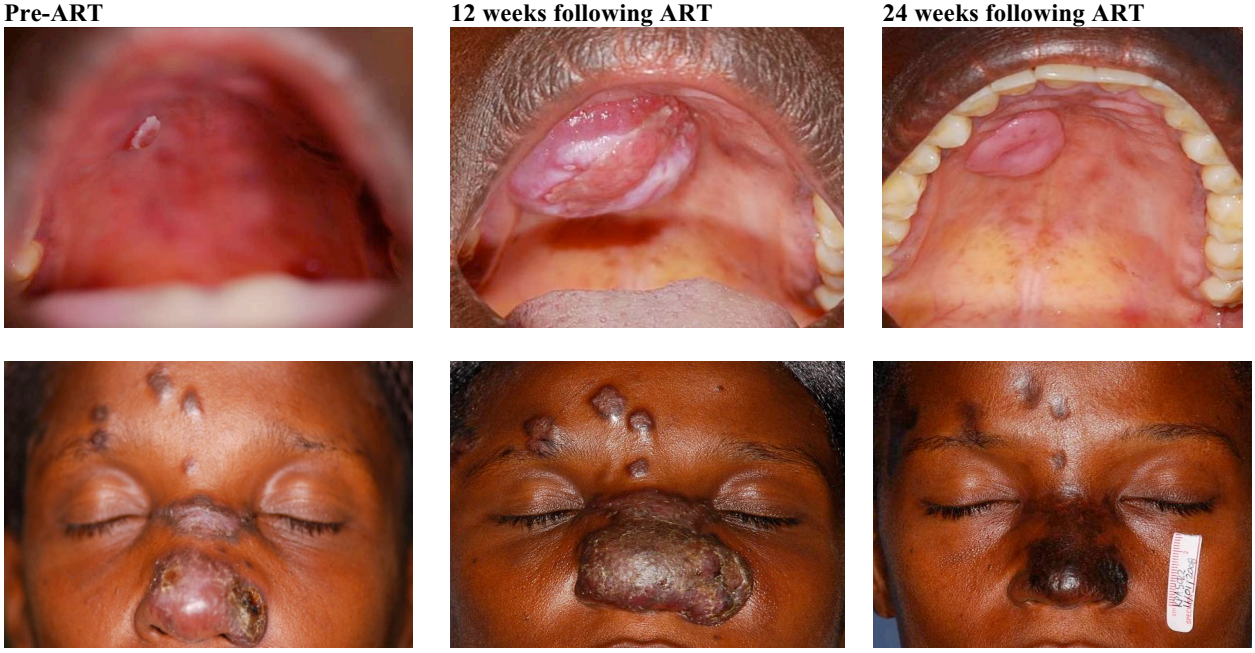
Background: Immune reconstitution inflammatory syndrome (IRIS) is a set of conditions, characterized by findings of inflammation, which occur in HIV-infected patients after initiation of antiretroviral therapy (ART). It is believed to result from an overly exuberant response to residual opportunistic pathogens by the newly reconstituted immune system. Specific manifestations of IRIS depend upon the pathogen being targeted, but among the variants of IRIS, Kaposi's sarcoma-associated IRIS (KS-IRIS) is one of the least understood—especially in resource-limited settings where KS is epidemic. Now that ART is becoming available in sub-Saharan Africa, we have hypothesized that KS-IRIS is likely to be most relevant in this region. This is because of the high prevalence of AIDS-related KS in sub-Saharan Africa (i.e., large number of patients with AIDS-KS initiating ART) and because of factors that theoretically may predispose to KS-IRIS, specifically higher KS lesion burden and lower pre-ART CD4+ T cell count.

Methods: In Kampala, Uganda, we studied the incidence and spectrum of KS-IRIS in a randomized trial for the initial therapy of AIDS-related KS. Participants without indications for chemotherapy were randomized to one of two different ART regimens and then evaluated every 4 weeks for 48 weeks with a questionnaire, physical examination, and digital photography to record signs and symptoms compatible with KS-IRIS. KS-IRIS was defined as development of a) any of the following in pre-existing KS lesions: swelling, pain or tenderness, paresthesia, erythema, or warmth; or b) not otherwise explained subcutaneous nodules, node enlargement, edema, or pleural effusion.

Results: Of the first 30 subjects evaluated, 17 (57%) exhibited ≥ 1 sign or symptom compatible with KS-IRIS. The most common finding was lesion swelling (43%), and there were several instances of dramatic lesion enlargement followed by spontaneous reduction (see photos from 2 subjects). Other manifestations included lesion pain or pares-thesia (33%), warmth or erythema (23%), femoral or inguinal node enlargement with scrotal swelling (n=1), and pleural effusion (n=1). The most fulminant KS-IRIS case featured diffuse lesion swelling and new diffuse subcutaneous nodules; death ensued but the causative role of KS-IRIS is unknown. Of the three participants with KS-IRIS that did not resolve spontaneously and who were given chemotherapy, two had a good response to liposomal doxorubicin.

Pre-ART | **12 weeks following ART** | **24 weeks following ART**



Conclusion: In sub-Saharan Africa, KS-IRIS occurs at a clinically relevant frequency with a wide spectrum of manifestations. Many of the findings are difficult to distinguish in real time from natural KS progression, and even some of the most dramatic cases can be self-limiting. This, coupled with the general lack of effective chemotherapy for KS in resource-limited settings, makes patient management complicated when KS-IRIS is suspected. In this setting, diagnostic tests are thus urgently needed to distinguish IRIS-based disease from natural progression of KS.

Abstract O18

AIDS-ASSOCIATED KAPOSI SARCOMA IN UGANDA: RESPONSE TO TREATMENT WITH HIGHLY ACTIVE ANTIRETROVIRAL THERAPY AND CHEMOTHERAPY

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Background: Highly active antiretroviral therapy (HAART) alone or in combination with systemic chemotherapy has been shown to be effective therapy for AIDS-associated Kaposi sarcoma (KS) in resource-rich countries. It is not known whether HAART or chemotherapy regimens available in resource-poor regions are effective in areas where KS is hyperendemic and typically more aggressive. Therefore, we conducted a retrospective cohort study to evaluate clinical response among patients with AIDS-associated KS treated with HAART alone or in combination with chemotherapy in Uganda.

Methods: Records of patients with AIDS-associated KS who had attended the Infectious Disease Institute (IDI) in Kampala, Uganda, for HIV care between January 2004 and December 2006 were linked to records at the Uganda Cancer Institute (UCI). Patients ≥18 years were eligible if they had histologically or clinically confirmed KS, HIV infection, and ≥1 KS visit after the initial diagnosis prior to December 2006. Demographic and clinical information were abstracted from records at both institutions. CD4 T-cell count during follow-up and HAART information was obtained from the IDI, while chemotherapy details were obtained from the UCI. Cox's proportional hazards models were used to identify predictors of improvement and resolution of KS disease separately.

Results: We identified 177 patients with a diagnosis of KS and ≥1 KS visit after diagnosis at either the IDI or UCI. Approximately half (53%) were female and the median age was 35 years. At the time of KS diagnosis, 94 (50%) had a BMI <18.5 kg/m^2, 150 (85%) had a Karnofsky score ≥70, 95 (54%) had T1 tumor stage, 45 (25%) had macular lesions, 50 (28%) had nodular lesions, and 10 (6%) had fungating lesions. Ninety-six (54%) had KS lesions in >1 location and 66 (37%) had ≥10 lesions. The median CD4 T-cell count was 87 cells/mm^3 (Interquartile range (IQR): 17-230). One year following KS diagnosis, the cumulative probability of improvement was 0.71 (95% CI: 0.63-0.79) and resolution was 0.08 (95% CI: 0.03-0.13). After two years, the cumulative probability of resolution was 0.28 (95% CI: 0.17-0.39). In univariate analyses, none of the baseline characteristics (sex, age, employment status, body mass index (BMI), Karnofsky score, and CD4 T-cell count) were associated with either improvement or resolution. Three clinical factors were associated with improvement: having lesions on the upper extremities (HR=1.7, 95% CI: 1.1-2.6, p=0.001), lesions on the hard palate (HR=1.5, 95% CI: 1.0-2.3, p=0.05), and lesions in >1 location (HR=1.6, 95% CI: 1.0-2.5, p=0.05). Three different clinical factors were associated with a decreased risk of resolution in univariate analyses: having nodular lesions (HR=0.19, 95% CI: 0.04-0.87, p=0.03), lesions on the lower extremities (HR=0.38, 95% CI: 0.15-0.96, p=0.04), and ≥10 lesions (HR=0.30, 95% CI: 0.09-0.94, p=0.04). Both HAART and chemotherapy were associated with improvement of disease, but only HAART was associated with resolution in univariate analyses. In multivariate analyses, male sex was the only variable other than HAART and chemotherapy that was independently associated with increased risk of improvement (HR=2.0, 95% CI: 1.3-3.1, p=0.002). For resolution, having a low BMI (<18.5, HR=0.15, 95% CI: 0.06-0.39, p<0.0001) and lesions located on the lower extremities (HR=0.12, 95% CI: 0.03-0.43, p=0.001) were independently associated with a decreased risk of disease resolution. Among patients on HAART, those receiving efavirenz- and protease inhibitor-containing HAART regimens were 6.9 (95% CI: 1.8-27, p=0.006) and 14 times (95% CI: 1.2-172, p=0.04) more likely to experience disease resolution compared to those receiving Triomune (stavudine, lamivudine, nevirapine). There was a trend towards a better chance of KS resolution with increasing dosage of chemotherapy (HR=1.02, 95% CI: 1.00-1.05, p=0.1).

Conclusions: HAART, used alone or in combination with systemic chemotherapy, is effective therapy for epidemic KS in Uganda. While the majority of patients experience improvements in KS lesions during the first two years of therapy, a very small minority resolved their disease. Factors such as the burden and location of lesions, gender, and under-nutrition may impact the success of KS therapy. Our data also suggest that the individual components of HAART regimens may have differential effects on KS response, with the most widely available drug in resource-limited settings (Triomune) showing less effectiveness than other antiretroviral combinations. Additional studies are required to define the optimal treatment of KS in endemic areas.

Abstract O16

A POPULATION-BASED STUDY OF HOW CHILDREN ARE EXPOSED TO SALIVA IN AFRICA: IMPLICATIONS FOR KSHV TRANSMISSION

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Background: Kaposi's sarcoma-associated herpesvirus (KSHV) is endemic among most sub-Saharan African populations. In those regions with the highest seroprevalences, there is a steady increase in KSHV seropositivity with age among children indicating that horizontal non-sexual transmission in childhood is the primary means of spread. While it is known that saliva is the body fluid that most commonly harbors KSHV and is therefore an important conduit for KSHV transmission, there is scant information on how African children are exposed to saliva and whether this exposure is preventable.

Methods: In two settings in or near Durban, South Africa—Cato Manor, an urban community, and KwaXimba, a rural community—we first used qualitative methods to identify the range of acts by which children are exposed to saliva from others. We conducted focus groups and semi-structured interviews with prototypical individuals who have contact with children ≤ 6 years old, including mothers, fathers, grandparents, siblings, and traditional healers. We also performed participant observation, where we lived amongst families with children, observing and participating in their everyday activities. We then created a structured questionnaire to quantitate the prevalence of the various saliva-passing acts we identified in the qualitative work. The questionnaire was administered to a door-to-door population-based sample of mothers, fathers, grandmothers and siblings of children ≤ 6 years old residing in either Cato Manor or KwaXimba.

Results: The qualitative work uncovered a total of 14 different practices by which children are exposed to saliva. For the structured questionnaire, a total of 258 mothers, 198 fathers, 204 grandmothers, and 236 siblings (97 brothers and 139 sisters) of children ≤ 6 years old (N=896; 398 from Cato Manor and 498 from KwaXimba) were interviewed; there were no refusals. In general, there were a number of practices by which saliva is passed to children, and a variety of different caregiver types engage in such practices (see Table for representative acts). These acts include those that expose oral-respiratory mucosa to saliva, including ones that were previously appreciated (e.g., premastication of food) as well as those less recognized (e.g., blowing herbs via mouth into a child's nostrils). Most of these acts were to fulfill a certain function (e.g., to relieve congestion), but others were ritualistic (e.g., rubbing premasticated herbs on the head or face). Acts that involved exposure of cutaneous surfaces to saliva included use of saliva to soothe an insect bite or wound. Finally, there were several heretofore unappreciated acts involving exposure of anal-rectal mucosa to saliva (e.g., insertion of saliva-lubricated finger into rectum to relieve constipation). This was one of the acts that was practiced differentially according to caregiver type.

Percent of caregivers who reported ever practicing acts involving saliva passage to children ≤ 6 years old

Practice	Mothers N=258	Fathers N=198	Grandmothers N=204	Siblings N=236
Shared toothbrush or toothstick	14%	9%	22%	19%
Cleaned eyes or face with tongue	19%	2%	44%	8%
Used mouth/cloth soaked with saliva to soothe insect bite	18%	10%	28%	8%
Premastication of food	67%	44%	81%	68%
Shared sweets or candy	55%	67%	65%	87%
Blown herbs via mouth into nostril	5%	4%	23%	0.8%
Rubbed premasticated herbs on head or face	64%	76%	82%	39%
Pushed substance into rectum from mouth through pipe	10%	4%	25%	*n/a*
Inserted finger lubricated with saliva into rectum	15%	4%	28%	*n/a*

Conclusion: A variety of acts, practiced by a variety of persons of differing relation to children, expose children to saliva in Africa; there is no single predominant practice. This poses substantial challenges for epidemiologic work seeking to identify specific routes by which KSHV is spread. The saliva-passing acts include ones that expose oral-respiratory mucosa and cutaneous surfaces to saliva as well as acts that expose anal-rectal mucosa to saliva. The latter exposure has similarities to how homosexual men in resource-replete settings (who also have high KSHV seroprevalence) are exposed to saliva, providing speculation regarding a common route of KSHV transmission. While there are many acts that expose African children to saliva, the majority of these practices could be replaced by other actions and are therefore theoretically preventable.

Abstract O64

IMPLEMENTATION OF A "SEE AND TREAT" CERVICAL CANCER PREVENTION PROGRAM LINKED TO HIV CARE IN ZAMBIA

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Objective: To establish a public-sector "see and treat" cervical cancer prevention program in Zambia by linking services to an HIV care and treatment infrastructure.

Methods: We modeled our infrastructure after a successful PEPFAR-funded HIV care and treatment program and selected HIV-infected women as our initial target population. Zambian nurses underwent classroom and clinically-mentored training to become primary service providers for screening women for cervical lesions using visual inspection with acetic acid (VIA) and treatment with cryotherapy, when indicated. Women with cryotherapy-ineligible lesions were referred to the university hospital where physicians were trained to perform punch biopsy and loop electrosurgical excision procedure (LEEP) for histologic evaluation. We utilized telecervicography for distance consultation as well as reviewing digital images weekly for quality assurance and continuing education. Patients with invasive cancer were referred for hysterectomy, radiation or palliation, depending on the stage of their disease

Results: Between January 2006 and October 2007 we established 14 prevention sites in outlying government-operated public health clinics and a modern outpatient evaluation center. During this 22-month period 8,823 women were screened, 41.5 percent of whom were HIV-infected. The 15 specially-trained nurses independently managed 83.3 percent of clients in the outlying clinics and referred the remaining 16.7 percent for further evaluation. Four physicians managed the outpatient evaluation center, performing punch biopsy or LEEP, the latter with minimal intra- and post-operative complications. Pathologic analysis confirmed 144 high-grade lesions (CIN2/3) and 149 invasive cancers (58% micro invasive).

Conclusions: We successfully established the first phase of a population-based "see and treat" cervical cancer prevention program in Zambia by linking the services to an HIV care and treatment program, integrating them into government-operated public health clinics and utilizing task-shifting and distance consultation to optimize care provision.

Abstract O58

PROFILING OF CELLULAR AND VIRAL MICRORNAS IN KAPOSI SARCOMA AND VIRAL-ASSOCIATED LYMPHOMA

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MicroRNAs are regulated by gene alteration at the DNA level, transcriptional regulation, and mature miRNA processing via Dicer. Thus far, few studies have simultaneously assessed all three levels of regulation. Using real-time quantitative polymerase chain reaction (QPCR)-based arrays, changes in gene copy number, pre-miRNA and mature miRNA levels for a large set of primary effusion lymphomas (PELs) and primary Kaposi Sarcoma biopsies (KS) has been determined; this includes miRNA gene alterations and concordant changes in pre-miRNA and mature miRNA expression levels. The real-time QPCR based approach confirmed many of the KSHV viral and cellular miRNAs previously cloned from PEL. However, array-based profiling also uncovered many novel PEL–specific miRNAs, since cloning-based approaches are not always saturating. The miRNA expression pattern for neither viral nor cellular miRNAs has hitherto been determined for KS. Furthermore, comprehensive SNP analysis of the viral miRNAs has been profiled to further examine the effects of sequence and processing. This defines the miRNA signature of PEL, KS, KSHV-infected cancers and experimental models. It shows that the transcriptional regulation of pre-miRNA as well as mature miRNA levels contribute non-redundant information that can be used in the classification of human tumors.

Abstract O82

PROFILING VIRAL AND HOST MICRORNA EXPRESSION IN CELLS INFECTED WITH KSHV AND EBV

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MicroRNAs are small non-coding RNAs of around 22 nucleotides that post-transcriptionally regulate gene expression. MicroRNAs have important functions in embryogenesis, hematapoiesis and carcinogenesis. Virally encoded microRNAs have been identified in EBV and KSHV and recent data suggest a role for both viral and host microRNAs in pathogenesis. We have developed a custom microarray to detect expression of all human and viral microRNAs. Probes are 60 mer oligonucleotides containing a 40 nucleotide non genomic linker sequence. Four replicates of each probe are represented on the array and eight arrays are printed on each slide. The arrays are printed by Agilent ensuring excellent quality control. We have used this array to profile viral and host microRNAs in KSHV in primary effusion lymphoma (PEL) cells infected with KSHV alone or KSHV and EBV, and in KSHV infected and uninfected endothelial cells. The effect of KSHV reactivation on viral and host microRNA expression was determined by induction of viral replication by an adenovirus vector expressing KSHV ORF 50, the master switch of lytic replication.

KSHV encoded microRNAs were detected in PEL cell lines during latency and levels of expression did not substantially change after reactivation. The EBV co-infected PEL cell lines also expressed high levels of the EBV encoded BART2 microRNAs but not the BHRF1-3 microRNAs. Interestingly, KSHV reactivation caused an increase of EBV encoded microRNAs. PEL lines display a unique cellular microRNA expression pattern which may contribute to their post-germinal center arrested phenotype.

In addition, we detected for the first time viral and cellular microRNA expression patterns in two different endothelial cell lines (TIVE and SLK) latently infected with KSHV. KSHV infection leads to a marked induction of human microRNA expression including several microRNAs with known roles in carcinogenesis. Ongoing studies include microRNA profiling of EBV infected B cells and lymphoma cell lines as well as KSHV infected primary B cells.

Viral microRNA are expressed in infected cells and likely modulate both viral and host genes relevant to lymphomagenesis. EBV and KSHV infection also upregulate expression of host microRNAs previously shown to play a role in tumorogenesis.

Abstract O31

RAPAMYCIN REDUCES PRIMARY EFFUSION LYMPHOMA PROGRESSION BY TARGETING VEGF PRODUCTION AND VEGF RESPONSES

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Kaposi's sarcoma herpesvirus (KSHV)-infected primary effusion lymphoma (PEL) typically presents as a malignant effusion in body cavities that disseminates to distant sites. There is a need for new therapies for PEL as most patients rapidly succumb in spite of high-dose chemotherapy. We examined the potential utility of Rapamycin for PEL treatment. We found that the downstream effectors of the mammalian target of Rapamycin (mTOR) p70S6k and S6 are constitutively phosphorylated in PEL cells, and that Rapamycin inhibits this constitutive p70S6k and S6 phosphorylation. Rapamycin reduces PEL proliferation but is not cytotoxic for PEL cells. Intraperitoneal injection of PEL cells in NOD/SCID mice causes experimental effusion lymphoma. Rapamycin delayed PEL development in this model, markedly reduced accumulation of ascites ($P=0.009$), prevented formation of solid tumor masses, and a significantly extended mouse survival ($P<0.001$). However, Rapamycin did not eradicate PEL in mice. We examined the mechanisms by which Rapamycin reduces PEL progression in this mouse model. Levels of VEGF, which promotes vascular permeability and is critical to the accumulation of body cavity fluids, were significantly reduced in ascites of Rapamycin-treated mice compared to controls ($P=0.009$). Rapamycin inhibited VEGF-induced phosphorylation of VEGF receptor (R) 2 in endothelial cells and activation of the downstream effectors of VEGFR2 phosphorylation src and enos (endothelial nitric oxide synthase). Rapamycin did not alter KSHV genes transcription in PEL cells, and only insignificantly reduced levels of IL-10, the principal growth factor for PEL, in ascites of PEL-bearing mice. Reduction of VEGF secretion by PEL and impairment of endothelial cell responses to residual VEGF likely explain reduced accumulation of ascites in Rapamycin-treated mice. The failure of Rapamycin to significantly reduce IL-10 levels in PEL-bearing mice and to promote PEL cell death likely explain PEL persistence in mice treated with Rapamycin. The successful use of Rapamycin to reduce PEL effusion and disease progression by reducing VEGF secretion and endothelial cell responses to VEGF illustrates a novel application of mTOR inhibition that targets the tumor microenvironment rather than the tumor cells, and is applicable to the treatment of PEL and other malignancies characterized by ascites accumulation and increased vascular permeability.

Abstract O22

TARGETING THE PI3K/AKT/MTOR PATHWAY IN KSHV-ASSOCIATED CANCERS

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Kaposi's sarcoma-associated herpesvirus (KSHV) is linked to three different human cancers: Kaposi's sarcoma (KS), primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD). We have previously reported that the PI3K/Akt/mTOR pathway is critical for the survival of KSHV-infected endothelial cells and B cells, and have demonstrated that Rapamycin/Sirolimus, an inhibitor of mTOR, can induce PEL cell death *in vitro* and *in vivo* (Sin et al., Blood. 2007. 109(5):2165-73). We have now extended these findings and demonstrate that therapeutic targeting of other members of the PI3K/Akt/mTOR signal transduction pathway can also induce cell death in PEL *in vitro* and inhibit tumor growth in murine xenograft models. Importantly, some of these novel drug candidates have passed clinical trials for other indications and can therefore be tested for efficacy against KS and AIDS-associated lymphomas.

