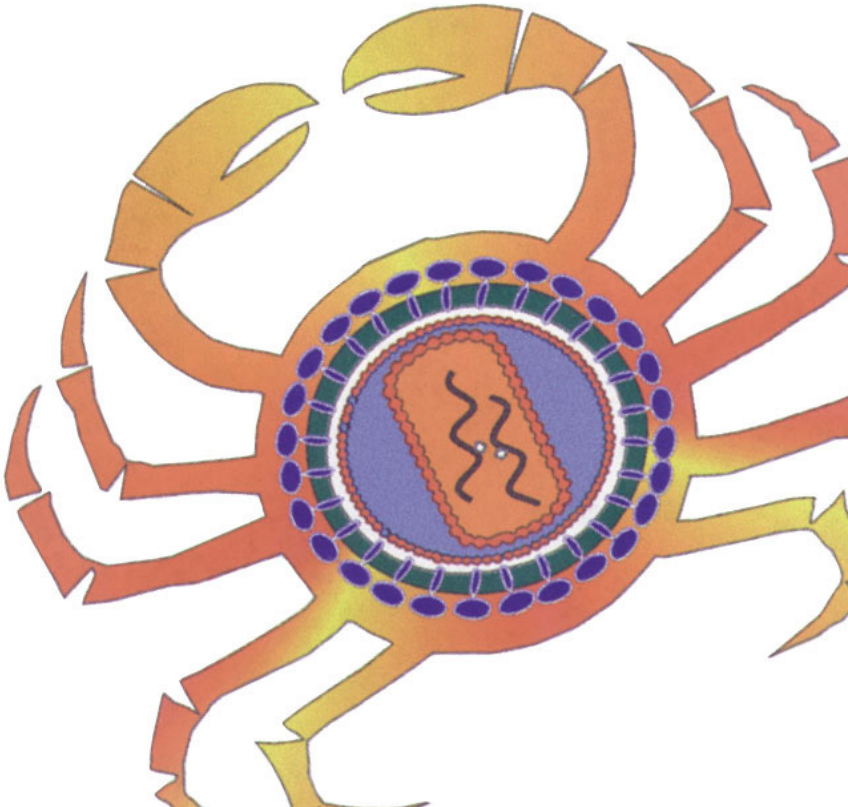
National Cancer Institute

Office of HIV and AIDS Malignancy

14th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies

November 12-13, 2013

Lister Hill Auditorium
NIH Main Campus
Bethesda, Maryland



U.S DEPARTMENT OF HEALTH AND HUMAN SERVICES

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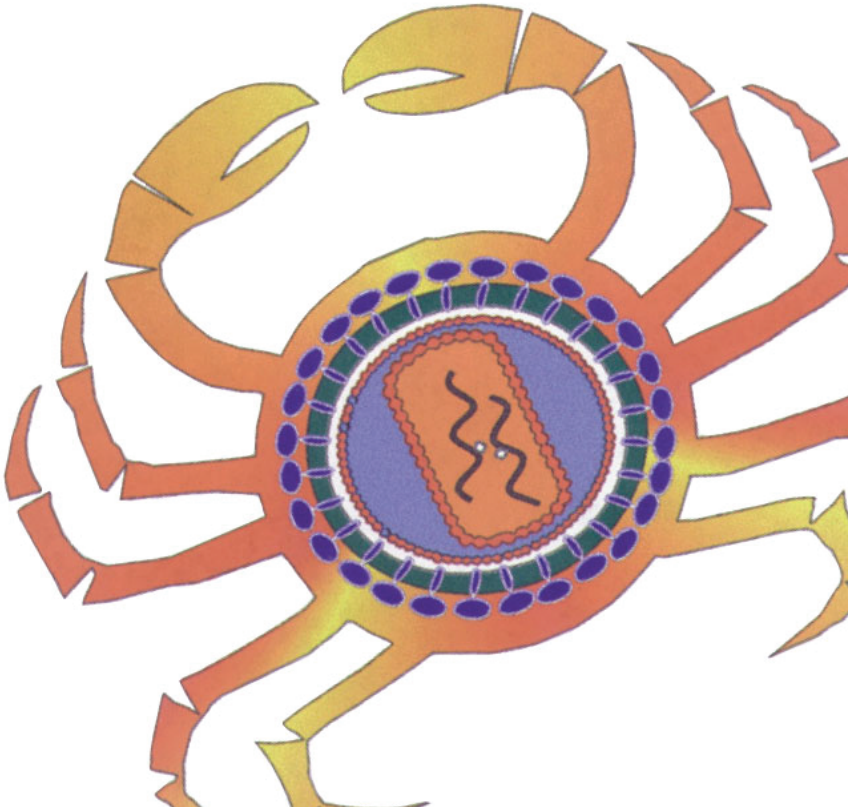

U.S DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Program

November 12

8:00 a.m. - 8:15 a.m. **Poster Setup** (posters to stay up for the entire meeting)

8:15 a.m. - 8:30 a.m. **Opening Remarks: Day 1**
Robert Yarchoan, M.D.
Office of HIV and AIDS Malignancy
National Cancer Institute, NIH, USA

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

8:30 a.m. - 9:30 a.m. **HPV Vaccines**
Moderator: T-C Wu, M.D., Ph.D.
Johns Hopkins University, USA

8:30 a.m. - 9:00 a.m. ***Plenary: L2 as a Target for Prophylactic Human Papillomavirus Vaccination***
Richard Roden, Ph.D.
Johns Hopkins University, USA

9:00 a.m. - 9:30 a.m. ***Plenary: HPV Vaccination in HIV-Infected Men and Women***
Joel Palefsky, M.D.
University of California, San Francisco, USA

9:30 a.m. - 10:15 a.m. **Oral HPV**
Moderator: Isaac R. Rodriguez-Chavez, Ph.D.
National Institute of Dental and Craniofacial Research, NIH, USA

9:30 a.m. - 9:45 a.m. ***HIV-Induced Epithelial-Mesenchymal Transition in Oral Mucosal Epithelial Cells Facilitates HPV Infection***
Sharof M. Tugizov, D.V.M., Ph.D., D.Sc.
University of California, San Francisco, USA

9:45 a.m. - 10:00 a.m. ***HIV-Related Immunosuppression Is Associated With Higher Incidence of Oral HPV, But Not Oral HPV Clearance***
Daniel C. Beachler, M.S.P.H.
Johns Hopkins University, USA

10:00 a.m. - 10:15 a.m. ***HIV Tat Increases HPV16 Infectivity Independent of Oral Keratinocyte Terminal Differentiation***
Jennifer Webster-Cyriaque, D.D.S., Ph.D.
The University of North Carolina at Chapel Hill, USA

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

10:45 a.m. - 12:15 p.m. **Pathogens and Host Interactions**
Moderator: Corey Casper, M.D., M.P.H.
Fred Hutchinson Cancer Research Center, USA

