National Cancer Institute

10th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies:

Basic, Epidemiologic and Clinical Research

Presented by the Office of AIDS Malignancy Program and the Office of International Affairs

October 16–17, 2006

Marriott Bethesda North Hotel and Conference Center, North Bethesda, Maryland

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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PROGRAM

Monday, October 16

8:00 AM–6:00 PM **Poster Presentations**

8:00 **Opening Remarks and Welcome**
Kishor Bhatia, PhD, MRCPath
National Cancer Institute, NIH, Bethesda, MD, USA

8:15 **P1: Viral Malignancies and an International Perspective**
John Ziegler, MD, MSc
University of California, San Francisco, Comprehensive Cancer Center, USA

9:00 AM–10:00 AM **KSHV and Kaposi's Sarcoma (KS)**
Moderator: *Denise Whitby, PhD*

9:00 **P2: Modulation of Cell Signaling and Angiogenesis by KSHV**
Blossom Damania, PhD
University of North Carolina at Chapel Hill, USA

9:30 **P3: AIDS-Associated Kaposi's Sarcoma (KS) at 25: A Model for the Evaluation of Targeted Antiangiogenesis Therapy**
Susan Krown, MD
Memorial Sloan-Kettering Cancer Center, New York, NY, USA

10:00 AM **Break**

10:20 AM–12:05 PM **Session 1: Kaposi's Sarcoma–Associated Herpesvirus (KSHV/HHV-8): Pathogenesis of Disease and Pathogenesis-Based Therapy**
Moderators: *Robert Yarchoan, MD, and Andrew Grulich, PhD*

10:20 Activation of Kaposi's Sarcoma–Associated Herpesvirus (KSHV) to Lytic Replication by the Cytotoxic Chemotherapy Drugs Vincristine and Doxorubicin
Kazushi Nakano, MD, National Cancer Institute, Bethesda, MD, USA

10:35 Identification of Novel NFκB Inhibitors in Primary Effusion Lymphoma Cells
Ethel Cesarman, MD, PhD, Weill Medical College of Cornell University, New York, NY, USA

10:50 Rapamycin is Efficacious against Primary Effusion Lymphoma (PEL)
Dirk Dittmer, PhD, University of North Carolina at Chapel Hill, USA

11:05 Cyclooxygenase-2 (COX-2) Induced by KSHV Early During *In Vitro* Infection of Target Cells Plays a Role in the Maintenance of Latent Viral Gene Expression
Neelam Sharma-Walla, PhD, Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA

Session 1, continued

11:20 Intracellular KSHV Load Determines Early Loss of Immune Synapse Components
Laura Adang, PhD, University of Virginia, Charlottesville, USA

11:35 HHV-8 Infects and Replicates in Primary Cultures of Activated B Lymphocytes Through DC-SIGN
Giovanna Rappocciolo, PhD, University of Pittsburgh, PA, USA

11:50 KSHV-LANA Stabilizes c-Myc by Activating ERK1/2 and Inhibiting GSK-3
Jianyong Liu, MD, PhD, Johns Hopkins School of Medicine, Baltimore, MD, USA

12:05 PM Lunch

1:25 PM–2:30 PM Lymphoma and EBV as a Therapeutic Target

1:25 **Introductory Remarks**
Elliott Kieff, MD, PhD
Harvard Medical School, Boston, MA, USA

1:30 **P4: InterLymph: An International Collaboration on the Epidemiology of Non-Hodgkin Lymphoma**
Wendy Cozen, DO, MPH
Keck School of Medicine, University of Southern California, Los Angeles, USA

2:00 **P5: Pathogenesis of B Cell Lymphomas: Implications in the Context of AIDS**
Gianluca Gaidano, MD, PhD
Amedeo Avogadro University of Eastern Piedmont, Novara, Italy

2:30 PM–3:15 PM Session 2: Lymphoma and Epstein-Barr Virus (EBV): New Insights and Treatments
Moderators*: Kevin Howcroft, PhD, and Sam Mbulaiteye, MD*

2:30 Elevated Activation-Induced Cytidine Deaminase (AID) Expression Preceding the Diagnosis of AIDS-Associated Burkitt's Lymphoma
Marta Epeldegui, David Geffen School of Medicine at UCLA, *Los Angeles, CA, USA*

2:45 Development of a Therapeutic Vaccine for HIV-associated Hodgkin's Lymphoma
Rajiv Khanna, PhD, Queensland Institute of Medical Research, Brisbane, Australia

3:00 EBV Gene Transcription Kinetics During Viral Reactivation by Bortezomib in Cell Lines and in a Clinical Setting
Rachel Bagni, MS, NCI-Frederick, MD, USA

3:15 PM Break

3:30 PM–4:30 PM **Session 3: Clinical Management of AIDS-Associated Lymphoma**
Moderator: *Alexandra Levine, MD, and Richard Ambinder MD, PhD*

3:30 Randomized Phase II Trial of Infusional EPOCH Chemotherapy Given Either Concurrently with or Sequentially Followed by Rituximab in HIV-Associated Lymphoma: AIDS Malignancy Consortium Trial 034
Joseph Sparano, MD, Montefiore-Einstein Cancer Center, Bronx, NY, USA

3:45 Abbreviated EPOCH-Rituximab Therapy with HAART Suspension Is Highly Effective and Tolerable in AIDS Related Lymphoma
Kieron Dunleavy, MD, National Cancer Institute, Bethesda, MD, USA

4:00 Dose Modified Oral Chemotherapy for AIDS-Related Non-Hodgkin's Lymphoma (AR-NHL) in East Africa: Impact on CD4+ count and HIV-1 replication; and Retrospective Look at Similar Regimen In Pre-HAART Era in the USA
Walter Mwanda, MBChB, MD, University of Nairobi College of Health Sciences and Kenyatta National Hospital–Case Research Collaboration, Kenya

4:15 Discussion

4:35 PM–6:00 PM **Adjourn to Posters**
Authors of AB#1–41 please stand by your poster.

Tuesday, October 17

8:00 AM–6:00 PM **Poster Presentations**

8:10 **Administrative Remarks**
Geraldina Dominguez, PhD

8:15 AM–10:15 AM **HPV, Disease and Vaccine**
Moderator: *Joel Palefsky, MD, FRCP*

8:15 **P6: HPV Infection and Cancer in Normal and Immunologically Impaired Hosts**
Douglas Lowy, MD
National Cancer Institute, NIH, Bethesda, MD, USA

8:45 **P7: HPV Infection in HIV-Positive Women**
Silvia Franceschi, MD
International Agency for Research on Cancer, Lyon, France

9:15 **P8: HPV VLP Vaccine: Clinical Trial Results and Implementation Challenges**
Diane Harper, MD, MPH, MS
Norris Cotton Cancer Center, Dartmouth Medical School, Hanover, NH, USA

9:45 **P9: Development of a Broadly Protective HPV Vaccine Based on L2**
Richard Roden, PhD
Johns Hopkins School of Medicine, Baltimore, MD, USA

10:15 AM **Break**

10:35 AM–12:00 PM **Session 4: Human Papillomavirus (HPV): Diverse Sites of Infection with Implications to Treatment and Prevention**
Moderators: *T-C Wu, MD, PhD, and Elizabeth Read-Connole, PhD*

10:35 Human Papillomavirus (HPV) Infection of the Anus Is More Prevalent and Diverse than Cervical HPV Infection Among HIV-Infected Women in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN Study)
Erna Kojic, MD, The Miriam Hospital, Providence, RI, USA

10:50 Six-Month History of Oral Versus Cervical Human Papillomavirus Infection
Gypsyamber D'Souza, PhD, Johns Hopkins University, Baltimore, MD, USA

11:05 Clinical Profile of HIV-Positive Women with Cervical Cancer in India
Aruna Alahari, MD, Tata Memorial Hospital, Mumbai, India

11:20 A High Prevalence of High Risk Human Papillomavirus and Cervical Dysplasia in HIV Seropositive Women in a Urban South African Cancer Cohort (SACCC)
Cynthia Firnhaber, MD, University of Witwatersrand, Johannesburg, South Africa

11:35 Prevalence of Cervical Dysplasia in HIV-Positive Women in Jos, Nigeria
Patricia Agaba, MD, AIDS Prevention Initiative in Nigeria, Jos University Teaching Hospital

Session 4, continued

11:50 Infrared Coagulator (IRC) for Treatment of High Grade Squamous Intraepithelial Neoplasia (HSIL) of the Anal Canal in HIV Infected Individuals: A Pilot Study (AMC 032)
Elizabeth Stier, MD, Boston Medical Center, MA, USA

12:05 Interaction of HPV Pseudovirus with the Murine Female Genital Tract and Identification of Compounds That Can Potentiate or Inhibit *In Vivo* Infection
Jeffrey Roberts, PhD, NCI-Frederick, MD, USA

12:20 PM Lunch

1:30 PM–2:30 PM Inflammation, Immunity, and Malignancies
Moderator: *Elliott Kieff, MD, PhD*

1:30 **P10: A Role for the Chemokine Receptor CXCR4 in the Homing of Kaposi's Sarcoma–Associated Herpes Virus (KSHV)–Infected Cells**
Giovana Tosato, MD
National Cancer Institute, NIH, Bethesda, MD, USA

2:00 **P11: Liver and Inflammation**
Snorri S.Thorgeirsson, MD, PhD
National Cancer Institute, NIH, Bethesda, MD, USA

2:30 PM Break

2:50 PM–4:30 PM Session 5: Emerging Themes in HIV/AIDS Malignancies
Moderators: *Catherine Godfrey, MD, and Mostafa Nokta, MD, PhD*

2:50 Conservation of Virally-Encoded MicroRNAs in the Kaposi's Sarcoma-Associated Herpesvirus (KSHV) in Primary Effusion Lymphoma Cell Lines and in Patients with Kaposi's Sarcoma or Multicentric Castleman's Disease
Vickie Marshall, MS, NCI-Frederick, MD, USA

3:05 EBV Encoded Micro RNAs in Endemic and HIV-Related Burkitt's Lymphoma
William Harrington, MD, University of Miami, FL, USA

3:20 Tumor Recognition and Cytolysis by the CD45RA-/CD27- Effector Subset of Human VGVD2 T Cells
Andrew Hebbeler, PhD, Institute of Human Virology, Baltimore, MD, USA

3:35 Association of Cells with Natural Killer (NK) and NKT Immunophenotype with Incident Cancers in HIV-Infected Women
Marek Nowicki, PhD, Keck School of Medicine, University of Southern California, Los Angeles, USA

3:50 Risk of Cancers during Interrupted Antiretroviral Therapy: Malignant Outcomes in the SMART Study
Donald Abrams, MD, San Francisco General Hospital, University of San Francisco, CA, USA

Session 5, continued

4:05 Detection and Typing of Mucosal and Cutaneous Human Papillomaviruses in AIDS-Related Conjunctival Neoplasia in Uganda
Franco Buonaguro, MD, National Cancer Institute "Fond. Pascale," Naples, Italy

4:20 Persistent Kaposi's Sarcoma in a Population Extensively Treated with Antiretroviral Agents and Chemotherapy: Characterizing the Predictors of Clinical Response
Huong Nguyen, PhD, University of Washington, Seattle, USA

4:35 PM–6:00 PM **Adjourn to posters**
Authors of AB#42–64 please stand by your poster.

Continuing Medical Education

Accreditation Statement

The National Institutes of Health/Foundation for Advanced Education in the Sciences (NIH/FAES) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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ACSR

AIDS AND CANCER SPECIMEN RESOURCE

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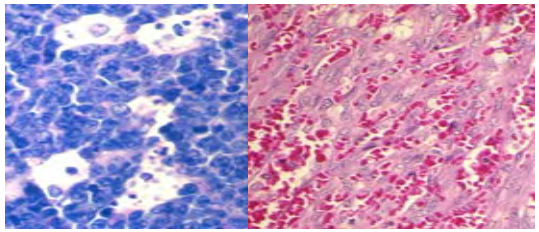

AIDS Lymphoma **AIDS Kaposi's Sarcoma**

The AIDS and Cancer Specimen Resource contains more than 100,000 individual specimens and associated clinical information.

Examples of fresh, frozen, or fixed specimens include:

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

Linkages with repositories of:

- Women's Interagency HIV Study (WIHS)
- Multicenter AIDS Cohort Study (MACS)
- National NeuroAIDS Tissue Consortium (NNTC)
- Specialized international collections

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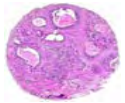

TMA Core Size 1.5 mm

- Hundreds of tissue samples can be assembled into a single TMA
- Opportunity for examination of large numbers of tumors
- HIV infected tissues and related malignancies along with non-HIV related controls

Tissue Resource/Informatics Interface

HIVbase® ***ACSResource***

Software designed to store, link and manipulate many HIV data types.

- Biological data integration
- Modeling of biological systems from tissues to genes
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- Examine HIV sequence variation in tissues and cancers
- Easily provide for large-scale sequence analysis studies
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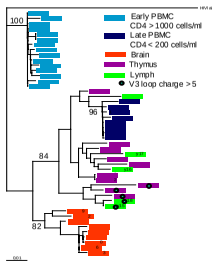

EMAIL: john.ziegler@ucsf.edu **AB# P1**

AIDS-ASSOCIATED MALIGNANCIES AND AN INTERNATIONAL PERSPECTIVE

ZIEGLER JL.
Comprehensive Cancer Center, University of California, San Francisco, San Francisco, California, USA.

From a global perspective, about 15% of human malignancy is attributed to an infectious cause. The advent of HIV/AIDS 25 years ago was heralded by para-epidemics of Kaposi's sarcoma (KS), non-Hodgkin lymphoma (NHL), and possibly some forms of Hodgkin lymphoma, raising suspicions that HIV-induced immune suppression uncovered a viral etiology. Although some lymphomas are linked to Epstein-Barr virus, KS has long resisted attempts to impugn an infectious etiology. A prescient combination of epidemiology (showing that KS behaved like a sexually transmitted disease) and molecular biology (using differential techniques to reveal a gamma herpesvirus) led quickly to the indictment of Kaposi's sarcoma herpesvirus (KSHV or HHV-8) as the causative microbe. Molecular virology revealed putative oncogenes, host-virus relationships (including latency and the virus receptor), and potential mechanisms of oncogenesis in the lymphatic endothelial target cells. Seroepidemiology connected areas of high KSHV prevalence with KS and suggested modes of transmission. KS and NHL incidence fell dramatically in populations treated with HAART as a result of improved immune function. But KS remains a major clinical problem in developing countries where both HIV and KSHV are endemic and antiretroviral therapy is not yet available to all. From a public health standpoint, avoidance of HIV is the best way to avert "epidemic" KS, and a KSHV vaccine would be spurious. NHL remains a clinical problem in HIV-infected patients, but it is an order of magnitude less common than KS, and its viral etiology is more suspect.

Seminal work in the 1970s blazed the trail of the viral etiology of carcinoma of the uterine cervix. Beral first showed that cervical cancer behaved like an STD in 1974, and zur Hausen suggested human papillomavirus as the putative oncovirus. It is now indisputable that cervical cancer is caused by certain strains of HPV, along with anorectal cancer and penile cancer. The availability of an effective HPV vaccine holds great promise for anogenital cancer control, especially in developing countries where cervical cancer is most prevalent. The relationship of cervical cancer rates to the HIV epidemic is controversial, partly because of the long incubation period and a lack of association with immune suppression.

A common virus-associated cancer, hepatocellular carcinoma, seems unrelated to HIV infection, despite the clear etiological link to HBV and HCV infection. This is probably because of the long incubation period, the necessity for intervening liver cirrhosis, and the influence of cofactors such as dietary aflatoxin. Other cancers, such as testicular seminoma and lip cancer, have been linked more tenuously to the HIV epidemic, but infectious causes are not established. Of interest in this regard is squamous carcinoma of the conjunctiva, known to have a 13-fold association with HIV infection in tropical latitudes where it is highly prevalent. Thus far, a search for a viral etiology (including HPV) has not been rewarding.

The link between HIV and viral-induced cancers has given insights into oncoviral biology. An immune response to oncogenic virus would normally be protective and might avert infection and malignant transformation. But perversely, inflammation can be pro-carcinogenic, especially via cytokines mediated by the innate immune response. Thus, transcription factors such as NF-κB and cytokine mediators such as TNF-ά and prostaglandins have been linked to tumor promotion. We have learned a great deal about viral latency and viral strategies to evade host defenses, such as herpesvirus miRNA that downregulates apoptosis and HIV *vif* that counters the cytidine deaminase antiviral response. We have learned that HIV itself thrives on the inflammatory response, creating a difficult task for vaccinology. But research in this field can produce a potential triumph, as with the new HPV vaccine. Although a devastating epidemic, HIV has taught us much about infectious causes and control of cancer, as we shall witness in this conference.

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MODULATION OF CELL SIGNALING AND ANGIOGENESIS BY KSHV

DAMANIA B, WANG L, DITTMER DP, TOMLINSON CC, and FAKHARI FD.
Lineberger Cancer Center and Department of Microbiology & Immunology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.

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). The KS lesion expresses high levels of angiogenic factors and is comprised of a mixed cell population including endothelial cells that are infected with KSHV. We find that the KSHV K1 protein is expressed in KS lesions and can immortalize and extend the lifespan of primary human umbilical vein endothelial cells (HUVEC) in culture. Vascular endothelial growth factor (VEGF) is critical for the survival of endothelial cells, and we show that expression of K1 in endothelial cells resulted in increased levels of secreted VEGF and the activation of key signaling pathways, including the VEGF-VEGF receptor (VEGFR) and the phosphatidyl-inositol-3′-OH-kinase (PI3K) pathway. Since activation of the PI3K pathway is critical for transformation of many human cells, we suggest that PI3K activation by K1 is involved in endothelial cell immortalization and contributes to KSHV-associated tumorigenesis. We also report that K1 enhances angiogenesis *in vivo* and increases tumor vasculature and tumor size. Finally, we have also examined the contribution of signaling pathways to KSHV angiogenesis and tubule formation.

EMAIL: krowns@mskcc.org **AB# P3**

AIDS-ASSOCIATED KAPOSI'S SARCOMA (KS) AT 25: A MODEL FOR THE EVALUATION OF TARGETED ANTIANGIOGENESIS THERAPY

KROWN SE.
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From the early days of the AIDS epidemic, Kaposi's sarcoma, which was among the first opportunistic illnesses described in association with HIV infection, was shown to regress after treatment with agents that subsequently were found to inhibit angiogenesis. Interferon alfa, which we first showed in 1981 could induce tumor regression in some patients with KS, was only later shown to be a potent inhibitor of angiogenesis, particularly when used at low doses. Similarly, the administration of certain cytotoxic chemotherapeutic agents, which were administered at low doses in an effort to prevent excessive myelotoxicity in HIV+ patients with poor marrow reserves, may have inadvertently resulted in superior angiogenesis inhibition than more conventional doses of the same agents. Later, various other agents were chosen for evaluation in KS specifically because of their angiogenesis-inhibitory activities. These included thalidomide, interleukin-12, the matrix metalloproteinase inhibitor COL-3, synthetic retinoids, and certain investigational agents that inhibit VEGF signaling. All of these agents have been reported to induce KS regression in some patients. Sadly, however, these trials did not include tumor biopsies to determine whether the putative targets had been affected in those patients whose tumors responded or if they failed to be affected in those whose tumors progressed.

Unlike most other solid tumors that require invasive procedures to directly monitor the effects of targeted treatment on tumor cells, KS's primarily cutaneous location provides an unparalleled opportunity to safely and easily obtain serial tumor samples for monitoring during therapy. To capitalize on this opportunity, more recent studies have incorporated pre- and on-treatment biopsies to assess the effects of therapy on molecular targets within tumor specimens. Examples include ongoing clinical trials with imatinib mesylate (Gleevec), an inhibitor of the c-kit and PDGF receptors, and sorafenib (Nexavar), an inhibitor of multiple tyrosine kinases associated with tumor angiogenesis, and a planned trial of the mTOR inhibitor, sirolimus (rapamycin). These and other anticipated studies in KS reflect a growing collaboration between clinical investigators and basic scientists, with the aims of translating insights into KS pathogenesis into improved clinical management and confirming their clinical relevance.

EMAIL: wcozen@ccnt.usc.edu **AB# P4**

INTERLYMPH: AN INTERNATIONAL COLLABORATION ON THE EPIDEMIOLOGY OF NON-HODGKIN LYMPHOMA

COZEN W.
Department of Preventive Medicine and Pathology and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, USA.

Unlike epidemiologic studies of other neoplasms, studies of NHL have been hampered by changing classification systems, heterogeneity of the phenotype, the relative rarity of the disease(s), and limited tools for assessing accurate historical exposures. To address these problems, a group of international investigators who were just completing individual case-control studies decided to pool their resources in 2000 and formed the International Lymphoma Epidemiology Consortium (InterLymph). The large numbers and varied populations of the member studies help to overcome the limitations encountered by individual investigators. Working groups established to focus on major risk factors hold monthly conference calls and annual meetings to develop collaborative proposals and brainstorm about hypotheses. Through specific projects and continued scientific dialogue, the InterLymph group has arrived at some consensus on what is currently known about NHL epidemiology and what are the most promising areas to target for further research.

The incidence of NHL increased approximately 4% per year over the last half of the twentieth century among both males and females. Although HIV/AIDS certainly contributed to this increase among younger males, the reasons for the increase in other groups is not known. Older males and females (ages 60–79) continue to experience increases, but the incidence in other age groups has leveled off in recent years. Differences between NHL subtype incidence rates by gender, socioeconomic status, and race/ethnicity suggest that at least some of the etiologic factors are distinctive.

The most well-established risk factors for non-AIDS related NHL are acquired (transplant-related) and genetic immunodeficiency. Findings from recent case-control studies suggest that more subtle immune alterations may play a role. There is mounting evidence that a history of autoimmune disease associated with a prominent B-cell response (i.e., rheumatoid arthritis) is associated with an increased risk that appears to be related to pathogenesis. Chronic infections, especially those acquired in childhood, are strongly associated with increased risk of specific NHL subtypes. Examples include Helicobacter pylori, Epstein-Barr virus, HTLV, Campylobacter jejuni, and Borrelia burgdorferi. Hepatitis C has been associated with NHL in several recent epidemiologic studies, but neither Simian virus 40 nor BK virus is related to NHL risk.

Measures of childhood crowding have generally been reported to increase risk, especially for DLBCL. These could be surrogates for increased childhood exposure to a specific infection or, alternatively, for global exposure to antigen, such as endotoxin. Multiple studies report that atopic conditions, especially hay fever, are associated with a decreased risk of NHL. Because atopy and childhood crowding are inversely correlated, it is unclear which exposure is driving the increased risk. The specific factor responsible for the association between farming and NHL has been debated for decades: some new evidence indicates that exposure to pesticides may be an underlying cause. However, early childhood farm exposure is also associated with decreased atopy and increased antigen/endotoxin exposure, which has a demonstrable effect on children's immune systems. Thus the relationships between the risk factors appear to be consistent and support a role for early childhood immune-related exposures in NHL etiology.

Other environmental risk factors of current interest include chemical exposures, particularly benzene; sun exposure; tobacco use; diet; and obesity. Contradictory evidence from various case-control studies on the importance of these risk factors is being followed up by pooled studies within InterLymph to confirm or refute associations. Prior reports of a decreased risk associated with alcohol use have recently been confirmed in an InterLymph pooled study.