Abstract O23

HIGH RESOLUTION PROFILING OF DNA COPY NUMBER AND GENE EXPRESSION CHANGES IN AIDS-RELATED LYMPHOMA

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The incidence of B cell non-Hodgkin lymphoma (NHL) is increased substantially in the HIV-1-infected immunosuppressed population. Clinically, AIDS-related lymphoma (ARL) is more aggressive and has a worse prognosis than in non-immunocompromised patients, though there has been significant improvement in the post-HAART era. While HIV-induced immunosuppression, chronic antigenic stimulation, and cytokine overproduction may contribute to differences in disease progression and outcome, distinct genetic changes in ARL may also mediate these effects. Chromosomal DNA copy number alterations are known to play a major role in lymphomagenesis and have been studied in non immunocompromised patients for some NHLs.

To determine whether ARL has distinct molecular features and pathogenetic mechanisms, we assessed genome-wide copy number changes and gene expression profiles using 24 HIV+ cases with B cell NHL obtained from the AIDS and Cancer Specimen Resource (ACSR). High resolution aCGH was performed using the 250 K NspI SNP platform (Affymetrix). Selecting for frequent aberrations present in >20 percent of the cases, 43 chromosomal gains and 30 chromosomal losses were identified. Many of these regions replicated copy number changes previously reported for high-grade B cell NHL, including: gains of X, 12, 11q, 8q, 2p16.1, 9p11.2, 17q21, and 3p; and losses of 1p36, 4q23, 9p21.3, 13q34, and 17q23. The aberrant regions ranged in size from 12 kb to 6.5 Mb, providing concise boundaries for these intervals, which harbor a relatively small number of genes. Several novel recurrent regions were also identified, including a loss of 7q21.2-q22.1, and gains of 4p16.1, 15q11.2, and 19p13.2. To identify coordinate changes in gene expression associated with the chromosomal aberrations, gene expression profiles were generated using the Human Genome U133 Plus 2.0 Array (Affymetrix). This approach identified specific candidate genes for these intervals that may contribute to ARL pathogenesis. Gene expression profiles were also used to cluster the ARL cases. Gene signatures that reliably distinguish activated B-cell (ABC) like Diffuse Large B Cell Lymphoma (DLBCL), germinal center B-cell (GCB) like DLBCL and Burkitt lymphoma (BL), were applied to the ARL gene expression profiles.

The ARL samples showed no correlation with the BL gene signature. In contrast, the ABC and GCB gene signatures divided the ARL samples into two distinct groups with either a predominantly ABC- or GCB-type expression. Assigning ABC and GCB phenotypes to these groups of samples, Goeman's global test found a highly significant association ($p = 0.00012$) of the ABC and GCB phenotypes with the DLBCL ABC and GCB predictor gene set. The classification of AIDS-related DLBCLs into distinct ABC and GCB groups has significant implications given the differences in pathogenesis, biology, and survival for these two subtypes of DLBCL.

Abstract O28

HIV INDUCES THE EXPRESSION OF ACTIVATION-INDUCED CYTIDINE DEAMINASE (AICDA) IN B CELLS THROUGH A DIRECT INTERACTION BETWEEN VIRION-ASSOCIATED CD40L AND CD40

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NHL is a common AIDS-associated cancer. NHL is thought to occur due to errors in Class Switch Recombination (CSR) and Somatic Hypermutation (SHM); both of these events occur in Germinal Center (GC) B cells. Activation-Induced Cytidine deaminase (AICDA) is an enzyme required for both CSR and SHM. Since errors in both CSR and SHM lead to the seminal molecular lesions in NHL development, it is thought that AICDA plays a central role in the genesis of these cancers. It has been shown by us and others that several oncogenic viruses (EBV, HCV, HPV) can induce AICDA expression. We have also shown that AICDA expression in PBMC is elevated prior to AIDS-NHL diagnosis. Additionally, several studies have shown that exposure of B cells to HIV can result in their activation.

Based on this, we assessed the ability of HIV to induce AICDA expression in normal human B cells. We hypothesized that the HIV virion itself might be inducing AICDA expression, through a direct interaction between the virus and B cells involving the ligation of CD40 on B cells by CD40L. CD40L classically induces AICDA expression in B cells. It is known that CD40L is incorporated into the HIV envelope membrane. We observed that HIV grown in PBMC induces AICDA mRNA expression in B cells and that these virions express CD40L. Additionally, we created HIV that do not express CD40L, as well as HIV that does contain CD40L. Only viruses expressing CD40L induced AICDA expression in B cells. AICDA expression in B cells exposed to viruses expressing CD40L was abrogated by anti-CD40L blocking antibody, but not by exposure to AZT.

In conclusion, HIV viruses that express CD40L on their surfaces induce AICDA expression in B cells, and this induction is due to a direct interaction between the CD40L on these virions and CD40 on B cells. Also, HIV infection of the B cells does not play a role in this induction. CD40L-expressing viruses induced AICDA expression at both the mRNA and protein levels. These findings are of great interest as they confirm a direct role for HIV in B cell activation, and in the induction of a gene (AICDA) that plays a central role in NHL development. Therefore, HIV has the potential to contribute to NHL development through a direct interaction with B cells.

Abstract O83

EXPRESSION AND FUNCTION OF THE CHEMOKINE, CXCL13, AND ITS RECEPTOR, CXCR5, IN AIDS-ASSOCIATED NON-HODGKIN'S LYMPHOMA

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AIDS-associated Non-Hodgkin's lymphoma (AIDS-NHL) remains a problem even in the era of effective anti-retroviral therapy. Recent studies have suggested that the chemokine, CXCL13, and its receptor, CXCR5 may play a role in B cell tumors (non-AIDS-associated). Normally, CXCL13 is expressed in secondary lymphoid tissues and directs the homeostatic movement of CXCR5(+) B cells through these areas.

To evaluate the role that CXCL13 and CXCR5 might play in AIDS-NHL, serum of individuals (n=46) who ultimately developed AIDS-NHL was obtained from the Multicenter AIDS Cohort Study (MACS) at UCLA. The AIDS-NHL serum specimens tested were collected at a mean of 8.9 months prior to NHL diagnosis (SD = 7.9 months). Sera from AIDS (non-lymphoma), healthy HIV-positive, and HIV-negative control subjects were also included in the study. The mean CXCL13 level in the AIDS-NHL group (158 pg/ml, SD = 153) was ~50 percent higher than the AIDS control group (98.4 pg/ml, SD = 70.9, P = 0.02). Furthermore, CXCL13 levels correlated with sCD44 levels in the AIDS-NHL group (R = 0.31, P = 0.04), but not in the AIDS control group (R = 0.07; P = 0.7, data not shown); we previously showed that sCD44 levels are elevated prior to AIDS-NHL development. CXCL13 levels in the AIDS-NHL group were also ~2.5 times greater than levels in the HIV-positive group, and ~7 times greater than levels in the HIV-negative group (P < 0.001 for both comparisons).

Next, tissue arrays were obtained from the AIDS & Cancer Specimen Resource (ACSR) that contained numerous sections of primary AIDS-NHLs, including both the Burkitt and diffuse large cell subtypes. By immunohistochemistry, all primary AIDS-NHLs (24/24) expressed CXCR5, and 22/24 of the AIDS-NHL specimens also showed expression of CXCL13. Cell lines derived from primary AIDS-NHL tumors also showed strong expression of CXCR5, and occasionally, low levels of expression of CXCL13. AIDS-NHL cell lines also demonstrated chemotaxis towards CXCL13.

These results indicate that CXCL13 and CXCR5 may play a role in the biology of AIDS-NHL, possibly by affecting the movement of pre-malignant and/or malignant B cells.

Abstract O12

INCIDENCE AND RISK FACTORS OF HIV-ASSOCIATED NON-HODGKIN-LYMOPHMA IN THE ERA COMBINED ANTI-RETROVIRAL THERAPY. A EUROPEAN MULTI-COHORT STUDY

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Background: Incidence and risk factors of HIV-associated non-Hodgkin lymphoma (NHL) in the era of combined anti-retroviral therapy (cART) have not been well defined. We analyzed incidence and risk factors for HIV-related NHL in the era of cART within the framework of a large European multi-cohort collaborative study.

Methods: We analyzed the data of HIV-infected adult patients (over 16 years old) who were cART naïve at inclusion and started cART after January 1, 1998. cART was defined as regimen with at least three antiretroviral drugs. Patients had to have at least one CD4 cell count measurement after January 1, 1998, and before start of HAART or diagnosis of NHL. Both patients developing Primary Brain Lymphoma and systemic NHL were included in the analysis. Incidence rates were calculated based on the Poisson distribution; risk factors were estimated using crude and adjusted Weibull models, with random effects to account for heterogeneity between cohorts. Models with time varying covariates were used to explore the effect of CD4 cells counts and plasma HIV-RNA loads over time. The database included a total of 67,659 patients. Seventeen percent of patients (11,354) were excluded from the analysis because they did not meet the inclusion criteria outlined above.

Results: We included 56,305 patients from 22 cohort studies across Europe. During 212,042 person-years of follow up, 583 patients developed NHL. The incidence in patients not on cART was 519 (95% CI 448 to 602) per 100,000 person-years compared to 229 (95% CI 208 to 252) per 100,000 person-years in those on cART. The incidence of Primary Brain Lymphoma was 56.7 (95% CI 36 to 89) per 100,000 person-years in patients not on CART and 24 (95% CI 18 to 33) per 100,000 person years in patients on cART. The incidence of systemic Non-Hodgkin Lymphoma other than Primary Brain Lymphoma was 463 (95% CI 395 to 541) per 100,000 in patients not on cART and 205 (95% CI 185 to 227) per 100,000 person years in patients on cART. In cART naïve patients the risk for NHL increased with age, high plasma HIV-RNA loads and decreasing CD4 cell counts. In patients receiving cART risk factors for developing NHL were low CD4 cell counts, higher age, belonging to the transmission risk group men having sex with men and previous diagnosis of Kaposi Sarcoma.

Conclusions: Combined anti-retroviral therapy reduces the risk of developing NHL. In the era of cART more advanced immunodeficiency is the dominant risk factor for developing NHL both in patients receiving and not receiving cART for treatment of HIV infection.

Abstract O11

DEVELOPMENT AND APPLICATION OF A REAL TIME PCR ASSAY FOR DETECTION AND QUANTIFICATION OF MERKEL CELL VIRUS (MCV) IN ARCHIVED FORMALIN FIXED PARAFFIN EMEBEDDED TISSUE SAMPLES OF MERKEL CELL CARCINOMA AND OTHER CANCERS

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Background: Merkel cell carcinoma (MCC) of the skin is a highly malignant primary cutaneous neuroendocrine malignancy. Older individuals, patients undergoing immunosuppressive therapy for organ transplant, and patients with HIV infection who are immunosuppressed are at a higher risk for developing MCC. MCC may share etiologic influences with other malignancies, and increased risks for other cancers in MCC patients have been reported. Feng et al recently identified a new human polyoma virus, Merkel Cell Virus (MCV), in MCC. The discovery of MCV raises important questions. Is MCV obligatory for MCC? The absence of the viral genome in 20 percent of the 10 MCC cases in the index study suggests that some MCC may not be associated with MCV. What is the natural reservoir for this virus? Feng et al demonstrated low levels of detection in skin samples from non-disease controls. How prevalent is an MCV latent or active infection? Can detection be carried out in archived formalin fixed paraffin embedded (FFPE) tissue samples of MCC to clarify the association between MCV and MCC? Until such time as tools for serology are available polymerase chain reaction (PCR) based detection methods, particularly those that can effectively be applied to small and FFPE samples, will be valuable.

Methods: A real time PCR assay for MCV was developed using a known source of fresh, frozen MCC with confirmed integrated MCV kindly provided by Dr. Patrick Moore, University of Pittsburgh. The assay readily and reproducibly amplified MCV DNA. To test the assay in FFPE tissues, we assembled a 25-case series of primary and metastatic MCC archived from 1994 to 2008. A tissue microarray (TMA) was constructed to confirm the MCC diagnosis by a battery of immunohistochemistry tests. These 25 FFPE samples included MCC from 22 individual patients some with and some without known immunodeficiency. Duplicate diagnostic blocks were available from nine patients. The PCR samples were coded off site so the identity and interrelationships of the samples were unavailable to persons performing the PCR assay. In addition to reagent controls, we included DNA from 12 colon carcinomas and 20 breast carcinomas.

Results: The MCV real-time PCR assay had excellent linearity with an input of genomic DNA in the range of 10 ng to 0.1 ng corresponding to 1000 to 10 cells. With 40 cycles of amplification, DNA from peripheral blood lymphocytes (PBL) used as a negative control reproducibly scored negative for amplification of MCV. This assay readily and reproducibly amplified MCV DNA from the known source of MCV in fresh, frozen MCC. We demonstrated that this PCR assay could detect MCV in as few as 10 cells. No DNA controls and PBL samples used as negative controls yielded a Ct of 40 as expected. The Ct values for the confirmed MCC FFPE samples ranged from 18 to 40, with a mean value of 31, demonstrating heterogeneity in the association of MCV with MCC. PCR assay was readily able to amplify MCV independent of the age of the MCC tissues. All duplicate MCC tissues showed strong concordance in detection. Level of MCV DNA associated in duplicate biopsies was tightly concordant in six of nine. Diagnostic tissue from one patient included three independent sites, biopsied at different time points in the course of the disease. MCV was detected in two of these biopsies but the third axillary metastatic MCC tissue was negative. An inverse correlation was suggested between patient survival and the level of MCV DNA observed. MCV DNA was not detected in nine colon cancer tissues, but a low level (Ct 38) of MCV DNA was reproducibly detected in three of 20 breast cancers.

Conclusion: We have developed and validated a PCR assay to reliably detect and quantify MCV DNA from archived FFPE tissues. Using this newly developed real time PCR assay, we confirmed the association of MCV with MCC and demonstrated heterogeneity of MCV association with MCC. Furthermore, this PCR assay suggests that MCV can be detected in DNA from tissues other than MCC and thus might be useful in assessing the prevalence of MCV in various malignancies and body sites. Much remains to be done, including investigation of 1) correlations of MCV positivity in MCC with other biomarkers and 2) the possibility that MCC tissues demonstrate immunohistochemical cross-reactivity with available polyoma T virus reagents, both of which are in progress.

Abstract O37

AN INVASION MECHANISM FOR HUMAN PAPILLOMAVIRUS RELATED CANCERS: HPV 16 E6 DEGRADES PTPN13 ALLOWING ENHANCED MAP KINASE SIGNALING

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Oncogenic forms of human papillomavirus (HPV), most commonly HPV 16, are a causative factor in more than 90 percent of cervical and 25 percent of head and neck squamous cell carcinomas (HNSCCs). We have recently described a novel function of the PDZ binding motif of the high risk HPV 16 E6 protein in that it physically associates with and causes degradation of a non receptor protein tyrosine phosphatase (PTPN13). Here, we describe an important synergy between PTPN13 loss and Ras activating oncogenes that results in enhanced signaling through the Ras/RAF/MEK/Erk cascade. We show that in a syngeneic mouse model of tonsillar squamous cell carcinoma, E6 or shRNA mediated PTPN13 loss synergizes with ErbB2 for invasive growth of mouse tonsil epithelial cells in vivo. Examination of signaling pathways downstream of ErbB2 and Ras revealed that in mouse and human epithelial cells, PTPN13 loss correlates with enhanced MAP Kinase activity. Transfection experiments in HEK 293 cells showed that co-expression of ErbB2, EGFR, or H-Ras^{V12} with PTPN13, as compared to an empty vector control, resulted in decreased levels of phospho-Erk and phospho-MEK, while a phosphatase null PTPN13 mutant was unable to inhibit MAP Kinase signaling. Through analysis of human tumor samples, we have identified a subset of HPV negative HNSCC's that have functionally significant PTPN13 phosphatase domain mutations. Finally, we have shown MAP Kinase inhibition by pharmacologic agent U0126 results in decreased phospho-Erk and inhibition anchorage independent growth in tumorigenic cell lines that have lost PTPN13, either through expression of E6 or downregulation by shRNA. These findings suggest an important synergy between PTPN13 loss and MAP Kinase activating cellular oncogenes commonly found in HPV related cancers. Inhibition of the MAP Kinase pathway may provide a potential therapy based on a viral mechanism of transformation.

Abstract O10

GENERATION OF VFLIP TRANSGENIC MICE: A MODEL TO STUDY KSHV-ASSOCIATED LYMPHOMAGENESIS

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Primary effusion lymphoma (PEL) is a distinct subtype of aggressive Non-Hodgkin's lymphoma (NHL), specifically associated with infection by Kaposi's sarcoma-associated herpesvirus (KSHV). Several *in vitro* observations suggest that vFLIP, a protein expressed during latency, is an important viral oncogene. It is essential for the survival of KSHV-infected PEL cells, mainly by constitutively activating the NF-κB pathway.

To assess the role of vFLIP in the pathogenesis of PEL, we developed transgenic mouse models expressing vFLIP in B-cells. The experimental approach used has been a conditional recombinant activation of vFLIP, by using the ROSA26 knock-in system. A specifically restricted expression of the transgene in CD19+ B-cells has been achieved by crossing the ROSA26.vFLIP knock-in mice with other mice expressing Cre recombinase under the control of the CD19 promoter. These mice have also been crossed with the LANA transgenic mice to assess a potential synergistic effect between these two KSHV latent proteins in the lymphomagenic process of PEL. vFLIP expression in the CD19+ B-cells results in splenomegaly, with an increase in both T and B-cells, and with a relative increase of the T *versus* B-cell ratio. Although primary follicles were enlarged, the expression of vFLIP in the CD19+ B-cells results in lack of germinal center formation in the spleen, lymph nodes and intestine, and in partially impaired class-switching recombination. These results indicate that, by constitutively activating the NF-κB pathway in pre-germinal center B-cells expressing CD19, the normal B-cell differentiation is impaired, and provide clues about possible aberrant differentiation in PEL cells.

Abstract O14

IMMUNODEFICIENCY, HIV RNA PLASMA VIRAL LOAD AND RISK OF AIDS-DEFINING AND NON-AIDS-DEFINING NEOPLASIA, ANRS CO3 AQUITAINE COHORT (1998-2006)

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Background: The risk of neoplasis is increased in HIV-infected subjects. Beside traditional determinants of cancer occurrence, a specific role of HIV-related immunosuppression is strongly suspected and a more complex relationship between HIV and antiretroviral therapy (ART) cannot be excluded. Our objective was to disentangle the relationship between some frequently diagnosed cancers in HIV-infected patients and immunosuppression, HIV and ART exposure.

Methods: Patients from the ANRS CO3 Aquitaine Cohort were included in this study if they had a duration of follow-up of at least three months, at least two follow-up visits recorded within the study period (1998 to 2006) and if one HIV RNA plasma viral load (VL) was collected within the first follow-up visit. Durations of exposure were calculated as the time durations with CD4 count <200 and 500 cells/mm^3 or VL >500 copies/mL. Multivariate modelling was based on extended Cox proportional hazards models for time-time dependent covariates and delayed entry (at time of first VL measurement). ART exposure was defined as the prescription of at least three antiretroviral drugs.

Results: Among the 4,194 patients included, 61 cases of Non-Hodgkin's lymphoma, 41 Kaposi's sarcoma, 41 bronchopulmonary and upper respiratory tract cancers, 20 skin cancers, 18 cases of Hodgkin's disease, 16 hepatocarcinomas and 14 anal cancers were reported during the study period. Kaposi's sarcoma was independently associated with each year spent with CD4 <200 (Hazard ratio [HR] = 1.53; 95% CI: 1.23 – 1.90; $p < 0.001$), each year of ART exposure (HR = 0.74; 95% CI: 0.61 – 0.90; $p < 0.003$) and male gender (HR = 5.26; 95% CI: 1.66 – 16.66; $p < 0.006$). Non-Hodgkin's lymphoma was associated with each year spent with HIV RNA >500 (HR = 1.34; 95% CI: 1.19 – 1.51; $p < 0.001$), each year with CD4 <200 (HR = 1.31; 95% CI: 1.12 – 1.53; $p < 0.001$), and each year of ART exposure (HR = 0.86; 95% CI: 0.75 – 0.99; $p < 0.03$). Hepatocarcinoma was independently associated with each year spent with CD4 <500 (HR = 1.31; 95% CI: 1.06 – 1.63; $p = 0.012$). Anal cancer was also independently associated with each year spent with HIV RNA >500 copies/mL (HR = 1.31; 95% CI: 1.02 – 1.68; $p = 0.033$). Regarding the associations between skin, anal and bronchopulmonary cancers and CD4 <200, the adjusted analyses showed p-values of 0.058, 0.112 and 0.13, respectively).

Conclusion: Together with immunosuppression, HIV VL may be independently associated with an increased risk of some cancers, AIDS-defining or not. Due to the limited statistical power to investigate several types of cancers that are still relatively infrequent, our results need to be confirmed by further studies, possibly collaborative and including lower-income country cohorts. Moreover, maintaining a high CD4 count, a strict control of HIV VL with fully suppressive ART could have a direct and measurable impact in preventing the currently predictable increasing occurrence of cancer in HIV-infected patients, in addition to other prevention policies.

Abstract O21

INFLUENCE OF HIV-RELATED IMMUNODEFICIENCY ON THE RISK OF HEPATOCELLULAR CARCINOMA

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Objective: To investigate HIV-related immunodeficiency as a risk factor for hepatocellular carcinoma (HCC) among persons infected with HIV, whilst controlling for the effect of frequent co-infection with hepatitis C and hepatitis B viruses.

Design: A case-control study nested in the Swiss HIV Cohort Study (SHCS).

Methods: Twenty-six HCC cases were identified in the SHCS or through linkage with Swiss Cancer Registries, and were individually matched to 251 controls by SHCS centre, gender, HIV-transmission category, age and year at enrolment. Odds ratios (OR) and corresponding confidence intervals (CI) were estimated by conditional logistic regression.