10:45 a.m. - 11:15 a.m. ***Plenary: Potential Role of Graft-Versus-Host Reaction in Reducing the HIV-1 Reservoir***
Daniel R. Kuritzkes, M.D.
Brigham and Women's Hospital, USA

11:15 a.m. - 11:30 a.m. ***Variation in Viral Gene Expression Distinguishes Two Subtypes of Kaposi Sarcoma***
Dirk P. Dittmer, Ph.D.
The University of North Carolina at Chapel Hill, USA

11:30 a.m. - 11: 45 a.m. ***Characterization of HHV-8 Gene Expression in Kaposi Sarcoma Tumors and Correlation With Clinical Presentation and Outcomes***
Warren Phipps, M.D., M.P.H.
Fred Hutchinson Cancer Research Center, USA

11:45 a.m. - 12 noon ***Prevalent High-Risk HPV Infection and Vaginal Microbiota in Nigerian Women***
Clement A. Adebamowo, M.D.
Institute of Human Virology
University of Maryland School of Medicine, Baltimore, USA

12 noon - 12:15 p.m. ***Unmasking Lymphoma Immune Reconstitution Inflammatory Syndrome Among HIV-Infected Individuals in the Center for AIDS Research Network of Integrated Clinical Systems***
Satish Gopal, M.D.
The University of North Carolina at Chapel Hill, USA

12:15 p.m. - 1:45 p.m. **Lunch**

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

1:45 p.m. - 2:45 p.m. **Cancer Burden in Low and Middle Income Countries**
Moderator: Sam Mbulaiteye, M.D.
National Cancer Institute, NIH, USA

1:45 p.m. - 2:15 p.m. ***Plenary: Harnessing Cancer Registry and HIV Databases in Low and Middle Income Countries***
Diego Serraino, M.D.
IRCCS Centro di Riferimento Oncologico, Italy

2:15 p.m. - 2:45 p.m. ***Plenary: HIV and Cancer Survival in Uganda***
Anna E. Coghill, Ph.D., M.P.H.
National Cancer Institute, NIH, USA

2:45 p.m. - 3:30 p.m. **Break and Poster Session** (Lister Hill cafeteria closes at 3:00 p.m.)

3:30 p.m. - 5:30 p.m. **KSHV Biology**

Moderators: Denise Whitby, Ph.D.
National Cancer Institute, NIH, USA

Dirk P. Dittmer, Ph.D.
The University of North Carolina at Chapel Hill, USA

3:30 p.m. - 3:45 p.m. ***Kaposi Sarcoma Herpesvirus (KSHV) vFLIP Induces Systemic Endothelial Proliferation and a Proinflammatory Phenotype In Vivo***
Gianna Ballon, M.D.
Weill Cornell Medical College, USA

3:45 p.m. - 4:00 p.m. ***Human Herpesvirus 8 Infection Induces Polyfunctional B Lymphocytes Producing Cytokines and Chemokines That Drive Kaposi's Sarcoma***
Charles R. Rinaldo, Ph.D.
University of Pittsburgh, USA

4:00 p.m. - 4:15 p.m. ***Kaposi Sarcoma-Associated Human Herpesvirus (KSHV) Latency-Associated Nuclear Antigen (LANA) Undergoes Cleavage by Caspases Following Exposure of Cells to Oxidative Stress***
David A. Davis, Ph.D.
National Cancer Institute, NIH, USA

4:15 p.m. - 4:30 p.m. ***Regulation of Kaposi Sarcoma Herpesvirus (KSHV) Encoded Viral Interleukin 6 (vIL-6) by X-Box Binding Protein 1 (XBP-1)***
Duosha Hu, M.D., Ph.D.
National Cancer Institute, NIH, USA

4:30 p.m. - 4:45 p.m. ***RNA-Independent Activation of RIG-I by Deamidation***
Pinghui Feng, Ph.D.
University of Southern California, USA

4:45 p.m. - 5:00 p.m. ***KSHV-Dependent Activation of Platelet Derived Growth Factor Receptor Signaling Is an Oncogenesis Driver and a Therapeutic Target in Kaposi's Sarcoma***
Enrique A. Mesri, Ph.D.
University of Miami, USA

5:00 p.m. - 5:15 p.m. ***Using Proteomics to Understand Human Target Genes of KSHV MicroRNAs***
Joseph M. Ziegelbauer, Ph.D.
National Cancer Institute, NIH, USA

5:15 p.m. - 5:30 p.m. ***KS-Detect: A Complete "Sample-In, Answer-Out" Solution to the Diagnosis of Kaposi's Sarcoma***
Ethel Cesarman, M.D., Ph.D.
Weill Cornell Medical College, USA

5:30 p.m. **End of Day 1**

November 13

8:00 a.m. - 8: 15 a.m. **Poster Viewing**

8:15 a.m. - 8:20 a.m. **Welcoming Remarks: Day 2**
Geraldina Dominguez, Ph.D.
National Cancer Institute, NIH, USA

8:20 a.m. - 8:30 a.m. **Fogarty International Center's HIV Research Training Program**
Jeanne McDermott, Ph.D., M.P.H.
Fogarty International Center, NIH, USA

8:30 a.m. - 9:30 a.m. **Hepatitis C Virus**
Moderator: Ren Sun, Ph.D.
University of California, Los Angeles, USA

8:30 a.m. - 9:00 a.m. ***Plenary: Hepatitis C and Hepatocellular Carcinoma: New Model Systems and Insights Into Pathogenesis***
Stanley M. Lemon, M.D.
The University of North Carolina at Chapel Hill, USA

9:00 a.m. - 9:30 a.m. ***Plenary: Natural Courses and Management of Chronic Viral Hepatitis B or C in HIV-Infected Patients***
Pei-Jer Chen, M.D., Ph.D.
National Taiwan University Hospital, Taiwan

9:30 a.m. - 10:15 a.m. **Clinical Trials and Correlative Studies**
Moderator: Alexandra M. Levine, M.D.
City of Hope National Medical Center, USA

9:30 a.m. - 9:45 a.m. ***Results of a Phase I Study of Lenalidomide in Patients With AIDS-Associated Kaposi Sarcoma (AMC 070)***
Kelly Shimabukuro, M.D.
University of California, San Diego, USA

9:45 a.m. - 10:00 a.m. ***Antiretrovirals for Kaposi's Sarcoma (ARKS): A Randomized Trial of Protease Inhibitor-Based Antiretroviral Therapy for AIDS-Associated Kaposi's Sarcoma in Sub-Saharan Africa***
Jeffrey N. Martin, M.D., M.P.H.
University of California, San Francisco, USA

10:00 a.m. - 10:15 a.m. ***Studies in Primary Cultures of Human Hepatocytes and Computer Simulations Provide Guidance for Dosing of Anticancer Drugs in Patients Treated With HAART Drugs***
Raman Venkataramanan, Ph.D.
University of Pittsburgh, USA