Perhaps the most intriguing recent work is in the area of genetic risk factors. There is evidence to suggest a modest level of familiality, suggesting that genetic risk factors may be important. InterLymph group members have pursued genetic studies individually and collectively using the emerging powerful genetic technology. To date, studies implicate several pro-inflammatory immune response genes, including TNF-α and IL-10, in the etiological pathway. Preliminary evidence suggests that genes in the oxidative stress and DNA repair pathways may also be important. The next important steps will be evaluation of interaction between environmental and genetic risk factors, and of the effect of genetic risk factors on prognosis and survival. With the combined resources and talent of the InterLymph group, progress on a more complete understanding of NHL etiology should be forthcoming.

EMAIL: gianluca.gaidano@med.unipmn.it **AB# P5**

PATHOGENESIS OF B-CELL LYMPHOMAS: IMPLICATIONS IN THE CONTEXT OF AIDS

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Non-Hodgkin lymphoma (NHL) represents one of the most frequent malignancies associated with human immunodeficiency virus (HIV) infection, and since 1985 NHL are recognized as an acquired immunodeficiency syndrome (AIDS) defining illness. Although the incidence of HIV-related NHL (HIV-NHL) has diminished since the introduction of highly active antiretroviral therapy (HAART), NHL constitute an increasing proportion of AIDS-defining events diagnosed in recent years. As a consequence, HIV-NHLs are likely to become proportionately more important as a cause of morbidity and mortality among HIV-infected patients. The vast majority of HIV-NHL are clinically aggressive monoclonal B-cell lymphomas displaying distinctive clinical features, including widespread extent of disease at presentation, poor prognosis and frequent involvement of extranodal sites. According to body location and histological criteria, the pathologic spectrum of HIV-NHL includes systemic HIV-NHL, primary central nervous system lymphoma (HIV-PCNSL), primary effusion lymphoma (HIV-PEL), and plasmablastyc lymphoma (HIV-PBL) of the oral cavity. Systemic HIV-NHLs are histologically classified into HIV-related Burkitt/Burkitt-like lymphoma (HIV-BL/BLL) and HIV-related diffuse large B-cell lymphoma (HIV-DLBCL).

The clinico-biological heterogeneity of HIV-NHL might reflect the presence of multiple pathogenetic pathways that have been only partially elucidated so far. Various factors are hypothesized to contribute to HIV-NHL pathogenesis, including opportunistic viral and bacterial infections, chronic B-cell hyperactivation enhancing the generation of genetic lesions, deregulation of cytokine production and HIV itself. Structural analysis of the variable region of immunoglobulin variable genes (IGV) rearranged in HIV-NHL can provide insights into the mechanisms involved in the neoplastic transformation of B-cells. A biased usage of IG heavy chain variable genes (IGHV) and/or IG light chain variable genes families or gene segments suggest restricted antigen/superantigen binding. Moreover, analysis of IGV mutational profile may provide information on the pressure imposed by the stimulating antigen on the expanding clone.

A critical role for antigen stimulation in HIV-NHL pathogenesis is suggested by experimental and clinical observations. First, follicular hyperplasia and oligoclonal serum hypergammaglobulinemia have been observed in HIV infected individuals, and serum immunoglobulins exhibiting specificities for both HIV-associated proteins and non-viral determinants, including autoantigens, have been isolated from such patients. Second, HIV gp120 is a natural ligand for a subset of IGHV3 genes and, therefore, may act as a superantigen for IGHV3 expressing B-cells. Finally, production of Ig with specificities for HIV-associated proteins and autoantigens has been observed in a number of HIV-NHL. By analyzing the mutational profile and usage of IGHV, IGKV, and IGLV genes in a large series of HIV-NHL, we have shown an abnormal distribution of IGV gene usage in HIV-NHL, suggesting the presence of selective forces acting on the IGV repertoire expressed by HIV-NHL. Analysis of IGV gene usage in HIV-NHL showed evidence of a highly skewed IGHV repertoire in specific clinico-patologic categories of the disease.. The role of antigen stimulation in the pathogenesis of most HIV-NHL is further supported by a mutational profile suggesting a tendency to maintain antigen binding and antigen selection in more than 50% of IGV mutated HIV-NHL. These features are at variance with those observed in other lymphomas associated with immunodeficiency, namely posttransplant lymphoproliferative disorders, whose molecular features suggest a minor role for antigen stimulation. In particular, the different role exerted by B-cell receptor stimulation in the pathogenesis of HIV-NHL and PTLD is suggested by the presence of IGV rearrangements inactivated by crippling mutations introduced by SHM in nearly a quarter of PTLD, whereas crippling mutations of IGV rearrangements are a very rare finding among HIV-NHL (3%). Our results show that 93% of HIV-NHL have highly mutated IGV genes, documenting the origin from B cells that have persistently experienced the germinal center (GC) reaction. Because ongoing somatic hypermutation (SHM) of IGV genes is a rare event in HIV-NHL, conceivably these lymphomas are histogenetically related to B-cells that have terminated the GC reaction. HIV-NHL devoid of SHM are restricted to a fraction of HIV-PCNSL with large cell immunoblastic plasmacytoid morphology and to a fraction of plasmablastic lymphoma of the oral cavity. The origin of theses HIV-NHL subsets can be traced to naïve B cells that have not experienced the GC reaction and microenvironment. Because both HIV-PCNSL with large cell immunoblastic plasmacytoid morphology and PBL of the oral cavity express well-established markers of post-GC B cells, these findings indicate that a fraction of HIV-NHL may represent the transformation of B cells experiencing a preterminal differentiation independent of the GC reaction.

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HPV INFECTION AND CANCER IN NORMAL AND IMMUNOLOGICALLY IMPAIRED HOSTS

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Infection by high-risk HPVs, especially HPV16 and 18, is etiologically involved in virtually all cases of cervical cancer, as well as to a variable proportion of several other cancers, including the majority of anal cancers. Most HPV infections are self-limited, with the increased risk of progression to pre-cancer and cancer being associated with persistent infection. Immunocompromised hosts, such as patients with HIV/AIDS or organ transplants, are at increased risk of persistent HPV infection and HPV-associated cancers. However, HAART treatment of patients with HIV/AIDS has not been associated with a substantial reduction in the incidence of HPV-associated cancers, in contrast to tumor types associated with some other infections. Thus, HPV-associated tumors are likely to continue to represent an important part of the cancer burden of patients with HIV/AIDS, especially as HAART is permitting patients to live longer.

The recently approved prophylactic HPV vaccine has the potential to prevent the majority of serious HPV infections. However, it does not appear to alter the natural history of prevalent infection. Thus, it will be necessary to continue to rely upon, and to emphasize, screening techniques that can identify potentially serious prevalent HPV infections. No trials of the prophylactic vaccine have been reported in immunocompromised hosts. If adolescents who are HIV-positive can mount a strong humoral response to the vaccine, it seems likely that it would be protective for this group. There is also evidence that MSM continue to acquire new anal HPV infection; if the vaccine is immunogenic in this group, it might reduce the risk of infection by the viruses targeted by the vaccine. A substantial proportion of the HPV infections that develop in organ transplants may represent reactivation of latent infection; it could be important to determine whether vaccinating them prior to transplantation might reduce their risk of persistent infection.

Patients with HIV/AIDS are often infected with HPV types that are not targeted by the current prophylactic vaccine. In a recent discovery, an *in vitro* bioassay that measures the initial steps of HPV infection showed that carrageenans potently inhibit a broad spectrum of genital HPV types. Carrageenans are inexpensive sulfated polysaccharides that are widely used in foods, and their gelling properties have led to their incorporation into some over-the-counter sexual lubricants. Even when diluted a million-fold, some of these lubricants can inhibit HPV *in vitro.* Carrageenans have also been reported to inhibit HIV infection *in vitro,* but at concentrations that are about 1,000 times greater than those that inhibit HPV. Thus, carrageenans are candidate topical microbicides to prevent HIV and/or HPV infection. If clinical trials were to show that carrageenans could prevent HPV infection, their ability to inhibit many HPV types suggests that carrageenans could be useful as an adjunct to the prophylactic vaccine.

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HPV INFECTION IN HIV-POSITIVE WOMEN

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Objective(s): Women infected with human immunodeficiency virus (WHIV) have a high prevalence of human papillomavirus (HPV) infection and are infected with a broader range of HPV types than HIV-negative women. It is unknown to what extent these different types are associated with high-grade squamous intraepithelial lesions (HSIL) and cancer.

Design and Methods: Meta-analysis of HPV type-specific prevalence among WHIV, stratified by cervical cytology (normal, atypical squamous cells of undetermined significance [ASCUS]/low-grade squamous intraepithelial lesions [LSIL], HSIL) and geographical region.

Results: 5,578 WHIV were identified from 20 studies, representing largely North America but also Africa, Asia, Europe and South/Central America. For 3,230 WHIV with no cytological abnormalities, prevalence was 36.3% for any HPV and 11.9% for multiple HPV types. The six most common high-risk HPV types were 16 (4.5%), 58 (3.6%), 18 (3.1%), 52 (2.8%), 31 (2.0%) and 33 (2.0%). HPV16 was also the most common type in 2,053 WHIV with ASCUS/LSIL and 295 with HSIL. WHIV with HSIL were significantly less likely to be infected with HPV16 (Odds ratio = 0.6, 95% confidence interval: 0.4–0.7) than the general female population with HSIL. In contrast, WHIV with HSIL were significantly more likely to be infected with HPV11, 18, 33, 51, 52, 53, 58, and 61 and with multiple HPV types.

Conclusion(s): The proportion of women with HPV16 rose with increasing severity of cervical lesions among WHIV. Nevertheless, HPV16 remained underrepresented in WHIV with HSIL, who showed, compared to the general female population with HSIL, a higher proportion of other HPV types.

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HPV VLP VACCINES: CLINICAL TRIAL RESULTS AND IMPLEMENTATION CHALLENGES

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Virus like particle vaccines specific for the L1 protein of two oncogenic HPV types have been tested in phase IIb and III randomized controlled clinical trials for a bivalent (types 16/18) and a quadrivalent (types 6/11/16/18) vaccine. The phase IIb trials have focused on establishing safety, immunogenicity and continued efficacy in cohorts of North American and Brazilian women 15–26 years old. Immunogenicity levels remain sustained above natural infection titers for both vaccines: bivalent vaccine: 17- and 14-fold above natural infection titers for HPV types 16 and 18, respectively, at 4.5 years; and quadrivalent vaccine: 17 and 2-fold higher for 16/18 respectively at 3 years. All women remained seropositive for HPV 16 and 18 at 4.5 years of follow up in the bivalent vaccine trial. Seropositivity at 3 years for the quadrivalent vaccine was reported as 100% for HPV 16 and 76% for HPV 18. Descriptive efficacy for protection against HPV 16/18-related 4–6 month persistent infection was higher than 90% and against HPV 16/18 related CIN was 100% for both vaccines through their respective follow-up.

The phase III trials are powered to detect efficacy differences between vaccine and placebo recipients for type specific HPV infection: incident and persistent (defined as 4-6 month and 12 month); and for type specific HPV related cervical intraepithelial neoplasia (CIN), vaginal intraepithelial neoplasia (VaIN) and vulvar intraepithelial neoplasia (VIN) grades 1-3, as well as the squamous and adeno-associated anogenital carcinomas. The phase III trials have enrolled over 12,000 women for each vaccine study from clinic sites around the world. In addition, a NIH based study will establish vaccine safety, immunogenicity and efficacy in the context of population health.

Exploratory analyses have indicated some degree of cross protection for incident phylogenetically related oncogenic HPV type infections by the VLP vaccines. Efficacy analyses using endpoints of persistent infection and CIN are ongoing. Antibody formation to phylogenetically related oncogenic HPV types (cross- neutralization) by the VLP vaccines has also been demonstrated. Both phase IIb and III trials continue to follow women over time for evidence of sustained phylogenetically related HPV type-specific antibody titers and efficacy against infection/disease.

Immunobridging trials based solely on antibody titers measured in children indicate an immunogenic response that is assumed to endure and confer infection/disease protection in later life. Duration of vaccine efficacy is unknown at this time, as is the immune correlate of protection. The effect on duration of efficacy of the different vaccine adjuvants used in the two vaccine products (AS04 in the bivalent vaccine; alum in the quadrivalent vaccine) is unknown at this time. Immunobridging trials to women as old as 55 years indicate similar fold increases in titer responses above natural infection as in younger women. Efficacy trials in women 25–55 years are ongoing for both vaccines.

Efficacy trials either recently started or planned include male associated HPV 16/18 cancer precursors, immunocompromised women (HIV/AIDS) and trials combining HPV vaccines with other recommended adolescent vaccines. Immunogenicity trials in infants are also planned.

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DEVELOPMENT OF A BROADLY PROTECTIVE HPV VACCINE BASED ON L2

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Cancer of the uterine cervix is the second leading cause of cancer death in women, and its toll is greatest in low resource populations that lack screening programs to detect precursor lesions. Persistent infection with 'high-risk' genotypes of Human papillomavirus (HPV) is necessary, though not sufficient, to cause cervical carcinoma, and therefore HPV vaccination provides an opportunity to profoundly impact cervical cancer incidence worldwide. A recently licensed HPV subunit vaccine comprising L1 virus-like particles generated from HPV types 6 and 11 (low risk types associated with genital warts) and HPV types 16 and 18 (high-risk types associated with cancer) in yeast protects women from genital warts and the precursor lesions of cervical carcinoma related to these HPV genotypes. Protection with L1 VLP vaccines shows strong HPV type restriction, and at least 15 high-risk HPV genotypes are associated with cervical cancer. It has been suggested than a vaccine comprising the eight most prevalent HPV types detected in cancer may be required for >90% protection against cervical cancer. An alternative approach to highly multivalent vaccine preparations for broad protection is the identification of a conserved and cross-protective antigen. Vaccination with the minor capsid protein L2 is protective in animal models. Protection is mediated by neutralizing antibodies, although the titers produced by L2 vaccination are much lower than for L1 VLP vaccines. However, unlike L1-specific neutralizing antibodies, L2-specific neutralizing antibodies are broadly cross-neutralizing. Indeed, L2 vaccines can provide cross-protection in animal models; vaccination with HPV16 L2 protects against challenge with either cottontail rabbit papillomavirus or rabbit oral papillomavirus, two very distantly related types. Vaccination of patients with L2 induces low titers of cross-neutralizing antibodies. Therefore, efforts to improve the immunogenicity of L2 and development of L2 vaccines for clinical testing are underway in our laboratory. The ability to produce L2 in E. coli and the potential to use a single antigen suggest promise as a low cost alternative or complement to highly multivalent L1 VLP vaccines. A low-cost vaccine is important for introduction in developing countries that carry ~80% of the burden of cervical cancer. Broad protection across all oncogenic HPV types is important for eventual eradication of cervical cancer and reduction in Pap screening. Immune-suppressed patients also suffer from disease associated with unusual HPV types, and therefore a broadly protective vaccine may be particularly advantageous in this setting.

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A ROLE FOR THE CHEMOKINE RECEPTOR CXCR4 IN THE HOMING OF KAPOSI'S SARCOMA-ASSOCIATED HERPES VIRUS (KSHV)–INFECTED CELLS

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The G protein-coupled receptor CXCR4 and its unique chemokine ligand, stromal-derived factor-1 (SDF-1), play essential roles in hematopoiesis, lymphocyte homing, pre-B–cell growth, and angiogenesis. SDF-1 is locally active in tissues where it regulates cell recruitment from the bloodstream to tissues and cell movement within tissues through chemokine gradients sensed by CXCR4-expressing cells. SDF-1 is not active in the bloodstream where it is rapidly degraded by specific enzymes. CXCR4 can function as a co-receptor for T-cell tropic HIV-1 and can contribute to tumor cell homing to metastatic sites. In patients with AIDS, the presence of cell-associated KSHV DNA in blood, but not free virus, is predictive of the subsequent development of Kaposi's sarcoma (KS), the most common malignancy in AIDS. Thus, it is likely that KSHV-infected cells or the virus they may locally produce are involved in KS pathogenesis. The rare KSHV-infected cells in the circulation have been identified as B cells and monocytes, cell types that constitutively express a functional CXCR4. Unlike much of the capillary endothelium, skin capillary endothelium expresses SDF-1, which is displayed diffusely on the endothelial cell surface in association with cell surface heparan sulfate that protects it from enzymatic degradation. KSHV-infected PEL cells, used in lieu of the rare circulating B cells naturally infected with KSHV in infected individuals, express an active CXCR4, which triggers the specific arrest of KSHV-infected cells under physiological sheer flow conditions found in capillary blood flow. In addition, in the presence of soluble SDF-1 gradients, SDF-1 expressed on the capillary endothelium can promote transendothelial migration of KSHV-infected cells. By triggering the specific adhesion of circulating KSHV-infected cells and by favoring their transmigration to the extravascular space in the skin, SDF-1 may serve to dictate the preferential occurrence of KS in the skin. Less frequently than in the skin, lymph nodes are affected with KS and in advanced AIDS also the lung and the gastrointestinal tract. The high endothelial venules of lymph nodes are SDF-1 positive, but not the normal capillaries of the gastrointestinal tract or the lung. Vascular endothelial growth factor (VEGF)-A, which is induced by hypoxia, promotes SDF-1 expression in endothelial cells, suggesting that capillaries in the gut and lung may also express SDF-1 in hypoxic conditions. These results raise the possibility that drugs that alter SDF-1/CXCR4 interactions may prove useful in preventing KS or reducing its dissemination.

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GENOMIC DECODING OF HUMAN LIVER CANCER

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Much is known about both the sequential cellular changes that precede the formation of hepatocellular carcinoma (HCC) and the etiological agents (i.e. HBV, HCV infection, and alcohol) responsible for the majority of HCC. Nevertheless, the molecular pathogenesis of HCC is not well understood. Also, a staging system that reliably separates patients with early HCC as well as intermediate to advanced HCC into homogeneous groups with respect to prognosis does not exist. We have investigated the possibility that variations in gene expression of HCC at diagnosis would permit the identification of distinct subclasses of HCC patients with different prognoses. We applied three independent but complementary approaches for data analysis to uncover subclasses of HCC and the underlying biological differences between the subclasses. Unsupervised classification methods based solely on gene expression patterns revealed two subclasses of HCC strongly associated with the length of patients' survival. Also, when the classifiers used in a training set to optimized classification of the tumors were applied to the validation set, all the classifiers successfully separated poorer survival patients (cluster A) from longer survival patients (cluster B). Furthermore, application of a univariate Cox regression model was used to identify individual genes whose expression is highly correlated with the length of survival. Application of survival-associated genes for subclass prediction was highly accurate, as illustrated by the fact that averaged gene expression indices from the selected 406 "survival genes" were sufficient to segregate the two subclasses even without the use of sophisticated prediction models.

The variability in the prognosis of individuals with HCC may result from activation of different oncogenic pathways during tumorigenesis and/or from a different cell of origin. We have addressed whether the transcriptional characteristics of HCC can provide insight into the cellular origin of the tumor. We integrated gene expression data from rat fetal hepatoblasts and adult hepatocytes with HCC from human and mouse models. Individuals with HCC who shared a gene expression pattern with fetal hepatoblasts had a poor prognosis. The gene expression program that distinguished this subtype from other types of HCC included markers of hepatic oval cells, suggesting that HCC of this subtype may arise from hepatic progenitor cells. Analyses of gene networks showed that activation of AP-1 transcription factors in this newly identified HCC subtype might have A key role in tumor development.

These findings support the notion that multiple molecular pathways dictate the development and different clinical outcomes of HCC. These findings also indicate that the molecular features of HCC, such as prognostic gene expression signatures, are present at the time of diagnosis. Therefore, the use of gene expression profiling promises to improve molecular classification and prediction of outcomes in HCC. Furthermore, molecular stratification of individuals with HCC into homogeneous subgroups may provide opportunities for the development of new treatment modalities.

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ACTIVATION OF KAPOSI'S SARCOMA–ASSOCIATED HERPESVIRUS (KSHV) TO LYTIC REPLICATION BY THE CYTOTOXIC CHEMOTHERAPY DRUGS VINCRISTINE AND DOXORUBICIN

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KSHV is the causative agent of Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman's disease (MCD). These tumors are frequently treated with cytotoxic chemotherapy drugs, either alone or in combination. Several cytotoxic cancer drugs have previously been reported to induce lytic replication of Epstein-Barr virus (EBV), and bortezomib has been reported to induce lytic replication of KSHV (Feng WH et al., *J Virol* 78, 1893, 2004; Brown HJ et al., *Antivir Ther* 10, 745, 2005). However, the effect of other cytotoxic drugs on KSHV has not been reported. In this study, we assessed the potential of several anticancer drugs to activate KSHV.

In initial experiments, we found that vincristine and doxorubicin induced expression of the lytic switch gene RTA (ORF50) in BCBL-1 and JSC-1 PEL lines, as assessed by Western blot. Activation was observed at doses that were minimally toxic to these lines in short-term culture (doxorubicin as low as 25 nM; vincristine as low as 10 nM). In addition, these drugs induced expression of viral IL-6 (vIL-6), as assessed by Western blot. By contrast, cyclophosphamide, methotrexate, and gemcitabine had minimal or inconsistent activity in initial screening experiments. When exposed to vincristine, a substantial percentage of BCBL-1 cells expressed RTA and vIL-6 as assessed by immunofluorescence. Using a luciferase reporter assay, vincristine activated transcription from the promoter of the viral switch gene, RTA, in KSHV-negative 293T cells (1.85-fold increase at 80 nM vincristine, compared with 2.37 fold increase with 1.25 mM butyrate). We previously showed that hypoxia and hypoxia-inducible factor (HIF) induce lytic activation of KSHV, and we considered the possibility that vincristine might activate KSHV through HIF. However, this did not appear to be the case, as cells exposed to vincristine had decreased levels of HIF-1 alpha as compared to control cells. Kinases expressed as part of the lytic replication of KSHV can phosphorylate zidovidine (AZT) and ganciclovir (GCV), and in additional experiments, the cytotoxicity of doxorubicin in BCBL-1 or JSC-1 cells was found to be enhanced by co-exposure to AZT or GCV.

Vincristine and doxorubicin are active in KS and are sometimes used as part of the therapy for PEL and MCD. The results of these experiments raise the possibility that KSHV lytic activation (and associated cell death) may contribute to the activity of these drugs in KSHV-associated tumors. Moreover, the results suggest that the anti-tumor effect of these drugs in KSHV-associated tumors might be potentiated through simultaneous administration of AZT and/or GCV. On the other hand, they also suggest that patients with KSHV-associated tumors that are treated with certain cytotoxic chemotherapy drugs could possibly manifest effects of KSHV-associated or encoded cytokines such as vIL-6.

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IDENTIFICATION OF NOVEL NF-κB INHIBITORS IN PRIMARY EFFUSION LYMPHOMA CELLS

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Activated NF-κB is a critical mechanism by which lymphoma cells infected by KSHV are protected from apoptotic stress. vFLIP is the viral protein largely responsible for the constitutive NF-κB activity and is essential for primary effusion lymphoma (PEL) cell survival. Using a subclone of the BC-3 PEL cell line that stably expresses firefly luciferase under the control of an NF-κB promoter (BC3/NFκB-luc), we performed high throughput screening (HTS) of compound libraries to look for inhibitors of vFLIP/NF-κB in PEL cells. The first stage of assay optimization was done using the NCI Training Set, which includes 230 well-characterized anti-cancer agents. The list of compounds that showed greater than 90% inhibition included agents known to influence various steps of the signal transduction pathway, in addition to many DNA binding compounds. Screening of the diversity set at 5 μM picked up 60 hits (with ≥ 50% inhibition) from a total of 1,981 compounds. Compounds from the original plates were selected and tested again with a serial dilution to confirm the activity. To further test these compounds, we introduced a renilla luciferase controlled by a constitutive promoter (retroviral LTR) to obtain a double reporter cell line (BC3-REN#3). Expression of firefly and renilla luciferase was evaluated after treatment with the 60 compounds, and 3 compounds showed preferential inhibition of firefly luciferase in the double-reporter cell line and/or preferential inhibition of the BC3/NFκB-luc cell line when compared to a control non-lymphoid cell line with constitutive luciferase expression (U251-pGL3). Analogs of these three compounds (105 in total) were further tested in BC3-REN#3 cells, and three analogs were identified with increased activity/specificity for NF-κB. One of the compounds identified so far has shown dose-dependent inhibition of NF-κB in PEL cells, as evaluated independently by electrophoretic mobility shift assays (EMSA). Further testing is ongoing to determine whether these compounds specifically inhibit NF-κB initiated by vFLIP or if they can inhibit NF-κB initiated by cellular signals. For eventual therapeutic applications, inhibition of a viral protein would provide the advantage of making a compound more specific and less toxic. Alternatively, new inhibitors of cellular proteins involved in the NF-κB pathway would be useful for *in vitro* dissection of this pathway and potentially for the treatment of various malignancies that depend on NF-κB for tumor cell survival.