Results: All cases and 53 percent of controls (92% of controls among intravenous drug users [IDU]) were positive for hepatitis B superficial antigen (HBsAg) or antibodies against HCV (anti-HCV). HCC cases included 14 IDU (three positive for HBsAg, 13 for anti-HCV), and 12 men having sex with men (MSM)/heterosexual/others (11 positive for HBsAg, three for anti-HCV), revealing a strong relationship between HIV transmission route and hepatitis viral type. Latest CD4+ cell count was significantly associated with HCC (OR for lowest *versus* highest tertile=4.26, 95% CI: 1.18-15.5). This effect was concentrated among MSM/heterosexual/others (OR=18.2, 95% CI: 1.61-207) rather than IDU (OR=1.79, 95% CI: 0.39-8.23). HAART use was not significantly associated with HCC risk (OR for ever *versus* never=0.59, 95% CI: 0.18-1.91).

Conclusions: More than CD4+ cell counts increased the risk for HCC among persons infected with HIV, an effect that was particularly evident for HBV-related HCC arising in non-IDUs.

Abstract O44

CISPLATIN AND RADIATION THERAPY INDUCES AN IMMUNOLOGIC CLEARANCE OF HPV-POSITIVE HEAD AND NECK CANCER

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HPV is currently the most identifiable cause of head and neck squamous cell cancer (HNSCC). Intriguingly, although these tumors present at an advanced stage multiple studies have shown that they are more curable compared to HPV- HNSCC. To better understand why these more advanced tumors are curable, we have examined the response to treatment of HPV-positive cancer with radiation and cisplatin.

We have created a syngeneic mouse model of HPV-positive and HPV-negative HNSCC by transforming mouse primary tonsil epithelial cells with either HPV oncogenes or a non-antigenic RNAi strategy that affects similar oncogenic pathways. Using these transformed cells we examined the effect of radiation on HPV-positive and HPV-negative tumors in immune competent and immune incompetent mice. In addition to the mouse cells we also examined responses in human cancer cell lines. The results from our in vitro clonogenic survival assays demonstrate that HPV-positive cells are more resistant to radiation and cisplatin therapy compared to their HPV-negative counterparts. This result was consistent for human cancer cell lines, HPV transformed primary tonsil keratinocytes and HPV transformed mouse primary tonsil keratinocytes. Surprisingly the reverse sensitivity was observed in HPV-positive tumors after radiation and cisplatin therapy in vivo. HPV tumors were much more sensitive in vivo and at 20 gray of radiation HPV-positive tumors were eradicated compared to the HPV-negative counterpart that showed persistent growth. In the same manner, cisplatin therapy in vivo was able to result in a cure of HPV-positive tumor but not HPV-negative tumors. To understand whether an immune response could explain this enhanced eradication, we repeated the same studies in syngeneic mice lacking an ability to mount a cytolytic t-cell response. In these immune incompetent mice neither radiation nor cisplatin resulted in a cure. Adoptive transfer of wild-type immune cells into the immune incompetent mice restored immune clearance during cisplatin treatment. Our results prove that HPV-positive tumors are not more curable based on an increased epithelial sensitivity to cisplatin or radiation therapy, but rather that these therapies induce a tumor clearing immune response to this antigenic cancer. The implications from these results may lead to novel therapies that enhance tumor eradication for HPV-positive cancers.

POSTER ABSTRACTS (Listed Numerically)

Abstract 1

A RETROSPECTIVE ANALYSIS OF HIV-ASSOCIATED KAPOSI'S SARCOMA IN PATIENTS WITH NON-DETECTABLE HIV VIRAL LOADS AND CD4+ COUNTS GREATER THAN 300CELLS/µL

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In the HAART era, the incidence of HIV-associated Kaposi's sarcoma (KS) has declined precipitously for countries with ready access to anti-retrovirals. Patients with newly diagnosed KS typically have low CD4+counts and high HIV viral loads (VLs). Several recently published reports (*NEJM* 2007;357:1352–3, *NEJM* 2008;358:535-6, *AIDS* 2008;22:551-2) suggest that patients with KS may require treatment despite effective HAART and that KS may progress even in the setting of suppressed HIV VLs and adequate CD4+ counts.

To investigate this further, we examined the demographic and HIV-related clinical data of 91 KS patients attending our HIV outpatient clinic between 1996 and 2008. Twenty of the 91 patients (22 %) had either newly diagnosed KS or persistent or progressive disease despite CD4+ counts >300 cells/µL and undetectable HIV VLs. Nineteen of these 20 patients were males. The median age was 43 years (range 25 to 59), the median time since onset of HIV infection was 156 months (range 24 to 276) and the median duration of HAART was 60 months (range 12 to 144). Nine (45%) patients had a KS stage of T0S0, five (25%) had T1S0, three (15%) had T0S1, three (15%) had T1S1; no patient had KS visceral involvement. All 20 patients received specific anti-KS treatment in addition to HAART including liposomal doxorubicin (65%), paclitaxel (15%), radiation (20%) and novel clinical agents (25%). After a median follow up of 52 months (range 6 to 120), eight (40%) had complete regression of KS, six (30%) had partial regression, one (5%) had stable disease and five (25%) had KS progression. In this retrospective analysis, a substantial proportion of KS patients had undetectable HIV VLs and CD4+counts greater than the level typically associated with opportunistic infections and required systemic anti-ks therapy. This raises important questions regarding the mechanisms of KS progression and the management of KS in such patients.

Abstract 2

AIDS-ASSOCIATED PLASMABLASTIC LYMPHOMA PRESENTING AS A POORLY DIFFERENTIATED ESOPHAGEAL TUMOR: A DIAGNOSTIC DILEMMA

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Plasmablastic lymphoma (PBL) is a rare form of diffuse large B-cell lymphoma characterized by weak or absent expression of conventional B-cell markers and strong expression of plasma cell markers. It is strongly associated with HIV and Epstein Barr Virus (EBV) infection, and shows an unusual tropism to the oral cavity. Herein we describe a patient with AIDS who presented with weight loss and dysphagia owing to a large ulcerative gastroesophageal mass. His radiographic and endoscopic findings and long history of cigarette consumption suggested esophageal carcinoma. The patient had a history of multidrug resistant HIV and had been placed on salvage HAART (tenofovir, emtricitabine, ritonavir and atazanavir). Despite recent weight loss of 15 pounds, his CD4+ count had improved from 50 to 180 cells/μL and his HIV viral load, previously >100,000 copies/ml was now undetectable. Biopsy demonstrated a poorly differentiated tumor staining negatively to routine lymphoid markers including CD20. However, gene rearrangement studies confirmed a B-cell process and a more detailed immunohistochemistry analysis revealed the cells expressing CD138 (plasma cell antigen). In situ hybridization studies were positive for EBV but negative for Human Herpes Virus type-8. These findings were diagnostic of PBL and the patient was treated with combination chemotherapy consisting of liposomal doxorubicin, cyclophosphamide and etoposide. After six cycles of chemotherapy, his dysphagia and weight loss resolved and a positron emission tomogram showed complete resolution of the esophagogastric mass. The patient remains in complete remission 12 months later.

Our report underscores the importance of a broad array of viral and molecular studies needed to establish the diagnosis of PBL, which may mimic a variety of entities including carcinoma, melanoma, Kaposi's sarcoma, plasmacytoma and primary effusion lymphoma. Furthermore, our patient's diagnosis of lymphoma within 1 year of HAART initiation, and in the context of a rapidly improving CD4+ cell count and non-detectable HIV viral load may represent a case of immune reconstitution syndrome associated Non-Hodgkin's lymphoma.

Abstract 3

FOUR YEAR SURVIVAL IN UNTREATED AIDS RELATED-KAPOSI SARCOMA (AIDS-KS) IN JOS, NIGERIA

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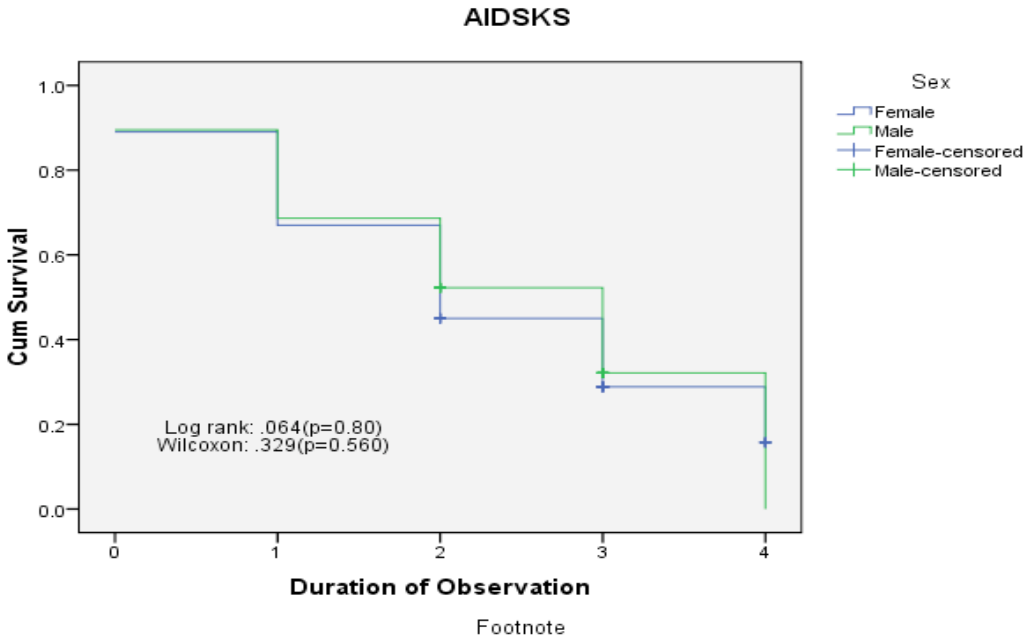
Background: AIDS-KS remains a significant cause of morbidity and mortality especially in sub-Saharan Africa in the face of ART scale-up. We compare survival over a four-year period between HIV-infected men and women with untreated AIDS-KS receiving care in Jos, Nigeria.

Patients and Methods: The Jos University Teaching Hospital HIV cohort has more than 10,500 adult patients enrolled for care. We prospectively collect routine data on individuals, and during the study 175 patients presenting with AIDS-KS were followed up. We compared survival, clinical, immunologic and virologic characteristics between male and female patients receiving HAART (two NRTIs and one NNRTI). Comparison of variables between groups was by χ^2 test for nominal variables. Survival was calculated from the day of enrollment until death or the date of last follow-up using Kaplan-Meier method.

Results: One hundred and three (58.8%) were females while 72 (41.2%) were males, giving a male: female ratio of 1:1.6. The mean age was 35±7 and 40±7 for females and males respectively (p, <0.001). Median CD4 count was 105 and 114 cells/mm^3 (p, 0.76) while HIV RNA was 43,113 and 80,310 (p, 0.01) median copies/ml for females and males respectively at baseline. Mean duration of observation was similar for both sexes (2.3±0.9 years) with 18.4% of females and 13.9% of males having history of use of HAART. Seventy-five percent (75%) of the females and 80 percent of the males had disseminated cutaneous disease and more than 40 percent of the male had nodular lesions compared with 25.5 percent of the females. The probability of survival was similar for both sexes.

Conclusion: Despite the availability of HAART, AIDS-KS continues to significantly affect morbidity and mortality in HIV-infected patients in our setting. Provision of specific treatment for AKS may improve overall outcome.

Kaplan-Meier plot for HIV+ patients with untreated AIDS-KS in Jos, Nigeria stratified by sex



Abstract 4

MALIGNANCIES IN HIV INFECTED CHILDREN AT A TERTIARY CANCER HOSPITAL IN INDIA

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Aim: To study the spectrum of malignancies in human immunodeficiency virus (HIV)-infected children and the clinical outcome of patients with these tumors.

Method: An observational study was done of pediatric patients diagnosed with cancer and who were HIV-infected at the Tata Memorial Cancer Hospital, a tertiary referral cancer centre in Mumbai, India. The study period was 2001 to 2007. Data regarding demographic profiles, types of cancers, stage of cancer, treatment and outcome, immune status was analyzed. We used gender and age-specific proportions of pediatric cancer that were recorded in the Tata Hospital cancer registry in 2002 to estimate an expected number of pediatric cancers among HIV positive pediatric cancer patients during the 2001 to 2007. The proportional incidence ratio (PIR) was calculated.

Results: The hospital diagnosed 475 patients including adults and children with HIV and cancer between 2001 and 2007. Among them there were 11 children with HIV infection and cancer. All children except one were male. The median age was 7 years (range 4 to 12 years). All patients were HIV-infected by vertical transmission. Malignancy was the presenting illness in four (36.3%) patients, after which the parents were diagnosed to be HIV-positive. All patients were HBsAg and HCV negative. CD4 counts were done in seven patients and the CD4 percentage was less than 14 percent in two patients. None of the children received HAART prior to being diagnosed with cancer. Four patients were started on concomitant chemotherapy and HAART. Nine patients (81.8%) had Non-Hodgkin's lymphoma (NHL); there was one case (9%) of B–ALL (acute lymphatic leukemia) and one case (9%) of Hodgkin's disease. Among the NHL patients the histology included four cases of diffuse large B-cell lymphoma (DLBCL), two cases of plasmablastic and two cases of Burkitt's lymphoma, and one case of High grade lymphoma. One-third (33.33%) of the patients had extra nodal disease and 66.66% of patients had advanced disease (stage III and IV). The PIR for NHL in male children was 9.71 (95% CI 4.19–19.13). Out of the 11 patients, seven (63.6%) received cancer directed treatment. Three patients received chemotherapy and radiotherapy and four patients received only chemotherapy.

One patient received prophylactic GCSF throughout chemotherapy and three received only with some cycles of CT after development of neutropenia. Adverse events included febrile neutropenia (71.4%), candidiasis (42.8%), diarrhea (42.8%), otitis (28.5%), CMV entero-colitis (28.5%), varicella (14.2%), pulmonary tuberculosis (14.2%), mucositis (71.4 %), and hemorrhagic cystitis (28.5%). Of the seven patients who received treatment, two (28.5 %) showed complete response, three (42.8%) had progressive disease, one (14.2 %) was lost to follow up and one patient (14.2%) is currently on therapy. Of the 11 patients, five expired: four patients died to disease progression and one patient died of infectious complication. The overall survival was 22.2 percent at 1 year.

Conclusions: NHL is the most common cancer among HIV-infected children and the PIR was significantly increased. Cancer may be the presenting AIDS-defining illness in HIV-infected children. Malignancies in children present at an advanced stage and have a poor prognosis. Significant immune suppression was not commonly seen. Association of HIV with cancers among children must be kept in mind by pediatricians especially in NHL. There should be a high index of suspicion for cancers among HIV-infected children.

Abstract 5

SUPPRESSION OF GALECTIN-3 IN KSHV INFECTED DMVEC CELLS AND KAPOSI'S SARCOMA: IMPLICATIONS FOR TUMORIGENESIS

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The Galectins are a family of proteins that share an affinity for Beta-galactoside containing glycoconjugates. Galectin-3 has been implicated in tumor progression and metastasis. It is also known that in prostate, ovarian and breast cancer, down regulation of Galectin-3 is associated with malignancy. Kaposi's sarcoma (KS) is characterized as an angioproliferative tumor of vascular endothelial cells and produces rare B cell lymphoproliferative diseases in the form of primary effusion lymphomas (PEL) and some forms of Multicentric Castleman's Disease (MDC). Kaposi's Sarcoma-Associated Herpesvirus also known as KSHV or Human Herpesvirus type 8 (HHV8) is the etiological agent of KS. We have observed suppression of galectin-3 expression in Kaposi's sarcoma (KS). Here we demonstrate that galectin-3 protein expression is down-regulated 20-fold in KSHV infected dermal microvascular endothelial cells (DMVEC) cells. We show loss of Galectin-3 staining by dual labeled immunofluorescence in latency associated nuclear antigen (LANA) positive spindle cells. We also find reduced levels of galectin-3 expression in LANA positive spindle cell regions in archival KS tissue. There is also transcriptional suppression of Galectin-3 message in KSHV infected DMVEC cells compared to mock infected controls. We demonstrate that KSHV vFLIP is the likely viral gene that targets galectin-3 downregulation in HeLa cells. In pleural effusion lymphoma cell lines (PEL), we observe different levels of galectin-3 expression associated with varying levels of KSHV replication. The search for novel host cell factors that may contribute to the overall pathogenesis of KS is essential for early detection of KS and development of innovative therapies for treatment.

Abstract 6

VALUE OF CD44 IMMUNOSTAINING (IHC) AS A SURROGATE IN THE DIFFERENTIATION OF MYC POSITIVE BURKITT LYMPHOMA (BL) AND BURKITT LYMPHOMA-LIKE (BLL) FROM MYC NEGATIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) IN A RESOURCE CONSTRAINED CLINICAL SETTING

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Background: Both BL and DLBCL are prevalent in HIV/AIDS patients and the correct classification of these two subtypes of Non-Hodgkin's lymphomas (NHL) particularly between DLCBL with high proliferation and BL, is critical to chemotherapy choice. Transcriptional gene expression profiling of sporadic and endemic BL by Stein et al (Berlin) identified a molecular signature for BL that included a down regulation of CD44 expression in a group of lymphomas from Africa. Immunophenotyping of formalin-fixed paraffin-embedded (FFPE) BL tissues by this group demonstrated difficulties in correctly classifying BL using morphology, BCL-2 (immunohistochemistry - IHC) presence and MYC (fluorescent in situ hybridization - FISH) absence. The differential expression of CD44, albeit non-membranous, suggests an intricate regulatory circuit that allows for low expression, supporting the possibility that CD44 plays a role in BL/BLL dissemination. CD44 (IHC) could be a valuable marker to aid classification of tumors whose morphologic and phenotypic overlap is among BL, BLL and DLBCL. CD44 absence clearly separates MYC+ BL/BLL and MYC- DLBCL. DLBCL, Hodgkin's lymphoma (HL) and normal lymphocytes from lymphoid mantle/marginal cell and interfollicular T-cell-rich zones should be strongly CD44 positive.

Materials and Methods: We evaluated 128 FFPE lymphoma tissue biopsy collected at St. Mary's Lacor Hospital, Gulu, Uganda, Africa, from 1994 to 2007 from tissue microarray (TMA) blocks constructed on site using the UNITMA Quick-Ray System (Seoul, South Korea). The completed TMA blocks were sectioned and stained for H&E, IHC including: CD44, CD43, CD45, CD45RO, MUM-1, CD138, TdT, CD5, CD3, CD20, CD79a, CD10, BCL-2, BCL-6, KI67 (MIM-1), HHV-8 (LANA-1), IgM, CD30, CD15, CD68, CD23, Vimentin, CD34, EMA, CD34, Cyclin D1, BIM and p53; in situ hybridization (ISH) for EBV (EBER) and kappa and lambda light chains and FISH break apart assay for C-MYC translocation.

Results: Of the 128 core samples collected (one per case), 107 could be interpreted. Ninety-two had results for CD44; 15 could not be read for CD44 due to missing tissue or necrosis. Seventy-one (66.4%) were negative for significant CD44 staining of tumor cells. Included were: 53 BL, 10 Burkitt lymphoma-like (BLL) and eight other (two small cell lymphomas, one marginal cell lymphoma, one lymphoblastic lymphoma, one follicular lymphoma, two normal tissues and one alveolar rhabdomyosarcoma). Twenty-one (19.6%) core samples were CD44 positive. Included were four DLBCL and 17 other (two small cell lymphomas, one gut associated lymphoma, one anaplastic large cell lymphoma, one histocyte rich lymphoma, one peripheral T cell lymphoma, three lymph nodes, three HD, two follicular lymphomas, and three normal tissues). Of note, supporting tissue in some BLL samples were positive for CD44 unlike the BL group, but the BLL tumor cells did not show membrane staining as seen with the DLBCL cells. C-MYC (FISH) probe produced no signals in the 42 biopsies collected prior to 2003. The 27 BL/BLL samples from 2003 to 2007 were C-MYC positive (17 or 73.9%) or C-MYC negative (six or 26.1%) except for four instances where the tissue core section was not present on the test slide. DLBCL samples were C-MYC negative. Most BL core sections (89.6%) and BLL core sections (90%) were EBV positive while all DLBCL core sections were EBV negative. The BL/BLL core sections were BCL-2 negative and usually BCL-6 positive (87.5 %).

Conclusion: CD44 absence on BL/BLL cells aligned C-MYC translocation, EBV-positive tumor cells and absence of BCL-2 with the BL group. The DLBCL group was strongly positive for CD44 cell membrane staining and variably positive for BCL-2, MUM-1 and CD10. Where BL/BLL presented as infiltrating cells into various supporting tissues rather than as monomorphic tumor, CD44 staining was insufficient to distinguish the BL/BLL cells but could be used along with other tests such as CD20 and BCL-6 to characterize this subtype. Our results suggest that CD44 is of value when used along with tumor cell morphology, as a clarifying additional test or as a surrogate for C-MYC testing in resource constrained settings to assure accurate separation of BL/BLL from DLBCL.

Abstract 7

EVALUATION OF EPSTEIN-BARR VIRUS (EBV) AND HUMAN HERPES VIRUS-8 (HHV-8) IN HIV-ASSOCIATED PERSISTENT GENERALIZED LYMPHADENOPATHY (PGL)

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Background: Human immunodeficiency virus (HIV) infection is associated with persistent generalized lymphadenopathy (PGL) resulting from polyclonal B cell activation with significant circulating Epstein-Barr virus (EBV). Does HHV-8 contribute to the hyperplasia when present? Unlike EBV, seroprevalence of HHV-8 in the HIV-negative U.S. population is low. Kaposi's sarcoma (KS) in HIV infected is thought to reflect "de novo" HHV-8 infection, not reactivation. Does primary HHV-8 infection present as a polyclonal B cell activation manifested as PGL such as other HHV-8 associated co-morbidities like primary effusion lymphoma and multicentric Castleman's disease? This study examines the association of HHV-8 (LANA-1) with B cells in HIV-associated PGLs.