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

10:45 a.m. - 12:15 p.m. **EBV and Lymphomagenesis**

Moderators: Elliott D. Kieff, M.D., Ph.D.
Harvard Medical School, USA

Richard F. Ambinder, M.D., Ph.D.
Johns Hopkins University School of Medicine, USA

10:45 a.m. - 11:15 a.m. ***Plenary: Immune Activation and Inflammation Biomarkers and Risk for AIDS-NHL***
Otoniel Martinez-Maza, Ph.D.
University of California, Los Angeles, USA

11:15 a.m. - 11:30 a.m. ***Differential Expression and Prognostic Utility of Immunophenotypic Markers in Diffuse Large B-cell Lymphoma From Patients With and Without HIV Infection***
Chun R. Chao, Ph.D.
Kaiser Permanente Southern California, USA

11:30 a.m. - 11:45 a.m. ***Targeting Sphingosine Kinase Induces Apoptosis and Regression of Virus-Associated Lymphoma In Vivo***
Chris M. Parsons, M.D.
Louisiana State University Health Sciences Center, USA

11:45 a.m. - 12 noon ***The HIV-1 Matrix Protein and AIDS-Related Lymphoma***
Mark K. Lafferty, Ph.D.
Institute of Human Virology, University of Maryland School of Medicine, USA

12 noon - 12: 15 p.m. ***Characterizing Survival in the Absence of LMP1-Mediated NFκB Signaling in the Model of EBV-Driven AIDS Lymphoma***
Alexander Price
Duke University, USA

12:15 p.m. - 2:00 p.m. **Lunch**

1:00 pm. - 2:00 p.m. **Poster Session** (Day 2 presenters to stand by their posters)

2:00 p.m. - 2:45 p.m. **Lung Cancer**

Moderator: Missak Haigentz, M.D.
Albert Einstein College of Medicine, USA

2:00 p.m. - 2:30 p.m. ***Plenary: Chronic Inflammation and Lung Cancer***
Anil K. Chaturvedi, Ph.D.
National Cancer Institute, NIH, USA

2:30 p.m. - 2:45 p.m. ***Inflammatory Biomarkers and CT-Detected Lung Nodules: Potential Implications for Lung Cancer Screening of HIV-Infected Patients***
Kristina Crothers, M.D.
University of Washington School of Medicine, USA

2:45 p.m. -3:30 p.m. **Break and Poster Session** (Lister Hill cafeteria closes at 3:00 p.m.)

3:30 p.m. - 5: 30 p.m. **Epidemiological Studies**

Moderators: Michael J. Silverberg, Ph.D., M.P.H.
Kaiser Permanente, USA

Eric Engels, M.D., M.P.H.
National Cancer Institute, NIH, USA

3:30 p.m. - 3:45 p.m. ***Applying the Methods of Causal Inference to HIV-Associated Malignancies: Estimation of the Impact of Antiretroviral Therapy on Kaposi's Sarcoma Incidence in East Africa via a Nested New User Cohort Analysis***
Aggrey S. Semeere, M.D.
University of California, San Francisco, USA

3:45 p.m. - 4:00 p.m. ***Impact of Kaposi's Sarcoma on Survival Among HIV-Infected Adults in Africa in the Era of Antiretroviral Therapy***
Stephen B. Asiimwe, M.D.
Mbarara Regional Referral Hospital, Mbarara, Uganda

4:00 p.m. - 4:15 p.m. ***Prevalence of HIV Infection Among U.S. Hodgkin Lymphoma Cases***
Meredith S. Shiels, Ph.D., M.S.
National Cancer Institute, NIH, USA

4:15 p.m. - 4:30 p.m. ***Risk of Non-Hodgkin Lymphoma Subtypes in People Infected With HIV During the HAART Era***
Todd M. Gibson, Ph.D.
National Cancer Institute, NIH, USA

4:30 p.m. - 4:45 p.m. ***Time Trends of Cancer Mortality Rates Among Men in the Veterans Aging Cohort Study***
Robert Dubrow, M.D., Ph.D.
Yale School of Public Health, USA

4:45 p.m. - 5:00 p.m. ***Epidemiologic Contributions to Recent Cancer Trends Among HIV-Infected People in the United States***
Hilary A. Robbins, M.S.P.H.
National Cancer Institute, NIH, USA

5:00 p.m. - 5:15 p.m. ***Cancer Treatment Disparities in HIV-Infected Individuals in the United States***
Gita Suneja, M.D.
University of Pennsylvania, USA

5:15 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
National Institutes of Health
Building 10, Room 6N-106
10 Center Drive
Bethesda, MD 20892-1868
(301) 496-0328
(301) 480-5955 Fax
robert.yarchoan@nih.gov

Geraldina Dominguez, Ph.D.
Program Director
Office of HIV and AIDS Malignancy
National Cancer Institute
National Institutes of Health
Building 31, Room 3A-33
31 Center Drive
Bethesda, MD 20892-2440
(301) 496-4995
(301) 480-4137 Fax
domingug@mail.nih.gov

Program Committee

Richard F. Ambinder, M.D., Ph.D.
Director
Division of Hematologic Malignancies
Professor of Oncology
School of Medicine
Johns Hopkins University
Bunting-Blaustein Building, Room 390
1650 Orleans Street
Baltimore, MD 21231
(410) 955-8839
(410) 955-0960 Fax
ambinri@jhmi.edu

Kishor Bhatia, Ph.D., FRCPath
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 20892-2440
(301) 496-4995
(301) 480-4137 Fax
bhatiak@mail.nih.gov

Pragna Patel, M.D., M.P.H.
Medical Epidemiologist
Division of HIV/AIDS Prevention
Centers for Disease Control and Prevention
MS E-45
1600 Clifton Road
Atlanta, GA 30333
(404) 639-6132
(404) 639-6127 Fax
plp3@cdc.gov

Corey Casper, M.D., M.P.H.
Associate Member
Vaccine and Infectious Disease Division
Fred Hutchinson Cancer Research Center
Associate Professor of Medicine, Epidemiology and Global Health
University of Washington
Medical Director, Infection Control
Seattle Cancer Care Alliance
MS M1-B140
1100 Fairview Avenue, North
Seattle, WA 98109
(206) 667-4600
(206) 667-1965 Fax
ccasper@fhcrc.org

Ethel Cesarman, M.D., Ph.D.
Professor, 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

Dirk P. Dittmer, Ph.D.
Professor
Program in Global Oncology
Department of Microbiology and Immunology
Lineberger Comprehensive Cancer Center
Center for AIDS Research
Carolina Center for Genome Sciences
The University of North Carolina at Chapel Hill
Mary Ellen Jones Building, Room 715
CB 7290
Chapel Hill, NC 27599-7290
(919) 966-7960
(919) 962-8103 Fax
dirkdittmer@me.com