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RAPAMYCIN IS EFFICACIOUS AGAINST PRIMARY EFFUSION LYMPHOMA (PEL)

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The antitumor potency of the mTOR inhibitor rapamycin (sirolimus) is the subject of intense investigations. Primary effusion lymphoma (PEL) appears concomitant with Kaposi's sarcoma as an AIDS and Kaposi's sarcoma-associated herpesvirus (KSHV) linked neoplasm. We find (i) that rapamycin is efficacious against PEL in culture and in a murine model; (ii) that mTOR, it's activator Akt, and mTOR's target p70S6 kinase are phosphorylated in PEL; (iii) that KSHV transcription is unaffected; but (iv) that inhibition of IL-10 signaling correlates with drug sensitivity. Moreover, IL-10 was established as a PEL-specific marker gene. This validates sirolimus as a new treatment option for PEL and the inhibition of paracrine effectors as potential new targets for sirolimus in KSHV-associated cancers.

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CYCLOOXYGENASE-2 (COX-2) INDUCED BY KSHV EARLY DURING *IN VITRO* INFECTION OF TARGET CELLS PLAYS A ROLE IN THE MAINTENANCE OF LATENT VIRAL GENE EXPRESSION

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Infection of human dermal microvascular endothelial (HMVEC-d) and fibroblast (HFF) cells by KSHV provides an excellent *in vitro* model system to study viral latency. KSHV infection is characterized by the induction of pre-existing host signal cascades, sustained expression of latency associated genes, transient expression of a limited number of lytic genes including the lytic cycle switch ORF50 gene, and reprogramming of host transcription regulating several proinflammatory responses. COX-2 was one of the host cell gene that was highly up-regulated at 2 and 4h post-infection (PI) of HMVEC-d and HFF cells. Since COX-2 is an important mediator of inflammatory and angiogenic responses, here, we characterized the COX-2 stimulation and its role in KSHV infection. KSHV induced a robust COX-2 expression which reached a maximum at 2h PI in HMVEC-d cells and at 8h PI in HFF cells, and significantly higher levels were continuously detected up to 72h PI of observation. Constitutive COX-1 protein levels were not modulated by KSHV infection. Moderate levels of COX-2 were also induced by UV-KSHV and by glycoproteins gB and gpK8.1A; however, viral gene expression appears to be essential for the increased COX-2 induction. High levels of PGE2, a COX-2 product, were released in the infected culture supernatants. PGE2 synthase, catalyzing the biosynthesis of PGE2, also increased and inhibition of COX-2 by NS-398 and indomethacin drastically reduced the PGE2 and PGE2 synthase levels. COX-2 inhibition did not affect KSHV binding or internalization or trafficking to the infected cell nuclei. However, latent ORF73 gene expression and ORF73 promoter activity were significantly reduced, and this inhibition was relieved by exogenous supplementation with PGE2. In contrast, lytic ORF50 gene expression and ORF50 promoter activity were unaffected. These studies demonstrate that COX-2 and PGE2 play roles in facilitating latent viral gene expression, and the establishment of latency, and suggest that KSHV has evolved to utilize the inflammatory responses induced during endothelial cell infection for the maintenance of viral latent gene expression.

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INTRACELLULAR KSHV LOAD DETERMINES EARLY LOSS OF IMMUNE SYNAPSE COMPONENTS

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Lifelong infection is a hallmark of all herpesviruses and their survival depends on countering host immune defenses. The human γherpesvirus, Kaposi's sarcoma-associated herpesvirus (KSHV), encodes an array of proteins that contribute to immune evasion, including modulator of immune recognition 2 (MIR2), an E3 ubiquitin ligase. Exogenously expressed MIR2 down-regulates surface expression of several immune synapse proteins, including MHC class 1, ICAM1 (CD31), and PECAM (CD54). Although immunofluorescence assays detect this lytic gene in only 1–5% of cells within infected cultures, we have found that *de novo* infection of naïve cells leads to the down regulation of these immune synapse components in a major proportion of the population. Investigating the possibility that low levels of MIR2 are responsible for this down-regulation in the context of viral infection, we found that a) MIR2 transduction recapitulated the patterns of surface down-regulation following *de novo* infection, b) both MIR2 promoter activation and immune synapse component down-regulation were proportional to the concentration of KSHV added to the culture, and c) MIR2-specific siRNA reversed the down-regulation effects. Finally, using a sensitive, high-throughput assay to detect levels of the virus in individual cells, we also observed that down-regulation of MHC class I and ICAM-1 correlated with intracellular viral load. Together, these results suggest that the effects of MIR2 are gene dosage dependent and that low levels of this viral protein contributes to the widespread down-regulation of immune modulating cell-surface proteins during the initial stages of KSHV infection.

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HHV-8 INFECTS AND REPLICATES IN PRIMARY CULTURES OF ACTIVATED B LYMPHOCYTES THROUGH DC-SIGN

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Human herpesvirus 8 (HHV8/KSHV) is the etiological agent of Kaposi's sarcoma (KS). In addition to targeting endothelial cells in KS, it targets B cells in primary effusion lymphoma and multicentric Castleman disease, and can be detected in B cells from the peripheral blood of KS patients. However, B cells are relatively resistant to *in vitro* infection with HHV-8. Attempts to infect immortalized B cell lines have been successful only when viral DNA was directly introduced into the cells, where virus is maintained as an episome, and can be reactivated with specific agents and transmitted to other cells. We hypothesize that the lack of permissive infection of B cells *in vitro* is due to a lack of the appropriate receptor for infection. We have recently shown that DC-SIGN, a C-type lectin first identified on dendritic cells (DC), is a receptor for HHV-8 on DC and activated macrophages *in vitro*. Moreover, B lymphocytes from peripheral blood and tonsils express DC-SIGN, and this expression significantly increases after B cell activation mediated by CD40 ligand (CD40L) and interleukin 4 (IL4). In the present study we show that activated blood and tonsil B cells could be productively infected with HHV-8 *in vitro* as detected by increase in the level of viral DNA in the infected cell pellets and cell culture supernatants, and the presence of lytic (K8.1 A/B, ORF59) and latency-associated (LANA) viral proteins by immunofluorescence. Resting B cells did not support productive HHV-8 infection. Expression of viral proteins and DNA replication, as well as binding of radioactive HHV-8 to B cells, was inhibited by pretreatment of the B cells with anti-DC-SIGN mAb or mannan. HHV-8 could not enter B cell lines expressing DC-SIGN lacking the transmembrane domain, supporting that entry of HHV8 into B cells is mediated by endocytosis. In conclusion, expression of DC-SIGN on activated blood and tonsil B cells is a portal for productive, lytic HHV-8 replication. This has important implications in determining reservoirs for HHV-8 in vivo and designing strategies for preventing HHV-8 infection and associated cancers.

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KSHV-LANA STABILIZES C-MYC BY ACTIVATING ERK1/2 AND INHIBITING GSK-3

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KSHV-LANA is expressed in all KSHV-associated tumors, including KS and PEL. The c-Myc transcription factor is a powerful regulator of cell proliferation, differentiation and apoptosis; it is activated and stabilized by ERK1/2 phosphorylation, and primed for degradation by GSK-3 phosphorylation. c-Myc is frequently dysregulated in human tumors through gene amplification, chromosomal translocation and mutation. We found that although c-myc is wild-type in PEL cell lines, its half life is similar to that of mutant c-Myc in EBV positive lymphoma cell lines. LANA mediated stabilization of c-Myc was shown in LANA converted TIME cells. A mechanistic analysis showed (1) c-Myc bound to LANA; mapping experiments revealed that aa 147–aa 220 of c-Myc are essential for interaction with LANA. (2) In transfected cells LANA increased endogenous ERK1/2 activity, which in turn leads to c-Myc phosphorylation and stabilization. (3) LANA-associated nuclear GSK-3 is mainly phosphorylated and inactivated at Ser9. Consequently phosphorylation of c-Myc by GSK-3 is inhibited by LANA. Thus LANA can increase c-Myc levels through beta-catenin accumulation and stabilize c-Myc by the combination of ERK1/2 activation and GSK-3 inhibition. LANA modification of c-Myc function may contribute to KSHV tumorigenesis

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ELEVATED ACTIVATION-INDUCED CYTIDINE DEAMINASE (AID) EXPRESSION PRECEDING THE DIAGNOSIS OF AIDS-ASSOCIATED BURKITT'S LYMPHOMA

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Non-Hodgkin's lymphoma (NHL) is the second most common cancer is HIV+ subjects following Kaposi's Sarcoma (KS). There are several subtypes of AIDS-NHL: Burkitt's lymphoma (BL), large cell lymphoma (LCL), immunoblastic plasmacytoid lymphoma (IBL), central nervous system (CNS) lymphoma, and primary effusion lymphoma (PEL), which differ in the fraction of tumors that are EBV+, as well as in the nature of the central molecular lesions thought to result in cancer. In addition, many AIDS-NHL are thought to occur due to errors in class switch recombination (CSR) and somatic hypermutation (SHM), processes that normally occur in germinal center (GC) B cells. B cells require the expression of the activation induced cytidine deaminase (AID) gene in order for CSR and SHM to occur in the GC. Since errors in CSR and SHM are believed to play a role in the development of AIDS-NHL, the aberrant *AID* expression may contribute to the development of NHL. Therefore, we hypothesized that *AID* expression would be elevated in HIV+ subjects who went onto develop NHL. *AID* expression was quantified using Taqman RT-PCR in PBMC collected and viably frozen at pre-NHL diagnosis MACS study visits from subjects who developed AIDS-NHL (n=16) as well as HIV+ subjects who had AIDS (n=17), and HIV-negative (n=16) controls. Longitudinal analysis indicated that *AID* PBMC expression was elevated in specimens collected prior to NHL diagnosis: *AID* expression was more than 5-fold higher in those whop developed NHL, when compared to AIDS controls (p=0.04), and more than 10-fold elevated when compared to HIV-negative controls (p=0.01). Of the 16 AIDS-NHL cases in which *AID* expression was measured, six developed BL, five LCL, and five CNS lymphomas. When segregated by NHL subtype, marked differences in PBMC *AID* expression were noted: *AID* expression in pre-NHL PBMC specimens was significantly higher (approximately 100 fold) in those who developed BL, utilizing longitudinal analysis taking into account multiple time points, when compared to those who developed non-BL NHL subtypes (p=0.002). Elevated *AID* expression was seen over a period of several years preceding BL diagnosis. BL is associated with *MYC:IgH* chromosomal translocations, the frequency of which is known to be elevated in cells that express *AID.* Therefore, these results are consistent with increased B cell activation leading to chronically elevated *AID* expression, preceding the appearance of BL in HIV+ subjects.

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DEVELOPMENT OF A THERAPEUTIC VACCINE FOR HIV-ASSOCIATED HODGKIN'S LYMPHOMA

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As HIV-infected individuals survive longer, there has been no substantial change in the incidence of certain HIV-associated malignancies including the Epstein-Bar virus (EBV)-associated Hodgkin's Lymphoma (HL). Important in the current context is the fact that HL is the most common non-AIDS defining tumour in the HIV population. Two powerful tools, irradiation and multi-agent chemotherapy have emerged as the mainstays for the treatment of HIV-related HL. However, these antineoplastic treatments display high levels of toxicity and induce immunosuppression which further compromises the immunodeficiency of HIV-infected patients and facilitates the onset of opportunistic infections and/or evolution of HIV infection. The presence of EBV in the malignant cells provides a unique opportunity to develop therapeutic vaccines based on viral epitopes and thus provides a more advantageous approach when treating a larger cohort of patients. We have developed a replication-incompetent adenoviral vaccine, which encodes multiple HLA class I-restricted CTL epitopes from LMP1 and LMP2 covalently linked to glycine-alanine repeat deleted EBNA1 as a polyepitope vaccine and have assessed its efficacy in a model in which quasi-HL cells are proliferating in mice under conditions of immunosuppression (CD4 T cell-deficient) as might occur in HIV patients. Immunization with this polyepitope vaccine consistently generated strong EBNA1 and LMP-specific CTL responses in both immunocompetent and CD4 T cell-deficient HLA A2/Kb mice, which can be detected by both *ex vivo* and *in vivo* T cell assays. Furthermore, we also show that *in vitro* stimulation with polyepitope vaccine can completely reverse the functional impairment of EBV-specific T cell responses in HL patients. These expanded T cells displayed strong lysis of malignant cells expressing LMP1, LMP2 and EBNA1 CTL epitopes. More importantly, this adenoviral vaccine was also successfully used to reverse the outgrowth of human tumours expressing LMP1. These studies demonstrate that a replication-incompetent adenovirus polyepitope vaccine is an excellent tool for the induction of protective CTL response directed towards multiple LMP CTL epitopes restricted through common HLA class I alleles prevalent in different ethnic groups where EBV-associated malignancies are endemic.

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EBV GENE TRANSCRIPTION KINETICS DURING VIRAL REACTIVATION BY BORTEZOMIB IN CELL LINES AND IN A CLINICAL SETTING

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Inhibition of the 26S proteasome by bortezomib results in altered degradation pathways for many regulatory proteins. Bortezomib is known to increase apoptosis through the activation of JNK and stabilization of p53. Downregulation of NF-κB through impaired degradation of IκBα by the proteasome also results in an increase in apoptosis and a decrease in cell proliferation and angiogenesis. Recently approved by the FDA for use in myeloma, bortezomib has shown well tolerated anti-cancer effects in many different cancers. It has also been shown to induce lytic replication of gamma-herpesviruses *in vitro*.

To further elucidate the kinetics of EBV reactivation upon treatment with bortezomib we assayed EBV transcription using a whole genome EBV transcript real-time PCR assay. We also assayed EBV transcription in a patient before, during and after bortezomib treatment.

We used bortezomib to induce EBV lytic replication in two latency type III B cell lines, HCL-B and HCL-P. FACS analysis has confirmed that these two cell lines differ in the percentage of cells that are in lytic replication when grown under standard conditions. Treatment of these two cell lines over a 36h time course with 500ng/mL bortezomib resulted in a rapid decrease in cell viability accompanied with an increase in EBV gene transcription and EBV DNA. In the HCL-B cell line, before treatment with bortezomib, 0-5% of cells were positive for the EBV lytic marker, Zta, and upon treatment, EBV transcription occured in an ordered and reproducible cascade. In the HCL-P cell line, where 10-25% of cells are positive for the EBV lytic protein Zta before treatment with bortezomib, further lytic transcription is induced upon treatment. These cell lines provide two *in vitro* model systems to further investigate bortezomib treatment of EBV latent versus EBV lytic diseases.

We also assayed samples from a patient with an EBV-related polymorphic B cell lymphoma being treated with bortezomib. The EBV gene transcription profile at three different time points shows an increase in EBV viral transcription between time points 1 and 2 with bortezomib treatment followed by a decrease in EBV viral transcription at the latest time point after bortezomib was discontinued. EBV viral load decreased from 1,700,000 copies/ml to 180,000 copies/ml following 4 doses bortezomib (1.3 mg/m^2/dose) given with ganciclovir 5 mg/kg intravenously. These data are consistent with the induction of EBV gene transcription during viral reactivation and a possible antiviral effect of ganciclovir.

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RANDOMIZED PHASE II TRIAL OF INFUSIONAL EPOCH CHEMOTHERAPY GIVEN EITHER CONCURRENTLY WITH OR SEQUENTIALLY FOLLOWED BY RITUXIMAB IN HIV-ASSOCIATED LYMPHOMA: AIDS MALIGNANCY CONSORTIUM TRIAL 034

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In HIV-associated B-cell lymphoma, previous studies have shown that: (1) infusional EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) is an effective regimen (CR 74%) (Blood 2003; 101: 4653), (2) rituximab (R) increases the risk of infectious death when added to CHOP (CHOP 2% vs. R-CHOP 15%; p=0.035) without a significant improvement in CR rate (CR 47% CHOP vs. 58% R-CHOP; p=0.147) (Blood 2005; 106: 1538), and (3) R + infusional CDE (cyclophosphamide, doxorubicin, and etoposide) is highly effective (CR 70%) (Blood 2005; 105: 1891). We report the results of a randomized phase II trial of infusional EPOCH given either concurrently with R (R-EPOCH) or sequentially prior to R (EPOCH⇒R). All patients received R (375 mg/m2) prior to each cycle of EPOCH (Blood 2003; 101; 4653) in the R-EPOCH arm (maximum 6 cycles), or R weekly x 6 weeks following the completion of up to 6 cycles of EPOCH in the EPOCH⇒R arm. The trial was powered to detect an increase in CR rate from 50% to 75% for either experimental arm (2-sided alpha 0.10, one sided beta 90%) All patients received *Pneumocystis carinii* prophylaxis, filgrastim or pegfilgrastim, and fluconazole and quinolones. Antiretroviral therapy was left to the discretion of the treating physician. A preliminary analysis for 80 of the first 110 patients enrolled is shown, with an updated analysis to be presented at the meeting.

	R-EPOCH	**EPOCH⇒R**
No.	40	40
Median CD4	198/μL	188/μL
Age adjusted IPI (0–1 vs. 2–3)	46%/54%	40%/60%
Stage I-II/III-IV	15%/85%	27%/73%
Elevated serum LDH	65%	65%
Age adjusted IPI (0–1 vs. 2–3)	46%/54%	40%/60%
Histology (DLBCL vs. Other)	60%/40%	75%/25%
CR/CRu Rate	24 (60%)	15 (38%)
95% Confidence Intervals	(43%, 75%)	(23%, 54%)
Worst Grade Adverse Event		
Grade 3	11 (28%)	13 (33%)
Grade 4	14 (35%)	9 (23%)
Grade 5	1 (3%)	2 (5%)

There was one-case of secondary leukemia (t11q23) occurring one year after therapy began. These preliminary findings confirm previous reports suggesting the effectiveness of R+ infusional chemotherapy in HIV-associated lymphoma with an acceptable safety profile, and provide rationale for continued accrual to a phase III trial comparing concurrent R-chop vs. concurrent R-EPOCH in immunocompetent patients with intermediate-grade b-cell lymphoma (c50303). Further follow up will be required to determine the effectiveness of R-EPOCH compared with our previous experience with R-CHOP in patients with HIV-associated lymphoma.

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ABBREVIATED EPOCH-RITUXIMAB THERAPY WITH HAART SUSPENSION IS HIGHLY EFFECTIVE AND TOLERABLE IN AIDS-RELATED LYMPHOMA

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While adding Rituximab (R) to CHOP chemotherapy may improve tumor response, the benefit may be offset by increased infectious deaths in patients with low CD4 cell counts (Kaplan et al. Blood 2005;106:1538). We hypothesized that the addition of R to EPOCH will improve tumor kill, allow fewer chemotherapy cycles and reduce toxicity. Patients received EPOCH-R (in mg/m^2/d etoposide 50, vincristine 0.4 and doxorubicin 10 all CIV d 1-4; and in mg/m2 cyclophosphamide 750 IV day 5, prednisone 60 po days 1-4 and rituximab 375 IV d 1, 5; and G-CSF sc d 6-15). Prophylactic IT MTX x 6 was administered and HAART was discontinued on all cycles. Cyclophosphamide was adjusted based on absolute neutrophil count (ANC) nadir. Response was assessed by CT and PET and patients received 1 cycle beyond CR for a minimum of 3 cycles. So far the characteristics of 30 enrolled patients are: median (range) age 41 (9-61) years; IPI 3 (0-4); ECOG PS 1 (1-4), CD4 count 213 (0-674) cells/mm3; HIV viral load 55,900 (0-6,080,000) RNA copies/mL; male sex 25 (83%); LDH > N 22 (73%); stage IV 20 (67%) and histology DLBCL 26 (87%) and Burkitt lymphoma 4 (13%). Of 28 evaluable patients (2NE), median (range) cycles given is 3 (3-5) with CR/CRu in 25 (89%) and PR in 1 (3%) patients. All 4 patients with Burkitt lymphoma are in continuous remission. At 35 months median potential follow-up, PFS and OS are 80% and 65%, respectively. For patients with CD4 > and < 100 cells/mm3 OS is 93% and 28%, respectively. IPI did not impact OS and PFS. We assessed the predictive value of early (after cycle 2 or 3) PET scanning on subsequent relapse. This was evaluated in 23 patients in follow-up. 0 of 13 patients with a negative PET study progressed (100% negative predictive value) whereas 2 of 10 patients with a positive PET progressed (20% positive predictive value). One death from MAI occurred on treatment and toxicity over 91 cycles of therapy included fever/neutropenia on 27 (30%), ANC < 500/mm3 on 36 (40%), and platelets < 50,000 on 21 (23%) cycles. EPOCH-R was associated with less CD4 loss - median 128 cells/mm3 (range +154 to -639) compared to EPOCH alone (median 189 cells/mm3 (range +19 to -973)(Little et al. Blood 2003;101:4653). Abbreviated EPOCH-R is highly effective with acceptable tolerability in ARL and enables the administration of fewer treatment cycles (median 3 versus 6). Patients with CD4 < 100/mm3 have good tumor control with EPOCH-R with a PFS of 61% at 35 months, but survival continues to be limited by HIV-associated complications. In contrast, patients with high CD4 counts > 100/mm3 have an extremely favorable outcome with EPOCH-R. EPOCH-R was effective in all 4 patients with Burkitt lymphoma. Early PET scanning has a high negative but low positive predictive value for subsequent relapse. Accrual continues.

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DOSE MODIFIED ORAL CHEMOTHERAPY FOR AIDS-RELATED NON-HODGKIN'S LYMPHOMA (AR-NHL) IN EAST AFRICA: IMPACT ON CD4+ COUNT AND HIV-1 REPLICATION; AND RETROSPECTIVE LOOK AT SIMILAR REGIMEN IN PRE-HAART ERA IN THE USA

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Background: Dose-modified chemotherapy for AR-NHL in the pre-HAART era has been shown to be equally efficacious and less myelotoxic [N Engl J Med 1997;336:1641 (mBACOD); J Clin Oncol 2001;19:2171 (mCHOP)]. In resource-constrained settings, intravenous chemotherapy and supportive care of the AIDS / cancer patient are challenging (J Natl Cancer Inst 2002;94:718). With majority of the patients in East Africa (EA) having no access to antiretroviral therapy (ARV), it is critical to have an understanding of the immunologic effects of anticancer therapy on underlying HIV infection. We also sought to compare the natural history of these patients with the identical oral chemotherapy regimen in the USA (J Clin Oncol 1993;11:1691; Am J Hematol 2001;66:178) during comparable therapeutic eras (pre-HAART).

Methods: We embarked on a pilot feasibility trial of dose-modified oral chemotherapy [lomustine 50 mg/m2 D1 (C#1 only); VP-16 100 mg/m2 D1-3; and cyclophosphamide / procarbazine 50 mg/m2 each D22-26 at 6-week intervals (1 cycle) for 2 cycles] in HIV-infected patients w biopsy-proven lymphoma in EA.