Methods: HIV-positive serum samples from four women and 18 men (nine African-American, one African (woman) and 12 Caucasian) with available matching lymph nodes (eight axillary, eight groin, two cervical, two mandible, one supraclavicular, and one lung) constituted the study set of 22 individuals. Serum samples were examined for HHV-8 antibodies. The lymph nodes were examined histologically for HHV-8 using LANA-1 immunohistochemistry (IHC) and EBV using EBER in situ hybridization (ISH).

Results: Three sera had positive HHV-8 titers: 1). 1:1240 in a Caucasian man, age 28, with a 1.0 cm hyperplastic axillary lymph node with prominent vascular proliferation and an area in the capsule with HHV-8+ endothelial cells. No LANA-1+ cells were present within the germinal centers or paracortical areas. Clinical KS was present at the time of the biopsy. 2). 1:640 in African woman, age 47, with a 2.2 cm axillary lymph node with giant follicular hyperplasia showing many EBER+ cells in paracortical areas and focal LANA-1 positive germinal center cells and few positive paracortical plasma cells. Pleural lymphoma developed 6 months after this biopsy. 3). 1:320 in an African/American man, age 46, who had a 0.6 cm groin lymph node, both LANA-1 and EBV negative. Neither lymphoma nor KS developed during the following 7 years. Hyperplastic lymph nodes from HHV-8 seronegative patients were LANA-1 negative but EBER+ (13 of 19). EBV negative nodes were small (0.6-0.3 cm), groin lymph nodes.

Conclusions: PGL is associated with EBV positive cells in the paracortical areas of hyperplastic lymph nodes. HIV-positive patients with HHV-8 positive serology had large, medium, and small lymph nodes. The HHV-8 seropositive African woman's hyperplastic lymph node showed EBV(EBER) positive cells in the paracortical regions and a few HHV-8 (LANA-1)+ B cells in the germinal centers and a few positive plasma cells in the paracortical areas demonstrating that HHV-8 can be present in B cells. Reactivation of HHV-8 in the African woman with HIV is more likely than "de novo" infection. Significant HHV-8 associated lymph node hyperplasia in the absence of EBV appears uncommon. PGL biospecimens are available from the AIDS and Cancer Specimen Resource (ACSR) for further study.

Abstract 8

THERAPEUTIC OPTIONS IN AIDS RELATED KAPOSI'S SARCOMA: A 5-YEAR NIGERIAN REVIEW

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Objective: To assess the beneficial effects of some of the available therapeutic agents in the management of AIDS-related Kaposi's sarcoma in a resource limited setting.

Patients/Method: The study was conducted between 2003 and 2007 at Ahmadu Bello University Teaching Hospital, a tertiary referral center in Zaria, Nigeria. There were 37 histologically diagnosed KS. All the cases were HIV-1 antibody positive by parallel ELISA method (Immunocomb and Genie II).. Complete blood count was carried out by either standard manual and automated methods (Advia® 60). CD4+ T lymphocytes enumerated using Dynabeads or Cyflow. Facilities for KS herpes virus type 8 serological screening were not available. Other ancillary investigations were carried out. The modalities of treatment include antiretroviral therapy (ART), Chemotherapy and Surgical excision.

Result: During a 5-year period, 37 antiretroviral naïve patients were recruited into this study. Men were predominantly affected, with a male to female ratio of 2.3:1. Cutaneous lesions were the earliest and commonest mode of presentation in all the patients. Visceral involvement could not be assessed due to lack of appropriate endoscopic biopsy tools. The mean packed cell volume was 0.28 and a mean CD4+ T Lymphocyte counts of 262.6-cells/µl of blood. Eight patients died pre-evaluation to commencement of any form of therapy due to late hospital presentation (extensive and progressive disease), nine patients were lost to follow up after commencement of ART and or chemotherapy. Five patients who had localized cutaneous KS lesions were on ART alone. Of the remaining 15 that had chemotherapy, five had single agent (Vincristine 1.4mg/m2 every 2 weeks for six cycles) at $12 per cycle and only one had vinblastine alone, while eight had polychemotherapy, (Adriamycin 10mg/m2, Bleomycin 10U/m2 and Vincristine 1.4mg/m2 every 2 weeks for six cycles except for one who discontinued due to cost) at $89 per cycle. Complete remission was achieved in two patients and partial remission in the remaining six patients that received polychemotherapeutic ABV regimen (partial remission defined as 50 percent regression in tumor size, improvement in clinical status and CD4 count) compared to those who had single agent chemotherapy or ART alone (no remission was achieved). The last patient was a 9-year-old girl who was treated with ART and surgical excision of the localized lesions. Management is hampered by late hospital presentation, presence of other co-morbid conditions such as tuberculosis, affordability and availability of the recommended choice of therapeutic agents in country where majority of the population subsists on less than $1 per day.

Conclusion: These finding suggest that ABV regimen remains an effective treatment option in resource limited settings where the internationally approved chemotherapeutic agents such as Paclitaxel, Liposomal doxorubicin and immune modulators (alpha interferon) are beyond the reach of the majority of the population.

Abstract 9

DENDRITIC CELL-MEDIATED INFECTION OF PRIMARY B CELLS WITH KSHV

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Circulating B lymphocytes are the major reservoir of KSHV infection in infected subjects. However, B cell lines and primary B cells are resistant to direct KSHV infection *in vitro*. In addition, primary B cells are difficult to propagate for more than a few days. In this study, we combined a novel primary B cell propagation method with efficient infection mediated by dendritic cells to study KSHV *de novo* infection of primary B cells *in vitro*.

Primary monocyte-derived dendritic cells (MDDCs) or plasmacytoid dendritic cells (pDCs) were pulsed with KSHV for 4 hours at which point KSHV DNA was readily detectable. Uptake of KSHV was significantly reduced by pre-incubating cells with antibodies to integrins α3, β1 and DC-SIGN. Autologous B cells were grown on a feeder layer of irradiated NIH3T3 cells transduced with a human CD40L retroviral vector. KSHV+ DCs were co-cultivated with primary B cells for 4–8 hours and then separated by CD19+ immunomagnetic isolation. B cell cultures were maintained on feeder cells for >30 days and monitored for KSHV infection.

Efficient KSHV infection of primary B cells was mediated by both MDDCs and pDCs. KSHV LANA protein (ORF73) was detected by IFA in 2–15 percent of B cells through day 14. Viral gene expression analysis using a KSHV whole genome virus array showed establishment of latent KSHV infection followed by spontaneous reactivation of lytic viral replication in the primary B cell cultures.

These studies suggest that dendritic cells play an important role in the transmission and pathogenesis of KSHV in infected subjects as well as demonstrating a powerful *in vitro* model for studying KSHV infection of B cells.

Funded by NCI Contract N01-CO-12400.

Abstract 13

SURVIVAL AND PROGNOSIS OF HIV-ASSOCIATED NON-HODGKIN-LYMOPHMA IN THE ERA OF COMBINED ANTI-RETROVIRAL THERAPY, A EUROPEAN MULTI-COHORT STUDY

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Background: Since the introduction of combined anti-retroviral therapy (cART), survival of patients with HIV-associated NHL improved dramatically. We examined survival and HIV-related prognostic factors of patients with HIV-related NHL in the era of cART within the framework of a large European multi-cohort collaborative study.

Methods: We analyzed the data of HIV-infected adult patients (age > 16 years) who developed a NHL after January 1, 1998. We included patients who were cART naïve at inclusion and started cART after January 1, 1998. Only patients who started cART at some point during lifetime were included in the present analysis. cART was defined as regimen with at least three antiretroviral drugs. Patients had to have at least one CD4 cell count measurement after January 1, 1998, and before or within 7 days of NHL diagnosis. Survival and prognostic factors were estimated using crude and adjusted Weibull models, with random-effects accounting for heterogeneity between cohorts.

Results: We observed 67,659 HIV-infected patients. Of 1,176 patients who developed NHL, 847 (72%) NHL patients from 22 collaborating cohorts across Europe were included in the present analysis. The 329 (28%) NHL patients who did not meet the inclusion criteria outlined above were excluded. After 1 year, 66 percent (95% CI 63%–70%) of patients with NHL other than Primary Brain Lymphoma (PBL) and 54 percent (95% CI 43%–65%) of patients with PBL were alive. Negative predictive factors for survival were diagnosis of PBL, low CD4 cell count nadir and history of injection drug use.

Conclusions: In the era of cART two-thirds of patients diagnosed with HIV-related NHL other than PBL survive for longer than 1 year after diagnosis. Survival is poorer in patients diagnosed with PBL.

More advanced immunodeficiency is the dominant prognostic factor for mortality in patients with HIV-related NHL.

Abstract 15

A PILOT STUDY ON THE DISTRIBUTION OF HUMAN PAPILLOMAVIRUS GENOTYPES AND HPV-16 VARIANTS IN CERVICAL NEOPLASTIC LESIONS FROM ECUADORIAN WOMEN

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Introduction: Human papillomaviruses (HPVs) are the cause of cervical intraepithelial neoplasia and invasive carcinomas of the uterine cervix. The distribution of specific HPV genotypes varies greatly across populations and HPV surveys have been performed in different geographical regions to apply appropriate vaccine strategies. The aim of this study was to determine the spectrum of HPV genotypes and HPV-16 variants among women with cervical lesions living in Ecuador.

Methods: A total of 71 cases have been analyzed, including 32 chronic cervicitis, 29 cervical intraepithelial neoplasia grade 1, and 10 cervical intraepithelial neoplasia grade 2–3. HPV sequences were detected by broad spectrum consensus-primer-pairs MY09/MY11 and GP5+/GP6+-based polymerase chain reaction and characterized by nucleotide sequence analysis.

Results: Overall, 31 (43.7%) cases were HPV-positive with prevalence rates of 37.5 percent, 44.8 percent and 60 percent in patients with chronic cervicitis, cervical intraepithelial neoplasia grade 1 and cervical intraepithelial neoplasia grade 2–3, respectively. Among the positive cases, the most common genotypes were HPV 16 (64.5%) and HPV 81 (29%) followed by HPV 31, 53, 56, and 58, in descending order of prevalence. Seventeen (85%) HPV-16 isolates were classified as European and three (15%) as African 1 variant on the basis of nucleotide signature present within the MY09/MY11 L1 sequence.

Discussion: The results suggest that 1) HPV 16 has a very high prevalence among women with cervical lesions in Ecuador; therefore, an effective HPV-16 based vaccine should prevent the development of cervical cancer in a large proportion of Ecuadorian women; and 2) HPV type 81, which has not been included in the most used detection systems and has not been searched for in the majority of epidemiological studies on HPV survey, is very frequent among women with cervical lesions in Ecuador and among HIV-positive women in Brazil and Italia (Cerqueira et al., 2007; Tornesello et al., 2008) underscoring the need to target a wide range of HPV types in cervical cancer screening programs.

Abstract 17

REGULATORY T CELLS ARE PRESENT IN KAPOSIS SARCOMA AND INCREASINGLY FREQUENT IN ADVANCED DISEASE

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Background: Regulatory T cells (Tregs) are thought to play a crucial role in preventing and controlling hyperactive immune responses in malignancies and inflammatory disease. The role of Tregs in Kaposi's sarcoma (KS) has not been explored and is of particular interest in that this disease demonstrates characteristics of both inflammation and malignancy. We examined the presence and frequency of Tregs in KS tissue samples compared to normal skin. In addition, we compared presence and frequency of Tregs across three distinct histopathologic stages of KS. The histopathologic comparisons included the earlier patch and plaque stages, and the most advanced, nodular stage of KS.

Methods: Regulatory T cells are characterized by the expression of FOXP3, CD4 and CD25. A total of 15 cutaneous KS samples were obtained from different patients. Of the total 15 KS samples, breakdown of histopathologic subtypes included 6 samples from patches, 4 samples from plaques, and 5 samples from nodules. Eight samples from normal skin served as controls. Immunohistochemical and immunofluorescent assays and image analysis were performed on all samples.

Results: The frequency of FOXP3+ cells in all stages of KS was significantly higher compared to normal skin with means ± standard deviation of 43.4 ± 47.8 FOXP3+ cells/mm² in KS versus 4.56 ± 12.5 FOXP3+ cells/mm² ($p<0.001$). This difference remained significant when comparing each individual stage to normal skin ($p <0.001$ for nodular and plaque stages versus normal skin, $p=0.002$ for patch stage versus normal skin). The number of FOXP3+ cells was highest in the nodular stage 70.3 ± 47.8 FOXP3+ cells/mm² compared to both patch 29.3 ± 50.8 $p=0.001$ and plaque 27.8 ± 33.2 $p<0.001$stages. The frequency of FOXP3+ cells in patch and plaque stages was not significantly different.

Conclusions: Tregs are present in KS and are increasingly frequent in advanced disease. This finding of increased Tregs in the most advanced stage of KS is a phenomenon that has also been demonstrated in other malignancies including melanoma, ovarian cancer, and hepatocellular carcinoma. Tregs might play a critical role in suppressing the KS-specific immune response and contributing to the unchecked proliferation that is characteristic of KS. In addition, our finding that Tregs were markedly increased in the most advanced stage of KS suggests that regulatory T cells may also play a key role in KS progression. Ultimately, targeted regulatory T cell immunotherapy may lead to improved treatment response and prognosis.

Abstract 19

EARLY EVENTS OF B-CELL RECEPTOR SIGNALING ARE NOT ESSENTIAL FOR THE PROLIFERATION AND VIABILITY OF AIDS-RELATED LYMPHOMA

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We have evaluated whether targeting the Src family kinase cascade, an early component of B-cell receptor (BCR) signaling, is an effective strategy to treat AIDS-related lymphoma (ARL). Src kinases are activated after ligation of the BCR and they phosphorylate downstream signaling proteins in tyrosine residues relaying B-cell signaling cascades that lead to B cell activation and proliferation. These kinases play an important role in lymphoma pathogenesis. We have shown that Src kinases are constitutively active in diffuse large cell lymphoma (DLBCL) cells occurring in immunocompetent individuals and inhibition of these kinases using dasatinib inhibits proliferation of the lymphoma cells.

Therefore, we postulated that targeting Src tyrosine kinases pharmacologically would also inhibit the survival and growth of the ARL cells. We tested the effect of dasatinib in 11 ARL cell lines, including six primary effusion lymphomas, three EBV(+) DLBCL (immunoblastic) lymphomas, one EBV(-) DLBCL, and one EBV(+) Burkitt lymphoma. Cell proliferation and viability in the presence of increasing doses of dasatinib were determined by the MTT assay. In contrast to DLBCL in HIV-negative individuals, most of which show sensitivity to dasatinib in the nanomolar range, none of the ARL cell lines tested showed sensitivity at doses as high as 1 uM. One EBV(+) Hodgkin lymphoma cell line was also evaluated, and found to be resistant to dasatinib treatment.

Non-AIDS DLBCLs have activation of SRC family kinases (SFK). The activity of SFK including Src, Lyn, Hck and Blk are invariably inhibited in both sensitive and resistant DLBCL cell lines, whereas the activity of two downstream signaling molecules, Syk and PLCγ2, are inhibited by dasatinib only in sensitive cell lines. To determine the molecular events that occur in ARL after dasatinib treatment in comparison to non-AIDS HIV DLBCL, we performed immunoblot analyses and phosphospecific flow cytometry. Both primary effusion lymphoma (KSHV+) cell lines evaluated (BC2 and VG-1) revealed very low basal levels of total phosphotyrosine, which did not change upon treatment with dasatinib. In contrast, the EBV-associated (LCL-JP06 and BCKN-1) and the virus-negative ARL cell line (BCHN-1) had significantly higher basal tyrosine kinase activity. The HL cell line, L591 has low but detectable level of phosphotyrosines. In these non-PEL cell lines, dasatinib was able to inhibit tyrosine phosphorylation at doses between 10 to 50 nM. In cell lines that had total tyrosine phosphorylation, basal phosphorylation of Src and Lyn was detected, and their activities were efficiently inhibited by treatment with dasatinib.

When we examined ARL cell lines for phosphorylation of Syk and PLCγ2, in those that have little or no basal phosphotyrosines including the PEL cell lines (BC2 and VG-1) and the HL cell line L591, cells did not respond to dasatinib treatment. In contrast, the DLBCL cell line BCHN-1 that had basal tyrosine phosphorylation, pSyk and p-PLCg2 responded to BCR stimulation and dasatinib treatment in a similar fashion to the control DLBCL cell lines. However, in spite of this molecular response, this cell line did not respond to the inhibitor at cellular level as no inhibition in proliferation or viability was detected.

Our results indicate that in ARLs, inhibition of BCR signaling is not detrimental to cellular survival or proliferation. These results suggest that viral proteins may provide survival and proliferation signals through interaction with cellular proteins that are further downstream from these early events of BCR signaling. Lack of inhibition by dasatinib was unexpected and in marked contrast to observations made in DLBCL occurring in immunocompetent individuals. These findings have therapeutic as well as pathobiological implications. From the therapeutic standpoint, while dasatinib is likely to be beneficial in lymphoma patients without HIV infection, this approach is unlikely to be successful in patients with AIDS.

Abstract 20

IMMUNOPHENOTYPIC ANALYSIS OF AIDS-RELATED DIFFUSE LARGE B-CELL LYMPHOMA AND CLINICAL IMPLICATIONS IN PATIENTS FROM AIDS MALIGNANCIES CONSORTIUM CLINICAL TRIALS 010 AND 034

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Diffuse large B cell lymphoma represents a clinically heterogeneous disease, and several immunohistochemical strategies have been shown to help prognosticate clinical outcome. These include subdivision into germinal center (GC) and non-germinal center (non-GC) subtypes, proliferation index (measured by expression of Ki67), and expression of BCL-2, FOXP1 or Blimp-1/PRDM1. We sought to determine whether immunohistochemical analyses of biopsies from DLBCL patients with HIV infection are similarly relevant for prognostication.

We examined 82 DLBCLs from uniformly treated AIDS patients in AMC 010 (CHOP or CHOP-rituximab) and AMC 034 (EPOCH-rituximab) clinical trials, and compared the immunophenotype with survival data, Epstein Barr virus (EBV) positivity and CD4 counts. There was no significant difference in survival or CD4 counts between the patients with GC and non-GC subtypes of DLBCL, regardless of inclusion of rituximab in the treatment regimen. EBV assessment showed that this virus can be found in both subtypes of DLBCL, although less frequently in the GC subtype, and does not affect survival.

We also evaluated expression FOXP1, which is an independent adverse prognostic marker when expressed in immunocompetent patients with DLBCL, as well as expression of Blimp-1/PRDM1 and BCL-2. Expression of FOXP1, Blimp-1/PRDM1 or BCL-2 did not correlate with the outcome in patients with AIDS-related DLBCL. The only predictive immunohistochemical marker was found to be Ki67, where a higher proliferation index was associated with better survival suggesting a better response to therapy in patients whose tumors had higher proliferation rates. These data indicate that with current treatment strategies for lymphoma and control of HIV infection, commonly used immunohistochemical markers may not be clinically relevant in HIV-infected DLBCL patients.

Abstract 24

MARIJUANA USE AND CERVICAL HPV / NEOPLASIA

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Recent research suggests that marijuana use may be positively associated with risk of human papillomavirus (HPV)-associated oropharyngeal cancer, and the immunomodulatory effects of cannabinoids are considered a possible mechanism. Were marijuana to have systemic effects on HPV-associated tumorigenesis it would be of major concern, and might be especially harmful in immunologically susceptible populations such as HIV-positive women.

We studied the effect of marijuana use on cervical HPV natural history and cervical squamous intraepithelial lesions (SIL) among HIV-positive and HIV-negative women in the Women's Interagency HIV Study (WIHS), a large prospective cohort study. HPV DNA testing by PCR and Pap smears were conducted semi-annually. Prevalent HPV and cervical SIL were analyzed using logistic regression with GEE. Persistence of HPV was analyzed using Cox regression.

Of the 3,499 women in the WIHS, 1,414 reported ever using marijuana. There were no associations between HPV prevalence and either current (OR=0.98 95%CI=0.90-1.07), frequent (current daily use: OR=0.98 95CI=0.90-1.07), or sustained (daily use for more than 3 years: OR=1.03, 95%CI=0.90-1.19) marijuana use, controlling for age, race, HIV status, CD4 cell count, number of sexual partners in the last 6 months, tobacco use and cervical treatment. Nor were there effects on prevalence of SIL, or on the persistence of cervical HPV infection. Results were similar among HIV-negative and HIV-positive women.

Our data do not support an effect of marijuana on cervical HPV infection, persistence or risk of cervical dysplasia. If there is an effect of marijuana use on oral HPV-associated tumorigenesis, it may be a local effect.

Abstract 25

BURKITT'S LYMPHOMA: DIFFERENTIAL KILLING OF EPSTEIN-BARR VIRUS (EBV) (+) AND EBV(-) BURKITT LYMPHOMA CELLS IN VITRO AND DOSE-DEPENDENT LYTIC INDUCTION BY BORTEZOMIB IN VIVO

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Bortezomib shows *in vitro* activity against a variety of lymphoid malignancies. It also is known to induce lytic cycle gene expression in several EBV associated malignancies. We compared its activity in killing isogenic EBV(+) and EBV(-) Akata cells, two Burkitt's lymphoma cell lines, in order to assess whether activation of viral lytic gene expression might augment killing achieved in the absence of virus. Cells were treated with bortezomib, ranging in concentration from 10 nM to 300 nM, for durations of 2, 24, 48, and 96 hours. Cell viability was determined by trypan blue exclusion, and changes in cell viability were characterized by comparison to untreated Akata cells cultured in parallel. The changes in cell viability resulting from the presence of bortezomib were dose and time dependent. Whereas low doses of bortezomib showed parallel killing effects on EBV(+) and EBV(-) tumor cells, higher doses appeared to be more toxic to EBV(+) cells. These higher doses were associated with a rapid increase in viral DNA copy number. In a murine xenograft model, we assessed activation of lytic infection measured as a function of the ability to concentrate [^{125}I]FIAU. Uptake of [^{125}I]FIAU increased with increasing bortezomib dose in the range of 0.5 - 2.0 g/g body mass at 30 hours post bortezomib treatment. These findings are consistent with a dose-response relationship for bortezomib and EBV lytic infection in EBV(+) Burkitt's lymphoma cell lines and with the possibility that lytic induction directly augments killing of tumor cells.

