12th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI)

April 26-27, 2010
Lister Hill Auditorium
NIH Main Campus

http://oham.cancer.gov/
12th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI)

April 26-27, 2010
Lister Hill Auditorium
NIH Main Campus

http://oham.cancer.gov/
12th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI)

April 26-27, 2010
Lister Hill Auditorium
NIH Main Campus

http://oham.cancer.gov/
Acknowledgements

Program Committee for Scientific Input

NCI Office of Communications and Education for cover art

and

National Institute of Dental and Craniofacial Research for financial support
Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The George Washington University Medical Center and the National Institutes of Health. The George Washington University Medical Center is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement
The George Washington University Medical Center designates this educational activity for a maximum of 5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Policy on Speaker and Provider Disclosure
The George Washington University Medical Center has a disclosure policy whereby everyone in a position to control the content of an educational activity must disclose all relevant financial relationships with commercial interests. In addition, speakers must also disclose any unlabeled/unapproved uses of drugs or devices that they plan to discuss in their presentation(s). Individuals who fail to disclose potential conflicts of interest are disqualified from participation in planning or implementing this CME activity. Potential conflicts of interest are resolved and documented. Detailed disclosure will be made in the activity handout materials.

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

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

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

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

Robert Yarchoan, MD
Dr. Yarchoan disclosed that he has a Material Transfer Agreement with Johnson and Johnson

Geraldina Dominguez, PhD
Nothing to disclose

Robert Yarchoan, MD
Dr. Yarchoan disclosed that he has a Material Transfer Agreement with Johnson and Johnson

Geraldina Dominguez, PhD
Nothing to disclose

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

PROGRAM COMMITTEE*

Richard F. Ambinder, MD, PhD
Nothing to disclose

Leona Ayers, MD
Nothing to disclose

Kishor Bhatia, PhD, FRCPath
Nothing to disclose

John T. Brooks, MD
Nothing to disclose

Corey Casper, MD, MPH
Nothing to disclose

Ethel Cesarman, MD, PhD
Nothing to disclose

Dirk Dittmer, PhD
Nothing to disclose

Robert W. Eisinger, PhD
Nothing to disclose

Eric A. Engels, MD, MPH
Nothing to disclose

Joe Harford, PhD
Nothing to disclose

Rebecca Liddell Huppi, PhD
Nothing to disclose

Elliott D. Kieff, MD, PhD
Nothing to disclose

Alexandra M. Levine, MD, MACP
Dr. Levine disclosed a consulting relationship with Genentech and a speakers bureau relationship with Abbott Laboratories

Richard Little, MD
Nothing to disclose

Douglas Lowy, MD
Dr. Lowy disclosed that he receives royalties via the NIH for an invention that the NIH licenses to Merck and GlaxoSmithKline

Sam Mbulaiteye, MD
Nothing to disclose

Mostafa Nokta, MD, PhD
Nothing to disclose

Joel Palefsky, MD, FRCP(C)
Dr. Palefsky disclosed that he is a consultant, advisory committee member, and independent contractor with Merck.

C. David Pauza, PhD
Nothing to disclose

Elizabeth Read-Connole, PhD
Nothing to disclose

Isaac R. Rodriguez-Chavez, PhD, MS, MHS
Nothing to disclose

Sylvia Silver, DA
Nothing to disclose

Michael J. Silverberg, PhD, MPH
Dr. Silverberg disclosed that he is an independent contractor with Pfizer and Merck.

Joseph Sparano, MD
Nothing to disclose

*The program chairs and committee were tasked with identifying program content and speakers. The course director conducted the meeting with the best interest of the learning needs in mind. Both chairs and all committee members completed disclosure documents. Any potential conflicts that arose were mitigated by either 1) self-recusal, or 2) concurrence by the committee that the content identified was scientifically sound and without bias and that the speakers identified would deliver balanced scientific presentations on raw data and sound evidence and make no commercial recommendations. It has been determined that no conflicts of interest exist in this role.
Denise Whitby, PhD  
Nothing to disclose

Frank Ruscetti, Ph.D.  
Nothing to disclose

T-C Wu, MD, PhD  
Nothing to disclose

Rengaswamy Sankaranarayanan, M.D  
Nothing to disclose

Accredited Faculty

Christopher Buck, Ph.D.  
Nothing to disclose

Don Ganem, M.D.  
Dr. Ganem disclosed a consulting relationship with 3V, Kearny Venture Partners and Novartis. After a review of his presentation it was determined that he will discuss raw data only and make no recommendations.

Clifford Gary, Ph.D.  
Nothing to disclose

Aisha O. Jumaan, Ph.D., M.P.H.  
Nothing to disclose

Ari Melnick, M.D  
Nothing to disclose

Eugene Mutimura, Ph.D.  
Dr. Mutimura will discuss CareHPV which is under development and for investigational use only. He has no financial relationships to disclose

Robert Newton, M.B.B.S., D.Phil., FFPH  
Nothing to disclose

Joel Palefsky, M.D., FRCP(C)  
Dr. Palefsky disclosed that he is a consultant, advisory committee member, and independent contractor with Merck. After a review of his presentation it was determined that he will discuss raw data only and make no recommendations.

Groesbeck P. Parham, M.D  
Nothing to disclose

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

April 26

8:00 a.m. - 8:15 a.m.  Poster Setup (Day 1 Posters)

8:15 a.m. - 8:30 a.m.  Welcome and Plenary Introduction
Robert Yarchoan, M.D.
Office of HIV and AIDS Malignancy
National Cancer Institute, NIH, USA

8:30 a.m. - 9:00 a.m.  HPV Vaccination in HIV-Positive Men and Women—Challenges and Opportunities
Joel Palefsky, M.D., FRCP(C)
University of California, San Francisco, USA

9:00 a.m. - 10:30 a.m.  Session 1: Cervical Cancer Control in Developing Countries
Moderators:  Joe B. Harford, Ph.D.
           National Cancer Institute, NIH, USA
           Joel Palefsky, M.D., FRCP(C)
           University of California, San Francisco, USA

9:00 a.m. - 9:30 a.m.  Cervical Cancer Control in Developing Countries: Impact of HIV Infection
Rengaswamy Sankaranarayanan, M.D.
International Agency for Research on Cancer, France

9:30 a.m. - 10:00 a.m.  Cervical Cancer Screening With Point-of-Care Rapid HPV Testing and Visual Inspection With Acetic Acid in HIV-Positive and HIV-Negative Rwandan Women
Eugene Mutimura, Ph.D.
Women’s Equity in Access to Care and Treatment, Rwanda

10:00 a.m. - 10:15 a.m.  UAB/CIDRZ Cervical Cancer Prevention Program in Zambia
Groesbeck P. Parham, M.D.
University of Alabama at Birmingham, USA

10:15 a.m. - 10:30 a.m.  Factors Impacting Introduction of HPV Vaccination in Low-Resource Settings
Aisha O. Jumaan, Ph.D., M.P.H.
PATH, USA

10:30 a.m. - 10:45 a.m.  Questions and Answers (directed at all speakers)

10:45 a.m. - 11:00 a.m.  Break: Coffee and Poster Viewing
11:00 a.m. - 12:30 p.m.  

Session 2: KSHV Biology  
Moderators: Denise Whitby, Ph.D.  
NCI-Frederick, USA  
Dirk Dittmer, Ph.D.  
The University of North Carolina at Chapel Hill, USA  

11:00 a.m. - 11:30 a.m.  
Infection of Primary Lymphoid Cells by KSHV: Novel Mechanisms of Immune Control of KSHV in the Lymphoid Compartment  
Donald E. Ganem, M.D.  
University of California, San Francisco, USA  

11:30 a.m. - 11:45 a.m.  
Bim Nuclear Translocation and Inactivation by HHV-8 Interferon Regulatory Factor 1  
John Nicholas, Ph.D.  
Johns Hopkins University School of Medicine, USA  

11:45 a.m. - 12 noon  
Hsp90 Is a Viable Therapeutic Target in the Treatment of KSHV-Associated Primary Effusion Lymphoma  
Utthara Nayar, M.S.  
Weill Cornell Medical College, USA  

12 noon - 12:15 p.m.  
Upregulation Angiopoietin-like 4 by Viral G Protein-Coupled Receptor Promotes Angiogenesis and Vascular Permeability in Kaposi’s Sarcoma  
Silvia Montaner, Ph.D., M.P.H.  
University of Maryland, USA  

12:15 p.m. - 12:30 p.m.  
KSHV Regulation of Fibulins in Kaposi’s Sarcoma: Implications for Tumorigenesis  
Donald James Alcendor, Ph.D., M.S.  
Meharry Medical College, USA  

12:30 p.m. - 1:00 p.m.  
Lunch (lunch on your own or pre-bought lunch box)  

1:00 p.m. - 2:00 p.m.  
Poster Viewing (presenters stand by posters)  

2:00 p.m. - 3:30 p.m.  
Session 3: New and Old Viruses—Impact on Chronic Diseases  
Moderators: C. David Pauza, Ph.D.  
Institute of Human Virology, University of Maryland School of Medicine, USA  
Kishor Bhatia, Ph.D., FRCPath  
National Cancer Institute, NIH, USA  

2:00 p.m. - 2:30 p.m.  
Repeated Detection of Infectious Xenotropic Murine Virus-Related Virus (XMRV) in Human Neoplasia and Neuroimmune Diseases  
Frank Ruscetti, Ph.D.  
National Cancer Institute, NIH, USA
2:30 p.m. - 3:00 p.m.  
**Merkel Cell Polyomavirus and Two Novel Polyomaviruses Are Chronically Shed From Human Skin**  
Christopher Buck, Ph.D.  
National Cancer Institute, NIH, USA

3:00 p.m. - 3:15 p.m.  
**HIV-Associated Salivary Gland Disease: A Role for BK Virus**  
Liesl K. Jeffers, Ph.D.  
The University of North Carolina at Chapel Hill, USA

3:15 p.m. - 3:30 p.m.  
**Bacteria-Mediated Reactivation of Gammaherpesviruses**  
Jennifer Webster-Cyriaque, D.D.S., Ph.D.  
The University of North Carolina at Chapel Hill, USA

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

4:00 p.m. - 5:15 p.m.  
**Session 4: Clinical Trials Data in HIV/AIDS-Associated Malignancies**  
Moderators: Alexandra M. Levine, M.D., M.A.C.P.  
City of Hope National Medical Center, USA

- Richard F. Little, M.D.  
National Cancer Institute, NIH, USA

4:00 p.m. - 4:15 p.m.  
**Phase II AIDS Malignancy Consortium (AMC) Trial of Imatinib in AIDS-Associated Kaposi’s Sarcoma**  
Henry B. Koon, M.D.  
Case Western Reserve University, USA

4:15 p.m. - 4:30 p.m.  
**Rituximab Combined With Liposomal Doxorubicin in HIV-Infected Patients With Severe Kaposi Sarcoma-Associated Herpes Virus-Associated Multicentric Castleman Disease**  
Thomas Uldrick, M.D., M.S.  
National Cancer Institute, NIH, USA

4:30 p.m. - 4:45 p.m.  
**The KAART Trial: A Randomized Controlled Trial of HAART Compared to the Combination of HAART and Chemotherapy in Treatment-Naïve Patients With HIV-Associated Kaposi Sarcoma in KwaZulu-Natal, South Africa**  
Thomas Uldrick, M.D., M.S.  
National Cancer Institute, NIH, USA

4:45 p.m. - 5:00 p.m.  
**Distinct Profiles of Antibodies to Kaposi Sarcoma-Associated Herpesvirus Antigens in Patients With Kaposi Sarcoma, Multicentric Castleman Disease, and Primary Effusion Lymphoma**  
Peter D. Burbelo, Ph.D., M.A.  
National Institute of Dental and Craniofacial Research, NIH, USA
5:00 p.m. - 5:15 p.m.  

**Pooled Analysis of AIDS-Malignancy Consortium Trials Evaluating Rituximab Plus Either CHOP or Infusional EPOCH Chemotherapy in HIV-Associated Non-Hodgkin’s Lymphoma**  
Stefan K. Barta, M.D.  
Montefiore Medical Center, Einstein Cancer Center, USA

5:15 p.m.  

**End of Day One**

---

**April 27**

8:00 a.m. - 8:15 a.m.  
**Poster Setup (Day 2 Posters)**

8:15 a.m. - 8:25 a.m.  
**Opening Comments**  
Geraldina Dominguez, Ph.D.  
National Cancer Institute, NIH, USA

8:25 a.m. - 8:30 a.m.  
**Plenary Introduction**  
Eric A. Engels, M.D., M.P.H.  
National Cancer Institute, NIH, USA

8:30 a.m. - 9:00 a.m.  
**Epidemiology of HIV-Associated Cancers: New Findings From the Long-Term Followup of Cohorts on HAART**  
Gary Clifford, Ph.D.  
International Agency for Research on Cancer, France

9:00 a.m. - 10:00 a.m.  
**Session 5: Epidemiology of HPV-Associated Cancers**  
Moderators: John Brooks, M.D.  
Centers for Disease Control and Prevention, USA  
Eric Engels, M.D., M.P.H.  
National Cancer Institute, NIH, USA

9:00 a.m. - 9:15 a.m.  
**Cervical Cancer Epidemiology Among HIV-Infected Women in North America**  
Gypsyamber D’Souza, Ph.D.  
Johns Hopkins Bloomberg School of Public Health, USA

9:15 a.m. - 9:30 a.m.  
**Progression of Cervical Neoplasia in HIV-Seropositive Women With and Without Antiretroviral Therapy in Johannesburg, South Africa**  
Cynthia S. Firnhaber  
Right to Care, USA

9:30 a.m. - 9:45 a.m.  
**Persistence of Anal Squamous Intraepithelial Lesions and Anal HPV Infection in HIV-Infected Patients Despite Immune Restoration Under cART**  
Christophe Antoine Piketty, M.D., Ph.D.  
Georges-Pompidou Hospital, Paris, France
9:45 a.m. - 10:00 a.m.  
*Risk of Anal Cancer in HIV-Infected Patients and HIV-Uninfected Controls in North America*  
Michael J. Silverberg, Ph.D., M.P.H.  
Kaiser Permanente Northern California, USA

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

10:30 a.m. - 11:00 a.m.  
**Plenary Introduction**  
Sam M. Mbulaiteye, M.D.  
National Cancer Institute, NIH, USA

**HIV and Cancer in Children**  
Robert Newton, D.Phil., M.B.B.S., FFPH  
University of York, United Kingdom

11:00 a.m. - 12 noon  
**Session 6: International Partnerships**  
Moderators: Corey Casper, M.D., M.P.H.  
Fred Hutchinson Cancer Research Center, USA

Sam M. Mbulaiteye, M.D.  
National Cancer Institute, NIH, USA

11:00 a.m. - 11:15 a.m.  
**Integrative Proteomics and Genomics Supports a Role for Interferon Gamma in the Pathogenesis of Kaposi Sarcoma and Finds Multiple Candidate Diagnostic Proteins for Early Detection or Prevention**  
Lynn M. Amon, Ph.D.  
Fred Hutchinson Cancer Research Center, USA

11:15 a.m. - 11:30 a.m.  
**Malignant Lymphoma Incidence and HIV-Related Lymphoma Subtypes in the Western Cape of South Africa, 2002-2009**  
Leona W. Ayers, M.D.  
Ohio State University, USA

11:30 a.m. - 11:45 a.m.  
**HPV Genotype and EGFR Activation in Conjunctival Carcinoma Among HIV Patients in East Africa**  
Scot C. Remick, M.D.  
West Virginia University, USA

11:45 a.m. - 12 noon  
**Visual Inspection and HPV-Based Cervical Cancer Screening for HIV-Infected Women in Pune, India**  
Vikrant Sahasrabuddhe, Dr.P.H., M.B.B.S.  
Vanderbilt University, USA

12 noon - 12:30 p.m.  
Lunch (lunch on your own or pre-bought lunch box)

12:30 p.m. - 1:30 p.m.  
Poster Viewing (presenters stand by posters)
Session 7: EBV Biology and Lymphomagenesis
Moderators: Elliott D. Kieff, M.D., Ph.D.
Harvard Medical School, USA

Ethel Cesarman, M.D., Ph.D.
Weill Cornell Medical College, USA

1:30 p.m. - 2:00 p.m.  
**Epigenetic and Transcriptional Programming and Therapy in B Cell Lymphomas**  
Ari Melnick, M.D.
Weill Cornell Medical College, USA

2:00 p.m. - 2:15 p.m.  
**An ATM/Chk2-Mediated DNA Damage Responsive Signaling Pathway Suppresses Epstein-Barr Virus Transformation of Primary Human B Cells**  
Micah Luftig, Ph.D.
Duke University School of Medicine, USA

2:15 p.m. - 2:30 p.m.  
**TNFAIP3(A20) Genetic Alterations in AIDS-Related Lymphomas**  
Lisa Giulino, M.D.
New York Presbyterian Hospital, Weill Cornell Medical College, USA

2:30 p.m. - 2:45 p.m.  
**C/EBPbeta Mediates Bortezomib-Induced EBV and KSHV Lytic Gene Expression**  
Courtney O’Farrell
Johns Hopkins University School of Medicine, USA

2:45 p.m. - 3:00 p.m.  
**Elevated Serum Levels of CXCL13 Precede HIV-Associated Non-Hodgkin’s Lymphoma**  
Shehnaz K. Hussain, Ph.D.
University of California, Los Angeles, USA

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

3:30 p.m. - 4:45 p.m.  
Session 8: Cancers in the Era of Combination Antiretroviral Therapy
Moderators: Richard F. Ambinder, M.D., Ph.D.
Johns Hopkins University School of Medicine, USA

Joseph Sparano, M.D.
Albert Einstein College of Medicine, USA

3:30 p.m. - 3:45 p.m.  
**Decreased Risk of Breast Cancer Associated With X4-Tropic HIV**  
Nancy A. Hessol, M.S.P.H.
University of California, San Francisco, USA

3:45 p.m. - 4:00 p.m.  
**HIV-Related Hodgkin Lymphoma in the Era of Combination Antiretroviral Therapy: Incidence, Outcome, and Evolution of CD4+ T Cell Lymphocytes**  
Matthias Egger, M.D., M.S., FFPHM DTM & H
Institute of Social and Preventive Medicine, University of Bern, Switzerland
4:00 p.m. - 4:15 p.m.  **Risk of HIV-Associated Hodgkin Lymphoma During the First Months After Initiation of Combination Antiretroviral Therapy**
Emilie Lanoy, M.D.
INSERM, France

4:15 p.m. - 4:30 p.m.  **Non-AIDS-Defining Cancer Mortality Among People With AIDS in Italy**
Antonella Zucchetto, Sc.D.
National Cancer Institute Centro di Riferimento Oncologico, Italy

4:30 p.m. - 4:45 p.m.  **Phase IIA Trial of 1% Topical Cidofovir for Treatment of High-Grade Perianal Squamous Intraepithelial Neoplasia in HIV-Infected Men and Women (AMC046)**
Elizabeth A. Stier, M.D.
Boston Medical Center, USA

4:45 p.m.  **Meeting Adjourned**
Program Committee

Program Co-Chairs

Robert Yarchoan, M.D.
Director
Office of HIV and AIDS Malignancy
Chief
HIV and AIDS Malignancy Branch
Center for Cancer Research
National Cancer Institute
Bethesda, Maryland
yarchoan@helix.nih.gov

Geraldina Dominguez, Ph.D.
Program Director
Office of HIV and AIDS Malignancy
National Cancer Institute
Bethesda, Maryland
domingug@mail.nih.gov

Program Committee

Kishor Bhatia, Ph.D., MRCPath
Director
AIDS Malignancy Program
Office of HIV and AIDS Malignancy
National Cancer Institute
Bethesda, Maryland
bhatiak@mail.nih.gov

Joe Harford, Ph.D.
Director
Office of International Affairs
National Cancer Institute
Bethesda, Maryland
harfordj@mail.nih.gov

Elliott D. Kieff, M.D., Ph.D.
Harriet Ryan Albee Professor of Microbiology and Molecular Genetics
Co-Director, Channing Laboratory
Harvard Medical School
Boston, Massachusetts
ekieff@rics.bwh.harvard.edu

Richard F. Ambinder, M.D., Ph.D.
Director, Division of Hematologic Malignancies
Professor of Oncology
Johns Hopkins University School of Medicine
Baltimore, Maryland
ambinri@jhmi.edu

Alexandra M. Levine, M.D.
Chief Medical Officer
City of Hope National Medical Center
Duarte, California
alevine@coh.org

Douglas Lowy, M.D.
Branch Chief
Laboratory of Cellular Oncology
Center for Cancer Research
National Cancer Institute
Bethesda, Maryland
drl@helix.nih.gov

Sam Mbulaiteye, M.D.
Principal Investigator
Infections and Immunepidemiology Branch
National Cancer Institute
Bethesda, Maryland
mbulaits@mail.nih.gov

Joel Palefsky, M.D., FRCP(C)
Professor
Laboratory Medicine, Medicine, and Stomatology
Director, Clinical Research Center
University of California, San Francisco
San Francisco, California
joelp@medicine.ucsf.edu

Elizabeth Read-Connole, Ph.D.
Program Director
Cancer Etiology Branch
National Cancer Institute
Bethesda, Maryland
bconnole@mail.nih.gov
Denise Whitby, Ph.D.  
Viral Oncology Section  
AIDS and Cancer Virus Program  
SAIC-Frederick  
NCI-Frederick  
Frederick, Maryland  
whitbyd@mail.nih.gov

Corey Casper, M.D., M.P.H.  
Associate Professor of Medicine  
University of Washington  
Assistant Member  
Fred Hutchinson Cancer Research Center  
Seattle, Washington  
casper@fhcrc.org

Richard Little, M.D.  
Senior Investigator  
Clinical Investigations Branch  
National Cancer Institute  
Bethesda, Maryland  
littler@mail.nih.gov

Dirk Dittmer, Ph.D.  
Associate Professor  
University of North Carolina at Chapel Hill  
Chapel Hill, North Carolina  
dirk_dittmer@med.unc.edu

T-C Wu, M.D., Ph.D.  
Departments of Pathology, Oncology, Obstetrics and Gynecology and Molecular Microbiology and Immunology  
Johns Hopkins University School of Medicine  
Baltimore, Maryland  
twu1@jhmi.edu

Robert W. Eisinger, Ph.D.  
Director of Scientific and Program Operations  
Chair  
Therapeutics Coordinating Committee  
Office of AIDS Research  
National Institutes of Health  
Bethesda, Maryland  
be4y@nih.gov

Mostafa Nokta, M.D., Ph.D.  
Director  
AIDS Cancer Clinical Program  
Office of HIV and AIDS Malignancy  
National Cancer Institute  
Bethesda, Maryland  
noktam@mail.nih.gov

Rebecca Lidell Huppi, Ph.D.  
Program Director  
Office of HIV and AIDS Malignancy  
National Cancer Institute  
Bethesda, Maryland  
liddellr@exchange.nih.gov

Michael J. Silverberg, Ph.D., M.P.H.  
Research Scientist  
Division of Research  
Kaiser Permanente  
Oakland, California  
Michael.J.Silverberg@kp.org

Eric Engels, M.D., M.P.H.  
Senior Investigator  
Division of Cancer Epidemiology and Genetics  
National Cancer Institute  
Bethesda, Maryland  
engelse@exchange.nih.gov

Joseph Sparano, M.D.  
Professor of Medicine and Women’s Health  
Montefiore-Einstein Cancer Center  
Bronx, New York  
jspar@montefiore.org

C. David Pauza, Ph.D.  
Professor and Assistant Director  
Institute of Human Virology  
University of Maryland School of Medicine  
Baltimore, Maryland  
cdpauza@ihv.umaryland.edu

Ethel Cesarman, M.D., Ph.D.  
Professor  
Pathology and Laboratory Medicine  
Weill Cornell Medical College  
New York, New York  
ecesarman@med.cornell.edu
Leona Ayers, M.D.
AIDS and Cancer Specimen Resource
Professor Pathology
College of Medicine
The Ohio State University
Columbus, Ohio
ayers.1@osu.edu

John Brooks, Ph.D.
Leader
Clinical Epidemiology Team
Division of HIV and AIDS Prevention
Centers for Disease Control and Prevention
Atlanta, Georgia
zud4@cdc.gov

Isaac R. Rodriguez-Chavez, Ph.D., M.S., M.H.S.
Director
AIDS and Immunosuppression Program, IBIDB, DER
National Institute of Dental and Craniofacial Research
Bethesda, Maryland
isaac@nidcr.nih.gov

Sylvia Silver, D.A.
Professor of Pathology
Associate Dean for Health Sciences
The George Washington University
School of Medicine and Health Sciences
Washington, D.C.
ssilver@gwu.edu
A Resource for Your Research

AIDS and Cancer Specimen Resource

Examples of Specimens:
- Kaposi’s sarcoma
- Non-Hodgkin’s lymphoma
- Hodgkin’s lymphoma
- Genito-urinary system dysplasia
- Non-HIV malignancy controls

The ACSR Offers Tissue Micro-Arrays (TMA)
- Hundreds of tissue samples can be assembled into a single TMA
- HIV infected tissues and related malignancies along with non-HIV related controls
- TMA’s available include Kaposi’s sarcoma and AIDS lymphoma

Specimens:
- Kaposi’s Sarcoma
- Non-Hodgkin’s lymphoma
- Hodgkin’s lymphoma
- Genito-urinary system dysplasia
- Non-HIV malignancy controls

Frontal cortex with HIV-encephalitis stained with HIV p24
Large cell lymphoma stained with CD68 (blue) and PCNA (brown)
Annotated HIV+ DLBCL TMA

http://acsr.ucsf.edu

For more information, contact either:
Debra Leiolani Garcia
ACSR Central Operations and Data Coordinating Center
415-206-5268
dgarcia@acsr.ucsf.edu

or
Rebecca L. Huppi, PhD
NCI/Office of HIV & AIDS Maligna
301-496-4995
liddellr@exchange.nih.gov

Sponsored by the National Cancer Institute
Plenary Speaker Abstracts
Background
HIV-positive men and women are at increased risk of anogenital human papillomavirus (HPV) infection, intraepithelial neoplasia, and invasive cancer. Prophylactic vaccination of young women with virus-like particle-based vaccines has been shown to be safe and effective to prevent HPV infection and HPV-associated disease due to vaccine HPV types among women naive to HPV vaccine types pre-vaccination. HPV vaccination therefore has the potential to prevent HPV-associated disease in high-risk HIV-positive individuals. Issues related to vaccinating this population include safety and efficacy of HPV vaccination among men in general; safety and immunogenicity of vaccination in HIV-positive men and women; and the degree to which exposure to HPV prior to vaccination will affect vaccine efficacy.

Materials and methods
Merck 020 was performed to study the safety and efficacy of quadrivalent HPV vaccine (qHPV, HPV 6, 11, 16, and 18) in healthy HIV-negative males aged 16-26 years. The study included 3463 heterosexual men (HM) and 602 men who have sex with men (MSM) with a history of no more than 5 lifetime sexual partners. Prevention of external genital infection and associated lesions was studied in the entire population. Prevention of anal HPV infection and HPV-associated anal lesions was studied in MSM only. AMC 052 was performed to study the safety and immunogenicity of qHPV in HIV-positive MSM.

Results
Data from Merck 020 show that qHPV is effective to prevent persistent external genital HPV 6/11/16/18 infection and external genital condyloma acuminatum in men. qHPV was also effective to prevent persistent anal HPV 6/11/16/18 infection in MSM, anal condyloma acuminatum, and high-grade anal intraepithelial neoplasia (AIN 2+). There were no vaccine-related serious adverse events. AMC 052 showed that qHPV was safe in HIV-positive MSM. More than half were naive to each of the vaccine HPV types individually at baseline, and nearly all seroconverted in response to vaccination. Titers were relatively low in Merck 020 and AMC 052 among MSM, regardless of HIV status, when compared with HM in Merck 020. The relatively low titers among MSM in Merck 020 did not adversely affect vaccine efficacy in this group.

Conclusions
qHPV is effective to prevent anogenital HPV infection and HPV-associated lesions in HIV-negative males. HPV vaccination appears to be safe and immunogenic in HIV-positive individuals. Additional safety studies are in progress in HIV-positive women. Efficacy studies are planned to determine the clinical utility of HPV vaccination in the HIV-positive population.

Acknowledgements
AMC 052 and Merck 020 study teams.
Cervical cancer is a major public health problem in developing countries of sub-Saharan Africa, South and Southeast Asia, and Latin America, despite its high preventability by screening and human papillomavirus (HPV) vaccination. Four-fifths of the estimated annual global burden of 500,000 new cases and 280,000 deaths occur in these countries, due to lack of effective screening programs. It is the leading cause of cancer death among women in these countries. Persistent infection with one of the high-risk types of oncogenic HPV infection has been established as a necessary cause of cervical cancer, exposures related to sexual and reproductive behavior such as increasing parity, early age at sexual intercourse, multiple sexual partners, and hormonal contraceptives, as well as smoking, are other established risk factors. Women infected with human immunodeficiency virus (HIV) have an increased risk of cervical cancer precursor lesions such as high-grade cervical intraepithelial neoplasia (CIN 2 and 3 lesions) and cervical cancer. HIV-positive women have higher prevalence of HPV infection, repeated HPV infection and more persistent infection due to immuno-suppression, leading to higher frequencies of cervical neoplasia. The association between HIV infection and invasive cervical cancer (ICC) is complex. Whereas studies in Europe and the United States have shown a 5- to 8-fold increased risk of ICC among HIV-infected women or women suffering from acquired immunodeficiency syndrome (AIDS), such evidence is limited in Africa, where treatment for HIV is limited and the lifespan of HIV-positive women is too short for cervical cancer to develop. Although a high risk of CIN and cervical cancer in HIV-positive women has been demonstrated in Senegal, where a relatively high prevalence of HIV-2 infection occurs, a study from South Africa showed no increased risk of cervical cancer associated with HIV and there have not been significantly higher incidence rates associated with HIV epidemic in developing countries, particularly sub-Saharan Africa. This may be due to the natural progression of HIV disease to opportunistic infections leading to premature death before the onset of ICC in the absence of widespread use of potent antiretroviral treatment. The control of cervical neoplasia among HIV-infected women will be discussed in the context that more than half of the 16 million HIV-infected women in the world are living in sub-Saharan Africa, where they have poor access to both screening and antiretroviral therapy.

Control of cervical neoplasia among HIV-positive women is challenging. The risk of cervical neoplasia has remained high and stable during the last decade in HIV-infected women, and incidence did not decrease with improving CD4 cell counts in women receiving antiretroviral therapy. Although the prevalence of HPV 16 and 18, the two vaccine preventable types, among women with cervical cancer does not differ among HIV-positive and -negative women, the current HPV vaccines will have no impact in HIV-infected women as they have no therapeutic effect. Whether cervical cancer screening is as efficient among HIV-infected women as in the general population is still being debated. The use of HPV DNA tests may be less specific in immuno-compromised women and might not be as efficient as in the general population. No universally accepted consensus exists for primary screening methods, screening intervals, thresholds for proceeding to diagnosis, and treatment or method of treatment. Screening seems to be less effective in preventing cervical cancer among HIV-infected women due to high risk of HPV infection, repeated HPV infection, and high recurrence rates following treatment of CIN, due to immunosuppression. Available evidence on the outcome of treatment for CIN among HIV-infected women is limited, but suggests that standard treatments for CIN are associated with high rates recurrence, despite multiple treatments, ranging from 20% to 70% in HIV-positive women; however, most treatment failures are low-grade CIN. That most HIV-infected women in developing countries have no access to screening and treatment, and the currently available screening approaches are less effective, underscores the importance of searching and establishing optimal screening and treatment approaches to control cervical cancer among them.

Patrick Mulindwa¹, Xiaotao Cai², Philip Castle³, Qiu hu Shi⁴, Eugene Mutimura⁵, Paul Eder⁶, Joseph Vyankadondera¹, Laura Bell⁶, Howard Strickler⁷, Robert Burk², Kathryn Anastos⁵,⁷,⁸

¹National University of Rwanda, Faculty of Medicine, Department of Obstetrics and Gynecology, Kigali, Rwanda
²Data Solutions LLC, Bronx, NY, USA
³National Cancer Institute, Bethesda, MD, USA
⁴New York Medical College, Valhalla, NY, USA
⁵Women’s Equity in Access to Care and Treatment, Kigali, Rwanda
⁶Qiagen, Rockville, MD, USA
⁷Albert Einstein College of Medicine, Bronx, NY, USA
⁸Montefiore Medical Center Bronx, NY, USA

Background

Human papillomavirus (HPV), the cause of cervical cancer, is more common in HIV+ than in HIV- women. Like most sub-Saharan African countries, Rwanda has a dual burden of HIV infection and high cervical cancer rates. We determined the prevalence of high-risk (HR) HPV infection and visible cervical abnormalities in HIV+ and -negative women in urban and periurban Rwanda.

Methods

1303 HIV+ and 1713 HIV- Rwandan women were screened for cervical disease with point-of-care HR-HPV testing (CareHPV, Qiagen) and visual inspection with acetic acid (VIA) in a screen-and-treat protocol.

Results

HIV-positive women were more likely than HIV-negative women to test positive for HR-HPV (31.7% vs. 9.1%, p<0.0001) and to test positive by VIA (11.4% vs. 8.1%, p=0.003). Among HIV+ women, CD4 count was associated with testing HR-HPV positive but not VIA+ (figure). In multivariate analyses, factors significantly associated with HR-HPV detection were age (P<0.0001), number of lifetime sex partners (<0.0001), and HIV status (p<0.0001, OR 4.05, confidence interval (CI), 3.18, 5.14). Only age and HPV infection were associated with VIA positivity, and HIV-infection did not predict VIA+ results (OR 1.04, CI 0.77, 1.43, p=0.51). Antiretroviral therapy, used by 77% of the HIV+ women, was not associated with testing HR-HPV or VIA positive.

Conclusion

In this study of 3016 Rwandan women previously unscreened for cervical abnormalities, HR-HPV was associated with HIV infection and CD4 count, but VIA was not. Further study with clinically relevant outcomes is necessary to determine whether VIA is an adequate screening methodology for HIV+ women.

Figure 1. High-Risk HPV and VIA findings by CD4 count and HIV-serostatus.
P4. UAB/CIDRZ Cervical Cancer Prevention Program in Zambia

Groesbeck P. Parham1,2,3, Mulindi H. Mwanahamuntu2,3, Vikrant V. Sahasrabuddhe4, Kristin E. King5, Krista S. Pfaendler6, Victor Mudenda7, Gracilia Mkumba2,3, Benjamin Chi1,2, Sharon Kapambwe2,3, Carla Chibwesha1,2, Michael L. Hicks7, Jeffrey S.A. Stringer1,2

1University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA
2Center for Infectious Disease Research in Zambia, Lusaka, Zambia
3University Teaching Hospital, Lusaka, Zambia
4Vanderbilt University School of Medicine, Nashville, TN, USA
5University of Michigan, Ann Arbor, MI, USA
6University of Cincinnati, Cincinnati, OH, USA
7Michigan Cancer Institute, Pontiac, MI, USA

Background
Women persistently infected with oncogenic HPV genotypes, severely immunosuppressed from HIV, and without access to effective cervical cancer prevention services are at high risk for developing cervical cancer precursors that, if left untreated, will likely progress to invasive cervical cancer. Such are the circumstances that characterize large numbers of HIV-seropositive women residing in low-income nations whose lifespans are being prolonged because of expanded access to modern HIV care and treatment.

Methods
We implemented nurse-led screen-and-treat services at 15 public-sector sites (11 urban, 4 rural) in Zambia, co-located with ART programs. Nurses evaluated patients using visual inspection with acetic acid (VIA) and digital cervicography. Depending on the surface morphology of acetowhite lesions, patients with VIA positive tests were offered same-day cryotherapy or referred to the University Teaching Hospital for further evaluation. We estimated program effectiveness by modeling the total number of cervical cancer deaths prevented among the screened population of HIV-seropositive women as a result of our early detection and treatment interventions.

Results
Between January 2006 and December 2008, we screened 21,010 women, of whom 6,572 (31%) were HIV seropositive. In HIV-seropositive women, VIA tests were positive in 3,523 (54%), 2,062 were eligible and offered same-day cryotherapy, and 1,603 underwent the procedure. An additional 1,461 were referred for further evaluation and pathology was available on 715. Clinical, pathologic, and surgical staging of the 715 women revealed 151 with normal/benign histology, 214 with low-grade cervical intraepithelial neoplasia (CIN 1), 235 with high-grade cervical intraepithelial neoplasia (CIN 2/3), and 115 invasive cancers. 69% of the invasive cancers were early stage (stage 1A-1B), and 78% of those were Stage 1A (microinvasive). Using published estimates of disease progression and cure/prevention rates, and assuming all women receive treatment, we estimate that our program prevented 203 deaths from invasive cervical cancer cases among the 6,572 HIV-infected women screened. Overall, one cancer death was prevented for every 32 HIV-seropositive women screened.

Conclusions
A nurse-led, service-oriented VIA-based cervical cancer screening program linked to same-day cryotherapy and referral for excisional biopsy has the potential to prevent deaths from cervical cancer in HIV-seropositive women. Although we face programmatic challenges, low-cost screening saves many lives and should be considered for implementation elsewhere.
Factors Impacting Introduction of HPV Vaccination in Low-Resource Settings

A. Jumaan¹, N. Le², E. Mugisha³, I. Ramos⁴, A. Bingham¹, C. Levin¹, D.S. Lamontagne¹
¹PATH, HPV Vaccines: Evidence for Impact project, Seattle, WA, USA
²PATH, HPV Vaccines: Evidence for Impact project, Hanoi, Vietnam
³PATH, HPV Vaccines: Evidence for Impact project, Kampala, Uganda
⁴PATH, HPV Vaccines: Evidence for Impact project, Lima, Peru

Introduction
HPV vaccines against HPV types 16 and 18, which are associated with 70 percent of cervical cancer cases, have the potential to reduce cervical cancer if they are used widely among sexually naive girls, especially in developing countries where the disease burden is greatest. However, there are challenges in implementing HPV vaccination within current EPI programs in these countries, including lack of vaccine delivery mechanisms for young adolescent girls, cost associated with and feasibility of delivering the vaccines, and acceptance of vaccines that target sexually transmitted infections. The PATH HPV Vaccines: Evidence for Impact project implemented HPV vaccination in selected areas of three low- and middle-resource countries.

Objective
Evaluate HPV vaccination coverage, feasibility, acceptability, and implementation costs of different delivery strategies.

Methods
Sociocultural research and health system assessment results guided the design of HPV vaccine delivery strategies. Evaluation studies included a modified WHO two-stage cluster survey for coverage; focus groups and key informant interviews for acceptability; vaccination observation, interviews, and focus group discussions for feasibility; and micro-costing using ingredients approach and supplementary expenditure records to estimate costs.

Results
Vaccine delivery included school and clinic-based strategies with HPV vaccines delivered vertically or in combination with other health services. Vaccine coverage varied by region and strategy and ranged from 53 percent to 94 percent. Acceptability was high due to government and EPI support; community trust in vaccines, and comprehensive sensitization and mobilization. Delivery was feasible due to collaboration and planning between health centers and schools for coordinated implementation, and strengthening of cold chain systems. Implementation costs varied by country and strategy used in each country.

Conclusion
Our data suggest that high HPV vaccination coverage can be achieved. Acceptance of the vaccine was also high and the delivery strategies were feasible. Implementation costs are within the range of other vaccination campaign strategies.
Kaposi’s sarcoma (KS)-associated herpesvirus (KSHV) is a B-lymphotropic herpesvirus whose primary site of replication is the oropharynx, reflecting infection of tonsillar B cells (and possibly oral epithelium). Primary tonsillar explants are infectable in vitro. Although viral entry into both T and B cells is observed in such cultures, T cells do not support either spontaneous or induced lytic replication, while B cells spontaneously produce substantial amounts of infectious virus. When mixed cultures of primary T and B cells are exposed to KSHV, little spontaneous virus production is observed, but virus production can be enhanced by (1) removal of T cells from the mix or (2) treatment of the mixed culture with cyclosporine A. Adding back T cells to purified infected B cells efficiently suppresses KSHV production, and examination of isolated T cell subsets indicates this activity is attributable primarily to CD4-positive T cells. The suppressive activity (1) requires T cell activation, but not prior exposure to KSHV antigen, (2) requires direct cell-cell contact, (3) is not MHC-restricted, and (4) does not result in killing of the target cell. We propose that oropharyngeal T cells activated by a variety of stimuli can recognize ligands on latently infected target cells, leading to signaling events that downregulate lytic reactivation, most likely by promoting latent infection.
P7. Repeated Detection of Infectious Xenotropic Murine Virus-Related Virus (XMRV) in Human Neoplasia and Neuroimmune Diseases

Francis Ruscetti1, Vincent Lombardi2, Max Pfost2, Kathryn Hagen2, Judy Mikovits2
1Laboratory of Experimental Immunology, NCI-Frederick, Frederick, MD, USA
2Whittemore-Peterson Institute, University of Nevada, Reno, NV, USA

Background
In 2006, sequences of a novel human retrovirus, XMRV, were identified and reported to be associated with a subset of hereditary prostate cancer. Although the public health implications of this finding were not immediately clear, two recent papers show XMRV is clearly a health concern. One clearly shows that XMRV expression in the proliferating prostate stroma and epithelium of prostate cancer patients [1]. The second describes the detection of XMRV in about two-thirds of patients diagnosed with chronic fatigue syndrome [2]. We will present data that in these and other neuroimmune diseases and cancers, the host mounts a humoral response to XMRV and infected patients are viremic.

Methods
A combination of classical retroviral methods, including RT-PCR, full-length genomic sequencing, immunoblotting of viral expression in activated PBMC, passage of infectious virus in plasma and PBMC to indicator cell lines, and presence of antibodies to XMRV in plasma, allowed XMRV detection in more than 75% of the CFS patients studied. Since then, several publications in Europe using DNA-PCR of blood products failed to detect XMRV sequences in patients with either disease and have created considerable controversy. Reliable methods for the biological and molecular amplification to detect XMRV in unstimulated blood cells and plasma have been developed. Some DNA-PCR negative patient blood samples represent false negatives and molecular analysis using DNA from unstimulated blood cells is not yet sufficient for XMRV identification.

Results
In mice, viruses related to XMRV cause B-cell lymphoma usually by insertional mutagenesis activating a cellular oncogene as well as causing chronic neurological diseases. We will present a case of development of such B cell lymphoma in CFS patients. XMRV-infected individuals with both neuroimmune disease and cancer develop an immune response to XMRV. The isolation of infectious XMRV from prostate cancer patients will be shown for the first time. Pathogenic consequences of this infection will be discussed.

Conclusion
XMRV, a retrovirus of unknown pathogenic potential is infectious in humans.

References
Merkel Cell Polyomavirus and Two Novel Polyomaviruses Are Chronically Shed From Human Skin

Rachel Schowalter, Katie Pumphrey, Adam Moyer, Diana Pastrana, Christopher Buck
Tumor Virus Molecular Biology Section, Laboratory of Cellular Oncology, National Cancer Institute, NIH, Bethesda, MD, USA

Background

In the nearly four decades since the human polyomaviruses BKV and JCV were discovered, there have been conflicting reports concerning their possible associations with various forms of human cancer. Although both viruses can cause various forms of cancer in animal model systems, investigation of their possible association with human cancers has been complicated by the fact that nearly all humans harbor chronic kidney infections with one or both viruses. In contrast to BKV and JCV, it is increasingly clear that the recently discovered Merkel cell polyomavirus (MCV) plays a causal role in the development of a rare but highly lethal form of skin cancer called Merkel cell carcinoma (MCC). The discovery of MCV’s association with MCC has sparked a resurgence of interest in the possible roles polyomaviruses may play in causing human cancer.

Results

Emerging PCR-based evidence suggests that MCV DNA segments can commonly be detected on various skin surfaces of healthy adult subjects. To investigate the genetic characteristics of commonly circulating strains of MCV, we developed an improved rolling circle amplification technique to clone full-length MCV genomes from skin swab samples contributed by 14/35 (40%) healthy subjects. The results provide the first apparently wild-type full-length MCV isolates and show that commonly circulating MCV strains closely resemble strains found in tumors. The RCA-based analysis also serendipitously revealed the existence of two previously unknown human polyomaviruses, which we have named epsilon polyomavirus-1 (EPV1) and EPV2. The two EPVs occupy a common phylogenetic branch that is distant from MCV and other previously identified human polyomaviruses.
Persons infected with HIV are now known to be at increased risk for all cancers known or suspected to have an infectious cause, an effect believed to be primarily mediated by lowered host immunity via the depletion of CD4+ cells. Whereas Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) were recognised as AIDS-defining illnesses early in the HIV epidemic, the influence of declining CD4+ count on other infection-related cancers has taken longer to establish, undoubtedly because the association is weaker. Following improved survival made possible by combined antiretroviral therapy (cART), however, data from cohorts of PHIV followed up in the cART era are slowly accruing to show that declining CD4+ count both worsens the natural history of infection with carcinogenic viruses, and impacts negatively on the risk for an increasingly wide range of cancers including Hodgkin lymphoma, and cervical, anal, and liver cancer.

Indeed, the introduction of cART has greatly influenced the overall pattern of cancer incidence in people with HIV. The decrease in the prevalence of severe immunodeficiency resulted in a rapid reduction in KS and NHL incidence. Furthermore, there is increasing evidence for a slow increase in the burden of non-AIDS-defining cancers (NADCs) in the cART era. Nevertheless, NADC incidence, even in the immunocompetent population, is strongly associated with increasing age, and the huge shifts in age distribution seen in HIV-positive cohorts make adequately age-standardized comparisons of NADC incidence in the pre- and post-cART periods difficult.

To this end, the latest published epidemiologic research on HIV and cancer risk in the era of cART will be reviewed, and some relevant new data on trends in cancer risk from the Swiss HIV Cohort study will be presented.
Relative to adults, there are few published data from analytical studies on the risk of cancer in HIV-infected children, primarily because both cancer and HIV infection are less common in children than in adults. It is notable that the spectrum of cancers affecting children in the general population is different from that in adults. Furthermore, unlike adults, the great majority of HIV-infected children acquire the virus in the first months of life, while the immune system is developing and before exposure to many other immunological challenges.