Results: A total of 49 pts (21 Uganda; 28 Kenya) were treated on study. The majority of pts were female (59%) with median age 39 yrs (range 18-64); poor PS (2 or 3) – 63%; high grade lymphoma (69%); advanced stage (III or IV) – 69%; and B symptoms (79%). At study entry median CD4 count was 200/µL and HIV-1 viral load 97,973 copies/ml. Eighteen pts (36%) had access to ARV. A total of 78 cycles of therapy were administered (median 2; range 0.5–2). The regimen was well tolerated. There were 4 episodes of febrile neutropenia and 3 treatment-related deaths (6% mortality rate). Overall objective response rate was 77% (CR/uCR 56%); median survival 12.3 months; and 18 patients remain alive as of 7/11/06. Important differences in the natural history of AR-NHL in EA vs. USA (n=40) include more women, B-symptoms, and prior OIs; poorer ECOG PS, higher LDH and lower albumin. Oral chemotherapy had modest effect on CD4 counts and no adverse effect on underlying viral replication.

Conclusions: Dose-modified oral chemotherapy is efficacious, has comparable outcome to that in the US in pre-HAART era, an acceptable safety profile, and is pragmatic in the resource-limited setting. Further investigation of the oral regimen vs. mCHOP is warranted.

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HUMAN PAPILLOMA VIRUS (HPV) INFECTION OF THE ANUS IS MORE PREVALENT AND DIVERSE THAN CERVICAL HPV INFECTION AMONG HIV-INFECTED WOMEN IN THE STUDY TO UNDERSTAND THE NATURAL HISTORY OF HIV/AIDS IN THE ERA OF EFFECTIVE THERAPY (SUN STUDY)

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Background: Genital HPV infection is highly prevalent and persistent in women with HIV infection; however, the ecology of anal HPV infection in such women has not been well characterized.

Methods: The SUN Study is an on-going prospective cohort study of HIV-infected patients receiving care at clinics in Denver, Minneapolis, Providence, and St. Louis. At baseline, all patients completed a behavioral risk questionnaire and providers collected, among other specimens, cervical ThinPrep® cytobroom sweeps (women only) and Dacron® anal swabs for HPV detection and genotyping using Roche Linear Assay.

Results: Among the first 99 women enrolled in the study, median age was 40 years, 84% were receiving HAART, 92% had CD4 cells counts ≥ 200 cells/mm3 and 48% had undetectable viral loads. History of any anal sex was reported by 41% of women (8% within the last 6 months). HPV was detected significantly more often in anal (92%) than in cervical (85%) samples ($p = 0.03$) but did not differ significantly among women reporting a history of anal sex compared with women who did not (86% vs. 95% of anal samples, $p = 0.17$; and 78% vs. 87% of cervical samples, $p = 0.24$). High risk (HR) types were detected in 80% of anal and 66% of cervical samples ($p < 0.01$) and low risk (LR) types in 76% of anal and 60% of cervical samples ($p < 0.01$), respectively. HPV 16 and 18 were detected in 27% of anal and 15% of cervical samples ($p = 0.02$). Among women with CD4 counts of < 200, 200–500, and > 500 cells/mm3, HR HPV was detected in 87%, 80%, and 80% of anal samples ($p = 0.42$), respectively, and in 75%, 68%, and 56%, of cervical samples ($p = 0.12$), respectively. The mean number of HPV types was greater in anal versus cervical samples for all types of HPV (4.1 vs. 2.1, $p \leq 0.01$), for HR types (2.3 vs. 1.1, $p \leq 0.01$), and for LR types (1.7 vs. 1.1, $p < 0.01$).

Conclusions: Among HIV-infected women, prevalence and diversity of HPV are greater in the anal canal than at the cervix. Although values were greater in women with lower CD4 cell counts, differences by CD4 cell count were not statistically significant. Studies in HIV-infected persons examining the clinical consequences of long-term anal HPV infection as well as of the utility of anal cancer screening methods (e.g., HPV detection, cytologic examination) should include women.

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SIX-MONTH HISTORY OF ORAL VERSUS CERVICAL HUMAN PAPILOMAVIRUS INFECTION

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Human papillomavirus (HPV) infection is etiologically associated with a subset of oral cancers, and yet, the natural history of oral HPV infection remains unexplored. The feasibility of studying oral HPV natural history was evaluated by collecting paired oral rinse and cervical vaginal lavage samples twice at a six-month interval from138 HIV-positive and 63 HIV-negative participants of the Women's Interagency HIV Study (WIHS). HPV genomic DNA was detected in oral and cervical samples by consensus primer PCR and type-specified for 37 HPV types. The six-month cumulative prevalence of oral HPV infection was significantly less than for cervical infection ($p < 0.0001$). HIV-positive women were more likely than HIV-negative women to have an oral (p=0.016) or cervical ($p < 0.001$) infection detected during the study. Oral HPV infections detected at baseline were as likely as cervical infections to persist for six months among HIV-negative women (60% versus 51%, $p = 0.70$) and marginally less likely to persist among HIV-positive women (50% versus 63%, $p = 0.07$). Factors that independently elevated odds for oral HPV persistence differed from cervical infection and included current smoking (OR=6 95%CI=1.2-66), age above 44 years (OR = 15 95% CI = 2.9-83), CD4 < 500 (OR = 8 95% CI = 1.3-50), and use of HAART therapy (OR = 13 95% CI = 1.0-185). The rate of incidently detected oral HPV infection was significantly lower than cervical infection among HIV-positive ($p < 0.001$) and HIV-negative women ($p < 0.001$). This study not only demonstrates that it is feasible to study the natural history of oral HPV infection with oral rinse sampling, but also indicates that oral and cervical HPV natural history may differ. New cervical HPV infections at the second visit were more common than new oral HPV infections.

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CLINICAL PROFILE OF HIV-POSITIVE WOMEN WITH CERVICAL CANCER IN INDIA

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Background: Cancer cervix is one of the commonest cancers of women in India. Effective intervention strategies for HIV in this group require data about the clinico-social profile of these patients. There is not enough data on simultaneous treatment of HIV and cervical cancer from India.

Methods: All HIV positive cancer cervix patients seen in the last three years were studied. Data of their demographic profiles, immune status, cancer stage, treatment received, response and outcomes were collected and analyzed.

Results: There were 36 patients with a median age of 40 years. 7(19.4%) patients were below 35 years. PIR for cancer cervix was 4.09 (95% C I 2.90-5.75). 27(75%) were illiterate and 20(55.5%) were from rural areas. All the women belonged to economically dis-advantaged strata with an average family monthly income of Rs 1344 (30$). 13(36.1%) of women had a history of chewing tobacco. 4 (11%) were previously known to be HIV positive, whereas the rest were diagnosed during work up for cancer. None of these women had any knowledge about HIV disease or its connotations. None of the patients had a previous PAP smear done. 2 patients had concurrent tuberculosis. All patients were HBsAg negative, and one patient tested positive for HCV. Three patients had documented opportunistic infections. 5 (29.4%) had CD4 counts < 200 cells/ cu mm. 33.3% of patients received ART. 58.3% of patients presented in late stage (stage III A-IV). 75% of the women received cancer directed treatment. Radiation therapy alone or in combination with chemotherapy was given in 27 patients. 55.5% had complete response. Incidence of radiation induced reactions was 60.4%. ART was well tolerated with no serious adverse event. One patient died due to complications of HIV.

Conclusion: Cancer cervix shows four times higher incidence in HIV positive females in India. As these patients belong to low socio-economic- educational strata, voluntary PAP smear is not utilized. Significant immune suppression is not common, and ART is well tolerated. The response to therapy appears lower and incidence of radiation reactions is higher than in those without HIV. Age of acquiring cancer cervix is much lower in the HIV positive population. Preventive strategies including HPV vaccination should take the socio-economic background and younger age of these patients into account.

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A HIGH PREVALENCE OF HIGH-RISK HUMAN PAPILLOMA VIRUS AND CERVICAL DYSPLASIA IN HIV-SEROPOSITIVE WOMEN IN A URBAN SOUTH AFRICAN CANCER COHORT (SACCC)

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Background: The HIV seroprevalence in South Africa (SA) is 12% with women carrying the majority of this burden. Cervical cancer is the seconding leading cancer in SA. The average HIV seronegative African woman has a 2.3% chance of developing cervical cancer in her life time. HIV disease is a known risk factor for cervical dysplasia and cancer. The environment is concerning for increasing morbidity and mortality to cervical cancer however little is known in regards to the epidemiology of cervical disease and HPV in this population We present data from the SACCC, a cohort of 750 women from a HIV clinic in an academic government hospital in Johannesburg South Africa.

Methods: A total of 750 women were screened for cervical disease using conventional cytology analyzed according to the Bethesda 2001 guidelines. For quality control, 5% of the slides were sent to University of North Carolina and a high rate of concordance was found (81%). High grade lesions were sent for colposcopies and approximately a 75% concordance rate was found with the pap smears. HPV DNA testing was performed with Roche Linear Blot Assay detecting 37 types including 22 high risk (HR) types

Results: The average age of the participants was 35.7 (range 19-55) with an average CD4 count is 254 (range 0-934). 71% of participants were on HAART and 71% had not had a previous Pap smear. 74% returned for their baseline cytology results. Most of the subjects (58%) reported less than 5 sexual partners, 30% had 5 to 10 partners while 6% reported more than 20 partners. The majority of subjects (54%) had abnormal Pap smears. Most (37%) had low grade cervical dysplasia; 17% were assessed as high grade, while two patients each had atypical glandular dysplasia and cervical cancer. HPV DNA was found in 95% of the 148 subjects assessed with 83% having 1 or more HPV high risk types. High risk HPV types represented a diverse range with all 22 high risk types detected. Types 16, 35, 53 were found in 30%, 20% and 19.6% respectively. One woman had a total of 13 types of HPV and another woman had 9 HR HPV types.

Conclusions: The results of the HPV typing in this sample from the cohort illustrates that the range of HR HPV is diverse and most patients carry more than one HR type. The high prevalence of abnormal cytology (2-9 times higher than is reported in the SA literature) highlights the need for improved access for pap smear screening for women with HIV especially given the epidemiology of HR HPV types detected. Also more information regarding HPV typing is needed to determine the most effective preventative vaccine strategy in resource limiting countries.

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PREVALENCE OF CERVICAL DYSPLASIA IN HIV-POSITIVE WOMEN IN JOS, NIGERIA

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Background: Women infected with the human immunodeficiency virus (HIV) are at increased risk for the development of dysplastic genital lesions. The incidence of cervical dysplasia has also been shown to be increased in HIV-infected women. A positive correlation has been described between cervical dysplasia, CD4+ count and HIV viral load (VL). This study describes the pattern of cervical dysplasia in a cohort of HIV-positive women in Jos, Nigeria.

Methods: A cross sectional study conducted at the ARV clinic of the Jos University Teaching Hospital. 369 women with Western blot confirmation of their HIV-1 status were recruited. Demographic data and Pap smears were obtained from all of them. CD4+ count by flowcytometry (Cyflow, Partec, Germany) and VL (Roche-Ampiclor® 1.5 assay) were measured on the same day the smears were taken. Univariate and multivariate analysis using Student's t test.

Results: The mean age was 33.9 ± 7.4 years. 147 (39.8%) were married with a median parity of 2 (range 0–12). The median number of lifetime sexual partners was 2 (range 0–100). Only 3 subjects (0.3%) reported ever having had a previous Pap smear. 114 (30.9%) were using HAART, with a mean duration of use of 14.7 ± 11.5 months (range 1–40 months).

The median CD4 cell count was 161 cells/mm^3 (range: 2 – 1515). 225 (60.9%) subjects had CD4 cell counts below 200 cells/mm^3. 291(78.9%) had detectable viral RNA with a median detectable level of 79,256 copies/ml (range 422 –2,052,083copies/ml). 107 (42.4%) had cytologic evidence of dysplasia; 56(22.2%) had mild, while 31(12.3%) and 20(7.9%) had moderate and severe dysplasia respectively. HPV changes were reported in 10.3% of the subjects.

Conclusion: In our population, there is a high prevalence of cervical dysplasia among HIV-infected women with significant correlation between CD4+ count and VL. The burden of HIV disease (using percentage of subjects with CD4 counts below 200cells/mm3) was also very high among our subjects.

EMAIL: elizabeth.stier@bmc.org **AB# 19**

INFRARED COAGULATOR (IRC) FOR TREATMENT OF HIGH-GRADE SQUAMOUS INTRA-EPITHELIAL NEOPLASIA (HSIL) OF THE ANAL CANAL IN HIV INFECTED INDIVIDUALS: A PILOT STUDY (AMC032)

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Objective: Treatments for HSIL of the anal canal include surgical ablation and/or excision under general anesthesia. These are associated with considerable morbidity and high rates of recurrence. An ideal treatment modality would be an office procedure, requiring minimal skill, and sufficient effectiveness so that patients can avoid more major surgical procedures. The IRC has been proposed as a potentially appropriate treatment device for this purpose The IRC is a therapeutic device that delivers short pulses of a narrow beam of visible and infrared light through a small contact tip applicator that is applied directly to the anal lesion. This light causes thermal coagulation that results in tissue necrosis. This multi-center study evaluated prospectively whether IRC used in the office setting is a safe and effective treatment for anal HSIL in HIV-infected individuals.

Methods: HIV-infected patients with discrete internal anal lesions positive for HSIL on biopsy, with positive margins, and a maximal lesion diameter of 1 cm. were offered office-based treatment with the IRC at participating AMC study sites. Study clinicians were certified for the IRC treatment procedure. The treatment is done during HRA. The lesions to be treated are infiltrated with 1% lidocaine with epinephrine. IRC is in direct contact with each lesion for 1.5 seconds and necrotic tissues are then debrided. IRC applications and debridement continue to the level of the submucosal vessels for each lesion.

Following the initial IRC ablation, patients were re-valuated at 3 months. Lesion(s) that persisted in a previously treated area could be retreated with the IRC within one month of that visit. . Patients were then seen every 3 months for a year from initial treatment and evaluated for persistence or recurrence with cytology and high resolution anoscopy (HRA) with biopsy. Persistent lesions were those that did not respond after 2 treatments with the IRC. Recurrent lesions were those that responded to treatment with the IRC, but in which HSIL was again detected in the treated areas.

Results: Eighteen patients, 16 men and 2 women, participated in the trial. The mean age was 44, median HIV RNA level was 75,000 copies/ml and mean CD4 count was 581/µl. Of the 18 patients, 10 had persistent disease at 3 months and were candidates for a second treatment. Eight were retreated and two were lost to follow-up.

A total of 44 HSIL lesions were treated. 11 (25%) of these lesions showed persistent HSIL at the 3 month visit and were retreated with the IRC. On average, 2.1 HSIL lesions were treated at each treatment visit.

Of the 18 patients, 12 (67%) showed a complete response 1 year after initial treatment. Of the remaining 6, 4 had persistent HSIL after the second treatment, 2 recurred after an initial response (at 6 and 13 months), and 2 were lost to follow-up.

HPV 16 was the most common HPV type identified and was detected in 11 patients during at least 1 visit. There was no consistent change in HPV type or intensity in patients before and after treatment with the IRC. There were no clear correlations in HPV type or intensity between patients with persistence, clearance or recurrence of HSIL lesions.

Twelve patients reported adverse events related to the procedure. Six patients reported moderate protalgia, 4 patients had mild anal discomfort, 11 patients reported mild anal/rectal bleeding and 1 patient had moderate rectal bleeding. No severe adverse events were reported that were related to the procedure.

Conclusions: IRC is a well-tolerated, effective method of treating discrete anal canal HSIL lesions in HIV-infected patients. A larger study to better characterize the efficacy of the IRC in the management of HSIL in HIV- infected individuals is warranted.

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INTERACTION OF HPV PSEUDOVIRUS WITH THE MURINE FEMALE GENITAL TRACT AND INDENTIFICATION OF COMPOUNDS THAT CAN POTENTIATE OR INHIBIT *IN VIVO* INFECTION

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The species specificity of papillomaviruses has meant that animal models of papillomavirus (PV) infection have focused either on the study of animal PV's in their natural hosts or on transgenic mice that express one or more papillomavirus genes. The experimental animal PV models have the further limitation that none involves transmission to the female genital tract, the site of most HPV-induced cancers. Using HPV16 pseudoviruses encapsidating fluorescent reporter genes to infect the murine cervicovaginal epithelium, we have overcome the barrier of species specificity and have now established an animal model system to mimic the sexual transmission of HPV's. Previous *in vitro* studies of HPV pseudoviruses have shown that they recapitulate the early steps of the viral infectious process.

For the *in vivo* infectivity assay, we studied the effects of various cellular parameters to develop a system that results in consistent HPV pseudovirus infection of the female mouse genital tract and permits qualitative histological analysis by confocal microscopy and quantitative analysis of the entire female reproductive tract using whole-organ fluorescence imaging. Initially we found that the intact epithelium lining the reproductive tract, including the monolayer columnar epithelium of the endocervix, was highly resistant to infection. However, gentle mechanical disruption of the genital mucosa with a cytobrush dramatically potentiated infection. Consistent with this finding, fluorescent dye-coupled capsids preferentially bound the basement membrane of disrupted epithelia. Systemic progesterone treatment, which thinned the gential epithelium, increased susceptibility, suggesting that hormonal status of the genital tract may influence acquisition of infection.

In this model, we found that intravaginal exposure to commercial spermicides containing the nonionic surfactant, nonoxynol-9 (N-9), which is known to reduce the barrier function of the genital epithelium, markedly and consistently increased susceptibility to infection, even in the absence of mechanical disruption. A possibly analogous susceptibility to HIV infection has been previously reported in some clinical studies that involve N-9. We also examined the effects of carrageenan in the *in vivo* model. In recently reported *in vitro* studies (Buck, et al. PLoS Pathog. 2006 Jul;2(7):e69), we found that this compound, which is an inexpensive sulfated polysaccharide that is widely used as a food additive and is also present in several commercial sexual lubricants, is a potent inhibitor of a wide range of genital HPV pseudoviruses. Carrageenan is also reported to inhibit HIV infection *in vitro*, but HPV is about one thousand times more sensitive. In the mouse genital tract assay, commercially available carrageenan-based sexual lubricants were able to protect against HPV pseudovirus challenge after cytobrush or after N-9 treatment. Finally, we found that immunization with an L1 VLP-based vaccine was effective at preventing infection, demonstrating the fidelity of the model and its potential for testing new vaccine candidates.

In summary, we have established a reproducible animal model for genital transmission of HPV that can be used to examine basic and clinically relevant issues of HPV biology. The carrageenan results suggest that a clinical trial to test the ability of this compound to inhibit the acquisition of genital HPVs may be warranted. If such studies validate its efficacy against a wide range of genital HPV types, carrageenan might have utility as an adjunct to the L1 VLP vaccine, whose protection is limited mainly to the HPV types in the vaccine. Such an effect might be especially useful in populations at risk of acquiring HIV infection, as HIV infected women are frequently co-infected with a wide range of genital HPV types.

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CONSERVATION OF VIRALLY ENCODED MICRORNAS IN THE KAPOSI'S SARCOMA–ASSOCIATED HERPESVIRUS (KSHV) IN PRIMARY EFFUSION LYMPHOMA CELL LINES AND IN PATIENTS WITH KAPOSI'S SARCOMA OR MULTICENTRIC CASTLEMAN'S DISEASE

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Background: MicroRNAs are small noncoding RNAs that post-transcriptionally regulate gene expression. KSHV encodes 12 distinct microRNA genes, all located within the latency-associated region that is highly expressed in all KSHV-associated malignancies.

Methods: We amplified, cloned, and sequenced a 2.8 kbp–long region containing a cluster of 10 miRNAs plus a 646-bp fragment of K12/T0.7 containing the remaining two miRNAs from five primary effusion lymphoma-derived cell lines from 16 patients. The patients included 2 Classic KS, 11 AIDS-KS (8 from the USA, 1 from Europe, 3 from Africa, and 4 from Central/South America) and 2 MCD. Additionally, we analyzed the K1, ORF 75, and K15 genes in order to determine sub-types and performed a phylogenetic analysis.

Results: Phylogenetic analysis of the 2.8-kbp microRNA region revealed two distinct clusters of sequences, a major (A/C) cluster and a variant (B/Q) cluster. The variant cluster included sequences from three subjects of African origin and both MCD patients. Some microRNAs were highly conserved, while others had changes that could affect processing and, therefore, biological activity.

Conclusions: These data demonstrate that microRNA genes are under tight selection *in vivo* and suggest that they contribute to the biology and possibly pathogenesis of KSHV.

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EBV ENCODED MICRORNAS IN ENDEMIC AND HIV-RELATED BURKITT'S LYMPHOMA

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Epstein-Barr Virus (EBV)–encoded microRNAs have been identified, but their functions are as yet undefined. We build on previous findings by analyzing the expression of five EBV-encoded microRNAs (BARTs 1 and 2 and BHRFs 1-1, 1-2, and 1-3) in latency I and latency III primary Burkitt's lymphoma (BL) cell lines and in primary unmanipulated B-cell lymphoma clinical specimens. We demonstrate a marked induction BHRF1-3 miRNA in latency III cells derived from isogenic latency 1 BL. We further demonstrate miRNA expression in a variety of primary unmanipulated B-cell lymphomas, including EBV-associated endemic type BL, HIV-related BL, and diffuse large B-cell lymphoma. Finally, we present evidence that BHRF1-3 miRNA targets and represses the expression of the potent T-cell chemotactic factor, interferon inducible chemokine CXCL11/I-TAC, and that this repression can be relieved by delivering BHRF1-3 anti-sense RNA oligonucleotides. We propose that the targeted suppression of CXCL11/I-TAC by BHRF1-3 miRNA may serve as a counter immunosurveillance mechanism in EBV type III lymphomas. Studies of EBV miRNA in primary lymphomas from a highly endemic region for EBV (Northeastern Brazil) are in progress.

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TUMOR RECOGNITION AND CYTOLYSIS BY THE CD45RA-/CD27- EFFECTOR SUBSET OF HUMAN VG2VD2 T CELLS

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Peripheral blood lymphocytes bearing the gamma/delta T-cell receptor (gd TCR) are important for regulating immunity to pathogens and for tumor surveillance. The $Vg2Vd2^{+}$ subset recognizes B non-Hodgkin's lymphoma or Kaposi's sarcoma cells. Proliferative expansion plus acquisition of effector function is driven by exposure to tumor cells, phosphoantigens, or direct signaling through the T-cell receptor with additional stimuli including Toll-like receptor 2 agonists. Vg2-Jg1.2Vd2 T-cell recognition of tumor cells is polyclonal and overlaps substantially with the subset that responds to phosphoantigens, encouraging the use of phosphoantigen or aminobisphosphonate treatment in cancer patients with at least minimal effector cell populations. However, chronic HIV infection leads to a targeted depletion of Vg2-Jg1.2Vd2 T cells. This targeted depletion likely reflects chronic stimulation and loss via activation-induced cell death and is common in persons with HIV infection among all cohorts tested so far. Once this depletion becomes extensive, even prolonged antiretroviral therapy fails to reconstitute the Vg2-Jg1.2Vd2 T-cell subset. Thus, a continuing process of active Vg2-Jg1.2Vd2 T-cell depletion enforces a specific and chronic immunodeficiency. Persons with HIV are impacted in this arm of immunity with a concomitant loss of tumor immunity that is linked to a drastic increase in the risk for B NHL and KS.