Eric A. Engels, M.D., M.P.H.
Senior Investigator
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Executive Plaza South, Suite 7076
6120 Executive Boulevard
Bethesda, MD 20892
(301) 496-8115
(301) 402-0817 Fax
engelse@exchange.nih.gov

Rebecca Liddell Huppi, Ph.D.
Program Director
Office of HIV and AIDS Malignancy
National Cancer Institute
National Institutes of Health
Building 31, Room 3A-33
31 Center Drive
Bethesda, MD 20892-2440
(301) 496-4995
(301) 480-4137 Fax
liddellr@exchange.nih.gov

Elliott D. Kieff, MD, PhD
Harriet Ryan Albee Professor of Microbiology and Molecular Genetics
Harvard Medical School
Director, Infectious Diseases
Brigham and Women's Hospital
181 Longwood Avenue
Boston, MA 02115
(617) 525-4252
(617) 525-4257 Fax
ekieff@rics.bwh.harvard.edu

Alexandra M. Levine, M.D., MACP
Chief Medical Officer
Professor of Hematology/HCT
City of Hope National Medical Center
1500 East Duarte Road
Duarte, CA 91010
(626) 471-7213
(626) 471-7200 Fax
alevine@coh.org

Richard F. Little, M.D., M.P.H.
Senior Investigator
Head, Hematologic and AIDS-Related Malignancies and Hematopoietic Stem Cell Transplantation
Clinical Investigations Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Executive Plaza North, Room 7025
MSC 7436
6130 Executive Boulevard
Bethesda, MD 20892
(301) 496-2522
(301) 402-0557 Fax
littler@mail.nih.gov

Sam Mbulaiteye, M.D.
Principal Investigator
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Executive Plaza South, Room 7080
6120 Executive Boulevard
Bethesda, MD 20892-7248
(301) 594-7825
(301) 402-0817 Fax
mbulaits@mail.nih.gov

Mostafa Nokta, M.D., Ph.D.
Director
AIDS Cancer Clinical Program
Office of HIV and AIDS Malignancy
National Cancer Institute
Building 31, Room 3A-33
31 Center Drive
Bethesda, MD 20892-2440
(301) 496-4995
(301) 480-4137 Fax
noktam@mail.nih.gov

Joel Palefsky, M.D., FRCP(C)
Professor
Department of Medicine
University of California, San Francisco
Box 0126
M-1203
505 Parnassus
San Francisco, CA 94118
(415) 476-1574
(415) 476-0986 Fax
joelp@medicine.ucsf.edu

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

Elizabeth Read-Connole, Ph.D.
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

Sylvia Silver, D.A.
Director
East Coast AIDS and Cancer Specimen Resource
Professor of Pathology
The George Washington University
School of Medicine and Health Sciences
2300 I Street, NW
Washington DC 20037
(202) 994-2945
(202) 994-5056 Fax
ssilver@gwu.edu

Michael J. Silverberg, Ph.D., M.P.H.
Research Scientist
Division of Research
Kaiser Permanente
5th Floor
2000 Broadway
Oakland, CA 94612
(510) 891-3801
(510) 891-3508 Fax
michael.j.silverberg@kp.org

Joseph Sparano, M.D.
Professor of Medicine and Women's Health
Albert Einstein College of Medicine
Montefiore Medical Center-Weiler Division
1825 Eastchester Road
Bronx, NY 10461
(718) 904-2555
(718) 904-2892 Fax
jsparano@montefiore.org

Denise Whitby, Ph.D.
Senior Scientist and Principal Investigator
Viral Oncology Section
AIDS and Cancer Virus Program
SAIC-Frederick, Inc.
NCI-Frederick
P.O. Box B
Frederick, MD 21701
(301) 846-1714
(301) 846-7119 Fax
whitbyd@mail.nih.gov

T-C Wu, M.D., Ph.D.
Departments of Pathology, Oncology, Obstetrics and Gynecology, and Molecular Microbiology and Immunology
Johns Hopkins School of Medicine
Cancer Research Building II, Room 309
1550 Orleans Street
Baltimore, MD 21231
(410) 614-3899
(443) 287-4295 Fax
twu1@jhmi.edu

Erle S. Robertson, Ph.D.
Professor of Microbiology
Director
Tumor Virology Training Program
Program Leader, Tumor Virology
Abramson Cancer Center
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA 19104
(215) 746-0114
(215) 746-0115 Fax
erle@upenn.edu

Missak Haigentz, M.D.
Associate Professor of Clinical Medicine
Albert Einstein College of Medicine
Montefiore Medical Center
Hofheimer Building, Room 100
111 East 210th Street
Bronx, NY 10467
(718) 920-4826
mhaigent@montefiore.org

Denise Galloway, Ph.D.
Interim Director
Human Biology Division
Fred Hutchinson Cancer Research Center
Room C1-105
P.O. Box 19024
1100 Fairview Avenue, North
Seattle, WA 98109-1024
(206) 667-4500
(206) 667-5815 Fax
dgallowa@fhcrc.org

Ashlee Moses, Ph.D.
Associate Professor
Oregon Health & Science University
Vaccine and Gene Therapy Institute
505 NW 185th Avenue
Beaverton, OR 97006
(503) 418-2712
(503) 418-2713 Fax
mosesa@ohsu.edu

Ren Sun, Ph.D.
Professor
University of California, Los Angeles
Factor Building, Room 10-155
650 Charles E. Young Drive, South
Los Angeles, CA 90095
(310) 794-5557
rsun@mednet.ucla.edu

Makeda J. Williams, Ph.D., M.P.H., CHES
International Program Officer
Center for Global Health
National Cancer Institute
National Institutes of Health
Executive Plaza North, Suite 100
6130 Executive Boulevard
Bethesda, MD 20892
(301) 451-1445
(301) 496-3954 Fax
willimak@mail.nih.gov

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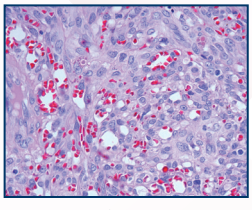
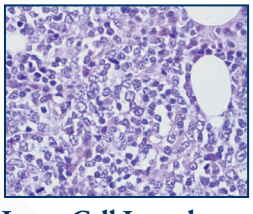
- Squamous cell carcinoma
- Adenocarcinoma
- Sarcoma
- Germ cell tumors
- Primary effusion lymphomas
- Lymphadenopathy
- Opportunistic infections
- HIV+ and HIV- controls



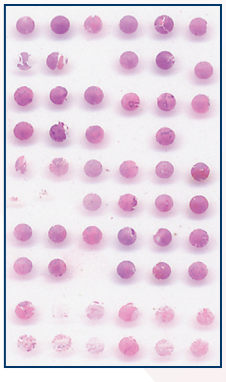
Kaposi's Sarcoma



Large Cell Lymphoma

Tissue Micro-Arrays (TMA)