A U.S. study showed that, subsequent to a diagnosis of AIDS, children were at an increased risk of NHL, Kaposi’s sarcoma, and leiomyosarcoma. However, the numbers of cases of certain cancer sites or types remain small, hence the need for new and larger studies. Despite the fact that HIV infection is more prevalent in parts of sub-Saharan Africa than elsewhere, there are few data from Africa that indicated the scale of the excess risk of cancer in HIV-infected as compared to uninfected children. The results from studies in Uganda, Malawi, and South Africa indicate that HIV infection increases the risk of Kaposi’s sarcoma and lymphoma, although results relating to endemic Burkitt lymphoma are equivocal. Notably, no association between infection with HIV and lymphoid leukemias, for which an underlying infectious etiology has been suggested, has yet been identified.
Epigenetic deregulation of genes through aberrant DNA methylation has been widely reported in cancer. Epigenetic patterning of genes plays a central role in mediating cell phenotypes. Normal differentiation of stem cells into various terminally differentiated cell types is only possible because of epigenomic programming acquired during the process of cell differentiation. Erasing these epigenomic marks returns cells to a stem cell-like phenotype. Tumor phenotype is equally dependent on epigenomic programming as are normal tissues. Identification of tumor-specific epigenetic programs is crucial to understanding the biology and phenotype and developing specifically targeted therapeutic strategies. In order to identify the epigenetic patterns underlying human tumors we have performed epigenomics profiling studies on cohorts of patients with leukemias and lymphomas. The data demonstrate that aberrant epigenetic programming is a universal event occurring in all tumors, and that epigenetic signatures can identify new subtypes of disease with specific biological and clinical features and serve as biomarkers to predict risk.
Oral Speaker Abstracts
01. **Bim nuclear translocation and inactivation by HHV-8 interferon regulatory factor 1**

Young Choi, John Nicholas  
Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Viral replication efficiency is in large part governed by the ability of viruses to counteract pro-apoptotic signals induced by infection of host cells. In HHV-8, one group of proteins acting to suppress the host’s innate defenses is the set of four viral interferon regulatory factors (vIRFs 1-4), which act to block cellular IRF activities in addition to targeting and inhibiting p53 and other inducers of apoptosis. We observed that in a large proportion of endothelial cells supporting lytic reactivation, the normally cytoplasmic pro-apoptotic BH3-only protein Bim, a negative regulator of HHV-8 productive replication, was localized in the nucleus. Nuclear localization of Bim could be induced in cells cotransfected with vIRF-1, and confocal microscopy identified co-localization of vIRF-1 and Bim in the nuclei of lytically reactivated cells. Physical association of vIRF-1 and Bim was identified in co-precipitation experiments using both transfected cell lysates and purified recombinant vIRF-1 and Bim. In vitro binding studies using a series of truncation and point variants of vIRF-1 enabled precise mapping of the Bim-interacting residues (Bim-binding domain, BBD) of vIRF-1. Wild-type, but not mutated, BBD fused to a nuclear localization signal was sufficient to induce Bim nuclear translocation in transfected cells; BBD-mutated vIRF-1 proteins were unable to do so or to protect cells from Bim-induced apoptosis. Depletion of endogenous vIRF-1 led to reductions in virus production and increased apoptosis in lytically reactivated endothelial cultures, while transduced expression of wild-type vIRF-1 promoted virus production and inhibited apoptosis. Experimental utilization of Bim-refractory vIRF-1 variants revealed the importance of vIRF-1:Bim interaction, specifically, for pro-replication and anti-apoptotic activity of vIRF-1. Furthermore, blocking of the interaction with cell-permeable peptide corresponding to the Bim-binding region of vIRF-1 confirmed the relevance of vIRF-1:Bim association to vIRF-1 pro-replication activity. To our knowledge, this is the first report of an IRF protein that interacts with a Bcl-2 family member and of nuclear sequestration of Bim or any other member of the family as a means of inactivation. Our data reveal a novel mechanism utilized by a virus to control replication-induced apoptosis and suggest that inhibitory targeting of vIRF-1:Bim interaction may provide an effective antiviral strategy.
Hsp90 is a viable therapeutic target in the treatment of KSHV-associated primary effusion lymphoma

Uttara Nayar1, Pin Lu1, Jelena Vider2, Leandro Cerchietti3, Gabriela Chiosis4, Lynn Wang1, Ronald Blasberg2,5, Ethel Cesarm1
1Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY, USA
2Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
3Department of Medicine, Weill Cornell Medical College, New York, NY, USA
4Department of Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
5Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Background
Hsp90 is a chaperone protein that binds client proteins involved in the regulation of cell survival and apoptosis signal transduction, including Akt, IKK complex, Apaf-1, survivin, CDKs, and KSHV vFLIP. This binding is necessary to maintain proper protein folding, assembly, transport, and function. A lack of Hsp90 results in protein misfolding, ubiquitination, and degradation. KSHV vFLIP was identified as a viral gene that is responsible for NF-κB-dependent anti-apoptotic gene expression in primary effusion lymphoma (PEL) cells [1]. In particular, the IKK signaling complex consisting of IKKα, IKKβ, IKKγ, vFLIP, and Hsp90 in the case of PEL cells was demonstrated as essential for survival in these cells. As Hsp90 forms part of the IKK signalosome in PEL cells, the Hsp90 inhibitor geldanamycin was previously tested in these cells and has been shown to inhibit activity of this complex in vitro. However, geldanamycin is of limited therapeutic potential due to its undesirable pharmacophysiology. We tested a new purine-scaffold Hsp90 inhibitor with high selectivity for tumor versus normal cell Hsp90, which is water-soluble with high oral bioavailability and excellent therapeutic window [2,3].

Materials and methods
We evaluated the sensitivity of several KSHV infected and uninfected cell lines to treatment with this inhibitor, called PU-H71. We performed viability and NF-κB reporter luciferase assays. Immunoblot analyses to cellular and viral proteins were done to assess the effect of PU-H71. Finally, we used a mouse PEL xenograft model and in vivo imaging to assess tumor responses to PU-H71.

Results
We found all KSHV-positive PEL cell lines to be exquisitely sensitive when compared to uninfected lymphoma cells, with growth inhibition at IC50s in the nanomolar range. PU-H71 was shown to induce PEL cell death by apoptosis and autophagy within 48 hours of treatment. Western blot analysis indicated that the IKK signaling complex components vFLIP and IKKγ were degraded upon PU-H71 treatment, leading to destabilization of the complex, and inhibition of NF-κB signaling, as confirmed by reporter luciferase assay. PU-H71 was further tested in a mouse xenograft model of PEL and shown to inhibit progression of tumor spread and confer a significant survival advantage (p<0.02) in these mice.

Conclusions
Our findings suggest that Hsp90 inhibition with PU-H71 is a promising targeted approach for the treatment of PEL and warrants further preclinical and clinical investigation.

References
O3. Upregulation of angiopoietin-like 4 by viral G protein-coupled receptor promotes angiogenesis and vascular permeability in Kaposi’s sarcoma

Tao Ma1, Bruno C. Jham1, Jiadi Hu1, Eitan R. Friedman1, John R. Basile1,2, Akrit Sodhi3, Silvia Montaner1

1Department of Oncology and Diagnostic Sciences, University of Maryland, Baltimore, MD, USA
2Greenebaum Cancer Center, University of Maryland, Baltimore, MD, USA
3Wilmer Eye Institute, Johns Hopkins School of Medicine, Johns Hopkins University, Baltimore, MD, USA

Background
Kaposi’s sarcoma (KS) is an enigmatic vascular tumor thought to be a consequence of dysregulated expression of the human herpesvirus-8 (HHV-8 or KSHV)-encoded G protein-coupled receptor (vGPCR) [1]. Both human and vGPCR experimental KS lesions are characterized by prominent angiogenesis and vascular permeability attributed to the paracrine release of angiogenic mediators, most notably vascular endothelial growth factor (VEGF). To date, the relative contribution of these paracrine mediators to the angiogenic and exudative phenotype of KS lesions remains unclear. Here we show that vGPCR upregulated angiopoietin-like 4 (ANGPTL4) (Figure 1 A,B,C) plays a prominent role in promoting the angiogenesis and increasing vascular permeability in this tumor. Inhibition of ANGPTL4 effectively blocks vGPCR promotion of angiogenesis and vascular permeability in vitro and tumorigenesis in vivo (Figure 1 D,E,F,G,H).

Conclusion
These observations suggest that ANGPTL4 is a previously unrecognized target for the treatment of patients with KS. As angiogenesis and increased vessel permeability are common themes in all solid tumors, these results may have a broad impact on our understanding and treatment of cancer.

Acknowledgements
This work was supported by grant R01CA119911 (National Cancer Institute, NIH). We thank Histoserv, Inc., for its assistance in the processing of the murine tissues. BCJ is a recipient of a predoctoral fellowship from the CNPq-Brazil.

References
Kaposi’s sarcoma (KS) is an angioproliferative tumor of vascular endothelial cells and produces rare B cell lymphoproliferative diseases in the form of primary effusion lymphomas (PELs) and some forms of Multicentric Castleman’s Disease (MCD). Kaposi’s sarcoma-associated herpesvirus, also known as KSHV or human herpesvirus type 8 (HHV8), is the etiological agent of KS. Fibulins are extra-cellular matrix (ECM) proteins involved in cell adhesion, proliferation, migration, invasion, and angiogenesis, and have been linked to progression of several cancer types. However, to our knowledge, they have not been studied in KS. We examined fibulin-2 because we found it to be significantly downregulated by microarray analysis in KSHV-infected DMVEC cells. Here we demonstrate that fibulin-2 protein expression is downregulated 50-fold in 10 day KSHV-infected dermal microvascular endothelial cells (DMVEC) with a 26-fold reduction in fibulin-2 message. By time-course transcriptional analysis there was consistent reduction of fibulin-2 message accompanied by an increase in KSHV latency associated nuclear antigen (LANA) transcription. Of the fibulins assayed, fibulins -2, -5, and -3 were downregulated over time in KSHV infected DMVEC, while fibulins 1C and 1D were upregulated, with no change in fibulins 4, 6, and 7. In pleural effusion lymphoma cell lines that express different levels of KSHV lytic replication, we observed no detectable fibulin-2 expression. Tissue microarrays representing patch/plaque and nodular forms of KS from 86 different patients were shown to be statistically significant for downregulation of fibulin-2 in virus-infected LANA positive cells by dual labeled immunohistochemical staining. This represents the first study that examines fibulin-2 expression in KSHV-infected DMVEC and KS to determine whether suppression of this ECM protein plays a role in KS tumor progression. Understanding the interactions between KSHV and the fibulin family of extra-cellular matrix proteins that modulate angiogenesis cancer cell proliferation, migration and invasion could lead to development of novel therapies for treatment of KS.
HIV-associated salivary gland disease (HIV-SGD) is disfiguring and causes significant morbidity in the HIV population. Evidence detailing the epidemiology of HIV-SGD suggests the involvement of a viral opportunist in its pathogenesis, yet the specific etiology of HIV-SGD remains unclear. To determine the role for an opportunistic virus as the etiologic agent of HIV-SGD, we hypothesized that HIV-SGD was a manifestation of primary infection or reactivation with a DNA tumor virus, BKV, during immune suppression. The central hypothesis of this work is that viral pathogenesis is essential to the development of salivary gland disease. Results show for the first time that polyomavirus, BKV, is associated with HIV-SGD. BKV DNA, RNA, and protein were consistently detected in salivary gland biopsies and in the peripheral blood and oral fluids from HIV-SGD patients and not in control subjects. To confirm the in vivo findings, an in vitro model was created whereby parotid and submandibular salivary gland cells were productively infected with BKV, demonstrating each part of the viral life cycle. Salivary gland tropism was confirmed and the BKV receptor on salivary gland cells was defined. BKV transmission and pathogenesis is not well understood. Importantly, these studies suggest a role for BKV in HIV-SGD and that BKV transmission may occur via the oral route. The long-term goal of this project is to make critical strides toward understanding the etiology of SGD in order to go beyond the ineffective palliative treatment that is currently the standard of care.

Acknowledgement
This work was supported by NIDCR OHARA 1 U01 AI068636-01.
06. Bacteria-mediated reactivation of gammaherpesviruses

Terry Morris¹, Fang Gu, RoShaunna Rothwell⁴, Jennifer Webster-Cyriaque¹,²,³,⁴
¹Lineberger Cancer Center, University of North Carolina, Chapel Hill, NC, USA
²Division of Infectious Disease, University of North Carolina, Chapel Hill, NC, USA
³Department of Microbiology and Immunology, University of North Carolina School of Medicine, Chapel Hill, NC, USA
⁴Department of Dental Ecology, University of North Carolina School of Dentistry Chapel Hill, NC, USA

Significant morbidity is associated with the synergistic and inhibitory interactions of bacteria, viruses, parasites, and fungi. The oral cavity, gut, and genitourinary tract are home to many of these organisms and are the site of virus-associated malignancies that affect millions worldwide. Yet little is known with regard to the cellular and molecular interactions of viral pathogens with the normal flora as well as the interactions among pathogens themselves. Our laboratory is interested in understanding the role of factors present within the immediate environment that may influence reactivation of persistent infection and pathogenesis. Our central hypothesis is that viral-bacterial interactions foster enhanced pathogen replication and modulation of the immune response in the mouth, GI tract, and genito-urinary tract. The detection of replicating virus in these tissues has incited investigation into the relationship between bacterial infection and herpesviral reactivation. We hypothesized that bacterial end-products including short chain fatty acids (SCFA), lipopolysaccharide (LPS), and lipoteichoic acid (LTA) secreted by oral bacteria initiate viral reactivation from latency. Latently infected EBV, KSHV, and MHV 68 cell lines were incubated with crude spent media containing secreted SCFA, and components of bacterial pathogens (E. faecalis, Bacteriodes, Prevotella, Porphomonas, and Fusobacterium Nucleatum). Cells were then assayed for viral promoter activation, promoter-protein interactions, and state of infection. Following incubation with crude spent media, viral immediate early promoters were activated, the viral early genes were upregulated as determined by RT PCR and western blot, and linear genomes were detected. HDAC inhibition activity as well as protein kinase C activity increased significantly following treatment with bacterial spent media. KSHV and EBV were consistently reactivated by bacterial metabolites but the mechanism of reactivation was both bacteria, virus, and cell type specific. Interestingly, EBV was preferentially reactivated following toll like receptor stimulation while KSHV and HSV-1 reactivation occurred following HDAC inhibition. In conclusion, these studies provide significant insights to gammaherpesreactivation that may occur in vivo via pathogen-pathogen interaction.

Acknowledgements
This work was supported by NIDCR OHARA 1 U01 AI068636-01, AAE fellowship to Dr. Gu, and NIH F31 GM070115-02 to Dr. Rothwell.
Background
KS is a disease of multifocal vascular proliferation that requires infection with the KS herpes virus (KSHV/HHV-8). Activation of the c-kit and platelet derived growth factor (PDGF) receptors by autocrine and paracrine mechanisms follows KSHV infection of endothelial cells. Partial KS regression in 5/10 patients was observed in a pilot study using the c-kit/PDGF-R inhibitor imatinib (Novartis Pharmaceuticals), and 3/4 biopsies showed PDGF inhibition, suggesting this agent has activity in AIDS-related KS.

Methods
The primary objective was to estimate the response rate of KS to imatinib in AIDS-related KS. Secondary objectives included investigation of predictors of response and imatinib pharmacokinetics in patients on cART. Patients were treated with imatinib 400 mg/day orally for up to 12 months with the option to dose escalate to 600 mg/day at 3 months if disease was stable. Plasma concentrations of CCL5 (RANTES), IFNγ, IL-6, and FGF-β at baseline, day 8, and day 28 were measured using the Mesoscale platform to assess the utility of these growth factors as biomarkers.

Results
Thirty patients were treated at 12 AMC sites. Median CD4 count was 263 (19-819). 79% had undetectable HIV RNA. Ten (33.3%) showed partial response, 6 (20%) had stable disease, and 7 (23.3%) showed KS progression by modified AIDS Clinical Trial Group response criteria. Treatment was well tolerated. Nine patients completed 52 weeks of imatinib and the median treatment duration was 22.5 weeks (0.3-52.7). Only 5 patients (16.7%) discontinued therapy due to adverse events including grade 3 hypophosphatemia (2), allergic reaction (1), cellulitis (1), depression (1), and grade 4 elevation of CK (1). Pharmacokinetic analysis of the AUC ratios (using day 1 and 15 sampling) demonstrated that actual imatinib AUC levels were significantly higher than predicted (P=0.036), but there was no difference between actual and predicted AUC for the active metabolite (P=0.441), suggesting the antiretroviral regimens influenced imatinib metabolism. While baseline levels of CCL5 and IFNγ and changes in the levels of IL-6 and FGF-β correlated with response in our pilot study, none of these growth factors predicted response in this larger study.

Conclusion
Imatinib has activity in AIDS-related Kaposi’s sarcoma. The potential interactions with antiretroviral drugs did not correlate with increased toxicity. Thirty percent of patients showed long-term clinical benefit and remained on imatinib for the entire year. These results suggest this regimen is well tolerated and may be an alternative to cytotoxic chemotherapy for some patients with AIDS-related KS.

Acknowledgements
This work was supported by U01 CA121947, R21 CA108251, and Novartis Pharmaceuticals.
O8. Rituximab combined with liposomal doxorubicin (R-Dox) in HIV-infected patients with severe Kaposi sarcoma-associated herpes virus (KSHV) associated multicentric Castleman disease (MCD)

Thomas Uldrick¹, Mark Polizzotto¹, Deirdre O’Mahoney¹, Karen Aleman¹, Kathy Wyvill¹, Seth M. Steinberg², Stefania Pittaluga³, Vickie Marshall⁴, Denise Whitby⁵, Giovanna Tosato⁴, Richard F. Little¹, Robert Yarchoan¹

¹HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA
²Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA
³Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA
⁴Laboratory of Cellular Oncology, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA
⁵Viral Oncology Section, AIDS and Cancer Virus Program, National Cancer Institute, Bethesda, MD, USA

Background
MCD is characterized by inflammatory symptoms, splenomegaly, adenopathy, hypoalbuminemia, hyponatremia, and cytopenias. MCD in HIV-infected patients is generally KSHV-associated. No standard therapy exists. Rituximab has activity, but monotherapy may be insufficient in severe disease and can be associated with worsening of Kaposi’s sarcoma (KS).

Methods
Patients with symptomatic MCD received rituximab 375 mg/m² plus liposomal doxorubicin 20 mg/m² every 21 days until substantial clinical improvement or disease progression. This regimen is being evaluated prospectively within an MCD natural history protocol. Additional therapy, employing agents with antiviral activity (discussed below), was generally employed to consolidate or maintain responses. Clinical, biochemical, and radiographic responses were evaluated using protocol-defined criteria. Overall complete response (CR) required normalization of all MCD-related abnormalities.

Results
Patient characteristics: 12 (1 woman, 11 men) patients completed R-dox. Median age, 43 (34-55); median number of prior therapies 2 (0-8). Diffuse adenopathy (12); median spleen (cm), 18.5 (12.5-28). Concurrent KS (5). All were receiving concurrent combination antiretroviral therapy. Baseline laboratory values, median (range): CD4 cells/μL, 291 (21-1598); C-reactive protein (mg/dL), 9.9 (0.4-21); albumin (mg/dL), 2.7 (1.5-3.3); sodium (mEq/L), 133 (126-136); platelets (K/μL), 70 (10-377); hemoglobin (gm/dL), 9.4 (6.8-12.2). Median cycles received 4.5 (3-9).

Table 1. Best response with R-Dox.

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Stable Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>12 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Biochemical</td>
<td>10 (83%)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Radiographic</td>
<td>6 (50%)</td>
<td>6 (50%)</td>
<td>-</td>
</tr>
<tr>
<td>Overall</td>
<td>3 (25%)</td>
<td>6 (50%)</td>
<td>3 (25%)</td>
</tr>
</tbody>
</table>

With 9 patients receiving additional therapy after R-dox; IFNα (6), high-dose zidovudine + valganciclovir (2), additional liposomal doxorubicin (1); 6 additional patients achieved overall CR (total 75%). KS responded in 4/5 (80%). With 31.4 months median potential followup (actual 5.5+ to 47+), estimated 2-year progression-free survival and overall survival are 61.1% and 78.6%, respectively. 8/12 (67%) remain symptom free, while 3 had recurrent MCD flares (months 7, 10, 17) responding to additional R-Dox. One had progressive MCD and worsening KS during cycle 6 and died at month 6. At autopsy, primary effusion lymphoma was discovered. One patient died at month 17 of sepsis unrelated to therapy. Select toxicities: 9 infusion reactions (Gr. 1 = 3, Gr. 2 = 4, Gr. 3 = 2) with the first dose of rituximab; 6/60 cycles complicated by neutropenia (Gr. 2 = 5, Gr. 3 = 1), no infectious complications.

Conclusions
R-Dox is effective in treating severe KSHV-MCD or MCD with concurrent severe KS. Evaluation of R-Dox in KSHV-MCD is ongoing.
The KAART Trial: a randomized controlled trial of HAART compared to the combination of HAART and chemotherapy in treatment-naïve patients with HIV-associated Kaposi sarcoma (HIV-KS) in KwaZulu-Natal (KZN), South Africa

A. Mosam1, F. Shaik1,2, T.S. Uldrick2,3, G.H. Friedland4, D.T. Scadden5, J. Aboobaker1, H.M. Coovadia6
1Department of Dermatology, Nelson R Mandela School of Medicine, University of KwaZulu Natal, South Africa
2CAPRISA and SA-Columbia Fogarty AITRP, USA
3Columbia University, New York, NY, USA
4Yale University School of Medicine, New Haven, CT, USA
5Harvard Medical School, Boston, MA, USA
6Victor Daitz Chair of HIV/AIDS Research, University of KwaZulu Natal, South Africa

Background
KS is the most common cancer in people with HIV/AIDS, affecting both men and women in sub-Saharan Africa. Without HAART, mortality is high. Given poor access to HAART and prevalent HIV and KS-associated herpesvirus co-infection, advanced HIV-KS is an increasing problem in KZN. This is the first prospective study evaluating the impact of HAART and the role of early chemotherapy in HIV-KS in Africa.

Methods
We performed a randomized, controlled, open-label trial comparing HAART to the combination of HAART and chemotherapy (CXT) in treatment-naïve patients with biopsy-confirmed HIV-KS, recruited from the dermatology clinic at King Edward VIII Hospital, KZN, South Africa. Patients were stratified by ACTG risk group. HAART was stavudine, lamivudine, and nevirapine. CXT consisted of HAART plus bleomycin (10 U/m²), doxorubicin (20 mg/m³), and vincristine (1.4 mg/m²). Responses were evaluated by ACTG criteria. We performed an intention-to-treat comparison between arms of KS clinical responses at month 12 (Fisher exact test), rate of response (Mantel-Haenszel rate ratio), and overall survival (log-rank test). ACTG prognostic criteria were evaluated (Cox proportional hazard regression). Toxicity was monitored using DAIDS criteria. Adherence was assessed by a 7-day recall questionnaire. Toxicities, adherence, and changes in CD4 and HIV-1 viral load were compared between arms (Fisher exact test).

Results
Baseline characteristic: 310 patients were screened, with 112 (62 women, 50 men) randomized; 59 to HAART and 53 to CXT arm. Mean age 34 (20-63 yrs). 89% had advanced disease (T1 disease), 93% poor risk by ACTG criteria, 58% with CD4 <200, 42% had a history of co-morbid infection; commonly tuberculosis (34%). Responses: The overall response rate (complete responses plus partial responses) at month 12 was 39% in the HAART arm and 66% in the CXT arm (p=0.005). The CXT arm had a 2.7 times faster response rate (p<0.001). Overall survival at 12 months was 76%, with no significant differences between arms (p=0.49). ACTG TIS staging was validated (p=0.03), with systemic illness the most significant prognosticator of overall survival. There were no significant differences in CD4 improvement, HIV viral load decay, adverse events, or adherence between arms.

Conclusion
HAART dramatically improves overall survival in African patients with HIV-KS compared to historic controls. Addition of chemotherapy improves response rates in patients with advanced (T1) HIV-KS.
O10. Distinct profiles of antibodies to Kaposi sarcoma-associated herpesvirus antigens in patients with Kaposi sarcoma, multicentric Castleman’s disease, and primary effusion lymphoma

Peter D. Burbelo¹, Alexandra T. Issa¹, Kathryn H. Ching¹, Kathleen M. Wyvill³, Richard F. Little³, Michael J. Iadarola¹, Joseph A. Kovacs², Robert Yarchoan³

¹Neurobiology and Pain Therapeutics Section, Laboratory of Sensory Biology, NIDCR, NIH, Bethesda, MD, USA
²Critical Care Medicine Department, Clinical Center, NIH, Bethesda, MD, USA
³HIV and AIDS Malignancy Branch, Center for Cancer Research, NCI, NIH, Bethesda, MD, USA

Clinical Background
Kaposi sarcoma-associated herpesvirus (KSHV), also called human herpesvirus-8 (HHV-8), is the causative agent of all forms of Kaposi sarcoma (KS), as well as two rare B-cell HIV lymphoproliferative disorders, primary effusion lymphoma (PEL) and multicentric Castleman’s disease (MCD). Like other herpesviruses, KSHV has two phases of gene expression, latent and lytic. In KS, many of the KSHV-infected spindle cells express only latent genes, while a small percentage express lytic genes. By contrast, a substantial percentage of MCD cells express lytic KSHV genes. The majority of PEL cells express KSHV latent genes, but in addition can show limited expression of certain lytic genes. Given the differential expression of KSHV lytic and latent proteins in KS, PEL, and MCD, we hypothesized that different antibody profiles to KSHV antigens might distinguish these diseases.

Materials and methods
Antibodies were evaluated in sera from patients or volunteers under IRB-approved protocols at the NIH Clinical Center, NIAID, and the NCI including from 35 patients with KS, 14 with both MCD and KS (MCD+/KS+), 6 with MCD but no KS (MCD+/KS), 5 with PEL, and 34 KSHV-uninfected controls. Luciferase Immunoprecipitation Systems (LIPS) was used for profiling antibodies to latent and lytic KSHV antigens.

Results
Using LIPS, antibodies against the lytic antigen K8.1 were 5-fold higher in MCD than in KS patients. In contrast, markedly higher antibodies to v-cyclin, a latent KSHV gene, were found in the KS and PEL patients compared to the MCD. Antibodies to another latent antigen, LANA, were also markedly higher in the KS compared to the MCD patients. Antibodies to the sum of latent antigens v-cyclin and LANA were 27-fold higher in KS compared to MCD patients (p<0.0001). The sum of anti-v-cyclin and anti-LANA antibody titers discriminated patients with KS without MCD from those with MCD and KS with 93% sensitivity and 83% specificity.

Conclusion
These results suggest that antibody responses to lytic and latent KSHV antigens differ between KS, MCD, and PEL.

Acknowledgements
The authors thank the patients who volunteered for these studies. This work was supported by the Intramural Research Program of the NIH, National Institute of Dental and Craniofacial Research, NIH Clinical Center, and National Cancer Institute and, in part, by a Bench to Bedside award from the NIH Clinical Center.
O11. Pooled analysis of AIDS Malignancy Consortium (AMC) trials evaluating rituximab plus either CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin’s lymphoma

Stefan K. Barta1, Jeannette Y. Lee2, Joseph A, Sparano3, Lawrence D. Kaplan1, Ariela Noy4
1Montefiore-Einstein Cancer Center, Bronx, NY, USA
2University of Arkansas, Little Rock, AR, USA
3University of California, San Francisco, CA, USA
4Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Background
Two consecutively performed randomized studies by the AMC evaluating chemoimmunotherapy for the treatment of HIV-associated NHL include AMC010 [1] (Concurrent Rituximab [R] + CHOP vs. CHOP, N=150) and AMC034 [2] (Concurrent R+EPOCH vs. Sequential EPOCH →R; N=106). In AMC010, the addition of Rituximab to CHOP was associated with an increased risk of infectious death (15% vs. 2%, p=0.035) without a significant improvement in complete response (CR) rate (58% vs. 47%; p=0.147), event-free survival (EFS), or overall survival (OS). In AMC034, the CR rate met its primary efficacy endpoint in the concurrent arm (73%; 95% confidence intervals [CI] 58%, 85%) but not the sequential arm (55%; 95% CI 41%, 68%).

Methods
We performed a pooled analysis of these two consecutive trials including patients treated with R-CHOP and concurrent R-EPOCH in order to determine the influence of the age-adjusted International Prognostic Index (aaIPI), CD4 count (<100/μL vs. >100/μL), and treatment (CHOP vs. EPOCH) as variables.

Results
The characteristics and outcomes of the study populations are shown in table 1. Patients treated with R-EPOCH tended to have better outcomes in both the low and high-risk IPI groups.

| Table 1. Patient characteristics and outcomes. |
| R-CHOP | R-EPOCH |
| No. | 99 | 51 |
| CD4<100/μL | 41% | 31% |
| High aaIPI risk (2-3 factors) | 59% | 69% |
| Mean age (years +/- standard deviation) | 43.5 (± 8.3) | 42.6 (±8.4) |
| CR rate | | |
| Low risk aaIPI (0-1 factors) | 76% (60%, 88%) | 88% (62%, 98%) |
| High risk aaIPI (2-3 factors) | 45% (32%, 58%) | 60% (42%, 76%) |
| 2 year EFS | | |
| Low risk aaIPI (0-1 factors) | 57% (36%, 73%) | 81% (51%, 93%) |
| High risk IPI (2-3 factors) | 30% (18%, 43%) | 59% (41%, 74%) |
| 2 year OS | | |
| Low risk aaIPI (0-1 factors) | 66% (43%, 82%) | 87% (57%, 97%) |
| High risk aaIPI (2-3 factors) | 36% (23%, 50%) | 62% (44%, 76%) |

In a multivariate analysis that included pooled data from both consecutive studies, features that were significantly associated with improved EFS, OS, and CR rate included low aaIPI score and baseline CD4 count of at least 100/μL. Additionally patients treated with concurrent R-EPOCH exhibited improved EFS and OS even when adjusted for prognostic covariates including aaIPI score and CD4 count (Table 2).
Table 2. Multivariate analysis regarding the outcomes event-free survival (EFS), overall survival (OS) and rate of complete or unconfirmed complete remission (CR/CRu).

<table>
<thead>
<tr>
<th></th>
<th>EFS p-value</th>
<th>OS p-value</th>
<th>CR/CRu p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>aIPI score (0-1 vs. 2-3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.32 (0.17, 0.57)</td>
<td>0.28 (0.14, 0.56)</td>
<td>4.58 (1.96, 10.69)</td>
</tr>
<tr>
<td>CD4 (&gt;100 vs. &lt; 100/μL)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>0.42 (0.26, 0.69)</td>
<td>0.37 (0.22, 0.63)</td>
<td>2.70 (1.26, 5.79)</td>
</tr>
<tr>
<td>R-EPOCH vs. R-CHOP</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.117</td>
</tr>
<tr>
<td></td>
<td>0.40 (0.23, 0.69)</td>
<td>0.38 (0.21, 0.69)</td>
<td>1.90 (0.85, 4.22)</td>
</tr>
</tbody>
</table>

Conclusions
These findings suggest that treatment outcomes may be superior with concurrent R-EPOCH compared with R-CHOP, and support the design of an ongoing Phase III trial comparing concurrent R-EPOCH with R-CHOP in immunocompetent patients with diffuse, large B-cell lymphoma (NCT00118209). This analysis provides additional level 2 evidence supporting the use of concurrent R-EPOCH in patients with HIV-associated lymphoma.

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

References
**Day 2 Oral Speaker Abstracts**

**012. Cervical cancer epidemiology among HIV-infected women in North America**

Gypsyamber D'Souza1, Yuezhou Jing1, Howard Strickler10, Michael Silverberg2, Eric Engels3, Ronald Bosch4, John T. Brooks5, Robert Dubrow6, Joseph Eron7, Kelly Gebo8, M. John Gill9, Bob Hogg11, Mari Kitahata12, Marina Klein13, Richard Moore8, Sean Rourke14, Alison G. Abraham1

1Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
2Kaiser Permanente Northern California, Oakland, CA, USA
3Division of Cancer Epidemiology and Genetics, NCI, NIH, Bethesda, MD, USA
4Department of Biostatistics, Harvard University, Boston, MA, USA
5Centers for Disease Control and Prevention, Atlanta, GA, USA
6Division of Chronic Disease Epidemiology Yale University, New Haven, CT, USA
7Division of Infectious Diseases, School of Medicine, University of North Carolina, Chapel Hill, NC, USA
8Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA
9Department of Medicine, University of Calgary, Calgary, Canada
10Department of Epidemiology, University of California at San Francisco, San Francisco, CA, USA
11BC Centre for Excellence in HIV/AIDS, Vancouver, Canada
12Department of Medicine, University of Washington, Seattle, WA, USA
13McGill University, Montreal, Canada
14Department of Psychiatry, University of Toronto, Toronto, Canada

**Background**

Initial studies suggest immunosuppression may be associated with the increased rates of precancerous cervical lesions observed in HIV-infected compared with HIV-uninfected individuals, but few studies have large enough populations to study the effect on invasive cancer. To characterize the incidence of cervical cancer among HIV-infected women in the HAART era, we examined data from the NA-ACCORD HIV cohort collaboration of IeDEA.

**Materials and methods**

This analysis includes data from 13 North American cohorts of HIV-infected women that collected clinically confirmed or cancer registry-linked data on invasive cervical cancer. Cervical cancer-free women were followed from the first HAART era CD4+ measurement (1996 onwards) until the earliest of: cervical cancer diagnosis, lost to followup, death, or December 2007. Incidence rate overall, by calendar period, and by first CD4+ cell count after 1995 (baseline) were standardized for age using the 2000 U.S. standard population.

**Results**

Among the 16,467 HIV-infected women free of disease at baseline, 102 cases of invasive cervical cancer were reported, yielding an age-standardized incidence rate of 114 per 100,000 person-years (95% CI: 88–139). Of those cases, 40 (39%) were HAART-naive at the time of diagnosis. Among women ≤39, 40-49, and ≥50 years of age the incidence rates were 122, 142, and 89 per 100,000 person-years, respectively. The age-standardized incidence rates by calendar periods for 1996-1999, 2000-2003, and 2004-2007 were 133, 152, and 87 per 100,000 person-years, respectively, showing no trend. The age-standardized incidence rates by baseline CD4+ categories of ≥350, 200-350, and <200 cells/μL were 68, 113, and 185, respectively, indicating an increasing rate with declining CD4+ cell count (P<0.001). Among 13,716 HIV-negative women free of disease in these cohorts, there were 10 invasive cervical cancers for an incidence of 11.3 per 100,000 person-years (95% CI 6.6-23), similar to the age-adjusted SEER population incidence of 8.2 per 100,000 person-years.

**Conclusions**

In this large collaboration of North American HIV cohorts, the estimate of cervical cancer incidence was almost 10-fold higher among HIV-infected than uninfected women in these cohorts. Although an effect of increased sexual risk-taking in HIV-infected women and/or differences in screening cannot be excluded, the strong association with lower baseline CD4+ cell count suggests a single low CD4 measurement may predict increased cervical cancer risk. It is unclear whether improvements in HIV-therapies during the HAART era have influenced cervical cancer rates; although no significant trend in incidence was observed over time, a decrease was observed in 2004-07.

**Acknowledgement**

This work is presented on behalf of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA.
O13.  Progression of cervical neoplasia in HIV-seropositive women with and without antiretroviral therapy in Johannesburg, South Africa

Cynthia Firnhaber¹, Daniel Westreich², Doreen Schulz¹, Sophie Williams³, Pam Michelow⁴, Mark Faesen³, Simon Levin³, Jennifer Smith²
¹Department of Medicine, University of Witwatersrand, Johannesburg, South Africa
²Department of Epidemiology, University of North Carolina, Raleigh, NC, USA
³Right to Care, Johannesburg, South Africa

Background
HIV-seropositive women have a higher risk of oncogenic HPV infection, cervical neoplasia, and cervical cancer than HIV-seronegative women. As HIV-seropositive women begin to live longer due to effective highly active antiretroviral therapy (HAART), their risk of developing cervical cancer may increase. Little data exist regarding the progression of cervical neoplasia in HIV seropositive women from sub-Saharan Africa.

Methods
A longitudinal observational study of 2,106 HIV-seropositive women was performed to determine progression rates of cytological outcomes in a government HIV clinic in Johannesburg, South Africa, stratified by use of HAART. The 2001 Bethesda grading system was to classify conventional Pap smear diagnoses. The effect of HAART use at initial visit on rate of progression of cervical neoplasia was determined using multivariate Poisson regression to obtain incidence rate ratios (IRRs) adjusted for age, CD4 count, history of STDs, use of hormonal contraception, parity, number of lifetime sex partners, and age at first sexual contact.

Results
The cohort comprised 741 HIV-seropositive women with at least two visits more than 6 months apart. Mean followup time among these women was 565 days (median 449 days; intraquartile range 382-698 days). Among women with a normal baseline Pap (n=326), 76 (23%) progressed to LSIL or HSIL, at a rate of 16.0 (95% CL 12.8, 20.0) per 100 woman-years. Among women with LSIL at baseline Pap (n=275), 46 (17%) progressed to HSIL at a rate of 10.8 (95% CL 8.1, 14.4) per 100 woman-years. Of the remaining 140 women with HSIL at baseline Pap who not assessed treatment before repeat Pap smear, none progressed to cancer. In multivariate Poisson regression, women receiving HAART at baseline visit were less likely to progress than women not receiving HAART at baseline (IRR=0.60, 95% CL 0.41, 0.87). Results were similar regardless of baseline Pap result, and using multivariate Cox proportional hazards models (hazard ratio, 0.55, 95% CL 0.38, 0.80). In addition, lower CD4 counts were associated with higher rates of cervical neoplastic progression, although results were imprecise.

Conclusion
This is one of the first reports of progression rates of cervical neoplasia among HIV-positive women. These rates among women from South Africa are concerning. There is an urgent need for broad-reaching screening/treatment in Africa.
O14. Persistence of anal squamous intraepithelial lesions and anal HPV infection in HIV-infected patients despite immune restoration under cART

C. Piketty1, E. Lanoy2, A. Si-Mohamed1, B. Cochand-Priolet3, S. Trabelsi2, P-M. Girard4, R. Tubiana5, L. Abramowitz6, E. Tartour1, C. Rouzioux1, L. Weiss1, D. Costagliola1,2,5, and the Valparaiso Study Group
1Hôpital Européen Georges Pompidou, Paris, France
2INSERM U943 - UPMC UMR S943, Paris, France
3Hôpital Lariboisière, Paris, France
4Hôpital Saint Antoine, Paris, France
5Hôpital Pitié Salpêtrière, Paris, France
6Hôpital Bichat-Claude Bernard, Paris, France
7Hôpital Necker, Paris, France
8Université Paris 5, René Descartes, Paris, France

Background
A high prevalence of anal squamous intraepithelial lesions (ASIL) and HPV infection have been observed in HIV-infected MSM in the pre-cART era. To date, the impact of cART on the natural history of HPV infection and ASIL is poorly documented.

Methods
94 HIV-infected MSM naïve of cART were enrolled in a longitudinal study before starting a first-line regimen of cART. Each patient provided anal samples for cytology, histology, and HPV DNA testing at baseline, month 12, and month 24 of cART. HPV DNA was detected by real-time PCR and Roche Linear Array assay. Anal cytologic was processed by the Thin Prep method (Hologic). CD4+ and CD8+ T cell responses to HPV-16 E6 and E7 proteins were measured in a subgroup of individuals exhibiting HPV-16 anal infection at inclusion.

Results

Table 1. The median age of the patients was 39.7 years (33.2-43.5). Baseline and month 12 cytologic and/or histologic results.

<table>
<thead>
<tr>
<th></th>
<th>CD4/mm³ median (Q1-Q3)</th>
<th>Plasma HIV RNA log10 copies/mL</th>
<th>VL &lt;50</th>
<th>Prior AIDS event</th>
<th>Visible lesion</th>
<th>Presence of condyloma</th>
<th>Anal SIL</th>
<th>Low-grade SIL; High-grade SIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>299 (242 – 342)</td>
<td>4.8 (4.17 – 5.26)</td>
<td>1%</td>
<td>4 (4%)</td>
<td>40/94 (43%)</td>
<td>23/94 (25%)</td>
<td>51 (54%)</td>
<td>30 (32%); 8 (9%)</td>
</tr>
<tr>
<td>M12</td>
<td>500 (411 – 575)</td>
<td>1.6 (1.6 – 1.6)</td>
<td>93%</td>
<td></td>
<td>25/71 (35%)</td>
<td>5/71 (7%)</td>
<td>41 (58%)</td>
<td>24 (34%); 10 (14%)</td>
</tr>
</tbody>
</table>

Prevalence of low-grade SIL, high-grade SIL, and HPV infection was similar at M12 compared to baseline. Among patients with normal cytology and/or histology at baseline, 44% progressed to SIL at M12 whereas 31% of patients with ASIL at baseline exhibited a regression at M12. Specific anti-HPV CD4 T cell responses were mostly undetectable both at baseline and M12.

Table 2. Baseline and month 12 virological results.

<table>
<thead>
<tr>
<th></th>
<th>Number of HPV</th>
<th>Number of high-risk and low-risk type</th>
<th>High risk HPV</th>
<th>HPV-16</th>
<th>HPV-18</th>
<th>HPV-16 DNA log10 copies/10⁶ cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>5 (2 – 7)</td>
<td>3 (2 – 5); 2 (1 – 4)</td>
<td>83 (90%)</td>
<td>49 (53%)</td>
<td>28 (30%)</td>
<td>6.1 (5.3 – 7.1)</td>
</tr>
<tr>
<td>M12</td>
<td>5 (2 – 6)</td>
<td>3 (1 – 4); 2 (1 – 4)</td>
<td>59 (87%)</td>
<td>28 (41%)</td>
<td>15 (22%)</td>
<td>6.1 (2.0 – 7.2)</td>
</tr>
</tbody>
</table>

At month 12, prevalence of anal HPV DNA detection was similar than at baseline. High-risk HPV was detected at month 12 in 92% of the patients with high-risk HPV infection at baseline. Low-risk HPV was detected at month 12 in 91% of the patients with low-risk HPV infection at baseline. HPV-16 and HPV-18 were detected at month 12 in 13% and 3.7% of patients with no HPV-16 and HPV 18 infection at baseline, respectively. HPV-16 was detected in 100% and 70% of high-grade SIL at baseline and month 12, respectively.

Conclusion
Our results demonstrate a high prevalence and incidence of ASIL and anal HPV infection in HIV-infected MSM despite CD4 reconstitution under cART. These data suggest that all HIV-positive MSM, even under antiretroviral therapy, remain at risk of anal SIL.
O15. Risk of anal cancer in HIV-infected patients and HIV-uninfected controls in North America

Michael J. Silverberg1, Bryan Lau2, Yuezhou Jing2, Gypsyamber D’Souza2, Eric A. Engels1, John Gill4, James J. Goedert3, Gregory D. Kirk35, Amy Justice67, Robert Dubrow17
1Kaiser Permanente Northern California, Oakland, CA, USA
2Johns Hopkins School of Public Health, Baltimore, MD, USA
3National Cancer Institute, Rockville, MD, USA
4University of Calgary, Calgary, Alberta, Canada
5Johns Hopkins School of Medicine, Baltimore, MD, USA
6Yale School of Public Health, New Haven, CT, USA
7Yale School of Medicine, New Haven, CT, USA

Background
Studies have provided conflicting data for calendar trends in anal cancer among HIV+ individuals, one of the most frequent cancers in this population. Our objective here was to compare the risk of anal cancer between HIV+ and HIV- individuals in North America, and how this relationship has changed over time.

Methods
We conducted a cohort study involving 12 cohorts from North America followed between 1996 and 2007. Anal cancer incidence rates were compared between HIV+ men who have sex with men (MSM), HIV+ non-MSM (including women), and HIV- individuals. We calculated rate ratios (RRs) using multivariable Poisson regression with adjustment for age, sex, race/ethnicity (26% imputed), and calendar era. We next determined whether the adjusted RR for HIV+ compared with HIV- controls has changed over time. Since only a subset of cohorts contributed HIV- controls, we also computed age- and sex- and race-standardized incidence ratios (SIR) using national U.S. SEER rates.

Results
Cohort-specific HIV+ anal cancer incidence rates ranged across cohorts from 0 to 154 cases per 100,000 person-years. The cohort-specific prevalence of MSM explained 58% of the total variability in rates. Overall, there were 111 anal cancer diagnoses among 15,907 HIV+ MSM, 38 diagnoses among 18,239 HIV+ non-MSM, and 79 diagnoses among 115,469 HIV- individuals. The corresponding adjusted RRs were 66.6 (95% CI: 36.9-120.2) for HIV+ MSM and 23.4 (95% CI: 11.9-46.1) for HIV+ non-MSM compared with the HIV- control group. For both HIV+ MSM and non-MSM, the RR was highest in 1999-2002, but the RR decreased for both groups in the most recent calendar era, 2003-2007 (Table), although the differences were not statistically significant (p>0.2) comparing RRs across eras. Inferences were similar for SIRs.

Table. Anal cancer RR (95% CI) for HIV+ MSM and HIV+ non-MSM compared with HIV- controls (reference) and national US SEER rates.

<table>
<thead>
<tr>
<th></th>
<th>RR (MSM)</th>
<th>RR (non-MSM)</th>
<th>SIR (MSM)</th>
<th>SIR (non-MSM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996 to 1998</td>
<td>97.7 (12.3-774.3)</td>
<td>12.0 (0.7-195.5)</td>
<td>63.5 (29.0-120.6)</td>
<td>10.2 (0.3-56.9)</td>
</tr>
<tr>
<td>1999 to 2002</td>
<td>114.7 (35.3-372.8)</td>
<td>35.2 (9.8-126.5)</td>
<td>117.3 (84.5-158.5)</td>
<td>26.4 (11.4-52.0)</td>
</tr>
<tr>
<td>2003 to 2007</td>
<td>48.1 (23.6-98.2)</td>
<td>19.7 (8.8-44.1)</td>
<td>77.7 (59.3-100.0)</td>
<td>26.4 (14.8-43.5)</td>
</tr>
</tbody>
</table>

Conclusions
Despite an aging HIV+ population with presumed longer exposure to the oncogenic effects of human papillomavirus, the relative incidence of anal cancer among HIV+ individuals in the most recent calendar era has not increased. It is possible that improvements in immune function resulting from effective antiretroviral therapy contributed to this result.

Acknowledgements
The abstract is submitted on behalf of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).
**O16. Integrative proteomics and genomics supports a role for interferon gamma in the pathogenesis of Kaposi sarcoma and finds multiple candidate diagnostic proteins for early detection or prevention**

Lynn Amon1, Jennifer Gross1, Jackson Orem2, Innocent Mutyaba2, Warren Phipps3,5, Kurt Diem6, Meei-Li Huang6, Lawrence Corey3,4,6, Martin McIntosh1, Corey Casper1,3,5,7,8

1Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
2Uganda Cancer Institute, Kampala, Uganda
3Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
4Clinical Research Divisions, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
5Department of Medicine, University of Washington, Seattle, WA, USA
6Department of Laboratory Medicine, University of Washington, Seattle, WA, USA
7Department of Epidemiology, University of Washington, Seattle, WA, USA
8Department of Global Health, University of Washington, Seattle, WA, USA

**Background**

Kaposi sarcoma (KS) is a common and morbid condition among persons with HIV infection. Strategies for preventing KS or designing better treatment regimens would be aided by the identification of biomarkers for development or progression of KS. Due to the vascular and often disseminated nature of KS, proteomic signatures detected from and specific to KS tumors may yield viable candidate diagnostic protein markers and insights into the pathogenesis of KS.

**Methods**

Flash-frozen punch biopsies from cutaneous samples of tumor and normal skin of individuals having epidemic (HIV-positive) or endemic (HIV-negative) KS were profiled using tandem mass spectrometry. Protein data were integrated with previously existing databases relevant for prioritizing diagnostic marker candidates, including plasma proteome data of cancer-free individuals, normal endothelial cells, and microarrays profiling the miRNA of KS, normal skin, KSHV-infected endothelial cells, and uninfected cells.