Abstract 29

KAPOSI SARCOMA INCIDENCE IN THE SWISS HIV COHORT STUDY BEFORE AND AFTER HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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Between 1984 and 2006, 12,959 people with HIV/AIDS (PWHA) in the Swiss HIV Cohort Study contributed a total of 73,412 person years of follow-up, 35,551 of which derived from PWHA treated with highly active antiretroviral therapy (HAART). Out of 597 incidents of Kaposi sarcoma (KS) identified, 52 were among HAART users.

Cox regression was used to estimate hazard ratios (HR) and corresponding 95 percent confidence intervals (CI). KS incidence fell abruptly from 1996 to 1998 to reach a plateau at 1.4 per 1000 person years afterwards. Men having sex with men (MSM) and birth in Africa or the Middle East were associated with KS in both non-users and users of HAART, but the risk pattern by CD4 cell count differed. Only very low CD4 cell count (<50 cells/µl) at enrolment or at HAART initiation were significantly associated with KS among HAART users. The HR for KS declined steeply in the first months after HAART initiation and continued to be low 7 to 10 years afterwards (HR, 0.06; 95% CI, 0.02–0.17). Out of 52 KS cases among HAART users, 33 out of 52 (63.5%) KS cases among HAART users arose among PWHA who had stopped treatment or used HAART for less than 6 months.

Abstract 30

KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS DISRUPTS ADHERENS JUNCTIONS AND INCREASES ENDOTHELIAL PERMEABILITY BY INDUCING DEGRADATION OF VE-CADHERIN

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Kaposi's sarcoma (KS) is a vascular tumor of proliferative endothelial cells caused by infection of Kaposi's sarcoma-associated herpesvirus (KSHV). Aberrant vascular permeability is a hallmark of KS manifested as multifocal edematous skin and visceral lesions with dysregulated angiogenesis and vast inflammatory infiltrations. In this study, we showed that KSHV infection increased the permeability of confluent endothelial monolayers to serum albumin, blood-derived cells, KSHV-infected cells and KSHV virions. KSHV-induced permeability was associated with the disruption of adherens junctions and degradation of vascular endothelial (VE)-cadherin protein. Ultraviolet irradiation that inactivated KSHV virions and cycloheximide that blocked *de novo* protein synthesis failed to reverse KSHV-induced disruption of adherens junctions. However, soluble heparin that blocked KSHV entry into cells completely inhibited KSHV-induced permeability. Furthermore, KSHV-induced degradation of VE-cadherin was dose-dependent on the internalized virus particles. Together, these results indicate that KSHV infection induces vascular permeability by inducing VE-cadherin degradation during virus entry into cells. KSHV-induced aberrant vascular permeability could facilitate virus spread, promote inflammation and angiogenesis, and contribute to the pathogenesis of KSHV-induced malignancies.

Abstract 32

THE ROLE OF THE TRAF2/3 BINDING SITE IN LMP1 AND CD40 SIGNALING

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The Epstein-Barr virus encoded protein, LMP1, is a viral mimic of the cellular protein CD40. In comparison to CD40, LMP1 signals to B lymphocytes in an amplified and sustained manner. LMP1 signaling is thought to contribute to the development of lymphoma in patients afflicted with HIV or in transplant recipients who are immunosuppressed. CD40 uses TRAF2 as a positive mediator of its signaling, while TRAF3 serves as a negative regulator. Interestingly, LMP1 uses TRAF3 as a positive mediator of its signaling. CD40, not LMP1, signaling has been shown to degrade TRAF2 and 3. Currently, lack of LMP1-induced TRAF degradation is thought to result in exaggerated LMP1 signals. Because LMP1 binds TRAF2 with less affinity than CD40 and TRAF2 is needed for inducing CD40-mediated TRAF2 and 3 degradation, it was thought that relative affinity for TRAF2 controls the disparate ways in which CD40 and LMP1 use and degrade TRAFs 2 and 3, and that this in turn results from the different sequences of the TRAF2/3 binding sites of the two receptors. However, our recent studies reveal that TRAF binding affinity and TRAF binding site sequence only partially dictates CD40 versus LMP1 signaling properties. We have been studying signaling via hybrid molecules that have had their TRAF binding sites switched so that CD40 contains the TRAF binding site of LMP1 and LMP1 contains the CD40 TRAF binding site. Examination of TRAF binding and degradation, cytokine production, IgM secretion, and the activation of c-Jun kinase and NF-kB revealed that some events are strongly dictated by TRAF binding site sequences, others partially regulated, and still others appear independent of TRAFs 2 and 3.

Abstract 33

KSHV SEROPREVALENCE, AND BLOOD AND SALIVA VIRAL LOADS IN THE HIV-INFECTED POPULATION OF SOUTH TEXAS

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Kaposi sarcoma (KS) is the most common neoplasm in HIV-infected subjects, and is associated with infection by Kaposi's sarcoma-associated herpesvirus (KSHV). Our previous studies have shown that KSHV epidemiology in South Texas is distinct with an increased KSHV seroprevalence in blood donors and unique distribution of KSHV genotypes in KS subjects. However, KSHV epidemiology in the HIV-infected population in South Texas remains undefined.

In this cross sectional study, we examined specific antibodies to KSHV latent nuclear antigen (LANA) by immunofluorescence antibody assay (IFA) and to KSHV lytic antigen ORF65 by ELISA in 25 HIV-infected KS subjects, 314 HIV-infected subjects, and 335 HIV-negative subjects. Relative antibody titers to ORF65 were estimated based on optical density values (O.D.). Blood and saliva viral loads were also determined in KSHV-seropositive subjects by quantitative real-time PCR. Antibodies to KSHV antigens were detected in 25 (100%) KS subjects, 114 (36%) HIV-infected subjects and 65 (19%) HIV-negative subjects. KS subjects had higher antibody titers to ORF65 compared to HIV-infected and -negative subjects (median O.D. 0.76 versus 0.47 and 0.27; p= 0.0017 and 0.0001, respectively). Antibody titers in HIV-infected subjects were also significantly higher than HIV-negative subjects (p = 0.0001).

Among the HIV-infected subjects, males had higher KSHV seroprevalence than females (42%, 95% CI: 35.6–47.4% versus 8%, 95% CI: 0.5–15.8%, p<0.0001). Compared to subjects with >400 CD4+ T cell counts, those with <200 CD4+ T cell counts had higher KSHV seroprevalence (OR=2.59, 95% CI: 1.4-4.80, p=0.017) and higher antibody titers (median O.D. 0.48 versus 0.32; p= 0.001). KSHV blood and saliva viral loads were detected in 12 (48%) and 9 (36%) of 25 KS subjects, 16 (26%) and 12 (19%) of 62 HIV-positive KSHV-seropositive subjects, and none of the HIV-negative KSHV-seropositive subjects, respectively. Among the KS subjects, KSHV blood and saliva viral loads were detected more frequently in those with active KS than those without active KS (81.8%, 95% CI: 48.2–97.7% and 54.5%, 95% CI: 23.3–83.2% versus 18%, 95% CI: 2.2–51.7% and 45%, 95% CI: 16.7–76.6%, p =0.004 and 0.05, respectively). Together, these results indicate that HIV infection and the status of HIV disease might modulate KSHV infection and replication, and impact the development of KS.

Abstract 34

ELEVATED RISK FOR SQUAMOUS CELL CARCINOMA OF THE CONJUNCTIVA AMONG ADULTS WITH AIDS IN THE UNITED STATES

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Squamous cell carcinoma of the conjunctiva (SCCC) has been associated with HIV infection in equatorial Africa, but the evidence for association with HIV in developed countries, where SCCC is rarer, is controversial. We investigated the risk for SCCC and other eye cancers in the updated U.S. HIV/AIDS Cancer Match Registry Study. We calculated standardized incidence ratios (SIRs) to estimate excess risk for SCCC, primary ocular lymphoma, ocular Kaposi sarcoma (KS), and other eye tumors among 491, 048 adults (age > 15 years or older) with HIV/AIDS diagnosed from 1980 to 2004. We calculated relative proportions (per 10^5) to gain insight into risk factors. We identified 73 eye cancers (15 SCCC, 35 primary ocular lymphoma, 17 ocular KS, and 6 other). Overall SIRs were elevated for SCCC (SIR, 12.2, 95% CI 6.8 - 20.2), primary ocular lymphoma (21.7, 95% CI 15.1-30.2), and ocular KS (109, 95% CI 63.5 -175). Risk for SCCC was elevated regardless of HIV acquisition category, CD4 lymphocyte count, and time-relative to AIDS-onset. Relative proportions of SCCC risk were highest with age ≥50 ($8/10^5$), Hispanic ethnicity ($7/10^5$), and residence in regions with high solar ultraviolet radiation ($10/10^5$). We show significantly increased incidence of SCCC among persons with HIV/AIDS in the United States. The associations with age and geography are in accord with etiological role for ultraviolet radiation in SCCC.

Abstract 35

BURKITT LYMPHOMA IN BRAZIL IS CHARACTERIZED BY GEOGRAPHICALLY DISTINCT CLINICO-PATHOLOGICAL FEATURES AND LACK OF p53 MUTATIONS

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Burkitt lymphoma (BL) is a highly aggressive non-Hodgkin lymphoma with a consistent MYC translocation. Epstein Barr virus (EBV) has been associated with BL at different frequencies depending on the clinical variant and geographic regions. This is a large-scale study of BL in Brazil, including 234 patients from five geographic regions that are widely disparate socioeonomically, including both the pediatric (61.1%) and adult (37.6%) populations. EBV was present in 52.5 percent of all BL cases, varying from 28.6 percent in the South to 76.4 percent in the North. Most of the cases were EBV type A. The frequency was higher in the pediatric group and EBV association within this age range predominated in all regions except the South. p53 protein expression was observed in 16.2 percent and only rare cases showed p63 expression. BL in Brazil is regionally distinct, has a low incidence of p53 over expression and a higher than expected association with EBV in sporadic cases.

Abstract 36

BORTEZOMIB-INDUCED ENZYME-TARGETED RADIOTHERAPY (BETR) FOR AIDS-RELATED MALIGNANCIES: EFFICACY ASSESSMENT BY MONTE CARLO AND DOSIMETRY MODELING

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The Epstein-Barr virus (EBV) is associated with AIDS-induced lymphomas and Kaposi's sarcoma, and in most patients with these tumors, the viral genome serves as a nearly tumor-specific target. BETR therapy proposes to use Bortezomib to induce Epstein-Barr virus (EBV)-thymidine kinase (TK) expression, which can be targeted with iodine labeled 2'-fluoro-2'-deoxy-beta-D-5-iodouracil-arabinofuranoside (FIAU). Monte Carlo is an established procedure for simulating radioactive decay and obtaining the absorbed dose distribution from a spatial configuration of radionuclide decays. We present here the Monte Carlo simulation and dosimetry modeling of spherical tumors using GEANT4 for BETR to examine the issue of efficacy relative to percentage of cells induced to express viral TK, in particular for a level of 1 percent, which is the typical percentage of virally infected tumor cells for the AIDS-induced lymphomas.

We constructed a spherical tumor model of spherical cells (15m diameter) in a hexagonal lattice of varying sizes (~10, 20, 50, and 150 cells per side). ^{131}I is randomly allowed to decay according to three different models with varying degrees of ^{131}I cell uptake: 100 percent of cells, 10 percent of cells, and 1 percent of cells containing ^{131}I. The energy deposited in each cell is collected and the dose to each cell calculated. Validation was performed, in part, by checking the MC-derived distribution of decaying ^{131}I within the cells, and the spatial distribution of cells.

The model can be scaled to the tumor size by maintaining the correct ratio of decaying particles to cells and by increasing the amount of deposited energy per decay. The scaling factor comes from simple spherical modeling results, and reflects the fact that the ionizing particles have more distance to deposit energy as the tumor size increases. Also due to the large energy deposition range of ^{131}I (~1mm) compared to the cell size, we observe little difference in the dose distribution per cell between the different percentages of active cells.

The analysis suggests that potential therapeutic efficacy, as measured by the mean absorbed dose and spatial dose distribution in the tumor will be independent of the fraction of cells in the tumor that express viral TK and concentrate ^{131}I-FIAU. The development of a kinetic model is the next step in this effort to assist in assessing the feasibility of porting Bortezomib-induced viral TK uptake of ^{131}I-FIAU to clinical trials. The kinetic model features multi-step kinetics including Bortezomib uptake, TK expression and [^{131}I]FIAU absorption and retention.

Abstract 38

IDENTIFICATION OF B-CELL LYMPHOMAS IN THE CAT/FELINE IMMUNODEFICIENCY VIRUS MODEL PRIOR TO THE DEVELOPMENT OF MACROSCOPIC OR HISTOLOGIC TUMORS: AN ANIMAL MODEL FOR AIDS-RELATED NON-HODGKIN'S LYMPHOMA

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Feline immunodeficiency virus (FIV) is a lentivirus homologous to HIV and shares many structural, biochemical and genomic characteristics with HIV, as well as the ability to induce disease naturally in the host species. FIV is a well-established animal model of HIV pathogenesis that causes immune compromise in domestic cats with a disease course that mimics the disease observed in humans with HIV. Further, FIV-positive cats develop an AIDS-like syndrome with opportunistic infections and cancer. B-cell lymphomas are the most frequently reported neoplasia in both naturally and experimentally infected FIV-positive cats. These lymphomas have a high frequency of extranodal occurrence and histologically resemble Non-Hodgkin's lymphoma (NHL) in humans.

Immunologic dysregulation of mucosal sites such as the intestine is well-established in HIV/FIV pathogenesis, however, the magnitude and significance of long-term mucosal perturbations had not been assessed in FIV. Thus, this study evaluated 14 cats that had been experimentally infected with FIV from 4–7 years duration to elucidate long-term mucosal pathogenesis of FIV. Intraepithelial lymphocytes (IEL) and lamina propria lymphocytes (LPL) of the small intestine were assessed at euthanasia for phenotypic and functional characteristics associated with immune function. Surprisingly, abnormal B-cells were discovered in some of the initial samples. Therefore, the focus of the study was expanded to assess for the presence of lymphoma in these cats.

We found two of 14 cats had grossly evident lymphoma in their gastrointestinal tract. Of the remaining 12 cats without macroscopic or histologic evidence of lymphoma, eight were further assessed for the presence of lymphoma. Seven were identified to have neoplastic B-cells in the absence of lesions. B-cell receptor clonality was confirmed in five of seven samples.

Our results show that 1) neoplastic B-cells can be identified in a significant proportion of chronically FIV-positive cats prior to the development of clinical lymphoma, and 2) that the FIV cat model is a potentially valuable animal model for elucidating pathogenesis as well as identifying biomarkers for spontaneously occurring AIDS-related NHL.

Support: NIH/NIAID K08 AI056984 (KEH).

Abstract 39

TOBACCO, ALCOHOL AND USE OF OTHER RECREATIONAL DRUGS WITHIN HIV-INFECTED TREATED COHORTS: THE IeDEA WEST AFRICA COLLABORATION

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Background: Cardiovascular diseases and cancers are an emerging problem among HIV-infected persons once Highly Active Antiretroviral Therapy (HAART) is used for prolonged periods of time. Tobacco and alcohol consumption are well-known risk factors of many non-AIDS classifying cancers but are poorly documented in sub-Saharan Africa. We aimed to estimate the prevalence of cancer risk behaviors classifiable as addictions (tobacco, alcohol and recreational drugs) among HAART-treated HIV-infected patients in the West African region.

Method: A cross-sectional survey was conducted in eight adult centers participating to the International epidemiological Database to Evaluate AIDS (IeDEA) in West Africa collaboration (five in Abidjan, Côte d'Ivoire, two in Bamako, Mali and one in Cotonou, Benin). During a 4-week period, especially trained health workers administered to HAART-treated patients a standardized and validated questionnaire assessing current and past smoking status, alcohol drinking and use of selected recreational drugs.

Preliminary Results: From May 21 to June 6, 2008, 813 HIV-infected patients on HAART participated to the first phase of this study (194 men and 619 women). In Côte d'Ivoire, 57.2 percent (95% CI +/- 6.8%) of men reported a current or a past history of smoking and 23 percent (95% CI +/-5.8%) admitted being current smokers. Of the group, 43.1 percent (95% CI +/-7%) declared current alcohol consumption during the last year and 56.7 percent (95% CI +/-6.9%) declared alcohol intake before this last year. In Ivoirian women, 5.3 percent (95% CI +/-1.7%) declared a current or a past history of smoking and 1.4 percent (95% CI +/-0.9%) admitted being current smokers. In Ivoirian women, 24.6 percent (95% CI +/-3.4%) declared current alcohol consumption during the last year and 37.0 percent (95% CI +/-3.8%) declared alcohol intake before this last year. In Mali, 81.1 percent (95% CI +/-12.4%) of men declared a current or past history of smoking, 48.6 percent (95% CI +/-16.1%) being current smokers. Of the Mali men, 5.4 percent declared current alcohol consumption during the last year and 16 percent declared alcohol intake before this last year. In Malian women, 6.3 percent (95% CI +/-4.6%) declared a current or past history of smoking, with 2.7 percent being current smokers. In Malian women, 3.7 percent declared current alcohol consumption during the last year and 4.3 percent declared alcohol intake before this year. The full data set will comprise data on 1,400 HAART-treated patients in Côte d'Ivoire, 600 in Mali and 400 in Benin and will be correlated with socio-demographic, clinical and therapeutic characteristics.

Discussion: This information will help 1) at the patient level to provide targeted educational support to HAART-treated patients on these addictions; 2) at the population level to provide reliable estimates of the long-term impact of such consumptions on the prognosis of these African patients.

Abstract 40

ANAL AND CERVICAL CYTOLOGIC ABNORMALITIES AMONG HIV-INFECTED WOMEN IN THE ERA OF HAART

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Background: Cervical human papillomavirus (HPV) infections and abnormal cervical cytology are more prevalent and persistent in HIV-infected compared with uninfected women. Less is known about anal HPV infections and abnormal anal cytology in women and whether findings in the cervix correlate with findings in the anus. The correlation between cytology and histology in the anal area has been even less studied. Here we evaluate the prevalence of anal and cervical cytologic abnormalities and evaluate if the abnormal cytology is associated with abnormal histology as evaluated by biopsies.

Methods: This is a cross sectional study of HIV-infected patients receiving care at the Miriam Hospital, Providence, Rhode Island. All women that were due for the annual cervical Pap smear were offered to participate in the study. Each participant had cervical and anal swabs for cytopathologic examination (Pap tests) and cervical and anal cytobrush and swab obtained for HPV typing. Any abnormal cytology was followed up with a colposcopy and anoscopy respectively and biopsies obtained.

Results: Cervical and anal cytology results were available for 80 women. Mean age was 43 years (range 24–60), and race was 50 percent white, 34 percent African American, 14 percent Hispanic, 10 percent other. The median CD4 count was 564 cells/mm^3 (range 44 to 1470 cells/mm^3). Fourteen women (18%) were antiretroviral naïve, 64 women (80%) were taking antiretroviral therapy, and two had an unknown medication history. The mean HIV viral load was 18,318 copies/mL, 56 percent of the women had an undetectable HIV viral load. The prevalence of an abnormal cytology (atypical squamous cells of undetermined significance [ASCUS], low- or high-grade squamous intraepithelial lesions [SIL]) in anus or cervix was 40 percent (32 out of 80 women); 22 percent in the anus, and 26 percent in the cervix (not statistically significant). Eight out of 32 women (25%) had an abnormal cytology at both anatomical areas, 10 of 32 (31%) women had an abnormal anal cytology only, and 14 of 32 (44%) women had an abnormal cervical cytology only. Up to date, 5 out of 18 women with an abnormal anal cytology have undergone anoscopy with biopsy results that were all normal. Nine women out of the 22 women that had an abnormal cervical Pap smear have had a colposcopy with biopsy and only one cervical intraepithelial neoplasia II.

Conclusions: Preliminary results in this cohort of HIV-infected women with a high mean CD4 cell count shows that there is a high prevalence of abnormal cytology and it is similar in both cervix and anus. The majority of women had abnormal cytology in either anus or cervix but not both. A limited number of women have undergone histology sampling, and all but one had normal results. Additional biopsies have been scheduled and HPV typing is being analyzed.

Abstract 45

MDM2-DEPENDENT INHIBITION OF P53 IS REQUIRED FOR EPSTEIN-BARR VIRUS B CELL GROWTH TRANSFORMATION AND INFECTED CELL SURVIVAL

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Epstein-Barr virus (EBV) growth transformation of primary B lymphocytes into indefinitely proliferating lymphoblastoid cell lines (LCLs) depends on the concerted activities of a subset of viral proteins expressed during latency. EBV drives quiescent B cells into S phase and consequently a host response is activated that includes expression of p53 and its target genes. Since LCLs retain wild-type p53, it was of interest to determine what contribution the p53 pathway may have in controlling established LCL growth and EBV-mediated transformation of primary B cells.

We found that liberation of p53 through chemical antagonism of one of its major ubiquitin ligases, MDM2, led to apoptosis of established LCLs and suppressed EBV-mediated transformation of primary B cells. The activation of latent p53 induced target genes associated with apoptosis and was antagonized by constitutive NFκB activity in LCLs. Furthermore, the NFκB-dependent antagonism of p53 was not at the p53-dependent transcriptional level, but rather involved increasing the level of steady-state MDM2 protein. The consequence of these effects through NFκB is to increase the MDM2/p53 ratio, thereby sensitizing cells to MDM2 antagonism. This mechanism, likely through increased MDM2 translation, may provide a novel means by which NFκB activating oncogenes suppress wild-type p53 activity and overcome the oncogenic stress checkpoint. Furthermore, the acquisition of Nutlin-sensitivity in EBV-infected cells provides a novel system for studying the pathways that dictate LCL survival and regulate EBV transformation. Finally, MDM2 antagonists may be considered alone or in combination with NFκB inhibition for therapeutic intervention in EBV-associated malignancies expressing wild-type p53.