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ASSOCIATION OF CELLS WITH NATURAL KILLER (NK) AND NKT IMMUNOPHENOTYPE WITH INCIDENT CANCERS IN HIV-INFECTED WOMEN

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Background: Evidence indicates that immunosuppression is associated with the development of certain cancers. The pathogenesis of HIV disease includes an alteration in innate immunity, mediated through NK and NKT cells. Evaluation of innate immune status in HIV patients prior to cancer diagnosis may identify the specific immunologic events leading to the development of malignant disease.

Methods: We evaluated the association between immunophenotypically defined NK, NKT, and CD8+ cell percentages and incident malignancies in 1,817 HIV-positive women in the Women's Interagency HIV Study (WIHS) who were followed for a median of 7.5 years.

Results: A total of 52 incident cancers of 20 different sites were identified. Compared to cancer-free women, cancer cases were older ($p < 0.01$), more likely to be anti-HCV seropositive ($p = 0.02$), and had higher baseline median HIV RNA levels than controls. The CD8+, NK, and NKT percents at baseline were not related to cancer risk. However, when time-dependent values for NKT cells were used, higher levels of NKT cells were associated with a reduced risk of cancer (adjusted hazard ratio = 0.67, 95% CI = 0.50, 0.89 per NKT percentage point).

Conclusions: In addition to the loss of CD4+ lymphocytes and an increased risk of opportunistic infections, co-infected individuals may also experience aberrations in innate immunity, including NKT and NK cell function and number. In time-dependent analyses, increased numbers of NKT cells were associated with a reduced risk of cancer. HIV-induced innate immune dysfunction may contribute to the eventual emergence of cancer in the setting of genetic alterations and altered immunosurveillance.

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RISK OF CANCERS DURING INTERRUPTED ANTIRETROVIRAL THERAPY: MALIGNANT OUTCOMES IN THE *SMART* STUDY

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Background: The SMART study, an international collaboration supported by the NIAID, NIH, demonstrated an increased risk of HIV disease progression and death in patients on a CD4-guided antiretroviral therapy (ART) strategy (drug conservation, DC; stop ART CD4>350, (re)start ART CD4<250) compared to those on continuous ART (viral suppression, VS). We describe malignant outcomes by type and their predictors.

Methods: Cancers were classified as AIDS-defining (ADC) and non-AIDS-defining (NADC). Rates are per 100PY. Proportional hazards regression models were used to compare treatment groups and to study the association of baseline predictors (demographic characteristics, CD4+ and HIV-RNA levels) with cancer within each treatment group. Hazard ratios (HR), 95% confidence intervals (CIs), and two-sided p-values are cited.

Results: A total of 5472 pts were enrolled from 318 sites in 33 countries. The majority (95%) were ART experienced (median six years prior ART use). The mean age was 44 years; 27% were women and 29% black. At baseline, median CD4 was 597 cells/mm^3, nadir CD4 was 250 cells/mm^3, 72% had HIV RNA ≤ 400 and 24% prior AIDS diagnosis. Average follow-up (F-U) was 16 months (range up to 4 years), with approximately 3,700 person-years (PYS) of F-U in each group; 1.3% of pts were lost to F-U. ART was used for 33% and 94% of the time by pts in DC and VS arms, respectively. Pts in the DC and VS arms spent 32% and 7% of follow-up at CD4 < 350 cells/mm^3 and spent 9% and 2% at CD4 < 250 cells/mm^3, respectively. Forty percent of pts were current smokers. Major SMART endpoints and malignant endpoints are shown below.

Endpoint	DC n(rate)	VS n(rate)	HR (DC/VS)	95% CI, (P-value)
Major SMART Endpoints				
Opportunistic disease (OD) or death	120(3.3)	47(1.3)	2.6	1.9–3.7, (<0.0001)
Death any cause	55(1.5)	30(0.8)	1.8	1.2–2.9, (0.007)
Cancer Endpoints				
ADC or non-ADC	44(1.2)	29(0.8)	1.5	1.0–2.5, (0.07)
ADC	12(0.3)	2(0.1)	6.0	1.4–27.0, (0.02)
KS	7(0.2)	1(0.0)	7.0	0.9–57.1, (0.07)
NADC	33(0.9)	27(0.7)	1.2	0.7–2.1, (0.41)
Cancer Death (ADC or NADC)	13(0.4)	6(0.2)	2.2	0.8–5.7, (0.11)

Cutaneous malignancies were the most frequent NADC (8 DC, 7 VS), followed by lung cancers (6 DC, 2 VS). Among VS pts, older age (HR = 2.4 per 10 year older; $p < 0.0001$) and smoking (HR = 4.9; $p = 0.0003$) were predictors of NADC. Among DC pts, older age (HR = 2.3; $p < 0.0001$) was associated with NADC. Baseline CD4+ count and HIV RNA and nadir CD4+ were not associated with cancer (ADC or NADC) in either treatment group.

Conclusions: The incidence of ADC, but not NADC, was greater in the DC than in the VS arm. Older age and tobacco use were associated with higher likelihood of developing malignant outcomes in the VS arm.

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DETECTION AND TYPING OF MUCOSAL AND CUTANEOUS HUMAN PAPILLOMAVIRUSES IN AIDS-RELATED CONJUNCTIVAL NEOPLASIA IN UGANDA

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Introduction: The role of human papillomaviruses (HPVs) in the etiology of genital cancers is well established. In the conjunctiva neoplasia, which has become common in regions of sub-Saharan Africa, particularly during the AIDS epidemic, early reports suggested a probable role for high-risk mucosotropic HPVs, and more recently, the presence of *Epidermodysplasia Verruciformis* (EV)–related HPVs has been claimed. The object of our study was to elucidate the role of such viruses by identification and characterization of HPV sequences present in conjunctival lesions at different stages of malignancy along with the HIV immunodeficiency status.

Methods: We have used a combination of eight pairs of PCR primers to examine 86 conjunctival tumor biopsies (ranging from conjunctival intraepithelial lesions grade 1 [CIN1] to invasive conjunctival squamous cell carcinoma [ICSCC]) and 63 conjunctival non-neoplastic control tissues from Ugandan subjects. HPV genotypes were identified by nucleotide sequencing analysis of amplified DNAs and homology searches with the BLAST software. HIV status was identified by serologic methods.

Results: We have detected 18 HPV-positive samples, including 17 (19.8%) conjunctival neoplasia and 1 (1.6%) control sample ($P = 0.0019$). The BLAST analysis of L1-consensus primer region allowed the identification of two mucosal (6 and 18 types) and six EV-related (HPV38 and PPHL1FR14b, 20, DL473, DL267, PPHL1FR, and HPV38) HPVs. A putative new HPV sequence (CJ198), with a < 90% homology to all known HPVs, was identified in one ICSCC and in a CIN1 sample. Phylogenetic analysis allocated the putative new HPV-CJ198 within the EV-HPV Beta-group. There was no statistically significant difference in the distribution of genotypes among ICSCC and CIN3 subjects according to their HIV serological status.

Discussion: Although HIV-related immunodeficiency is associated with incidence increase of both conjunctival neoplasia and HPV detection, HIV infection does not alter ICSCC etiopathogenetic mechanisms. The EV-related HPVs groups are the predominant types in conjunctival neoplasia biopsies in both HIV-negative and -positive subjects. The multiplicity of HPV types detected and the identification of a new HPV type of unknown oncogenicity suggest the need to conduct more investigation on the role of HPVs in conjunctival tumors.

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PERSISTENT KAPOSI'S SARCOMA IN A POPULATION EXTENSIVELY TREATED WITH ANTIRETROVIRAL AGENTS AND CHEMOTHERAPY: CHARACTERIZING THE PREDICTORS OF CLINICAL RESPONSE

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Background: The use of highly active antiretroviral therapy (HAART) in areas where its availability is widespread has led to dramatic declines in the incidence of Kaposi's sarcoma (KS). KS, however, remains the most common cancer worldwide in patients with AIDS. Even where HAART is widely available, its effect in persons with preexisting KS has not been extensively described. We sought to characterize the experience of patients with KS in the era of HAART and determine the predictors of clinical response.

Methods: All patients with KS cared for at an urban HIV Clinic in Seattle, Washington, who are enrolled in the University of Washington (UW) HIV Cohort were identified through the UW HIV Information System. Patients with at least one visit after January 1996 had the opportunity to initiate HAART and were eligible for inclusion. All charts were reviewed to confirm KS diagnosis, stage, chemotherapy use, and documentation of change in the clinical appearance of KS. Laboratory (CD4 T-cell count and HIV plasma RNA level) and pharmacy records (antiretroviral therapy (ART) dispensation dates) were electronically abstracted. Year of KS diagnosis was categorized into three calendar periods to represent changes in availability of different HAART regimens. We performed univariate analysis using Cox regression of the following baseline variables: KS stage (T1 vs. T0), chemotherapy (ever vs. never use), KS diagnosis period (1996–1998, 1999–2001, and 2002–2006 vs. 1993–1995), HIV plasma RNA level (≥ 100,000 and missing data vs. < 100,000), CD4 T-cell count (> 200 and missing data vs. ≤ 200), prior ART history, and prior HAART history. All variables that were statistically significant by univariate analysis were included in the multivariable model to determine variables independently associated with KS improvement.

Results: In the 13-year period between January 1993 and February 2006, 91 patients had a confirmed diagnosis of KS and ≥ 1 visit after January 1996. The majority were male (99%), were white (70%), and reported sex with men (68%). At KS diagnosis, 48 (53%) had extensive (T1) and 43 (47%) had moderate (T0) disease. The median CD4 T-cell count at diagnosis was 50 (interquartile range (IQR) 10–160), and the median log HIV RNA level was 5.04 (IQR 4.11-5.55). 46 (51%) received chemotherapy following diagnosis. After 36 months of follow-up, 26 (29%) patients were reported to have improvement in their KS disease. The median time to KS improvement from diagnosis was not reached. In the multivariable model that included KS diagnosis period, HIV plasma RNA level, CD4 T-cell count, and prior HAART history, KS diagnosis period and plasma RNA level were independently associated with KS improvement. KS improvement was significantly higher with increasing calendar period in which KS was diagnosed, (1996-1998, hazard ratio (HR) = 1.8, 95% CI: 0.2, 19.9; 1999–2001, HR = 3.2, 95% CI: 0.3, 33.3; 2002–2006, HR = 10.5, 95% CI: 1.0, 114.3; compared with 1993-1995, $p < 0.01$). Patients with high HIV plasma RNA level (> 100,000) at baseline were less likely to experience KS improvement (HR = 0.3, 95% CI: 0.1, 0.8, $p = 0.02$).

Conclusions: Three years following diagnosis, most patients with HIV-associated KS have persistent disease despite the widespread use of HAART and chemotherapy. The complexity of current HIV treatment regimens and the confounding associated with observational studies makes inferences about the efficacy of specific ART agents challenging. Randomized clinical trials are needed to determine the optimal treatment strategies for HIV-infected persons with KS.

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KAPOSI'S SARCOMA-ASSOCIATED HERPES VIRUS (KSHV) INDUCES A SUSTAINED NFKB ACTIVATION DURING INFECTION OF HUMAN DERMAL MICROVASCULAR ENDOTHELIAL CELLS THAT IS ESSENTIAL FOR VIRAL GENE EXPRESSION AND FOR THE INDUCTION OF CYTOKINES AND GROWTH FACTORS

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Kaposi's sarcoma (KS) is classified as a chronic inflammation-associated malignancy, and KS lesions consist of spindle-shaped endothelial cells, inflammatory cells, growth factors, and cytokines. *In vitro* KSHV infection of human dermal microvascular endothelial (HMVEC-d) and fibroblast (HFF) cells results in the induction of pre-existing host signal cascades, sustained expression of latency-associated ORF73 (LANA-1), ORF72, and K13 genes; transient expression of a limited number of lytic genes, including the lytic cycle switch ORF50 (RTA) gene; and reprogramming of host transcriptional machinery, including several pro-inflammatory inflammatory cytokines, and growth and angiogenic factors. NFkB is a key factor involved in the regulation of cytokines, growth factors, cell proliferation, and survival and has been shown to play roles in the maintenance of KSHV latency in B lymphoma cells. Here, we examined the induction of NFkB during *de novo* infection of primary HMVEC-d and HFF cells. NFkB induction was observed as early as 5–15 min post KSHV infection. Significant reduction in NFkB activation was observed by pre-incubating virus with heparin. Rapid early translocation of p65–NFkB into the infected cell nuclei was detected by IFA, EMSA, and p65 ELISA. Inhibition of IkB phosphorylation by Bay 11-7082 inhibited this activation. A persistent level of KSHV-induced NFkB was observed during 72-h period of observation. In contrast, ERK1/2 was highly activated during the earlier time points, and p38MAPkinase was activated only during the later time points. Inhibition of NFkB did not have any effect on KSHV entry into the cells, and in contrast, the expression of viral latent (ORF73) and lytic (ORF50) genes was significantly reduced. Several transcription factors were activated during KSHV infection, and inhibition of NFkB affected the Jun D, Jun B, phospho-c-jun, cFos, and FosB. Cytokine arrays detected the induction of inflammatory cytokines in the infected cell supernatant, several of which were inhibited by Bay treatment. Together, these results suggest that during *de novo* infection, KSHV induces the sustained levels of NFkB to regulate viral and host cell genes, including cytokines, thus possibly regulating the establishment of latent infection. Exploring the link between NFkB, virus, and host gene expression will provide strategies to influence KSHV gene expression and infection.

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INDUCTION OF SPINDLE–CELL MORPHOLOGY IN HUMAN VASCULAR ENDOTHELIAL CELLS BY HUMAN HERPES VIRUS 8–ENCODED VFLIP K13

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Human Herpes Virus 8 (HHV8), also known as Kaposi's sarcoma associated herpes virus (KSHV), is linked to the development of Kaposi's sarcoma, a disease characterized by the presence of distinctive proliferating spindle-like cells. Although HHV8 can induce spindle-cell transformation of vascular endothelial cells *in vitro*, the viral gene(s) responsible for this phenotype remain to be identified. We demonstrate that expression of HHV8-encoded vFLIP K13 is sufficient to induce spindle-cell phenotype in human umbilical vein endothelial cells (HUVEC), which is associated with the activation of the NF-κB pathway and can be blocked by Bay-11-7082, a specific inhibitor of this pathway. K13 induces the expression of several genes known to be upregulated in HHV8-transformed vascular endothelial cells, such as IL-6, IL-8, CXCL3, RDC1, COX-2, and DUSP5. Furthermore, similar to K13, HHV8-induced spindle-cell transformation of HUVEC is associated with NF-κB activation and can be blocked by Bay-11-7082. Thus, ectopic expression of a single latent gene of HHV8 is sufficient for the acquisition of spindle-cell phenotype by vascular endothelial cells, and NF-κB activation plays an essential role in this process.

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TARGETED DISRUPTION OF KSHV ORF57 IN THE VIRAL GENOME IS DETRIMENTAL FOR THE EXPRESSION OF ORF59, K8ALPHA, AND K8.1 AND THE PRODUCTION OF INFECTIOUS VIRUS

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Kaposi's sarcoma-associated herpesvirus (KSHV) ORF57 regulates viral gene expression at the post-transcriptional level during viral lytic infection. To study its function in the context of the viral genome, we disrupted KSHV ORF57 in the KSHV genome by transposon-based mutagenesis. The insertion of the transposon into the ORF57 exon 2 region also interrupted the 3′ untranslated region of KSHV ORF56, which overlaps with the ORF57 coding region. The disrupted viral genome, Bac36-delta57, did not express ORF57, ORF59, K8alpha, or K8.1 after butyrate induction and could not be induced to produce infectious viruses in the presence of valproic acid, a histone deacetylase inhibitor and a novel KSHV lytic cycle inducer. However, the mutant genome was able to express PAN RNA. The ectopic expression of ORF57 partially complemented the replication deficiency of the disrupted KSHV genome and the expression of the lytic gene ORF59. The induced production of infectious virus particles from the disrupted KSHV genome was also substantially restored by the simultaneous expression of both ORF57 and ORF56; complementation by ORF57 alone only partially restored the production of virus, and expression of ORF56 alone showed no effect. Altogether, our data indicate that in the context of the viral genome, KSHV ORF57 is essential for ORF59, K8alpha, and K8.1 expression and infectious virus production.

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INVOLVEMENT OF CYCLIN-DEPENDENT KINASES IN KSHV GENE EXPRESSION

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During latent infection, the Kaposi's sarcoma–associated herpesvirus (KSHV) genome replicates as extra-chromosomal episomes and a restricted number of viral genes are expressed. The KSHV genome, similar to other herpesviruses, is likely to be in a chromatin-like state in latently infected cells as positioned nucleosomes have been observed on a few regions of the KSHV genome. As modification of histone tails, including phosphorylation, is important in control of gene expression, we propose that the KSHV chromatin is phosphorylated by the virally encoded cyclin complexed with a cellular cyclin-dependent kinase (CDK) to control latent and lytic gene expression. We have demonstrated that v-Cyclin/CDK complexes immunoprecipitated from the KSHV+ cell line, BCBL-1, phosphorylate histone H3 on a physiologically relevant site, which was suppressed by a pharmacological inhibitor of CDKs, Cyc202. Two CDKs targeted by Cyc202, CDK1 and CDK9, bound to v-Cyclin in GST-pull-down assays, suggesting that either or both CDKs mediate phosphorylation of histone H3. We further show by ChIP-chip analysis that phosphorylated histone H3 is associated with the KSHV genome *in vivo,* and treatment of BCBL-1 cells with Cyc202 reduced the levels of phosphorylated histone H3 associated with the KSHV genome. Treatment of BCBL-1 cells inhibited the latent expression of LANA as well as lytic gene expression following induction. Our results demonstrate that phosphorylated histone H3 is associated with the KSHV genome in latently infected cells and that v-Cyclin bound to CDK1 or CDK9 mediates this phosphorylation. This is the first demonstration of a cyclin-dependent kinase phosphorylating histone H3 and that v-Cyclin forms a complex with CDK9. As CDK9 is a component of p-TEFb, a complex important in transcription elongation, the interaction of v-Cyclin with CDK9 suggests that v-Cyclin/CDK9 may phosphorylate the C-terminal domain of RNA polymerase II and regulate transcription elongation. These studies have led us to propose a mechanism of action of v-Cyclin in KSHV gene expression.

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HUMAN HERPESVIRUS (HHV)–8 K1 SUPPRESSES FAS-MEDIATED APOPTOSIS AND BINDS TO THE FAS COMPLEX

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Kaposi's sarcoma–associated herpesvirus (KSHV or HHV-8) is associated with multicentric Castleman's disease, primary effusion lymphoma (PEL), and Kaposi's sarcoma. Malignant tumors are frequently associated with resistance to Fas-mediated apoptosis, which is a common obstacle to the successful treatment of many different types of cancers. Oncoprotein K1 encoded by HHV-8 is a transmembrane protein with an immunoreceptor tyrosine-based activation motif (ITAM) sequence in its short cytoplasmic domain, which is constitutively phosphorylated (J Natl Cancer Inst Monogr. 28; 15–23, 2001). We have found that K1-expressing cells are resistant to apoptosis and K1 directly binds Fas to inhibit apoptosis. K1-transfected BJAB cells were resistant to Fas-induced apoptosis but not to other apoptosis-inducing stimuli, including tumor necrosis–related apoptosis-inducing ligand or radiation. K1 transgenic mice showed lymph node hyperplasia and large spleens. Nine out of 12 K1 transgenic mice survived injection of 0.3 μ/gram activating anti-Fas (Jo2) antibody, whereas 13 out of 22 control mice died with hepatocyte apoptosis ($p = 0.03$). In mice transfected with K1 vector, K1 bound to Fas in liver tissue and protected liver cells against apoptosis induced by agonistic anti-Fas antibody. We prepared deletion and point mutants of K1 and Fas to map their respective binding sites. Immunoprecipitation-immunoblotting analysis of the transfectant cell lysates showed that binding occurred through the extracellular domains of K1 and Fas. Also, we have found that preligand assembly domain-deleted Fas mutants (amino acids 1–66 deleted) still bind to K1. These results support the presence of an apoptosis regulatory system based on Fas-protein interactions. By characterizing this mechanism, we will lay the foundation of an apoptosis regulatory pathway that may explain apoptosis resistance of many cancers.

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MODULATION OF THE KSHV LYTIC PROGRAM BY DEACETYLASE INHIBITORS

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Kaposi's sarcoma (KS) and primary effusion lymphoma (PEL) are opportunistic tumors that occur at high incidence in patients with HIV/AIDS. In both, the primary etiologic agent is Kaposi's sarcoma–associated herpesvirus (KSHV, HHV8). Typical of any herpesvirus, KSHV takes advantage of two contrasting programs of viral gene expression (lytic and latent) to sustain a lifelong colonization of the host and to disseminate to new hosts through viral shedding. In KS and PEL, the majority of tumor cells remain latently infected and are resistant to cytotoxic chemotherapy and antiherpetic drugs such as ganciclovir. Very little is known about the physiological cues that determine the extent of lytic replication and how this relates to disease progression. Numerous studies point to a strong positive correlation between KSHV viremia (presence of virus in cell free fluids) and clinical outcomes of AIDS-KS. Understanding the mechanistic basis of the switch between latency and lytic replication is therefore of paramount importance.

Protein acetylation has emerged as a major regulator of biological processes and involves the addition or removal of acetyl groups on lysine or arginine residues by acetylase and deacetylase enzymes respectively. Studies of latently infected PEL cells have shown that deacetylase inhibitors (butyrate, trichostatin A) are among the most potent inducers of lytic replication. The prevailing view is that these compounds act by increasing the acetylation of viral and/or cellular proteins that regulate expression of viral open reading frame 50 (ORF50), the gene encoding the lytic switch protein RTA. Once made to sufficient levels, RTA is capable of inducing transcription of many lytic genes, leading to production of infectious virions. Recent work from our laboratory and others suggests this is only part of the full story. We find that transcriptional activation by RTA is itself regulated in an acetylation- and promoter-dependent manner. In the absence of acetylation, RTA activates an inducible promoter (LT_i) upstream of the latency genes cluster encoding LANA, vFLIP, vCyclin, kaposin, and 12 microRNAs. Treatment with deacetylase inhibitors suppresses activation of this promoter and simultaneously enhances activation of typical lytic promoters such as PAN/Nut1. Suppression of LT_i is mediated by the CSL (CBF-1, RBP-Jκ) binding sites within LT_i and requires LANA. We propose that deactylase inhibitors function as potent reactivation agents because of their ability to stimulate RTA expression and at the same time block activation of a subset of RTA-responsive genes that are incompatible with lytic replication. A variety of deacetylase inhibitors are found in the environment, either as abundant metabolic products of bacterial fermentation (e.g. short-chain fatty acids) or as agents of chemotherapy for cancer or various neurological disorders. In patients with AIDS-KS, these factors are likely to influence the frequency of viral reactivation (i.e. viremia) and thus the prognosis. Because of their ability to sensitize latently infected tumor cells to killing, deacetylase inhibitors also offer tremendous potential as therapeutic agents, especially if used in combination with antiherpetic drugs.