**Results**

In a comparison of 13 HIV+ tumor punch biopsies to 5 HIV+ normal samples, 5100 total proteins were identified. We have identified proteins abundant in the majority of tumor samples and absent from normal skin and plasma of cancer-free individuals that may serve as candidate diagnostic markers. Aligning the data with KS tissue expression data produced 72 proteins that were over-abundant in KS samples in both proteomic and transcriptomic datasets. Most notably, a third of those proteins (24 total) are known to interact with interferon gamma (IFNγ) (enrichment p-value<10^{-8}). Gene symbols are shown in Figure 1. This finding is consistent with previous observations on the importance of IFNγ in endothelial cell proliferation and expression in KS tumors. We are currently evaluating these results further, including conducting other experiments intended to compare the KS proteomics signatures that distinguish 6 HIV+ and 6 HIV- KS tumors. Preliminary results from these analyses will be presented as well.

**Conclusions**

The combined use of genomic and proteomic interrogation of biopsy material from KS tumors has revealed a large set of proteins that are overexpressed in KS compared to normal skin and provides a set of candidate diagnostic proteins for the prevention or early detection of KS. These data are also useful in exploring hypotheses regarding the pathogenesis of KS and relating those mechanisms to their role in endemic and epidemic disease.
Malignant lymphoma incidence and HIV-related lymphoma subtypes in the Western Cape of South Africa, 2002-2009

E. Akin Abayomi1,3, Avril Sommers1, Ravnit Grewal1, Gerhard Sissolak1, Fatima Bassa1, Deborah Maartens1, Peter Jacobs1, Cristina Stefan1, Leona W. Ayers2,3
1Division of Haematology, Stellenbosch University, Cape Town, South Africa
2Department of Pathology, The Ohio State University, Columbus, OH, USA
3Sub-Saharan Africa Lymphoma Consortium

Background
The incidence of malignant lymphomas (ML) in the Western Cape, a province of South Africa (SA), with a population of 5 million and an estimated HIV prevalence of 15% (census report 2002) has not been previously documented. Highly active antiretroviral therapy (HAART) was introduced into the public patient sector in 2004, with 28% estimated coverage by 2007 (UNAIDS/WHO 2008). People living with HIV (PLWH) have 60-200 times increased risk of developing HIV-related lymphoma (HRL). Therefore, based on HIV prevalence, HRL would be expected to increase but is undocumented.

Materials and methods
We reviewed all patients diagnosed with ML from the Tygerberg Academic Hospital catchments area in the Western Cape of SA for years 2002-2009. In this timeframe 606 cases of ML were identified, of which 488 were HIV-negative and 118 HIV-positive. ML were subtyped according to WHO classification (2008) based on cell or tissue morphology and molecular and immunophenotypic platforms.

Results
ML cases increased each year from 2002 to 2005 and remain elevated in both the HIV-negative and HIV-positive patients through 2009. HRL increased from 5% in 2002 to 30% in 2009 with a profile of subtypes differing from the HIV-negative cases. ML subtypes of HIV-negative (488) and HIV-positive (118) cases are shown in Table 1.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>%HIV-</th>
<th>%HIV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt lymphoma</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Small cell lymphoma</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Mucosa-associated lymphoid tissue (MALT)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>T-cell lymphoma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Primary effusion lymphoma and Castleman’s disease</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Conclusions
ML cases increased from 2002 to 2009 including a dramatic increase in HRL, currently at 29% of all cases. This changing pattern of subtypes in PLWH presents new challenges to histopathology diagnosis as well as a clinically more therapeutically difficult patient population. Burkitt lymphoma, the most common HRL, is among emerging subtypes, along with plasmablastic lymphoma, not previously seen in this geographic region. We anticipate the continued rise in HRL cases as PLWH live longer with HAART. Emergence of more aggressive lymphoma subtypes inevitably poses a major strategic health concern in the region. We participate in the Sub-Saharan Africa Lymphoma Consortium [http://www.ssalc.org] to expand the understanding of HRL in this region of the world.
**018. HPV genotype and EGFR activation in conjunctival carcinoma among HIV patients in East Africa**

S.C. Remick¹, J.J. Yu¹, P. Fu², J.J. Pink², D. Dawson², J. Wasman², J. Orem³, W.O. Mwanda⁴, Y. Guo¹, X. Liang¹, W.P. Petros¹, R.T. Mitsuyasu⁵, H. Wabinga⁶

¹Mary Babb Randolph Cancer Center and Molecular Medicine Core Facility, Schools of Medicine and Pharmacy, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, WV, USA
²Departments of Biostatistics and Epidemiology, Medicine, and Pathology, Center for AIDS Research, and Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH, USA
³Uganda Cancer Institute, Makerere University, School of Medicine, Kampala, Uganda
⁴Department of Pathology, Kenya National Hospital, University of Nairobi, Nairobi, Kenya
⁵Department of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
⁶Department of Pathology, Makerere University, School of Medicine, Kampala, Uganda

**Purpose**

There is a substantial growth in the number of HIV patients with conjunctival squamous cell carcinoma in East Africa. However, the etiologic mechanism is unclear and therapeutic options are very limited. We hypothesized that this unique AIDS-associated malignancy would harbor human papillomavirus and involve activation of the EGFR signaling pathway. Positive findings would identify etiologic causes and provide clinical guidance to improve treatment.

**Experimental design**

Expression of p-MAPK/MAPK, p-Akt/Akt, and p-EGFR/EGFR in cell nucleus and cytoplasm of 38 FFPE specimens was assessed by immunohistochemistry; HPV genotype was detected by qPCR; EGFR mutation was assessed by DNA sequencing; and EGFR mRNA expression was measured using relative qPCR. Statistical analyses included two-sided Fisher exact test or chi-square test, Spearman correlation coefficient, and ANOVA.

**Results**

HPV 18 was found in 23 of 38 (61%) samples, with HPV 16 double-genotype in 6 patients. Immunohistochemistry and qPCR data suggest that activation and expression of the EGFR signaling pathway are related to disease progression of conjunctival cancer. The associations of cytoplasmic p-MAPK and cytoplasmic p-Akt with tumor invasiveness were significant (p = 0.05 and 0.028, respectively). Nuclear p-EGFR appeared only in invasive tumors. A significant positive association between EGFR expression and disease invasiveness was observed (p=0.01). A SNP in 10 patients and one missense mutation were found within EGFR tyrosine kinase domain. Statistical analysis indicates that patients with measurable EGFR expression more likely harbor EGFR mutations, compared to those with negative EGFR expression (35.3% vs. 0%).

**Conclusions**

Our data indicate a relationship between HPV infection and EGFR signaling in patients with AIDS-associated squamous cell carcinoma of the conjunctiva. HPV infection and EGFR activation/alteration may contribute to and sustain the high prevalence of the cancer in East Africa. Our findings support clinical trials that involve HPV vaccination, with application of therapeutic agents that target the EGFR pathway. These clinical strategies may reduce the incidence of conjunctival carcinoma among HIV patients in equatorial Africa.

**Acknowledgements**

This work was supported in part by NIH grants CA121947, CA70081, and CA43703.
019. Visual inspection and HPV-based cervical cancer screening in HIV-infected women in Pune, India

Vikrant Sahasrabuddhe1, Ramesh Bhosale2, Bryan Shepherd1, Cathy Jenkins1, Anita Kavatkar2, Rohini Kelkar4, Seema Sahay3, Arun Risbud3, Sten Vermund1, Sanjay Mehendale2
1Vanderbilt University, Nashville, TN, USA
2Byramjee Jeejeebhoy Medical College, Pune, India
3National AIDS Research Institute, Pune, India
4Tata Memorial Center, Mumbai, India

Background
Visual inspection with acetic acid (VIA) and human papillomavirus (HPV) testing are being explored as alternatives to cervical cytology (Pap smears) for cervical cancer screening in India and other resource-limited settings. However, there are limited data on utility and acceptability of these screening approaches for detection of cervical intraepithelial neoplasia (CIN) among HIV-infected women.

Methods
We conducted a cross-sectional study among n=303 consenting non-pregnant HIV-infected women in Pune, India. All participants underwent independent and simultaneous screening with VIA, cytology, and collection of HPV samples (by both self-collected samples and clinician collected samples, analyzed using Digene Hybrid Capture-2™ (HC2) assay). Independent diagnostic assessment by colposcopy was conducted in the same visit and histopathology was performed if clinically indicated. We compared the measures of test performance for VIA-positive test results and “cytology-positive” detection of any squamous intraepithelial lesions (SIL), at the ≥CIN2 diagnostic threshold. We also performed multiple imputation analysis to derive predictions for missing values of histopathology to account for potential verification bias, using data from VIA, cytology, and colposcopy results and compared simulated measures of screening test performance. We compared patient preferences, HPV detection rates, and measures of agreement between two HPV sample collection approaches (self-sampling versus sample collection during pelvic examination).

Results
The median age of the HIV-infected participants was 30 years (interquartile range, IQR: 27-34), and their median CD4+ cell count was 343/μL (IQR: 244–495). VIA was positive in 84/303 (27.7%). Cytology revealed normal results in 131 (53%), ASCUS in 11 (4.5%), LSIL in 87 (35.2%), and HSIL in 18 (7.3%) of the 247 evaluable slides. VIA has higher sensitivity compared to cytology: 80% vs. 60% (based on conventional gold standard) and 70% vs. 69% (based on multiple imputations for missing histopathology). The specificity of VIA was also higher than cytology (83% vs. 65% and 82% and 70%, based on the conventional and imputation methods, respectively). The detection rates of HR-HPV positive test results were comparable in self versus clinician collected samples overall [44.1% (130/295) vs. 41.8% (124/297), p=0.6]. The pair-wise agreement between the two HPV sampling approaches was high [88.1%] and the kappa statistic of 0.76 (95% C.I.: 0.68-0.83) denoted substantial agreement beyond chance. A higher proportion of women found self-sampling to cause absolutely no discomfort (61% vs. 51%, p=0.01) and no pain (59% vs. 42%, p=0.01) than pelvic examination.

Conclusions
VIA performed similar to or better than cytology among HIV-infected women in Pune, India. With sensitivity for ≥CIN2 lesions consistently at or above 70%, and with the ability to link screening and testing in the same visit, VIA can be a useful independent primary screening test for HIV-infected women in low-resource settings. Clinic-based self-collection of HPV compared favorably in comparison to sample collection through clinic-based pelvic examination, signifying importance of further research to explore field acceptability and operational aspects of HPV-based screening.

Acknowledgements
All collaborators of the HIV-HPV-Cervical Cancer Prevention Research Consortium in India.
O20. An ATM/Chk2-mediated DNA damage responsive signaling pathway suppresses Epstein-Barr virus transformation of primary human B cells

Pavel Nikitin1, Chris Yan1, Eleonora Forte1, Alessio Bocedi1, Jay Tourigny1, Amee Patel2, Sandeep Dave2, Katherine Hu1, Jing Guo1, David Tainter1, Olena Rusyn1, Micah Luftig1

1Department of Molecular Genetics and Microbiology, Center for Virology, Duke University School of Medicine, Durham, NC, USA
2Duke Institute for Genome Sciences and Policy, Duke University, Durham, NC, USA

Epstein-Barr virus (EBV) infection of primary B cells leads to the outgrowth of indefinitely proliferating lymphoblastoid cell lines (LCLs). However, the efficiency of immortalization is less than 10% of infected cells. We hypothesize that a robust innate tumor suppressor response prevents long-term outgrowth of the majority of infected cells. In this study we identify the DNA damage response (DDR) as a major component of this response. EBV infection of primary B cells activated hallmarks of the DDR including phosphorylated ATM, Chk2, g-H2AX, and 53BP1 foci. DDR activation was not due to lytic viral DNA replication nor did its marks co-localize with latent viral episomes. Rather, EBV induced a period of hyper-proliferation early after infection responsible for DDR activation. Microarray data supported the transient activation and subsequent attenuation of proliferation and DDR-associated mRNAs during LCL outgrowth. Importantly, activation of this pathway suppressed transformation as small molecule antagonism of the DNA damage responsive kinases ATM and Chk2 increased EBV transformation efficiency. Thus, we propose a model whereby EBV infection initially drives aberrant cellular DNA replication activating an anti-proliferative DNA damage response. Long-term outgrowth depends on attenuation of this hyper-proliferative signal through full latency III gene expression.
021. TNFAIP3(A20) genetic alterations in AIDS-related lymphomas

Lisa Giulino1,2, Susan Matthew3, Wayne Tam4, Amy Chadburn3, Gianna Ballon3, Sharon Barouk3, Giuseppina Antonicelli4, Lorenzo Leoncini4, Ethel Cesarman3

1Department of Pediatrics, New York Presbyterian Hospital – Cornell, New York, NY, USA
2Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
3Department of Pathology, Weill Cornell Medical College, New York, NY, USA
4Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
5Department of Human Pathology and Oncology, University of Siena, Siena, Italy

Background
AIDS-related lymphomas (ARLs), which include Burkitt lymphoma and diffuse large B cell lymphoma (DLBCL), are a heterogeneous group of lymphoproliferative disorders that occur in the setting of HIV-mediated immune suppression. A subset of cases are associated with Epstein-Barr virus (EBV) infection. EBV expresses latent viral oncoproteins that constitutively activate the transcription factor NF-κB, a potent inducer of genes involved in promoting B cell survival and proliferation [1].

In immunocompetent individuals, lymphomas that are not associated with EBV can also display increased NF-κB activity, and recent reports have described mutations in regulators of NF-κB. One of the frequently mutated regulatory genes is TNFAIP3, which encodes A20, a ubiquitin modifying enzyme involved in the termination of NF-κB signaling. Mutations resulting in the inactivation of A20 have been found in a significant proportion of marginal zone lymphomas [2], classical Hodgkin’s lymphomas and primary mediastinal B cell lymphomas [3], and DLBCLs [4]. In ARL the role of NF-κB activation and the incidence of mutations in A20 have not been described.

Materials and methods
We evaluated archival formalin-fixed paraffin-embedded tissue samples of AIDS-related lymphoma for genetic alterations in A20. Tissue was collected through an international collaboration between Weill Cornell Medical College in New York, NY, and Siena University in Siena, Italy. A tissue microarray with 48 cases of ARL was prepared, and characterization of viral status and lymphoma subtype were determined by immunohistochemistry and in situ hybridization for Epstein-Barr encoded RNA (EBER). Fluorescent in situ hybridization (FISH) was used to evaluate for genomic deletions in A20, and translocations of cMYC, BCL-2, and BCL-6. Direct sequencing of the coding region of A20 was performed to evaluate for additional mutations.

Results
FISH was performed on 48 cases of ARL. Of 21 cases with successful hybridization loss of heterozygosity at the A20 locus was observed in 6 cases (28%). Cases with A20 deletion included three diffuse large B cell lymphomas, two Burkitt lymphomas, and one Burkitt-like lymphoma. Two cases were positive for EBER but all were negative for latent membrane protein-1 (LMP-1). Partial sequencing of approximately 70% of the A20 coding regions in 23 cases did not reveal additional mutations.

Conclusions
A20 may represent a tumor suppressor gene in a subset of AIDS-related lymphomas. Inactivation of A20 may be an alternative mechanism of NF-κB upregulation in the absence of LMP-1.

References
C/EBPbeta mediates bortezomib-induced EBV and KSHV lytic gene expression

Courtney O’Farrell, Meir Shamay, Nene Kalu, Richard F. Ambinder
Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD, USA

Bortezomib is a proteasome inhibitor used clinically for the treatment of multiple myeloma and mantle cell lymphoma and is being evaluated for the treatment of AIDS-related lymphoma and Kaposi’s sarcoma in the AIDS Malignancy Consortium. Activation of herpes zoster infection is a well-recognized complication of bortezomib therapy. In previous work, we have shown that bortezomib is a potent inducer of EBV and KSHV lytic gene expression and demonstrated a novel approach to therapy that leverages this activation to facilitate tumor imaging and treatment.

In an effort to better understand the relevant pathways, we confirmed that bortezomib at 20 nM concentrations induces expression of EBV and KSHV immediate early genes (EBV ZTA, KSHV RTA) as assessed by immunoblot and by reverse transcriptase PCR for the associated transcripts. Bortezomib activates EBV ZTA promoter expression and KSHV RTA promoter expression in reporter assays. Bortezomib does not alter C/EBPalpha protein level as assessed by immunoblot but does lead to increased C/EBPbeta. C/EBPbeta includes activating isoforms (LAP) and an inhibitory isoform (LIP). In reporter assays, we show that C/EBPbeta LAP activates the EBV promoters whereas LIP is inhibitory. In ChIP assays we show that bortezomib treatment leads to increased C/EBPbeta binding to the ZTA promoter. Mutation of the binding sites abolishes activation of the promoter associated with bortezomib treatment. In order to determine whether C/EBPbeta expression simply tracks with lytic viral gene expression or plays a key role in mediating such expression, we created a tet-regulated C/EBPbeta knockdown. In the presence of doxycycline, C/EBPbeta is suppressed, and bortezomib lytic induction of EBV as measured by increases in ZTA mRNA, ZTA protein, and viral DNA copy number are all blunted. Induction of lytic viral gene expression in EBV Akata cell lines by anti-Ig treatment is also blunted.

These results suggest that C/EBPbeta family members play a key role in mediating activation of EBV and KSHV lytic infection following bortezomib and other inducers.

Acknowledgements
This work is supported by P30CA06973 and P50CA96888.

References
023. Elevated serum levels of CXC L13 precede HIV-associated non-Hodgkin’s lymphoma

Shehnaz K. Hussain¹,², Daniel Widney³, Lisa Jacobson⁴, Elizabeth C. Breen⁵, Alexandra Levine⁶, Roger Detels¹, Zuo-Feng Zhang¹,², Otoniel Martínez-Maza¹,²,⁷,⁸
¹Department of Epidemiology, University of California, Los Angeles, CA, USA
²Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA, USA
³Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
⁴Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA
⁵Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
⁶City of Hope Comprehensive Cancer Center, Duarte, CA, USA
⁷Department of Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
⁸UCLA AIDS Institute, Los Angeles, CA, USA

Introduction
CXCL13 (BCA-1, BLC), a chemokine constitutively expressed by cells in secondary lymphoid organs, promotes the chemotaxis of B cells to secondary lymphoid organs. There is accumulating evidence that CXCL13 is aberrantly expressed in a variety of lymphomas; thus we sought to define the longitudinal expression pattern of CXCL13 preceding a non-Hodgkin’s lymphoma (NHL) diagnosis in the setting of HIV.

Methods
A nested case-control study was conducted in the setting of two large prospective cohort studies of the natural and treated history of HIV and AIDS, the Multicenter AIDS Cohort Study (MACS) and the Women’s Interagency HIV Study (WIHS). Archival, pre-cancer diagnosis serum specimens from NHL cases (180 MACS and 30 WIHS) and HIV-seropositive matched controls (180 MACS and 109 WIHS) were assayed for CXCL13 by ELISA. Visit-matched sera from case-control pairs were obtained when available from three time windows preceding NHL diagnosis in the case: 3-5 years pre-NHL (closest to 4 years), 1-3 years pre-NHL (closest to 2 years), and 0-1 year pre-NHL (closest to 0.5 year). These data were analyzed using multivariate conditional logistic regression models to obtain adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for each unit increase in log-transformed CXCL13 for each of the three study visits.

Results
CXCL13 levels were significantly elevated at all three time points preceding the clinical recognition of NHL, 3-5 years: OR=3.66 (95% CI, 2.34-5.74); 1-3 years: OR=6.62 (95% CI, 3.78-11.6); and 0-1 year: OR=3.68 (95% CI, 2.27-5.98). Subgroup analyses revealed that CXCL13 was more strongly associated with systemic NHL compared to central nervous system NHL, and EBV-negative compared to EBV-positive tumors.

Conclusions
These data suggest that CXCL13 may be a biomarker for NHL in the setting of HIV, and is more strongly associated with systemic, EBV-negative tumors. Studies are currently under way to further characterize the role CXCL13, and its receptor CXCR5, in lymphomagenesis.
Background
HIV envelope (env) protein binds to CCR5 and/or CXCR4 chemokine receptors on lymphocytes, resulting in cell infection and death. CXCR4 is also commonly and highly expressed on neoplastic breast duct cells. Binding of X4-env protein, but not R5-env protein, can induce apoptosis of neoplastic breast cells. We hypothesized that CXCR4-tropic HIV may account for the reduced breast cancer incidence observed in HIV-infected women in the United States before widespread use of effective antiretroviral therapy.

Methods
This was a retrospective case-control study of women who developed breast cancer during 1993-2008 in the WIHS and HERS longitudinal studies. Cases were HIV-infected women who had stored plasma samples within 24 months (before or after) of a confirmed breast cancer diagnosis and who had HIV viral load ≥500 copies/mL. Three HIV-infected women controls, without breast cancer, were matched to each case based on age (±2 yrs) and date (±6 months) of plasma specimen collection. The Monogram Biosciences Trofile assay was used to classify women who had X4-tropic (including X4/R5-tropic) versus exclusively R5-tropic HIV. Unadjusted and adjusted conditional logistic regression models were used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for breast cancer associated with tropism, contemporaneous HIV viral load and CD4 count, antiretroviral therapy, and classical breast cancer risk factors.

Results
22 breast cancer cases and 66 matched controls met the inclusion criteria and had valid HIV tropism results. Only 2 (9.1%) breast cancer cases had CXCR4-using HIV, compared to 19 (28.8%) of the matched controls. In unadjusted analysis of 19 variables, breast cancer was inversely associated with CXCR4-using HIV (p=0.05), and marginally associated with menstrual status (p=0.08). In multivariate analysis adjusted for CXCR4-using HIV and menstruation in the past 12 months, both variables were significantly associated with reduced odds of breast cancer (CXCR4-tropic HIV ORadj=0.10, 95% CI 0.01-0.93; menstruation in the past 12 months ORadj=0.07, 95% CI 0.005-0.92). Other classical breast cancer risk factors, HIV viral load, CD4 cell count, antiretroviral therapy, and race/ethnicity had no detectable impact on these associations.

Conclusions
These results support the hypothesis that the low breast cancer incidence observed in women with HIV/AIDS is specifically tied to circulating variants of HIV that bind to and signal through CXCR4, a receptor that is commonly expressed on hyperplastic and neoplastic breast duct cells. These findings suggest novel pathogenic interactions between viral proteins and neoplastic breast cells in vivo and invite new approaches for treating CXCR4-expressing malignancies.

These results will be presented as a poster at the 101st Meeting of the American Association for Cancer Research, Washington, DC, April 17-21, 2010, and the abstract will be published in the 2010 Proceedings of the American Association for Cancer Research.
HIV-related Hodgkin lymphoma in the era of combination antiretroviral therapy: incidence, outcome, and evolution of CD4+ T cell lymphocytes

Matthias Egger
COHERE Lymphoma Working Group
Institute of Social and Preventive Medicine, University of Bern, Switzerland

Clinical background
HIV-infected patients are at increased risk to develop Hodgkin lymphoma (HL). We examined the incidence and risk factors for HL, the evolution of CD4 cell counts before HL diagnosis and prognosis of patients with HIV-related HL and in the era of combined antiretroviral therapy (cART) in the Collaboration of Observational HIV Epidemiological Research Europe (COHERE).

Patients and methods
40,168 adult HIV-1 infected patients who started cART in one of 16 prospective cohort studies in Europe were included. Incidence rates per 100,000 person-years, Kaplan-Meier estimates of cumulative incidence and survival, and adjusted hazard ratios from Weibull random-effects models, with 95% confidence intervals (CIs), were calculated. CD4 counts over time were compared between patients who were free of AIDS, on cART and developed HL (cases), and control patients. Cases and controls were matched 1:5 for cohort, age, sex, risk group, CD4 cell count at start of cART, and HIV-1 RNA at reference date, defined as HL diagnosis (cases), or at identical length of followup since start of cART (controls). We used multilevel linear regression to model changes in CD4 cell counts after start of cART and during the year before reference date and tested for differences between slopes in cases and controls. The analysis was repeated for patients with non-Hodgkin lymphoma (NHL).

Results
During 159,133 person-years of followup, 78 patients were diagnosed with HL. The crude incidence rate of HL was 50.4 per 100,000 person-years for patients who developed HL before starting cART (17 cases) and 48.7 per 100,000 person-years in patients who were already on cART (61 cases). Age, gender, CDC clinical stage, CD4 cell count, and HIV-1 RNA viral load at baseline (start of observation) were not significantly associated with the risk of HL. During a median followup of 18 months (IQR 4.8-34.8 months) 12 of 78 patients with HL died. Survival was 88% (95% CI 77-94) at 1 year and 81% (95% CI 68-89) at 2 years. A total of 18 HL patients were matched to 79 controls. At HL diagnosis, 16 of 18 cases (89%) had undetectable viral loads (<500 copies/ml). The evolution of CD4 cell counts before reference date differed: in HL patients the CD4 cell count increased after start of cART (+126 cells per year) but declined during the year before the HL diagnosis (-99 cells per year). In controls the CD4 cell counts increased throughout (+57 cells per year). Slopes differed significantly during the year before the HL diagnosis (p=0.003), but not after start of cART (p=0.944); see Figure 1. In NHL patients, the CD4 cell count increased after start of cART (+131 cells per year) and remained stable during the year before the NHL diagnosis (-16 cells per year). In controls CD4 cell counts increased throughout (+38 cells per year).

Conclusions
HL incidence rates were similar in cART treated and untreated patients. CD4 cells declined before HL diagnosis in patients on cART, despite undetectable viral load. In contrast, in NHL patients CD4 cell counts did not sharply decrease in the year before NHL diagnosis. Patients on successful cART who experience a sudden decline of CD4 counts should be investigated for HL.

Figure 1. Evolution of CD4 cells in Hodgkin lymphoma cases and matched controls.
O26. Risk of HIV-associated Hodgkin lymphoma during the first months after initiation of combination antiretroviral therapy

E. Lanoy¹, P.S. Rosenberg², F. Fily³, A.S. Lascaux⁴, V. Martinez⁵, M. Partisani⁶, I. Poizot-Martin⁷, E. Rouveix⁶, E.A. Engels², D. Costagliola¹,9, J.J. Goedert²

¹INSERM, U943, Paris, France; UPMC Univ Paris 06, UMR S943, Paris, France
²Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA
³Service des Maladies Infectieuses et de Réanimation Médicale, CHU Pontchaillou, Rennes, France
⁴Département d’immunologie clinique, Hôpital Henri-Mondor, Créteil, France
⁵Service de Médicine Interne, AP-HP, Hôpital Antoine Béclère, Clamart, France
⁶Centre de soins de l’infection à VIH, Hôpitaux Universitaires, Strasbourg, France
⁷Unité CISIH Sud Hématologie VIH, Hôpital Sainte-Marguerite, Marseille, France
⁸Service de Médecine 5, Hôpital Ambroise-Paré, Boulogne, France
⁹Service de Maladies Infectieuses et Tropicales, AP-HP, Groupe hospitalier Pitié-Salpêtrière, Paris, France

Background

Since the advent of combination antiretroviral therapy (cART), several studies have described an increase in the incidence of Hodgkin lymphoma (HL). This increase has been postulated to be linked with immunologic mechanisms occurring at cART initiation. Relationships between the CD4 cell count and the risk of HL have also been investigated. Our study aimed to evaluate the risk of HL by use of cART and its duration.

Materials and methods

From the French Hospital Database on HIV (FHDH-ANRS CO4), a large prospective hospital cohort, we studied the incidence of HL in 1992-2007 according to the duration of cART exposure: no cART and year<1996, no cART and year ≥1996, [0;1], [1;2], [2;3], [3;6] and ≥6 months. Relative rates (RR) of HL were estimated using Poisson regression models for the duration of cART exposure, adjusted for age, sex and exposure group, migration from sub-Saharan Africa, AIDS stage, and CD4 cell count.

Results

Our study included 286,806 person-years (PY) of followup and 187 HL cases. The incidence of HL was not associated with the period: 0.79, 0.60, and 0.64 per 1000 PY before 1996, in 1996-1999, and since 2000, respectively (p=0.55). Risk of HL was significantly related to cART (p=0.008), being especially high during the first 3 months of use (Table 1). The association remained after adjustment for age, sex and exposure group, migration, and AIDS stage (p=0.006), but not in the model accounting for CD4 cell count (p=0.058). A peak of HL incidence was observed for 50-99 CD4 cell count and the association between risk of HL and CD4 cell count remained significant in the multivariate model (Figure 1, p<10⁻⁶).

Table 1.

<table>
<thead>
<tr>
<th>No of diagnoses</th>
<th>Incidence per 1000 PY</th>
<th>Crude RR 95%CI</th>
<th>Adjusted RR Model 1* 95%CI</th>
<th>Adjusted Model 2** 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>no cART and year&lt;1996</td>
<td>43</td>
<td>0.58</td>
<td>1.35 [0.84;2.18]</td>
<td>1.14 [0.7;1.85]</td>
</tr>
<tr>
<td>no cART and year≥1996</td>
<td>28</td>
<td>0.79</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>[0;1]</td>
<td>6</td>
<td>2.01</td>
<td>3.48 [1.48;8.17]</td>
<td>3.09 [1.31;7.28]</td>
</tr>
<tr>
<td>[1;2]</td>
<td>2</td>
<td>0.68</td>
<td>1.19 [0.29;4.89]</td>
<td>1.05 [0.25;4.33]</td>
</tr>
<tr>
<td>[2;3]</td>
<td>7</td>
<td>2.35</td>
<td>4.11 [1.85;9.13]</td>
<td>3.62 [1.62;8.08]</td>
</tr>
<tr>
<td>[3;6]</td>
<td>8</td>
<td>0.94</td>
<td>1.63 [0.76;3.46]</td>
<td>1.43 [0.67;3.05]</td>
</tr>
<tr>
<td>≥6</td>
<td>93</td>
<td>0.58</td>
<td>1.00 [0.69;1.43]</td>
<td>0.83 [0.57;1.2]</td>
</tr>
</tbody>
</table>

*adjusted for age, sex and exposure group, migration for sub-Saharan Africa, AIDS stage. **adjusted for variables in model 1 and CD4 cell count.
Conclusion
Our results support that the early cART effect on the risk of HL is largely explained by CD4 count.

Acknowledgement
This abstract is presented on behalf of the FHDH-ANRS CO4.
**027. Non-AIDS-defining cancer mortality among people with AIDS in Italy**

Antonella Zucchetto¹, Barbara Suligoi², Silvia Bruzzone³, Angela De Paoli¹, Simona Pennazza⁴, Jerry Polesel¹, Luigino Dal Maso¹, Giovanni Rezza⁵, Diego Serraino¹

¹Unit of Epidemiology and Biostatistics, National Cancer Institute “Centro di Riferimento Oncologico”, Aviano, Italy
²Department of Infectious Diseases, COA, National Institute of Health, Rome, Italy
³Direzione centrale per le statistiche e le indagini sulle istituzioni sociali, Servizio Sanità e Assistenza, National Institute of Statistics, Rome, Italy

**Background**

Mortality due to non-AIDS-defining cancers (NADCs) among HIV-positive patients, in the era of highly active antiretroviral therapies, has yet to be completely defined. To estimate the excess risk of death for each NADC among people with AIDS (PWA), in comparison with the general population, we conducted a population-based study in Italy.

**Materials and methods**

Between 1999 and 2006, 10,391 Italian citizens (≥15 years of age) had been diagnosed with AIDS in Italy. These PWAs constituted the population included in our study. Death certificates were retrieved through a record-linkage with the mortality databases at the National Institute of Statistics. This allowed the extraction of information about PWA dates of death, up to December 31, 2006. The underlying cause of death, for each deceased PWA, was identified following the International Classification of Diseases, 10th revision (ICD-10), applied also for the general population. The excess risks of death for each NADC were therefore estimated through standardized mortality ratios (SMRs) with 95% confidence intervals (CIs), in comparison with the Italian general population.

**Results**

Among 3,209 deceased PWA, 7.4% had died of NADCs, with an SMR of 6.6 (95% CI 5.8-7.5). Significantly elevated excess risks of death were found for a broad range of cancers, notably for Hodgkin lymphoma (SMR=174), cancers of liver (SMR=11.1), brain (SMR=10.0), head and neck (SMR=8.2), lung (SMR=5.9), and myeloma and leukemias (SMR=5.9). SMRs were higher among injecting drug users (IDUs) (SMR=15.5 for all NADC) than among other HIV-transmission categories (SMR=4.8), above all for liver cancer (SMR=65.2 among IDUs; SMR=2.8 among non-IDUs).

**Conclusions**

We found particularly elevated SMRs for NADCs among PWA, with several excess risks of death that were higher than those expected, based on NADC incidence recorded in Italy [1]. This finding could be explained by the joint effect of an increased incidence of some malignancies, markedly those related to smoking and viral infections, and of their poorer prognosis among PWA versus the general population.

**Reference**

Objective
Treatments for high-grade perianal intraepithelial neoplasia (PAIN 2-3), include surgical ablation/excision and have significant morbidity and recurrence rates. Cidofovir, a cytidine nucleotide analogue, has broad-spectrum antiviral activity. This multicenter study prospectively evaluated the efficacy, safety, and tolerability of topical cidofovir for treatment of PAIN 2-3 in HIV-positive individuals.

Methods
HIV-positive patients with biopsy-proven PAIN 2-3 ≥ 3 cm² were eligible. Subjects applied 1% topical cidofovir for 6 two-week cycles consisting of 5 consecutive days of treatment and 9 days without treatment. Subjects were evaluated every 2 weeks. High-resolution anoscopy and biopsy were performed 6 weeks after the last cycle. Results were scored as stable disease (SD), partial response (PR) (> 50% reduction in size), complete response (CR), or progressive disease (PD) based on size and histology.

Results
24 men and 9 women were enrolled. Mean age was 33 years, median HIV RNA level was <75 copies/ml, and mean CD4 count was 440/µl. HPV DNA was detected in intra-anal swabs of 31 of 32 (97%) subjects with analyzable specimens. The most common type was HPV16 (44%).

27 (82%) subjects completed treatment per protocol—CR: 4 (15%); PR: 12 (44%); SD: 9 (33%); PD: 2 (7%) (1 with a superficially invasive cancer and 1 with new PAIN 2-3). Six subjects did not complete treatment because of discomfort (1), poor compliance (4), and CR after 4 cycles (1).

26 of 33 subjects (79%) reported adverse events likely related to treatment. Most were mild or moderate, including self-limited, localized, superficial ulcerations in the disease area (2 mild, 19 moderate, 1 severe), discomfort (4 mild, 14 moderate), itching (1 mild, 3 moderate), and bleeding (6 mild). Seven (21%) had mild transient proteinuria.

Conclusions
Topical cidofovir is a well-tolerated and effective treatment for PAIN 2-3 in HIV-positive patients. A larger study is warranted.
Poster Abstracts – Day 1
1. A proportion of germinal center and memory B cells express the latency-associated nuclear antigen (LANA) throughout chronic infection in vivo

Michael S. Nealy, Carrie B. Coleman, Haiyan Li, Scott A. Tibbetts
Center for Molecular and Tumor Virology, Department of Microbiology and Immunology, Louisiana State University Health Sciences Center, Shreveport, Louisiana, USA

An integral feature of gammaherpesvirus infections is the ability to establish lifelong latency in B cells. During latency, the viral genome is maintained as an extrachromosomal episome, with stable maintenance of the episome in dividing cells mediated by the critical viral proteins LANA for Kaposi’s sarcoma-associated herpesvirus (KSHV) and EBNA-1 for Epstein-Barr virus (EBV). Although EBNA-1 is known to be expressed in multiple B cell subsets, it is believed that the expression of episome maintenance proteins is turned off in the predominant long-term latency reservoir of resting memory B cells, suggesting that chronic gammaherpesvirus infection is maintained in a primarily dormant state. However, the kinetics of LANA/EBNA-1 expression in individual B cell subsets throughout a course of infection has not been previously examined. The infection of mice with murine gammaherpesvirus 68 (MHV68, HV68) provides a useful small-animal model to determine the specific cellular and molecular events that occur in vivo during the establishment of lifelong gammaherpesvirus latency. In work presented here, we describe the use of a heterologously expressed enzymatic marker to define the types of B cells that express the LANA homolog mLANA during chronic MHV68 infection. Our data demonstrate that mLANA is expressed in a stable proportion of infected B cells throughout chronic infection. Expression of mLANA was detected in naïve follicular B cells, germinal center B cells, and memory B cells throughout infection, with germinal center and memory B cells accounting for more than 80% of the mLANA expressing cells during the maintenance of latency. These findings suggest that the maintenance phase of latency is an active process involving proliferation of latently infected germinal center and memory B cells.
2. AIDS-related Kaposi’s sarcoma: outcomes after initiation of highly active antiretroviral therapy under routine conditions in Zimbabwe

Bradley Nelson¹, Margaret Borok², Tariro Makadzange², Tafadzwa Mhlanga², Thomas Campbell¹
¹Department of Medicine, University of Colorado, Denver, Aurora, CO, USA
²Department of Medicine, University of Zimbabwe, Harare, Zimbabwe

Background
Additional information on the outcomes of patients with AIDS-related Kaposi’s sarcoma (AIDS-KS) on highly active antiretroviral therapy (HAART) in resource-limited settings is needed. This study evaluated outcomes in AIDS-KS patients after initiation of HAART in Zimbabwe.

Methods
A retrospective cohort of 124 patients from the Parirenyatwa Hospital Kaposi’s Sarcoma and Opportunistic Infections (OI) Clinics was studied. 31 patients with AIDS-KS were matched 1:3 to 93 non-KS AIDS patients based on date of initiation of HAART, gender, and age. The primary endpoint was loss to care, defined as failure to attend clinic or refill prescriptions for 3 months or longer. Secondary endpoints were weight gain at 6 months, change in CD4+ count within 1 year, and final CD4+ count within 1 year of initiating HAART. Eligibility criteria included a minimum of 6 months of followup in the OI Clinic and less than 2 months of previous HAART prior to beginning therapy through the OI Clinic. A two-step model-selection strategy using KS status, gender, age, WHO performance status, OI disease burden, medical aid, employment, education, pre-treatment cotrimoxazole use, pre-treatment weight, and pre-treatment CD4+ count was used to identify factors associated with loss to care. On the initial univariate analysis, KS status, medical aid, and pre-treatment cotrimoxazole use had a p<0.15 and were included in the final multivariate analysis.

Results
AIDS-KS and non-KS patients did not differ significantly in baseline characteristics except for pre-treatment CD4+ count (196 vs. 92 cells/mm³; p=0.005). On the multivariate analysis, KS status (p=0.016, HR: 4.11, CI: 1.31-12.92) and having medical aid were significant predictors of loss to care (p=0.048, HR: 3.84, CI: 1.02-14.44). At a median followup of 632 days, 37.5% of AIDS-KS patients were lost to care compared to 16.1% of non-KS patients. AIDS-KS patients had significantly worse weight gain than non-KS patients (+0.78% vs. +4.18%, p=0.023). Change in CD4+ count (p=0.149) and final CD4+ count (p=0.729) were not significantly different between study groups. Amongst AIDS-KS patients, retained patients (n=20) had significantly higher pre-treatment CD4+ counts than patients lost to care (n=11) (232 vs. 122 cells/mm³, p=0.048).

Conclusions
After initiating HAART, AIDS-KS patients experienced greater loss to care and poorer weight gain than matched non-KS patients, suggesting that, under routine conditions in Zimbabwe, AIDS-KS patients have worse intermediate- and long-term clinical outcomes than non-KS AIDS patients. AIDS-KS patients retained in care had higher pre-treatment CD4+ counts than patients lost to care, indicating that early intervention with HAART may improve outcomes in AIDS-KS patients.
3. Caspase-7 cleavage of Kaposi sarcoma-associated herpesvirus ORF57 confers a cellular function against viral lytic gene expression

Vladimir Majerciak¹, Michael Kruhlak², Pradeep K. Dagur³, J. Philip McCoy Jr.³, Zhi-Ming Zheng¹

¹HIV and AIDS Malignancy Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
²Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
³Flow Cytometry Core, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA

Background
Host persistent infection by Kaposi sarcoma-associated herpesvirus (KSHV) is etiologically linked to the development of Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. Like other gammaherpesviruses, KSHV establishes a long-term latency in infected cells upon primary infection. The latent infection can be reactivated in a small proportion of latently infected cells, leading to limited production of infectious virus. However, factors which restrict KSHV reactivation from latency and lytic replication remain unknown.

Results
We found that virus reactivation in KSHV latently infected B cells derived from cavity-based B-cell lymphoma by various inducers is associated with induction of apoptosis. We also showed that virus reactivation leads to a specific activation of initiator caspase-8 but not caspase-9. The activation of caspase-8 pathway in infected cells results in cleavage of KSHV ORF57, a viral early protein essential for KSHV multiplication. ORF57 is cleaved at the aspartate residue at position 33 from the N-terminus by caspase-7 in the cytoplasm of infected cells. Caspase-7 cleavage of ORF57 is prevented by pan-caspase inhibitor z-VAD, caspase-3 and caspase-7 inhibitor z-DEVD, and caspase-7 siRNAs. Interestingly, the caspase-7 cleavage site 30DETD33 in ORF57 is not cleavable by caspase-3, although both enzymes use DEXD as a common cleavage site. B cells with lytic KSHV infection and caspase-7 activation exhibit a greatly reduced level of ORF57. In a majority of the cells expressing active caspase-7 no detectable ORF57 appeared. Upon cleavage with caspase-7, ORF57 is deficient in promoting the expression of viral lytic genes. In contrast, the inhibition of caspase-7 cleavage of ORF57 in KSHV⁺ BCBL-1 cells by z-VAD, z-DEVD, or caspase-7 siRNA increased expression of viral lytic genes and production of cell-free virus particles.

Conclusion
Collectively, our data provide the first compelling evidence that caspase cleavage of an essential viral protein ORF57, as a result of apoptosis triggered by virus reactivation, may represent a cellular defense mechanism against lytic KSHV infection.

Warren Phipps¹, Jackson Orem⁶,², Innocent Mutyaba⁶,², James Ferrenberg², Misty Saracino², Meei-Li Huang², Jeff Vieira², Anna Wald¹,³,⁵, Larry Corey¹,³,⁵, Corey Casper¹,³,⁴,⁵
¹Department of Medicine, University of Washington, Seattle, WA, USA
²Department of Laboratory Medicine, University of Washington, Seattle, WA, USA
³Department of Epidemiology, University of Washington, Seattle, WA, USA
⁴Department of Global Health, University of Washington, Seattle, WA, USA
⁵Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
⁶Uganda Cancer Institute, Kampala, Uganda
⁷Makerere University, College of Health Sciences, Kampala, Uganda

Background
Human herpesvirus 8 (HHV-8) replication is necessary for KS tumor growth and maintenance, and the detection of replicating HHV-8 in the peripheral blood predicts the development of KS [1]. Quantities of HHV-8 lytic and latent mRNA vary in KS biopsy tissue [2,3], suggesting that differences in lytic gene expression may be important in tumor pathogenesis and could have clinical significance. We evaluated lytic and latent mRNA transcripts in KS tumors from Ugandans with epidemic KS, and examined associations between HHV-8 gene expression in tumors, KS morphology, and systemic viral replication.

Methods
KS biopsy specimens were obtained from 13 treatment-naive, HIV-positive Ugandans with histologically confirmed KS. Participants also collected oral swabs daily and plasma samples weekly over 4 weeks to quantify HHV-8 replication. HHV-8 mRNA gene transcripts, including 2 lytic genes (K8 and ORF50) and 1 latent gene (ORF73), and GAPDH were quantified in biopsy specimens using RT-PCR; total RNA was determined by optical density. Only specimens with total RNA >10 ng and GAPDH threshold cycle (Ct) <35 were included in the analysis. HHV-8 mRNA log copies were normalized to the total ng of RNA in samples.

Results
HHV-8 mRNA gene transcripts were detected in all 13 KS biopsy samples. In all samples, the quantity of mRNA from lytic genes (K8 or ORF50) exceeded that of ORF73 when adjusted for total RNA recovered, though in two samples the amount of ORF73 mRNA exceeded the amount of ORF50 mRNA. The quantity of HHV-8 mRNA detected was highly correlated within samples (K8 and ORF50 Spearman coefficient (Sp)=0.92; K8 and ORF73 Sp=0.78; ORF50 and ORF73 Sp=0.84). Tumors of nodular morphotype had a lower proportion of lytic genes detected compared to macular morphotype (K8/ORF73 p=0.04; ORF50/ORF73 p=0.07). The quantity of K8, ORF50, and ORF73 mRNA in KS biopsies was positively associated with the detection of oral HHV-8 (K8 p=0.003; ORF50 p<0.001; ORF73 p=0.002). The quantity of lytic K8 and ORF50 mRNA, but not latent ORF73 mRNA, was also positively associated with the quantity of HHV-8 detected in saliva (K8 p=0.06; ORF50 p=0.06).

Conclusions
KS tumors in our cohort express a preponderance of lytic HHV-8 gene products. The quantity of lytic HHV-8 mRNA detected in KS tumors is associated with tumor morphotype and the detection of replicating HHV-8 in the oropharynx. Quantification of HHV-8 mRNA from KS tissue may provide insight into the pathophysiology of KS and could help predict disease progression and response to treatment.
References


5. **Concurrent human herpesvirus 8 and 6a viremia in end-stage AIDS as uncovered by NextGen sequencing**

Kristen M. Tamburro\(^1\)\(^2\), Jessica Poisson\(^3\), Debasmita Roy\(^1\)\(^2\), Amy Lucas\(^4\), Sang-Hoon Sin\(^1\), Nadia Malouf\(^3\), Vincent Moylan\(^3\), Blossom Damania\(^1\), Stefan Moll\(^4\), Charles van der Horst\(^1\)\(^4\); Dirk P. Dittmer\(^1\)

\(^1\)Department of Microbiology and Immunology, Lineberger Comprehensive Cancer Center, Center for AIDS Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
\(^2\)Curriculum in Genetics and Molecular Biology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
\(^3\)Department of Pathology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
\(^4\)Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Kaposi sarcoma-associated herpesvirus (KSHV) cancers are AIDS defining, but high-level viremia is infrequent. We observed plasma viral load of 5,300,000 copies/ml, the highest yet, despite <5 skin lesions and no lymphoma. NextGen sequencing uncovered HHV6a. This is the first report of systemic HHV6a/KSHV co-viremia. Epstein-Barr virus loads (EBV) and human cytomegalovirus loads (HCMV) were negligible at <250 copies/ml and 647 copies/ml, respectively. We therefore conclude that the patient died of acute KSHV/HHV6 reactivation disease.

**Acknowledgements**

This work was supported by NIH grants DE018304 and CA121947 (AIDS Malignancy Consortium).
6. Current epidemiology of KSHV infection in American men who have sex with men

Nazzarena Labo[^1^,2], Wendell Miley[^1], Maya Kesler[^2], Lisa Jacobson[^2], Denise Whitby[^1]

[^1]: AIDS and Cancer Virus Program, Viral Oncology Section, SAIC-Frederick, NCI-Frederick, Frederick, MD, USA
[^2]: Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD, USA

**Background**

The introduction of highly active antiretroviral therapy (HAART) has resulted in a dramatic decline in the incidence of AIDS-associated Kaposi sarcoma (KS) among men who have sex with men (MSM). The decline had been associated with increased CD4+ cell counts; however, the effect of HAART on the epidemiology of the Kaposi sarcoma-associated herpesvirus (KSHV) has not been investigated. We describe here the prevalence of KSHV in HIV infected and uninfected MSM across time periods of different prevailing HAART usage.