- Hundreds of tissue samples can be assembled into a single TMA
- Opportunity for testing of multiple cases on a single slide
- HIV infected tissues and related malignancies, along with non-HIV related controls



For more information contact:
Debra Leiolani Garcia
ACSR Central Operations and Data Coordinating Center
415.206.5268 • CODCC@acsr.ucsf.edu

P1. L2 as a Target for Prophylactic Human Papillomavirus Vaccination

Richard Roden
Johns Hopkins University, Baltimore, MD

Oncogenic human papillomavirus (HPV) types, of which 14 types have been identified, are the etiologic agent for 5% of all cancer world-wide, including cervical, vaginal, vulval, anal, penile and oropharyngeal cancers. HIV co-infection is linked to more aggressive and recalcitrant disease that is associated with a greater diversity of HPV types, and higher rates of HPV-associated cancer. The HPV minor capsid protein L2 plays a necessary role in infection and is a candidate protective antigen. Vaccination with L2 elicits antibodies that neutralize diverse oncogenic HPV types, albeit a lower titer than the type-restricted elicited by L1 virus-like particles (VLPs). Notably, L2 vaccines can be produced as a single cross-protective antigen in bacteria, potentially lowering the cost of manufacture as compared to the licensed HPV vaccines, Gardasil and Cervarix, which are multi-type L1 VLP produced in yeast or insect cells respectively. A broad spectrum and low cost HPV vaccine is needed to address the critical public health need in developing countries because they suffer 80% of the global cervical cancer burden. The licensed L1 VLP-based vaccines are currently unaffordable for sustained and widespread implementation in developing countries where they are urgently needed. Further, the licensed L1 VLP vaccines target only two of the 15 known oncogenic HPV types (HPV16 and HPV18 that together cause ~70% of cervical cancer cases), triggering ongoing efforts to develop more multivalent formulations, including a nine-valent L1 VLP vaccine currently in advanced clinical testing. Our objective is to produce an HPV vaccine based on a single antigen, L2, in bacteria that is affordable in low resource countries and protects against all oncogenic HPV types.

A neutralizing epitope (RG-1) that is mapped to amino acid residues 17–36 of L2 is recognized by these broadly cross-protective antibodies. Multimeric antigens constituting repeats of defined L2 immunogenic domains, encompassing the RG-1 epitope and other conserved neutralizing epitopes from diverse HPV types were produced in bacteria and explored as candidate pan-oncogenic preventive HPV vaccines. Results indicated that the breadth and titer of cross-neutralizing antibodies can be increased when L2 is presented in a multivalent form. L2 multimers induced robust antibody responses against diverse HPV types including those not directly targeted by the vaccine. Neutralizing antibodies were persistent several months following immunization in both rabbits and mice. Additionally, animals vaccinated with an L2 multimer vaccine adjuvanted with alum were protected from challenge by multiple diverse HPV types.

Complete unit operation for a simple, straightforward, robust and scalable production platform involving fermentation and purification of the broad spectrum HPV L2 vaccine candidate from recombinant bacteria has been developed by Shantha Biotechnics (Hyderabad, India). Alum-based stable formulations that elicit strong immune responses were optimized and shown to provide protection in animal models. The simplicity of manufacturing process, high yields and pre-clinical results from animal models suggest promise to meet the challenge of delivering an affordable vaccine. The progress toward development of an L2-based second generation HPV vaccine will be presented.

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P2. HPV Vaccination in HIV-Infected Men and Women

Joel Palefsky
University of California, San Francisco, San Francisco, CA

HIV-infected men and women are at increased risk of anogenital and oral HPV infection and HPV-associated cancers at these anatomic sites. Vaccination of HIV-infected men and women has the potential to reduce the risk of these cancers if the vaccine is administered prior to initial exposure to the HPV types in the vaccine. HIV-infected men and women may benefit from vaccination but several issues need to be considered, including safety, immunogenicity and efficacy to prevent disease. The target population for HPV vaccination is 11-12 years, but it is recommended for routine use as early as 9 years and up to age 26 years. Many HIV-infected men and women are older than 26 years.

Safety has now been evaluated in several HIV-infected cohorts in the U.S., including children (IMPAACT P1047), adult women over the age of 26 years (ACTG 5240) and adult men who have sex with men over the age of 26 years (AMC 052). Safety has also been evaluated in adult HIV-infected Indian women in Tamil Nadu (AMC 054). The safety profile of the vaccine appears to be similar to that reported in HIV-uninfected populations, and there do not appear to be any HIV-specific adverse events, such as vaccine-associated increase in HIV viral load or reduction in CD4+ level.

Another key consideration is the immunogenicity of the vaccine in HIV-infected men and women. Results differ from population to population but overall the percentage who seroconvert after vaccination is very high. Titers to individual HPV types have been lower for some HPV types than seen in healthy young men and women, but most have been well above what are likely to be protective levels. The impact of having lower peak titers on duration of protection is not yet known.

Few studies have evaluated efficacy of HPV vaccination in HIV-infected men and women to prevent HPV-related cancer. Many HIV-infected men and women will have had prior exposure to vaccine HPV types when they present for possible vaccination, and thus would be expected to have limited efficacy. Surprisingly, however, more than half of HIV-infected MSM, with a mean age of 44 years, were "naïve" to HPV 6, 11, 16 or 18 as defined by being DNA-negative n the anal canal and sero-negative to these types. Since it is possible, if not probable, that many of these sero-negative individuals were previously sero-positive and sero-reverted over time, it remains unclear as to whether HPV vaccination offers clinical benefit to these individuals.

Taken together, HPV vaccination should be a high priority for HIV-infected men and women age 26 or younger, and should ideally be administered prior to the onset of sexual activity. HPV vaccination is safe and immunogenic in HIV-infected individuals. Given the high proportion of "naïve" individuals over 40 years of age and the lower titers seen in HIV-infected males and females, future studies should examine the duration and kinetics of vaccine-induced antibody responses in HIV-infected men and women.