Abstract 48

GENETICALLY RESTRICTED HIV-1 SUB POPULATIONS ARE ASSOCIATED WITH AND MIGRATE WITHIN METASTATIC SITES OF AIDS-RELATED LYMPHOMA

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Background: AIDS-Related Lymphoma (ARL) is a disease mediated in part by HIV-infected macrophages and persists despite current HIV therapy protocols. The primary difference between lymphoma seen in non HIV-infected individuals and ARL is that ARL is uniformly high grade and widely metastatic. This fact, coupled with finding almost 50 percent of tumors have HIV expressing macrophages, has created interest in studying a potential viral component to lymphoma evolution. The expansion of HIV quasispecies *in vivo*, which can be evaluated using a variety of computational algorithms, allows precise assignment of viral evolutionary relationships when applied to sequences obtained from multiple sites of infection. In this study, we used an advanced HIV phylodynamic approach to track the evolution of ARL metastasis in a multisite autopsy study and identified a significant relationship between HIV dynamics and lymphoma progression.

Methods: Multi-site frozen autopsy specimens were obtained through the AIDS and Cancer Specimen Resource (ACSR) from patients who died with ARL. A variety of lymphoid and non-lymphoid tissues were classified as abnormal or normal by histology examination and stained with antibodies to CD68, MAC 387 and HIV p24. Quantitative HIV genetic studies qualified diseased and non diseased tissues to having > 1 copy of HIV/2000 genomic equivalents for further genetic analyses. We extracted 406 HIV-1 genomes, spanning the 3' *env-LTR* segment of HIV that were sequenced from multiple sites from two multi-site autopsies. Viral dynamic analyses included phylogeny, migration assessment, population growth and selection studies using advanced bioinformatics methodologies.

Results: Detailed phylogenetic analysis clearly showed distinct subpopulations of tumor and non-tumor viruses with lymph node viruses moving between both groups. Gene flow analysis showed that viruses from normal tissues rarely migrated to lymphoma tissues ($p<0.0001$). This evidence strongly indicates a relationship between specific HIV genetic variants and the development of tumors. Additionally, a 10-fold faster evolution of viruses was found within lymphoma tissues as compared to normal tissues (median effective viral population in lymphoma tissue = 60,000 compared to 6,000 in normal tissue) and up to a four-fold increase in purifying selection in lymphoma viruses indicated that the lymphoma virus was both fast replicating and genetically stable (non-tumor dN/dS = 1.23 compared to tumor dN/dS = 0.26).

Conclusions: The results strongly support the existence of a fast replicating lymphoma-related virus, distinct from other circulating viruses in two patients who died with metastatic ARL. The positive selection of viral sequences in one of the cases suggests a non-random association of a lymphoma specific viral element within viruses associated with tumor metastasis. Earlier studies that localized HIV to tumor associated macrophages suggests that this viral evolution is relatively specific for a macrophage pool of viruses and hence might be relatively resistant to current HAART therapies dedicated at blocking primary infection rather than eradicating macrophage associated infection. These data suggest the addition of drugs that target infected macrophages may influence the evolution of ARL. Sequences that cluster with ARL versus non tumor sites within these two individuals are currently being evaluated to test whether a true lymphoma virus might evolve in the context of ARL lymphomagenesis.

Abstract 50

GENETIC RESISTANCE TO GAHV-2 INDUCED LYMPHOMA IN THE CHICKEN MODEL

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Oncogenic herpesvirus infections contribute to the occurrence of lymphomas in the human population. Genetic makeup has a role in susceptibility, but the basis of resistance and susceptibility is not well understood. To gain insight into how genetic resistance occurs in an animal model we have been studying the lymphomas that form in chickens following infection with gallus herpesvirus 2 (GaHV-2), the virus that causes Marek's disease. A significant association between MHC haplotype and the incidence of Marek's disease in chickens was recognized more than 30 years ago. Through mapping crossover breakpoints in two MHC recombinant haplotypes (*BR2* and*BR4*) that differ in the incidence of Marek's disease we have identified *BG1* as an MHC gene with a major influence in the occurrence of GaHV-2-associated lymphoma in the chicken. BG1 is an Ig-family type I transmembrane protein containing an ITIM motif. The *BG1*BR2* and *BG1*BR4* alleles differ only in the 3'-untranslated region (3'-UTR) with the longer 3'-UTR of the susceptible *BR4* allele containing unique sequence. In dual firefly/renilla luciferase reporter assays we found that the 3'-UTR of the *BR4* suppresses translation of the firefly reporter gene in LMH cells activated with PMA. The 3'-UTR of *BR2* is far less inhibitory under the same conditions.

This experiment suggests that the 3'-UTR of the susceptible allele may have a negative influence on the expression of BG1 protein in vivo. We are currently investigating the possibility that microRNA binding to the longer 3'-UTR results in reduced BG1 expression and increased tumors. *BG1* expression in cultured cells rapidly decreases in the presence of virus (avian poxvirus only tested so far). If BG1 sends an inhibitory signal as the ITIM suggests, then down-regulation of BG1 by viral infection may result in the availability of more activated cells for viral replication. With more cells infected the likelihood of transformation increases. (Supported by NIH/NCI R21 CA105426)

Abstract 51

AKT/TSC/mTOR ACTIVATION BY THE KAPOSI'S SARCOMA-ASSOCIATED HERPERSVIRUS G PROTEIN-COUPLED RECEPTOR: NOVEL THERAPEUTIC TARGETS FOR THE TREATMENT OF KAPOSI'S SARCOMA

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The identification of the Kaposi's sarcoma (KS)-associated herpesvirus (KSHV) as the viral etiologic agent for KS has provided an opportunity to uncover its molecular pathogenesis and to identify new therapeutic targets for this neoplasm. The expression of only one KSHV gene, *vGPCR*, is able to induce KS-like sarcomas in mice, suggesting that *vGPCR* may be the viral gene responsible for the development of KS.

Here, we demonstrate that dysregulation of Akt/TSC2/mTOR by the KSHV vGPCR is essential for KS sarcomagenesis. *In vitro*, cells overexpressing vGPCR showed constitutive signaling of Akt/TSC/mTOR. Immunohistochemical analysis of vGPCR experimental and human KS tissues revealed high levels of phosphorylated Akt and S6 ribosomal protein. Of interest, the treatment of allografts established upon injection of endothelial cells overexpressing KSHV vGPCR with the specific mTOR inhibitor, rapamycin, blocked tumor growth, providing a molecular explanation of the efficacy of rapamycin in the regression of KS lesions in patients with iatrogenic KS. Moreover, a novel dual inhibitor of PI3Kα and mTOR, PI-103, was able to inhibit vGPCR tumorigenesis *in vitro* and *in vivo*. Exposure of vGPCR expressing cells to this compound blocked the phosphorylation of Akt, its downstream substrates, and mTOR suggesting that combinatorial inhibition of mTOR and p110α may represent an effective therapeutic alternative for KS patients. All together, these results suggest that specific inhibitors of Akt/TSC/mTOR represent valuable therapeutic alternatives for Kaposi's sarcoma.

Abstract 52

EXTRACELLULAR MATRIX PROMOTES PATHOGENIC TREATMENT OF AIDS-ASSOCIATED KAPOSI'S SARCOMA AT HÔPITAL GENERAL IN YAOUNDÉ, CAMEROON

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With the extensive rollout of comprehensive antiretroviral therapy (ART) now accelerating in sub-Saharan Africa, the epidemiology, treatment and clinical outcomes of AIDS-associated malignancies is rapidly evolving. This expansion, largely enabled by PEPFAR (President's Emergency Plan for AIDS Relief) and the Global Fund to fight AIDS, Tuberculosis and Malaria, is dramatically increasing access to complicated medical interventions in individuals who would otherwise be unable to afford them. Attitudes and expectations of patients and their care-providers are fortunately moving away from the former paradigm of "can't do this in Africa." Populace expectation of having access to life-prolonging treatments is becoming the new paradigm. AIDS has led the way in this paradigm shift but a movement for concurrently reinforcing chemotherapy of AIDS-related malignancies has also been empowered by the massive ART rollout.

In this presentation, we highlight the changes that are occurring in both the Medical Oncology Unit and in the AIDS Treatment Center at Hôpital General, in Yaoundé, Cameroon. Hôpital General is a typical state-run hospital with limited resources and a difficult-to-manage number of ill patients, including impressive numbers of patients with AIDS and AIDS-associated malignancies. During a 12-month period, we systematically conducted HIV testing of all 632 patients with a confirmed new malignancy; 52 (8.2%) were HIV-positive. Concurrent HIV prevalence in the general population was ~5.5 percent. Of these 52 HIV-positive patients with a documented malignancy, 14 (27%) had Kaposi's sarcoma (KS), 8 (15.4%) lymphoma, 7 (13.5%) breast cancer, 3 (5.7%) oropharyngeal cancer, 2 (3.9%) ovarian cancer.

In a subsequent 12-month period, we identified 57 additional KS patients of whom 50 (88%) were HIV-positive. Among KS-positive or HIV-positive patients who received both anti-KS chemotherapy by protocol (doxyrubicin, bleomycin, vincristine), and concurrent ART, the time to quantifiable recovery was markedly shorter compared to recovery times in patients who received only anti-KS chemotherapy. These findings have prompted a change in AIDS-associated malignancy management at our institution. These patients are now co-managed in the same clinic by medical oncologists and experts in ART. With the recent expanded access to ART we believe that this synergy in case management will increase the quality and the number of life years in this ever-expanding population.

Abstract 56

PROTEIN TYROSINE PHOSPHATASE NONRECEPTOR 13 (PTPN13) IS TARGETED BY HUMAN PAPILLOMAVIRUS 16 E6 IN CERVICAL EPITHELIUM

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Objectives: The Post Synaptic density protein-95/ Drosophila disc large/Zonula occludens (PDZ) domain binding motif of human papillomavirus (HPV) E6 correlates with malignant transformation for high risk HPV. Recent evidence in our lab has shown that HPV16 E6 binds and degrades PTPN13 in a PDZ binding motif-dependent manner in HPV-positive head and neck squamous cell cancer. The loss of PTPN13 results in invasive growth when combined with Ras expression. The purpose of this study is to investigate PTPN13 expression in normal and malignant cervical epithelial cells, and to evaluate its role in cervical cancer.

Methods: PTPN13 expression was measured by Western blotting in primary cultures of normal and high-risk HPV-infected human cervix and foreskin keratinocytes, in non-tumorigenic HPV 31b positive cells, in HPV positive (CaSki, SiHa) and HPV-negative (C-33A) cervical carcinoma cell lines. Immunohistochemistry with PTPN13 (C-20): sc-1138 antibody was performed on cervical tissue specimens. Primary human cervical cultures and C33A cells were transduced with recombinant adenovirus containing HPV16 E6, E7, and mutant lacking the PDZ domain binding motif (E6Δ146-151). SiHa and Caski cells were transfected with plasmid containing PTPN13. PTPN13 loss was induced in C33A cells using shRNA strategy. Morphologic features, in vitro growth rate, and anchorage independent growth were evaluated. RTPCR was used to measure E6 and E6* expression.

Results: Normal cervical epithelial cells, foreskin keratinocytes and the HPV-negative C-33A cancer cell line express PTPN13. HPV-positive cancer cell lines, as well as cervical and foreskin epithelial cells containing HPV 16, 18, 31 show significant loss of PTPN13 expression. Cells transduced with HPV16 E6Δ146-151/E7 do not survive in vitro compared to cells transduced with HPV E6/E7. PTPN13 loss is E6 PDZ dependent and appears to be associated with integration of E6/E7 into the host genome. Re-establishment of PTPN13 in SiHa and Caski cells decreased colony formation efficiency in soft agar by 21($p=0.0031$) and 68 percent($p=0.0001$) respectively. Loss of PTPN13 via shRNA in C33A cell line increases its colony formation efficiency 133 times ($p=0.0001$) in soft agar.

Conclusion: PTPN13 may play an important role as a tumor suppressor in HPV-mediated cervical carcinogenesis. Understanding of this PDZ dependent mechanism may lead to development of targeted molecular therapy against HPV-positive cervical cancer.

Abstract 57

HEPATOSPLENIC T-CELL LYMPHOMA IN A YOUNG MAN WITH CROHN'S DISEASE: CASE REPORT AND LITERATURE REVIEW

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ABSTRACT: Hepatosplenic T-cell lymphoma (HSTCL) is a rare form of peripheral T-cell lymphoma associated with an aggressive clinical course, a typically poor response to treatment, and an exceedingly high mortality rate. Recent reports suggest there are an excess number of cases of HSTCL in young patients with Crohn's disease who are treated with purine analogues (azathioprine or 6-mercaptopurine) with or without the addition of infliximab, a tumor necrosis factor-alpha inhibitor. We report the case of an 18-year-old man who developed HSTCL after five years of treatment with 6-mercaptopurine. He died seven months after diagnosis despite high-dose chemotherapy and autologous stem cell transplantation. Through a literature review, we identified an additional 12 cases of HSTCL in Crohn's patients. In all, 12 of 13 patients were male (92%). All patients were treated with either azathioprine or 6-mercaptopurine, and 8 of 13 (62%) had concomitant treatment with infliximab. The median age at diagnosis of HSTCL was 18 years (range, 12-35 years). Four case reports included details about treatment regimens. Two patients received induction chemotherapy followed by high-dose chemotherapy plus alemtuzumab and subsequent unrelated allogeneic stem cell transplantation. Both patients died within six weeks of transplantation. One patient received standard lymphoma induction chemotherapy but died from infectious complications associated with neutropenia. One patient received standard lymphoma induction chemotherapy without improvement. The patient underwent splenectomy and died after developing a subphrenic abscess. Following the diagnosis of HSTCL, the median survival for all 13 patients was only nine months (range, 5 days to 12 months). Additional research and improved post-marketing surveillance are needed to better understand the possible role of purine analogues and infliximab in promoting HSTCL and what can be done to prevent the occurrence of this devastating malignancy in young Crohn's patients.

Abstract 60

CLINICAL CHARACTERISTICS AND OUTCOME OF CHILDREN WITH HIV AND BURKITT'S LYMPHOMA IN UGANDA

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Background: Characteristics of children with Burkitt's lymphoma (BL) and HIV infection have not been clearly described in Africa before.

Method: We reviewed records at Uganda Cancer Institute (UCI) for years 1994-2004, to compare clinical features and outcome of BL in children who are HIV-positive and HIV-negative). As statistical methods we used student t-test, chi-square and Kaplan-Meier's to compare both groups.

Results: Of 1462 records of children retrieved, 228 met the eligibility criteria and were reviewed (158 HIV-negative, 70 HIV-positive). There were 139 (61%) males and 89 (39%) females. The mean age was 6.9 years (HIV-positive 6.7, HIV-negative 7.1). One hundred seventy one cases (75%) had facial tumor (HIV-positive 71.4%, HIV-negative 76.6%). HIV-positive children presented significantly with extra facial disease (lymphadenopathy 67%, hepatic masses 51%, and thoracic masses 10%). Presentation with advanced stage disease occurred more frequently in HIV-positive patients compared to HIV-negative patients. Treatment response rates to chemotherapy were similar irrespective of HIVstatus. However, overall survival was poorer in HIV-positive patients with a median survival of 11.79 months (*P*- value < 0.000, 95% CI 8.65 – 14.92).

Conclusions: BL in Uganda present frequently with facial disease irrespective of HIV status. However HIV-positive BL also present commonly with extra facial sites, mainly lymphadenopathy. There is no difference in response to treatment with chemotherapy, but HIV-positive BL patients have poorer survival. There is need for further characterization of BL in Uganda to understand the role HIV in disease process and outcome.

Abstract 61

COLON ADENOCARCINOMA IN HIV INFECTED PATIENTS

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Background: Non AIDS-defining cancers (NADC) have emerged as a growing problem in the HIV-positive population, especially given that HIV-infected patients are living longer with antiretroviral therapy (ART). HIV-Tat protein appears to have oncogenic properties in colorectal cancer cells *in vitro*. To date, there has been no large series studying HIV-associated colon adenocarcinoma. Therefore, the aim of this study was to examine the clinicopathologic features of this NADC in a series of HIV-positive patients.

Methods: Cases of HIV-associated colon adenocarcinoma (excluding anorectal location and non-epithelial cancers) were accrued from the personal archives of the authors and from case reports with available information published in the literature. Available data regarding demographics (age, gender), HIV acquisition, ART use, immunosuppression (AIDS and/or CD4 count), cancer location, pathology (tumor grade, TNM stage), and outcome were extracted and analyzed.

Results: A total of 15 patients were identified, including five personal cases and 10 published reports. Patients were an average age of 42 years (range 25–67) and predominantly male (M:F 12:3), of which six were known intravenous drug users and four homosexual. Most (59%) carcinomas involved the right colon, and less frequently the sigmoid (25%), transverse (8%) or entire (8%) colon. Tumor differentiation ranged from grade 1 (17%), to grade 2 (50%) and grade 3 (33%) carcinomas. Most (62%) were stage 4 cancers, and less often stage 3 (23%) or 2 (15%) malignancies. Metastases when present were mainly to the liver, but included the lung, ascites and subcutaneous tissue. Many (62%) individuals died shortly (within 1–26 months) after their cancer diagnosis. Immunosuppression (AIDS diagnosis and/or CD4 <200 cells/mm^3) noted in eight (53%) individuals did not appear to correlate with tumor grade, stage, nor an adverse outcome. Neither did ART use, which was reported in eight (53%) of these patients.

Conclusion: Adenocarcinoma of the colon should be added to the growing list of NADC. These data show that HIV-infected patients manifesting with colon cancer tend to be younger than their HIV-negative counterparts, with a male predominance. HIV-associated immunosuppression and prior exposure to antiretroviral therapy do not appear to have a major impact on tumor biology or patient outcome. Frequent involvement of the right colon suggests that colorectal cancer screening of the entire colon should be offered to HIV-infected individuals.

Abstract 62

PATHOLOGY OF RITUXIMAB-INDUCED KAPOSI SARCOMA FLARE: ROLE OF B-CELL DEPLETION

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Background: Kaposi sarcoma (KS) flare (exacerbation) may occur following therapy with corticosteroids, as part of the immune reconstitution inflammatory syndrome seen with highly active antiretroviral therapy (HAART), and after rituximab therapy. The exact mechanism responsible for iatrogenic KS flare is unclear. Therefore, the aim of this study was to investigate the pathologic features in cases of AIDS-associated KS flare.

Methods: Two cases of AIDS-associated cutaneous KS flare were identified following rituximab therapy. Tissue biopsies obtained from these KS flare lesions were compared to similar controls (AIDS-KS samples of similar stage from patients who had not received rituximab) by means of immunohistochemistry using vascular makers (CD34, CD31), monoclonal antibodies to human Herpesvirus-8 (HHV-8) gene products (LNA-1, K5), as well as B-lymphocyte (CD20) and T-lymphocyte (CD3, CD4, CD8) markers.

Results: One patient was a 36-year-old male, HIV-positive for 2 years (CD4 T-lymphocyte count 363 cells/mm3; HIV viral load >100,000 copies/ml), and the other a 44-year-old male, HIV-positive for 5 years (CD4 T-lymphocyte count 443 cells/mm3; HIV viral load <75 copies/ml), who had both received rituximab therapy for multicentric Castleman disease. The former manifested with cutaneous KS after 7 days, and the later patient with skin and lymphadenopathic KS flares within 3 months of receiving rituximab. In the control cases both CD3 and CD20 cells were present, with a preponderance of T-lymphocytes identified. In the KS flare specimens, there were only T-cells present with a notable absence of B-lymphocytes. In all control and flare KS cases T-cell subsets showed CD8 > CD4. CD20+ B-cell depletion in the KS flare case of the 36-year-old patient occurred concomitantly with activation of the HHV-8 immediate early gene protein K5. KS flares in both patients were successfully treated with liposomal doxorubicin and valganciclovir.

Conclusion: Rituximab-induced KS flare appears to be related to a modification in the host immune system, most notably with complete absence of B lymphocytes in the KS lesion. B-cell depletion with rituximab in patients at risk for KS development may activate HHV-8, resulting in unwanted KS flare. Effective management of iatrogenic KS flare therefore depends upon the control of HHV-8 viremia in conjunction with specific chemotherapy for KS.

Abstract 63

HIV-ASSOCIATED BLADDER CANCER: DIAGNOSIS AND MANAGEMENT

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Introduction: Chronic HIV infection has been associated with an increased incidence of non AIDS-defining cancers. To date, only a limited number of cases of bladder cancer have been reported in association with HIV infection. Therefore, the aim of this study was to investigate a series of HIV-associated bladder cancer cases.

Methods: A retrospective study was performed involving HIV positive patients with concomitant bladder cancer, combining cases from multiple institutions with published case reports. Data were extracted regarding patient demographics (age, gender), HIV status (CD4+ cell count, HIV viral load), clinical presentation, pathology, cancer treatment, and outcome. Accrued data were analyzed using descriptive statistics.

Results: A total of 11 patients were identified with an average age of 53 years (range 33 to 67), most of whom were male (M:F 9:2). Their median CD4 cell count was 280 cells/mm^3 (range 106 – 572 cells/mm^3) and median HIV load <50 copies/mL (range <50 – 665,000 copies/mL). Five (45%) patients smoked tobacco, two had recurrent cystitis, two had bladder calculi, and one patient had previous pelvic radiation therapy for cervical cancer. Nine (82%) presented with hematuria. Less common presentations included lower abdominal pain, irritative urinary symptoms (frequency, urgency and/or dysuria), and weight loss. Most cases (10/11) had transitional cell carcinoma and one person had squamous cell carcinoma. At presentation, two cases had stage 0a disease, five had stage I disease, and two stage IV disease. Treatment with transurethral resection of bladder tumor (TURBT) was followed by intravesical or systemic chemotherapy, cystectomy and/or radiation. Intravesical mitomycin C or epirubicin was used, despite the fact that BCG in one case did not cause complications. Several patients (64%) were alive following therapy, although many (71%) suffered from local relapse and metastatic disease.

Conclusion: Bladder cancer should be added to the growing list of Non-AIDS defining cancers likely to be encountered in HIV-infected patients now living longer with controlled HIV disease. Afflicted patients are likely to present at a younger age and with only mild immunosuppression. Hematuria, dysuria, frequency and/or urgency in an HIV-infected patient warrants complete evaluation, including a work up for bladder cancer. Although most patients presented with early stage disease, the course for their bladder cancers was notable for frequent relapses and subsequent metastases. HIV positive individuals should be counseled on the potential risks (e.g., smoking) of bladder cancer.