**Subjects, materials, and methods**

The serostatus of 4159 participants in the prospective Multicenter AIDS Cohort Study (MACS) was ascertained using two ELISAs, detecting antibodies against the latently associated nuclear antigen (LANA) and the lytic antigen encoded by ORFk8.1, respectively. KSHV seropositivity was defined as positivity in either assay. The calendar period between 1984 and 1990 was defined as untreated era, while the periods 1990-1995 and 1995-2001 were defined as pre-HAART era and HAART era, respectively. Because the last wave of enrollment in the MACS that occurred in 2001 involved a distinct change in study demographics, a fourth period, 2001-2009 was defined as current era.

**Results**

The study population was composed of 2920 HIV-positive and 1239 HIV-negative subjects. The prevalence of KSHV was 54.6% overall (95% CI: 53.0-56.1%), 67.8% (95% CI: 66.0-69.5%) in HIV+ and 23.5% (95% CI: 21.1-25.9%) in HIV- subjects. When examining the cohort by calendar time, the prevalence was 52.9% (95% CI: 51.2-54.6%) in the untreated era, 67.5% (95% CI: 59.3-75.1%) in the pre-HAART era, 52.7% (95% CI: 35.4-69.9%) in the HAART era, and 59.7% (56.0-63.4%) in the current era.

**Conclusions**

The overall prevalence of KSHV in MSM enrolled in the MACS did not vary significantly from 1984 through 2009, indicating that the decline in incidence of KS seen over the same calendar periods in this population is not associated with a decline in KSHV prevalence. The observation is significant because of the potential excess morbidity risk associated with KSHV in an aging population, particularly among HIV/ KSHV co-infected individuals, notwithstanding effective anti-HIV treatment. To elucidate the mechanisms sustaining the high prevalence of KSHV amongst MSM, KHSV incidence in time and risk factors associated with KSHV infection are being investigated.
Cytosine methylation in the HPV16 3’ L1/ 5’LCR region characterized from anal epithelia of HPV-HIV coinfected men

D.J. Wiley¹, P. Barman¹, E. Masongsong, D. Elashoff², HIPVIRG Study Group³, F. Coutlee³
¹School of Nursing, University of California, Los Angeles, Los Angeles, CA, USA
²David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
³Centre Hospitalier de L’Université de Montréal, Hopital Notre-Dame, Montréal, Québec, Canada

Anal specimens derived from 83 HIV-HPV16 co-infected men were analyzed for cytosine methylation using bisulfite modification, PCR amplification, cloning, and sequencing. Data were processed using the ClustalW alignment algorithm within BiQ Analyzer Software and input into SAS 9.2 to generate heat maps and histograms. Approximately 10 clones were characterized for each specimen across 81 CpA, CpT, CpC (denovo methylation) and 10 CpG sites within the 3’-L1 and 5’LCR region of HPV16 genomes. Analyses were confined to 64 denovo cytosine residues and 10 CpGs outside the primer annealing regions. Clinical outcome evaluation by a single examiner showed seven men with no anal intraepithelial neoplasias (AIN), 26 with AIN-1, and 50 with AIN-2. Data showed the average prevalence (standard deviation) of methylcytosines was 11% (0.3) across 7,553 bases/residues and did not vary across maintained or denovo cytosine groups, i.e., 6,723 denovo sites and 830 CpGs. Evaluation by a single examiner using cytology and histology showed 7 with no anal intraepithelial neoplasias (AIN), 26 showed AIN-1, and 50 showed AIN-2. Mean and median prevalence of denovo and CpG methylation were closely approximated across AIN groups. Maxima were observed in two regions: 7111 to 7119, and 7505 to 7514 that showed a methylcytosine prevalence of 24% (0.4), and 18% (0.4), respectively. Logistic regression suggests that with each year of age, risk for moderate-severe methylation >30% at each site decreases; however, among smokers risk for ≥30% methylation increases. Specifically, moderate cytosine-methylation decreased by 5% (OR=0.95, 95% CI, (0.92, 0.99) for each year of age, centered around the mean of the sample. Smokers were nearly twice as likely to show moderate cytosine methylation overall (OR=1.9, (1.1, 3.3) and these estimates did not vary across CpG-denovo sites. Although not statistically significant, moderate cytosine methylation was inversely associated with grade of AIN in these data (when compared to high-grade, low-grade and no AIN showed OR=1.5 (0.8, 2.7) and 2.0 (0.9, 4.5), respectively, p=0.2).

Figure 1. Heatmap of Methylcytosines in the 3’L1 and 5’LCR Region of HPV16.
Human papillomaviruses (HPV) remain a serious world health problem due to their association with anogenital and oral cancers and warts. While over 100 HPV types have been identified, only a subset is associated with malignancy. HPV16 and 18 are the most common oncogenic types, while HPV6 and 11 are the most common types responsible for anogenital warts. These four types cause up to 90% of HPV-associated disease. While other quantitative PCR (qPCR) assays can be used to detect oncogenic HPV, there is no single tube assay that distinguishes the most frequent oncogenic types and the most common types found in warts. A qPCR assay was developed that allowed for detection and quantitation of these 4 HPV types. Type-specific primer pairs and TaqMan probes allowed single tube multiplex reactions to be performed. Each HPV type was detected over a range from $2 \times 10^1$ to $2 \times 10^6$ copies/reaction, providing a reliable method of quantitating type-specific HPV. A Sybr Green-based qPCR assay was developed that utilizes degenerate primers targeting the E1 region of all HPVs. These assays were run in parallel with PCR/sequence gold standard on 76 oral cancers from HIV-negative individuals. Cervical and oral washes were collected from 25 HIV-positive women and 90 HIV-positive men, respectively, being screened for anogenital neoplasia. Samples were analyzed using the newly developed assays. Of the 115 samples, 16% were HPV positive. Cervical washes contained HPV types 44, 67, 35, and 68 and oral specimens contained HPV types 16, 11, 32, 6, 55, 73, and 70. These results indicate that these assays can be used to detect and quantitate HPV in clinical samples obtained by noninvasive measures.

Acknowledgement
This work was supported in part by NIDCR OHARA 1 U01 AI068636-01.
Development of a proteomic platform for EBV and KSHV serological screening

Leyao Wang¹, Dasheng Zheng¹, Jian Zhu², Gangling Liao¹, Crystal Woodard², C-J Chiou¹, Gary Hayward¹,³, Prashant Desai¹,³, Richard Ambinder¹,³, Heng Zhu²,³, S. Diane Hayward¹,³

¹Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD, USA
²Department of Pharmacology, Johns Hopkins School of Medicine, Baltimore, MD, USA
³Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD, USA

In the context of HIV infection, there is an increased susceptibility to EBV- and KSHV-associated malignancies. Evaluating a possible role for specific humoral responses to individual viral proteins in the control of viral load and prevention of EBV or KSHV related disease development in this population has been hampered by the limited availability of suitable screening reagents.

We have developed a protein array platform that can be utilized for EBV and KSHV serological screening. The array consists of EBV and KSHV proteins printed onto glass slides. All eighty-four EBV open reading frames and eighty-six KSHV open reading frames were cloned into bacterial vectors and the inserts validated by DNA sequencing in both directions. Authenticated inserts were transferred to a yeast vector that expresses proteins as N-terminal GST-fusions. Seventy-nine EBV proteins and eighty-one KSHV proteins were successfully purified from yeast. First-generation EBV/KSHV protein arrays have been printed with these proteins plus a variety of control proteins that include GST, and human IgG, IgM, and IgA.

Glycosylation of viral proteins may affect immunogenicity. To evaluate this aspect, EBV and KSHV virion glycoproteins are being expressed in insect cells modified with the human glycosylation machinery. Once purified, these proteins will be added to the EBV/KSHV protein arrays.

The ability to compare serological responses to the complete repertoire of individual EBV and KSHV encoded proteins should provide new insight into B cell mediated immune regulation of these viruses.
10. DNA ploidy, cell proliferation, and HIV/EBV association in Tanzanian malignant lymphomas

Amos Mwakigonja1,2, German Wannhoff2, Thomas Heiden3, Anna Porwit4, Peter Biberfeld5, Ephata Kaaya1,2
1Department of Pathology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
2Department of Oncology- Pathology, Karolinska University Hospital, Solna/Karolinska Institute, Stockholm, Sweden
3Otto-Heubner-Center for Pediatrics, Charité Campus, Virchow-Klinikum, Berlin, Germany
4Department of Pathology, Radiumhemmet, Karolinska University Hospital, Solna, Stockholm, Sweden

Background
Malignant lymphomas (ML) are increasingly important causes of morbidity and mortality in sub-Saharan Africa including Tanzania, possibly due to HIV and AIDS. However, the biological characterization ML including their HIV and Epstein-Barr virus (EBV) association as well as DLBCL subtypes in Tanzania is still sketchy. This prevents diagnostic/prognostic comparison as well as application of established therapeutic protocols.

Materials and methods
Selected archival, diagnostic ML biopsies (N=60) collected at Muhimbili National Hospital (MNH), Dar es Salaam, Tanzania, between 1996 and 2006 and their corresponding clinical/histopathological notes were analyzed by histopathology; immunohistochemistry (IHC) using CD20, CD3, CD30, CD10, MUM1p, BCL-6, BCL-2, and Ki-67 cell markers; flow-cytometry (FC) for DNA ploidy; and in situ hybridization (ISH) (n=25) for EBV-encoded RNA (EBER). Available sera (N=35) were screened by ELISA for HIV antibodies.

Results
Out of the evaluated cases, 27 were diffuse large B-cell lymphoma (DLBCL) of which a slight majority (55.6%, n=15/27) had activated B cell-like (ABC) and 44.4% (12/27) had germinal center B cell-like (GCB) immunophenotype, although this was not statistically significant (p-value 0.547, Chi² Test). Overall, 40% (24/60) ML were aneuploid mostly (63.0%, 17/27) the DLBCL and T-cell lymphoma (TCL) [54.5%, 6/11] which differences were not statistically significant (p-value 0.06, Chi² Test). DNA index (DI) of FC-analyzed ML ranged from 1.103 to 2.407 (median=1.51) and most (75.0%) aneuploid cases showed high (>40%) cell proliferation by Ki-67 reactivity (p-value 0.031, statistically significant, Fisher’s Exact Test). The majority (51.4%, 19/37) of EBER ISH analyzed lymphoma biopsies were positive (p-value 0.87, not statistically significant, Chi² Test). Of the serologically tested lymphomas 40.0% (14/35) were HIV positive, mostly with high (≥40.0%) Ki-67 reactivity [p-value=0.05, statistically significant, Pearson Correlation].

Conclusions
Lymphomas at MNH appear to have frequent aneuploidy and EBER positivity as well as high DNA indices and tumor proliferation (Ki-67). DLBCL phenotype heterogeneity was similar to that observed in other countries suggesting applicability of established intervention approaches. HIV was apparently associated with high lymphoma cell proliferation but extended studies are needed to clarify this.
11. EBV-induced miR-34a functions to stimulate transformed B cell growth

Eleonora Forte1, Christina Chang1, Jason Tourigny1, Eva Gottwein1, Bryan Cullen1, Sandeep Dave2, Micah Luftig1
1Department of Molecular Genetics and Microbiology, Center of Virology, Duke University School of Medicine, Durham, NC 27712, USA
2Duke Institute for Genome Sciences and Policy, Duke University, Durham, NC, USA

Background

Epstein-Barr virus (EBV) is a member of the -herpesvirus family estimated to infect 90% of the world’s population. Despite the high prevalence of infection, EBV-associated malignancies are largely kept in check by a strong cytotoxic T cell immune response. However, EBV causes lymphoproliferative disease in immune-deficient individuals and plays a role in the pathogenesis of African Burkitt lymphoma, Hodgkin’s disease, and nasopharyngeal carcinoma. In vitro, EBV infection of B cells results in proliferation and outgrowth of indefinitely proliferating lymphoblastoid cell lines (LCLs). Thus, LCLs represent a viable model for the pathogenesis of EBV-associated malignancies.

microRNAs are small noncoding RNAs that post-transcriptionally regulate gene expression to control a variety of processes including development, cell cycle, and immunity. Their role in EBV transformation and lymphomas is currently not well understood.

Results

Using a miRNA microarray, we identified a number of cellular miRNAs that were over- or under-expressed comparing resting CD19+ B cells to EBV-infected, proliferating B cells and immortalized LCLs. In particular, we focused on miR-34a, whose expression was induced by EBV. This miRNA has been previously reported to be a pro-apoptotic target of p53 implicated in the response to DNA damage. Surprisingly, contrary to its regulation in other cell types, miR-34a was not found to be p53 responsive in LCLs. In order to understand the functional role of this miRNA in EBV transformation, we constructed a miRNA sponge. miR-34a knockdown in LCLs showed that these cells depend on normal miR-34a expression to proliferate and to aggregate.

Conclusions

miR-34a is important for efficient growth and survival of EBV-transformed cells, in contrast to its tumor suppressive role in carcinoma and sarcoma-derived cell lines.
Background
Human gamma-herpesviruses, Epstein-Barr virus (EBV or HHV-4), and Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8), are associated with several malignancies, especially in persons with immunodeficiency conditions, such as human immunodeficiency virus (HIV) infection and AIDS. Tumorigenesis of gamma-herpesviruses is associated with the persistence of infection. Thus, vaccination to inhibit viral infection will reduce the frequency of virus-associated cancers. However, currently there are no effective vaccines available for KSHV or EBV.

Materials and methods
Mouse infection with murine gamma-herpesvirus 68 (MHV-68) has been used an experimental model to explore and test proof-of-principle vaccination strategies. In this model, vaccines targeting individual viral proteins or based on heat inactivated MHV-68 confer only modest protective effects. A live attenuated virus, which allows for the presentation of the full repertoire of viral antigens, will effectively elicit both humoral and cellular immunity. However, the primary concern using a live virus as a vaccine for EBV and KSHV is the tumorigenicity associated with the persistent infection. Therefore, we constructed and tested the protective efficacy of a live attenuated MHV-68 virus (AC-RTA) that is deficient in latency using the mouse infection model. AC-RTA was generated by replacing the genes required for persistent infection with a constitutively expressed viral transcription activator, RTA, which dictates the virus to lytic replication.

Results
We have shown that AC-RTA undergoes lytic infection without establishing latency in mice. More importantly, this latency deficient virus, AC-RTA, is able to prevent challenge infection of the wild-type virus. Next, we aim to genetically modify AC-RTA to reduce its lytic replication capacity without compromising the immunogenicity. The strategy is to delete a group of viral immune evasion genes that inhibit the type I interferon responses and block the MHC class I antigen presentation. This new vaccine virus, DIP (deficient in immune evasion and persistent infection), will be evaluated for its preventive and therapeutic efficacy.

Conclusions
DIP represents a vaccine strategy for preventing infection of human gamma-herpesviruses. The "proof-of-concept" study in the mouse infection model is necessary to provide fundamental insights into the development of vaccines for the tumor-associated human herpesviruses.
13. Elevated serum levels of heat shock protein 70 precede the development of AIDS-non-Hodgkin lymphoma in carriers of the common and highly conserved HLA-B8-DR3 haplotype

Brahim Aissani1, Otoniel Martinez-Maza2,3, Sadeep Shrestha1, Elizabeth Breen4, Lisa Jacobson6, Richard Kaslow1,6

1Departments of Epidemiology and Medicine, University of Alabama at Birmingham, AL, USA
2Departments of Obstetrics and Gynecology, University of California, Los Angeles, CA, USA
3Microbiology, Immunology and Molecular Genetics, University of California, Los Angeles, CA, USA
4Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA
6Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA

Background
Polymorphisms in the tumor necrosis factor (TNF) and lymphotoxin alpha (LTA) genes, by themselves or in combination with nearby specific human leukocyte antigen (HLA) loci, have been associated with classical and AIDS-related non-Hodgkin lymphoma (NHL). However, whether those gene variants represent true etiologic factors remains uncertain because they are part of the conserved and extended HLA-B*08-containing AH8.1. Building on recent observations linking the MHC-encoded heat shock protein 70 (Hsp70) to lymphomagenesis, we hypothesized that concomitant carriage of presumably high TNF and Hsp70 producing gene variants on AH8.1 may predispose HIV-infected individuals to AIDS-NHL. To test this hypothesis, we have compared Hsp70 serum levels in the years preceding the diagnosis of AIDS-NHL in carriers vs. non-carriers of AH8.1.

Materials and methods
A Caucasian case-control sample (n=169 pairs) was nested in the Multicenter AIDS Cohort Study (MACS). Cases are participants diagnosed with AIDS-NHL prior to April 2002, matched 1:1 with HIV+ NHL-free controls on duration of HIV infection and availability of serum samples at time points 3-5 years; 1-3 years; and <1 year prior to NHL diagnosis. Typed loci are HLA-B, HLA-DRB1, and 6 MHC class III single nucleotide polymorphisms (SNPs) from TNF and complement factor gene clusters. Hsp70 levels were measured by an ultra-sensitive ELISA. Extended MHC haplotypes were estimated via the EM-algorithm and were modeled as fixed main and interaction (with time) effects in a mixed linear model with adjustment for the CD4+ counts at the time of NHL diagnosis separately in cases and controls. A random model was fitted to account for the different levels of Hsp70 at the earliest time point.

Results
No MHC haplotype was associated with a change in Hsp70 levels in cases or controls during the 5 years preceding NHL. However, when the study was restricted to the subset of cases who developed NHL as their AIDS-defining condition (vs. NHL subsequent to another AIDS-defining condition), carriage of AH8.1 haplotypes was significantly (p=0.0002-0.006) associated with increasing Hsp70 levels in the cases but not in the matched controls. Conversely, the common HLA-B7-DR15 haplotype appears to be protective and associated with decreasing Hsp70 levels.

Conclusion
An altered level of Hsp70 may be a component of the AH8.1-mediated pathogenetic pathway in AIDS NHL, perhaps through the action of Hsp70 as a B-cell stimulatory molecule. Investigation of Hsp70 promoter variants in AIDS-NHL is a worthy undertaking, especially if the association can be replicated in larger studies.
14. **Epigenetic deregulation of IGF2 and cervical cancer precursors in HIV+ and HIV- patients**

Cathrine Hoyø¹, Francine Overcash¹, Zhiqing Huang², Olola Oneko³, Brandi Vaquez⁴, Joseph Obure⁵, Pendo Mlay⁶, John Bartlett⁵, Brenda Hernandez⁶, Susan K. Murphy²

¹Department of Community and Family Medicine, Duke University, Durham, NC, USA
²Department of Obstetrics and Gynecology, Duke University, Durham, NC, USA
³Department of Obstetrics and Gynecology, Kilimanjaro Christian Medical Center, Moshi, Tanzania
⁴Kilimanjaro Christian Medical Center–Duke Women’s Health Collaboration, Moshi, Tanzania and Durham, NC, USA
⁵Department of Medicine, Duke University, Durham, NC, USA
⁶Cancer Research Center of Hawaii, University of Hawaii, Honolulu, HI, USA

**Introduction**

Early detection and aggressive treatment programs to prevent cervical carcinoma in situ (CIS) and invasive uterine cervical cancer (ICC) have been available for more than 30 years with more than 80% population coverage. Despite this, 11,000 cases of ICC and 40,000 cases of CIS continue to be diagnosed in the United States annually. Women of African descent are at >2-fold higher risk of invasive cervical cancer death compared to other ethnic groups.

**Objective**

The overarching goal is to develop epigenetic biomarkers that can be used for early identification of aggressive cases likely to result in invasive cervical cancer and death.

**Methods**

We conducted a hospital-based, case-control study comprising 26 women with ICC, 18 with CIN2/3/HSIL and 41 with normal cytology, at Kilimanjaro Christian Medical Center in Moshi, Tanzania. We analyzed methylation of three regions in the IGF2/H19 imprinted domain known to regulate the expression of imprinted IGF2. Aberrant methylation is associated with IGF2 deregulation, including changes in expression, loss of imprinting, and neoplasia.

**Results**

At the IGF2/H19 imprint center upstream of H19, methylation profiles for all women with no evidence of cervical abnormality or those with CIN2-CIN3 were within normal ranges (40%-60%), while 23% with invasive cancer had hypermethylation. In contrast, 25% of the CIN2/3 cases were abnormally hypomethylated at the IGF2 DMR in IGF2 intron 2, and the methylation profile worsened in the invasive cervical cancer cases with 64% having an abnormal methylation profile. A similar trend was found for the regulatory region in IGF2 intron 6. Stratifying these analyses by HIV status in ICC revealed that aberrant intragenic IGF2 hypomethylation was observed only among women without HIV. These associations persisted after adjusting for HPV genotype.

**Conclusion**

Our findings suggest that regulation of IGF2 is substantially altered in CIN2 or worse via epigenetic alterations. DNA methylation profiles of these regions may be markers of risk of progression especially in HIV- women. The findings support our hypothesis that epigenetic deregulation of this imprinted gene could be useful in discriminating women with dysplasia likely to progress.
15. Epstein-Barr virus (EBV)-associated miRNAs are important for the maintenance of EBV transformed B cells

Sarah Linnstaedt, Eva Gottwein, Micah Luftig, Bryan Cullen
Department of Molecular Genetics and Microbiology, Duke University, Durham, NC, USA

The human oncogenic gamma-herpesvirus, Epstein-Barr virus (EBV), infects approximately 95% of the adult human population and causes B-cell lymphomas in immune-compromised individuals, such as AIDS patients. EBV transforms primary human B cells into indefinitely proliferating lymphoblastoid cell lines (LCLs) in vitro, which represents an important model system for the transformation of B cells by EBV. EBV encodes 25 viral miRNA, but their role in virus replication and pathogenesis is unclear. Three of these miRNAs, miR-BHRF1-1, miR-BHRF1-2, and miR-BHRF1-3, are expressed during the latency III stage of EBV, the EBV gene expression pattern observed in AIDS-associated B cell lymphomas and LCLs. We have performed functional studies examining the roles of the three BHRF1 miRNAs during the transformation of primary B cells by EBV in vitro as well as in the maintenance of the transformed state in established LCL cultures. Our preliminary data suggest that at least one EBV miRNA is necessary for LCL outgrowth. EBV is also known to up-regulate a number of cellular microRNAs, including miR-155, and our preliminary data also suggest a role of miR-155 in the maintenance of LCLs. We are currently examining the mechanisms by which EBV and cellular microRNAs contribute to the growth and maintenance of LCLs. Together, our data point to a role for EBV-encoded and EBV-induced miRNAs in EBV-induced cell transformation.
16. Gamma-tubulin and 53BP1 as candidate biomarkers of human papillomavirus-associated anal dysplasia

Ken S. Ho¹, Richard Day², Amy Perkins², Jia Xu², Shih-Fan Kuan³, Anette Duensing³, Ross D. Cranston¹, Stefan Duensing⁴
¹Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, USA
²Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA
³Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
⁴Cancer Virology Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA

Background
HIV+ men who have sex with men (MSM) are at increased risk of developing anal squamous cell carcinoma. High-grade anal intraepithelial neoplasia (HG-AIN or AIN2/3) is the consequence of persistent infection with high-risk human papillomaviruses and is a precursor to cancer. No biomarkers exist to identify patients with HG-AIN at risk of malignant progression. We investigated two candidate biomarkers of genomic instability, gamma-tubulin and 53BP1, in a series of anal biopsies from HIV+ MSM by immunofluorescence microscopy. Gamma-tubulin staining is used to assess centrosome abnormalities as a potential source of cell division errors and aneuploidy, while staining for 53BP1 nuclear foci reflects the presence of DNA double strand breaks.

Materials and methods
Anal biopsies were obtained from HIV+ MSM undergoing high-resolution anoscopy and reported using the Bethesda 2001 classification system as AIN1 through 3 or carcinoma. Normal colonic tissue served as controls. The percentage of cells with abnormal centrosome number (more than two per cell) and DNA damage-associated 53BP1 foci was assessed and correlated with the histopathological diagnosis. Eighty-eight biopsies were stained for gamma-tubulin, and ninety biopsies were stained for 53BP1.

Results
The mean percentage of cells with abnormal centrosomes was 1.5% in AIN1, 1.3% in AIN2, and 0.9% in AIN3. No controls showed centrosome aberrations. A single biopsy diagnosed as carcinoma contained 16.1% cells with abnormal centrosomes. The mean percentage of cells with abnormal 53BP1 foci was 2.5% in controls, 17% in AIN1, 18.5% in AIN2, and 5.2% in AIN3. Higher levels of abnormal 53BP1 foci were seen in AIN1 and AIN2 compared to controls based on pair-wise comparisons between control and AIN1 (p=0.0008) and control and AIN2 (p=0.0030) using the Mann Whitney test. Lower levels of 53BP1 foci were seen in AIN3 compared to AIN1 and 2 based on pair-wise comparisons between AIN1 versus AIN3 (p=0.0034) and between AIN2 versus AIN3 (p=0.0056).

Conclusion
The levels of centrosome aberrations were generally low in AIN1 through 3 and were increased in carcinoma, suggesting that centrosome abnormalities may not occur until malignant progression. DNA damage-associated 53BP1 foci were increased in AIN1 and 2 when compared to controls, whereas AIN3 showed lower levels of 53BP1 foci. These results are consistent with previous studies suggesting that the DNA damage response represents an early barrier against malignant progression. Further prospective studies assessing the predictive value in particular of 53BP1 as a biomarker in HPV-associated anal neoplasia are warranted.
17. **Human herpesvirus type 8 variants in Kaposi’s sarcoma before and after AIDS era**

Maria Lina Tornesello¹, Benon Biryahwaho², Robert Downing², Angelo Hatzakis³, Elvio Alessi⁴, Marco Cusini⁴, Vincenzo Ruocco⁵, Giovanna Loquercio¹, Edward Katongole-Mbidde², Luigi Buonaguro¹, Franco M. Buonaguro¹

¹Molecular Biology and Viral Oncology & AIDS Reference Centre, National Cancer Institute “Fondazione Pascale”, Naples, Italy
²Uganda Virus Research Institute, P.O. Box 49, Entebbe, Uganda
³University of Athens, Athens, Greece
⁴Institute of Dermatological Sciences, University and IRCCS Ospedale Maggiore, Milan, Italy
⁵Department of Dermatology, Second University of Naples, Naples, Italy.

**Background**

Human herpesvirus 8 (HHV-8) variants have been found heterogeneously distributed among human populations living in diverse geographic regions, but their differential pathogenicity in Kaposi’s sarcoma (KS) development remains controversial. The aim of the present study was to analyze variations of HHV-8 genomes in tumor biopsies collected before and in the course of HIV epidemic (1971 - 2008), from patients with classic, iatrogenic, endemic as well as epidemic KS living in Africa, Europe, and North America.

**Materials and methods**

DNA samples have been extracted from cutaneous KS lesions of 68 patients living in Africa (n=23, Cameroon, Kenya and Uganda), Europe (n=34, Greece and Italy), and North America (n=11). The identification and characterization of HHV-8 variants has been based on PCR amplification followed by direct nucleotide sequencing and phylogenetic analysis of the highly conserved ORF 26 and T0.7, the hypervariable ORF K1, as well as on the analysis of P and M alleles of the K14.1/15 locus.

**Results**

Among the 23 African samples, the majority of HHV-8 ORF 26 variants clustered with the subtype R (n=12) and B (n=5). Conversely, the viral sequences obtained from 45 European and North European tumors belonged mainly to subtype A/C (n=36). In general HHV-8 and K1 variant clustering paralleled that of ORF 26 and T0.7. Genotyping of the K14.1/15 loci revealed a large predominance of P subtype in all tumors.

**Conclusions**

Although the virus has genetic regions of high variability, approaching that of HIV-1 env gene, the HHV-8 subtypes remained stably distributed before and after the AIDS epidemic. These results suggest that the increased incidence of epidemic KS in low-incidence countries was not related to the spreading of high pathogenic HHV-8 variants, furthermore, suggest the presence of other cofactors in high risk KS countries pre-existing in pre-AIDS era [1].

**Acknowledgements**

We thank the late Prof SK Kyalwazi (Mulago Hospital, Kampala, Uganda), Prof VA Ngu (Univ., Yaounde, Cameroon), Prof B Safai (Sloan-Kettering/Memorial Hospital New York City, USA), Prof. N Mueller (Harvard School of Public Health, Boston, USA) and Prof G Giraldo (Natl Cancer Inst. Fond. Pascale, Napoli, Italy), for patients enrollement.

**Reference**

18. Inhibition of KSHV-associated lymphoma engraftment in SCID mouse by morpholino oligomers

Yuchen Nan, Deendayal Patel, Yanjin Zhang
Department of Veterinary Medicine and Maryland Pathogen Research Institute, University of Maryland, College Park, MD, USA

Kaposi’s sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8, is associated with several malignant disorders, including Kaposi’s sarcoma, primary effusion lymphoma (PEL), and multicentric Castleman’s disease. We have explored peptide-conjugated antisense phosphorodiamidate morpholino oligonucleotides (PPMOs) against KSHV and found effective PPMOs in inhibition of KSHV gene expression in cell culture. PPMOs are single-stranded DNA analogues that have a modified backbone and penetrate cells readily. In this study, we further tested the PPMOs in a SCID mouse model to assess their effect on engraftment and growth of PEL cells. PEL cells were engrafted into SCID mice via intraperitoneal route. PPMO was administered at the same time and repeated every other day for 10 doses. The mice were observed and scored for ascites development. The tumor cell burden was assessed by flow cytometry. Administration of anti-vIL-6 PPMO protected the mice from lymphoma development, while those mice receiving a control PPMO developed ascites and had high ratio of PEL cells in peritoneal lavage. The results demonstrate that PPMO against key KSHV genes can potently reduce KSHV replication and growth of PEL cells in SCID mice. Further exploration of PPMOs in the animal model is warranted.
19. **Kaposi’s sarcoma-associated herpesvirus (KSHV) serum DNA not associated with subsequent non-Hodgkin’s lymphoma (NHL) risk**

Dan Beachler¹, Lan Lin Gellert,² Rich Ambinder³, Lisa Jacobson¹, Gypsyamber D’Souza¹
¹ Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
² Department of Oncology, Johns Hopkins Hospital, Baltimore, MD, USA

**Background**

Non-Hodgkin’s lymphoma (NHL) is a diverse group of cancers, elevated in HIV-infected individuals. Kaposi’s sarcoma-associated herpesvirus (KSHV) is found in a subset of NHL tumors, and could therefore be a cause of NHL. However, antibody testing for KSHV has limited sensitivity and specificity and studies have not associated KSHV antibodies with NHL odds. KSHV DNA in serum is a more specific marker of KSHV infection.

**Methods**

We performed a nested case-control study in the Multicenter AIDS Cohort Study, including 155 incident NHL cases occurring between 1984 and 2006 and non-cancer controls matched by study entry and time at risk. KSHV DNA was tested in pre-diagnostic serum from within 5 years before diagnosis using real-time quantitative PCR. Risk factors for NHL were evaluated with conditional logistic regression models.

**Results**

NHL cases were significantly more likely to have Kaposi sarcoma, and had more advanced HIV disease as indicated by lower CD4 cell count at study baseline and greater reduction in CD4 from baseline to HAART era than their matched controls (each p<0.01). Detection of KSHV DNA in pre-diagnostic serum was more common among NHL cases than controls (14% vs. 6.5%, p=0.03). However, among cases and controls who had detectable KSHV DNA, the median KSHV viral load (406 vs. 324, p=0.39) was comparable. After adjusting for age, baseline CD4 cell count, and CD4 change, KSHV serum DNA was no longer significantly associated with odds of NHL (OR=1.5, 95% CI=0.53-3.9). Similarly null associations were observed among the subset of participants with serum within 1 year before diagnosis, by NHL sub-type, and when stratified by history of Kaposi sarcoma (Table 1). To better match for stage of disease, we performed a second analysis among 76 NHL cases who developed NHL after AIDS diagnosis, matching these cases to controls by time since AIDS diagnosis. KSHV serum DNA prevalence was similar among these AIDS NHL cases and matched controls (14% vs. 9.2%, p=0.32). KSHV seroprevalence was also not associated with odds of NHL.

**Conclusions**

We found no significant independent association between KSHV DNA in pre-diagnostic serum with overall odds of NHL in this nested case control study. This research suggests that, similar to KSHV antibodies, KSHV serum DNA does not have predictive value for NHL risk and KSHV is not a primary cause of NHL in HIV-positive men who have sex with men.

**Table 1.** Comparison of KSHV DNA and KSHV seropositivity among 155 HIV-positive incident NHL cases compared to 155 HIV-positive matched controls.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>KSHV serum DNA: ≥1 copy detected</td>
<td>310</td>
<td>2.3 (1.1-5.1)</td>
<td>1.5 (0.53-3.9)</td>
</tr>
<tr>
<td>Among subset with serum within 1 year before diagnosis</td>
<td>130</td>
<td>1.2 (0.37-3.9)</td>
<td>0.81 (0.14-4.7)</td>
</tr>
<tr>
<td>Among subset without Kaposi sarcoma diagnosis</td>
<td>216</td>
<td>4.0 (1.13-14)</td>
<td>1.9 (0.37-9.6)</td>
</tr>
<tr>
<td>Among those developing NHL after AIDS</td>
<td>152</td>
<td>2.0 (0.60-6.6)</td>
<td>2.0 (0.55-7.0)</td>
</tr>
<tr>
<td>KSHV antibodies: seroprevalent</td>
<td>252</td>
<td>1.3 (0.68-2.5)</td>
<td>0.85 (0.36-2.0)</td>
</tr>
</tbody>
</table>
Cancerous cells transformed by KSHV infection manifest an increased expression of both viral and human interleukin 6 (IL6). Although increased IL6 appears important to maintain cancer cell proliferation, what causes IL6 increase in the tumor cells by KSHV infection remains largely unknown. KSHV mRNA transcript accumulation protein (MTA or ORF57) has been characterized as a multifunctional protein in regulation of viral gene expression.

In seeking for genome-wide RNA targets of MTA by the CLIP assay, we identified viral IL6 (vIL6) as an MTA target which contains an MTA response element (MRE). MTA enhanced both vIL6 and human IL6 (hIL6) expression and cells with a MTA-null KSHV genome displayed a deficiency in vIL6 expression during virus lytic induction. Mutations in the vIL6 MRE identified its role in translational enhancement of vIL6, suggesting that vIL6 is translationally regulated in a sequence-specific manner. Unexpectedly, Ago2 which is a major component in RISC was found in RNA-protein pulldown assays by using MRE-RNA oligomers. Bioinformatics analysis showed that the identified vIL6 MRE contains a functional seed match to miR-1293. Ectopic expression of miR-1293 prevented vIL6 expression. Mutation of the miR-1293 seed match in the MRE or by ectopic expression of MTA could diminish the translational repression of vIL6 mediated by miR-1293 in vitro and in vivo, resulting in enhancement of vIL6 expression. Furthermore, we demonstrated that hIL6 expression is also under control by miR-608 binding to a similar MRE in the corresponding region. Through interaction with a RISC component Ago2, MTA prevents miRNA-mediated recruitment of IL6 mRNA into RISC, thereby relieving the translational repression.

Together, our results suggest the existence of a highly conserved miRNA pathway in cells in prevention of cytokine-induced cell proliferation and compelling evidence of how an oncogenic virus invades this pathway to induce cell proliferation and tumorigenesis during virus infection.
21. **KSHV activation, human and viral IL-6 production, and other cytokine dysregulation: Association with the symptomatology of KSHV-associated multicentric Castleman’s disease**

Mark N. Polizzotto, Thomas S. Uldrick, Victoria Wang, Karen Aleman, Kathleen M. Wywill, Vickie Marshall, Stefania Pittaluga, Dierdre O’Mahony, Denise Whitby, Giovanna Tosato, Seth M. Steinberg, Richard F. Little, Robert Yarchoan

**Background**
KSHV-associated multicentric Castleman’s disease (MCD) is a frequently fatal lymphoproliferative disorder characterized by inflammatory flares of fever, cytopenias, hypoalbuminemia, hyponatremia, and splenomegaly. Most cases occur in HIV-infected patients. KHSV viral interleukin-6 (vIL-6), human IL-6 (hIL-6), and possibly other proinflammatory cellular cytokines are believed to contribute to the pathophysiology of MCD flares.

**Methods**
We identified MCD patients with clinical flares. KHSV viral load (VL) in peripheral blood mononuclear cells, vIL-6, and the cellular cytokines IL-6, IL-1β, IL-8, IL-10, IL-12p70, interferon gamma, and tumor necrosis factor alpha were measured during flares and remissions to identify parameters best characterizing flares. The assay for vIL-6 was modified from Aoki Y. et al., Blood, 97, 2526, 2001; the cutoff of detection was 1560 pg/ml. Factors statistically associated with flares (p<0.01) were explored in relationship to common disease manifestations with multiple linear regression models.

**Results**
20 patients (18 male, 2 female) were studied during 33 flares (range 1-3 per patient) and, in 18 patients, remission with therapy. Median (range) values of key parameters during flares included hemoglobin 9.9 mg/dL (6.8-14.4); platelet count 97 K/μL (6-377); sodium 133 mEq/L (127-143); albumin 2.7 mg/dL (1.2-3.9); spleen size 14.5 cm (9-28); temperature 38 °C (36.1-40.5); CD4 count 240 cells/μL (24-1319); HIV VL <50 copies/mL (<50-64100). Flares were associated with elevated KSHV VL (median 23448 copies/mL; range 0-3913043; p<0.0001 compared with remission), vIL-6 (2575 pg/mL; <1560-20497; p=0.0039), hIL-6 (24.2 pg/mL; 1.4-171.5; p=0.0034), hIL-10 (783.9 pg/mL; 2.8-26021; p=0.0027), and hIL-1β (1.3 pg/mL; 0-11.3; p=0.0074). In two of the 33 flares vIL-6 was elevated but hIL-6 was not; in 14 hIL-6 was elevated but vIL6 was undetectable; and in 15 both were elevated. Neither was initially elevated in 2 flares, but hIL-6 later became elevated in both. Disease manifestations did not differ among flares with differing vIL-6/hIL-6 profiles. In multiple regression analysis, elevated KSHV VL was the strongest predictor of level of hemoglobin (p<0.0001), sodium (p<0.0001), albumin (p<0.0001), and spleen size (p=0.0002); hIL-6 the strongest predictor of thrombocytes (p=0.0011), and KHSV and hIL-6 together the strongest predictors of body temperature (p<0.0001). For hemoglobin, but not other parameters, vIL-6 and hIL-6 in combination were stronger predictors than either independently (p=0.0002), though less strong than KSHV VL alone.

**Conclusions**
KSHV activity, vIL-6 production, and associated human hIL-6 dysregulation are key determinants of the clinical manifestations of MCD. vIL-6 and hIL-6 each appear sufficient to induce flares without the other. hIL-10 and hIL-1β are also elevated in MCD flares, but their contribution to symptomatology remains to be determined.
The skin contains two types of dendritic cells (DC), Langerhans cells (LC), which reside in the epidermis in close contact with keratinocytes, and dermal dendritic cells (DDC), resident in the dermis. LC and DDC process cutaneous antigens and migrate out of the skin into the draining lymph nodes to present antigens to T and B cells. Recent reports showed that LC and DDC play an important role in certain virus infections, such as HIV-1 and HSV. Because of the strategic position of LC and DDC at mucosal sites of infection and the ability of these cells to capture pathogens, we hypothesized that these cells could be infected with KSHV and have an important role in the development of Kaposi’s sarcoma. We have previously shown that KSHV enters monocyte-derived dendritic cells (MoDC) through DC-SIGN, resulting in a nonproductive infection. We have now generated LC and DDC from pluripotent cord blood CD34+ precursors by culture with GM-CSF, TNF, and TGF-B to obtain LC, and GM-CSF, TNF, and IL4 to generate DDC. These expressed the typical phenotype of LC, i.e., CD207pos, CD14pos, CD11b neg, CD1apos, HLA-DRpos, DC-SIGN neg, and dermal DC, i.e., DC-SIGNpos, CD14neg, CD11bpos, CD1apos, HLA-DRpos, langerin neg. We found that both LC and DDC supported productive infection with KSHV. Strikingly, while the level of viral DNA replication increased only 4-fold in infected DDC by 24h, we observed a >1 log10 increase in levels of viral DNA in LC. Anti-DC-SIGN mAB inhibited viral infection of DDC as detected by expression of viral proteins and viral DNA, while blocking of langerin on LC did not interfere with viral entry and replication. Infection with KSHV did not alter cell surface expression of langerin on LC, but downregulated expression of DC-SIGN on DDC, as we previously reported for MoDC. Cytokine production in infected LC and DDC was also altered compared to uninfected cells, with an increase in the levels of IL-8, IL-6, and IL-10 in the infected cells. These results indicate that KSHV can target both LC and DDC for productive infection and alter their function, supporting a role for these dermal DC in KSHV infection and pathogen.
23. **KSHV-mediated ROS induction defines novel therapeutic targets in Kaposi’s sarcoma**

Lucas E. Cavallin¹, Qi Ma², Pascal Goldschmidt-Clermont², Enrique A. Mesri¹

¹Viral Oncology Program, Sylvester Comprehensive Cancer Center and Department of Microbiology and Immunology, University of Miami Miller School of Medicine, Miami, FL, USA

²Vascular Biology Institute, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA

**Background**

Kaposi’s sarcoma herpesvirus (KSHV) is the etiological agent of Kaposi’s sarcoma (KS). Understanding the interplay of viral and host factors in KS carcinogenesis is critical for the rational development of new therapies. Reactive oxygen species (ROS) have a recognized broad function in oncogenesis mediated by signaling cascades leading to the Rac1 activation of NADPH oxidases (Nox) [1]. ROS play a role in cell cycle regulation and angiogenesis, yet the specific molecular events linking ROS and these cancer hallmarks are still elusive. KSHV encodes a constitutively active G protein-coupled receptor (vGPCR) [2], which triggers KS-like sarcomagenesis via Rac1 [3]. It has been shown that Rac1-activated mutant induces tumors resembling Kaposi’s sarcoma by a ROS-mediated mechanism in transgenic mice [4,5]. Moreover, Rac1 is overexpressed in AIDS-KS lesions and in KSHV-infected mECK36 tumors, pointing to a role for KSHV-induced Rac1-mediated production of ROS in KS pathogenesis [5]. The current study explored the induction of oxidative stress pathways in the KSHV-induced mouse model mECK36.

**Results**

vGPCR expression led to the upregulation of the c-sis/PDGFB oncogene in a dose-dependent manner in mECK36. PDGFB upregulation was dependent on Rac1 and ROS since it was suppressed by the Rac1 inhibitor EHT1864 and the ROS scavenger N-acetyl cysteine (NAC). PDGF activated oxidative signaling in a Rac/Nox/ROS-dependent manner in latently infected cells, leading to the upregulation of important genes for proliferation and angiogenesis, such as c-Myc and VEGFA through the activation of the STAT3 transcription factor. Treatment with antioxidant NAC and PDGF receptor inhibitors (imatinib and sunitinib) proved effective in inhibiting KSHV-induced tumorigenesis in the mECK36 mouse model.

**Conclusions**

Our results show a novel KSHV-driven oncogenic mechanism mediated by PDGF-B, whereby KSHV infection induces and exploits ROS production. ROS can be targeted therapeutically by using the NAC antioxidant or FDA-approved PDGF receptors inhibitors. Imatinib clinical responses in AIDS-KS could be due to PDGF-receptor inhibition of ROS production and warrant further clinical trials and molecular exploration of these new molecular therapeutic and prevention targets in AIDS-KS.

**References**


24. **MicroRNA analysis in human papillomavirus (HPV)-associated cervical neoplasia and cancer**

Amy S. Gardiner¹, William C. McBee, Jr.², Robert P. Edwards², Marshall Austin², Jamie L. Lesnock², Rohit Bhargava³, Richard Guido², Saleem A. Khan¹

¹Department of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
²Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Reproductive Sciences, Magee-Women’s Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA, USA
³Department of Pathology, Magee-Women’s Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA, USA

MicroRNAs (miRNAs) are ~22 nt single-stranded, non-protein-coding RNAs that generally negatively regulate their target mRNAs at a posttranscriptional level. Differential expression of miRNAs has been observed in many human cancers. To study their potential role in the pathogenesis of human papillomavirus (HPV) type 16-associated cervical neoplasia and cancer, we analyzed miRNA expression in cervical tissue from the normal cervix, moderate/severe dysplasia, and invasive squamous cell carcinoma. Using RNA from 6 cervical cancers, 3 dysplasias, and 4 normal samples and the TaqMan® MicroRNA Arrays, we found that 18 miRNAs were overexpressed and 2 underexpressed in cervical cancer compared to the normal cervical tissue (p<0.05). We further found that 9 miRNAs (miRs-16, 21, 106b, 124, 135b, 223, 301b, 449a, and 141) were consistently overexpressed and 2 miRNAs (miRs-218 and 433) were consistently underexpressed in cervical cancer compared to the normal tissue. MiRNA expression in dysplasia samples was most similar to the normal tissue, with the exception of the overexpression of miR-16, miR-141, and miR-449a, and the underexpression of miR-218 and miR-433. Our results suggest that five miRNAs may have potential as markers for progression of dysplasia to invasive cervical disease.
25. Phase II AIDS Malignancy Consortium (AMC) trial of topical halofuginone in AIDS-associated Kaposi’s sarcoma (KS): clinical and biological effects using a novel intra-patient control design

Susan E. Krown¹, Barbara Fingleton², Jeannette Y. Lee³, Merrill J. Egorin⁴, Henry B. Koon⁵ for the AIDS Malignancy Consortium
¹Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
²Department of Cancer Biology, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA
³Department of Biostatistics, University of Arkansas Medical School, Little Rock, AR, USA
⁴Departments of Medicine and Pharmacology, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA
⁵Ireland Cancer Center, Case Western Reserve University, Cleveland, OH, USA

Background
KS is a disease of multifocal vascular proliferation. Matrix metalloproteinases (MMPs) and type I collagen play critical roles in angiogenesis and are potential targets. Halofuginone (Tempostatin™), a synthetic quinazolinone alkaloid derivative, induced anti-angiogenic, anti-metastatic and anti-proliferative effects in preclinical studies. It inhibits several essential stages of angiogenesis: endothelial cell proliferation, MMP2 expression, BM invasion, ECM deposition by newly formed vessels, synthesis of type I collagen during angiogenic sprouting, and bFGF-induced neovascularization. These data suggested that halofuginone might have activity in KS.

Methods
The AMC developed a novel trial design with a blinded intra-patient vehicle control. Halofuginone was supplied by Collgard Biopharmaceuticals Ltd (Atlanta, GA) to the NCI-DCTD under a CRADA as a 0.01% w/w ointment. Twelve KS lesions were divided into two groups of six, designated Group A and Group B. Tubes designated A and B containing either halofuginone or matching placebo ointment were supplied in a blinded fashion. Ointment A was applied to Group A lesions and ointment B to Group B lesions twice daily. Lesion response was assessed every 4 weeks for Group A and B lesions individually, and global response assessed both treated and untreated disease. Tumor biopsies obtained at baseline and from both Group A and B lesions during treatment were studied for expression of type I collagen by ISH and of MMP2 and VEGF by IHC. A patient subset had blood sampling after 8 weeks to evaluate systemic absorption.