P3. Potential Role of Graft-Versus-Host Reaction in Reducing the HIV-1 Reservoir

Timothy J. Henrich and Daniel R. Kuritzkes
Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Long-term remission of HIV-1 infection has been reported in a patient who underwent myeloablative allogeneic hematopoietic stem cell transplant (HSCT) for acute myeloid leukemia using cells from a donor homozygous for the Δ32 mutation in CCR5. The lack of functional CCR5 on donor stem cells likely played an important role in achieving virologic control in this patient, but other factors including graft-versus-host reaction, may have contributed to reduction in the viral reservoir and long-term HIV-1 control. We examined the effect of allogeneic HSCT with CCR5+ donor cells following a reduced-intensity conditioning regimen on the peripheral blood viral reservoir in two HIV-1 infected patients with lymphoma, and studied the protective effects of antiretroviral therapy (ART) on donor cells. HIV-1 DNA was readily detected in PBMC before and 2-3 months after HSCT but subsequently became undetectable (a >3-4 $\log_{10}$ reduction of HIV DNA copies/10^6 peripheral blood mononuclear cells); HIV-1 was also undetectable by a sensitive viral outgrowth assay. The loss of detectable HIV-1 correlated temporally with full donor chimerism and development of graft-versus-host disease (GVHD) that required treatment with immunosuppressive therapy, and was sustained for up to 4.5 years while the patients remained on ART. The loss of detectable HIV-1 DNA after full donor chimerism strongly suggests that latently infected host cells were replaced by donor cells that were protected from HIV-1 infection by ART. Graft-versus-host reaction may have played a significant role in reducing the viral reservoir by clearing infected host cells. Preliminary results of an analytical treatment interruption (ATI) showed no rebound in plasma viremia after 8 and 16 weeks, respectively. Longer follow-up during ATI is needed to assess the extent of viral reservoir reduction.

P4. Harnessing Cancer Registry and HIV Databases in Low and Middle Income Countries

Diego Serraino
Unit of Epidemiology and Biostatistics, IRCCS Centro di Riferimento Oncologico, Aviano, Italy

Worldwide, low or middle income countries (i.e., countries other than Western and Central Europe, North America and Oceania), particularly sub-Saharan Africa, account for more than 90% of adults and children living with HIV infection and AIDS, 95% of yearly new HIV infections and 98% of deaths due to HIV/AIDS. In contrast with the geographic distribution of HIV/AIDS, our knowledge on the impact of HIV infection on cancer stems in the largest part from investigations conducted in high income countries; only 5% of all the studies on HIV-associated cancers have been carried out in sub-Saharan Africa, and very few in other low/middle income countries. Moreover, population-based studies on HIV and cancer in these countries are rare, because of the paucity of cancer registries – 1% of the African and 4% of the Asian populations are covered by cancer registries, in contrast to 33% of European, 73% of Oceania and 80% of the North American populations. HIV and AIDS registries are also poorly implemented, making record linkage studies of HIV and cancer databases difficult to implement in low/middle income countries.

In high income countries, a large number of population-based studies that linked cancer registries and HIV/AIDS registries or databases have strongly contributed to delineate the patterns of AIDS-associated cancers (ADCs) and of non-AIDS-defining-cancers (NADCs). While the impact of HIV on ADCs in Africa and in other low/middle income countries is similar, though less strong, than in the West, sparse data have precluded a thorough comparison of NADCs. Patterns of NADCs seem, however, to differ from those observed in the West (e.g., the dramatic increase of squamous cell carcinoma of the conjunctiva in Africa that has no counterpart in the West, and that has been recognized as caused by HIV by the IARC in 2009). It is known that behavioral and environmental factors account for a large part of NADCs in high income countries, whereas infections have a key role in NADCs in low/middle income ones – thus the impact of HIV on cancers in these areas is likely to be different.

This presentation aims to delineate the potential importance of linking cancer and HIVAIDS registries in low/middle income countries to improve our understanding of the relationship between immunosuppression (HIV-induced) and cancer. Accordingly, a briefly highlight of the enormous contribution of record linkage studies of cancer and HIV registries to our knowledge of HIV-related cancers will introduce the description of the current status of population-based cancer registration and of HIV/AIDS monitoring in low/middle income countries. Discussed topics include the need of better data—from a developing country perspective, sub-Saharan Africa and India in first place—to depict the burden, trend and future direction of HIV associated cancers ad their implications for access to treatment; the quality of information captured, the level at which such information is captured, and problems in transmission of data on HIV positive people. The relationship with specialized research cancer centers in the West, where etiological studies can be carried on at molecular level, will also be discussed.

P5. HIV and Cancer Survival in Uganda

Anna E. Coghill
National Cancer Institute, National Institutes of Health, Bethesda, MD

HIV infection is associated with cancer risk. This relationship has resulted in a growing cancer burden, especially in resource-limited countries where HIV is highly prevalent. Little is known, however, about how HIV affects cancer survival in these settings. We therefore investigated the role of HIV in cancer survival in Uganda. Eligible cancer patients were residents of Kyadondo County, ≥18 years of age at cancer diagnosis, and diagnosed between 2003 and 2010 with one of the following: breast cancer, cervical cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, or esophageal cancer. The risk of death during the year after cancer diagnosis was compared between cancer patients with and without evidence of HIV infection using Cox proportional hazards regression.

HIV-infected cancer patients in Uganda experienced a more than two-fold increased risk of death during the year following cancer diagnosis compared to HIV-uninfected cancer patients (HR=2.28; 95% CI 1.61-3.23). This association between HIV and one-year cancer survival was observed for both cancers with (HR=1.54; 95% CI 1.04-2.34) and without (HR=2.68; 95% CI 1.20-5.99) an infectious etiology. HIV-infected cases diagnosed prior to widespread ART availability in Uganda experienced the poorest one-year cancer survival compared to HIV-uninfected patients. These findings extend the established relationship between HIV and excess cancer risk to include a role for HIV in cancer outcomes for both cancers with and without an infectious etiology in a resource-limited, HIV-endemic setting.

P6. Hepatitis C and Hepatocellular Carcinoma: New Model Systems and Insights Into Pathogenesis

Stanley M. Lemon
The University of North Carolina at Chapel Hill, Chapel Hill, NC

Persistent infection with hepatitis C virus (HCV) is now the leading cause of hepatocellular carcinoma (HCC) in the United States and many other developed nations. It is also responsible for increased rates of liver cancer in persons living with HIV/AIDS. HCV is a plus-strand RNA virus with no potential for integration of its genetic material into the host genome. The mechanism(s) by which it promotes liver cancer are controversial and likely differ from other models of viral carcinogenesis. Liver cancer typically develops after decades of persistent HCV infection. Chronic inflammation resulting from immune responses against infected hepatocytes is associated with apoptosis, enhanced hepatocellular proliferation, progressive fibrosis and cirrhosis. Cirrhosis is an important risk factor for HCC independent of HCV infection, and a majority of HCV-associated HCC arises in the setting of cirrhosis. However, a significant minority arises in the absence of cirrhosis, indicating that cirrhosis is not an absolute prerequisite for cancer. Several lines of evidence suggest that direct, HCV-specific mechanisms are also involved in hepatocellular carcinogenesis in addition to the indirect effects of inflammation and fibrosis. There is growing evidence from in vitro studies that HCV disrupts both retinoblastoma protein and p53 functions and thus shares attributes in common with many DNA tumor viruses. Consistent with this, transgenic mice expressing the HCV polyprotein under the control of the albumin promoter develop liver cancer in the absence of inflammation or immune recognition of the transgene. However, current understanding of the mechanisms by which HCV promotes hepatic carcinogenesis is limited by the lack of permissive small animal models in which the impact of viral proteins expressed in the context of infection can be studied directly. Chimpanzees are the only animal species other than humans that are naturally susceptible to infection with the virus. Novel humanized mice expressing receptor proteins essential for HCV infection, or immunodeficient mice with chimeric livers containing human hepatocytes do support the complete viral lifecycle. Cancer has yet to be observed in such models, however, possibly because of the absence of an immune response to HCV, a limited extent of viral replication, and/or insufficient time. AFC8 (DKO)-hu mice engrafted with CD34+ fetal hematopoietic stem cells and EpCAM+ hepatoblasts represent an alternative model with perhaps greater potential for the development of cancer. These animals achieve up to 18% liver chimerism, are permissive for HCV replication, induce a human HCV-specific T cell response, and develop hepatic fibrosis when infected with HCV.