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BLOCKADE OF EXPRESSION OF VIRAL INTERLEUKIN 6 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, such as Kaposi's sarcoma, primary effusion lymphoma (PEL), and multicentric Castleman's disease (MCD). Like other herpesviruses, KSHV displays a tightly regulated program of gene expression with two modes of infection: latent and lytic. In lytic infection, KSHV encodes regulatory proteins altering the expression of viral and cellular genes during virus infection and reactivation. Many of these genes are homologous to cellular genes, and these viral gene products play a variety of roles in KSHV-associated pathogenesis by disrupting cellular signal transduction pathways, cell growth, apoptosis, and cell cycle control. One of the genes is ORF-K2, encoding viral interleukin 6 (vIL-6), an early lytic gene product homologous to human interleukin 6 (hIL-6) that is highly expressed in infected hematopoietic cells. The hIL-6 is a pro-inflammatory cytokine, as well as an autocrine/paracrine growth factor that stimulates growth and proliferation of B cells, induces growth arrest and differentiation of macrophages, and also has anti-apoptotic activity. The vIL-6 is capable of substituting for hIL-6 in its growth factor and anti-apoptotic activity and can induce hIL-6 expression. Thus, vIL-6 is believed to be a major contributor to PEL and MCD pathogenesis. In the current study, a novel approach is employed to effectively block translation of vIL-6 mRNA via phosphorodiamidate morpholino oligonucleotides (PMOs). PMOs are analogs of short DNA oligonucleotides with modified chemical structures, resulting in highly specific binding to target sequences and stable presence in the host. Through Watson-Crick base pairing, PMOs can stericly block translation of target mRNA. PMOs are new generation of antisense compounds with a track record of safety and bioavailability that sets them apart from other antisense chemistries and suggests promising clinical application. In this study, a PMO against vIL-6 was designed and tested on two KSHV-infected PEL cell lines, BCBL-1 and BC-1. Immunofluorescence assay (IFA) with vIL-6–specific antibodies was conducted to detect vIL-6 expression in the PEL cells. IFA showed that the number of vIL-6–positive cells in the cells treated with the vIL-6 PMO was reduced in comparison with cells treated with a control PMO. Subsequently, Western blot was performed, and its results confirmed the reduction of vIL-6 expression and found that the suppression was in a dose-dependent manner. To detect the changes of hIL-6 after PMO treatment, enzyme immunoassay was performed, and it was found that hIL-6 expression was reduced in cells treated with vIL-6 PMO in comparison with cells treated with the control PMO. The result indicates that vIL-6 PMO is effective in blocking the expression of vIL-6 and that the reduction of vIL-6 leads to the decrease of hIL-6. Further studies are being conducted to explore the effects of this ablation on KSHV replication.

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SUBNANOMETER STRUCTURE AND ATOMIC MODELING OF A GAMMAHERPESVIRUS CAPSID REVEALS HIGHLY ADAPTED STRUCTURAL ELEMENTS BUILT ON A CONSERVED BACTERIOPHAGE FOLD

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Gammaherpesviruses, including the human pathogens Epstein-Barr virus (EBV) and Kaposi's sarcoma–associated herpesvirus (KSHV), are DNA tumor viruses that form a subfamily of the Herpesviridae. Little is known about their structural divergence and conservation due to difficulties in isolating these viruses. We report an 8-Å resolution capsid structure of the rhesus monkey rhadinovirus (RRV), a gammaherpesvirus highly homologous to EBV and KSHV. This is the first gammaherpesvirus structure to reach subnanometer resolution, revealing distinct secondary structural elements of the capsid proteins of this enormous molecular machine while also providing sufficient constraints to allow the construction of a pseudo-atomic model of the upper domain of major capsid protein (MCP) associated with gammaherpesvirus-specific molecular interactions. Our model revealed a conserved, 50-Å–long helix that plays a key role in upper subunit association in MCP hexons and a highly variable, loop-forming amino-acid sequence segment that is responsible and accounts for the unique pattern of external tegument protein interactions observed in gammaherpesviruses. The demarcation of molecular boundaries has made possible the identification of various molecular interactions among MCP molecules and the clamping triplexes and has provided numerous insights into the potential molecular mechanisms employed by the capsid proteins to adopt drastic conformation changes needed during assembly and maturation. Therefore, tumor herpesviruses have evolved the upper-laying domains of the capsid proteins to adapt gammaherpesvirus-specific structures or functional roles while retaining, at the innermost capsid floor region, a molecular fold and architectural design that trace back to some DNA bacteriophages.

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TARGETED PROFILING OF KAPOSI'S SARCOMA AND KSHV-ASSOCIATED LYMPHOMA

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Kaposi's sarcoma–associated herpesvirus (KSHV) causes Kaposi's sarcoma (KS) as well as KSHV-associated lymphoma. We developed real-time QPCR arrays to profile viral transcription in KS and found that this information can be used to stratify otherwise identical KS biopsies based upon the degree of lytic mRNA levels. This aided in the diagnosis of KS. Here, we have used the same strategy to develop targeted arrays for therapy-relevant cellular pathways such as the NFkappa-B and p53 pathways. We find that NFkappa-B targets are activated in KS and that this approach can be used to understand the response of PEL to current and experimental therapies.

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IS AIDS-RELATED KAPOSI'S SARCOMA CHIMERIC?

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Kaposi's sarcoma (KS) is a rare soft tissue malignancy that occurs with relatively high frequency in immunosuppressed transplant recipients and in patients with AIDS. A recent study conducted in Italy found 5 of 8 transplant-related KS tumors bearing donor-derived antigens, suggesting parenteral transmission of KS as whole cells, engraftment, and development into chimeric tumors. Whether whole KS cells could be transmitted sexually and engraft in immunocompromised hosts is unknown. We investigated the hypothesis that KS whole cells may also be transmitted into immunocompromised recipients via heterosexual acts by testing KS lesions occurring in female patients with AIDS from Africa for the presence of the Y-chromosome–specific sex-determining sequence (SRY). Matched normal tissue from KS lesions was used as negative controls. Detection of SRY sequence in tumor, but not in normal control tissue, would suggest chimeric tumors. Among 25 unique tumor-normal sample pairs tested, none tested positive for SRY sequence. Our results do not exclude sexual cellular transmission of KS, but they suggest that if it occurs, it is rare.

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TRANSMISSION OF KAPOSI'S SARCOMA HERPES VIRUS (KSHV) BETWEEN SOUTH AFRICAN MOTHERS AND CHILDREN

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Background: Kaposi's sarcoma–associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is now accepted as the etiological agent for Kaposi's sarcoma (KS) and other haematological malignancies. Unlike in Europe and the United States, where KSHV is rare and regarded as a sexually transmitted infection, in Africa KSHV is very common and affects the heterosexual population and young children. In this study we assess whether KSHV with or without HIV co-infection in South African mothers is associated with higher KSHV seropositivity in their children.

Methods: Sera obtained from children and their mothers who were involved in paternity disputes were tested using two enzyme linked-immunosorbent assays for lytic KSHV K8.1 and latent KSHV Orf73 antigens. Subjects positive for either of the assays were deemed to be seropositive for KSHV.

Results: KSHV seroprevalence was 15.9% (204/1287) in children and 29.7% (350/1179) in mothers. The risk of KSHV seropositivity was significantly higher in children between 1.5 years and 10 years born to KSHV-seropositive mothers compared to those born to KSHV-seronegative mothers (OR = 1.9; 95% CI 1.3–3.0), and the risk increased with the age of the children. The HIV status of mothers was marginally associated with increased risk of KSHV seropositivity in their children (OR = 1.6; 95% CI 1.0–2.6, p = 0.07). Also, HIV-positive subjects had significantly higher lytic and latent KSHV antibody levels than HIV-negative subjects. Although KSHV antibody titres were higher in HIV-positive mothers compared with HIV-negative mothers, it is not clear whether HIV-infection promotes increased shedding of KSHV among mothers and therefore transmission to children or whether HIV infected children are more susceptible to infection by KSHV.

Conclusion: The risk of acquisition of KSHV in children is higher among children of KSHV-seropositive mothers. While KSHV seroprevalence was significantly higher in both children and mothers who were HIV-positive, the HIV status of the mother was only marginally associated with increased risk of KSHV seropositivity in the child.

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CLINICAL AND VIROLOGIC CHARACTERISTICS OF EPIDEMIC AND ENDEMIC KAPOSI'S SARCOMA IN UGANDAN MEN AND WOMEN

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Introduction: Kaposi's sarcoma (KS) has been recognized as a common tumor in Uganda for several decades. Concurrent with the HIV epidemic, KS has emerged as the leading cause of cancer in Uganda. Replication of Kaposi's sarcoma–associated herpesvirus (KSHV) has been shown to be important in the genesis and persistence of KS lesions. We sought to characterize the relationship between KSHV replication patterns and the clinical presentation of KS and to contrast KSHV replication in persons with endemic and epidemic KS.

Methods: Participants with biopsy-proven KS were recruited from the Uganda Cancer Institute and the Infectious Disease Institute, Mulago Hospital, Kampala, between May 2005 and July 2006. HIV serostatus was confirmed by rapid enzyme immunoassay testing. HIV-positive participants with a CD4 count < 200 and/or who had already initiated antiretroviral therapy were excluded. A standardized form was used to record demographic characteristics and document initial KS lesions as described by participants. A complete physical exam was performed by trained physicians to document size, location, and character of KS lesions. Plasma samples were collected weekly and salivary samples collected daily over a 28-day period. KSHV plasma viremia and salivary shedding were quantified using real-time polymerase chain reaction. The Fisher's two-sided exact test and the Student's t-test were used to determine differences in KS presentation, response to therapy, and viral replication in participants with endemic and epidemic KS.

Results: Twenty (50%) of 40 participants with KS were HIV positive. The median CD4 count among HIV-positive patients was 409 (range 240–1,062). The mean age was similar in persons with epidemic KS (34.9 ± 8.6 years) and endemic KS (33 ± 11.3 years). The majority of participants in both groups were men (80% epidemic KS, 75% endemic KS). Participants with epidemic KS were significantly more likely to have lesions on the trunk (35% vs. 5%, $p = 0.04$), or to have an abnormal oral (35% vs. 5% $p = 0.04$) or lymph node exam (65% vs. 10%, $p < 0.001$). The leg was the most common site of the first lesion in both epidemic KS (60%) and endemic KS (75%). Women with epidemic KS were significantly less likely to present with KS lesions on the lower extremities than men (44% vs. 87%, $p = 0.01$). Persons with endemic KS noted their first lesion significantly earlier than those with epidemic KS (mean time 4.5 years vs. 1 year prior to enrollment, $p < 0.01$). Combination vincristine and bleomycin was the most common chemotherapeutic intervention, utilized in 35% of participants with endemic KS and 30% with epidemic KS. Of those participants who received chemotherapy, complete resolution was more common in persons with endemic KS vs. epidemic KS (25% vs. 0%, $p = 0.04$). Improvement without resolution was seen in 50% of endemic KS and 80% of epidemic KS patients. Radiotherapy was more commonly utilized by persons with endemic KS (30% vs. 0% of epidemic KS patients, $p = 0.05$).

The frequency of HHV-8 viremia as detected by PCR in plasma was similar in epidemic and endemic KS (75% vs. 57%, p=0.62). Rates of viremia did not vary by the site of KS clinical presentation. KSHV was detected in the oropharynx of 8 (73%) of 11 patients with epidemic KS, and 4 (57%) of 7 of patients with endemic KS ($p = 0.62$). There was a trend toward women with KS being less likely than men to harbor replicating KSHV either in the peripheral blood (25 vs. 80%, $p = 0.07$) or oropharynx (33% vs. 73%, $p = 0.25$), but this analysis was limited by small numbers.

Conclusions: The clinical presentation, response to therapy, and HHV-8 replication patterns of persons with KS in Uganda may vary by HIV status and gender. Persons with HIV-associated KS more often present with lesions in the oral cavity or trunk and have concurrent lymphadenopathy, and they had a poorer response to chemotherapy. Ugandan women with KS were less likely to present with lower extremity lesions and tended to have HHV-8 detected in the peripheral blood and oropharynx less frequently than men. These findings may allow for improved recognition and treatment of KS in Uganda and also point towards important factors in the pathophysiology and virology of KS.

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AIDS-RELATED KAPOSI'S SARCOMA: MANAGEMENT CONSTRAINTS IN ABUTH ZARIA, NIGERIA

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Objective: To assess some diagnostic and treatment constrains in a resource-limited setting.

Patients: The study was carried out between January 2003 and January 2005 in the Haematology HIV subspecialty clinic at ABUTH, a tertiary referral centre and one of the sites of the Nigerian federal government anti-retroviral treatment centre. Prospective clinic-based assessment of patients was carried out. There were 24 histological diagnosed Kaposi's sarcoma (KS) patients.

Method: All of the patients were HIV-1–antibody positive by double ELISA method (ImmunoComb and Genie II); Western blot or PCR were not available. Complete blood count was carried out by standard manual methods (no automated haematology analyzer) and CD4+ T lymphocytes enumeration by the Dynabeads method (no standard flow cytometry). Facilities for KS herpes virus type 8 serological screening were not available. The modalities of treatment include HAART, chemotherapy and surgical excision.

Result: Over a period of three years, 24 patients were seen. Male adult patients predominated, with a male-to-female ratio of 2.8:1. One childhood KS was reported in a 9-year-old girl. The ages ranged from 9 to 70 years. Cutaneous lesions were the earliest and most common mode of presentation in 88.8% of the patients. Visceral involvement could not be assessed due to lack of bronchoscopic and gastrointestinal endoscopic biopsy tools. The mean packed cell volume was 0.25L/L, and the mean CD4+ T lymphocyte counts of 142.6-cells/µl of blood. At the time of analysis, 8 patients were lost to follow-up, 6 were dead before commencement therapy, and only 10 were still being seen. Of these 10, 5 were only on HAART, 3 had single-agent chemotherapy (vincristine) at $12 per course, and only 1 had combination chemotherapy, (Adriamycin, bleomycin, and vincristine) at $71 per course, with a minimum of six courses required. The child had surgical excision of the few cutaneous lesions. Therapy with HAART and chemotherapy induced some tumour regression but more so with combination chemotherapy. Addition of immune modulators (alpha interferon) has not been practicable due to cost. Therapy is hampered by ignorance, poverty, lack of some diagnostic tools, and inability to afford the recommended choice of therapeutic agents in a country with a gross domestic product (GDP) per capita of $330–348 where 70.2% of the population subsists on less than $1 per day.

Conclusion: In Nigeria, the majority of the AIDS-related Kaposi's sarcoma presentation and diagnosis in the hospital is late, which might be due to several factors, mainly poverty. This yields disappointing results for the patients, their families, and the attending clinician. Improved outcome might be achieved by health education, good standard of living, provision of diagnostic tools, and availability and reduction in the cost of newer therapeutic agents.

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USE OF AN INTERACTIVE MULTIMEDIA COMPUTER SYSTEM TO REDUCE SMOKING AMONG AN ETHNICALLY DIVERSE COHORT OF HIV-INFECTED AND AT-RISK WOMEN

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Background: With the introduction of HAART, there has been a substantial decline in mortality among HIV infected persons, but solid tumor cancers remain an important cause of non-HIV-related deaths. Smoking is implicated as a key risk factor for cancer death among HIV+ and at risk seronegative individuals. With smoking prevalence rates of 50% or more among HIV+ women, smoking cessation interventions are critical. We report preliminary data in the Chicago Women's Interagency HIV Study (WIHS) cohort on application of the Transtheoretical Model computer expert system (CES), an interactive multimedia computerized feedback program demonstrating high efficacy in population-based cessation trials.

Methods: HIV+ and at-risk smokers enrolled in the Chicago WIHS cohort were invited to participate in a computerized smoking education and feedback program. At baseline, participants completed paper and pencil surveys of smoking demographics, nicotine dependence, and perceived stress. The computer program collected smoking stage, decisional balance, temptations to smoke, processes of change, and program satisfaction at baseline, with a second CES contact after six months. As part of the WIHS study, sociodemographics; behavioral, including drug and alcohol use; psychosocial, including symptoms of depression; and detailed clinical and laboratory measures are collected biannually

Results: Among 80 participants enrolled to date, baseline smoking stage included 38% in Precontemplation, 41% in Contemplation, and 21% in Preparation. Mean age was 41.8 years; 89% were African American, and 72% were HIV+. Mean stress score (measured by Perceived Stress Scale-10) was 18.2, and mean depression score (measured by CES-D) was 17.1 with 26% reporting current drug use. On average, participants smoked for 21 years and 35.2% were highly dependent smokers (as measured by Fagerstrom Test for Nicotine Dependence). After orientation to the program, all enrollees were able to work independently with the computer system and rated the first session as helpful (91%), interesting (91%), and making them more interested in quitting (89%). To date, 55% have completed a 6-month follow-up CES session; 30% advanced their stage, 11% regressed, and 59% remained in the same stage. 7/16 baseline precontemplators, 4/20 baseline contemplators, and 2/8 baseline preparation stage smokers advanced their stage. There were 4 (9.1%) self-reported quits between the baseline and first follow-up exposure.

Conclusions: In this cohort of female smokers who are HIV+ or at-risk, with high levels of perceived stress, depressive symptoms, and substance use, the majority (79%) were in pre-action stages. There were high levels of satisfaction with the program and evidence of early-stage advancement found in each of the baseline stages. These findings support tailoring of computerized smoking feedback.

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FOXP1 EXPRESSION IN AIDS-ASSOCIATED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): CORRELATION WITH PROGNOSTIC PARAMETERS IN PATIENTS FROM AIDS MALIGNANCIES CONSORTIUM TRIALS 010 AND 034

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Background: Microarray gene expression patterns of germinal center (GC) and non-germinal center (non-GC) correlate with survival in immunocompetent DLBCL patients. CD10, BCL6, MUM1, and CD138 phenotypic patterns are surrogates for genetic studies with comparable survival data: CD10+, BCL6+/−, MUM1− defines GC while CD10−, BCL6−, MUM1+/− identifies the poorer prognosis non-GC phenotype. FOXP1, a transcription factor differentially expressed in resting and activated B cells, is an independent adverse prognostic marker for DLBCL in immunocompetent patients. We examined AIDS-associated DLBCLs from uniformly treated HIV+ patients in AMC010 (CHOP vs. CHOP-rituxan) and AMC034 (EPOCH vs. EPOCH-rituxan) to determine if FOXP1 and/or the GC vs. non-GC phenotype are prognostic in this patient population.

Design: Slides of 32 and 30 AIDS-associated DLBCLs from AMC010 (closed) and AMC034 (data in analysis) patients, respectively, were available for FOXP1, CD10, BCL6, MUM1, BCL2, Ki-67 immunohistochemistry (IHC) and ISH for EBV (EBER). Antigen expression by >20% tumor cells was considered positive. GC phenotype was defined as CD10+, BCL6+/−, MUM1− ,while the non-GC cases were CD10−, BCL6−, MUM1+/−. FOXP1 expression was correlated with survival; BCL2, Ki-67 expression; and EBV status. Overall survival (OS) based on GC vs. non-GC phenotype was examined.

Results: IHC identified 26/53 FOXP1 as positive, 26/44 MUM1 as positive, 24/40 BCL6 as positive, 16/30 CD10 as positive, 22/37 BCL2 as positive, and 18/60 EBER as positive cases. 19 cases were classified as GC and 14 as non-GC. In AMC 010 patients, there was no mean OS difference between GC and non-GC groups ($p = 0.7$) or FOXP1+ (124 wks) and FOXP1− (127 wks) cases ($p = 0.8$; t-test). FOXP1 expression did not correlate with EBV positivity, BCL2, MUM1, BCL6, or CD10 expression; GC vs. non-GC phenotype; or proliferation rate based on Ki67 (chi-square).

Conclusions: FOXP1 expression in uniformly treated AIDS-associated DLBCLs, in contrast to immunocompetent DLBCLs, is not associated with significantly poorer prognosis based on OS. In addition, FOXP1 expression did not correlate with GC or non-GC phenotype; other known prognostic markers such as BCL2, Ki67; or EBV status. Furthermore, while AIDS-associated DLBCLs can be classified as GC or non-GC cases, this classification does not appear to correlate with prognosis in uniformly treated HIV-positive patients. Thus, useful prognostic markers in immunocompetent patients with DLBCL may not be relevant for the HIV-positive population, suggesting that patient immune status may be more important in predicting patient outcome than tumor biology.

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HIV/AIDS-RELATED LYMPHOMA IMMUNOPHENOTYPES IN BIOPSY SAMPLES FROM PATIENTS DURING PRE- AND POST-HAART TREATMENT PERIODS

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AIDS-associated malignant lymphoma tissue microarrays (TMAs) allow parallel immunohistochemical (IHC) testing for detection of genetic/protein targets and *in situ* hybridization (ISH) for other targets. Archived formalin-fixed paraffin-embedded tissues (FFPET) are a resource for rapid translation from molecular target discovery to clinical disease application. The NCI ACSR provides HIV/AIDS-related biological samples and negative controls to approved investigators. The inclusion in these TMAs of lymphoma tissues from the beginning of the AIDS epidemic in the USA allows a retrospective comparison of early lymphoma phenotypes (pre-HAART) with current lymphoma phenotypes. TMA blocks prepared by the ACSR from FFPET of AIDS-related lymphoma (108 cases), control lymphoma (1 case), and control lymph node (6 cases) from 1980–2005 were sectioned and stained with H&E, IHC (Dako): CD 45, CD3, CD20, CD10, CD138, MIB1, MUM-1, Bcl-6, and ISH for EBV (EBER) as part of an ACSR TMA quality control protocol. The results of IHC and ISH staining from pre- (1980–1995) and post- (1996–2005) HAART intervals were compared for patient demographics, immunophenotypes, and Epstein-Barr (EBER) presence within the lymphoma cells. Pre-HAART cases n = 65, (91% male) vs. post-HAART cases n = 43, (77% male). Age range of both groups was 21–62 years with a median age of 38 and 39 years respectively. Lymphomas in females increased (9% to 23%). Overall, 53% of lymphomas were found in cases 30–39 years of age. EBER-rich tumors decreased (31% to 21%). Plasmablastic or plasma cell-rich lymphomas with CD138 marker decreased (31% to 16%). CD10 decreased (23% to 9%). Frequency of other analytes increased: CD45 (52% to 77%), MUM-1 (22% to 42%), MIB-1 (57% to 95%), Bcl-6 (26% to 40%). There was little change in frequency of CD3 (26% to 33%) and CD20 (68% to 63%). Samples showed loss of target integrity within each time interval, but not necessarily over time. The number of women with HIV-related lymphoma has increased over the study period. The age at which lymphoma appears has not yet been extended with HAART, although the total number of lymphomas available has decreased in the post-HAART period. The change in the overall immunotyping analytes may represent an actual change in phenotypes, such as might be associated with a change in the prevalence of Epstein-Barr virus and/or Kaposi's sarcoma–associated virus (KSHV). Or changes in phenotypes may represent more highly differentiated tumors or better performance of stains in more recent tissue. Diminished molecular target integrity appears to be a function of individual sample potential/quality rather than sample age. The NCI ACSR provides HIV/AIDS-related biological samples and negative controls to approved investigators.

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METRONOMIC THERAPY FOR TREATMENT OF AIDS BURKITT'S LYMPHOMA IN A NOD/SCID LYMPHOMA XENOGRAFT MODEL

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Background: Myelotoxicity is a major complication following the delivery of cytotoxic therapy to treat AIDS-associated malignancies in resource-poor countries. Alternative approaches to the management of Burkitt's lymphoma and other AIDS-associated non-Hodgkin's lymphomas are needed in developing countries where there are limited resources to treat the complications associated with cytotoxic therapy. One possible approach is the use of so-called metronomic therapy. In this approach, cytotoxic drugs are given more frequently but at reduced dosages. This reduced dosage limits the myelotoxicity associated with cytotoxic drugs given at the maximum tolerated dose.