Results
Twenty-three patients were treated. Median CD4 count was 322 (2-693); 68% had undetectable HIV RNA. Treatment was well tolerated. Of 14 patients who completed 12 weeks of treatment, 26% (95% CI, 10%-48%) showed partial response in halofuginone-treated lesions and 17% in placebo-treated lesions (95% CI, 5%-39%), (P=0.689). Global response was 30% (95% CI, 13%-53%). None of 10 subjects showed detectable blood levels. Type 1 collagen message decreased significantly in halofuginone-treated lesions at week 4, whereas vehicle-treated lesions showed no change. VEGF protein expression decreased significantly in vehicle-treated lesions at week 4, whereas halofuginone-treated lesions showed no change. There were no differences in levels of MMP2 or VEGF protein between halofuginone- and vehicle-treated lesions. No changes in HIV RNA levels or CD4 counts were observed.

Conclusion
Although topical halofuginone appears ineffective for KS treatment, this study presents a novel design that could be applied to future studies using the patient as his own control to test a topical, non-absorbed agent.

Acknowledgements
This work was supported by U01 CA121947.
26. Preventing HHV-8 transmission and Kaposi’s sarcoma (KS) risk prediction and prognostication in resource-poor countries

Amos Mwakigonja1,2, Pawan Pyakurel2, Fatemeh Pak2, Parviz Kokhaei2, Peter Biberfeld2, Ephata Kaaya1,2
1Department of Pathology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
2Department of Oncology-Pathology, Karolinska University Hospital Solna/Karolinska Institutet, Stockholm, Sweden

Background
Kaposi’s sarcoma (KS) is the now most important AIDS-defining malignancy in sub-Saharan Africa including Tanzania, and human herpesvirus-8 (HHV-8) is necessary for its development. Detecting HHV-8 in biopsies and its antibodies in sera allows the confirmation of KS diagnosis and predicts its risk among blood transfusion (BT) and organ transplant recipients but this is not yet routine in most African countries. This impedes the provision of safe BT/organ donation as well as KS prevention. A cost-effective HHV-8 serological assay for routine use will help improve blood/organ safety and lower iatrogenic KS incidence in resource-poor countries.

Materials and methods
Consecutive archival (1990-2001) biopsies and their corresponding sera from African patients with KS, non-KS tumors, and non-neoplastic (reactive) lesions at Muhimbili National Hospital (MNH) were evaluated by histopathology, immunohistochemistry (IHC) for the HHV-8 latency-associated nuclear antigen (LANA), and serology for HIV and HHV-8 (ELISA) as well as for HHV-8 [immunofluorescence (IFA)].

Results
A total of 184 biopsies and corresponding sera from 120 KS (65%), 24 non-KS tumors (13%), and 40 non-neoplastic lesions (22%) were evaluated. Most sera (89.0%, 164/184) were HHV-8+ by either IFA or ELISA (p<0.001, highly statistically significant, Chi2 Test) and as expected the majority (68.3%, 112/164) were KS. HHV-8 serology tests by IFA and ELISA were mostly (92.4%, 73/79) concordant. Sensitivity, positive predictive value (PPV), and specificity were 98.6%, 93.5%, and 16.7% for IFA and 93.5%, 98.6%, and 50.0% for ELISA, respectively. All patients with early-stage KS were HHV-8 seropositive but two late-stage cases were seronegative despite LANA expression in their corresponding biopsies.

Conclusions
HHV-8 frequency at MNH appears to be very high and necessitates routine screening of blood/organ donors and recipients to prevent viral transmission and lower risk of iatrogenic KS development. IFA and ELISA serology tests appeared highly concordant and ELISA showed higher PPV and specificity in detecting anti-HHV-8 antibodies. Thus ELISA might allow affordable HHV-8 screening in resource-poor countries like Tanzania, with most lacking the cell culture and fluorescence microscopy facilities needed in IFA. The apparent tissue (LANA)-serum HHV-8 antibodies discrepancy in late-stage KS suggests that serum HHV-8 might not be a good indicator of this tumor’s development.

Acknowledgement
These studies were supported by Sida/SAREC of Sweden.
Relationship between salivary shedding and seropositivity for Kaposi’s sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV) among South African children and adults: insights on why EBV infection is ubiquitous and KSHV is not

Lisa Butler¹, Sheila Dollard², Minal Amin², Anisa Mosam³, Jeffrey Martin¹
¹Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA
²Centers for Disease Control and Prevention, Atlanta, GA, USA
³University of KwaZulu-Natal, Durban, South Africa

Background
In a recent population-based study of South African children, we found KSHV seroprevalence in children to be low (7%) and not associated with age, but EBV infection was nearly ubiquitous (96%). While saliva is known to be the main conduit for transmission of both KSHV and EBV, little is known about the comparative patterns of KSHV and EBV salivary shedding in Africa. To address whether differences in salivary shedding may account for the difference in seroprevalence, we assessed KSHV and EBV shedding in children and their caregivers in South Africa.

Methods
Participants were children ages 1.5 to 8.9 years and their primary female caregivers in a population-based sample in a rural and an urban community in KwaZulu-Natal Province, South Africa. KSHV antibody testing utilized a previously established algorithm featuring two enzyme immunoassays and one indirect immunofluorescence assay. Viral DNA in unstimulated saliva was detected by PCR targeting ORF25 for KSHV and the EBNA gene for EBV.

Results
Among 458 children, 33 (7%) were KSHV antibody-positive, of whom 30 had saliva available for testing. Of these 30, 70% were female, and median age was 4.3 years (IQR 2.5-8.2). Among the female caregivers, 84 (17%) were KSHV antibody-positive, of whom 80 had saliva available for testing. Of these 80, the median age was 34 years (IQR 26-51). Among KSHV-seropositive individuals, KSHV DNA was detected in saliva of 1/30 children (3.3%) and 9/80 (11.3%) adults (p=0.20). KSHV DNA was not detected in the saliva of any KSHV antibody-negative or -equivocal individual. EBV DNA was detected in the saliva of 83% (25/30) of children (p<0.001 compared to KSHV) and 60% (48/80) of adults (p<0.001 compared to KSHV). There was no association between viral shedding of EBV and KSHV in saliva (p=0.83). Examination of the determinants of salivary shedding found that both younger age (odds ratio=0.97 per year of age, p=0.01) and HIV infection (OR=4.0, p=0.01) were independently associated with EBV shedding but not with KSHV shedding.

Conclusions
EBV is present in saliva substantially more often than KSHV among KSHV/EBV-infected South African children and adults. The much higher prevalence of EBV in saliva may, at least in part, explain why EBV infection is ubiquitous and KSHV is not. Attention next needs to turn to comparative mechanisms of host control of viral salivary shedding. The effect of HIV on herpesvirus salivary shedding suggests yet another reason why widespread therapy of HIV infection would be useful.
T cell immunosenescence is associated with the presence of Kaposi’s sarcoma in antiretroviral treated human immunodeficiency virus-infected persons

Patrick Unemori1,2, Peter Hunt2, Kieron Leslie1, Elizabeth Sinclair2, Jeffrey Martin2, Steve Deeks2, Toby Maurer1
1Dermatology, University of California, San Francisco, San Francisco, CA, USA
2Internal Medicine, University of California, San Francisco, San Francisco, CA, USA
3Center for AIDS Research Core Immunology Laboratory, University of California, San Francisco, San Francisco, CA, USA

Background
We reported an atypical cohort of antiretroviral-treated patients who developed or had unremitting Kaposi’s sarcoma (KS) despite having undetectable viral loads and high CD4 cell counts. The KS course of these patients is indolent, resembling elderly or classical HIV- KS. Since HIV infection is associated with accelerated immunologic aging (“immunosenescence”), and since classical HIV- KS of the elderly may be related to age-associated T cell dysfunction, we hypothesized that T cell immunosenescence would be associated with the presence of this atypical KS.

Materials and methods
We identified 19 individuals on antiretroviral therapy (ART) who developed or had unremitting KS after an interval of at least 24 months with viral loads <75 copies RNA/mL and peripheral CD4 cell counts >300 cells/mm³. We also recruited 47 HIV+ KS-controls on ART with viral loads <75 copies RNA/mL and peripheral CD4 cell counts >300 cells/mm³. Global immunosenescence markers CD28 and CD57, as well as naïve cell phenotypic coexpression of CD27+/CD28+/CD45RA+, were examined in peripheral blood via flow cytometry.

Results
All cases and controls were men. Cases and controls were not significantly different with regard to CD4 or CD8 cell count and viral load, though age was significantly different (p<0.001, Table 1). Cases had a higher proportion of CD57+CD8+ T cells vs. controls (median of 41.5% vs. 27.7%, age-adjusted p=0.005). There was a trend suggesting that cases had a higher frequency of CD57+CD4+ T cells than controls (median of 7.4% vs. 3.7%, age-adjusted p=0.07). Cases also had a higher proportion of CD28-/CD4+ cells (median of 9.1% vs. 4.8%, age adjusted p=0.030) and CD28-/CD8+ cells (median of 60.5% vs. 51.3%, age adjusted p=0.044) vs. controls. Cases had a lower proportion of CD27+/CD28+/CD45RA+ naive CD8+ T cells vs. controls (median of 11.3% vs. 20.7%, age adjusted p=0.022). There was a trend suggesting that cases had a lower frequency of CD27+/CD28+/CD45RA+ naive CD4+ cells vs. controls (median of 23.0% vs. 32.2%, age adjusted p=0.11).

Table 1. Age and Markers of HIV Infection in HIV+ KS+ Cases and HIV+ KS- Controls.

<table>
<thead>
<tr>
<th></th>
<th>Number of Subjects (N)</th>
<th>Median Age (years)*</th>
<th>Median CD4 count (cells/mm³)</th>
<th>Median CD8 count (cells/mm³)</th>
<th>Median Viral Load (copies RNA/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+ KS+ Cases</td>
<td>19</td>
<td>54*</td>
<td>701</td>
<td>933</td>
<td>&lt;75</td>
</tr>
<tr>
<td>HIV+ KS- Controls</td>
<td>47</td>
<td>43*</td>
<td>521</td>
<td>1200</td>
<td>&lt;75</td>
</tr>
</tbody>
</table>

*p<0.05

Conclusion
The indolent KS observed among antiretroviral-treated patients is associated with a higher frequency of immunosenescent T cells, characterized by global immunosenescence markers and decreased numbers of naïve cells. These markers provide more evidence that KS in these patients may be a consequence of enduring HIV-associated T cell dysfunction and T cell immunosenescence. This association of immunosenescence in otherwise well-treated HIV infection with an AIDS-defining malignancy may provide important insights into the role of immune dysfunction as a cause of premature morbidity commonly observed in the HIV+ cohorts.
29. The angiogenic properties of Kaposi’s sarcoma-associated herpesvirus encoded G-protein coupled receptor are reduced by flavopiridol, an inhibitor of cyclin-dependent kinase 9

Harris McFerrin1, Magdelena Angelova2, Elizabeth Abboud1, Anne Nelson2, Aline Betancourt2, Gilbert Morris3, Bryan Shelby4, Cindy Morris2, Deborah Sullivan2
1Department of Biology, Xavier University of Louisiana, New Orleans, LA, USA
2Department of Microbiology and Immunology, Tulane University School of Medicine, New Orleans, LA, USA
3Program in Lung Biology, Department of Pathology, Tulane University School of Medicine, New Orleans, LA, USA
4NCIRD/DVD/MMRHLB/Herpesvirus Team, Centers for Disease Control and Prevention, Atlanta, GA, USA

Kaposi’s sarcoma-associated herpesvirus (KSHV/HHV8) has been identified as the etiologic agent of Kaposi’s sarcoma (KS), a multifocal highly vascularized neoplasm that is the most common malignancy associated with AIDS. Although highly active antiretroviral therapy has decreased the incidence of KS, it remains an incurable tumor for which there is no established treatment. Due to the vascular nature of KS, an anti-angiogenic therapeutic approach is attractive. The KSHV-encoded G-protein-coupled receptor (vGPCR) is required and sufficient to initiate angiogenesis and tumorigenesis. Recent evidence suggests that inhibition of P-TEFb, a transcriptional elongation factor composed of cyclin dependent kinase 9 (CDK9) and its regulatory partner cyclin T, is anti-angiogenic.

We hypothesized that flavopiridol, a novel inhibitor of CDK9, would inhibit vGPCR-induced angiogenesis by downregulating expression of angiogenic growth factors and/or Bcl-2. To test this hypothesis, in vitro and in vivo angiogenesis assays were carried out using primary human umbilical vein endothelial cells (HUVECs) transduced with either a control or a vGPCR-expressing retroviral vector and then treated with flavopiridol. Our results show that CDK9 activity is increased in vGPCR-expressing HUVECs and that pretreatment with 50 nM flavopiridol inhibited vGPCR-induced migration and capillary tubule formation. These results correlated with a significant decrease in expression of genes encoding the angiogenic factors VEGF-A and VEGF-C and the pro-survival factor Bcl-2. Initial studies to determine the molecular mechanisms by which CDK9 affects angiogenesis demonstrated that HUVECs treated with bFGF and VEGF had increased CDK9 activity as well as increased expression of the major isoform of Cdk9 and cyclin T. Although Cdk9 was described in the literature as a general transcription factor, we have observed that inhibition of CDK9 by flavopiridol decreased the expression of Bcl-2 but not p21 in HUVEC. Together these results suggest that CDK9 plays a role in mediating transcriptional regulation of vGPCR responsive genes and implicate CDK9 as a potential target to reduce vGPCR-enhanced endothelial cell survival, angiogenesis, and tumorigenesis. Experiments are currently under way to determine whether CDK9 is directly activated upon vGPCR expression and whether inhibition of CDK9 activity suppresses KSHV-enhanced angiogenesis and tumorigenesis in vivo.
The Kaposi’s sarcoma-associated herpesvirus E3 ubiquitin ligase K5 acts as a novel oncogene, altering cellular metabolism and signaling: implications for tumorigenesis

Roshan Karki, Sabine M. Lang, Robert E. Means
Department of Pathology, Yale University School of Medicine, New Haven, CT, USA

While it is clear that Kaposi’s sarcoma-associated herpesvirus (KSHV or HHV-8) is the causative agent of a number of malignancies including multicentric Castleman’s disease, primary effusion lymphoma, and Kaposi’s sarcoma (KS), the molecular mechanisms of tumor induction by this virus are still unclear. In part, KS lesion presentation is thought to be driven primarily through paracrine mechanisms and is mainly observed in immunocompromised patients. Monocyte subsets, including dendritic cells and macrophages, are crucial to immune system functionality and are also skewed in KS patients. The goals of this study were to investigate a potential role for the E3 ubiquitin ligase K5 of KSHV, which plays a role in viral immune evasion, in altering monocyte functionality, thereby contributing to KSHV-driven tumorigenesis.

A series of wild-type (WT) and mutant K5-expressing stable cell lines were generated in THP-1 monocytic cell line and examined. Surprisingly, these cells demonstrated a serum-dependent increased growth rate and a propensity to acidify the growth medium as compared to vector-THP-1 cells. Biochemical examination indicated that K5 induced aerobic glycolysis and other hallmarks of the “Warburg Effect,” including increased lactate production and glucose uptake. Observed increases in Akt and total cellular tyrosine phosphorylation, combined with the serum-dependence, suggested a role for receptor tyrosine kinases (RTKs). A human-RTK array demonstrated increased activation of the Flt-3, Axl, PDGFR-ß, and Flt-4 receptors in K5-expressing versus vector cell lines. Subsequent testing demonstrated increased sensitivity of K5-expressing THP-1 cells to growth arrest and apoptosis by sunitinib and increased ligand-dependent signaling. Dynamin inhibitor studies showed that K5 can target these RTKs from the surface to increase intracellular signaling. Additional molecular details will be presented.

Overall, our studies demonstrate that the KSHV K5 protein is acting as a novel oncogene – the first viral protein of its kind – to drive monocyte subset expansion and alter cellular metabolism, contributing to a pro-tumorigenic microenvironment. Intriguingly, the metabolic changes observed are caused by a single KSHV protein and thus serve as a useful model to study different aspects of KS pathology and its overall regulation of cellular metabolism. These studies also provide additional rationale for the currently ongoing clinical trials of sunitinib, Gleevec, and rapamycin for the treatment of KSHV-driven neoplasias. Finally, the ability of this viral E3 ubiquitin ligase to drive metabolic changes provides the tantalizing suggestion that a cellular ligase may be acting in a similar, either physiologic or oncogenic, manner.
31. The HIV nef protein within ARL is genetically and structurally distinct from those in the brain of patients with HAD

Susanna L. Lamers¹, Gary B. Fogel², Leanne Huysentruyt³, Art Poon⁴, Michael S. McGrath⁴
¹BioInfoExperts, Thibodaux, LA, USA
²Natural Selection Incorporated, San Diego, CA, USA
³Department of Medicine, University of California, San Francisco, San Francisco, CA, USA
⁴British Columbia Centre for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada

Background
Despite antiretroviral therapy, macrophages remain significant cellular reservoirs for HIV infection. Two fatal macrophage-mediated diseases still occur at a much higher rate in the HIV-infected and HAART-treated population: (1) AIDS-related lymphoma (ARL), a noninflammatory disease, and (2) HIV-associated dementia (HAD), an inflammatory disease. The frequency of HIV-infected macrophages in ARL is 50%. Macrophages are the primary HIV-infected cells in the brain. The mechanisms that lead to the development of these diseases are not understood. Because certain subtypes of HIV are associated with a higher prevalence of HAD, a viral genetic determinant for HAD development is likely. On the other hand, ARL development occurs fairly consistently across multiple HIV subtypes and genetic analysis has clearly differentiated ARL tissue-associated HIV from non-ARL tissue HIV within individuals. These facts raise two questions: (1) Are there tumor-specific genetic differences among HIV proteins that could influence the macrophage to accelerate ARL development? (2) How might HAD-associated and ARL-associated viruses differ at the genetic and structural levels? Our goal was to analyze HAD and ARL viral sequences and determine whether a disease association could be identified within viral proteins.

Methods
The AIDS and Cancer Specimen Resource (ACSR) archives tissue samples derived from well-documented cases of both ARL and HAD. Multisite autopsies of 7 patients with ARL, HAD, and other neurological and systemic disorders were identified at the ACSR. More than 20 sequences from each of 5 to 7 tissues from each patient were sequenced. The HIV nef sequence was used in multiple genetic analyses, including a neural net signature pattern analysis, a tertiary structural analysis, and an analysis of the stability of an HIV viral microRNA associated with apoptosis.

Results
Signature pattern analysis clearly separated ARL from HAD viruses and identified positions that may in concert produce specific pathological outcomes. HIV subtype D viruses are known to be associated with a high rate of HAD. Comparative tertiary structural analysis of nef showed that HAD viruses were more similar to HIV subtype D viruses than ARL viruses. ARL viruses were either missing or possessed a less stable miR-H1 structure compared to HAD viruses.

Conclusions
Our results show that HIV-associated diseases are likely related to specific viral genetic signatures and structures. Discovery of an ARL virus would enable the development of diagnostic tools and identify subsets of viruses to be targeted with drugs or vaccines.
The use of high-dose azidothymidine in combination with chemotherapy upfront is an effective treatment approach for gamma-herpes virus-related non-Hodgkin’s lymphomas

Ulas Darda Bayraktar¹, Eileen Bernal¹, Lisa Cabral¹, William J. Harrington Jr.¹, Dirk P. Dittmer², Juan Carlos Ramos¹
¹Division of Hematology/Oncology, University of Miami Miller School of Medicine, Miami, FL, USA
²Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background
Azidothymidine (AZT), a thymidine analogue, is an excellent substrate for gamma-herpes virus thymidine kinases (TKs). Our group previously demonstrated that AZT alone can inhibit NF-κB and disrupt EBV latency in primary low-passage Type I latency EBV+ Burkitt lines. The addition of hydroxyurea, which increases the intracellular levels of AZT monophosphate, synergized with AZT in Type III latency EBV+ immunoblastic lymphoma cell lines. The use of AZT in targeting gamma-herpes virus lymphomas is an attractive concept given that this drug is preferentially phosphorylated by EBV and HHV-8 TKs as compared to non-thymidine nucleoside analogues. The drugs methotrexate (MTX) and doxorubicin (DOX) also induce lytic expression of gamma-herpes viruses. MTX inhibits thymidylate synthase, thus blocking de novo synthesis of dTMP and increasing the likelihood of AZT incorporation into DNA. We have found that the combination of high-dose AZT with MTX, used alone or with alternating standard chemotherapy, can result in dramatic clinical responses and even cures in patients with poor prognosis gamma-herpes virus-related lymphomas.

Materials and methods
Ten patients with EBV-positive (9 HIV-positive) non-Hodgkin’s lymphoma (NHL) were treated with first-line MTX (3.0-4.5 g/m² IV on day 1) and AZT 1.5 g IV infusion q12 hours (days 1-4) every 3 weeks or alternated with other chemotherapy regimens, including EPOCH, or hyper CVAD between 2004-2009 at the discretion of the treating physician (Table 1). One patient (solid PEL) received AZT and MTX initially, and upon relapse 31 months later received DOX 20 mg/m² (Day 1), MTX 5 g/m² (Day 2), and AZT 750 mg twice daily with hydroxyurea 1 g daily (Days 2-5) under our new clinical trial.

Results
Clinical characteristics, response, and survival data of patients are summarized in Table 1. All patients were treated with high-dose AZT and MTX. Three patients with plasmablastic lymphoma (PBL) and 1 patient with BL also received alternating EPOCH; 2 BL patients received alternating hCVAD. Seven patients achieved CR. Two patients developed neutropenic fever. Median PFS in this cohort of patients has not been reached. Median OS was 31 months (95% CI: 0.0-84.8).

Conclusions
The combination of high-dose MTX/AZT is a promising and tolerable treatment for gamma-herpes virus-related lymphomas. A Phase II clinical trial with low-dose doxorubicin, MTX, AZT, and hydroxyurea for relapse EBV+ NHL is currently recruiting participants. Interim results and supporting laboratory data for using this gamma-herpes virus lytic approach will be presented at the meeting.
Upregulation of p18Ink4c expression by HPV E6 via p53-miR-34a pathway

Xiaohong Wang1, Craig Meyers2, Zhi-Ming Zheng1

1HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
2Department of Microbiology and Immunology, Penn State University School of Medicine, Hershey, PA, USA

Binding of p53 to miR-34a promoter activates the expression of tumor suppressive miR-34a. Our previous study demonstrated that oncogenic HPV infection downregulates miR-34a expression through degradation of p53 mediated by E6. In searching for miR-34a targets, we found that miR-34a mainly downregulates p18Ink4c, a CDK4/6 inhibitor induced by E2F transactivation. HPV18+ HeLa cells with ectopic miR-34a expression or by E6 siRNA knockdown-induced expression of miR-34a had a substantially reduced expression of p18Ink4c in a dose-dependent manner, but had no effect on p16Ink4a, another member of CDK4/6 inhibitor family. Further investigation showed an increased p18Ink4c level in cervical cancer tissues by western blotting as compared to normal cervix. By immunostaining of tissue arrays, an increased expression of p18Ink4c was found in 68% of cervical cancer tissues, but only in 6.6% of normal cervical tissues. Moreover, specific inhibition of miR-34a expression in CaSk i cells promoted the expression of p18Ink4c. Raft cultures with HPV16 or HPV18 infections also showed an increased p18Ink4c expression. In a reporter assay, we demonstrated that disruption of the miR-34a seed match from p18Ink4c promoted luciferase activity in the presence of ectopic miR-34a. As a cell cycle regulatory protein in normal cells, the increased p18Ink4c expression by E6-induced p53 destabilization and miR-34a reduction in cervical cancer would lead to suppress cell cycling and proliferation. However, viral E7 expressed in cervical cancer cells inactivates pRB and dissociates E2F from pRB, resulting in disruption of normal G1 checkpoint. Thus, an increased p18Ink4c in the cervical cancer cells would not affect the cell growth. To test this hypothesis, we knocked down p18Ink4c expression by siRNA in both HPV18-positive HeLa cells and HPV-negative HCT116 cells, a colon cancer cell line that contains an intact G1 checkpoint. As we predicted, knocking down p18Ink4c expression promoted the growth of HCT116 cells but had no effect on HeLa cells. Altogether, our data indicate that p18Ink4c is a miR-34a target and its increased expression in cervical cancer tissues can be used as a new biomarker for cervical cancer diagnosis and prognosis.
Poster Abstracts – Day 2
A higher proportion of squamous intraepithelial lesion of the cervix in symptomatic HIV-infected women at a tertiary health center in Tanzania

Joseph Obure, Pendo Mlay, Gileard Masenga, Olola Oneko, David Walmer

1Department of Obstetrics and Gynecology, Kilimanjaro Christian Medical Center and Kilimanjaro Christian Medical College, Moshi, Kilimanjaro, Tanzania
2Department of Maternal and Child Health, University of North Carolina Gillings School of Global Public Health, NC, USA
3Departments of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC, USA

Background

Many study reports have associated cervical squamous intraepithelial lesion (SIL) and HIV infection [1,2]. In Tanzania, however, there are limited and conflicting published reports on the association between HIV infection and SIL [3]. A study was conducted to determine the proportion and severity of SIL in HIV-infected women attending a cervical cancer screening clinic at Kilimanjaro Christian Medical Center (KCMC) in Tanzania. A total of 214 women 18 to 60 years old, among whom 99 (46.3%) and 115 (53.7%) were HIV-seropositive and HIV-seronegative, respectively, were recruited in the study. Blood samples were taken to associate SIL and degree of HIV infection by CD4+ T lymphocyte counts. Structured questionnaires with socio-demographic characteristics were administered while cervical smears were taken from all women to determine and grade the degree of SIL. High-grade and low-grade squamous intraepithelial lesions were regarded as abnormal smear. Overall proportion of SIL was 17%. Proportion of SIL among HIV-seropositive subjects was 32% versus 4% in seronegative subjects (OR=13.3, 95% CI=4.2-46.4) (see Table 1). Low CD4+ T lymphocyte cell count was associated with higher proportion of SIL (p=0.001) (see Table 2). The relationship between CD4+ T lymphocyte cell counts and the severity of cervical SIL was significant (p=0.007) (see Table 3). Marital status and number of lifetime sex partners were risk factors significantly associated with SIL (p=0.004 and 0.005, respectively). There was no association between SIL with age, education level, parity, or age at sex debut.

Table 1. Relationship between HIV serostatus and cervical SIL (n, 214).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Pap results</th>
<th>Chi-square</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SIL</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-seropositive</td>
<td>99</td>
<td>32 (32.3)</td>
<td>67 (67.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-seronegative</td>
<td>115</td>
<td>4 (3.5)</td>
<td>111 (96.5)</td>
<td>31.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: Pap = Papanicolous smear; SIL = Squamous Intraepithelial Lesion.

Table 2. Relationship between SIL and HIV disease progression according to CD4+ T lymphocyte count (cells/microL).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>PAP smear results</th>
<th>Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SIL</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>CD4+ T lymphocyte cell Count (cells/microL):</td>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Less than 200</td>
<td>31</td>
<td>18 (58.1)</td>
<td>13 (41.9)</td>
<td></td>
</tr>
<tr>
<td>200-499</td>
<td>49</td>
<td>32 (32.3)</td>
<td>38 (77.6)</td>
<td></td>
</tr>
<tr>
<td>500 or more</td>
<td>19</td>
<td>4 (3.5)</td>
<td>16 (96.5)</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Note: PAP = Papanicolous; SIL = Squamous Intraepithelial Neoplasia.
Table 3. Relationship between degree of SIL and degree of HIV progression (n=99).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>PAP smear results</th>
<th></th>
<th>Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HGL No. (%)</td>
<td>LGL No. (%)</td>
<td>Normal No. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ T lymphocyte cell count (cells/microliter):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 200</td>
<td>31</td>
<td>7 (22.6)</td>
<td>11 (35.5)</td>
<td>13 (14.9)</td>
<td></td>
</tr>
<tr>
<td>200-499</td>
<td>49</td>
<td>4 (8.2)</td>
<td>7 (14.3)</td>
<td>38 (77.6)</td>
<td></td>
</tr>
<tr>
<td>500 or more</td>
<td>19</td>
<td>1 (5.3)</td>
<td>2 (10.5)</td>
<td>16 (84.2)</td>
<td>14.0</td>
</tr>
</tbody>
</table>

Note: PAP = Papaniculous; HGL = High-Grade Squamous Intraepithelial Lesion; LGL = Low-Grade Squamous Intraepithelial Lesion.

Conclusion
SIL diagnosis was significantly associated with HIV infection with inverse relationship between HIV disease progression and degree of SIL. These findings underscore the need for HIV screening among women with SIL, and the need for cervical cancer screening in HIV-infected women. Marital status and number of lifetime sex partners were significant risk factors associated with SIL.

Acknowledgement
Special thanks to Prof. John Bartlett of Duke University (USA)-KCMC collaborations for entire funding of this work, Dr John Crump and Colleagues from KCMC Department of Obstetrics and Gynaecology for their contribution to this work.

References
Nonlinear Burkitt lymphoma risk patterns with age and CD4 lymphocyte count among persons with AIDS in the United States

Mercy Guech-Ongey¹, Eric A. Engels¹, William F. Anderson², Kishor Bhatia¹, Edgar P. Simard¹, Susan S. Devesa², Sam M. Mbulaiteye¹

¹Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD, USA
²Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD, USA

Background
Trimodal age-specific incidence rates for Burkitt lymphoma (BL) were observed in the U.S. general population, particularly among men. Because BL is AIDS-related, it is not known whether trimodal incidence peaks occur independently of immunosuppression. We therefore investigated age-specific BL incidence in persons with AIDS (PWA).

Methods
Crude and adjusted incidence rates, rate ratios (IRR), and 95% confidence intervals (95% CI) for BL and other non-Hodgkin lymphomas (NHLs) diagnosed during 4-60 months following AIDS diagnosis in the United States HIV/AIDS Cancer Match study (1980-2005) were assessed by age and CD4 lymphocyte counts using Poisson regression models. Two-tailed \( p \)-values < 0.05 were considered statistically significant.

Findings
We analyzed 306 incident cases (22 cases per 100,000 person-years) diagnosed among 567,865 PWA. The adjusted incidence rate ratio for BL among males was 1.6 times that among females and among non-Hispanic Blacks 0.4 times that among non-Hispanic Whites, but it was unrelated to HIV-transmission categories. The age-specific incidence rates for BL revealed at least two and perhaps three peaks during the pediatric and adult/geriatric years, whereas the incidence rates for other NHLs increased from childhood to adulthood. Compared to PWA aged 32-39 years, the adjusted incidence rate ratio (IRR) for BL was significantly elevated among PWA aged 0-19 years (2.3, 95% CI 1.2-4.4). The adjusted IRR for BL among PWA aged 20-31 years was significantly decreased (0.6, 95% CI 0.4-0.8), but the adjusted IRRs for BL among PWA aged 40-51 years, 52-59 years, and aged 60 years or older were not significantly different (1.0, 95% CI 0.8-1.3), (0.8, 95% CI 0.4-1.4), and (1.4, 95% CI 0.7-2.7), respectively. The risk for BL among PWA with <50 CD4 lymphocytes/µL was 0.3 (95% CI=0.2-0.6) of those with ≥250 CD4 lymphocytes/µL, whereas the incidence for other NHLs rose with decreasing CD4 lymphocyte counts.

Interpretation
Our findings strengthen the notion that bi/trimodal BL may occur independently of immunosuppression. The deficit of BL at low CD4 lymphocyte counts suggests that functional CD4 lymphocytes may be required for BL to develop.
AIDS-related lymphomas in Nigeria an emerging phenomenon

L. Salawu1, R.A. Bolarinwa1, O.O. Lawal2, A.A. Oyekunle1, O. Adeodu3, E.A. Adejuyigbe3, K.A. Adelusola4, N.O. Akinola1, M.A. Ndakotsu1, M.A. Durosinmi1
1Department of Haematology, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria
2Department of Surgery, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria
3Department of Paediatrics, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria
4Department of Morbid Anatomy, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria

Background
In comparison to the western world, aggressive non-Hodgkin’s lymphoma (NHL) including primary central nervous system (CNS) lymphoma, as AIDS-defining disease, is less common in sub-Saharan Africa even with its high HIV/AIDS prevalence. We studied the occurrence of HIV/AIDS-related lymphomas in Nigerian patients with a view toward highlighting the incidence.

Patients and method
Consecutive cases of histologically and/or cytologically confirmed lymphoma screened for HIV (after appropriate counseling) and seen between January 2003 and December 2009 were the subjects. Types and treatment outcome of lymphoma in the HIV-positive group were further studied. Data were analyzed using appropriate descriptive and inferential statistics.

Results
There were 161 cases comprising NHL, 42 (25.5%); HL, 15 (9.3%), and BL, 104, (64.6%). Seven (4.3%), aged 2-49 (median = 41) years were retroviral positive. Of these, 4 (3 males, 1 female, aged 28-49 (median = 38.5) years) had NHL, 2 (both females) HL, and 1 case, a 2-year-old boy with HIV since birth, had Burkitt’s and an HIV-positive mother. All, except one female with stage 1 HL, presented late (at least clinical stage IIIb). Three patients with NHL and 1 with late-stage HL succumbed to their disease within 1-3 weeks of hospital admission. The remaining 3 patients had been responding satisfactorily to chemotherapy (CHOP for NHL, ABVD for HL, and COM for Burkitt’s lymphoma.)

Conclusion
Compared to earlier reports from Nigeria, the AIDS-related lymphomas rate of 4.3% in the series indicated rising incidence. AIDS-associated BL of 0.1%, in spite of high background prevalence of Burkitt’s lymphoma (>60% of lymphomas), supported its relative rarity. With longer survival and longer immunosuppression, closely following up AIDS patients on HAART would be justified, as more cases of AIDS-related lymphomas may possibly emerge in the future.

Acknowledgements
AIDS-Associated Malignancies Management Team, OAUTHC ILE-IFE Nigeria.
**37. Attitude of health care providers in Abia State, Nigeria, to people living with HIV and AIDS**

Charles Adisa¹, Ugochukwu Onyeonoro¹, Aniele Agu¹, Ndukauba Eleweke¹, Umezurike Chisara²

¹Abia State University, Aba, Nigeria
²Christian Hospital, Nlagu, Nigeria

**Background**

In pursuit of the global commitment of universal access to HIV services, there has been rapid scale up of HIV programmes including care and support in Nigeria in the past few years. Consequently, more health care providers are increasingly being involved in the provision of HIV services; this however increases their risk of exposure to HIV infection. Most people accessing HIV services are also at risk of developing malignancies because they often present late as a result of stigma. Care providers attitude towards PLWHA has been shown to be the most important factor influencing uptake of HIV services [1]. The objective of this study is to ascertain health care workers knowledge of HIV and their attitude towards PLWHAs in Abia State, Nigeria.

**Methodology**

A cross-sectional, descriptive study, involving a total of 300 health care workers selected using stratified sampling technique from the list of registered health care workers in the State. Responses were elicited from them using semi-structured self-administered questionnaire on socio-demographic characteristics, knowledge of HIV/AIDS and attitude towards PLWHAs. Data collected was analyzed using Epi-info 3.5.1 version. IRB approval was obtained from Abia State University.

**Result**

The respondents included 135 nurses (52%), 56 doctors (21.7%), others were pharmacists, laboratory scientists and medical records officers. Almost all know that HIV is a blood transmissible infection. Over 50% believe that HIV transmission in health care settings is predominantly by sexual intercourse, while 40% of them consider recapping of needles as an important measure in preventing HIV transmission. 13% of them feel that their work do not expose them to the risk of acquiring HIV, and 40% do not think that increased uptake of HIV services increases their chance of acquiring HIV. Majority of them provide one form of HIV services in their facility or the other, but their facilities lack enough provisions to protect them from HIV infection. However, most health workers in the state expressed willingness to care for PLWHA, admit them into their facility, as well as work with an HIV positive colleague. However, less than 35% are not willing to share a meal with HIV person, buy food from a HIV positive shopkeeper.

**Conclusion**

These findings underscores the need to further educate health care providers in Abia State Nigeria on the risk of occupational exposure to HIV transmission, so as to improve their attitude towards PLWHA, which in turn may result in increased uptake of HIV services.

**Reference**

Cancer in HIV patients in Latin America and the Caribbean: characteristics in seven sites from the CCASAnet Cohort (IeDEA Region 2)

Valeria Fink1, Bryan Shepherd2, Firas Wehbe3, Claudia Cortés4, Brenda Crabtree5, Denis Padgett6, Maryam Shaffaee7, Mauro Schechter7, Eduardo Gotuzzo9, Carina Cesar1, Alejandro Krolewiecki1, Melanie Bacon10, Catherine Mc Gowan11, Pedro Cahn1, Daniel Masys12

1Fundación Huésped, Investigaciones Clínicas, Buenos Aires, Argentina
2Vanderbilt University, Biostatistics, Nashville, TN, USA
3Vanderbilt University, Nashville, TN, USA
4Universidad de Chile-Fundación Arriarán, Santiago, Chile
5Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran, Mexico, Mexico
6Instituto Hondureño de Seguro Social y Hospital Escuela, Tegucigalpa, Honduras
7GHESKIO/ Weill Medical College of Cornell University, Port au Prince, Haiti
8Universidade Federal do Rio de Janeiro, Projeto Praça Onze, Rio de Janeiro, Brazil
9Instituto de Medicina Tropical Alexander von Humboldt, Lima, Peru
10HJF-NIAID/DAIDS, Epidemiology, Bethesda, MD, USA
11Vanderbilt University, Infectious Diseases, Nashville, TN, USA
12Vanderbilt University, Biomedical Informatics, Nashville, TN, USA

Background
Cancer in the Latin American and Caribbean HIV+ population has not been comprehensively studied. CCASAnet includes sites from Argentina, Brazil, Chile, Haiti, Honduras, Mexico, and Peru [1]. With support from NIH and NCI, CCASAnet established a region-wide registry of cancer-related information on HIV+ individuals.

Methods
Retrospective cancer data from HIV+ patients was collected between 2007 and 2009. Cancer cases were identified by review of clinical charts and preexisting databases. A standardized case report form was developed by the Vanderbilt data coordination center. Data were entered via a secure online Web interface. Cancers were categorized as AIDS-defining and non-AIDS-defining cancers (ADC and NADC). Time relations between HIV diagnosis, ARV initiation, and cancer diagnosis were established. For computing cancer incidence after HAART initiation, we used data from HAART starters in the CCASAnet cohort [2]. Haiti’s data were analyzed separately considering available information.

Results
Of 463 cancers reported, 357 were ADC: 242 Kaposi’s sarcoma, 98 non-Hodgkin lymphoma, and 17 invasive cervical cancers. Most frequent NADC were Hodgkin lymphoma (16), breast cancer (15)(most from Haiti), skin cancer (11), anal cancer (6), and in situ cervical carcinoma (6). About half of the cancers were diagnosed prior to or within 1 year of HIV diagnosis. However, 73% of NADC and 45% of ADC were found >1 year after HIV diagnosis. ADC occurred more commonly prior to initiation of ARV therapy. Among patients previously exposed to ARV, time from ARV start until cancer diagnosis was longer for NADC than ADC (median: 2.48 vs. 0.5 years, p=<0.001). Survival probability for people with ADC was lower than for those with NADC but risk of death did not differ among both groups (p=0.51).

Among 3372 HAART recipients, 158 (4.7%) were diagnosed with 165 cancers during the followup period: 136 ADC and 29 NADC. 85 cases were diagnosed prior to or at HAART initiation (77 ADC, 8 NADC). Incidence of cancer after HAART initiation in 8080 person-years of followup (median=1.9, IQR=1-3.2 years) was 7.3 (95% CI=5.7-9.4) for ADC 47.6 (95% CI=32.2-70.5) in the first 2 months], and 2.6 (95% CI= 1.7-4) for NADC. For a 100-cell increase in CD4 at HAART initiation, relative risk of cancer decreased 31% (95% CI 13-45%).

Conclusions
Our findings on incidence and type of cancer in this cohort are consistent with reports from other regions, with variations among sites. Early HIV diagnosis and treatment should be improved considering the high number of ADC and concomitant cancers with HIV diagnosis or HAART initiation.
Acknowledgements
CCASAnet, IeDEA Region 2: Caribbean, Central and South America.

References


Apollinaire Horo1, Antoine Jaquet2, Badian Toure1, Didier K. Ekouevi234, Séverin Lenaud4, Benjamin Effi5, Annie J. Sasco2, Eugene Messou6, Emmanuel Bissagnienn6, Mamourou Kone1, François Dabis2
1Service de Gynécologie Obstétrique, CHU de Yopougon, Abidjan, Côte d’Ivoire
2INSERM CRE U 897, ISPED, Université Victor Segalen, Bordeaux, France
3Clinique MTCT+ Adultes, ACONDA, Abidjan, Côte d’Ivoire
4Programme PAC-CI, CHU de Treichville, Abidjan, Côte d’Ivoire
5Service d’Anatomo-Pathologie, CHU de Treichville, Abidjan, Côte d’Ivoire
6CePReF, ACONDA, Abidjan, Côte d’Ivoire
7Service de Maladies Infectieuses et Tropicales (SIMIT), CHU de Treichville, Abidjan, Côte d’Ivoire

Background
The ongoing scale-up of antiretroviral therapy (ART) in low-resource settings continues to improve the prognosis of HIV-infected individuals, necessitating a focus on long-term case management especially in women. Facing the particularly high burden of cervical cancer in sub-Saharan Africa, preventive measures are therefore becoming an integral component of a comprehensive approach to the management of patients. We describe here some of the operational aspects of a cervical cancer screening procedure based on visual inspection among HIV-positive women attending ART clinics in Abidjan.

Methods
A cross-sectional study is being conducted in two HIV clinics of Abidjan, since August 2009. A mobile team composed of three trained midwives and a senior gynecologist is in charge of proposing cervical screening based on visual inspection to all HIV-infected women attending participating clinics. Midwives are in charge to perform visual inspection of the cervix with acetic acid (IVA) and lugol’s iodine (IVL). Exclusion criteria are following: no previous cervical cancer or total hysterectomy, aged <25 or >59 years, pregnancy over 20 weeks. They refer positively screened women (IVA+ or IVL+) to a gynecologist in charge of the colposcopy examination (and biopsy if needed). Women with confirmed lesions are proposed an adapted treatment according to local available resources.

Results
Of the first 1,653 HIV-positive women, who attended the cervical screening consultations, 49 were not eligible and 103 were not assessable because of a prevalent cervical infection. The median age of the 1,501 screened women was 37 (IQR 32-43) years, and 1171 (78%) were on ART. 133 (9%) women were positively screened for cervical pre malignancy and referred for medical examination. 69 (4.6%, 95% CI 3.5-5.6) were confirmed by colposcopy and had histological investigation. Results of the 69 biopsy performed were as follows; 48 cervical intraepithelial neoplasia (CIN) of grade 1, 8 CIN grade 2 or 3, 2 invasive carcinoma and 10 nonmalignant findings. 22 patients were treated with cryotherapy, 16 were referred for surgical excision, and 31 were proposed a gynecological followup.

Conclusion
Several barriers were identified as limiting the ability of visual inspection used as a cervical screening method such as a high rate of cervical infection or a high rate of false-positive cervical lesions. Health care systems in West African countries cannot afford the financial and structural burdens of a conventional cervical screening program. Strategies adapted to HIV-infected women and relying on visual inspection appear feasible despite stated limitations and should be further evaluated.

Acknowledgement
This abstract is being submitted on behalf of the International Epidemiological Database to Evaluate AIDS in West Africa collaboration.
Background
Kaposi sarcoma (KS) is one of the most common pediatric cancers in sub-Saharan Africa. Few data are available about the clinical presentation or response to treatment of children with epidemic (HIV-associated) KS.

Methods
Medical records of all children with KS and HIV infection referred to the Uganda Cancer Institute from October 2004 to June 2007 were reviewed. Charts were abstracted for age, sex, location of KS lesions, biopsy results, CD4 T-cell counts, and KS treatment and outcome.

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>KS cases, n (percent)</td>
<td>73 (100%)</td>
<td>37 (50.7%)</td>
<td>36 (49.3%)</td>
</tr>
<tr>
<td>Age in years, median (range), n=56</td>
<td>10.1 (2 – 18)</td>
<td>9.3 (2 – 16)</td>
<td>11.0 (2 – 18)</td>
</tr>
<tr>
<td>CD4 T-cells/μL, median (IQR) n=36</td>
<td>210 (21 – 482)</td>
<td>165 (16 – 538)</td>
<td>263 (26 – 464)</td>
</tr>
<tr>
<td>Location of lesions n=42*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin involvement</td>
<td>20 (47.6%)</td>
<td>10 (45.5%)</td>
<td>10 (50.0%)</td>
</tr>
<tr>
<td>Oral cavity involvement</td>
<td>9 (21.4%)</td>
<td>4 (20.0%)</td>
<td>5 (22.7%)</td>
</tr>
<tr>
<td>Viscera involvement</td>
<td>5 (11.9%)</td>
<td>3 (15.0%)</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>25 (59.5%)</td>
<td>11 (55.0%)</td>
<td>14 (58.3%)</td>
</tr>
</tbody>
</table>

*Categories of lesion location not mutually exclusive.

Those children with lymphadenopathic KS were younger (mean difference 3.7 years; p = 0.01), and had higher CD4 T-cell counts (mean difference 242 cells/μL; p = 0.03) than those without lymph node involvement. CD4 T-cell count was not associated with KS presentations other than lymph node involvement (Figure 1).

Twenty children (62.5%) of the 32 patients with outcome data available had a complete resolution of KS. Eleven patients had a partial response, and only one patient had a documented lack of response. No association was apparent between outcome and age, sex, or type of KS presentation. Thirty (93.8%) of the 32 patients with outcome data available received cancer chemotherapy (10 with vincristine, 20 with vincristine plus bleomycin). No difference was observed in outcome with respect to whether cancer chemotherapy was used, or whether one or two drugs were given. Of those patients with a known outcome, a higher proportion had a complete resolution of KS among those who received any antiretroviral therapy (ART) regimen compared to those who did not receive ART (19 of 26 vs. 1 of 6; P=0.02).