P7. Natural Courses and Management of Chronic Viral Hepatitis B or C in HIV-Infected Patients

Pei-Jer Chen
National Taiwan University Hospital, Taiwan

HIV-infected patients frequent suffer from opportunistic infections and related deaths. Since the introduction of HAART, HIV replication is effectively controlled and the host immunity maintained, the causes of death among HIV patients receiving HAART changes. Liver-related death now accounts for the second important one. Most of the liver-related deaths are attributed to chronic hepatitis B or C virus coinfections. Worldwide, HCV infection frequency varied from 8-50% in HIV patients, and HBV co-infection ranges from 5-26%, depending on their geographic areas. As a consequence of common transmission routes, a significant proportion of HIV patients carried more than one hepatitis viruses (HBV and HCV, or even HBV, HCV and HCV coinfection). Those patients developed hepatitis episodes more frequently, and more likely to become cirrhosis and hepatic failure.

In the last decade, both anti-HBV and anti-HCV regimens become available and they have been incorporated into HAART to treat co-infected HIV patients. For those with HBV co-infection, the standard HAART is combined with Tenofovir (preferred) or Lamivudine. Long-term treatment effectively suppresses HBV replication and it also prevents HBV spreading. For HIV-patients with HCV co-infection and with adequate immune capacity, current therapy will combine pegylated interferon and ribavirin. Such regimen can cure HCV from the patients, up to 50%. Recently, small molecules targeting to HCV protease or RNA polymerase have been developed and their supreme efficacy confirmed in large clinical trials for single hepatitis C patients. These direct antiviral agents (DAA) can be applied to all HIV patients with HCV co-infection. Clinical trials are ongoing and results are highly expected.

In conclusion, the chronic viral hepatitis B or C co-infections in HIV patients can be effectively controlled or even eradicated by current or new regimens. We can envision a reduction of liver-related deaths in the near future.

P8. Immune Activation and Inflammation Biomarkers and Risk for AIDS-NHL

Otoniel Martínez-Maza
University of California, Los Angeles, Los Angeles, CA

HIV infection is associated with a marked increase in risk for non-Hodgkin lymphoma (NHL). However, the mechanisms that promote the development and growth of AIDS-related NHL (AIDS-NHL) are not fully understood. In work done in two prospective cohort studies of HIV/AIDS, the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS), we have measured serum levels of cytokines and other molecules associated with immune dysfunction in specimens collected during the years preceding AIDS-NHL diagnosis [1,2]. In multivariate analyses, it was seen that serum levels of several cytokines (IL6, IL10, TNFα, CXCL13, IP-10/CXCL10), soluble receptors (sCD27, sCD30, sCD23), immunoglobulin free light chains (FLC), C' reactive protein (CRP), and neopterin, were associated with an increase in risk for AIDS-NHL. Detectable IL4 was seen less frequently in those who developed AIDS-NHL. Additionally, distinct patterns of micro-RNA (miRNA) expression [3], as well as elevated expression of activation-induced cytidine deaminase (AICDA) [4] and of phenotypically aberrant B cells (CD10+, CD71+, CD86+ B cells) [5], were seen in peripheral blood mononuclear cells collected preceding AIDS-NHL diagnosis. It was seen that levels of some, but not all (IL6, CRP), of these biomarkers decreased after 1-2 years on combined multi-agent antiretroviral treatment (cART), in a study of those initiating cART in the MACS, but that post-cART levels of most biomarkers remained higher than seen in HIV-negative persons [6]. Interestingly, similar results were seen in NHL not associated with HIV infection, in studies done in the Women's Health Initiative (WHI) and in other cohorts. In the studies done in the WHI, women with pre-diagnosis serum biomarker levels in the highest vs lowest quartiles for CXCL13, sCD23, sCD27, or sCD30 were at increased risk for B cell NHL [7]. In work done in the AIDS Malignancies Consortium (AMC), the pre-treatment level of one of these molecules (CXCL13) was seen to be associated with response to therapy and overall survival in treated AIDS-NHL. Based on these results, it appears that immune activation, driven by T cells and/or monocytes/macrophages, occurs for a prolonged period of time preceding NHL diagnosis in HIV-positive, and perhaps HIV-negative, individuals, potentially contributing to the development and/or growth of these malignancies. Additionally cART may not lead to a reversion of many of these biomarkers to the levels seen in HIV-negative persons.

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P9. Chronic Inflammation and Lung Cancer

Anil K. Chaturvedi
National Cancer Institute, National Institutes of Health, Bethesda, MD

Lung cancer is the most common cause of cancer-related mortality in the U.S. general population. Tobacco smoking is the predominant risk factor for lung cancer, accounting for approximately 90% of all lung cancers. Additionally, chronic pulmonary inflammation is increasingly recognized as an important co-factor in lung carcinogenesis. Studies show that several indicators of inflammation, including chronic pulmonary infections (*Mycobacterium tuberculosis* and *Chlamydia pneumonia*e), pulmonary inflammatory conditions (asthma and chronic obstructive pulmonary disease), and polymorphisms in key inflammation genes (NFkappa B) are associated with increased risk of lung cancer. More recently, prospective epidemiologic studies have shown that circulating levels of several classes of inflammation markers, including acute-phase proteins (CRP and SAA), pro-and anti-inflammatory cytokines (IL-6, IL-8, sTNFRII and IL-1RA), chemokines (CXCL5/ENA78, CXCL13/BCA-1, CCL17/TARC, and CCL22/MDC), and growth and angiogenesis factors (TGF-A and CXCL9/MIG) are associated with a 2-3 fold increased risk of lung cancer, even after carefully accounting for the confounding effects of cigarette smoking. These epidemiologic studies, coupled with molecular and experimental studies, underscore an etiologic role for chronic inflammation in lung carcinogenesis.