Abstract 65

CLINICAL PRESENTATION OF EPIDEMIC KAPOSI'S SARCOMA DIFFERS BY GENDER IN KAMPALA, UGANDA

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Background: Previous work has shown that the incidence of AIDS-associated (epidemic) Kaposi sarcoma differs between men and women, suggesting that gender may influence the pathophysiology and presentation of KS. Despite some reports that epidemic KS in women is associated with more severe disease and worse prognosis, data on differences in the clinical manifestations of KS between genders are limited, particularly in regions of the world with high burdens of KS. Further, several different morphotypes of KS have been described in Africa, which are rare elsewhere in the world, including nodular and fungating KS. We examined clinical manifestations of KS in men and women in a retrospective cohort of HIV-infected persons with KS seen at the Infectious Diseases Institute (IDI) in Kampala, Uganda.

Methods: HIV-infected adults attending the IDI between January 2004 and December 2006 were included if they received a clinical or biopsy-confirmed diagnosis of KS. A standardized case report form was used to collect information on the clinical presentations of KS at the IDI. Data was obtained by a chart review and clinical characteristics described at the time of KS diagnosis were used in our evaluation. CD4 counts obtained closest to the KS diagnosis and within 6 months of the diagnosis date were included in the analyses.

Results: The cohort consisted of 197 adults with HIV and KS: 55 percent (108/197) were women and 45 percent (89/197) were men. KS was confirmed by histology in 62 percent (123/197) of cases. The median age was 34 years (range 18 to 61) for women and 35 years (range 21 to 57) for men (p=0.77). The median CD4 count was 58 cells/mm3 (IQR 11, 156) among women and 124.5 cells/mm3 (IQR 22, 254) among men (p=0.80).

In unadjusted analyses, women were more likely than men to have KS lesions involving the face (RR, 2.2; 95% CI, 1.2, 3.9), oral cavity (RR, 3.5; 95% CI, 1.5, 8.2), and hard palate (RR, 1.6; 95% CI, 1.1, 2.4). Women were less likely than men to have nodular lesion types (RR, 0.42; 95% CI, 0.24, 0.75), lower extremity lesions (RR, 0.81; 95% CI, 0.66, 0.99), and associated edema (RR, 0.54; 95% CI, 0.36, 0.80).

After adjusting for CD4 count, women remained more likely than men to present with lesions of the face (OR, 2.6; 95% CI, 1.2, 5.7) and oral cavity (OR, 3.5; 95% CI, 1.2, 9.9) and were less likely than men to have nodular lesion types (OR, 0.32; 95% CI, 0.14, 0.74).

Conclusions: Clinical manifestations of KS appear to differ between men and women in Uganda. These data suggest that gender affects the pathophysiology of KS, which may have implications for prevention, diagnosis, and treatment of KS. Prospective studies are needed to further evaluate differences in the clinical manifestations of KS and response to treatment between men and women.

Abstract 66

UNREMITTING KAPOSI SARCOMA IN HIV INFECTED PATIENTS WITH VIRAL SUPPRESSION ON ANTIRETROVIRALS

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Background: In large cohort studies, development of Kaposi Sarcoma (KS) in patients with HIV is usually associated with low CD4 count (23-129 cells/μl^3), high viral load (85,570 to 176,000copies/ml) and low CD4 nadir (upper range of 150 cells/µl, with a median of 78 cells/$\mu l.^3$). We report a series of 16 homosexual men that in spite of 2 years of sustained viral load suppression, stable CD4 counts over 300 cells/μl^3 on antiretroviral therapy (ART) and CD4 nadirs over 300cells/ μl^3, developed KS. Currently, the mainstay of treatment for KS is to maximize ART with respect to CD4 count and viral load. Despite adequate ART, the patients in this series have unremitting KS.

Methods: The patients in this series were referred to our practice at a specialized dermatology clinic in a university setting in San Francisco during a 33-month period from November of 2004 to July of 2007. The patients attracted our attention due to their continuing problems with KS despite good virologic and immunologic control of HIV.

Results: Our patients include 16 homosexual males from a variety of ethnic groups. The median age at presentation was 52.5 years (41–75 years). The median known duration of HIV at presentation was 17.5 years (4-25 years). All had a CD4 count of >300 cells/μl^3 at the time of diagnosis with KS and 12/16 had an undetectable viral load (<75 copies/ml). All have maintained a viral load below 300 copies/ml and a CD4 count of greater than 300 cells/μl^3 for the past 2 years. All patients presented with cutaneous lesions of KS. Seven had more than five lesions at presentation and nine had fewer than five lesions at presentation. Twelve were on ART at the time of KS diagnosis and all are on ART currently. The median length of time of antiretroviral therapy (ART) that includes a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) is 5 years (range 1 to 12 years). KS lesions have remained the same regardless of NNRTI switches to PI regimens. Five patients have undergone successful surgical excision of at least one KS lesion. One patient has experienced mild improvement with intralesional vinblastine and liquid nitrogen cryotherapy. Five patients have received radiotherapy resulting in regression of lesions. Two patients received liposomal doxorubicin infusions, which decreased the number, size, and pigmentation of KS lesions. Three of five patients who have applied topical alitretinoin twice daily have experienced mild improvement in size and color of lesions. None of the patients have had eruptive KS, organ involvement of KS or development of other opportunistic infections.

Conclusions: We believe that the patients in this series represent a new, atypical expression of KS that occurs despite viral suppression and good immune system function as measured by CD4 count and viral load. Given that these individuals are already maximized on their ART, the presence of KS in this population presents a clinical and prognostic conundrum. Based on our preliminary experience with these patients, it is our recommendation that they should be managed conservatively. First, the ART regimen should be reexamined to ensure maximum adherence. Given our observations so far, we do not believe that PIs provide any benefit over NNRTIs in the treatment of this form of KS. Second, we recommend radiation and/or chemotherapy (intralesional or systemic) only when lesions are painful or are located in areas that are highly visible and affect the patient's self image. Finally, given the stigma associated with KS as an AIDS-defining illness, it is important to provide reassurance to patients who develop KS despite high CD4 count and low viral load on ART that this form of KS seems to run a more indolent course despite its unremitting nature.

Abstract 68

CELLULAR GENE REGULATION BY K13/VFLIP OF KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS

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ORFK13/vFLIP of Kaposi's sarcoma-associated herpesvirus (KSHV) encodes a 188-amino acid protein, which binds with Iκb kinase gamma subunit (IKKγ) to activate the NFκB pathway. To gain insight into the changes induced by K13 in endothelial cells, we retrovirally expressed *ORFK13* in human umbilical vein endothelial cells (HUVECs) and examined by DNA microarray patterns of genes expression in control retrovirus- and K13 retroviral-infected HUVECs. As expected, expression of numerous NFκB-targeted genes increased and expression of a limited number of genes decreased in K13-expressing HUVECs compared to control. Genes with increased expression included pro-inflammatory chemokines, cytokines, and adhesion molecules. Consistent with these results, K13-expressing HUVECs promoted monocyte attachment *in vitro* more effectively than controls, an observation consistent with immunofluorescent staining of AIDS-KS tissue showing infiltration of CD68-positive monocyte/macrophages. These infiltrating CD68-positive cells displayed moderate expression of VEGF, suggesting that K13 expression in KSHV-infected cells contributes to monocyte/macrophages attachment and represents a source of VEGF for tumor cells. Additionally, retroviral gene expression of *ORFK13* caused a dynamic morphological change in HUVEC that turned into spindle-like cells, and altered endothelial formation of vascular structures on extracellular matrix. In another aspect, K13 retrovirus induced significant expression of human thymidine phosphorylase, which is also called platelet-derived endothelial cell growth factor (PD-ECGF). PD-ECGF can metabolize 5-fluoro-5-deoxyuridine (5-dFUrd) into 5-fluorouridine (5-FU), a thymidylate synthase inhibitor. When cytotoxity was measured, 5-dFUrd selectively killed K13-expressing HUVECs at low concentrations (0.1M), which did not affect the survival of control HUVECs. This observation has potential clinical implications for the treatment of KSHV-related malignancies where *ORFK13*/vFLIP is expressed and responses to current therapy are poor.

Abstract 69

HUMAN HERPESVIRUS 8 K1-DERIVED PEPTIDES DISRUPT THE INHIBITORY FAS-K1 COMPLEX AND RESTORE FAS RECEPTOR-MEDIATED APOPTOSIS

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Background: Human herpesvirus 8 (HHV-8) infection is associated with the development of primary effusion lymphoma, Kaposi's sarcoma, and multicentric Castleman's disease. The *K1* gene of HHV-8 is expressed in tumor cells as a transmembrane protein with an immunoglobulin-like domain in its ectodomain and an immunoreceptor tyrosine-based activation motif (ITAM). We demonstrated that K1 protein activates nuclear factor-kappa B (NF-κB), and K1 expression in transgenic mice stimulated accumulation of lymphatic cells and development of lymphoma. How K1 blocks apoptosis and induces hyperplasia and lymphomas is not known. We hypothesized that K1 contributes to lymphoma development partly by suppressing apoptosis, and that this suppression combined with its NF-κB activation produces lymphoma.

Results: We found that K1 binds to Fas and in turn, inhibits Fas-mediated apoptosis. We mapped the region that K1 uses to bind to Fas as an immunoglobulin (Ig) chain-like domain by expressing deletion mutants of K1. Overexpression of an Ig domain-containing protein CD79b competed with K1-Fas binding in a dose-dependent manner. Two 20-amino acid peptides (N251, N253) representing the Ig domain of K1 competed with K1-Fas binding in immunoprecipitation/immunoblotting analysis. The N251 and N253 peptides (100 μM) enhanced anti-Fas antibody (CH-11, 50 ng/mL)-induced apoptosis of BJAB lymphoma cells that expressed K1 but not that of vector-transfected BJAB cells. Ig-deleted K1 (K1dIg)-transfected mice were not protected (0/6), and K1-transfected mice were protected (7/10, $P < 0.01$) against the lethal effects of agonistic anti-Fas (Jo2) antibody. K1dIg expressed in mice did not form complexes with Fas, suggesting that the Ig domain is essential for K1-Fas binding and suppression of apoptosis.

Conclusion: Collectively, these results indicate that K1 potently blocks apoptosis, and that this effect is mediated through the Ig-like domain of K1. Because viral proteins mimic cellular proteins, these results predict the presence of functional cellular homologs of K1 that have key roles in death receptor regulation.

Abstract 70

KAPOSI'S SARCOMA HUMAN HERPESVIRUS K1 INTERFERES WITH FAS-MEDIATED APOPTOSIS AND STIMULATES CLONAL GROWTH AND LYMPHOID HYPERPLASIA

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Background: Infection with human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma associated herpesvirus, is associated with the development of primary effusion lymphoma and Kaposi sarcoma. A transmembrane protein of HHV-8, K1, is readily expressed in these tumors, and the expression of K1 alone causes hyperplasia of lymph nodes and lymphomas in mice. The exact mechanism of how K1 causes hyperplasia and lymphomas in K1-expressing mice is not known. The cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM) of K1 was previously shown to be involved in activation of nuclear factor-kappa B (NF-κB). Moreover, we have recently shown that K1 suppresses Fas-mediated apoptosis through its extracellular immunoglobulin-like domain and that K1-transfected mice survive a lethal dose of agonistic anti-Fas antibody (Jo2). We thus hypothesized that development of hyperplasia and lymphomas in K1-expressing mice is driven by alterations in Fas signaling.

Results: Gross examination of thoracic and abdominal cavities of transgenic mice with K1 expression driven by a ubiquitous promoter, which were sacrificed at 18 months of age, revealed enlarged cervical, mediastinal, renal, and mesenteric lymph nodes and spleens. Peyer patches were also enlarged and readily visible on the outer surface of the ileum. Out of 10 K1 mice, 90 percent developed lymphoid hyperplasia (> 3 mm) and 60 percent developed lymphomas, while all (26) control mice remained hyperplasia- and lymphoma-free. In the extreme cases, K1 mice developed liver or mesenteric tumors (four and four out of 10 mice, respectively). Spleens of 78 percent of K1 mice were enlarged at 18 months and were on average 3.5 times heavier than spleens of non-expressing control mice (332±200 mg versus 94±26 mg, $P < 0.03$). Hematoxylin and eosin staining of spleen sections showed expansion to the periarteriolar lymphocyte sheath with disruption of normal follicular architecture. Staining of spleen sections with anti-kappa and anti-lambda light chain antibodies revealed the presence of monoclonal foci in three out of three K1 mice (average six foci per single section of spleen), but none in the four control mice. Moreover, K1 protein was expressed in about 10 percent of splenic cells as judged from staining with anti-K1 antibody 2H5. To test the hypothesis that expression of K1 protein in spleens renders them resistant to Fas-mediated apoptosis, splenic cells of 6-month-old K1 mice (n=3) and matched controls (n=3) were isolated and incubated with 50 ng/mL of agonistic anti-Fas antibody Jo2. At 12 hours of treatment, only 4±1 percent of splenocytes from K1 mice versus 17±2 percent of control splenocytes were undergoing apoptosis ($P < 0.01$). At 24 hours of treatment, the difference was even more significant (11±0.6% versus 50±6%, $P < 0.005$). Splenocytes of K1 mice were indeed more resistant to Jo2 induced apoptosis than splenocytes from age-matched control mice. Of mice inoculated with a lethal dose of Jo2 antibody, three out of 12 K1 transgenic (30%) and 13 out of 22 control mice (60%) died ($P < 0.05$), further confirming the protective effect of K1 against Fas-mediated apoptosis.

Conclusion: Overall, these results confirm that K1 is associated with lymphoid hyperplasia and lymphoma and provide a plausible explanation. Interference of K1 with Fas-mediated apoptosis disrupts the normal life cycle of lymphocytes.

Abstract 71

CD74 ASSOCIATES WITH FAS AND INHIBITS FAS-MEDIATED APOPTOTIC SIGNALING

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Introduction: Resistance to Fas-mediated apoptosis is a key abnormality in immunodeficiency conditions and hematopoietic cancers, which interferes with the efficacy of currently available chemotherapy. Our prior research on human herpesvirus 8 oncoprotein K1 showed that K1 binds to Fas and interferes with activation of Fas-mediated apoptotic signaling (Wang, W, et al, *Blood* 2007; 109:5455–62). Herpesvirus proteins often mimic host proteins or their functions; we thus searched for endogenous host proteins associated with inactive Fas to identify potential regulators of Fas signaling.

Potential inhibitors of Fas were identified by immunodepletion of cell extracts from B-cell lymphoma-derived BJAB cells with activating anti-Fas antibody and by subsequent coimmunoprecipitation of proteins associated with nonactivated Fas. CD74, the invariant light chain of MHC II, was identifed in complex with inactive Fas by liquid chromatography tandem mass spectroscopy. Interestingly, overexpression of CD74 has been previously reported in hematopoietic cancers: in 43 of 66 cases of pediatric Non-Hodgkin lymphomas (Miles, R.R., et al., *Br J of Haematology*. 2007; 138: 64–71), in 8 out of 14 multiple myeloma-derived cell lines and B-cell lymphoma cell lines Raji and Ramos (Burton, J.D., et al., *Clin Cancer Res.* 2004; 10: 6606–6611), in 11 of 16 cases of leukemia (Kaddu, S., et al., *J Am Acad Dermatol.* 1999; 40: 966–978), as well as in 9 out of 11 cases of non-small-cell lung carcinoma (Ioachim, H.L., *Am J Surg Pathol.* 1996; 20: 64-71). CD74 expression in cancers was thus suspicious.

Methods/Results: Through overexpression of CD74 in Fas-positive HEK 293 cells and suppression of CD74 expression in BJAB cell using siRNA technology we have determined that cells overexpressing CD74 are more resistant to agonistic antibody CH-11-induced Fas-mediated apoptosis then their relative controls. We have also mapped the domain of CD74 required for association with Fas to a membrane-proximal region of CD74 by expressing deletion mutants. Transfection of mice with plasmid encoding full length CD74 protected mice from lethal challenge with agonistic anti-Fas antibody Jo2. All five of vector transfected mice died within six hours from challenge, while four out of five CD74 transfected mice survived the challenge ($P<0.05$).

Conclusions: Our results support the idea of an endogenous regulatory system of Fas-mediated apoptosis that utilizes transmembrane proteins interacting with Fas. We anticipate that specific blocking of the CD74-Fas interaction will sensitize CD74 overexpressing cancer cells to Fas-mediated apoptosis and thus will increase effectiveness of chemotherapy for hematopoietic cancers.

Abstract 72

INITIAL EXPERIENCE OF AN ANAL DYSPLASIA CLINIC FOR HIV-INFECTED MEN IN SEATTLE, WA

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Purpose: Anal dysplasia due to HPV infection is common in HIV-infected individuals and is a precursor to squamous cell cancer of the anus (SCCA). Herein, we describe our initial experience in assessing the incidence and severity of anal dysplasia in a newly formed anal dysplasia clinic in Seattle, WA.

Methods: We performed an IRB approved retrospective chart review of the first group of HIV seropositive individuals who underwent anal dysplasia screening with digital rectal examination, anal PAP cytology, and biopsy of disconcerting lesions. Demographic information (age, sex and race), CD4+ cell counts and HIV viral loads were recorded in conjunction with anal PAP cytology and anal biopsy results.

Results: During a seven-month start up period 150 HIV-positive men were evaluated. Their median age was 47 years (range 24 to 83 years), their median HIV viral load was <75 copies/mL (range <75-228,000 copies/mL), and their median CD4+ cell counts was 454 cells/UL (range 7-1663 cells/uL). One hundred and twenty-two patients (81%) were Caucasian, 12 (8%) were African American, three (2%) were Asian, nine (6%) were Hispanic, and for four (3%) race was not identified. Fifty (33%) had a normal PAP and normal exam/biopsy, five (3%) had an abnormal exam but either declined biopsy or had a health care condition that precluded biopsy, 48 (32%) had low-grade anal intraepithelial neoplasia (AIN), and 47 (31%) had high-grade AIN. One patient with high grade AIN was referred for surgical treatment and was noted to have micro-invasive SCCA. No patient experienced significant post-procedural complications (i.e. bleeding, pain, or infection). Patient tolerance and acceptance of the procedure was good and the majority of those who underwent screening have been compliant with follow up exams.

Conclusions: Anal dysplasia is common in HIV-infected men in our clinic with similar rates to those reported by other anal dysplasia clinics in urban U.S. cities. Creation of our anal dysplasia clinic has refined collaboration between HIV medicine (Internal Medicine, Hematology-Oncology, Infectious Diseases), and the departments of Gastroenterology and Surgery. The clinic is expanding rapidly with excellent community and provider support. We anticipate that the anal dysplasia clinic will allow our institution to participate in emerging HIV and HPV-related anal dysplasia clinical trials.

Abstract 74

EXPLORING KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS LATENT GENES' ROLE IN VIRAL LYMPHOMAGENESIS USING TRANSGENIC MICE

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Kaposi's sarcoma-associated herpesvirus (KSHV) is a human lymphotropic gammaherpesvirus and associated with Kaposi sarcoma as well as two B cell lymphoproliferative disorders: primary effusion lymphoma (PEL) and multicentric Castleman disease. We reported that the KSHV latency-associated nuclear antigen (LANA) transgenic mice developed splenic follicular hyperplasia and showed increased germinal center formation. Here we report that the KSHV LANA-induced B cell activation is CD19 dependent and LANA restores the marginal zone defect in CD19-/- mice. To test KSHV latent genes' role in viral lymphomagenesis, we generated mice expressing all KSHV latency-associated genes. All of the transgenic mice induced mature B cell activation. Further characterization of the mice expressing all KSHV latency-associated genes is currently underway.

Abstract 75

CERVICAL AND ANAL HPV INFECTION AND DYSPLASIA IN HIV-INFECTED WOMEN

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Background: HIV-infected women are at increased risk of cervical HPV infection and neoplasia. We investigated whether HIV-infected women are also at high risk for HPV infection of the anal canal and anal dysplasia.

Methods: We performed a pilot, prospective, observational study on 100 HIV-infected women presenting for routine HIV care. Subjects were interviewed and underwent cervical and anal testing with cytology and HPV with Hybrid Capture 2 assay (Digene Corporation, Gaithersburg, MD). High resolution anoscopy (HRA) or colposcopy were performed if indicated and subjects with high grade dysplasia were referred for treatment. Secondary analyses were performed to assess for associated risk factors for abnormal cervical or anal cytology or HPV infection such as CD4 T-cell count using SPSS for Windows, version 15.0.

Results:

- The average age of the subjects was 41 years and 78 percent of the women were currently on highly active antiretroviral therapy.
- The prevalence of high-risk HPV infection in the cervix was 24 percent and cervical cytological abnormality was 21.6 percent. Of the 24 patients with cervical HPV infection, 15 (62.5%) had cervical cytological abnormalities. (Fisher Exact Test, p= 0.0001).
- The prevalence of high risk HPV infection in the anus was 16 percent and anal cytological abnormality was 17 percent. Of the 16 patients with anal HPV infection, 10 (62.5%) had anal cytological abnormalities (Fisher Exact Test, p= 0.0001).
- Eleven of 24 women (46%) who had high risk HPV in the cervix also had high risk HPV detected in the anal canal (Fisher Exact Test, p= 0.0001). Eight of 21 women (38 percent) who had abnormal cervical cytology also had abnormal anal cytology (Fisher Exact Test, p= 0.0001).
- Subjects with anal HPV infection (mean CD4 count 349 cells/µl) had significantly lower mean CD4 counts compared to subjects without anal HPV infection (mean CD4, 555 cells/µl) (t test, p=0.007). Subjects with abnormal anal cytology (mean CD4 393 cells/µl) had significantly lower mean CD4 counts compared with subjects with normal anal cytology (mean CD4, 550 cells/µl) (t-test, p=0.007).
- Similarly, subjects with cervical HPV infection were significantly more likely to have lower mean CD4 count (394 cells/µl) compared to those without cervical HPV infection (564 cells/µl) (t-test, p=.01). Subjects with abnormal cervical cytology also had lower mean CD4 count (372 cells/µl) compared to women with normal cervical cytology (CD4, 549 cells/µl) (t-test, p=.004).
- Of the 16 patients who underwent colposcopy, eight had low-grade and five had high-grade cervical or vaginal dysplasia. Of the 11 women who underwent HRA, six had low-grade and three had high-grade anal dysplasia.