Methods: To test the feasibility of this approach for treatment of AIDS-Burkitt's lymphoma (BL), we first developed a preclinical model. We used the BL-7 cell line to engraft into NOD/SCID mice. The BL-7 cell line is derived from a biopsy from an AIDS patient with BL, is EBV-positive, has the characteristic c-myc translocation, and has limited passage *ex vivo.* Following engraftment of BL-7 into NOD/SCID mice, lymphomas were isolated and the phenotype of the resultant tumors was similar to the parental cell lines, suggesting that growth *in vivo* was not altering the phenotype of the cell lines. To determine whether metronomic dosing of cyclophosphamide (CTX) would be effective in the treatment of AIDS-BL, we engrafted NOD/SCID mice with the BL-7 cell line. To allow the tumors to establish prior to the initiation of chemotherapy, we did not start treatment until 27 days post-engraftment, which is half the average time for mice to succumb to tumors with this cell line. Four groups of mice were analyzed: BL-7 engrafted SCID mice were given saline i.p. every six days (control), CTX at 170 mg/kg i.p. every six days for seven treatments (metronomic i.p.), CTX at 40 mg/kg in the drinking water (metronomic oral), or CTX at 150 mg/kg i.p. three times per week followed by two weeks rest and repeated three times (maximum tolerated dose).

Results: The average time before mice were sacrificed due to tumor growth in the control mice was 56.8 days. When the last control mouse succumbed to tumor growth (65 days), we stopped the treatment of the remaining mice. Mice treated with the maximum tolerated dose of CTX survived until 204 days, when the experiment was terminated. No evidence of tumor growth was evident in any of the mice based on necropsy. Sixty percent of mice treated with the metronomic dose of CTX i.p. survived until 204 days without evidence of tumors. The remaining mice did not develop tumors until 193 and 194 days post-engraftment, approximately 137 days following the death of the control mice and cessation of treatment. Mice that received CTX in their drinking water succumbed to tumors but not until 92 days, almost double the time of the control mice indicating that even minimal levels of CTX in the drinking water had an anti-tumor effect. Weight loss in mice receiving metronomic doses was minimal compared to the mice that had received CTX at maximum tolerated doses.

Conclusion: This data indicates that metronomic scheduling of CTX given i.p. significantly enhanced the survival of BL-SCID mice compared to controls and was comparable to CTX given at the maximum tolerated dose. Collectively, these data demonstrate that primary BL cell lines derived from AIDS patients can be successfully engrafted into NOD/SCID mice and are suitable as a preclinical model to test new therapeutic approaches that will limit myelotoxicity.

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"PROMACS" IN CASES OF HIV+ AND HIV− LARGE CELL LYMPHOMA

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Background: Large cell lymphomas (LCL) are aggressive and quickly progressive and are among the most common of the lymphomas seen in AIDS patients. A preliminary evaluation of abnormal macrophages or "proliferative macrophages" in HIV+ and HIV− LCL was undertaken in this study. Such macrophages can be identified by colocalization of CD68 (marks macrophage cytoplasm) and PCNA (proliferation marker, nuclear staining).

Materials and Methods: Formalin-fixed and paraffin-embedded tissues from patients with LCL, both HIV+ and HIV−, were evaluated via the use of tissue microarrays (TMA). Analysis for p24 (an HIV antigen) by immunohistochemistry was performed. Double immunohistochemistry for CD68 and PCNA was performed to identify an abnormal macrophage population (colocalization of CD68 and PCNA). Normal tonsillar lymphoid tissue, without lymphoma or other significant pathology, was used as control tissue. Clinical outcome data was also evaluated.

Results: 29 cases of LCL were evaluated via use of TMA, 14 of which were clinically documented to be HIV+ (15 cases were HIV−). p24 concordance was seen with 7 of the 14 HIV+ cases, with staining noted in macrophage cytoplasm and not in lymphomatous cells; no p24 reactivity was noted in the HIV− cases. While macrophages were abundant in normal tonsillar lymphoid tissue, highlighting reactive germinal centers, no PCNA-positive promacs were noted. PCNA-positive promacs were frequent in cases of LCL, from both HIV+ and HIV− patients. Macrophage (CD68+) number per TMA core (0.6 mm in diameter) was significantly correlated with promac number in both HIV− and HIV+ cases of LCL ($p < .001$). Similarly, there was a trend towards higher numbers of promacs in patients who were HIV+ and in patients with shorter survival.

Conclusion/Discussion: In this preliminary study, documentation of a phenotypically abnormal population of macrophages was noted in cases of LCL (as compared to reactive control tissue, tonsillar tissue). These phenotypically abnormal macrophages, or promacs, were identified by colocalization of CD68 and PCNA. While macrophages were abundant in cases of high-grade lymphoma as well as in reactive germinal centers of normal tonsillar tissue, PCNA-positive promacs were found only in lymphomatous samples. Macrophage number per TMA core was significantly correlated with promac number in both HIV+ and HIV− cases of LCL ($p < .001$). Of note, though not statistically significant with the numbers at hand, a trend was seen to correlate numbers of promacs with HIV+ lymphomas (as opposed to HIV− cases). There also appears to be a trend toward significance wherein number of promacs is negatively correlated with survival time. Analysis of additional samples of LCL by TMA will be performed along with further accumulation of outcome data.

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HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) AS THE SOLE TREATMENT FOR AIDS-RELATED PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL): A CASE REPORT WITH IMPLICATIONS FOR TREATMENT

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AIDS-related PCNSL is a devastating manifestation of advanced HIV infection. Current prognosis for patients with untreated PCNSL is 1–3 months; with corticosteroids and whole-brain radiotherapy, survival is extended to a median of 3.5 months. Newer treatment paradigms are needed for this rare and devastating manifestation of advanced AIDS. Herein, we describe the clinical course of a patient with recently diagnosed AIDS. In the absence of adjuvant therapies, he achieved a complete remission (CR) after he began HAART. A 40-year-old man presented to medical attention with fevers, 30-lb. weight loss, and altered sensorium. He was subsequently diagnosed with *Pneumocystis jiroveci* pneumonia and HIV infection. His CD4+ count was 18 cells/µL and HIV viral load (VL) > 400,000 copies/mL. After three weeks of antibiotic therapy, his pulmonary infiltrates resolved, but he continued to have global cognitive deficits. A magnetic resonance imaging (MRI) study revealed a right temporal lesion which, on biopsy, proved to be diffuse large B-cell PCNSL. The patient began HAART but declined palliative whole-brain radiotherapy. Four months later, his CD4+ count had improved to 153 cells/µL and his HIV VL was < 75 copies/mL. At 18 months follow-up, he remains in CR with a CD4+ count of 220 cells/µL and a non-detectable HIV VL. His clinical course has been characterized by a return to normal muscle mass and gradual, but profound, improvement in cognition. Through a Medline literature review, we identified four additional cases of prolonged remission of AIDS-related PCNSL following HAART initiation and in the absence of chemotherapy or radiotherapy. Including our patient, all five were HAART naïve and PCNSL was their AIDS-defining and presenting illness. Three of the patients were male, and the sex of the remaining two patients was not stated; their median initial CD4+ count was 50 cells/µL (range, 2–220 cells/µL), and HIV VLs for four of the cases were not reported. All five individuals remain in CR at a median follow-up of 23.5 months (range, 13–32 months). Our patient's experience and those of these additional reports underscore the potential importance of a reconstituted immune system not just in the prevention but also in the control of AIDS-related PCNSL. Perhaps for the rare HIV-seropositive individual with PCNSL who is HAART naïve and who does not have severe or rapidly progressive neurologic signs or symptoms, HAART alone is a reasonable initial therapeutic option.

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DOSE-MODIFIED ORAL CHEMOTHERAPY FOR AIDS-RELATED NON-HODGKIN'S LYMPHOMA (AR-NHL) IN EAST AFRICA

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Background: Dose-modified chemotherapy for AR-NHL in the pre-HAART era has been shown to be equally efficacious and less myelotoxic [N Engl J Med 1997;336:1641 (mBACOD); J Clin Oncol 2001;19:2171 (mCHOP)]. In resource-constrained settings, intravenous chemotherapy and supportive care of the AIDS/cancer patient are challenging (J Natl Cancer Inst 2002;94:718).

Methods: We embarked on a pilot feasibility trial of dose-modified oral chemotherapy [lomustine 50 mg/m2 D1 (C#1 only); VP-16 100 mg/m^2 D1-3; and cyclo-phosphamide/procarbazine 50 mg/m^2 each D22-26 at 6-week intervals (1 cycle) for 2 cycles] in HIV-infected patients with biopsy-proven lymphoma in East Africa.

Results: A total of 49 pts (21 Uganda; 28 Kenya) were treated on study. The majority of pts were female (59%) with median age 39 yrs (range 18–64); poor PS (2 or 3) (63%); high-grade lymphoma (69%); advanced stage (III or IV) (69%); and B symptoms (79%). At study entry, median CD4 count was 200/µL and HIV-1 viral load 97,973 copies/ml. Eighteen pts (36%) had access to ARV. A total of 78 cycles of therapy were administered (median 2; range 0.5–2). The regimen was well tolerated. There were four episodes of febrile neutropenia and three treatment-related deaths (6% mortality rate). Overall objective response rate was 77% (CR/uCR 56%); median survival was 12.3 months; and 18 patients remain alive as of 7/11/06.

Conclusions: Dose-modified oral chemotherapy is efficacious, has comparable outcome to that in the United States in the pre-HAART era, has an acceptable safety profile, and is pragmatic in the resource-limited setting. Further investigation of the oral regimen vs. mCHOP is warranted.

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COMPARATIVE RETROSPECTIVE STUDY OF PATIENTS AT DIAGNOSIS WITH AIDS-RELATED NON-HODGKIN'S LYMPHOMA (AR-NHL) TREATED WITH ORAL CHEMOTHERAPY IN THE PRE-HAART ERA IN EAST AFRICA AND THE USA

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Background: Conditions in East Africa (EA) during the conduct (2001–2005) of our oral chemotherapy trial simulate the pre-HAART era (prior to 1996) in the USA. We sought to compare the natural history of AR-NHL in patients treated with the identical oral chemotherapy regimen in the USA and EA (see Mwanda et al. abstract) at comparable therapeutic eras (pre-HAART) in the AIDS pandemic.

Methods: We retrospectively analyzed 40 patients with AR-NHL treated with full dose oral chemotherapy (20 pts received G-CSF) in the pre-HAART era in the USA (J Clin Oncol 1993;11:1691; Am J Hematol 2001;66:178) with our 49 patients treated in EA, who received the identical dose-modified oral regimen (lomustine, VP-16, cyclophosphamide, and procarbazine).

Results: None of the patients in EA were homosexual or injection drug users (IDU), whereas 45% were homosexual and 34% IDU in the USA. There were no differences between EA and USA patients in age, clinical stage, and prior thrush at presentation. In EA, patients were more likely to be female (59% vs. 8%, $p < .0001$) and to have B symptoms (79% vs. 68%, $p = 0.034$), prior OI (65% vs. 38%, $p = .009$), higher LDH (median 554 vs. 289 U/L, $p = .01$), poorer ECOG PS (PS of 2/3 63% vs. 37%, $p = 0.016$), and lower albumin (median 3.2 vs. 3.6 g/L, $p = .035$). US patients were more likely to have lower CD4 count (median 84 vs. 200/μL, $p = .05$) and more extranodal sites of disease (> 1 50% vs. 29%, $p = .039$). Median survival in EA was 12.3 mos. and in the USA 6.75 mos. Both EA and USA groups were further analyzed by univariate and multivariate analysis. After controlling for effects of sex, B-symptoms, LDH, CD4, and IPI, multivariate analysis by Cox regression between the EA and USA cohorts revealed no significant differences. Baseline LDH, CD4, and IPI were still significant predictors of overall survival.

Conclusions: Important differences in the natural history of AR-NHL in EA vs. USA include more women, B-symptoms, and prior OIs; poorer ECOG PS; higher LDH; and lower albumin.

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LYMPHOMA EXPERIENCE IN A HOSPITAL-BASED HIV CLINIC FROM 1996 TO PRESENT

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We describe 21 cases of HIV-associated lymphoma in our clinic, which has followed approximately 1,500 individuals since 1996. Through direct physician contact and search of the medical records database, 21 patients were identified and their charts were reviewed. The most common transmission category of HIV was male-to-male sexual transmission (38%), followed by injection drug use (24%) and heterosexual contact (14%). In 5 patients (24%), the mode of HIV transmission was other (transfusion, bloodborne) or unknown. There were 18 (86%) men and 3 (14%) women. 18 patients (86%) had a history of smoking. 8 (38%) were coinfected with HCV. The median age at lymphoma diagnosis was 43 years (range: 28–60).

Classification of Lymphomas

Of the 21 cases, there were 16 cases of non-Hodgkin's lymphoma (NHL) and 5 cases of Hodgkin's lymphoma. 3 patients had more than one occurrence of lymphoma.

Diffuse large cell was the most prevalent subtype of NHL with 7 cases, followed by 5 cases of Burkitt's/Burkitt's-like NHL. There were 2 cases of primary effusion lymphoma (PEL) and 1 case of primary CNS lymphoma. One patient had an unspecified NHL successfully treated at another institution. Of the Hodgkin's cases, the histological breakdown was as follows: 2 nodular sclerosing, 1 nodular lymphocyte predominant, 1 mixed cellularity, and 1 unspecified.

Relationship of Lymphoma to HIV Clinical Course

In 6 patients, the diagnoses of HIV and lymphoma were made concurrently; lymphoma was their HIV/AIDS-presenting illness. In one patient, the diagnosis of lymphoma preceded the first positive HIV test by more than 2 years. 15 patients were known to be HIV+ at the time of lymphoma diagnosis, and 10 had used HAART for at least one year.

For the non-Hodgkin's lymphomas, the median CD4+ count at time of lymphoma diagnosis was 107 (range: 12-518). CD4+ count at lymphoma diagnosis was missing for 1 NHL patient. Median nadir CD4+ of NHL patients was 53 (0–334). For the Hodgkin's lymphomas, the median CD4+ count at lymphoma diagnosis was 200 (12-1155) and median nadir CD4+ was 159 (12–244). The majority of patients (67%) presented with B symptoms (unexplained weight loss, fever, or drenching night sweats). 6 patients have expired, 7 are receiving therapy, and 8 have completed therapy.

Conclusions

In our patient population, we have found that NHL is still the predominant type of lymphoma despite the use of HAART. Primary CNS lymphoma is rarely diagnosed in the HAART era. Most patients had received HAART for at least one year and therefore had been under care for their HIV infection prior to their lymphoma diagnosis. Despite the widespread use of HAART and demonstrated clinical benefits, HIV-infected patients still represent a population at risk for lymphoma.

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ANALYSES OF PROGNOSTIC FACTORS FOR SURVIVAL IN EAST AFRICAN PATIENTS WITH AIDS-RELATED NON-HODGKIN'S LYMPHOMA (AR-NHL) TREATED WITH DOSE MODIFIED ORAL CHEMOTHERAPY

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Background: The results of our feasibility trial of dose-modified oral chemotherapy for AR-NHL in East Africa are encouraging to frame/sustain alternative non-myelotoxic and pragmatic therapeutic strategies suitable for evaluation in the resource-constrained setting. To define a group of patients who may have a better outcome univariate and multivariate analyses of prognostic factors were performed.

Methods: Forty nine patients with AR-NHL received dose-modified oral chemotherapy. The following baseline variables were included as potential predictors of survival: age (≤ 60 vs. > 60 yrs.); sex; stage (≤ 2 vs. > 2); ECOG performance status (0/1 vs. 2/3); LDH (≤ 270 vs. >270 U/L); extranodal sites of involvement (≤ 1 vs. > 1 site); prior thrush; prior AIDS [wasting or opportunistic infection(s)]; A/B symptoms; mCHOP salvage chemotherapy (n = 10); antiretroviral (ARV) therapy (n = 18); and baseline albumin. International Prognostic Index (IPI), excluding LDH since not available for all patients (N Engl J Med 1993;329:987), and ACTG 142 prognostic variables (J Clin Oncol 1998;16:3601) were also analyzed.

Results: By univariate analysis, only LDH ($p = 0.0013$) was significantly related to overall survival (OS). Hypoalbuminemia and LDH affected event-free survival (EFS). By multiple regression, LDH and IPI were significantly related to OS ($p = 0.012$). Similarly, the hazard ratio of patients without and with ARV therapy was 17.45 ($p = 0.0007$); and the hazard ratio of patients with IPI 2 compared to those with IPI 0 was 6.62 ($p = 0.028$). LDH, ARV status, and IPI were significantly related to EFS. The complete response rate was 56%, and the objective response rate was 77%. Median OS and EFS were 12.3 and 7.9 months respectively.

Conclusions: For patients with AR-NHL in East Africa treated with dose-modified oral chemotherapy, IPI and not ACTG 142 prognostic covariates best predicts survival. Albumin (perhaps substituting for LDH since more readily tested in East Africa) and ARV status provide further independent prognostic information. These factors may further guide therapeutic options in future trials in resource-poor settings.

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EMAIL: viveksubbiah@gmail.com **AB# 51**

IMPLICATIONS OF ORAL CHEMOTHERAPY IN AFRICA FOR AIDS-RELATED NON-HODGKIN'S LYMPHOMA (AR-NHL)

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Background: As the AIDS pandemic advances, the burden of HIV disease and associated malignant complications is sharply increasing in regions of the world, such as sub-Saharan Africa, that are most affected (J Natl Cancer Inst 2002;94:718). It is imperative and now possible to begin to address practical therapeutic strategies for the treatment of AIDS-related neoplasms [East Afr Med J 2005;82(9/Suppl):S157–62].

Methods: Resources for transfusion and CSF support are extremely limited. It is prudent to avoid myelosuppressive therapeutic interventions, which is the overriding theme of our pathogenesis-based international research collaboration dedicated to AIDS malignancy.

Results: Advantages of oral chemotherapy are numerous. There are often hidden cost savings and time considerations of health care personnel in the resource-poor setting that are not as readily apparent in the resource-rich health care environment. The advantages of oral therapies include: (1) No requirement for intravenous (IV) access; (2) Time consumed by RNs and MD supervision for either short or long-term IV infusions is avoided; (3) No need for IV chemotherapy supplies—bags, tubing, antiseptic supplies, and dressings; (4) No pharmacy preparation; (5) No special training of health care personnel in chemotherapy administration and avoidance of risk of occupational exposure (needlestick injury). At the same time, greater patient education in oral chemotherapy is required to assure compliance, which has not been problematic in our experience. Until oral chemotherapy drugs are more broadly prescribed and utilized, some cost savings may be offset due to the expense of oral agents.

Conclusions: Dose-modified oral chemotherapy is an example of one approach of adapting oral treatment to a complex oncologic problem. Further investigation of the oral regimen vs. mCHOP in AR-NHL is warranted. In addition, other suitable and testable oral therapies should be evaluated in other solid tumors with the ultimate goal of extending better palliative systemic and perhaps life-prolonging therapies to patients with cancer in Africa.

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ABNORMALLY ELEVATED CASES OF PRECANCEROUS LESIONS OF THE CERVIX AMONGST RURAL CAMEROONIAN WOMEN

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Background: Cancer of the cervix is the commonest in Cameroonian women, representing 11% of all cancers diagnosed in the country. In most developed countries, cytological screening has led to a significant reduction in the incidence of and mortality from cervical cancer. In countries with lower participation compliance and in less developed health care systems, screening has been much less or not at all effective in reducing mortality. In developing countries like Cameroon, the cost of infrastructure and initial investment in organising cytological screening is prohibitive. The cost effectiveness of screening programmes based on alternative tests such as visual inspection following acetic acid application has already been investigated but not yet implemented because of poverty. So far, only 1/300 woman could be screened for cervical cancer. In the main cities like Yaoundé and Douala, the prevalence and incidence of clinical cervical cancers are very low or nonexistent, and it is known from our previous study that the prevalence of precancerous lesions of the cervix was 7%.

HIV is still a major public health problem in our country, with around 10% prevalence, and women are more infected than men. The role of HIV in the development of cervical cancer is documented, and in Cameroon, many patients can't undergo treatment and generally move to the rural areas where they will wait to die.

Materials and Methods: We carried out a free screening campaign in six rural Cameroonian villages using Pap smear.

Results: 800 women were enrolled. 10% had a precancerous lesion of the cervix. 75% of these lesions were high grade (HSIL), while 25% were low grade (LSIL). These lesions were observed at all ages from 15 years to even 80 years. These preliminary results are abnormally elevated compared to what was observed before the HIV/AIDS pandemic reached a critical level and compare with what is still observed in urban areas.

Conclusion: This preliminary study shows that there are abnormally elevated cases of precancerous lesions of the uterine cervix amongst rural Cameroonian women, probably due to the fact that most of the HIV/AIDS patients move into rural areas where they consult traditional doctors.

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CLINICO-PATHOLOGICAL CHARACTERIZATION OF ANORECTAL CARCINOMA IN ZARIA, NIGERIA: A PROSPECTIVE STUDY OF 16 PATIENTS

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Purpose: To investigate the clinical and pathological pattern of anorectal carcinoma seen in one large tertiary hospital in northern Nigeria.

Method: A prospective study of 16 consecutive patients seen in three years

Results: There were 10 males and 6 females, aged 25–81 years (median 49 years). No patient had a family history of cancer. Seven patients had symptoms for 12 months or less. Anal pain, bloody stool, and frank bleeding per rectum were present in 8 patients. Ten patients had locally advanced disease, and 4 had metastatic diseases to bones (1) and liver (3). Three patients were positive for HIV antibodies (1 with HIV 1 and 2 with HIV 1 & 2). The commonest histologic type seen is adenocarcinoma. Excisional biopsies were done in 5 patients; incisional biopsy histologic diagnosis only in 8, and 3 had palliative surgery. Nine patients received chemoradiation. Post-treatment evaluation six weeks after completion of treatment showed that 9 patients had complete remission. Overall, 6 patients are alive, 3 died after an average duration of 27.3 months, and 7 were lost to follow-up.

Conclusion: Most patients with anorectal carcinoma in our setting present late with locally advanced disease. The majority of the patients are HIV negative. Although the number of patients is small, complete remission is achievable in many instances using a multidisciplinary approach to treatment.

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ABNORMAL PAPANICOLAOU SMEARS IN HIV-INFECTED WOMEN AFTER HYSTERECTOMY

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Background: For non-HIV infected women with a history of hysterectomy, current guidelines for Papanicolaou (Pap) smear screening state that there is no benefit to performing Pap tests on women who have had a hysterectomy for a benign cause, have no cervix, and have no history of vaginal or cervical neoplasia (1). The same guidelines further state that women who have had a hysterectomy should continue to have Pap tests if they have a history of HSIL prior to hysterectomy. For these women, Pap tests should be done every two to three years until 65 to 70 years old, but can be discontinued after three negative/normal Paps (2). As for HIV-infected women with a history of hysterectomy, prior studies have demonstrated high rates of abnormal vaginal Pap smears (3). Guidelines recommend that HIV-infected women who have had a hysterectomy, especially those with a history of abnormal Pap smears, are at increased risk for SIL on vaginal cytological testing and should undergo regular Pap smear screenings (4). The objective of this study is to compare the incidence of abnormal Pap smear cytology in HIV-infected women who have had hysterectomies with that of HIV-infected women who have not had hysterectomies.

Methods: Participants were 112 women from an inner city HIV clinic, the majority of whom were African-American. All primary providers of HIV care were asked to identify women with prior hysterectomies and Pap smears within the last 10 years. We identified 29 women who had a history of hysterectomy as far back as 1975 who had Pap smear results from within the last 10 years. Charts were reviewed for confirmation of the hysterectomy and Pap smear results. We then compared these women with 83 women who had had Pap smears within the last nine years and no prior history of hysterectomy. Other data collected included demographics, date of HIV diagnosis, history of human papillomavirus infection, history of an AIDS-defining illness, CD4 count, and viral load, as well as history of intravenous drug use (IDU). An abnormal Pap smear was defined as any abnormal cytology, including atypical squamous cells of uncertain significance (ASCUS). The data were analyzed with Pearson's Chi-square test, two sample t tests, and multiple logistic regression.