Figure 1. CD4 T-cell count quartiles (boxes and whiskers) and outliers (dots) for those patients with and without KS involvement of the lymph nodes (A), skin (B), oral cavity (C), and viscera (D).
Conclusions
Compared to skin involvement, lymph node involvement of epidemic KS occurs at younger ages and at higher CD4 levels. This presentation may reflect recent infection with human herpesvirus 8 followed by a rapid progression to malignancy. Favorable response to treatment was observed in some cases, but the observed response rate was almost certainly biased by the large number of children lost to followup, among whom we expect disproportionately poor outcomes. Prospective studies are needed to determine optimal management.
41. Comparison of self-collected versus nurse-collected samples for detection of HPV-DNA among HIV-infected women in Pune, India

Vikrant Sahasrabuddhe1, Seema Sahay2, Rohini Kelkar3, Cathy A. Jenkins1, Bryan Shepherd1, Arun Risbud2, Ramesh Bhosale4, Robert Bollinger5, Sten Vermund1, Sanjay Mehendale2
1Vanderbilt University, Nashville, TN, USA
2National AIDS Research Institute, Pune, India
3Tata Memorial Center, Mumbai, India
4Byramjee Jeejeebhoy Medical College, Pune, India
5Johns Hopkins University, Baltimore, MD, USA

Background
Self-collection of samples for papillomavirus (HPV)-DNA testing may represent a noninvasive and discreet method for cervical cancer screening, especially among HIV-infected women whose screening options are often compromised by the dual burden stigma of HIV and gender and lack of health care access.

Methods
We conducted a cross-sectional study in Pune, India among n=303 consenting HIV-infected women who underwent a brief informational session about high-vaginal self-collection for HPV samples. The participants then undertook self collection using a Digene cervical sampler in a private room in the clinic. This was followed by collection of cervical samples by a pelvic examination (along with other screening tests) conducted by a female nurse. Participants also answered a brief acceptability survey after the screening examination. High-risk (HR) HPV-DNA detection was conducted using Digene Hybrid Capture-2™ (HC2) assay. We calculated detection rates and measures of agreement between the two tests and compared survey responses for acceptability of self-sampling versus sample collection during pelvic examination.

Results
The median age was 30 years (interquartile range, IQR: 27–34) and the median CD4+ T-cell count was 343/μL (IQR: 244–495). The detection rates of HR-HPV positive test results were comparable in self versus clinician collected samples overall [44.1% (130/295) vs. 41.8% (124/297), p=0.6], and did not statistically differ by age (i.e., >30 vs. ≤30 years) (44% vs. 41%, p=0.5), CD4+ cut-off (i.e., <200/μL vs. ≥200/μL) (43% versus 41%, p=0.6) or antiretroviral treatment (ART)-status (i.e., on ART vs. never on ART) (45% vs. 49%, p=0.6).

The pair-wise agreement between the two sampling approaches was high [88.1%] and the kappa statistic denoted substantial agreement beyond chance [kappa: 0.76 (95% C.I.: 0.68-0.83)]. Survey responses about acceptability between the two approaches revealed that in comparison to screening by pelvic examination, a higher proportion of women found self-sampling to cause absolutely no discomfort [51% vs. 61%, p=0.01] and absolutely no pain [42% vs. 59%, p=0.01]. However, over half (50.2%) still preferred screening through pelvic examination, a third (35.2%) preferred self-collection as the favored method for screening, while 14.3% had no preference of one sampling method over the other.

Conclusions
Clinic-based self-collection of HPV compared favorably in comparison to sample collection through clinic-based pelvic examination among HIV-infected women in Pune, India. Further research needs to be undertaken to explore acceptability of home-based versus clinic-based collection of HPV samples, and operational challenges that may be encountered in these approaches.
Cutaneous squamous cell carcinoma in HIV-infected patients: a report of two (2) cases.

O.P. Oluwole¹, J.O. Adeniran², J.O. Taiwo³, M.O.A. Samaila⁴
¹Department of Pathology, College of Health Sciences, University of Abuja, Nigeria
²Department of Surgery, University of Ilorin Teaching Hospital, Ilorin, Nigeria
³Department of Surgery, Federal Medical Centre, Lokoja, Kogi State, Nigeria
⁴Department of Pathology, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria

Cutaneous squamous cell carcinoma (SCC) is a malignant neoplasm of the keratinizing epidermal cells and it accounts for 20% of all cases of nonmelanoma skin cancer. Important etiologic factors to the development of SCC are host characteristics, such as male gender, age, skin pigmentation, and environmental elements, the most important being long-time exposure to sunlight. Other predisposing factors include ionizing radiation, exposure to UV light, exposure to chemical carcinogens and chronic immunosuppression which is not HIV-associated. Though cutaneous SCC had been reported in several regions of the body, we are reporting two cases of cutaneous squamous cell carcinoma in the penile shaft and left gluteal region.
43. Delay in anal cancer diagnosis as a non-AIDS-defining malignancy

Justine Cohen¹, John Stern², David Henry³
¹Department of Internal Medicine, Pennsylvania Hospital, University of Pennsylvania Health System, Philadelphia, PA, USA
²Department of Infectious Diseases, Pennsylvania Hospital, University of Pennsylvania Health System, Philadelphia, PA, USA
³Department of Hematology and Oncology, Pennsylvania Hospital, University of Pennsylvania Health System, Philadelphia, PA, USA

Background
Anal cancer is not considered an AIDS-defining malignancy (ADM). Nevertheless, the frequency of both anal intraepithelial neoplasia and invasive squamous cell carcinoma of the anus continues to increase in the HIV/AIDS population. As in cervical cancer, an ADM, numerous studies have established a causal relationship between high-risk types of human papillomavirus (HPV) infection and anal cancer [1]. In cervical cancer, the diagnosis is typically established at or near the time of HIV diagnosis [2]. The goal of this study was to evaluate and ascertain the interval from HIV diagnosis to anal cancer diagnosis.

Materials and methods
Medical records were retrospectively reviewed in 25 HIV+ patients with documented anal cancer. Cases were selectively analyzed using preexistent diagnosis dates of HIV infection. Surgical pathology reports were examined to corroborate the diagnosis of anal cancer.

Results
In all 25 patients, anal cancer was biopsy-proven between 1 and 25 years after a diagnosis of HIV infection, with a mean of 11.43 years (Table 1). Greater than 95% of patients were compliant on antiretroviral therapy at the time of cancer diagnosis. This study identified a considerable delay in anal cancer diagnosis in all cases (Figure 1).

<table>
<thead>
<tr>
<th>Years elapsed from HIV diagnosis to anal cancer diagnosis</th>
<th># of patients/Years elapsed</th>
<th>Cumulative number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>19</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>21</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>22</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>23</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
</tbody>
</table>
Conclusions
The frequency of anal cancer within the HIV/AIDS population continues to increase despite effective antiretroviral therapy. This study reveals that unlike cervical cancer as an ADM, there is a frequent lag in identifying anal cancer among HIV patients. Given the known progression of HPV to cancer despite antiretroviral therapy, it is imperative that health care providers include a closer examination of the perianal area on a regular and continuing basis. We believe that increased awareness of anal cancer in the setting of HIV/AIDS will lead to earlier recognition, timely treatment, as well as improved outcome and long-term survival.

References

Figure 1. Delay in anal cancer diagnosis in years by cumulative number of patients.
44. Diagnosis of HIV-related malignancies in resource-constrained settings of sub-Saharan Africa, a cautionary tale for non-Hodgkin’s lymphoma

Leona W. Ayers1,4, Robert Lukande2,3, Lynnette K. Tumwine2,4
1Department of Pathology, The Ohio State University, Columbus, OH, USA
2Department of Pathology, Makerere University, Kampala, Uganda
3AIDS and Cancer Specimen Resource, ACSR, NIH, USA
4Sub-Saharan Africa Lymphoma Consortium, SSALC, ACSR, OHAM, USA

Background
Non-Hodgkin’s lymphoma (NHL) subgroups, immunophenotypes, and genotypes have been defined in developed countries but how that information translates to resource-constrained sub-Saharan Africa medical settings is undocumented. Local published data on NHL subgroups come largely from retrospective clinical biopsy study sets of paraffin-embedded tissues filed in local pathology archives. Relatively poorer representation of the rural and low socioeconomic populations is likely in such data. Prospectively identified NHL subgroups using immunologic and molecular techniques in consecutive presentations of patients would best clarify NHL subgroups and confounding diagnoses.

Materials and methods
Approximately 456 cases of malignant lymphoma (ML) from both the sub-Saharan African Lymphoma Consortium and Mid-region AIDS and Cancer Specimen Resource (ACSR) projects in East Africa were examined for microscopic morphology and 30 monoclonal antibodies for common NHL antigens; Lana-1 for HHV-8 (immunohistochemical, IHC); in situ hybridization (ISH) for EBV-encoded RNA, kappa/lambda light chains (Ventana, Tucson, AZ); and fluorescent in situ hybridization (FISH) c-myc t(8;14) (Abbott/Vysis, Downer’s Grove, IL).

Results
There was a small but consistent population of other tumors that reduced the accuracy of both the clinical and histopathology diagnosis of NHLs including those given in Table 1.

Table 1. Confounding tumor look-alikes.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Subtype examples/confounding factors</th>
<th>Presentation or clinical classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infections</td>
<td>African histoplasmosis</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td></td>
<td>Entomophthoromycosis – Basidiobolus ranarum</td>
<td>NHL</td>
</tr>
<tr>
<td>Viral lymphadenopathy</td>
<td>HIV-1 lymphadenopathy, follicular hyperplasia</td>
<td>NHL</td>
</tr>
<tr>
<td></td>
<td>EBV lymphadenopathy or lymphoproliferative disorders</td>
<td>NHL</td>
</tr>
<tr>
<td></td>
<td>HHV-8 lymphoblastic lymphoma</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td></td>
<td>Castleman’s disease</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>Pediatric small round cell tumors</td>
<td>Undifferentiated neuroblastoma</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td></td>
<td>Primitive neuroectodermal tumors (PNET)</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>Lymphocyte predominant</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>Poorly differentiated</td>
<td>NHL</td>
</tr>
</tbody>
</table>

Conclusions
Clinical diagnosis of NHL is complicated by other pathological entities that lead to inaccuracies. Histopathology diagnosis based on hematoxylin and eosin (H&E) stained tissue morphology alone improves accuracy (vs. clinical diagnoses alone) but can provide additional inaccuracies due to tumor look-alikes. Caution is warranted in considering either clinical diagnosis or local histopathology diagnosis in a resource-constrained medical setting as accurate in the conduct of clinical treatment trials or epidemiology studies.
45. **Do people with AIDS develop cancer at younger ages than the general population?**

**Meredith S. Shiels, Ruth M. Pfeiffer, Eric A. Engels**
National Cancer Institute, Rockville, MD, USA

**Background**
Previous studies have reported that age at cancer diagnosis is far younger among persons with HIV than in the general population, suggesting that cancer development is “accelerated” in persons with HIV. However, these estimates were influenced by differences in population age structures, since there are fewer older people with HIV at risk for developing cancer. We compared ages at cancer diagnosis among people with AIDS and the general population, after adjusting for underlying population age differences.

**Methods**
The HIV/AIDS Cancer Match study links 15 U.S. HIV/AIDS and cancer registries. Using data from 338,349 persons with AIDS from 1980-2006, we compared observed cancers in persons with AIDS and the general population, and expected cancers calculated by applying general population rates from the cancer registry to followup time of persons with AIDS. Expected cancers represent cases that would occur in the general population if it had the same structure as the AIDS population, defined by age, sex, race, year, and registry. Median age at cancer diagnosis was estimated for each cancer.

**Results**
The proportion of person-time contributed by older persons (65+ years) was far smaller in the AIDS (1%) than in the general population (13%). Reflecting this difference, the median observed age at diagnosis for most cancers was ~15-30 years younger among people with AIDS than in the general population. However, after accounting for differences in age structure, observed and expected ages at diagnosis did not differ for most cancers. Observed ages at diagnosis were younger than expected (p<0.001) only for Kaposi sarcoma (median 37 vs. 44 years), non-Hodgkin lymphoma (39 years vs. 43 years), lung cancer (49 years vs. 53 years), and anal cancer (42 years vs. 45 years), and older for Hodgkin lymphoma (41 years vs. 38 years; p<0.001).

**Conclusions**
For most cancers, age at diagnosis is similar between people with AIDS and the general population, after accounting for the ages of the populations at risk. After controlling for differences in population structure, age at diagnosis remained slightly younger for only a few cancers among people with AIDS. These differences may reflect the effects of HIV in accelerating the development of some cancers where immunosuppression plays an important role. Alternatively, some age differences might reflect earlier exposure to other cancer risk factors among HIV-infected people (e.g., HPV infection, tobacco).
46. Epidemiology of malignancies in HIV patients at Kamuzu Central Hospital in Lilongwe, Malawi

Elizabeth Bigger1, Carol Shores3,4, Mina Hosseinipour3, Agnes Moses1, Albert Mwafongo1
1Department of Medicine, UNC Project, Lilongwe, Malawi
2Department of Otolaryngology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
3Department of Medicine, Division of Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
4Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Clinical background
Malawi lacks an operational cancer registry, thus reliable epidemiological data to develop evidence-based care and focused research. HIV, infecting approximately 20% of urban Malawians [1], contributes to the pathogenesis of cancers, particularly AIDS-defining malignancies (Kaposi’s sarcoma, non-Hodgkin’s lymphoma, and cervical cancer) [2,3,4]. As antiretroviral use expands and life expectancy increases, malignancies will become a more significant cause of morbidity and mortality in this population. To gain understanding about malignancies in Malawians, we designed a database to collect clinical data for all presenting cancer patients at Kamuzu Central Hospital (KCH) in Lilongwe, Malawi.

Methods
Patients with histologically confirmed or clinically diagnosed malignancies were identified at Kamuzu Central Hospital’s departments of Medicine, General Surgery, Gynecology, Dental, Pediatrics, and Ophthalmology. From September 2009, patients underwent interviews and medical chart reviews to complete database questionnaires. Collected information included demographic data (age, sex, race, home village), family history of malignancy, exposure to potential carcinogens (tobacco, alcohol, and marijuana use, water source, cooking materials, and insecticide exposure), past medical history (including HIV, malaria, tuberculosis, and schistosomiasis), tumor location, histology diagnosis, stage, and treatment received. The questionnaire data were entered into a Web-based metaclinics database and extracted into Microsoft Excel. Calculations and analysis were performed with Excel. The cancer database will continue until at least 2013.

Results
Thus far, 315 cancer patients have been identified, with 152 (48.3%) HIV positive, 36 (11.4%) ignorant of their HIV status, and 127 (40.3%) HIV-negative. For representation from different departments, there were 155 patients from Medicine, 62 from Surgery, 48 from Pediatrics, 32 from Gynecology, 13 from Ophthalmology, and 5 from Dental. Of the HIV-positive patients, 107 (70.4%) had Kaposi’s sarcoma, 14 (9.2%) had lymphoma, 13 (8.6%) had cervical cancer, 4 (2.6%) had breast cancer, 2 (1.3%) had esophageal cancer, 2 (1.3%) had squamous cell carcinoma of the penis, and 2 (1.3%) had conjunctival squamous cell carcinoma. More HIV patients with Kaposi’s sarcoma used tobacco and alcohol than HIV patients with other malignancies (Table 2). Among HIV-positive patients, 126 (82.9%) had a history of malaria infection, and 34 (22.4%) had a history of TB infection.

<table>
<thead>
<tr>
<th>HIV status, sex, and mean age for KCH cancer database patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cases</strong></td>
</tr>
<tr>
<td>HIV-positive</td>
</tr>
<tr>
<td>HIV-negative</td>
</tr>
<tr>
<td>All patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Distribution of malignancies, infectious disease history, and substance use of HIV patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kaposi’s sarcoma</strong></td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Tobacco</td>
</tr>
<tr>
<td>No Alcohol</td>
</tr>
<tr>
<td>Light Alcohol</td>
</tr>
<tr>
<td>Heavy Alcohol</td>
</tr>
<tr>
<td>TB</td>
</tr>
<tr>
<td>Malaria</td>
</tr>
</tbody>
</table>
Conclusions
The majority of registered patients came from the Medicine Department, suggesting possible under-reporting from other departments. Almost half of the diagnosed malignancies registered occurred in known HIV-positive patients with Kaposi’s sarcoma as the most common malignancy. Analysis of broader epidemiological data about malignancies of HIV patients in Malawi will aid future efforts for prevention and treatment.

References
HAART and response to therapy improve quality of life (QOL) of African patients with advanced HIV-associated Kaposi’s sarcoma (HIV-KS): a prospective analysis of QOL in the KAART trial

Anisa Mosam¹, F. Shaik²,³, T. Uldrick²,³, T. Esterhuizen¹, G. Friedland⁴, D. Scadden⁵, J. Aboobaker¹, H. Coovadia¹,⁶
¹University of KwaZulu Natal, Durban, South Africa
²CAPRISA and SA-Columbia Fogarty AITRP
³Columbia University, New York, NY, USA
⁴Yale University School of Medicine, New Haven, CT, USA
⁵Harvard Medical School, Boston, MA, USA
⁶Reproductive Health and HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa

Background
Quality of Life (QOL) assessment is important in oncology studies. Effect of therapy on QOL is important in HIV-KS, as decreasing morbidity is a goal of therapy. This is the first prospective study to evaluate the effect of HAART, +/- chemotherapy, on QOL in African patients with HIV-KS. Within the KAART study, we assessed the impact of HAART over 12 months in all patients, differences in QOL between arms, as well as associations between QOL and several clinical parameters.

Methods
KAART is a randomized, controlled, open label trial of HAART vs. HAART plus chemotherapy (CXT) in treatment-naive South African patients with HIV-KS. QOL outcomes were assessed prospectively in English or isiZulu using EORTC-QOL30. We evaluated intra-group changes between baseline and month 12 QOL scores (Wilcoxon rank sign test), changes between baseline and month 12 QOL scores between the two groups (Mann-Whitney test), and the relationship between clinical responses and global QOL (Kruskal-Wallis test). Given multiple comparisons, p-values <0.01 are considered statistically significant; 0.01< p <0.05 represent important trends.

Results
111 participants had QOL information. Median global health score (perfect score = 100) was 50 at baseline, improving to 67 at month 12 (p<0.001). Significant improvements in median scores from baseline to month 12 were seen in emotional, cognitive, and social scales, but not physical function and role function. Most symptom scales (fatigue, pain, dyspnea, insomnia, appetite, diarrhea, and constipation) showed significant improvement over time. Improvement in nausea was borderline (p=0.03). There were no statistically significant changes over time between arms; however role function (p=0.011) trended toward greater improvement in the CXT arm. Complete or partial response was associated with increased global health scores (p<0.001), while number or severity of adverse events, adherence, HIV viral load, or CD4 count were not.

Conclusion
African HIV-KS patients benefit significantly in their overall global health status, functioning and symptoms from HAART. Partial and complete responses to therapy are significant predictors of global health, and the role of early chemotherapy in advanced HIV-KS merits further investigation. Improving QOL is an important goal in the treatment of advanced KS in resource-limited settings. QOL results from this study inform treatment paradigms for management of African patients with HIV-KS.
High acceptance rate of anal pap screening despite limited knowledge about anal dysplasia among HIV+ MSM

Julia Seay¹, Timothy Sadiq², Katya Roytburd¹, Prema Menezes¹,2,3, E. Byrd Quinlivan¹,2,3,4
¹Center for Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
²Department of GI Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
³Center for AIDS Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
⁴Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background
Anal cancer in the general population is more prevalent in women, but in most HIV populations, MSM have the highest risk. Data suggest that screening can prevent invasive carcinoma. Use of routine cervical pap smears resulted in an 80% reduction in cervical cancer rates. The current study examines the effectiveness of a clinical intervention designed to increase anal dysplasia education, screening, and treatment for HIV+ MSM.

Methods
To assess anal dysplasia knowledge, sexual history/behavior, and attitudes about health care, a convenience sample of HIV+ MSM (≥18 years, English-speaking) being seen for routine care were asked to complete a questionnaire. The questionnaire assessed anal dysplasia knowledge and acceptance of screening anal pap utilizing a 5-point Likert-scale. Subjects were categorized as having anal dysplasia knowledge and accepting of anal pap smear if they answered “agree” or “strongly agree.” A chi-square analysis was conducted to determine whether those with anal dysplasia knowledge significantly differed from those who did not in terms of anal pap screening. Clinical information was abstracted from medical records.

Results
Of 142 subjects, 56% were Caucasian, 39% were African American, and 5% were of other ethnicities with a mean age of 44 years (SD 10.74 years) and eighth grade or higher reading level (88%). Most (92%) subjects were on ART with median HIV RNA <48 copies per mL and median CD4 534 cells/UL. Although less than half (39%) of the participants felt their current knowledge of anal dysplasia was sufficient to make decisions about detection and treatment, acceptance of anal pap smear screening was close to universal (93%). One-third of subjects (50) had undergone anal pap testing and of these, 44% had dysplasia. Knowledge of dysplasia was not significantly correlated with anal pap screening (p=.37).

Conclusions
We found a high acceptance rate of anal pap smear despite low rates of knowledge about anal dysplasia. Importantly, anal dysplasia knowledge did not differ between patients who had been previously screened for anal dysplasia and those who had not. These results suggest that the clinical intervention to increase anal dysplasia screening and treatment must also focus on patient education and awareness. The high acceptance rate of the anal pap test indicates that, if implemented effectively, anal dysplasia screening should be well received by patients.
HIV-associated primary lung cancer (LC) in the era of highly active antiretroviral therapy (HAART): a multi-institutional collaboration

Gabriela D’Jaen1, Liron Pantanowitz2, Mark Bower3, Susan Buskin4,5, Nancy Neil5,6, Erin Greco7, Timothy Cooley8,9, David Henry10, Jonathan Stem10, Bruce Dezube11, Justin Stebbing12, David Aboulafia1,5
1Division of Hematology/Oncology, Virginia Mason Medical Center, Seattle, WA, USA
2Department of Pathology, Baystate Medical Center, Tufts University School of Medicine, Springfield, MA, USA
3Chelsea & Westminster Hospital, London, UK
4Public Health-Seattle and King County, HIV/AIDS Epidemiology, Seattle, WA, USA
5University of Washington, Seattle, WA, USA
6ICON Clinical Research, San Francisco, CA, USA
7School of Public Health, University of California, Los Angeles, Los Angeles, CA, USA
8Section of Hematology/Oncology, Boston Medical Center, Boston, MA, USA
9Section of Hematology/Oncology, Boston University School of Medicine, Boston, MA, USA
10Joan Kernell Cancer Center, Philadelphia, PA, 19107, USA
11Department of Hematology/Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
12Imperial College, Charing Cross Hospital, London, UK

Background
HIV-infected individuals are at increased risk for primary LC. We wished to compare the clinico-pathologic features and treatment outcome of HIV-LC patients with HIV-negative LC patients. We also sought to compare smoking habits and immunologic features of HIV-LC patients with HIV-positive patients without LC.

Methods
A database of 75 HIV-positive patients with primary LC in the HAART era was established from an international collaboration. These cases were drawn from the archives of contributing physicians who subspecialize in HIV malignancies. Patient characteristics were compared with registry data from the Surveillance Epidemiology and End Results (SEER, n=169,091 participants) Program and with HIV-positive individuals without LC from the Adult and Adolescent Spectrum of HIV-related Diseases (ASD, n=36,569 participants) Project.

Results
The median age at HIV-related LC diagnosis was 50 years compared to 68 years for SEER participants (p<0.001). HIV-LC patients, like their SEER counterparts, most frequently presented with stage III (29% vs. 32%) and stage IV (55% vs. 48%) cancers, usually with adenocarcinoma (41% vs. 37%) or squamous carcinoma (32% vs. 20%) histologies. HIV-LC patients and ASD participants had comparable median nadir CD4+ cell counts (138 vs. 160 cells/μL). HIV-LC patients were, however, more likely to be smokers (99% vs. 76%; p<0.001) with a higher median pack-year history of cigarette consumption (41 vs. 14 pack-years; p<0.001). At LC diagnosis, their median CD4+ count was 340 cells/μL and 86% were receiving HAART. Sixty-three (84%) HIV-LC patients received cancer-specific treatments, but chemotherapy-associated toxicity was substantial. The median survival among HIV-LC patients and SEER participants both measured 9 months.

Conclusions
Smoking was tightly associated with the risk of HIV-LC. Most HIV patients were receiving HAART and had substantial immune reconstitution at time of LC diagnosis. They were able to receive LC treatments; their tumor types and overall survival were similar to SEER LC participants. However, HIV-LC patients were diagnosed with LC at a younger age than their HIV-negative counterparts. Future research should explore how screening and diagnostic and treatment strategies directed toward the general population may apply to HIV-positive patients at risk for LC.
50. HPV genotypes and association with cervical cytology and immune status in HIV-infected women in India

Vikrant Sahasrabuddhe¹, Arati Mane², Arun Risbud², Anita Kavatkar³, Usha Katti³, Seema Sahay², Ramesh Bhosale³, Sten Vermund¹, Sanjay Mehendale⁷
¹Vanderbilt University, Nashville, TN, USA
²National AIDS Research Institute, Pune, India
³Byramjee Jeejeebhoy Medical College, Pune, India

Background
Knowledge about HPV genotypes may inform rational design of prevention strategies for HIV-infected women in India and other developing country settings.

Methods
We analyzed cervical cytobrush samples using Linear Array HPV genotyping assay among n=267 non-pregnant HIV-infected women in Pune, India, and evaluated the association between high-risk (HR) HPV genotypes, cervical cytology status, and current CD4+ cell counts.

Results
The median (IQR) age was 31 (29-35) years and CD4+ cell count was 392/μL (242-581). HR-HPV genotypes were present in 106 [39.7% (95%CI: 33.8-45.6)], low-risk/unknown-risk HPV genotypes in 97 [36.3% (95%CI: 30.6-42.1)] women, while no HPV genotypes were detected in 126 [47.2% (95%CI: 41.2-53.1)] participants.

Among women with HSIL, HPV 16 (44%), HPV 53 (22%), and HPV 33 (22%) were the most common HR-HPV genotypes. HR-HPV genotypes were present in 100% of 9 women with HSIL, 77.1% in 35 with LSIL, 45% in 40 with ASCUS, and 26.6% in 169 women with normal cytology (Chi-square for trend: p<0.001). Severely immune-compromised women [CD4+ <200/μL] had higher HR-HPV prevalence [OR: 2.5 (95%CI: 1.2-5.5)], higher prevalence of LSIL/HSIL on cytology [OR: 2.5 (95%CI: 0.9-6.9)] and higher prevalence of HPV 16 [OR: 3.9 (95%CI: 1.3-12.0)] compared to HIV-infected women with CD4+ ≥500/μL. No significant difference was noted in HR-HPV prevalence among women currently on ART versus those never on ART [OR: 1.2 (95%CI: 0.7-2.0)].

Conclusions
The burden of HR-HPV infection, including HPV 16, correlated directly with severity of cytology and level of HIV-related immune suppression among HIV-infected women in India. HPV prevention strategies for HIV-infected women in India and other developing country settings should take into account the unique HPV type composition and the impact of immune suppression.
Background

Multiple myeloma (MM) is a non-AIDS related malignancy of an immunoglobulin (Ig)-secreting B cell (plasma cell) usually associated with older age. MM is characterized by the presence of a high concentration monoclonal Ig protein in serum, and excretion of free light chains (FLC) in urine. In the years preceding MM diagnosis, a small monoclonal Ig develops that may be detectable upon serum protein electrophoresis, resulting in a premalignant condition known as monoclonal gammopathy of undetermined significance (MGUS). In an individual with MGUS, there may also be abnormal levels of FLC. Increased circulating levels of Ig, other indicators of B cell hyperactivation, and B cell lymphoma are well-recognized features of HIV infection. There have also been several reports of increased prevalence of MGUS and a meta-analysis showing increased risk of MM among HIV-infected (HIV+) individuals. There are, however, little or no longitudinal data on HIV-associated Ig abnormalities, B cell activation, and MGUS. We have initiated a pilot study within the Multicenter AIDS Cohort Study (MACS), a prospective study of untreated and treated HIV infection and AIDS in the United States, to begin to examine Ig abnormalities associated with MGUS in HIV-uninfected (HIV-) and HIV+ homosexual men.

Materials and methods

Archived serum samples from the Los Angeles site of the MACS were obtained from 172 long-term HIV+ (8.1-18 years), HAART-naive subjects at the latest visit before initiating HAART, and from 166 HIV- subjects of similar age (31-62 years) and ethnicity (88% White, 8% Hispanic, 2% Black). Serum protein electrophoresis and quantitative IgG, IgM, IgA, kappa FLC, and lambda FLC assays were performed on all samples, followed by immunofixation when possible monoclonal protein or abnormal kappa/lambda FLC ratios were observed.

Results

Increased mean serum concentrations of IgG, IgA, IgM, kappa FLC, and lambda FLC (p<0.001) were seen in HIV+ subjects compared to HIV- subjects. Kappa/lambda FLC ratios were higher in HIV+ men (1.16 vs. 1.04, p<0.01), with a clear increase in the frequency of elevated (>1.65) ratios (11.0% vs. 1.8%). MGUS prevalence (defined as a monoclonal peak confirmed by immunofixation) was 0/166 (<0.6%) in HIV- and 4/172 (2.3%, p<0.05) in HIV+ MACS subjects.

Conclusions

MGUS is uncommon but increased among untreated HIV+ MACS subjects under 65 years of age. FLC levels and/or abnormal ratios may be more sensitive indicator(s) of Ig abnormalities associated with MGUS or MM. Longitudinal MACS studies are planned to examine FLC, MGUS, and B cell activation.
52. Immunohistochemically confirmed HHV-8-related lymphoproliferative disorders in Uganda

Lynnette K. Tumwine1,3, Robert Lukande1,3, Weiqiang Zhao2,3, Leona W. Ayers2,3
1Department of Pathology, Makerere University, Kampala, Uganda
2Department of Pathology, The Ohio State University, Columbus, OH, USA
3Sub-Saharan Africa Lymphoma Consortium (SSALC/NCI)

Background
Human herpesvirus-8 (HHV-8) infection is endemic in Uganda and has an estimated 36%-60% seroprevalence. This virus is in the oropharynx and peripheral blood of Ugandans with Kaposi’s sarcoma, and viremia is increased in those with HIV-1. While Kaposi’s sarcoma is widely recognized as both endemic and with HIV epidemic, HHV-8 associated lymphoproliferative disorders have not been previously reported in Uganda. Evidence for these disorders was sought in lymphoma surveys conducted by sub-Saharan African Lymphoma Consortium (SSALC) consortium members in Uganda.

Materials and methods
Samples of 456 malignant lymphoma and adenopathy cases in formalin-fixed paraffin-embedded (FFPE) blocks from the Uganda SSALC and the Uganda AIDS and Cancer Specimen Resource (ACSR) were examined for morphology and Lana-1 (immunohistochemical, IHC) for diagnosis of HHV-8 lymphoproliferative disorders. Samples were also tested (IHC and in situ hybridization, ISH) using 20 monoclonal antibodies for common NHL antigens, ISH for EBV-encoded RNA, and kappa/lambda light chains (ISH, Ventana, Tucson).

Results
Many but not all of reported HHV-8-related proliferative disorders were identified in this sample population. Those identified and remaining to be identified are listed in Table 1.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castleman’s disease</td>
<td></td>
</tr>
<tr>
<td>Unicentric varieties</td>
<td></td>
</tr>
<tr>
<td>Hyaline vascular variant</td>
<td>2</td>
</tr>
<tr>
<td>Plasma cell variant</td>
<td>1</td>
</tr>
<tr>
<td>Plasmablastic variant</td>
<td>1</td>
</tr>
<tr>
<td>Lymphocyte depleted</td>
<td>1</td>
</tr>
<tr>
<td>Multicentric varieties</td>
<td></td>
</tr>
<tr>
<td>Plasma cell variant</td>
<td>1</td>
</tr>
<tr>
<td>Plasmablastic variant</td>
<td>1</td>
</tr>
<tr>
<td>Lymphocyte depleted</td>
<td>1</td>
</tr>
<tr>
<td>Plasmablastic lymphoma (HHV-8 negative and positive)</td>
<td>2</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td></td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Plasmacytic lymphoproliferative disorder</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
</tr>
</tbody>
</table>

Conclusions
HHV-8 proliferative disorders excluding Kaposi’s sarcoma are present but generally not recognized by Ugandan clinicians and pathologists. Disorders are present in Uganda, especially in HIV-positive patients, in association with the high infection rates of both HIV-1 and HHV-8. Recognition is important because HHV-8 infection in HIV-1-positive patients associates with poor prognosis. Familiarity with the clinical presentation and tissue morphology of these disorders will likely result in recognition of the full range of reported HHV-8 proliferative complications. HHV-8-related lymphoma has increased prevalence in the HIV-1 infected. It arises and progresses in the face of highly active antiretroviral therapy immune reconstitution, making recognition of these disorders critical to patient care. We participate in the Sub-Saharan Africa Lymphoma Consortium [http://www.ssalc.org] to expand the understanding of HIV/AIDS-related malignancies and viral proliferative disorders in this region of the world.
53. Initial experience with topical fluorouracil (5-FU) for treatment of anal intraepithelial neoplasia (AIN) in HIV-positive patients

Sean M. Snyder¹, Lacey Siekas², David M. Aboulafia³, ⁴
¹Department of Graduate Medical Education, Virginia Mason Medical Center, Seattle, WA, USA
²Department of Gastroenterology, Virginia Mason Medical Center, Seattle, WA, USA
³Department of Hematology and Oncology, Virginia Mason Medical Center, Seattle, WA, USA
⁴Division of Hematology, University of Washington, Seattle, WA, USA

Background
Exposure to certain strains of human papilloma virus (HPV) promotes dysplasia in cells of the anal canal epithelium, leading to AIN, which is in turn a precursor to squamous cell carcinoma of the anus (SCCA). Patients with HIV infection who have anoreceptive intercourse are at heightened risk for acquiring HPV, AIN, and SCCA. The use of topical 5-FU to prevent the progression of lower genital tract neoplasia to invasive cervical carcinoma has been studied in both HIV+ and HIV- women. Although intravenous 5-FU is also commonly used for treatment of invasive SCCA, there has been little experience with the use of topical 5-FU as therapy for AIN.

Materials and methods
We retrospectively reviewed medical records from our anal dysplasia clinic. Our study population comprised 11 HIV+ men with biopsy-proven AIN who were treated with topical 5-FU. All patients were initially instructed to apply a pea-sized amount of topical 5-FU to the anus each night, to wash their hands afterwards, and to wipe away excess 5-FU in the morning. Patients reduced the frequency of application if they experienced undue local irritation.

Results
Patient data are summarized in Table 1. 6 of 11 (55%) patients showed improvement in clinical appearance. Anoscopy images for one of these patients before and after treatment are shown in Figures 1 and 2, respectively; note the diffusely verrucous appearance in Figure 1 (arrows).

While all patients had biopsies of the areas with the most clinically severe dysplasia pre-treatment, only 6 had biopsies post-treatment, and of those only 2 showed improvement in pathologic grade on biopsy. 6 (55%) patients decreased frequency of 5-FU application due to mild to moderate perianal irritation.

Conclusions
Patients tolerated topical 5-FU without significant side effects. Our results are preliminary, but suggest a role for topical 5-FU in reducing disease burden in anal dysplasia. While this therapy may not eliminate areas with the worst dysplasia, reducing disease burden may facilitate the use of destructive modalities to treat residual areas of high-grade dysplasia.

Table 1.

<table>
<thead>
<tr>
<th>Age range in years (median)</th>
<th>32-67 (45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On HAART (%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>CD4+ cell count/µL range (median)</td>
<td>35-730 (416)</td>
</tr>
<tr>
<td>HIV viral copies/mL range (median)</td>
<td>&lt;75-172,966 (&lt;75)</td>
</tr>
<tr>
<td>Treatment duration range (median)</td>
<td>7 wks-6 mo (20 wks)</td>
</tr>
<tr>
<td>Clinically improved (%)</td>
<td>6 (55%)</td>
</tr>
<tr>
<td>Perianal irritation (%)</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>Anal fissure (%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Perianal HSV (%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Decreased dosing frequency (%)</td>
<td>6 (55%)</td>
</tr>
<tr>
<td>Discontinued (%)</td>
<td>1 (9%)</td>
</tr>
</tbody>
</table>

- 123 -
54. **Kaposi sarcoma in South African children**

Cristina Stefan¹, David Stones², Linda Wainwright³, Rob Newton⁴

¹Department of Paediatrics and Child Health, Tygerberg Hospital and Stellenbosch University, Tygerberg, Cape Town, South Africa
²Department of Paediatrics and Child Health University of Free State Universitas Hospital, Bloemfontein, South Africa
³Department of Paediatrics and Child Health Chris Baragwanath Hospital, University of the Witwatersrand, Johannesburg, South Africa
⁴Epidemiology and Genetics Unit, Department of Health Sciences, University of York, York, UK

**Background**
The AIDS epidemic has contributed to an abrupt increase of the incidence of Kaposi sarcoma, especially in Sub-Saharan Africa, to values tens of times higher than in the pre-epidemic era. There is, however, very little literature concerning the clinical features of this disease and its management and outcome in HIV-positive children in Africa.

**Aim**
To examine retrospectively a series of 70 HIV-positive children with Kaposi sarcoma, from several centers in South Africa, in order to describe the usual clinical presentation as well as the management and its impact on the course of the disease.

**Patients and methods**
Data were analyzed from tumor registries and patient records in four South African hospitals from January 1998 to December 2009.

**Results**
The average age in this series was 73 months. The ratio of males to females was 1.65. The lesions were present on skin in 32 out of 63 cases (50.79%), alone or in combination with other sites. In 8 cases (12.69%) the tumor was localized exclusively in the mouth, in a further 8 patients (12.69%) exclusively in the viscera, and in 6 patients (9.52%) only in the lymph nodes. Tuberculosis was associated with Kaposi’s sarcoma in 9 cases out of 38 (23.68%). The mean CD4+ lymphocyte count was 440 (SD=385). Only 38 patients (54.28%) were taking combined antiretrovirals at the time of diagnosis. Twenty-nine cases (41.42%) received chemotherapy with Bleomycine, Vincristine, and Adriamycin, alone or in combination. While 32 patients (45.71%) died after an average of 4 months, the average followup period for the remaining children was 16 months, with a maximum of 57 months.

**Conclusions**
Most of the time the clinical diagnosis was suggested by the skin lesions; however, in a large percentage of cases the tumor was hidden in the mouth, viscera, or lymph nodes. The CD4+ lymphocyte count was not a predictor of Kaposi sarcoma. The mortality remains high in South Africa in spite of antiretroviral drugs and chemotherapy.
55. **Knowledge of HPV and cervical cancer among HIV-positive women in Lagos, Nigeria**

Rose Anorlu, Maymuna Adegbesan, Temitope Adaramewa
Lagos University Teaching Hospital, Lagos, Nigeria

**Background**

Cervical cancer is the second most common cancer among women in the world. In parts of Africa it is the most common cancer among women. The age-specific incident rate is in some parts of Africa. Persistent infection with high-risk human papillomavirus (HPV) is a necessary cause of cervical cancer and HIV is a known co-factor that enhances the oncogenic potential of HPV. Sub-Saharan Africa has the highest number of people living with HIV. In Nigeria there are about 4.5 million people living with HIV/AIDS; more than half are women. Women infected with HIV are at greater risk of persistent HPV infection and consequently at greater risk of the associated premalignant disease and cervical cancer. The objective of this study was to determine the knowledge of HIV-positive women on HPV and cervical cancer.

**Materials and methods**

Two-hundred women who attended an HIV clinic in Lagos in January 2010 and who consented to participate in the study were randomly selected. They were given self-administered questionnaires. The questionnaire sought to determine their sociodemographic characteristics and their knowledge of HPV, cervical cancer, and the HPV vaccine.

**Results**

183 completed the questionnaire. The mean age was 33.0±6.1 years (range 23-52 years). About one third (32.1%) had had post-secondary school education and almost a third were single. 117 (71.1%) had never been on any form of contraception. 127 (69.3%) had had the HIV test because they were very sick; only 16.7% had voluntary testing. The awareness of cervical cancer was poor. 74.4% had never had any form of cervical cancer screening. About 90% had never heard of HPV and 92.3% did not know that HPV causes cervical cancer, 82.1% did not know that HPV is contracted via sexual intercourse, and only 17.1% knew cervical cancer can be prevented by a vaccine.

**Conclusion**

The overall knowledge of cervical cancer and HPV in this high-risk population was very poor. There is a need to improve the knowledge of this disease among this population. Cervical cancer screening should be made available at little or no cost to them.
Liver cancers and other hepatic disease from the Adult/Adolescent Spectrum of HIV-related Diseases (ASD) Project

David Aboulafia1,2, Susan Buskin3,4, Elizabeth Barash1, John Scott5, Robert Wood3,6
1Department of Hematology and Oncology, Virginia Mason Medical Center, Seattle, WA, USA
2Division of Hematology, University of Washington, Seattle, WA, USA
3Public Health, Seattle and King County, WA, USA
4Department of Epidemiology, University of Washington, Seattle, WA, USA
5Department of Gastroenterology, University of Washington, Seattle, WA, USA
6Department of Infectious Disease, University of Washington, Seattle, WA, USA

Background
As individuals with HIV infection live longer due to highly active antiretroviral therapy (HAART), co-morbid conditions and infections, including liver cancers and viral hepatitis, warrant increased attention and action.

Materials and methods
The multisite ASD Project followed 29,491 HIV-infected individuals receiving medical care in 11 U.S. metropolitan areas for an average of 2.4 years and a total of 69,487 person-years. ASD collected data on the presentation, treatment, and outcomes related to HIV infection, including viral hepatitis screening and liver-specific complications including hepatic neoplasms. Data were restricted to the HAART era, 1998-2004.

Results
There were 25 participants with liver malignancies in the ASD cohort corresponding to a rate of 8.5 cancers/10,000 people living with HIV. Twenty two (88%) participants died and the remaining 3 were lost to followup. Fifteen (60%) of the 25 had hepatocellular carcinoma; 6 had metastatic adenocarcinoma, 1 each had lymphoma, hepatoblastoma, sarcoma, and poorly differentiated carcinoma. Thirteen of 25 (52%) individuals with liver malignancies were diagnosed with hepatitis C virus (HCV) and 10 (40%) with chronic hepatitis B virus (HBV) infection (including 2 participants with HBV and HCV co-infection). This corresponds to a relative risk of liver cancer among HCV and HBV infected individuals of 12.8 (95% confidence interval [CI] = 4.1-40.2) and 26.8 (95% CI = 8.1-88.9), respectively (relative to those without HBV or HCV diagnoses). The risk of malignancy in HIV-infected individuals with both HBV and HCV co-infection, relative to those with neither co-infection, was 16.8 (95% CI = 3.1-91.8). Four individuals did not undergo HBV or HCV screening, and their viral hepatitis serostatus remained undefined. Twelve percent of liver cancer patients also had a diagnosis of cirrhosis, relative to a 1 percent prevalence of cirrhosis overall (relative risk of liver cancer for those with cirrhosis = 10.2, 95% CI = 3.1-33.9). Incident liver disease and chronic HBV and HCV were diagnosed in 0.9, 1.8, and 4.7 per 100 person-years. HBV and HCV screening increased from fewer than 20% to over 60% during this period of observation (p<.001). Deaths occurred in 57% of those diagnosed with liver disease relative to 15% overall (p<.001). Overall, 10% of deaths occurred among individuals with a diagnosis of liver disease.

Conclusions
Despite care guidelines promoting screening for HBV and HCV, screening was not universally conducted or, if conducted, not documented. Due to elevated risks of liver cancer and other liver diseases, HCV and HBV screening and treatment of viral hepatitis among HIV-infected individuals should be a priority in the HAART era.
57.  Malignancies in HIV

Nikolay A. Belyakov1, Zinaida M. Zagdyn2, Vadim V. Rassochin1, Tatjana N. Trofimova3, Alexey Y. Kovelenov2, Robert Dubrow4, Robert Heimer4
1City AIDS Center, Saint Petersburg, Russia
2AIDS Center, Leningrad Region, Russia
3I.I. Mechnikov Medical Academy, Saint Petersburg, Russia
4Yale School of Public Health, Yale School of Medicine, New Haven, CT, USA

We identified all known cases of malignancy among HIV-infected patients admitted to the AIDS Center hospital in Saint Petersburg in 2004-2009 via statistical cards completed for each discharged or dying case with a final clinical and/or autopsy diagnosis. From a total of 19,410 patients admitted during this period, we identified 38 cases (0.2%). We randomly selected 42 patients without malignancy, also using statistical cards. The cancer cases included 15 (39.5%) AIDS-defining malignancies (ADMs) (9 cases of non-Hodgkin’s lymphoma [including one case of brain lymphoma], 3 cases of Kaposi’s sarcoma, and 2 cases of invasive cervical cancer), and 23 (60.5%) non-ADMs [Hodgkin’s disease (7 cases), lung cancer (3 cases), breast, rectal, larynx, and brain cancer (2 cases each), oral, stomach and penis cancer (1 case each), and cancer of unknown primary site (2 cases)]. All cases were confirmed histologically; the two brain tumors were diagnosed as oligodendroglioma and ependymoma.

Most of the cancer patients were men (73.7%), consistent with the population of patients visiting the AIDS Center. Most cases were diagnosed when patients sought medical care for cancer-related symptoms. About 60% of the subjects with malignancy died. Patients with ADMs were younger and had lower CD4 cell counts and lower HIV RNA loads than those with non-ADMs. There was no significant difference between the two groups in (a) the interval between HIV diagnosis and development of malignancy, (b) cancer survival, (c) HIV survival, and (d) frequency of death. The majority (55%) of the patients had stage III-IV malignancies; over half of the ADM cases and about one-third of non-ADM cases were untreated. When comparing patients who had malignancy with those who had no cancer, the latter were younger, less likely drug users and smokers, and had higher CD4 cell counts and lower frequency of death.

Conclusion
The small number of malignancies we identified suggests that malignancies, especially ADMs, in HIV-infected patients are under-diagnosed in Saint Petersburg. The majority of cancers were diagnosed at their end stages, and almost half of cancers remained untreated. Patients with malignancy had more risk factors and a more severe clinical picture than those with no malignancy. It is imperative that we conduct further research on malignancies in HIV-infected persons in Saint Petersburg, with a focus on determining whether under-diagnosis is occurring and, if so, reasons for under-diagnosis. Programs to enhance cancer screening interventions in HIV-infected patients in Saint Petersburg may be needed.
Malignant lymphoma subgroups from Zaria, Nigeria, reveal absence of HIV/AIDS-related plasmablastic lymphomas and HHV-8-related lymphoproliferative disorders

Yawale Iliyasu³, Weiqiang Zhao³, Leona W. Ayers³
¹Department of Pathology, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria
²Department of Pathology, The Ohio State University, Columbus, OH, USA
³Sub-Saharan Africa Lymphoma Consortium (SSALC/NCI)

Background
Prevalence of non-Hodgkin’s lymphoma (NHL) subgroups throughout Africa, particularly among persons with HIV/AIDS, is unknown but increases in Burkitt lymphoma, plasmablastic lymphoma, and HHV-8 proliferation disorders have been noted. SSALC, an AIDS and Cancer Specimen Resource (ACSR/NCI) project, seeks to define indigenous sub-Saharan NHL subtypes using WHO classification (2008). Omoti (Univ. Benin 2007) defined an overall malignant lymphoma (ML) rate: 13.4/100,000 (1990s) including 17% Hodgkin’s disease and 83% NHL but subgroups were not defined. Because regional HIV/AIDS prevalence is high, we subgrouped NHL and reviewed lymph node hyperplasia using stored material from Ahmadu Bello University Teaching Hospital in Zaria, Nigeria, to look for HIV/AIDS-associated lymphoid malignancies.