Conclusion: Anal and cervical HPV infections are common in HIV-infected women. HIV-infected women have high rates of anal and cervical dysplasia. These findings provide further data for developing anal cytology screening recommendations for this patient population.

Abstract 76

PROGNOSIS OF PATIENTS WITH AIDS-ASSOCIATED KAPOSI'S SARCOMA RECEIVING ANTIRETROVIRAL THERAPY +/- CHEMOTHERAPY IN KWAZULU-NATAL, SOUTH AFRICA: AN ANALYSIS OF 1-YR SURVIVAL DATA FROM NCT00380770

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Objective: AIDS-associated Kaposi's Sarcoma (KS) is an increasing public health problem in KwaZulu-Natal, South Africa. The optimal management of AIDS-associated KS in sub-Saharan Africa is unknown. NCT00380770 is a single center randomized clinical trial of 112 patients with AIDS-associated KS who received a nivirapine based antiviral regimen (ARV) alone, or with chemotherapy (doxorubicin, bleomycin and vincristine) between 2003 and 2007. We evaluated 1-year overall survival (OS) and the ACTG staging system in our study population.

Design: Cohort study.

Methods: Baseline TIS staging information is available for all patients. One-year survival data is available for 105 study subjects, with only seven subjects lost to follow-up. OS was evaluated using Kaplan-Meier hazard function methodology. Survival functions were generated for subjects with 0, 1, 2 and 3 adverse prognostic variables using the modified ACTG TIS staging system (CD4 cut-off = 150). Univariate and multivariate Cox proportional hazard regression was performed to evaluate the prognostic value of individual and combined variables on OS in the study cohort. Survival analysis was performed with Stata 10 for Macintosh.

Results: Baseline characteristics are listed in Table 1. One-year OS in the overall cohort was 76.6 percent. For subjects with 0, 1, 2 and 3 adverse prognostic risk factors, the one-year OS was 100 percent, 89 percent, 73 percent and 61 percent (Graph 1). Results from univariate and multivariate Cox proportional hazard regression analyses are listed in Table 2. For the Cox proportional hazards regression model including T, I, and S, the LR χ^2 (3) = 8.45, with p = 0.0375.

Table 1. Baseline Demographics		
Randomization	ARV 53% Combination 47%	
Sex	F 55% M = 45%	
Age Range	18-62	
Region	Urban 70% Rural 30%	
T	0 = 14%	1 = 86%
I	0 = 45%	1 = 55%
S	0 = 56%	1 = 44%

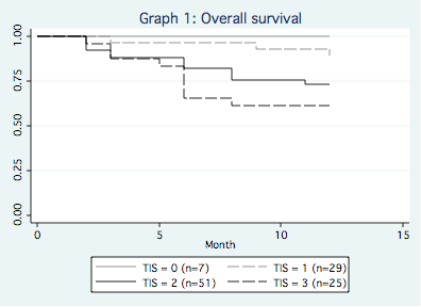

Table 2: Cox Proportional Hazard Regression

Prognostic Variable	Univariate		Multivariate	
T	HR = 2	p = 0.34	HR = 1.8	p = 0.44
I	HR = 2	p = 0.11	HR = 1.8	p = 0.16
S	HR = 2.7	p = 0.02	HR = 2.4	p = 0.04

HR = Hazard ratio of death for score of 1 compared to score of 0

In NCT00380770, 1-year OS in a cohort of AIDS-associated KS subjects in a resource limited setting is dramatically improved compared to historical sub-Saharan cohorts prior to the availability of ARVs. The ACTG Staging system is clinically useful in resource-limited settings. It is notable that for 86 percent T=1 disease and universal ARV use, HIV-associated systemic illnesses, which included 15 subjects with tuberculosis, is the most significant prognostic factor. Analysis of response rates, overall survival, adverse events, and quality-of-life between the two arms in NCT00380770 is ongoing.

Abstract 77

CD57+, A GLOBAL MARKER OF IMMUNOSENESCENCE, IS ELEVATED IN AN ATYPICAL COHORT OF PATIENTS WITH KAPOSI SARCOMA AND WELL-CONTROLLED HIV

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Background: Traditionally, KS has been associated with advanced age or with significant immunosuppression. We recently reported an atypical cohort of antiretroviral-treated HIV infected patients who developed cutaneous KS despite having undetectable plasma HIV RNA levels and high CD4+ T cell counts. The KS lesions seen in these patients were indolent and reminiscent of classical KS seen in the HIV-negative elderly. The mechanism of KS in the elderly remains undefined, but many have postulated a potential role of immunosenescence, which is generally defined as the gradual loss of immunologic function during advanced age. Given emerging evidence suggesting that prolonged periods of untreated HIV infection results in accelerated and perhaps irreversible "aging" of the immune system, we hypothesized that immunosenescence may account for the development of KS in otherwise young well-treated HIV infected individuals.

Methods: Peripheral blood was collected from two patient groups: (1) antiretroviral-treated HIV infected patients with undetectable viral loads who developed KS (n=10) and (2) treated patients with undetectable viral loads who did not develop KS (n=86). All KS cases had CD4 counts >300. Flow cytometry was performed on cyropreserved cells to determine the proportion of CD4+ and CD8+ T cells that were activated or senescent. CD38 and HLADR were used to measure activation and CD57 was used as a measure of immunosencence as this cell surface marker has been associated with shorter telomere length, a history of cell division, and decreased proliferative ability.

Results: Consistent with our initial hypothesis, in patients who had developed KS a higher percentage of CD4+ T cells expressed CD57than in those individuals who did not develop KS (median of 10.8% vs. 6.4% , P = p=0.03). Similarly, those with KS had higher percentage of CD8+T cells that expressed CD57 compared with those without KS (42% vs. 32%, P = 0.02). There was no difference in T cell activation markers between the KS and non-KS groups. The difference in CD57 expression between those with and without KS was not explained by age, gender or HCV co-infection.

Conclusion: In this study we find that a well recognized global immunosenescence marker (CD57) was elevated among patients with well-controlled HIV who developed KS as compared to comparable patients who do not develop KS. Collectively, these observations suggest that (1) HIV infection drives premature immunologic aging, (2) HAART does not fully reverse this process and (3) HIV associated immunosenescence may result in increased risk of the type of KS commonly observed in certain elderly populations. This association of immunosenescence and chronic well-controlled HIV in the setting of an AIDS-defining malignancy carries implications for adequacy of current immunologic monitoring of HIV progression. It also raises questions with regard to regulation of chronic inflammation and replication in the long-term management of HIV infection, and for the potential of immune-related morbidity in the aging population of HIV-positive patients.

Abstract 78

THE SPECTRUM OF HIV-ASSOCIATED CANCERS IN A SOUTH AFRICAN BLACK POPULATION: RESULTS FROM A CASE-CONTROL STUDY, 1995 – 2004

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Accumulating evidence confirms different patterns of HIV-associated cancers in developed and developing countries. We report results of risk for specific cancers associated with HIV-1 infection from an on-going case control study started in government hospitals in Johannesburg in 1995.

Cases consisted of cancers known or suspected to be associated with HIV infection: Kaposi sarcoma (n=333), Non-Hodgkin lymphoma (n=223), cancer of the uterine cervix (n=1586), Hodgkin lymphoma (n=154), cancers of anogenital organs other than cervix (n=157), squamous cell skin cancer (n=70), oral cavity and pharyngeal cancers (n=319), liver cancer (n=83), stomach cancer (n=142), leukaemias (n=323), myelomas (n=189), melanoma (n=53), lung cancer (n=363) and sarcomas other than Kaposi (n=93).

The comparison group comprised 3,717 patients with all other cancer types and 682 patients with cardiovascular diseases.

Odds Ratios (OR) were adjusted for age, sex, year of diagnosis, education level and number of sexual partners.

Significantly increased risks associated with HIV-1 infection were found for Kaposi sarcoma (OR=47.1, 95% CI= 31.9 - 69.8), Non-Hodgkin lymphoma (OR = 5.9, 95% CI = 4.3 – 8.1), cancer of the cervix (OR = 1.6, 95% CI = 1.3 – 2.0), Hodgkin lymphoma (OR = 1.6, 95% CI = 1.0 – 2.7), cancers of anogenital organs other than cervix (OR = 2.2, 95% CI =1.4 – 3.3) and squamous cell skin cancers (OR = 2.6, 95% CI = 1.4 – 4.9).

Our study results are supported by data from the pathology-based South African National Cancer Registry. In 2001 Kaposi sarcoma was recorded as the leading cancer in black males age 20 to 44 and in black females aged 20 to 29. From age 30, cervical cancers was the most common cancer diagnosed in black women.

The above figures reflect HIV-related cancers prior to the public health sector roll-out of ART (anti-retroviral therapy), which began in 2005.

Abstract 79

A SMALL ANIMAL MODEL FOR VIRUS-ASSOCIATED PULMONARY LYMPHOMA IN IMMUNE DEFICIENCY.

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Chronic infection of interferon gamma unresponsive mice (IFNgR-/-) with gammaherpesvirus 68 (gHV68) has been demonstrated to result in pulmonary and vascular disease. We performed detailed analysis of chronic infection and associated inflammation in the lungs of C57BL/6 and IFNgR-/- mice infected for 90 days. We established a quantitative scoring system of vascular inflammation, which demonstrated that significant inflammation occurred only in the lungs of infected IFNgR-/- mice. The inflammation was characterized by infected B cells, and in four cases to date, progressed into frank lymphoma between 5 and 9 months post-infection. Analysis of a mutant virus (unable to support efficient reactivation) further demonstrated that while infection of IFNgR-/- mice is required for pulmonary vascular inflammation and B cell lymphoma, ongoing production of infectious virus at 90 days after infection is not required, since infectious virus was detected only in the lungs of IFNgR-/- mice infected with wildtype virus and not those infected with mutant virus. Virus-infected cells, as detected by in situ hybridization for latently expressed transcripts, were present in the lungs of IFNgR-/- mice infected for 90 days, but not in infected C57BL/6 controls. Pulmonary lymphomas resulted from infection with either wildtype or mutant virus, and were composed primarily of latently infected B cells. These pulmonary lymphomas bear many similarities and striking immunohistochemical resemblance to the human pulmonary lymphomas, lymphomatoid granulomatosis and pyothorax-associated lymphoma. Interestingly, these human lymphomas are closely associated with chronic inflammation and with AIDS and non-AIDS immunodeficiency. These studies characterize a small animal model of gammaherpesvirus infection combined with immunodeficiency for further investigation of gammaherpesvirus-associated pulmonary lymphoma in humans.

Abstract 80

TRANSIENT INDUCTION OF LYTIC KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS (KSHV) GENES IN KSHV-INFECTED ENDOTHELIAL CELLS EXPOSED TO HYPOXIA

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Kaposi's sarcoma-associated herpesvirus (KSHV), also called human herpesvirus-8 (HHV-8) is the causative agent of Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), and a form of multicentric Castleman's disease (MCD). Two of these tumors, KS and PEL, tend to arise in areas of the body that are relatively hypoxic. Exploring this phenomenon, our group has previously found that KSHV in PEL tumor cell lines is activated to lytic replication by hypoxia and that certain KSHV genes are activated by hypoxia inducible factors (HIF-1 and HIF-2) through functional hypoxia response elements (HRE) (Davis et al., *Blood*, 2001, 15, 3244-50; Haque et al., *J. Virol.,* 2006*,* 80, 7037-51). KS tumor cells are thought to be derived from endothelial cells or their precursors, and in the current study, we have addressed the question of whether KSHV was similarly activated to lytic replication in KSHV-infected endothelial cells.

To investigate this, we infected primary dermal microvascular endothelial cells (DMEC) derived from human foreskin with a recombinant KSHV (rKSHV.219) that was engineered to contain red fluorescent protein (RFP) controlled by the lytic PAN RNA promoter as a lytic marker and green fluorescent protein under the control of human elongation factor 1-α promoter as a latent marker (gift of Dr. Jeff Vieira). Short-term (<24 hours) exposure of these KSHV-infected DMEC to hypoxia (1% O_2) resulted in an initial increase in the expression of KSHV lytic genes (including RTA and viral interleukin [IL]-6) and secretion of KSHV into the supernatant. However, when the infected DMEC were cultured in hypoxia for > 24 hours, there was a subsequent downregulation of KSHV lytic genes and of the production of virus despite continued upregulation of HIF-2 in the cells. We hypothesized that this late downregulation might be from production of one or more cellular factors with KSHV-suppressive activity in these cells upon exposure to hypoxia. We focused on IL-1β, IL-6, IL-8, tumor necrosis factor alpha (TNFα) and vascular endothelial growth factor (VEGF), as these are known to be produced by hypoxic endothelial cells and to be expressed by KSHV-infected cells *in vitro* and in KS lesions. IL-6, IL-1β and VEGF had no effect on lytic replication and IL8 increased replication in the KSHV-infected DMEC. However, TNFα blocked the expression of RTA, vIL6, ORF45 and K5 proteins and suppressed production of KSHV virions in the supernatant. Furthermore, when the cells were treated with blocking antibodies directed against human TNFα, KSHV lytic activation in the hypoxic DMEC was partially restored. Interestingly, established monolayers of KSHV-infected DMEC cells cultured in hypoxia out-survived normoxic cells cultured in parallel; this provided evidence that suppression of KSHV by TNFα was not simply from cell killing. These results suggest that production of TNFα by KSHV-infected endothelial cells may limit activation of lytic KSHV replication by hypoxia and that this effect may promote survival of KSHV-infected cells under hypoxic conditions and contribute to the pathogenesis of KS. This research was supported in part by the Intramural Research Program of the NIH, NCI.

Abstract 81

GEOGRAPHIC VARIATION OF THE PREVALENCE OF KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS AND RISK FACTORS FOR TRANSMISSION IN WOMEN FROM 8 COUNTRIES IN FOUR CONTINENTS

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Transmission routes of Kaposi's sarcoma-associated herpes virus (KSHV) in the general population are poorly understood. Sexual transmission appears to be common in homosexual men, but heterosexual transmission has not been clearly documented. This study aims to estimate the prevalence of KSHV in the female general populations of Argentina, Colombia, Costa Rica, Nigeria, Spain, Vietnam, Thailand and Korea to explore geographical variation and potential heterosexual transmission. Samples and questionnaire data were available from a study organized by the International Agency for Research on Cancer (IARC) to estimate the prevalence of distinct sexually transmitted infections. The study includes 10,963 women from 10 centers with questionnaire information available on socio-demographic, reproductive and sexual lifetime experiences, smoking habits. HPV DNA detection was previously measured. Antibodies against KSHV encoded K8.1 and orf73 were determined. Prevalence of antibodies to any of the two antigens k8.1 or orf73 was 13.9 percent with an important geographical variation (range= Nigeria 46%- 3.8% in Spain). Antibodies increased with increasing age particularly in high prevalent countries such as Nigeria, Colombia and Costa Rica. KSHV was not related to education, age at first sexual intercourse, number of sexual partners, number of children, patterns of use of oral contraceptives or presence of cervical HPV DNA. A decreased prevalence was observed with increasing number of cigarettes smoked per day (p=0.000).

The study provides reliable and comparable estimates of KSHV in diverse cultural settings across four continents and provides a powerful indication of absence of heterosexual transmission of KSHV.

Abstract 84

ACTIVATION OF INTERFERON SIGNALING PATHWAY IN PRIMARY EFFUSION LYMPHOMA CELLS BY INHIBITION OF VIRAL INTERFERON REGULATORY FACTOR 1 OF KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS

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Kaposi's Sarcoma-Associated Herpesvirus (KSHV), also known as human Herpesvirus 8, is associated with several malignant disorders, including Kaposi's sarcoma, primary effusion lymphoma (PEL) and multicentric Castleman's disease. KSHV ORF-K9 encodes viral interferon regulatory factor 1 (vIRF1), an early lytic gene product homologous to cellular interferon regulatory factors. The IRF family members are transcription regulatory factors that bind to interferon-stimulated response elements (ISRE) to regulate interferon-responsive genes involved in pathogen response, cytokine signaling, cell growth regulation, and hematopoietic development. As an oncogenic protein, vIRF1 potentially contributes to KSHV-driven malignancies. In this study, KSHV vIRF1 was suppressed with peptide-conjugated antisense phosphorodiamidate morpholino oligonucleotides (PPMO) and the effect was examined. PPMO are single-stranded DNA analogues that have a modified backbone and which penetrate cells readily. Treatment of PEL cells with anti-K9 PPMO led to reduction of vIRF1 expression. The anti-K9 PPMO also reduced expression of vIRF1 in 293 cells transiently transfected with a K9 plasmid. PEL cells that were treated with anti-K9 PPMO exhibited reduced RTA and vIL-6 expression and reduced level of KSHV DNA copies. The inhibition of vIRF1 in PEL cells led to elevation of protein levels of important genes in IFN signaling, including IRF3 and STAT1, indicating the activation of the pathway. The results demonstrate that targeting of vIRF1 mRNA with PPMO can potently reduce vIRF1 protein translation, and indicate that further exploration of these compounds in an animal model is warranted.

Abstract 85

ACTIVATION OF RSK AND ERK MAPK KINASES BY ORF45 OF KAPOSI'S SARCOMA–ASSOCIATED HERPESVIRUS

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Kaposi's sarcoma–associated herpesvirus (KSHV) is a human DNA tumor virus etiologically linked to Kaposi's sarcoma, primary effusion lymphoma, and a subset of multicentric Castleman's disease. Infection and reactivation of KSHV activates multiple MAPK pathways. Noticeably, the ERK/RSK activation is sustained late during KSHV primary infection and reactivation from latency, but the responsible viral factors and underlying mechanism was unknown. Open reading frame 45 (ORF45) of KSHV is an immediate early, phosphorylated, and tegument protein. Its unique temporal and spatial expression put it in the forefront of coping with host cellular environment. We recently reported that ORF45 interacts with p90 ribosomal S6 kinases (RSKs), a family of serine/threonine kinases that lie at the terminus of the ERK pathway, and strongly stimulates their kinase activities. We found that binding of ORF45 to RSK increases the association of ERK with RSK, such that ORF45, RSK, and ERK form complexes. The complexes shield active pERK and pRSK from dephosphorylation. As a result, the complex-associated RSK and ERK are activated and sustained at high levels. We also demonstrated that RSK and ERK are activated biphasically during KSHV primary infection and lytic replication cycle. We provided evidence that the reciprocal activation of ERK and RSK by ORF45 contributes to the sustained activation of ERK/RSK in KSHV lytic replication. We further demonstrated that ablation of RSK expression by SiRNA or inhibition of kinase activity by specific RSK inhibitors lead to lower KSHV lytic gene expression, reactivation, and virus production, suggesting an essential role of the RSK in KSHV lytic replication. Therefore, inhibition of RSK is likely to disrupt KSHV infection and be a potent target for therapy of KSHV associated diseases.

Abstract 87

INCREASING INCIDENCE OF KAPOSI'S SARCOMA IN BLACK SOUTH AFRICANS IN KWAZULU-NATAL, SOUTH AFRICA (1983 TO 2006)

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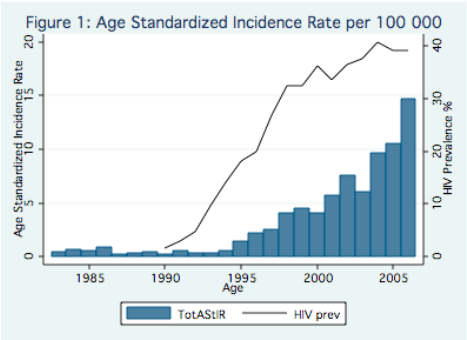
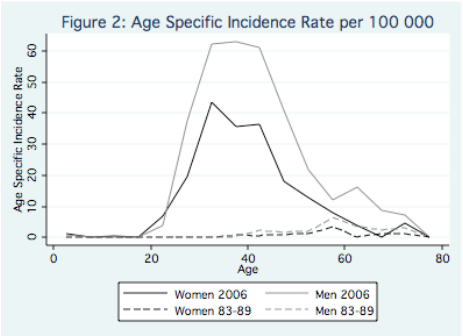
Objective: AIDS-associated Kaposi 's sarcoma (KS) is a common malignancy in regions with high HIV and Kaposi's Sarcoma-Associated Virus (KSHV) co-infection. This is exacerbated by limited access to antiretroviral therapy. Despite the dramatic increase in HIV in South Africa since the mid-1990s, little is known about the rates of AIDS-associated KS. Our objective is to estimate trends in the incidence of AIDS-associated KS in black South Africans in KwaZulu-Natal.

Design: Observational database analysis.

Methods: The incidence of KS (per 100,000) was estimated using anonymous administrative records for patients receiving care for KS through all public sector oncology clinics in KwaZulu-Natal, 1983 to 2006. Age-standardized incidence rates were calculated annually using provincial census data for the black population from 1985, 1996, 2001 and 2005. Age-specific rates were calculated for 1983-1989 (baseline) and for 2006 (generalized HIV epidemic).

Results: The age-standardized incidence of KS continues to increase in KwaZulu-Natal. Between 1983 and 2006, age-standardized incidence rates in men increased from 1.04 to 19.7 cases per 100,000, while in women they increased 50-fold, from 0.21 to 11.51 cases per 100,000. Overall, incidence has increased from 0.52 to 14.76 cases per 100,000 (Figure 1). This pattern of increase mirrors that of the HIV antenatal clinic seroprevalence for Kwazulu-Natal, which increased steadily from 1.6 percent in 1989 to 39 percent in 2006. In 2006, peak age-specific incidence in men is 63.1 cases per 100,000 and in women is 43.5 cases per 100,000 (Figure 2), with peaks shifting to the fourth and fifth decades of life, compared to a peak incidence between ages 55-60 in the pre-HIV era (1983-1989). During the last decade, the mean male:female ratio was 2.3.





Conclusions: Our estimates of KS incidence are based only on those who are referred to public sector oncologists, and exclude both early and late stage KS that would be treated by primary care providers or hospice, as well as those treated in the private sector. We therefore greatly underestimate the true incidence AIDS-associated KS in the province, and absolute rates cannot be compared directly to cancer-registry data from other African countries. Nonetheless, we demonstrate that the incidence of AIDS-associated KS continues to increase through 2006, and is a growing public health problem in KwaZulu-Natal, South Africa.

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