Results: 63 (56%) participants had a history of abnormal Pap smear. Eighteen were ASCUS, and 45 were higher-grade lesions. Rates of abnormal Pap smear were similar between women with hysterectomy (59%) and women without hysterectomy (55%). When abnormal Pap smears for women with a history of hysterectomy were compared to those for women with no history of hysterectomy, the odds ratio for an abnormal Pap smear in an HIV-infected woman after hysterectomy was 1.13 (ns). After controlling for hysterectomy status, women with a history of IDU had a higher risk of abnormal Pap than those without history of IDU (OR= 3.16, $p = 0.004$). Neither CD4 counts nor viral loads were associated with abnormal Pap.

Discussion: These data suggest that HIV-infected women with a history of hysterectomy are at the same risk for having an abnormal Pap smear as HIV-infected women with no history of hysterectomy. Traditionally, the Pap smear has been used to screen for cervical dysplasia; however, in HIV infected women without a cervix, the Pap smear can be used to screen for vaginal dysplasia. Women who have abnormal Pap smears and a history of hysterectomy can be referred for colposcopy of the vaginal vault with excision of any pathologic lesions. Of note, the risk for an abnormal Pap smear was independent of CD4 count and viral load. Therefore, clinicians should not rely on immunologic status as a predictor of an abnormal Pap smear. Additionally, the risk for an abnormal Pap smear increased in women with a history of IDU. This may be because a history of IDU is a marker for an increased number of sexual partners. HIV-infected women should receive annual Pap smears even if they have had a hysterectomy, regardless of CD4 count and viral load, and particularly if they have ever used injection drugs.

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HIGH-GRADE ANAL INTRAEPITHELIAL NEOPLASIA IN SURGICALLY EXCISED ANAL CONDYLOMATA IN MEN WHO HAVE SEX WITH MEN ACCORDING TO HIV SEROSTATUS

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Background: High-grade anal intraepithelial neoplasia (AIN) is considered the precursor of invasive anal squamous cell cancer. Anal condylomata, high-grade AIN, and anal squamous cell cancer are all more common in men who have sex with men (MSM), particularly those with HIV infection. This study investigates the prevalence of histologically confirmed high-grade AIN within surgically excised anal condylomata of MSM.

Methods: Records of a retrospective cohort of MSM with no history of high-grade AIN who had surgical excision of anal condylomata between 8/99 and 12/04 were reviewed for HIV serostatus, presenting anogenital symptoms, and surgical pathology results. CD4 cell counts and HIV viral loads in the HIV+ group, as well as any available anal cytology results in the six months prior to surgery, were also recorded. Differences were assessed using Chi-square test and Fisher's Exact Test where indicated.

Results: Of 237 MSM, 116 (49%) were HIV+ and 121 (51%) were HIV−. 90/237 (38%) of the entire cohort had anal condylomata harboring high-grade AIN on surgical pathology. High-grade AIN was found in 53% of the HIV+ group and in 23% of the HIV− group ($p < 0.0001$, Chi-square). In subjects in whom anal Pap smear data were available, high-grade cytology was present in < 50% of those with high-grade AIN on surgical pathology. Among HIV+ subjects, CD4 cell count and HIV viral load were unrelated to the risk of finding high-grade AIN on surgical pathology.

Conclusions: Anal condylomata requiring surgical excision frequently harbor high-grade AIN. The condylomata of HIV+ MSM have a significantly greater incidence of harboring such premalignant squamous lesions compared to the condylomata of their HIV− counterparts. Preoperative anal Pap smear results did not predict finding high-grade AIN within anal condylomata, regardless of HIV serostatus. Removal and careful pathologic examination of anal condylomata, along with careful clinical follow-up, could be an effective method of anal cancer prevention in MSM, particularly those with HIV.

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PREVALENCE OF GENITAL WARTS AMONG FEMALE HIV PATIENTS ATTENDING A SEXUALLY TRANSMITTED DISEASES CLINIC IN IBADAN, NIGERIA

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Background: Human papillomaviruses (HPV) selectively infect the epithelium of the skin and mucous membrane, producing warts, and have been implicated in the pathogenesis of cervical cancers in women. The prevalence of human immunodeficiency virus has been on the increase in Nigeria in recent years. Patients infected with HIV frequently have severe clinical manifestations of HPV. This study sought to determine the association between HIV infection and epithelial warts among patients presenting at the sexually transmitted diseases clinic in Ibadan, Nigeria.

Methods: A 5-year retrospective review of 202 case notes of female patients presenting at the clinic was carried out. The laboratory result for each patient was also reviewed. Data were analyzed using the SPSS (version 10) data editor. The Chi-square test was used to determine the level of association.

Results: 35 patients (17.3%) had positively reactive HIV results using the ELISA method. 137 (62.9%) had one form of warty growth or another. A history of genital warts had a significant association with HIV infection (p = 0.02).

Conclusion: Presence of epithelial warts is associated with HIV infection. Female HIV patients should therefore be advised to have cervical cancer screening tests.

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TRENDS IN HUMAN PAPILLOMAVIRUS (HPV) INFECTION AMONG HIV-POSITIVE WOMEN BEFORE THE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (PRE-HAART) AND HAART ERA IN A NIGERIAN CLINIC

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Background: The prevalence of HIV infection has been on the increase in Nigeria in recent times. HIV-positive patients frequently have anogenital malignancies due to HPV. HAART was introduced in anti-retroviral (ARV) centers in Nigeria in the year 2002. The aim of the study is to determine trends in incidence of anogenital malignancies among HIV-positive women in the pre-HAART and HAART eras.

Method: 541 case notes of HIV-positive female patients from January 1999 to December 2004 were analyzed by utilizing an ongoing observational database at the ARV center. Rate ratios, comparing incidence rates (number of malignancies per 1,000 person-years) were calculated.

Results: Twenty-four (4.43%) of the patients had one form of anogenital manifestation of HPV or the other. The incidence rate for HPV rose from 2.28 in the pre-HAART era to 6.40 in the HAART era (rate ratio = 3.15; 95% CI = 1.31–7.44; $p = 0.0002$).

Conclusion: There has been a significant rise in the incidence of HPV since the introduction of HAART. This may be due to the longer survival of HIV-infected patients, surpassing the latency period for the anogenital malignancies. Care providers should be more vigilant for HIV-associated malignancies as patients live longer.

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PRELIMINARY ASSESSMENT OF CONJUNCTIVAL SQUAMOUS CELL CARCINOMA AND HIV INFECTION IN NIGERIA

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Background: Conjunctival squamous cell carcinoma (SCC) is amongst the most prevalent ocular manifestations of human immunodeficiency virus (HIV) infection in developing countries. A rising incidence has also been noted in several African countries, which have been severely affected by the HIV/AIDS (acquired immunodeficiency syndrome) pandemic, where it is reported to occur at a frequency greater than 10 times the figure for non-infected individuals.

Methods: A preliminary review was carried out to evaluate the clinico-pathological features and management challenges in a series of 24 patients (13 males and 11 females) aged between 20 and 80 years with conjunctival squamous cell carcinoma. Information was obtained from surgical pathology records of the Pathology Department, Aminu Kano Teaching Hospital (AKTH), Kano, and clinical records of patients over a two-year period (2004–2005).

Results: Eleven (64.7%) of 17 patients tested for HIV were positive by ELISA and confirmed by Western blot. Their mean age and CD4 count was 40.6 years and 150 cells/mm^3 respectively. The mean age of non-infected cases was 42.5 years. Histologically, 16 (66.7%) were well, 6 (25%) moderately, and 2 (8.3%) poorly differentiated. The majority were treated by surgical excision and a few were treated by enucleation or exenteration. Follow-up was poor (mean period three months), and only 4 (36.4%) were able to receive antiretroviral treatment.

Conclusion: Conjunctival SCC is becoming an important cancer in Nigerian patients infected with HIV, similar to reports from other regions of Africa. It affects relatively young patients with a background of immunosuppression. Treatment is generally disappointing, partly due to patient default. There is a need for more studies to be performed to explore the relationship of this tumour with other confounding factors.

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SEROPREVALENCE OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION AMONGST CANCER PATIENTS

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Background: HIV/AIDS is a worldwide public health problem. In Africa, there were an estimated 26.3 million persons infected with HIV at the end of 2005; 25.8 million were in sub-Saharan Africa. The prevalence in Cameroon currently stands at 5.5%. The link between HIV/AIDS and certain cancers has been determined since the beginning of the pandemic in 1981, and increased risks for certain cancers were reported. Although a vast majority of research into the link between HIV/AIDS and cancer has been carried out in 'western' populations, these populations account for only a minority of the cases of AIDS occurring worldwide today. At a time when the management of HIV/AIDS and its infectious complications is constantly being improved by the use of highly active antiretroviral therapy (HAART) with consequent prolonged survival of these patients, malignant complications are becoming more frequent. We decided to carry out this study in a cancer treatment centre to determine the prevalence of HIV infection amongst the patients with confirmed cancer diagnosis.

Method: A cross-sectional survey was conducted over a period of nine months on 88 consenting patients with a confirmed diagnosis of cancer. The qualitative determination of HIV infection was done on blood specimens using Murex HIV Ag/Ab Combination GE41/42 kits. Statistical analysis was performed using Epi Info version 3.3.

Results: The total number of patients included in the study was 88. The average age of the subjects was 41.7±14.9 years (range 3 to 75 years). Twenty-six (26) different types of cancers were recorded, with the three most frequent being breast cancer, 25.0% (22/88); non-Hodgkin lymphoma, 20.5% (18/88); and Kaposi's sarcoma, 18.9% (16/88). The HIV prevalence was 28.4% (25/88). The mean age was 36.3 years, and the highest prevalence rate was noted in the age range 25–34years. Five different cancers were identified in HIV-positive patients. Kaposi's sarcoma, 60.0% (15/25), and non-Hodgkin lymphoma, 28.0% (7/25), were the AIDS-defining malignancies noted in the HIV-positive patients and the two most common neoplasias in these patients. Patients with Kaposi's sarcoma had the highest prevalence of HIV with 93.8% (15/16), with a male:female ratio of 4:1. The other cancers in the HIV-positive groups were breast, bladder, and colorectal cancer with 4.0% (1/25) prevalence each.

Conclusion: In conclusion, the overall prevalence of HIV infection in the cancer patients was high in this study, with Kaposi's sarcoma and non-Hodgkin lymphoma being the most frequent cancers associated with HIV infection. It is recommended that a larger, preferably multicentre study be carried out to ascertain the relationship between HIV infection and malignancies in Cameroon.

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CANCERS REPORTED IN HIV-POSITIVE PATIENTS IN YAOUNDE GENERAL HOSPITAL

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Introduction: 30 to 40% of patients with HIV are likely to have cancer in the course of development of the disease. This study carried out in Cameroon aimed to analyse the types of cancers reported in HIV-positive patients and to make an inventory of the antiretroviral treatments received by these patients.

Materials and Methods: Medical files were collected from October 2001 to September 2002 in the Medical Oncology Service of Yaoundé General Hospital according to the following criteria: a cancer confirmed by an anatomopathological test; a positive HIV test.

Results: The study included 52 subjects, 25 men (48%) and 27 women (52%), aged between 17 and 62 years, with a median age of 39.79 years. The first three cancers diagnosed included: 27 cases of Kaposi's disease (51.92%); 8 lymphomas (15.38%); and 7 adenocarcinomas of the breast (13.46%). 36 cancers out of 52 (69.23%) diagnosed in our sample were cancers known as virus-induced. Patients received isolated chemotherapy and surgery respectively in 29 (69.23%) and 6 (11.5%) cases and combined chemotherapy/surgery in 5 cases (9.6%). 12 cases (23.1%) received no cancer treatment.

Discussion: The types of cancers most often reported were Kaposi's disease, lymphomas, and breast cancer. Except breast cancer, these cancers are related to AIDS, which predicted a severe alteration of the immune system at the moment of diagnosis. Most HIV-positive patients with cancer (40/52) received an anticancer treatment. The cost of cancer treatment is often prohibitive in our context. Early detection and management of cancer, as well as the association of an antiretroviral treatment, can make it possible to reduce the duration of a treatment against cancer and affect its indication. 69.23% of the cancers of our sample are usually classified among cancers known as virus-induced cancers. It is proven today that HIV infection is an enabling factor of this type of cancers. Sexual transmission was most often reported in our study (28/52, 53.84%), especially concerning HHV8 and VHB viruses, which are respectively involved in the genesis of Kaposi's disease and primitive liver cancer.

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CHILDHOOD KAPOSI'S SARCOMA IN CAMEROON (CENTRAL AFRICA) PAST, PRESENT, AND FUTURE

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Background: Kaposi's sarcoma is epidemic in countries where human immunodeficiency virus (HIV) is prevalent, with an estimated prevalence of about 10% amongst HIV-infected patients. Prior to the HIV epidemic, Kaposi's sarcoma was already endemic in Cameroon and most common in older men as in some eastern African countries. Childhood Kaposi's sarcoma was rare. The first reported case of Kaposi's sarcoma in a child was described in a monograph by De Amics in 1882. Childhood Kaposi's sarcoma represented 0.57% of the cases of cancers reported in Cameroon by Jensen et al. between 1968 and 1974. In the eastern part of Africa, like in Uganda, Olweny et al. described 12 cases of childhood Kaposi's sarcoma between 1968 and 1974. With the advent of AIDS, childhood Kaposi's sarcoma has become more common, both in western and eastern Africa. Data from central Africa are not available.

Aim: The aim of this study is to show the past, present, and future of childhood Kaposi's sarcoma in a Central African country.

Material and Method: We retrieved the histologically confirmed cases of childhood Kaposi's sarcoma in Cameroon from January 1987 to April 2006.

Results: 42 cases of Kaposi's sarcoma were observed amongst children aged 3 months to 15 years, representing 4% of the total number of Kaposi's sarcoma cases observed during this period. The youngest child and the child's mother were HIV-positive. The male-to-female ratio was 2:1, and there are more females now than in the past. Seven cases of HIV-positive serology were observed in this series of children and their mothers. The most common site of involvement was cervical lymph nodes, but disseminated Kaposi's sarcoma was observed amongst HIV-positive children. Skin and lymph node involvement were observed in 2 cases. Histology showed advanced-stage Kaposi's sarcoma with HHV8 infection. These cases represent only 10% of the total number of Kaposi's sarcoma cases present in the country, as cancer registration is still scarce.

Conclusion: Rare in the past, childhood Kaposi's sarcoma is now common in Cameroon with the advent of AIDS, and if nothing is done, the prevalence will continue to increase.

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AIDS-ASSOCIATED MALIGNANCIES

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We investigated AIDS-related malignant diseases by analyzing data reported by the Republic Center "AIDS" and Republic Cancer Center. During the period from January 1, 2003 to January 6, 2006, 157 AIDS cases were reported, of which 32 patients had malignancies. All 32 AIDS-related malignancies were confirmed histological and/or cytological. The median age was 27 years (range 1–68). The male-to-female ratio was 25:7. The most frequent tumour was non-Hodgkin's lymphoma (NHL) (17 patients, 54.4%). 6 patients had Hodgkin's disease, 2 had malignant lymphoma, 3 had Kaposi's sarcoma, 1 had oesophageal squamous cell carcinoma, 1 had laryngeal carcinoma, 1 had hepatocellular carcinoma, and 1 had cutaneous melanoma.

In 17 cases of AIDS-associated non-Hodgkin's lymphoma, 12 patients were diffuse large cell lymphoma, 2 were Burkitt's lymphoma, 2 were poorly differentiated large cell lymphoma, and 1 was immunoblastic lymphoma. 10 patients with AIDS-related NHL presented with stage IV and 9 patients with extra nodal involvement. Median survival was five months, and the cause of death was most often progressive lymphoma and/or opportunist infection.

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CAUSES OF DEATH IN THE HAART ERA: PERSPECTIVES FROM A COMBINED HIV AND HEMATOLOGY/ONCOLOGY PRIMARY CARE PRACTICE

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Background: Over the past decade, HIV patient mortality has fallen dramatically, while the relative proportion of deaths from non-AIDS–defining illness (ADI) has increased. Heightened mortality in the HAART era is linked to substance abuse, mental illness, and poor treatment adherence. While large cohort studies reveal a changing pattern of mortality in the HAART era, they may overlook the details of intimate doctor-to-patient medical care in defining the causes of death.

Objective: To define the causes of death and to determine the factors heralding death among HIV-infected patients in a combined HIV and hematology/oncology practice that includes 600 seropositive individuals.

Methods: We conducted a retrospective review of medical records of all patients who died between the years 1996 and 2006. Abstracted data included patient demographics, causes of death, co-morbidities, treatment adherence, CDC AIDS classification, and relevant laboratory data. Chi-square was used for statistical analysis.

Results: Of 60 patient deaths, 57 (95%) patients were male, 16 (27%) were IV drug users (IDU), and 50% had significant mental illness. 44 (73%) patients had a C2/C3 CDC AIDS designation. The median time between HIV diagnosis and death was 11 years (range, 0–22). There were 33 (55%) patients with poor/moderate adherence. They were most likely to abuse drugs ($p = .0003$), to have mental illness ($p = .004$), and to die of an ADI ($p = .016$). The cohort's initial median HIV viral load (VL) was 33,000 c/ml (range, < 50 – > 750,000), and its initial median CD4+ count was 170 cells/µL (range, 2–800). The median HIV VL preceding death was 6,880 c/ml (range, < 50 – > 700,000), and the median CD4+ count preceding death was 79 cells/µL (range, 1–952). Among the 60 patients, 39 (65%) died from non-ADI, 18 (30%) died from ADI, and 3 (5%) died from both non-ADI and ADI. Among those in the non-ADI group, 15 (38%) died from malignancy, 8 (21%) from liver failure, 7 (18%) from pneumonia, and 9 (23%) from miscellaneous causes. Among those with ADI, 6 (29%) patients died from wasting, 5 (24%) from non-Hodgkin's lymphoma (NHL), 3 (14%) from progressive multi-focal leukoencephalopathy (PML), and 7 (33%) from miscellaneous causes. 11 of 60 patients (18%) died despite a non-detectable HIV VL. Their initial median CD4+ count was 125 cells/µL (range, 16–475), and their median pre-death CD4+ count was 216 cells/µL (range, 16–952). All of these patients died from non-ADI, malignancy being most common and responsible for 5 (45%) deaths in this group.

Conclusions: Non-ADI was the most common cause of death in the HAART era (malignancy > liver failure > pneumonia). Those with ADI most commonly died from wasting, NHL, and PML. Patients who at death had a non-detectable HIV VL invariably died from non-ADI. This cohort of patients had an initial CD4+ count lower than the recommended treatment threshold, perhaps reflecting late presentation or delay in treatment. Patients with the lowest adherence scores, particularly those with drug use and mental illness, predominate in this cohort, highlighting the importance of early testing, education, and psychosocial intervention.

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THE RISK OF LUNG CANCER AND OF LIVER CANCER IN HIV-POSITIVE INDIVIDUALS AND IN ORGAN TRANSPLANT RECIPIENTS IN SOUTHERN EUROPE

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For several cancer types, the role of immunosuppression is difficult to disentangle from the effect of baseline risk factors that strongly vary according to individual lifestyle and geographic area. Liver and lung cancers are among these cancers, and they have been inconsistently associated with an elevated risk among HIV-positive persons or transplant recipients. This study is part of a multicentre investigation aimed at better elucidating the link between cancer and immunosuppression in southern Europe. A multi-cohort longitudinal study was conducted in Italy and France, including 2,002 Italian HIV seroconverters, 6,072 French HIV-infected subjects, and 2,878 Italian solid organ transplant recipients (1,829 kidney, 682 heart, 325 liver, and 42 lung transplant recipients). Sex- and age-standardized incidence ratios (SIR) and 95% confidence intervals (CI) were computed to quantify the risk of lung cancer and of liver cancer in these people, as compared to the Italian and French general populations. The SIR for liver cancer was 9.4 (95% CI: 4.7–16.9) in HIV-infected persons and 4.1 in transplant recipients overall. The risk for liver cancer was not influenced by HAART treatment, whereas it was higher in recipients of liver transplants (27.1, 95% CI: 5.6–79.1) than among recipients of kidney (SIR = 3.9) or heart (SIR = 2.9) transplants. No significant differences emerged in SIR for liver cancer according to age, gender, or duration of immunosuppression. A nearly 2-fold significantly increased risk of lung cancer was noted in both HIV-positive persons (SIR = 1.7) and transplant recipients (SIR = 1.6). Subgroup analyses showed that the SIR for lung cancer was not related to HAART treatment, age, or sex of HIV-infected persons. Conversely, in transplant recipients, it was significantly elevated (SIR = 2.8, 95% CI: 1.8–4.1) among recipients of heart transplants. In Italy, infection with HBV or HCV is not an exclusion criteria for organ transplantation, and this fact may explain why an increased risk for liver cancer in transplant recipients has not been described elsewhere. Overall, our findings indicate that HIV-positive persons and transplant recipients have significantly increased SIR for liver cancer and for lung cancer. However, the results are inconclusive with regard to the role of immunosuppression, since the prevalence of the most important risk factors for lung cancer (i.e., cigarette smoking) or liver cancer (i.e., HCV and HBV infections) is likely to be higher in HIV-positive persons and in transplant recipients than in the general population.

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Function:
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How many of the previous conferences have you attended?
(1 through 9)

1. Do you think that the conference promoted any of the following outcomes?
   - Improve the flow of translational research, bedside to bench and bench to bedside. Yes or No
   - Provide an opportunity for networking Yes or No
   - Establish new collaborations Yes or No
   - Start new research projects Yes or No
   - Identify and promote research in Malignancies in HIV/AIDS nationally and internationally Yes or No

Scale: 1 = None or not at all 2 = Very little 3 = Moderately 4 = Considerably 5 = Completely N/A = Not applicable

Rating of Objectives and Program

2. Please rate the attainment of objectives:

a) To provide state-of-the-art information on the epidemiology, pathogenesis, and clinical aspects of malignancies associated with HIV. 1 2 3 4 5 N/A
b) To provide a basic biologic framework upon which to understand the malignancies associated with HIV. 1 2 3 4 5 N/A
c) To provide a forum where information can be exchanged, thereby serving to move the field more quickly than might otherwise be possible. 1 2 3 4 5 N/A
d) To provide a means by which new investigators may be drawn into the area of research related to AIDS malignancies. 1 2 3 4 5 N/A
e) To explore the how and why of AIDS-related neoplastic processes and also to determine what the commonalities are among the AIDS-related neoplasias. 1 2 3 4 5 N/A

3. The overall quality of the instructional process was an asset to the conference. 1 2 3 4 5 N/A

4. To what extent did participation in this activity enhance your professional effectiveness? 1 2 3 4 5 N/A

5. How useful did you find the following:
a) The abstracts and program booklet 1 2 3 4 5 N/A
b) The plenary talks 1 2 3 4 5 N/A
c) The short talks 1 2 3 4 5 N/A
d) The poster sessions 1 2 3 4 5 N/A

Please circle your answer.

6. Number of plenary lectures. Too many Just about right Too few
7. Number of oral abstract presentations Too many Just about right Too few
8. Did you like the format of the meeting? Yes No

Comments or recommendations:

Please continue on the next page

9. Was there a topic that was not covered? Yes No

   If yes, what was it?

10. Was there enough time for discussion? Yes No

    Comments or recommendations:

11. Should the conference be held Annually Bi-annually

    Comments or recommendations:

12. Do you have any additional comments or suggestions that would enhance the utility or impact of the Conference?

Please return completed meeting evaluation tool to the table at the Registration Desk

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