Materials and methods
Fifty-seven paraffin blocks were used to construct a tissue microarray (TMA), and whole tissue sections were H&E stained for morphology. TMA sections were stained using 30 monoclonal antibodies for common NHL antigens and Lana-1 for HHV-8 (immunohistochemical, IHC); in situ hybridization (ISH) for EBV-encoded RNA, kappa/lambda light chains (Ventana, Tucson, AZ), and fluorescent in situ hybridization (FISH) c-myc t(8;14) (Abbott/Vysis, Downer’s Grove, IL).

Results
There were 43 ML and 14 hyperplastic lymph nodes or reactive tissues. One lymph node was suspected for Castleman’s disease but Lana-1 was negative. Table 1 lists ML subgroups.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>N</th>
<th>%NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt lymphoma</td>
<td>19</td>
<td>51</td>
</tr>
<tr>
<td>Lymphoblastic lymphoma: (pre-B)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lymphoma not otherwise specified (NOS)</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>B-cell lymphoma, EBV+</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma, Activated B cell</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>NOS</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Malignant infiltrate (HHV-8 negative)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Reactive/normal tissue</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions
Subgrouping ML with Hodgkin’s disease (12%) and NHL (88%) is similar to the 2007 report from nearby Benin University. Burkitt lymphoma was the most common NHL at 51% followed by follicular lymphoma 16% and diffuse large B-cell lymphomas 14%. With the exception of Burkitt lymphoma, which is endemic in Nigeria, other NHL commonly associated with HIV/AIDS such as plasmablastic lymphoma and HHV-8 lymphoproliferative disorders were not identified.
59. Mortality after cancer diagnosis among HIV-infected individuals in the CFAR Network of Integrated Clinical Systems (CNICS)

Chad Achenbach1, Stephen Cole2, Corey Casper3, Mari Kitahata3, James Willig4, Michael Mugavero4, Michael Saag4
1Division of Infectious Diseases, Northwestern University, Chicago, IL, USA
2Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
3Division of Allergy and Infectious Diseases, University of Washington, Seattle, WA, USA
4Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, AL, USA

Background
Increased cancer risk has been well established in several HIV-infected populations. However, studies investigating mortality after a diagnosis of cancer have been limited in size, scope, and HIV-specific risk factors.

Materials and methods
CNICS is a cohort of over 20,000 HIV-infected adults in clinical care at eight U.S. sites. We included patients with chart review verified incident cancer diagnoses between 1996 and 2009. Non-AIDS defining cancers (NADC) were categorized as infection (HPV, EBV, or HBV/HCV)-related [1]: squamous cell anal, squamous cell oral cavity/pharynx, penis, vagina/vulva, Hodgkin’s, and liver; or non-infection-related: all other NADCs. Death was confirmed by the National Death Index and/or state death certificate data. We examined independent predictors of mortality by employing Cox proportional hazards regression models.

Results
918 adults with HIV and cancer were included in this analysis. 55% had AIDS-defining cancer (ADC), 15% had infection-related NADC, and 30% had non-infection related NADC. At cancer diagnosis, median age was 43 years, 50% were white, 86% male, 19% IDU, 21% HBV/HCV, 46% current smokers, and 56% current alcohol drinkers. Median CD4+ cell count was 192 cells/mm³ and HIV RNA was 3.6 log10 copies/ml. There were 395 deaths in 2,393 person-years of follow-up for a crude mortality rate of 16.5 per 100 person-years (95% CL: 15.0, 18.2). Adjusted hazard of mortality was significantly increased among individuals who were older, non-white, IDU, current or former smokers, had lower CD4+ cell count, higher HIV RNA, and non-infection related NADC (see Table 1). Figure 1 shows cumulative mortality after cancer diagnosis stratified by type of cancer.

<table>
<thead>
<tr>
<th>Mortality Hazard Ratio</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 years</td>
<td>1.23</td>
</tr>
<tr>
<td>White</td>
<td>0.77</td>
</tr>
<tr>
<td>Male</td>
<td>1.06</td>
</tr>
<tr>
<td>HBV/HCV</td>
<td>1.11</td>
</tr>
<tr>
<td>IDU</td>
<td>1.31</td>
</tr>
<tr>
<td>Smoking:</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
</tr>
<tr>
<td>Former</td>
<td>1.51</td>
</tr>
<tr>
<td>Current</td>
<td>1.45</td>
</tr>
<tr>
<td>Alcohol intake:</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
</tr>
<tr>
<td>Former</td>
<td>0.99</td>
</tr>
<tr>
<td>Current</td>
<td>0.78</td>
</tr>
<tr>
<td>HIV RNA, per log10 copies/ml</td>
<td>1.09</td>
</tr>
<tr>
<td>CD4 count:</td>
<td></td>
</tr>
<tr>
<td>&gt; 500 cells/mm³</td>
<td>1</td>
</tr>
<tr>
<td>200–500 cells/mm³</td>
<td>1.11</td>
</tr>
<tr>
<td>&lt; 200 cells/mm³</td>
<td>1.57</td>
</tr>
<tr>
<td>Summary cancer type:</td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>1</td>
</tr>
<tr>
<td>Infection-related NADC</td>
<td>0.78</td>
</tr>
<tr>
<td>Non-infection-related NADC</td>
<td>1.38</td>
</tr>
</tbody>
</table>

*Adjusted for all variables in the table.
Conclusions
In the era of ART, unique independent predictors of mortality among individuals with HIV and cancer were level of immune suppression, degree of HIV RNA replication, and non-infection-related type of cancer. These data highlight the need to improve prevention and management of NADC in this population.

Acknowledgements
These findings are presented on behalf of the CNICS. Funding for this study was provided by NIAID and NCI.

Reference

Figure 1. Mortality after cancer diagnosis for 918 HIV+ adults by cancer type. Non-infection-related NADC is solid line, ADC is dotted line, and infection-related NADC is dashed line.
Multiple oncogenic viruses identified in ocular surface squamous neoplasia in HIV-1 patients from a developing country outpatient clinic

Kenneth O. Simbiri¹, Masanao Murakami¹, Michael Feldman², Andrew Steenhoff³, Oathokwa Nkomazana⁴, Gregory Bisson⁵, Erle S. Robertson¹

¹Department of Microbiology, and Abramson Comprehensive Cancer Center, Tumor Virology Program, University of Pennsylvania, Philadelphia, PA, USA
²Pathology and Laboratory Medicine, Philadelphia, PA, USA
³Botswana-University of Pennsylvania Partnership, The Children’s Hospital of Philadelphia and the Center for AIDS Research, University of Pennsylvania, Philadelphia, PA, USA
⁴University of Botswana School of Medicine, Gaborone, Botswana
⁵Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA, USA

Background
Ocular surface squamous neoplasia (OSSN) is a conjunctival or corneal neoplastic growth that encompasses the conditions of simple dysplasia to conjunctival intraepithelial neoplasia (CIN) to invasive squamous cell carcinoma. Prior to the HIV pandemic, OSSN was noted to occur predominantly in the elderly, for whom it is the third most common oculoorbital tumor after melanoma and lymphoma. In Africa, OSSN is becoming more common, more aggressive, and more likely to affect young people. Several countries have noted a sharp rise in the incidence of OSSN in HIV-infected individuals such that OSSN, in parallel with the rise in HIV infection, is currently the most common oculoretinal tumor among adults in Africa. The underlying cause of this cancer in HIV-infected patients from Botswana is not well defined.

Method
DNA was extracted from 28 OSSN and 8 pterygia tissues, a benign neoplasia that may go on to develop into OSSN. The samples were analyzed for the presence of a number of human viruses including the tumor viruses HPV, EBV, KSHV, JC, and BK by PCR using consensus sequence primers. Type specific primers and sequencing using consensus GP5+ primers of HPV were used for the determination of HPV types. Tissues were further analyzed using in situ hybridization with specific viral probes and immunohistochemistry with antibodies against specific antigens encoded by these tumor viruses.

Results
DNA was extracted from the 28 OSSN tissues and the results showed that 83% were EBV positive, 75% were HPV positive, 70% were KSHV positive, 75% were HSV-1/2 positive, and 61% were CMV positive by PCR. Of the 8 pterygia tissues, 88% were EBV positive, 75% were HPV positive, 50% were KSHV positive, and 60% were CMV positive. None of the patients were JC or BK positive by PCR analysis. Furthermore, in situ hybridization and immunohistochemistry analyses identified HPV, EBV, and KSHV in the tissue samples. Of particular interest was the fact that greater than 50% of the patients were co-infected with more than one type of HPV as well as with EBV and KSHV.

Conclusion
We identified the known oncogenic viruses HPV, KSHV, and EBV in OSSN and pterygia tissues. The presence of these tumor viruses in OSSN in the HIV population suggests that they may be involved in the development of this malignancy. Further studies are necessary to characterize the molecular mechanisms associated with viral antigens and their potential role in development of SSN.
61. Prevalence of HIV among general surgical patients in southeastern Nigeria

Stanley Anyanwu, Gabriel Chianakwana, Eric Ihekwoaba
Department of Surgery, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria

Background
With the advent of HAART, many HIV patients are now living longer. It is expected that the incidence of HIV-related malignancies will increase, with additional burden of operating on HIV patients in areas of chronic severe shortages where minimum basic precautions may not always be feasible. We decided to assess the HIV prevalence in surgical patients and compare the periods 2001-04 and 2008-09.

Aim
To determine HIV seropositivity among elective general surgical patients at Nnamdi Azikiwe University Teaching Hospital, Nnewi.

Patients and methods
All surgical patients were sent for HIV screening as part of their workup for surgery. Patients testing positive were sent for further confirmatory tests.

Results
During the period 2008/09, 75 out of 2350 (3.25%) patients tested were positive for HIV. This compares with 78 out 2208 in the 3-year period 2001-04 (3.5%). Of this number, only 30.4% of these seropositive patients are receiving antiretroviral treatment. Males were affected more than the females and the reproductive age group [30-40] was the most affected.

Conclusion
The prevalence of HIV seropositivity among general surgical patients has remained the same over the past 10 years. The prevalence of 3-3.5% is significantly lower than the figures quoted from sentinel studies in Nigeria.
Background
Malignancies are features of late HIV presentation. In Nigeria the eligibility criteria for enrollment into ART programme is CD4 cell count ≤200 cells/mm³ or stage of IV of HIV/AIDS. Studies linking HIV/AIDS databases to cancer registries have shown a decrease in AIDS-related malignancies and an increase in non–AIDS-defining malignancies. However, in Nigeria, pattern and prevalence of malignancies among PLWHAs are understudied. The objective of this study was to determine the pattern and prevalence of HIV-associated malignancies among PLWHAs in Abia State, Nigeria.

Methodology
This was a retrospective review of records of PLWHAs assessing care in 3 selected ART centers in the State. The 3 centers which comprised 2 tertiary, and a secondary, health care facilities were purposely selected because they accounted for about 70% of the total client load of PLWHAs in the State. All records of patients who have accessed care in the facilities since 2007, when ART programme commenced in the State, were reviewed. Relevant data such as sex, age, CD4 cell count at first visit, clinical stage of HIV disease, year of enrollment, presence of OIs, and presence of malignancies were collected. Data collected were analyzed using SPSS version 15.

Results
Of the 896 patient’s record so far reviewed, 68% were females and 32% males. Mean age was 32.5±9.6 years for females and 44.9±11.7 years for males. 80% of them had their CD4 cell count at first visit recorded in their treatment card. The mean CD4 cell counts at presentation were 365.9±299.8 for females and 285±262.9 for males. 33.8% and 48.1% of the females and males, respectively, were eligible for ART based on CD4 cell count of ≤ 200 cells/mm³. The mean CD4 cell count at presentation for males eligible for ART was 78.1± 64.5 cells/mm³ compared with 91.7±60.5 cells/mm³ for females. No case of malignancy has been reported among those reviewed so far.

Conclusion
Although with CD4 cell count of <500 cell/mm³ one would have expected increasing prevalence of malignancies among the patients, none was so far reported. This is probably because the ART card/proforma used in capturing the data from enrolled patients has no provision to capture malignancies or HIV care providers and lacks resources required for diagnosis of cancers. There is therefore a need for health care providers to be properly trained to detect malignancies in PLWHA and also increase their indices of suspicion.
63. Reasons for not adhering to cervical cancer screening guidelines and HPV knowledge among HIV indeterminate midlife women (50-64 years old) whose last Pap test was >6 years ago

Lisa T. Wigfall1, Heather M. Brandt1, Donna L. Richter1, Wayne A. Duffus2,3, Saundra H. Glover1
1Arnold School of Public Health, University of South Carolina, Columbia, SC, USA
2Division of Infectious Diseases, University of South Carolina, School of Medicine, Columbia, SC, USA
3HIV/STD Division, South Carolina Department of Health and Environmental Control, Columbia, SC, USA

Background
Oncogenic human papillomavirus (HPV) infection is a main cause of cervical cancer. Annual Pap tests are recommended for HIV-positive women because their risk of developing cervical cancer, an AIDS defining illness, is increased [1]. Poor uptake of routine HIV testing combined with poor adherence to recommended Pap test screening guidelines among midlife women (50-64 years old) with late-diagnosed HIV infection increases their risk of being diagnosed with cervical cancer [2]. Women who miss opportunities for early initiation of effective antiretroviral therapy and early detection of precancerous cells face a double jeopardy of being diagnosed with HIV/AIDS and cervical cancer in late disease stages, when treatment is less successful.

Materials and methods
National Health Interview Survey (NHIS) 2008 data were analyzed to describe reasons for not adhering to recommended cervical cancer screening guidelines and HPV knowledge of midlife women who had never been tested for HIV and whose last Pap test was more than 6 years ago. Frequencies and weighted percents are reported.

Results
The sample included 224 midlife women. Of the 20% who had an abnormal Pap test (n=42), only 1 (<1%) reported having a previous diagnosis of HPV infection. A third (33%) did not have a Pap test in the past 6 years (n=65) because they had a hysterectomy, including 11% who had an abnormal Pap test (n=20). Only 12% (n=14) of those who did not have a hysterectomy (n=115) were planning to get a Pap test within a year. Most of these women (40%) had no specific reason for not having a more recent Pap test (Table 1). For many other women (32%), poor adherence was attributed to health care access issues (Table 1). HPV knowledge: 60% had heard of HPV (n=129); 64% knew HPV caused cervical cancer (n=82); 60% knew HPV was spread through sexual contact (n=79); and 85% did not think that HPV would go away without treatment (n=111).

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Abn Pap</th>
<th></th>
<th>No Abn Pap</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%b</td>
<td>n</td>
<td>%b</td>
<td>%b</td>
</tr>
<tr>
<td>No reason/didn’t think about it/put it off/didn’t get to it/don’t know</td>
<td>2</td>
<td>1.2</td>
<td>35</td>
<td>38.8</td>
<td>40.0</td>
</tr>
<tr>
<td>Cost was too expensive/no insurance/didn’t have a doctor</td>
<td>6</td>
<td>4.4</td>
<td>32</td>
<td>27.8</td>
<td>32.2</td>
</tr>
<tr>
<td>Didn’t need/doctor didn’t order it/not having any problems</td>
<td>2</td>
<td>3.7</td>
<td>17</td>
<td>11.5</td>
<td>15.2</td>
</tr>
<tr>
<td>Too painful, unpleasant, or embarrassing</td>
<td>1</td>
<td>0.9</td>
<td>4</td>
<td>2.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1.5</td>
<td>8</td>
<td>7.5</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Conclusions
Despite increased prevalence of HIV/AIDS, routine HIV testing is underutilized. Older adults are disproportionately burdened with late-diagnosed HIV infection. Early diagnosis of HIV and precancerous cervical cells due to HPV infection improves health outcomes for women. Dual HIV and cervical cancer prevention messages that target midlife women are needed.

References
64. Role of TP53 polymorphisms in sub-Saharan mucosal cancers

Franco M. Buonaguro, MariaLina Tornesello, Luigi Buonaguro
Istituto Nazionale Tumori “Fondazione” Pascale,” Naples, Italy

Background
The most common TP53 gene polymorphism, which alters amino acid sequence of the oncosuppressor p53 protein, is located at the codon 72, resulting in either Pro72 or Arg72 p53 variant. Several studies have associated, with controversial results, the prevalence of the Arg allele with different types of cancer. The aim of this report is to analyze the role of p53 polymorphisms in two mucosal (conjunctival and genital) HPV-associated cancers during HIV epidemic.

Distribution and role of TP53 Arg72 and Pro72 alleles in conjunctival neoplasia

Method
The study included 41 invasive conjunctival squamous cell carcinoma (ICSCC), 33 conjunctival intraepithelial neoplasia of grade 3 (CIN3), 33 of moderate grade (CIN1 and CIN2), and 115 controls from Uganda, a sub-Saharan country with the highest incidence rate of conjunctival neoplasia in the world, particularly in the era of AIDS.

Results
The TP53 Arg/Arg codon 72 genotype was detected in 21.9% of ICSCC and in 18.2% of CIN3 but only in 6% of CIN1-2 and in 5.2% of controls (P < 0.05). These data show an increased risk of ICSCC (odds ratio (OR)=6.2, 95% confidence interval (CI): 1.6-24.6) and CIN3 (OR=4.1, 95% CI: 1.0-18.0) associated with TP53 Arg homozygosity, not observed in CIN1-2 lesions (OR=0.8, 95% CI: 0.1-5.1). Moreover, the frequency of the Arg homozygosity was similar in HIV-positive and HIV-negative groups.

Discussion
The results suggest that TP53 Arg/Arg codon 72 genotype is a relevant risk factor for invasive squamous cell carcinoma of the conjunctiva and for CIN3 in the Ugandan population.

Distribution and role of TP53 Arg72 and Pro72 alleles in cervical neoplasia

Method
In the genital mucosal study, 78 penile squamous cell carcinoma biopsies (n = 17 from Uganda, n = 61 from Italy) and blood samples from 150 healthy controls (n = 57 from Uganda, n = 93 from Italy) have been analyzed for the arginine and proline allele distribution.

Results
Among Ugandan cases the heterozygous, proline homozygous and arginine homozygous genotype frequency was 41.2%, 52.9%, and 5.9%, respectively, and among controls was 40.3%, 54.4%, and 5.3%, respectively (P = 0.9917). Conversely, among Italian cases, genotype distribution was 42.6%, 4.9%, and 52.5%, and among controls was 34.4%, 7.5%, and 58.1%, respectively (P = 0.5343).

Discussion
No significant differences in arginine and proline allele distribution were observed when the cases were stratified by HPV status. Therefore, no evidence of association between homozygosity for p53 arginine and HPV-related or HPV-unrelated penile squamous cell carcinoma was observed.

Conclusions
The overall results from the combined data of these studies strongly suggest that (1) Arg homozygosity represents a relevant risk factor for low-risk HPVβ-related cancers, for which further co-carcinogenic factors are needed. (2) Arg homozygosity does not represent a significant risk factor for high-risk HPVα-related cancers, such as penile cancers.
The approach to individualized prediction of human papillomavirus (HPV) infection persistence/clearance in HIV-1-positive adolescent girls based on dynamics of CD4+ counts, viral load, and HAART

Julia Kravchenko1, Staci Sudenga2, Igor Akushevich3, Craig M.Wilson2, Sadeep Shrestha2
1Duke Comprehensive Cancer Center, Duke University, Durham, NC, USA
2Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA
3Center for Population Health and Aging, Duke University, Durham, NC, USA

Background
Several studies suggest that CD4+ T-cell count (CD4) is important in pathogenesis of human papillomavirus (HPV) infection in HIV-positive patients including HPV clearance. CD4 dynamics as well as other co-factors such as highly active antiretroviral therapy (HAART), HIV-1 RNA viral load (VL), demographics, behavioral risks and, clinical diagnosis allows for predicting the absolute probabilities of HPV clearance/persistence. The modeling approach allows for the utilization of complete datasets and does not require any additional essential assumptions about missing information and possible violations in study design.

Materials and methods
We analyzed 266 HIV-1 positive adolescent girls from the Reaching for Excellence in Adolescent Care and Health (REACH) cohort. At enrollment and every 6 months thereafter, cervical lavage samples were tested for HPV using MY09/MY11/HMB01-based PCR and 30 HPV type-specific probes. HIV-related clinical data and risk factors were recorded every 3 months. For analytic purposes, HPV types were categorized according to phylogenetic patterns into (1) 16/16-like, (2) 18/18-like, (3) other high risk (56/56-like), and (4) low risk. HPV clearance was defined by the absence of type-specific infection for two subsequent visits after infection. Maximum likelihood estimates based on the logistic-type model were developed for 3-month reconstructed probabilities of HPV clearance/persistent with CD4, VL, and HAART as the main predictors at the moment of examination.

Results
Figure 1A presents the clearance probability for HIV-positive patients depending on CD4 for HPV16/16-like, HPV18/18-like, HPV56/56-like, and low-risk HPV. HPV16/16-like infection has the lowest chance to be cleared by host at low CD4 levels. The probability of 3-month clearance was less than 20% for patients with CD4 <200, but increased gradually with CD4 increase but overall was slower than for HPV18/18-like, other high-risk, and low-risk HPV. Additionally, the 3-D plot in Figure 1B describes CD4 and log (VL) as predictors of probability of HPV16/16-like clearance: the lowest CD4 levels together with the highest VL were significant predictors for HPV persistence. The multiplicative effect of HAART showed tendency to decrease on HPV16/16-like clearance probability with increasing CD4 levels.

Conclusion
This approach could extend opportunities to understand the associations between CD4, VL, and HAART to develop the comprehensive approach to individualized prediction of HPV infection persistence/clearance in HIV-positive patients.

Figure 1. HPV infection clearance probability vs. (1A) CD4 counts and (1B) combination of CD4 and logarithm of HIV viral load (log(VL)).
The impact of aging on cancer burden in people with HIV/AIDS

Jerry Polesel1, Silvia Franceschi2, Barbara Suligoi3, Eugenio Paci for AIRTUM4, Antonella Zucchetto1, Diego Serraino1, Luigino Dal Maso1

1Cancer and AIDS Registries Linkage Study, Unit of Epidemiology and Biostatistics, IRCCS Centro di Riferimento Oncologico, Aviano, Italy
2International Agency for Research on Cancer, Lyon, Italy
3Department of Infectious Diseases, National Institute of Health, Rome, Italy
4Italian Association of Cancer Registries, Florence, Italy

Background
People with HIV/AIDS (PWHA) have higher risk of some cancers compared to the general population, with an approximately 2-fold increase for all non-AIDS-defining cancers (NADC). The widespread use of highly active antiretroviral therapy (HAART) has improved life expectancy of PWHA, exposing them to both aging and the prolonged exposure to cancer risk factors. A linkage study was therefore conducted to evaluate the impact of aging on the burden of cancer in this population.

Materials and methods
We performed an anonymous record linkage between Italian AIDS (21,951 cases) and Cancer Registries (17.3 million people, covering 30% of the general population). Crude incidence rates (IR), IRs directly standardized by sex and age, and age-specific IRs were estimated for NADCs in the pre-HAART (1986-1996) and in the HAART (1997-2004) periods.

Results
Crude IRs of NADCs increased 78% from pre-HAART to HAART period (IRs: 287 and 496 per 100,000, respectively). However, when aging of PWHA was taken into account through standardization, no difference emerged (standardized IRs: 352 and 379 per 100,000, respectively). Concerning specific cancer site/type, standardized IRs revealed an increase of liver (from 6 to 26 per 100,000; IR ratio: 4.6, 95% confidence interval, CI: 1.3-17.0) and lung cancers (from 37 to 65 per 100,000; IR ratio: 1.8, 95% CI: 1.0-3.2). No significant variation across periods emerged for Hodgkin lymphoma (IRs: 83 and 69 per 100,000 in pre- and HAART period; IR ratio: 0.8, 95% CI: 0.5-1.3). IRs of NADCs increased with age from 147 per 100,000 in PWHA aged 25-34 years to 1396 per 100,000 in those aged 55-69 years (Figure 1); however, the rise was smoother than in the general population. As a consequence, the excess of NADCs risk declined with age, peaking in PWHA aged 25-44 years (IRs ratio: 2.7) and disappearing in the oldest age group (IRs ratio: 1.1; 95% CI: 0.8-1.5).

Conclusions
The lack of any change in standardized IRs of NADCs across periods highlights the strong influence of PWHA aging on the observed upward trends of crude IRs. The aging of PWHA in HAART period, together with the age-related increase of cancer incidence, points to cancer as an increasing medical priority for this population in the near future. This calls for the intensification of cancer prevention strategies, notably smoking cessation and screening programs.

Table 1. All non-AIDS-defining cancers.

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Incidence Rates (per 100,000)</th>
<th>General Population People With HIV/AIDS</th>
<th>Incidence Rate Ratio (people with AIDS vs. general population) IR Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-34</td>
<td>100</td>
<td>2.7 (1.7-4.1)</td>
<td>95% CI</td>
</tr>
<tr>
<td>35-44</td>
<td>250</td>
<td>2.7 (2.2-3.3)</td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>500</td>
<td>1.9 (1.4-2.4)</td>
<td></td>
</tr>
<tr>
<td>55-69</td>
<td>1000</td>
<td>1.1 (0.8-1.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Type distribution of human papillomavirus in HIV-infected women with cervical intraepithelial neoplasia (CIN) stages 2 and 3 in Botswana

Doreen Ramogola-Masire1,2, Nicola M. Zetola1,2, Veronica de Klerk2, Barati Monare2, Bakgagi Ratshaa2, Gracious Ditlhabang2, Elisabeth Chibaya2, Metlha Nchunga2, Mukendi K. Kayembe2, Kurt T. Barnhart1, Cindy M. McGrath1, Harvey M. Friedman1,2
1Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA
2Botswana-UPenn Partnership, Gaborone, Botswana
3Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA, USA
4Department of Pathology, University of Pennsylvania, Philadelphia, PA, USA
5National Health Laboratory, Gaborone, Botswana

Background
Human papillomavirus (HPV) vaccines containing types 16 and 18 are remarkably effective in preventing cervical cancer associated with these HPV types. No information currently exists in Botswana concerning the HPV types causing precancerous or cancerous lesions.

Methods
The goal of this pilot project was to determine the HPV types causing precancerous cervical intraepithelial neoplasia (CIN) stages 2 and 3 in HIV-infected women in Gaborone, Botswana. HIV-infected women referred to our clinic with high-grade intraepithelial lesion (HSIL) on the Pap smear were enrolled in the study. Two specimens were obtained on all subjects, one for histopathology and the other for HPV typing. HPV typing was performed only if the histopathology results demonstrated CIN stage 2 or 3 disease. Histopathology results were corroborated at two sites: Lancet Laboratories (Johannesburg, South Africa) and University of Pennsylvania (Pennsylvania, United States). HPV typing was performed using linear array genotyping (CE-IVD, Roche Diagnostics).

Results
This is an interim analysis of an intended sample size of 100 women. We identified 30 HIV-infected women with CIN stages 2 or 3 between August 11, 2009, and January 29, 2010. The median age was 36 (interquartile range [IQR], 33 - 38) and the median CD4 cell count was 427 cells/mm³ (IQR, 360-560 cells/mm³). Of the 30 women enrolled, 28 (93%) had co-infection by multiple HPV types. HPV type 52 was found in the 2 (7%) women carrying a single type. 15 (50%) had HPV types 16, 18, or both. 25 (83%) women, including all the ones not carrying the 16 or 18 types, carried other high-risk HPV types. Among the other high-risk types, HPV types 33, 35, and 58 were the most prevalent, accounting for 7 (23%), 8 (27%), and 10 (33%) cases, respectively.

Conclusion
HPV 16 and 18 are the most common types in HIV-infected women with CIN 2 or 3 in Gaborone, Botswana. However, other high-risk HPV types may account for a significant number of advanced CIN lesions in this population.
Use of mobile telemedicine for cervical cancer screening of HIV-positive women in Gaborone, Botswana

Rachel H. Gormley¹, Kelly E. Quinley¹, Ting Shih², Zsofia Szep³, Ann Steiner⁴, Doreen Ramogola-Masire⁵, Carrie L. Kovarik²,₆
¹University of Pennsylvania School of Medicine, Philadelphia, PA, USA
²Click Diagnostics, Boston, MA, USA
³Department of Medicine, Division of Infectious Diseases, University of Pennsylvania Medical Center, Philadelphia, PA, USA
⁴Department of Obstetrics and Gynecology, University of Pennsylvania Medical Center, Philadelphia, PA, USA
⁵Botswana-UPenn Partnership, Women's Health Initiative, Gaborone, Botswana
⁶Department of Dermatology, University of Pennsylvania Medical Center, Philadelphia, PA, USA

Introduction and aims
Throughout the developing world, delivery of women’s health care, specifically cervical cancer screening, is limited by cost and access to trained personnel. Visual inspection with application of 4% acetic acid (VIA) is a practical, inexpensive alternative to cytology-based screening in areas where resources are limited. Mobile telemedicine using a cellular phone to photograph the cervix after VIA allows clinicians in “see and treat” cervical cancer screening clinics to capture high-quality images of the cervix, which can then be transmitted through the cellular network to a gynecology specialist located remotely. We present results of a prospective case-control study evaluating the accuracy of offsite (remote) expert diagnosis using mobile telemedicine photographic images of the cervix with VIA (PIA) in HIV-positive women in Gaborone, Botswana.

Methods and design
ClickDiagnostics has developed software (ClickDoc) specifically for remote diagnosis with the Samsung Soul U900 phone, which comes equipped with a 5 Megapixel camera. Ninety-five women presenting to Bontleng Clinic were enrolled and had (1) VIA evaluation by an onsite clinician, (2) an HPV (human papillomavirus) sample taken for PCR (polymerase chain reaction), (3) cervical photos taken with the Samsung phone camera, and (4) photos evaluated by original onsite clinician and by a remote gynecology specialist blinded to the initial visit. VIA and PIA results were categorized as “positive,” “negative,” or “indeterminate.” Percent agreement will be calculated for each pair of diagnostic impressions: (1) offsite gynecologist PIA to onsite clinician using VIA, (2) onsite clinician PIA to the same onsite clinician using VIA, (3) offsite gynecologist PIA to onsite clinician PIA. The HPV PCR results will also be compared to VIA findings of the onsite clinician and the PIA findings of the offsite gynecologist.

Results
All 95 subjects have been enrolled and final data analysis is currently under way. Preliminary concordance data will be presented, along with HPV correlation and prevalence data from PCR testing. We hypothesize that there will be significant concordance in the diagnosis of cervical lesions in HIV patients, when comparing the diagnosis of the onsite clinician to the diagnosis of the clinician evaluating the photos through telemedicine.

Conclusions
Women in sub-Saharan Africa often present with advanced cervical cancer, which is a result of poor screening, lack of appropriate referral, and HIV-HPV co-infection. In order to improve the availability of cervical cancer screening in Botswana, we propose the use of mobile telemedicine as an adjunct tool to visual screening techniques for cervical cancer. We aim to show that mobile telemedicine technology is a reliable method for diagnosing cervical lesions compared to in-person gynecological evaluation and that use of this technology has the potential to connect resource-poor cancer screening centers to remotely located gynecologists.
<table>
<thead>
<tr>
<th>Author Name</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abayomi, E.</td>
<td>17</td>
</tr>
<tr>
<td>Abboud, E.</td>
<td>29</td>
</tr>
<tr>
<td>Aboobaker, J.</td>
<td>09, 47</td>
</tr>
<tr>
<td>Aboulafia, D.</td>
<td>028, 49, 53, 56</td>
</tr>
<tr>
<td>Abraham, A.</td>
<td>012</td>
</tr>
<tr>
<td>Abramowitz, L.</td>
<td>014</td>
</tr>
<tr>
<td>Achenbach, C.</td>
<td>59</td>
</tr>
<tr>
<td>Adaramewa, T.</td>
<td>55</td>
</tr>
<tr>
<td>Adegbesan, M.</td>
<td>55</td>
</tr>
<tr>
<td>Adejuwibe, E.</td>
<td>36</td>
</tr>
<tr>
<td>Adelusola, K.</td>
<td>36</td>
</tr>
<tr>
<td>Adeniran, J.</td>
<td>42</td>
</tr>
<tr>
<td>Adeodu, O.</td>
<td>36</td>
</tr>
<tr>
<td>Adisa, C.</td>
<td>37, 62</td>
</tr>
<tr>
<td>Agu, A.</td>
<td>37, 62</td>
</tr>
<tr>
<td>Aissani, B.</td>
<td>13</td>
</tr>
<tr>
<td>Akinola, N.</td>
<td>36</td>
</tr>
<tr>
<td>Akushievich, I.</td>
<td>65</td>
</tr>
<tr>
<td>Alcendor, D.</td>
<td>04</td>
</tr>
<tr>
<td>Aleman, K.</td>
<td>08, 21</td>
</tr>
<tr>
<td>Alexi, E.</td>
<td>17</td>
</tr>
<tr>
<td>Ambinder, R.</td>
<td>022, 9, 19</td>
</tr>
<tr>
<td>Amin, M.</td>
<td>27</td>
</tr>
<tr>
<td>Amon, I.</td>
<td>016</td>
</tr>
<tr>
<td>Anastos, K.</td>
<td>P3, 024</td>
</tr>
<tr>
<td>Anderson, W.</td>
<td>35</td>
</tr>
<tr>
<td>Andrews, E.</td>
<td>8</td>
</tr>
<tr>
<td>Angelova, M.</td>
<td>29</td>
</tr>
<tr>
<td>Anorlu, R.</td>
<td>55</td>
</tr>
<tr>
<td>Antonicelli, G.</td>
<td>021</td>
</tr>
<tr>
<td>Anyanwu, S.</td>
<td>61</td>
</tr>
<tr>
<td>Austin, M.</td>
<td>24</td>
</tr>
<tr>
<td>Ayers, L.</td>
<td>017, 44, 52, 58</td>
</tr>
<tr>
<td>Bacon, M.</td>
<td>38</td>
</tr>
<tr>
<td>Ballon, G.</td>
<td>021</td>
</tr>
<tr>
<td>Barash, E.</td>
<td>56</td>
</tr>
<tr>
<td>Barman, P.</td>
<td>7</td>
</tr>
<tr>
<td>Barouk, S.</td>
<td>021</td>
</tr>
<tr>
<td>Barta, S.</td>
<td>011</td>
</tr>
<tr>
<td>Bartlett, J.</td>
<td>14</td>
</tr>
<tr>
<td>Basile, J.</td>
<td>03</td>
</tr>
<tr>
<td>Bassa, F.</td>
<td>017</td>
</tr>
<tr>
<td>Bayakhtar, U.</td>
<td>32</td>
</tr>
<tr>
<td>Beachler, D.</td>
<td>19</td>
</tr>
<tr>
<td>Bell, L.</td>
<td>P3</td>
</tr>
<tr>
<td>Belyakov, N.</td>
<td>57</td>
</tr>
<tr>
<td>Bernal, E.</td>
<td>32</td>
</tr>
<tr>
<td>Berry, J.</td>
<td>028</td>
</tr>
<tr>
<td>Betancourt, A.</td>
<td>29</td>
</tr>
<tr>
<td>Bhargava, R.</td>
<td>24</td>
</tr>
<tr>
<td>Bhatia, K.</td>
<td>35</td>
</tr>
<tr>
<td>Bhosale, R.</td>
<td>019, 41, 50</td>
</tr>
<tr>
<td>Biberfeld, P.</td>
<td>10, 26</td>
</tr>
<tr>
<td>Bigger, E.</td>
<td>46</td>
</tr>
<tr>
<td>Bingham, A.</td>
<td>P5</td>
</tr>
<tr>
<td>Biryahwaho, B.</td>
<td>17</td>
</tr>
<tr>
<td>Bissagni, E.</td>
<td>39</td>
</tr>
<tr>
<td>Bisson, G.</td>
<td>60</td>
</tr>
<tr>
<td>Blackman, M.</td>
<td>12</td>
</tr>
<tr>
<td>Blasberg, R.</td>
<td>02</td>
</tr>
<tr>
<td>Bocedi, A.</td>
<td>020</td>
</tr>
<tr>
<td>Bolarinwa, R.</td>
<td>36</td>
</tr>
<tr>
<td>Bollinger, R.</td>
<td>41</td>
</tr>
<tr>
<td>Borok, M.</td>
<td>2</td>
</tr>
<tr>
<td>Bosch, R.</td>
<td>012</td>
</tr>
<tr>
<td>Bower, M.</td>
<td>49</td>
</tr>
<tr>
<td>Brandt, H.</td>
<td>63</td>
</tr>
<tr>
<td>Breen, E.</td>
<td>023, 13, 51</td>
</tr>
<tr>
<td>Brooks, J.</td>
<td>012</td>
</tr>
<tr>
<td>Bruzzone, S.</td>
<td>027</td>
</tr>
<tr>
<td>Buck, C.</td>
<td>P8</td>
</tr>
<tr>
<td>Buonaguro, F.</td>
<td>17, 64</td>
</tr>
<tr>
<td>Buonaguro, L.</td>
<td>17, 64</td>
</tr>
<tr>
<td>Burbelo, P.</td>
<td>010</td>
</tr>
<tr>
<td>Burk, R.</td>
<td>P3</td>
</tr>
<tr>
<td>Buskin, S.</td>
<td>49, 56</td>
</tr>
<tr>
<td>Butler, L.</td>
<td>27</td>
</tr>
<tr>
<td>Cabral, L.</td>
<td>32</td>
</tr>
<tr>
<td>Cahn, P.</td>
<td>38</td>
</tr>
<tr>
<td>Cai, X.</td>
<td>P3</td>
</tr>
<tr>
<td>Campbell, T.</td>
<td>2</td>
</tr>
<tr>
<td>Casper, C.</td>
<td>016, 4, 40, 59</td>
</tr>
<tr>
<td>Castle, P.</td>
<td>P3</td>
</tr>
<tr>
<td>Cavallin, L.</td>
<td>23</td>
</tr>
<tr>
<td>Cerchietti, L.</td>
<td>02</td>
</tr>
<tr>
<td>Cesar, C.</td>
<td>38</td>
</tr>
<tr>
<td>Cesarman, E.</td>
<td>02, 021</td>
</tr>
<tr>
<td>Chadburn, A.</td>
<td>021</td>
</tr>
<tr>
<td>Chang, C.</td>
<td>11</td>
</tr>
<tr>
<td>Chi, B.</td>
<td>P4</td>
</tr>
<tr>
<td>Chianakwana, G.</td>
<td>61</td>
</tr>
<tr>
<td>Chibwesha, C.</td>
<td>P4</td>
</tr>
<tr>
<td>Ching, K.</td>
<td>010</td>
</tr>
<tr>
<td>Chiosis, G.</td>
<td>02</td>
</tr>
<tr>
<td>Chiu, C-J.</td>
<td>9</td>
</tr>
<tr>
<td>Chisara, U.</td>
<td>37</td>
</tr>
<tr>
<td>Choi, Y.</td>
<td>01</td>
</tr>
<tr>
<td>Christner, S.</td>
<td>07</td>
</tr>
</tbody>
</table>
Participants

Grewal R. Abayomi, M.D.
Professor
Head
Division of Haematological Pathology
Tygerberg Academic Hospital
Faculty of Health Sciences
University of Stellenbosch
Private Bag X3, Tygerberg 7505
Cape Town
South Africa
+27 21 938 5348
+27 21 938 4609 Fax

David Aboulafia, M.D.
Hematology/Oncology
Virginia Mason Medical Center
1100 9th Avenue
Seattle, WA 98111
(206) 341-1284
(206) 223-2382 Fax
hemdma@vmmc.org

Chad Achenbach, M.D., M.P.H.
Assistant Professor
Northwestern University
Division of Infectious Diseases
Center for Global Health
645 North Michigan Avenue
Suite 900
Chicago, IL 60611
(312) 695-5048
(312) 695-5088 Fax
c-achenbach@northwestern.edu

Clement Adebamowo, M.D., Sc.D.
Director
Office of Strategic Information, Research and Training
Institute of Human Virology
252 Herbert Macaulay Way
Abuja
Nigeria
cadebamowo@som.umaryland.edu

Charles Adeyinka Adisa, M.D., FACS
Abia State University
P.O. Box 12223 Umungasi Aba
Aba 234
Nigeria
234-8033377206
adisayinka@yahoo.com

Patricia Aladi Agaba, M.D.
Physician and Site Coordinator
Infectious Diseases Unit
AIDS Prevention Initiative Nigeria Plus
Jos University Teaching Hospital
P.M.B 2076
2 Murtala Mohammed Way
Jos, Plateau State
Nigeria
(240) 431 9586
ellagaba@yahoo.com

Viktor Agafonov, Ph.D.
Professor
Postgraduate Education Department of Oncology
Russian State Medical University
App 180
33 Corp 1 Millionshikova Street
Moscow 115446
Russia
+7 903 708 2061
bbogovski@rambler.ru

Brahim Aissani, Ph.D.
Assistant Professor of Epidemiology and Genetics
Department of Epidemiology
School of Public Health
University of Alabama at Birmingham
R220
1665 University Boulevard
Birmingham, AL 35294
(205) 975-8663
baissani@uab.edu
Luiz Carlos Alcantara, Ph.D.
Research Fellow
National Cancer Institute
National Institutes of Health
Building 41, Room C3-03
Bethesda, MD 20892
(240) 481-0522
alcantaralc@mail.nih.gov
Scientific Researcher
CPqGM/FIOCRUZ
Salvador, Ba
Brazil
55-71-9103-1962
lalcan@bahia.fiocruz.br

Donald James Alcendor, Ph.D., M.S.
Assistant Professor
Department of Microbiology and Immunology
Center for AIDS Health Disparities Research
Meharry Medical College
Hubbard Hospital, Fifth Floor
1005 Dr. D.B. Todd Jr. Boulevard
Nashville, TN 37208
(615) 327-6449
(615) 327-6929 Fax
dalcendor@mmc.edu

Karen Aleman
HIV and AIDS Malignancy Branch
National Cancer Institute
National Institutes of Health
Building 10, Room 6N-106
Bethesda, MD 20892
(301) 435-5621
(301) 402-7552 Fax
alemank@mail.nih.gov

Richard F. Ambinder, M.D., Ph.D.
Director
Division of Hematologic Malignancies
James B. Murphy Professor
Johns Hopkins School of Medicine
Cancer Research Building, Room 389
1650 Orleans Street
Baltimore, MD 21231
(410) 955-8839
(410) 955-0960 Fax
ambinri@jhmi.edu

Lynn M. Amon, Ph.D.
Staff Scientist
Computational Biology Program
Fred Hutchinson Cancer Research Center
M1-C108
P.O. Box 19024
Seattle, WA 98109-1024
(206) 667-7836
lamon@fhcrc.org

Kathryn Anastos, M.D.
Professor
Division of General Internal Medicine
Department of Medicine
Montefiore Medical Center
Second Floor
3311 Bainbridge Avenue
Bronx, NY 10467
(718) 515-2593
(718) 547-0584 Fax
kanastos@verizon.net

Rose Ihuoma Anorlu, M.D.
Associate Professor of Obstetrics and Gynaecology
Oncology and Pathological Studies Unit
Department of Obstetrics and Gynaecology
College of Medicine
University of Lagos
PMB 12003 Surulere
Lagos 1
Nigeria
2.3480230169e+012
rianorlu2004@gmail.com

Tony Antakly, Ph.D., D.Sc.
Professor
Department of Biochemistry
University of Montreal
Faculty of Medicine
Department of Biochemistry
P.O. Box 6128 Station Downtown
Montreal
Canada
(514) 343-5730
tony.antakly@umontreal.ca
Hossam Ashour, Ph.D.  
Research Fellow  
National Institutes of Health  
Apartment D33  
708 Lenmore Avenue  
Rockville, MD 20850  
hossamking@mailcity.com

Leona W. Ayers, M.D.  
Professor  
Department of Pathology  
College of Medicine  
Ohio State University  
Innovation Centre  
2001 Polaris Parkway  
Columbus, OH 43240  
(614) 208-5599  
(614) 293-8130 Fax  
ayers.1@osu.edu

Rachel Katherine Bagni, Ph.D., M.S.  
Scientist  
Head  
Molecular Detection Group  
Protein Expression Laboratory  
Advanced Technology Program  
SAIC-Frederick  
P.O. Box B  
Building 535, Room 428D  
Frederick, MD 21702  
(301) 846-5469  
bagnir@mail.nih.gov

Stefan K. Barta, M.D.  
Fellow, Hematology/Oncology  
Department of Oncology  
Albert Einstein College of Medicine  
Montefiore Medical Center  
111 East 210th Street  
Bronx, NY 10467  
(718) 920-4826  
sbarta@montefiore.org

Ulas Darda Bayraktar, M.D.  
Hematology/Oncology Fellow  
Division of Hematology/Oncology  
University of Miami  
1611 NW 12th Avenue  
Miami, FL 33136  
(305) 458-0998  
ubayraktar@med.miami.edu

Daniel Cline Beachler  
Department of Epidemiology  
Bloomberg School of Public Health  
Johns Hopkins University  
Apartment 3B  
1024 Chesapeake Drive  
Havre de Grace, MD 21078  
(717) 514-5540  
dbeachle@jhsphs.edu

Nikolay Alekseevich Belyakov, Sc.D.  
AIDS Center, Saint-Petersburg, Russia  
ul. Bumagnay,12  
Saint Petersburg 190020  
Russia  
+7 9219430130  
aidscenter@admiral.ru

Kishor Bhatia, Ph.D. FRCPath.  
Director  
AIDS Malignancy Program  
Office of HIV and AIDS Malignancy  
National Cancer Institute  
National Institutes of Health  
31 Center Drive  
Building 31, Room A33  
Bethesda, MD 20892  
(301) 496-4995  
bhatiak@mail.nih.gov

Jaswant S. Bhorjee, Ph.D.  
Program Director  
Office of Cancer Centers  
National Cancer Institute  
National Institutes of Health  
Suite 700  
6116 Executive Boulevard  
Bethesda, MD 20892  
(301) 435-9035  
(301) 402-0181 Fax  
bhorjeej@mail.nih.gov

Elizabeth Bigger, M.D.  
Fogarty International Clinical Research Fellow  
National Institutes of Health  
Clinical Research Fellow  
University of North Carolina at Chapel Hill  
6 Country Squire Lane  
Holmdel, NJ 07733  
(732) 946-9171  
e.bigger@gmail.com
Sunetra Biswas, M.S.
Ph.D Candidate
Viral Oncology
Room 389
1650 Orleans Street
Baltimore, MD 21287
(410) 955-8789
sbiswas2@jhmi.edu

Ioannis Bossis, Ph.D., M.S.
Assistant Professor of Virology and Epidemiology
Department of Veterinary Medicine
University of Maryland
8075 Greenmead Drive
College Park, MD 20742
(301) 314-8042
bossisi@umd.edu

Danny Branstetter, M.D., M.S.
Division of Infectious Diseases
Department of Medicine
Emory University
Grady Health System
341 Ponce de Leon Avenue, NE
Atlanta, GA 30308
(404) 616-2493
(404) 616-0592 Fax
dbranst@emory.edu

Elizabeth Crabb Breen, Ph.D.
Norman Cousins Center for Psychoneuroimmunology
Claude Pepper Older Americans Independence Center
David Geffen School of Medicine
University of California, Los Angeles
300 UCLA Medical Plaza, Room 3160A
Los Angeles, CA 90095-7076
(310) 206-5738
(310) 794-9247 Fax
ebreen@mednet.ucla.edu

Kenneth Bridbord, M.D., M.P.H.
Director
Division of International Training and Research
Fogarty International Center
National Institutes of Health
Building 31, Room B2C39
31 Center Drive
Bethesda, MD 20892-2220
(301) 496-1653
(301) 402-0779 Fax
bridbork@mail.nih.gov

John Brooks, M.D.
Leader
Clinical Epidemiology Team
Division of HIV and AIDS Prevention
Centers for Disease Control and Prevention
1600 Clifton Road, NE
Atlanta, GA 30329
(404) 639-3894
zud4@cdc.gov

Nancy Eileen Brown
Medical Editor
AIDS Clinical Trials Group
Social & Scientific Systems, Inc.
9800 Georgia Avenue
Suite 1200
Silver Spring, MD 20910
(301) 628-3368
nbrown@s-3.com

Gail Josephine Bryant, M.D.
Medical Officer
Resources and Training Review Branch
Division of Extramural Activities
National Cancer Institute
National Institutes of Health
Room 8107
MSC 8328
6116 Executive Boulevard
Bethesda, MD 20892-8328
(301) 402-0801
(301) 594-4074 Fax
gb30t@nih.gov

Christopher Buck, Ph.D.
Tumor Virus Molecular Biology Section
Laboratory of Cellular Oncology
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Building 37, Room 4118
9000 Rockville Pike
Bethesda, MD 20892-4263
(301) 594-7060
buckc@nih.gov
Peter D. Burbelo, Ph.D., M.A.
Neurobiology and Pain Therapeutics Section
Laboratory of Sensory Biology
National Institute of Dental and Craniofacial Research
National Institutes of Health
Building 49, Room 1C-20
49 Convent Drive
Bethesda, MD 20892
(301) 402-0778
(301) 402-0667 Fax
burbelop@nidcr.nih.gov

Beth Buschling
National Cancer Institute
National Institutes of Health
6116 Executive Boulevard
Bethesda, MD 20892
(301) 594-1119
buschlib@mail.nih.gov

Lisa M. Butler, Ph.D.
Assistant Professor
Department of Epidemiology and Biostatistics
University of California, San Francisco
Suite 1200
50 Beale Street
San Francisco, CA 94107
(415) 839-8434
lbutler@psg.ucsf.edu

Meisha Bynoe
Doctoral Candidate
Department of Pathology
Microbiology Program
Yale School of Medicine
LH304
310 Cedar Street
New Haven, CT 06520
(203) 785-7614
roshan.karki@yale.edu

Stacy Carrington-Lawrence, Ph.D.
Health Science Administrator
Office of AIDS Research
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director
National Institutes of Health
Suite 4000
MSC 9309
5635 Fishers Lane
Bethesda, MD 20892-9309
(301) 496-3677
carringtons@od.nih.gov

Corey Casper, M.D., M.P.H.
Associate Professor of Medicine
University of Washington
Assistant Member
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue, North
Mailstop M1-B140
Seattle, WA 98109
(206) 667-4600
(206) 667-1965 Fax
ccasper@fhcrc.org

Philip Castle, Ph.D., M.P.H.
Senior Investigator
National Cancer Institute
National Institutes of Health
Executive Plaza South, Suite 5026
6120 Executive Boulevard
Bethesda, MD 20892
(301) 435-3976
castlep@mail.nih.gov

Lucas Cavallin
Graduate Student
Microbiology and Immunology Program
University of Miami School of Medicine
Miami, FL 33136
(305) 243-6544
(305) 243-8309 Fax
lcavallin@med.miami.edu
Mary Allegra Cermak, M.F.A.
ACTG Community Coordinator
International Initiative
AIDS Clinical Trials Group Operations Center
12th Floor
8757 Georgia Avenue
Silver Spring, MD 20910
(301) 628-3312
(301) 628-3002 Fax
acermak@s-3.com

Ethel Cesarman, M.D., Ph.D.
Professor
Department of Pathology and Laboratory Medicine
Weill Cornell Medical College
1300 York Avenue
New York, NY 10065
(212) 746-8838
(212) 746-8816 Fax
ecesarm@med.cornell.edu

Samitabh Chakraborti, Ph.D.
Department of Microbiology and Immunology
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814
(301) 295-9620
samitabh.chakraborti@usuhs.mil

Pratip K. Chattopadhyay, Ph.D.
Room 5612
40 Convent Drive
Bethesda, MD 20892
(301) 594-8656
p chatttop@mail.nih.gov

William P. Clark, M.S.
Division of Extramural Activities
National Cancer Institute
National Institutes of Health
Room 8017
6116 Executive Boulevard
Bethesda, MD 20892
(301) 496-3336
clarkw2@mail.nih.gov

Gary Clifford, Ph.D.
Infections and Cancer Epidemiology Group
International Agency for Research on Cancer
150 Cours Albert Thomas
Lyon Cedex 08 F-69372
France
33 472738345
33 472738345 Fax
clifford@iarc.fr

Justine Cohen, D.O.
Internal Medicine Resident
Pennsylvania Hospital
University of Pennsylvania
Apartment 805
226 West Rittenhouse Square
Philadelphia, PA 19103
(215) 545-0416
justineco@gmail.com

Ross Cranston, M.D., FRCP
Assistant Professor
University of Pittsburgh
Keystone Building, Suite 510
3520 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-2900
rdc27@pitt.edu

Lu Dai, Ph.D.
Cell Biology and Anatomy
Medical University of South Carolina
Suite 1201
MSC 752
135 Rutledge Avenue
Charleston, SC 29425
(843) 792-1211
(843) 792-6680 Fax
gerked@musc.edu

Phillip J. Daschner, M.Sc.
Program Director
Cancer Etiology Branch
National Cancer Institute
National Institutes of Health
Executive Plaza North, Suite 5014
6130 Executive Boulevard
Bethesda, MD 20892
(301) 496-1951
(301) 496-2025 Fax
pd93u@nih.gov
Maria Teresa Demarco  
5601 Morning Ridge Court  
Rockville, MD 20852  
(301) 466-4501  
mtdemarco@gmail.com

Jennifer Dillow  
Clinical Trials Specialist  
Social & Scientific Systems, Inc.  
12th Floor  
8757 Georgia Avenue  
Silver Spring, MD 20910  
(301) 628-3344  
jdillow@s-3.com

Dirk Dittmer, Ph.D.  
Associate Professor  
Department of Microbiology and Immunology  
The University of North Carolina at Chapel Hill  
715 Mary Ellen Jones Building  
Campus Box 7290  
Chapel Hill, NC 27599  
(919) 966-7690  
(919) 962-8103 Fax  
ddittmer@med.unc.edu

Geraldina Dominguez, Ph.D.  
Program Director  
AIDS Malignancy Program  
Office of HIV and AIDS Malignancy  
National Cancer Institute  
National Institutes of Health  
Building 31, Room 3A/33  
31 Center Drive  
Bethesda, MD 20892  
(301) 496-3204  
(301) 480-4137 Fax  
domingug@mail.nih.gov

Gypsyamber D’Souza, Ph.D.  
Department of Epidemiology  
Johns Hopkins Bloomberg School of Public Health  
E6132B  
615 North Wolfe Street  
Baltimore, MD 21205  
(410) 502-2583  
gdsouza@jhsph.edu

Robert Dubrow, M.D., Ph.D.  
Associate Dean for Academic Affair and Associate Professor  
Division of Chronic Disease Epidemiology  
Yale School of Public Health  
P.O. Box 208034  
60 College Street  
New Haven, CT 06520-8034  
(203) 785-2853  
(203) 785-6980 Fax  
robert.dubrow@yale.edu

Yvonne Lolita Duglas-Tabor  
Division of Cancer Biology, Cancer Immunology, and Hematology  
National Cancer Institute  
National Institutes of Health  
Executive Plaza North  
6130 Executive Boulevard  
Bethesda, MD 20892  
(301) 496-7815  
duglasy@mail.nih.gov

Erica Yvonne Eaton, M.P.A.  
National Institute of Allergy and Infectious Diseases  
National Institutes of Health  
Critical Care Medicine Department  
Clinical Center  
National Institutes of Health  
Building 10, Room 2C145  
Bethesda, MD 20892  
(202) 785-4309  
eaton@mail.nih.gov

Matthias Egger, M.D., M.S., FFPH DTM & H  
Professor of Epidemiology and Public Health  
Institute of Social and Preventive Medicine  
University of Bern  
Department of Social and Preventive Medicine  
University of Bristol  
Finkenhuebelweg 11  
CH-3012  
Bern 3012  
Switzerland  
+41 31 631 3501  
+41 31 631 3520 Fax  
egger@ispm.unibe.ch
Eric A. Engels, M.D., M.P.H.
Senior Investigator
Division of Cancer Epidemiology and Genetics
Infections and Immunoepidemiology Branch
National Cancer Institute
National Institutes of Health
Executive Plaza South, Room 7076
Mail Stop 7248
6120 Executive Boulevard
Bethesda, MD 20892-7248
(301) 496-8115
(301) 402-0817 fax
eric.engels@nih.gov

Luis A Espinoza, Ph.D., M.S.
National Cancer Institute
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
(301) 435-3098
espinozala@mail.nih.gov

Valeria Irene Fink, M.D.
Clinical Research Area
Pasaje Peluffo 3932
Buenos Aires 1202
Argentina
54-11-4981-7777, ext. 114
54-11-4982-4024 Fax
valeria.fink@huesped.org.ar

Cynthia S. Firnhaber
Right to Care
984 Arapahoe Circle
Louisville, CO 80027
(913) 491-4593
cindy.firnhaber@righttocare.org

Eleonora Forte, Ph.D.
Department of Molecular Genetics and Microbiology
Center of Virology
Duke University School of Medicine
223 CARL Building
Research Drive
Durham, NC 27710
(919) 668-3123
eleonora.forte@duke.edu

Meg Fromuth, B.S.
Clinical Data Manager
AIDS Malignancy Consortium
EMMES Corporation
Suite 700
401 North Washington Street
Rockville, MD 20850
(301) 251-1161, ext. 2718
mfromuth@emmes.com

Donald E. Ganem, M.D.
Investigator
Howard Hughes Medical Institute
Professor of Microbiology and Medicine
University of California, San Francisco
Room HSW 1522
Box 0552
513 Parnassus Avenue
San Francisco, CA 94143-0552
(415) 353-9747
(415) 353-9788 Fax
ganem@cgl.ucsf.edu

Soren Gantt, M.D., Ph.D.
Assistant Professor
Department of Pediatrics
Division of Infectious Diseases
University of Washington
Children’s Hospital
Eighth Floor
1900 Ninth Avenue
Seattle, WA 98101
(206) 987-1160
(206) 884-7311 Fax
sganttt@uw.edu

Debra Leiolani Garcia, M.P.A.
Operations Director
University of California, San Francisco
AIDS and Cancer Specimen Resource
SFGH
1001 Potrero Avenue
Building 3, Room 207
San Francisco, CA 94110
(415) 206-5268
(415) 206-3765 Fax
dgarcia@acr.ucsf.edu
Amy S. Gardiner, M.S.
Department of Microbiology and Molecular Genetics
University of Pittsburgh School of Medicine
University of Pittsburgh
450 Technology Drive
Bridgeside Point II, 545
Pittsburgh, PA 15219
(412) 648-9019
asg18@pitt.edu

Mercy Guech-Ongey, Ph.D.
Postdoctoral Fellow
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Executive Plaza South, Suite 7078
6120 Executive Boulevard
Bethesda, MD 20892
(301) 594-7097
(301) 402-0817 Fax
guechome@mail.nih.gov

Lisa Giulino, M.D.
New York Presbyterian Hospital
Weill Cornell Medical College
525 East 68th Street
New York, NY 10065
(212) 746-5454

Kailash Gupta, Ph.D.
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Room 4153
6700B Rockledge Drive
Bethesda, MD 20892
(301) 515-8833
kgupta@niaid.nih.gov

Martha L. Hare, Ph.D., R.N.
Program Director
Center to Reduce Cancer Health Disparities
National Cancer Institute
National Institutes of Health
Suite 602
6116 Executive Boulevard
Bethesda, MD 20892
(301) 594-1908
martha.hare@nih.gov

Joe B. Harford, Ph.D.
Director
Office of International Affairs
National Cancer Institute
National Institutes of Health
Executive Plaza North, Suite 100
MSC 7301
6130 Executive Boulevard
Bethesda, MD 20892-7301
(301) 496-5534
(301) 496-3954 Fax
joe.harford@nih.gov

S. Diane Hayward, Ph.D.
Department of Oncology
School of Medicine
Johns Hopkins University
CRBI 308
1650 Orleans Street
Baltimore, MD 21287
(410) 955-2548
(410) 502-6802 Fax
dhayward@jhmi.edu

Rohan Hazra, M.D.
Pediatric, Adolescent, and Maternal AIDS Branch
Center for Research for Mothers and Children
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Room 4B11
6100 Executive Boulevard
Bethesda, MD 20892-7510
(301) 435-6868
hazrar@mail.nih.gov

David H. Henry, M.D.
Clinical Professor of Medicine
Pennsylvania Hospital
Department of Hematology/Oncology
Pennsylvania Oncology Hematology Associates
Second Floor
230 West Washington Square
Philadelphia, PA 19106
(215) 829-6513
(215) 829-6104 Fax
dhhenry@juno.com
Nancy A. Hessol, M.S.P.H.
Associate Professor
Departments of Clinical Pharmacy and Medicine
University of California, San Francisco
Second Floor
405 Irving Street
San Francisco, CA 94122
(415) 502-6281
(415) 476-8528 Fax
nancy.hessol@ucsf.edu

Ken Sujin Ho, M.D., M.P.H.
Fellow
Division of Infectious Diseases
University of Pittsburgh Medical Center
Falk 3A
200 Lothrop Street
Pittsburgh, PA 15213
(412) 965-9135
hok2@upmc.edu

Jim Hoxie, M.D.
Professor
Department of Medicine
Director
Penn Center for AIDS Research
Department of Medicine
Division of Hematology/Oncology
School of Medicine
University of Pennsylvania
Biomedical Research Building 11/111, Room 356
421 Curie Boulevard
Philadelphia, PA 19104
(215) 898-0261
hoxie@mail.med.upenn.edu

Cathrine Hoyo, Ph.D.
Associate Professor
Department of Community and Family Medicine
Suite 600
DUMC Box 104006
2200 West Main Street
Durham NC 27710
(919) 681-2441
(919) 684-5108 Fax
cathrine.hoyo@duke.edu

Rebecca Liddell Huppi, Ph.D.
Program Director
AIDS Cancer Clinical Program
Office of HIV and AIDS Malignancy
Office of the Director
National Cancer Institute
National Institutes of Health
Building 31, Room 3A-33
31 Center Drive
Bethesda, MD 20892
(301) 496-4995
(301) 480-4137 Fax
liddellr@exchange.nih.gov

Shehnaz K. Hussain, Ph.D.
Adjunct Assistant Professor
Department of Cancer Prevention and Control
University of California, Los Angeles
Res/SPH & JCCC
Box 956900, A2-125 CHS
Los Angeles, CA 90095-6900
(310) 825-8165
(310) 206-3566 Fax
skhussain@ucla.edu

Yawale Iliyasu, M.D.
Professor of Pathology
Department of Pathology
Ahmadu Bello University Teaching Hospital
PMB 06
Shika, Zaria, Kaduna State
Nigeria
234-803-314-6681
yawaleiliyasu@yahoo.com

Antoine Jaquet, M.D., M.P.H.
ISPED - INSERM U897
University Victor Segalen Bordeaux 2
33076 Bordeaux Cedex
Bordeaux 33076
France
+335 57 57 95 37
antoine.jaquet@isped.u-bordeaux2.fr
Liesl K. Jeffers, Ph.D.
Webster-Cyriaque Laboratory
Department of Microbiology and Immunology
The University of North Carolina at Chapel Hill
Campus Box 7290
116 Manning Drive
Chapel Hill, NC 27559-7290
(919) 843-5736
(919) 962-8103 Fax
lieslj@med.unc.edu

Denise Jenkins, M.B.A.
Office of HIV and AIDS Malignancy
National Cancer Institute
National Institutes of Health
Building 31, Room 3A-33
31 Center Drive
Bethesda, MD 20892
(301) 496-4995
denise_jenkins@nih.gov

Jose A. Jeronimo, M.D.
Director, Start-Up Project for HPV Diagnostics
Reproductive Health
PATH
Suite 200
2201 Westlake Avenue
Seattle, WA 98121
(206) 788-2413
(206) 285-6619 Fax
jjeronimo@path.org

Aisha O. Jumaan, Ph.D., M.P.H.
HPV Vaccines Project Director
PATH
1455 NW Leary Way
Seattle, WA 98107
(206) 285-3500
(206) 285-6619 Fax
ajumaan@path.org

Johnan A. Kaleeba, Ph.D.
Assistant Professor
Department of Microbiology and Immunology
Emerging Infectious Diseases Program
School of Medicine
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814
(301) 295-9621
(301) 295-3773 Fax
jkaleeba@usuhs.mil

Jeong-Gu Kang, Ph.D.
Visiting Research Fellow
HIV and AIDS Malignancy Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Building 10, Room 6N-106
10 Center Drive
Bethesda, MD 20892-1868
(301) 594-1383
kangj3@mail.nih.gov

Roshan Karki
Doctoral Candidate
Department of Pathology
Experimental Pathology Program
Yale School of Medicine
LH304
310 Cedar Street
New Haven, CT 06520
(203) 785-7614
roshan.karki@yale.edu

Richard A. Kaslow, M.D., M.P.H.
Professor of Epidemiology
Department of Epidemiology
School of Public Health
University of Alabama at Birmingham
220 Ryals Building
1665 University Boulevard
Birmingham, AL 35294-0022
(205) 975-8698
(205) 934-8665 Fax
rkaslow@uab.edu
Elliott D. Kieff, M.D., Ph.D.
Harriet Ryan Albee Professor of Medicine
Professor of Microbiology and Molecular Genetics
Co-Director, Channing Laboratory
Harvard Medical School
Suite 8
181 Longwood Avenue
Boston, MA 02115
(617) 525-4252
(617) 525-4251
ekieff@rics.bwh.harvard.edu

Henry B. Koon, M.D.
Assistant Professor of Medicine
Case Western Reserve University
Director, Medical Oncology Cutaneous Malignancy Program
Ireland Cancer Center/University Hospitals
WRB 2-143
2103 Cornell Road
Cleveland, OH 44106
(216) 368-1175
(216) 368-1166 Fax
henry.koon@uhhospitals.org

Jill Koshiol, Ph.D., M.S.P.H.
Research Fellow
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Executive Plaza South, Suite 7070
MSC 7248
6120 Executive Boulevard
Bethesda, MD 20892-7248
(301) 402-9508
koshiolj@mail.nih.gov

Carrie Kovarik, M.D.
Assistant Professor of Dermatology, Dermatopathology, and Infectious Diseases
University of Pennsylvania
Maloney Building, Room 2
3600 Spruce Street
Philadelphia, PA 19104
(215) 410-7341
carrie.kovarik@uphs.upenn.edu

Alexey Kovelenov, M.D., Ph.D.
Chief
AIDS Center, Leningrad Region
ul.Prof.Popova, 15/17
Saint Petersburg 197376
Russia
79112502879
akovelenov@mail.ru

Deborah Kraut, M.Ed.
Program Analyst
Office of AIDS Research
Office of the Director
National Institutes of Health
5635 Fishers Lane
Bethesda, MD 20892
(301) 496-4077
dk18n@nih.gov

Julia Kravchenko, M.D., Ph.D.
Duke Comprehensive Cancer Center
Duke University
Hock Plaza, Suite G05
Box 2732
2424 Erwin Road
Durham, NC 27705
(919) 668-3707
yk27@duke.edu

Susan E. Krown, M.D.
Member
Melanoma and Sarcoma Service
Department of Medicine
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10065
(212) 639-7426
(212) 717-3342 Fax
krowns@mskcc.org

Laurie T. Krug, Ph.D.
Assistant Professor
Department of Molecular Genetics and Microbiology
SUNY-Stony Brook University
130 Life Sciences Building
Stony Brook, NY 11794-5222
(631) 632-9055
(631) 632-9797 Fax
laurie.krug@stonybrook.edu
Ed Kyle  
Team Leader  
Division of Extramural Activities  
National Cancer Institute  
National Institutes of Health  
Room 8005  
6116 Executive Boulevard  
Bethesda, MD 20892  
(301) 594-1112  
kylee@exchange.nih.gov

Nazzarena Labo, M.D., M.P.H.  
AIDS and Cancer Virus Program  
Viral Oncology Section  
SAIC-Frederick  
NCI-Frederick  
1050 Boyles Street  
Frederick, MD 21701  
(301) 846-5939  
(301) 846-5588 Fax  
labon@mail.nih.gov

Patrick K. Lai, Ph.D.  
Health Scientist Administrator  
Immunity and Host Defense Study Section  
Division of Physiological and Pathological Sciences  
Center for Scientific Review  
National Institutes of Health  
Rockledge 2, Room 4208  
MSC 7812  
6701 Rockledge Drive  
Bethesda, MD 20892-7812  
(301) 435-1052  
(301) 480-4042 Fax  
lai@mail.nih.gov

Nicholas Langlois  
Scientific Committee Coordinator  
AIDS Clinical Trials Group  
Social & Scientific Systems, Inc.  
12th Floor  
8757 Georgia Avenue  
Silver Spring, MD 20910  
(301) 628-3370  
nlangois@S-3.com

Emilie Lanoy, M.D.  
INSERM  
National Institute of Health and Medical Research  
101, rue de Tolbiac  
75654 Paris Cedex 13  
France  
elanoy@ccde.chups.jussieu.fr

Alexandra M. Levine, M.D., M.A.C.P.  
Chief Medical Officer  
Deputy Director for Clinical Programs  
Comprehensive Cancer Center  
City of Hope National Medical Center  
1500 East Duarte Road  
Duarte, CA 91010  
(800) 826-4673  
alevine@coh.org

Sarah Linnstaedt, Ph.D.  
Duke University  
Department of Molecular Genetics and Microbiology  
7347 Doverty Court  
Raleigh, NC 27615  
(540) 809-9941  
sarah.linnstaedt@gmail.com

Richard F. Little, M.D.  
Senior Investigator  
Clinical Investigations Branch  
National Cancer Institute  
National Institutes of Health  
Executive Plaza North, Room 7025  
MSC 7436  
6130 Executive Boulevard  
Bethesda, MD 20892-7436  
(301) 435-9193  
(301) 402-0557 Fax  
richard.little@nih.gov

Micah Luftig, Ph.D.  
Assistant Professor  
Department of Molecular Genetics and Microbiology  
Duke University Medical Center  
CARL 224  
Research Drive  
Durham, NC 27710  
(919) 668-3091  
micah.luftig@duke.edu
Sasha Renee McClain  
AIDS and Cancer Virus Program  
SAIC-Frederick  
NCI-Frederick  
Room 428D  
P.O. Box B  
535 Sultan Drive  
Frederick, MD 21702  
(301) 846-5862  
sasha.mcclain@mail.nih.gov

Alicia McDonald, Ph.D., M.P.H.  
Postdoctoral Research Scientist  
Department of Epidemiology  
Mailman School of Public Health  
Columbia University  
Seventh Floor, Room 729  
722 West 168th Street  
New York, NY 10032  
(212) 342-0184  
am3398@columbia.edu

Harris Edward McFerrin, Ph.D.  
Assistant Professor  
Biology Department  
Xavier University of Louisiana  
NCF 404A  
1 Drexel Drive  
New Orleans, LA 70125  
(504) 450-1279  
hmcferri@xula.edu

Rosemary G. McKaig, Ph.D.  
Epidemiologist/Program Officer  
Division of AIDS  
National Institute of Allergy and Infectious Diseases  
National Institutes of Health  
6700B Rockledge Drive  
Bethesda, MD 20892  
(301) 594-6620  
(301) 402-3211 Fax  
rmckaig@niaid.nih.gov

Mary McLaughlin, R.N.  
Study Coordinator  
National Institute of Allergy and Infectious Diseases  
National Institutes of Health  
Building 10, Room 8C-404  
9000 Rockville Pike  
Bethesda, MD 20892  
(301) 435-8001  
(301) 496-1137 Fax  
mm149t@nih.gov

Robert E. Means, Ph.D.  
Assistant Professor of Pathology  
Director of Graduate Admissions  
Microbiology Program  
Department of Pathology  
Yale School of Medicine  
LH315B  
310 Cedar Street  
New Haven, CT 06520  
(203) 785-6160  
robert.means@yale.edu

Ari Melnick, M.D.  
Associate Professor  
Director  
Raymond and Beverly Sackler Center for Biomedical and Physical Sciences  
Departments of Medicine and Pharmacology  
Weill Cornell Medical College  
1300 York Avenue  
New York, NY 10065  
(212) 746-7643  
(212) 746-8866 Fax  
amm2014@med.cornell.edu

Enrique A. Mesri, Ph.D.  
Associate Professor of Microbiology and Immunology  
Viral Oncology Research Program  
Department of Microbiology and Immunology  
Sylvester Comprehensive Cancer Center  
University of Miami School of Medicine  
PAP Building, Suite 109B (R138)  
1550 NW 10th Avenue  
Miami, FL 33136  
(305) 243-5659  
(305) 243-8309 Fax  
emesri@med.miami.edu
Robert Newton, D.Phil., M.B.B.S., FFPH  
Clinical Epidemiologist  
Epidemiology and Genetics Unit  
Department of Health Sciences  
University of York  
Area 3, Sebohm Rowntree Building  
Helsinkiing, York YO10 5DD  
United Kingdom  
1904 321665  
1904 321899 Fax  
rob.newton@egu.york.ac.uk

Mary H. Nguyen, M.P.H.  
Health Scientist Administrator  
Office of AIDS Research  
National Institutes of Health  
Suite 4000  
MSC 9310  
5635 Fishers Lane  
Bethesda, MD 20892-9310  
(301) 594-4946  
nguyenmary@od.nih.gov

John Nicholas, Ph.D.  
Associate Professor  
Department of Oncology  
Viral Oncology Program  
Johns Hopkins University  
CRB-I, Room 309  
1650 Orleans Street  
Baltimore, MD 21287  
(410) 502-6801  
(410) 502-6802 Fax  
nichojo@jhmi.edu

Pavel Nikitin  
Graduate Student  
Department of Molecular Genetics and Microbiology  
Duke University Medical Center  
CARL 224  
Research Drive  
Durham, NC 27710  
(919) 668-3123  
pn14@duke.edu

Mostafa Nokta, M.D., Ph.D.  
Director  
AIDS Cancer Clinical Program  
Office of HIV and AIDS Malignancy  
National Cancer Institute  
National Institutes of Health  
Building 31, Room 3A-35  
31 Center Drive  
Bethesda, MD 20878  
(301) 496-4995  
mostafa.nokta@nih.gov

Courtney O’Farrell  
Ph.D. Candidate  
Viral Oncology  
Johns Hopkins University School of Medicine  
Room 384  
1650 Orleans Street  
Baltimore, MD 21287  
(410) 955-8789  
cofarre1@jhmi.edu

Ojoh Raphael Onum, M.D., M.B.B.S., FWACP  
APIN-HARVARD Clinic  
JOS University Teaching Hospital  
PMB 2076  
JOS, Plateau State 930001  
Nigeria  
234-8036667397  
raphaelojoh@yahoo.com

Francine M. Overcash, M.P.H.  
Research Analyst  
Community and Family Medicine  
Room 638  
DUMC Box 104006  
Erwin Square  
Durham, NC 27710  
(919) 684-5592  
(919) 684-5108 Fax  
francine.overcash@duke.edu
Joel Palefsky, M.D., FRCP(C)
Professor
Laboratory Medicine, Medicine, and Stomatology
Director
Clinical Research Center
University of California, San Francisco
M-1203
Box 0126
505 Parnassus Avenue
San Francisco, CA 94118
(415) 476-1574
(415) 476-5417 Fax
joelp@medicine.ucsf.edu

Groesbeck P. Parham, M.D.
Professor
Department of Medicine
University of Alabama at Birmingham
OHB538
619 19th Street
Birmingham, AL 35249-7333
(205) 934-1917
groesbeck.parham@cidrz.org

C. David Pauza, Ph.D.
Professor
Institute of Human Virology
Greenbaum Cancer Center
University of Maryland School of Medicine
Room N546
725 West Lombard Street
Baltimore, MD 21201-1009
(410) 706-1367
(410) 706-6212 Fax
cdpauza@ihv.umaryland.edu

Karen Sue Perkins, M.Ed.
Recreation Therapist
Clinical Center/Rehabilitation Medicine Department
National Institutes of Health
6515 Huntshire Drive
Elkridge, MD 21075
(301) 402-0283
kperkins@mail.nih.gov

Christophe Antoine Piketty, M.D., Ph.D.
Head
Department of Clinical Immunology
Georges-Pompidou Hospital
Assistance Publique-Hopitaux de Paris
20 Rue Leblanc
Paris 75015
France
+33 1 56 09 27 01
christophe.piketty@egp.aphp.fr

Rommy Pizarro, M.D.
Chair
Clinical Laboratory
Member
American Association for Chemical Chemistry
National Cancer Institute of Peru
Calle Ricardo Aicardi 169, Dpt 101
Chama, Santiago de Surco
Lima
Peru
(511) 449-3462
rommypizarro@yahoo.com

Jerry Polesel, Sc.D.
Statistician
Unit of Epidemiology and Biostatistics
National Cancer Institute
Centro di Riferimento Oncologico
Via Franco Gallini 2
Aviano, PN 33081
Italy

Mark Polizzotto, M.B., B.Med.Sc.
HIV and AIDS Malignancy Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Building 10, Room 6N-110
Bethesda, MD 20892-1868
(301) 402-1541
(301) 480-5955 Fax
Carolina Porras, M.S.
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Executive Plaza South, Suite 7073
6120 Executive Boulevard
Bethesda, MD 20892
(301) 435-4729
porrascg@mail.nih.gov

Ben Prickril, Ph.D.
International Programs Officer
National Cancer Institute
National Institutes of Health
Executive Plaza North, Suite 100
6130 Executive Boulevard
Bethesda, MD 20892
(301) 496-1081
prickril@mail.nih.gov

Zhiqiang Qin, Ph.D.
Department of Medicine, Infectious Diseases
Medical University of South Carolina
Room 1201
MSC 752
135 Rutledge Avenue
Charleston, SC 29425
(843) 792-3385
(843) 792-6680 Fax
gerked@musc.edu

Asimah Rafi, Ph.D.
Director, Regulatory Affairs
RCC Contractor for DAIDS
Technical Resources International, Inc.
Suite 650
6500 Rock Spring Drive
Bethesda, MD 20817
(301) 897-1712
arafi@tech-res.com

Doreen Ramogola-Masire, M.D.
Botswana UPenn Partnership
P.O. Box 404604
Broadhurst
Gaborone
South Africa
26772687480
doreen.masire@gmail.com

Juan Carlos Ramos, M.D.
Assistant Professor of Clinical Medicine
Department of Medicine
Division of Hematology/Oncology
Sylvester Cancer Center
Viral Oncology Program
Miller School of Medicine
University of Miami
D8-4
1475 NW 12th Avenue
Miami, FL 33136
(305) 243-6611
(305) 243-5239 Fax
jramos2@med.miami.edu

Giovanna Rappocciolo, Ph.D.
Research Assistant Professor
Department of Infectious Diseases and Microbiology
Graduate School of Public Health
University of Pittsburgh
604 Parran Hall
130 DeSoto Street
Pittsburgh, PA 15261
(412) 383-9590
giovanna@pitt.edu

Vadim Vladimirovich Rassokhin, M.D., Ph.D.
AIDS Center, Russia, Saint Petersburg
Bumagnaya Street 12
Saint Petersburg 190020
Russia
79119369301
ras-doc@mail.ru

Alex Ray
Viral Oncology Section
AIDS and Cancer Virus Program
SAIC-Frederick
NCI-Frederick
P.O. Box B
Frederick, MD 21702
(301) 846-5828
rayak@mail.nih.gov
Elizabeth Lee Read-Connole, Ph.D., M.S.
Program Director
AIDS Virus Studies
Cancer Etiology Branch
Division of Cancer Biology
National Cancer Institute
National Institutes of Health
Executive Plaza North, Suite 5016
6130 Executive Boulevard
Bethesda, MD 20892-7398
(301) 496-6085
(301) 496-2025 Fax
bconnole@mail.nih.gov

Erin Reid, M.D., M.S.
Associate Professor of Medicine
Moores Cancer Center
University of California, San Diego
3855 Health Sciences Drive
La Jolla, CA 92039-0987
(858) 822-6276
(858) 822-6288 Fax
egreid@ucsd.edu

Scot C. Remick, M.D.
Director
Mary Babb Randolph Cancer Center
School of Medicine
West Virginia University
Robert C. Byrd Health Sciences Center, South,
Room 1801
P.O. Box 9300
Morgantown, WV 26506-9300
(304) 293-0781
(304) 293-4667 Fax
sremick@hsc.wvu.edu

Rosemary Rochford, Ph.D.
Professor and Chair
Department of Microbiology and Immunology
SUNY Upstate Medical University
750 East Adams Street
Syracuse, NY 13066
(315) 464-5468
(315) 464-4417 Fax
rochforr@upstate.edu

Isaac R. Rodriguez-Chavez, Ph.D., M.S., M.H.S.C.R.
Director
AIDS and Immunosuppression Program
Integrative Biology and Infectious Diseases Branch
Division of Extramural Research
National Institute of Dental and Craniofacial Research
National Institutes of Health
Room 614
6701 Democracy Boulevard
Bethesda, MD 20892-4878
(301) 594-7985
(301) 480-8319 Fax
isaac@nidcr.nih.gov

Frank Ruscetti, Ph.D.
Head
Leukocyte Biology Section
NCI-Frederick
National Institutes of Health
Building 567, Room 251
Frederick, MD 21702-1201
(301) 846-1504
(301) 846-7034 Fax
ruscettif@mail.ncifcrf.gov

Jenica Ryu, M.D.
Physician
Rand Schrader Clinic
University of Southern California
1300 North Mission Road
Los Angeles, CA 90033
(323) 343-8255
jenicary@usc.edu

Vikrant Sahasrabuddhe, Dr.P.H., M.B.B.S.
Assistant Professor
Institute for Global Health
Vanderbilt University
Suite 750
2525 West End Avenue
Nashville, TN 37203
(615) 322-4377
(615) 343-7797 Fax
vikrant.sahasrabuddhe@vanderbilt.edu
Shuhei Sakakibara, Ph.D.
Research Fellow
National Cancer Institute
National Institutes of Health
Room 4134
37 Convent Drive
Bethesda, MD 20892
(301) 594-9597
sakakibs@mail.nih.gov

Lateef Salawu, M.D.
Physician
Department of Haematology and Blood Transfusion
Obafemi Awolowo University Teaching Hospitals Complex
P.M.B. 5538
Ile-Ife, 220005
Nigeria
+234 8033884177
+234 036 230141 Fax
lsalawu2002@yahoo.co.uk

Rengaswamy Sankaranarayanan, M.D.
Screening Group
Early Detection and Prevention Section
International Agency for Research on Cancer
150 Cours Albert Thomas
Lyons, Cedex 08 69372
France
33-472738599
33-472738518 Fax
sankar@iarc.fr

Deborah Scott, M.S.
Clinical Trials Specialist
AIDS Clinical Trials Group
Social & Scientific Systems, Inc.
8757 Georgia Avenue
Silver Spring, MD 20910
(301) 628-3327
dscott@s-3.com

Todd Seaman, Ph.D.
Webster-Cyriaque Laboratory
Department of Microbiology and Immunology
The University of North Carolina at Chapel Hill
Campus Box 7290
116 Manning Drive
Chapel Hill, NC 27559-7290
(919) 843-5736
(919) 962-8103 Fax
tseaman@med.unc.edu

Julia Seay
Study Coordinator
Infectious Diseases
The University of North Carolina at Chapel Hill
CB 7030
101 Manning Drive
Chapel Hill, NC 27514
(919) 843-7663
julia_seay@med.unc.edu

Diego Serraino, M.D.
Epidemiology Unit
IRCCS Centro di Riferimento Oncologico
Via Franco Gallini 2
Aviano 33084
Italy
+39 0434 659232	serrainod@cro.it

Hasnaa Shafik, M.D., Ph.D.
Program Director
Office of Cancer Centers
National Cancer Institute
National Institutes of Health
Room 7006
6116 Executive Boulevard
Bethesda, MD 20892
(301) 496-8531
shafikh@mail.nih.gov

Akbar Shahkolahi, Ph.D.
Social & Scientific Systems, Inc.
12th Floor
8757 Georgia Avenue
Silver Spring, MD 20910
(301) 628-3318
ashahkolahi@s-3.com
Meir Shamay, Ph.D.
Instructor
Viral Oncology Program
Johns Hopkins University
1650 Orleans Street
Baltimore, MD 21287
(410) 955-8839
mshamay1@jhmi.edu

Meredith Shiels, Ph.D., M.H.S.
Postdoctoral Fellow
Division of Cancer Epidemiology and Genetics
Infections and Immunoepidemiology Branch
National Cancer Institute
National Institutes of Health
Executive Plaza South, Suite 7059
6120 Executive Boulevard
Bethesda, MD 20892
(301) 402-5374
shielsms@mail.nih.gov

Sadeep Shrestha, Ph.D., M.S.
Assistant Professor
Department of Epidemiology
School of Public Health
University of Alabama at Birmingham
1600 University Boulevard
Birmingham, AL 35242
(205) 934 6459
sshresth@uab.edu

Sylvia Silver, D.A.
Professor and Associate Dean
George Washington University Medical Center
2300 I Street, NW
Washington, DC 20037
(202) 994-2945
sssilver@gwu.edu

Michael Silverberg, Ph.D., M.P.H.
Research Scientist
Division of Research
Kaiser Permanente Northern California
2000 Broadway
Oakland, CA 94612
(510) 891-3801
(510) 891-3805 Fax
michael.j.silverberg@kp.org

Kenneth Simbiri, Ph.D.
Department of Microbiology
University of Pennsylvania School of Medicine
202A Johnson Pavilion
3610 Hamilton Walk
Philadelphia, PA 19083
(215) 746-0116
simbiri@mail.med.upenn.edu

Dinah S. Singer, Ph.D.
Director
Division of Cancer Biology
National Cancer Institute
National Institutes of Health
Executive Plaza North
6130 Executive Boulevard
Bethesda, MD 20892
(301) 496-8636
(301) 496-8656 Fax
ds13j@nih.gov

Joseph Sparano, M.D.
Professor
Department of Medicine
Professor
Department of Obstetrics and Gynecology and Women’s Health
Jack D. Weller Hospital
Albert Einstein College of Medicine
Room 25-47-48
1825 Eastchester Road
Bronx, NY 10461
(718) 904-2555
(718) 904-2892 Fax
jsparano@montefiore.org

Cristina Daniela Stefan, M.D., Ph.D., MMED, FCP, CMO
Pediatric Oncologist
Department of Paediatrics and Child Health
Tygerberg Hospital
Stellenbosch University
73 Francie van Zyl Tygerberg
Cape Town 7550
South Africa
27 21 9389404
27 21 9389138 Fax
cs@sun.ac.za
Deborah Steffen  
Graduate Student  
Emerging Infectious Diseases Graduate Program  
Uniformed Services University of the Health Sciences  
B4121  
4301 Jones Bridge Road  
Bethesda, MD 20814  
(301) 295-9620  
deborah.steffen@usuhs.mil

Ann L. Steiner, M.D.  
Clinical Associate Professor  
Department of Obstetrics and Gynecology  
University of Pennsylvania  
Penn Medicine at Radnor  
Penn Health for Women  
250 King of Prussia Road  
Radnor, PA 19087  
(610) 902-2500  
(610) 902-2504 Fax  
ann.steiner@uphs.upenn.edu

Elizabeth A. Stier, M.D.  
Department of Obstetrics and Gynecology  
Boston Medical Center  
Sixth Floor  
85 East Concord Street  
Boston, MA 02118  
(617) 414-5175  
(617) 414-7300  
elizabeth.stier@bmc.org

Katharine M. Sturm-Ramirez, Ph.D.  
Program Officer  
Division of International Training and Research  
Fogarty International Center  
National Institutes of Health  
Building 31  
MSC 2220  
31 Center Drive  
Bethesda, MD 20892-2220  
(301) 496-9676  
(301) 402-0779 Fax  
sturmrak@mail.nih.gov

Melinda Tibbals, RAC  
EMMES Corporation  
Suite 700  
401 North Washington Street  
Rockville, MD 20850  
(301) 251-1161, ext. 2821  
mtibbals@emmes.com

William Timmer, Ph.D.  
Program Director  
Cancer Therapy Evaluation Program  
National Cancer Institute  
National Institutes of Health  
Executive Plaza North, Suite 7009  
MSC 7432  
6130 Executive Boulevard  
Bethesda, MD 20892-7432  
(301) 594-9796  
william.timmer@nih.gov

Natalie Tomitch, M.B.A., M.P.H.  
Health Scientist Administrator  
Office of AIDS Research  
Office of the Director  
National Institutes of Health  
Suite 4000  
5635 Fishers Lane  
Bethesda, MD 20892  
(301) 451-0098  
(301) 480-4746 Fax  
tomitchn@od.nih.gov

Tatiana Nikolaevna Trofimova, M.D., MRT, CT, Rg  
Professor  
Medical Academy  
Saint Petersburg AIDS City Center  
Bumagnaya Street 12  
Saint Petersburg 190020  
Russia  
79219933009  
78123363061 Fax  
trofimova-tn@avaclinic.ru
George Walter Turiansky, M.D.
Program Director
National Capital Consortium Dermatology Residency
Dermatology Service
Dermatology Department
Walter Reed Army Medical Center
National Naval Medical Center
U.S. Army
1507 Sanford Road
Silver Spring, MD 20902
(240) 353-6741
gwturiansky@verizon.net

Thomas Uldrick, M.D., M.S.
HIV and AIDS Malignancy Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Room 6N106
MSC 1868
10 Center Drive
Bethesda, MD 20892-1868
(301) 402-6296
(301) 480-5955 Fax
uldrickts@mail.nih.gov

Patrick Unemori, M.D., M.A.
HIV Fellow
Department of Dermatology
University of California, San Francisco
Ward 92
1001 Potrero Avenue
San Francisco, CA 94110
(415) 606-2109
patrick.unemori@ucsf.edu

Bhadrasain Vikram, M.D.
National Cancer Institute
National Institutes of Health
Executive Plaza North
6130 Executive Boulevard
Bethesda, MD 20892
(301) 496-6111
vikramb@mail.nih.gov

William Wachsman, M.D., Ph.D.
Associate Professor
Cancer Center
Division of Hematology-Oncology
University of California, San Diego and VASDHS
3350 La Jolla Village Drive
San Diego, CA 92161
(858) 552-8585, ext. 2628
(858) 552-7416 Fax
wwachsman@ucsd.edu

Leyao Wang, Ph.D.
Department of Oncology
School of Medicine
Johns Hopkins University
CRBI, Room 316
1650 Orleans Street
Baltimore, MD 21231
(410) 614-0594
(410) 502-6802 Fax
lwang7@jhmi.edu

Jennifer Webster-Cyriaque, D.D.S., Ph.D.
Associate Professor
Department of Dental Ecology
School of Dentistry
The University of North Carolina at Chapel Hill
Campus Box 7450
3310 Old Dental
Chapel Hill, NC 27599-7450
(919) 966-8911
cyriaquj@dentistry.unc.edu

John Weiser, M.D.
Clinical Associate Professor of Family and Social Medicine
Albert Einstein College of Medicine
Apartment 343
207 Park Drive
Boston, MA 02215
(917) 596-7009
jkweiser@gmail.com
Denise Whitby, Ph.D
Viral Oncology Section
AIDS and Cancer Virus Program
Office of the Director
NCI-Frederick
Building 535, FCRDC, 412
1050 Boyles Street
Frederick, MD 21702-9242
(301) 846-1714
denise.whitby@nih.gov

Lisa Tisdale Wigfall, Ph.D.
Institute for Partnerships to Eliminate Health Disparities
University of South Carolina
Suite 208
220 Stoneridge Drive
Columbia, SC 29208
(803) 251-2298
(803) 251-6327 Fax
lisa.wigfall@sc.edu

Dorothy JoAnn Wiley, Ph.D., M.P.H., R.N.
Associate Professor
School of Nursing
University of California, Los Angeles
Room 5-151
700 Tiverton Avenue
Los Angeles, CA 90095-6919
(310) 206-0606 Fax
dwiley@ucla.edu

May Wong, Ph.D.
Program Director, NeuroAIDS and Infectious Diseases
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Neuroscience Center, Room 2113
6001 Executive Boulevard
Bethesda, MD 20892
(301) 496-1431
mw132k@nih.gov

Ting-Ting Wu, Ph.D.
Department of Molecular and Medical Pharmacology
School of Medicine
Dental Research Institute
School of Dentistry
University of California, Los Angeles
CHS 23-120
650 Charles E. Young Drive
Los Angeles, CA 90095
(310) 267-2218
twu@mednet.ucla.edu

Robert Yarchoan, M.D.
Director
Office of HIV and AIDS Malignancy
Chief
HIV and AIDS Malignancy Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Building 10, Room 6N-106
MSC 1868
10 Center Drive
Bethesda, MD 20892-1868
(301) 496-0328
(301) 480-5955 Fax
yarchoan@helix.nih.gov

Suria Yesmin
Clinical Trials Specialist
Clinical Research and Bioscience
Social & Scientific Systems, Inc.
12th Floor
8757 Georgia Avenue
Silver Spring, MD 20910
(301) 628-3493
(301) 628-3302 Fax
syesmin@s-3.com

Zinaida Moyiseevna Zagdyn, Ph.D.
AIDS Center, Leningrad Region, Russia
Professor Popov’s Street 15/17
Saint Petersburg 196158
Russia
8 9217676947
dinmet@mail.ru
Li Zhang, M.D.
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health
Room 4N-07
5625 Fishers Lane
Bethesda, MD 20892
(301) 443-3755
lzhang@mail.nih.gov

Yanjin Zhang, Ph.D.
Assistant Professor
Department of Veterinary Medicine
University of Maryland
8075 Greenmead Drive
College Park, MD 20742
(301) 314-6596
zhangyj@umd.edu

Zhensheng Zhang, M.D.
National Institutes of Health
Building 10
10 Center Drive
Bethesda, MD 20892
(301) 435-4016
zz14h@nih.gov

Dasheng Zheng, Ph.D.
Department of Oncology
School of Medicine
Johns Hopkins University
CRBI 316
1650 Orleans Street
Baltimore, MD 21231
(410) 614-0594
(410) 502-6802 Fax
d.zheng@wh.iov.cn

Antonella Zucchetto, Sc.D.
Statistician
Epidemiology and Biostatistics
National Cancer Institute
Centro di Riferimento Oncologico
Via Franco Gallini 2
Aviano PN 33081
Italy
+39 0434 659354 Fax