Chronic inflammation could be particularly relevant in lung carcinogenesis among HIV-infected individuals, a group with a 2-4 fold higher incidence of lung cancer when compared to the general population. Several studies show that this elevated lung cancer incidence among HIV-infected individuals is not entirely explained by patterns of cigarette smoking. Consequently, HIV-related changes in pulmonary immunity, repeated pulmonary infections, HIV-related systemic inflammation and immune activation, and accelerated pulmonary damage from tobacco smoke have all been suggested as risk factors for increased lung cancer risk among HIV-infected individuals.

Oral Presentations

O1. HIV-Induced Epithelial-Mesenchymal Transition in Oral Mucosal Epithelial Cells Facilitates HPV Infection

Sharof M. Tugizov[1,2], Rossana Herrera[1], Piri Veluppillai[2], Deborah Greenspan[2], Joel M. Palefsky[1,2]

[1]Department of Medicine and [2]Department of Orofacial Sciences, University of California, San Francisco, San Francisco, CA

Background: The incidence of human papillomavirus (HPV)-associated malignant and non-malignant epithelial lesions in human immunodeficiency virus (HIV)-infected individuals is substantially higher than in HIV-uninfected individuals. HIV may increase the risk of mucosal HPV infection and progression of HPV-associated malignancy by induction of an epithelial-mesenchymal transition (EMT), which is a multistep epigenetic process characterized by loss of cell adhesion and increased proliferation and mobility of epithelial cells. EMT is important in cell differentiation during embryogenesis; however, it is also plays a critical role in the progression of epithelial neoplastic processes, including HPV-associated malignancies.

Materials and Methods: To model the effect of EMT on HPV infection, we used oral epithelial biopsies and oral keratinocytes from HIV-infected and HIV-uninfected individuals. EMT was defined as loss of adherens and tight junctions and induction of vimentin and transforming growth factor beta (TGF-β) expression. To study epithelial HPV entry we used HPV-16 pseudovirions (PsVs) containing a plasmid expressing red fluorescent protein (RFP). PsV penetration was evaluated using confocal microscopy to detect RFP fluorescence.

Results: Our data show that oral epithelial biopsies from HIV-infected individuals and oral keratinocytes from HIV-infected individuals that are grown in culture have multiple changes consistent with an EMT phenotype. In these epithelia the adherens and tight junctions were disrupted, vimentin expression was upregulated, and TGF-β, a key inducer of EMT, was overexpressed. Mitogen-activated protein kinase (MAPK) and epidermal growth factor receptor (EGFR), important players in the induction and maintenance of the EMT phenotype, were also activated. In contrast, normal keratinocytes from HIV-uninfected individuals did not have an EMT phenotype and, therefore, did not express TGF-β1 and vimentin and did not activate MAPK and EGFR. Exposure of TGF-β1-negative oral epithelial cells from HIç–uninfected individuals to HIV and HIV tat, gp120, and nef proteins led to induction of TGF-β1 expression and an EMT phenotype. In these cells cell junctions were disrupted and cell polarity was lost. HIV-associated EMT in oral keratinocytes led to infection of these cells by HPV-16 PsVs. In contrast, normal keratinocytes from HIV-negative individuals without the EMT phenotype were not infected by HPV-16 PsVs.

Conclusions: HIV-associated EMT in oral epithelia may facilitate HPV infection of oral keratinocytes and, therefore, may contribute to the increased incidence of HPV-associated malignancy in HIV-infected individuals.

O2. HIV-Related Immunosuppression Is Associated With Higher Incidence of Oral HPV, But Not Oral HPV Clearance

Daniel C. Beachler[1], Elizabeth A. Sugar[1], Joseph B. Margolick[1], Kathleen M. Weber[2], Howard D. Strickler[3], Dorothy J. Wiley[4], Ross D. Cranston[5], Robert D. Burk[3], Howard Minkoff[6], Susheel Reddy[2], Maura L. Gillison[7], Gypsyamber D'Souza[1]

[1]Johns Hopkins University, Baltimore, MD; [2]Cook County Health and Hospital Systems, Chicago, IL; [3]Albert Einstein, NY; [4]University of California, Los Angeles, Los Angeles, CA; [5]University of Pittsburgh, Pittsburgh, PA; [6]Maimonides Medical Center, Brooklyn, New York; [7]Ohio State University, Columbus, OH

Background: Oral HPV now causes the majority of oropharyngeal cancer in the United States, and is more prevalent in HIV-infected (HIV+) than HIV-uninfected (HIV-) individuals. The role of immunosuppression on the incidence and clearance of oral HPV is not well understood.

Materials and Methods: Semi-annual oral rinses were collected from HIV+ (328 men/433 women) and HIV- (222 men/247 women) participants in the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study for three years. Newly detected oral HPV type-specific infections were considered incident. An infection was considered cleared at first negative visit. Samples were tested for 37 HPV genotypes using the linear array and line blot hybridization, and risk factors were explored using Wei-Lin-Weissfeld modeling.

Results: Clearance of incident and prevalent oral HPV was common (12 month clearance: incident=83%, prevalent=51%), and similar between HIV+ and HIV- individuals (p=0.64). Clearance was lower among older individuals, current smokers, in MACS men compared to WIHS women (each p<0.05), but not in those with a reduced CD4 T cell count (p-trend=0.94, Table 1). 28% of participants had at least one incident oral HPV infection within 24 months, and the incidence was higher in HIV+ than HIV- (aHR=2.3, 95%CI=1.7-3.2), and in those with CD4<200 (aHR=6.0, 95%CI=2.7-13.3, Table 1), but not in those with a reduced nadir CD4 or higher RNA viral load after adjustment (p-trends>0.20). In HIV- individuals, oral HPV incidence was associated with performing oral sex on a higher number of recent partners, while in HIV+ individuals incidence was associated with performing oral sex on a higher number of lifetime partners (p-trends<0.01). In the 19% of participants reporting complete sexual abstinence throughout the study, oral HPV incidence was associated with HIV-infection, reduced CD4 T cell count, and a higher number of lifetime oral sex partners (all p<0.01). Results were similar when restricted to HPV16 or oncogenic types.

Table 1. HIV and Current CD4's Relationship to Oral HPV Prevalence, Incidence, and Clearance

	Adjusted OR (95%CI)	**Adjusted HR (95%CI)**	
	Baseline Prevalence	**Incidence**	**Clearance**
HIV-status + Current CD4			
HIV-negative	REF	REF	REF
Positive CD4>500 cells/μL	1.9 (1.4-2.6)	1.7 (1.3-2.3)	0.90 (0.75-1.1)
Positive CD4 200-499 cells/μL	2.6 (1.9-3.6)	2.4 (1.7-3.2)	0.87 (0.72-1.1)
Positive CD4<200 cells/μL	4.2 (2.8-6.3)	6.0 (2.7-13.3)	1.0 (0.64-1.6)
p-trend	<0.001	<0.001	0.94

Conclusions: The incidence of oral HPV was high, particularly in immunosuppressed HIV+ adults. However, the majority of prevalent and incident oral HPV infections cleared quickly regardless of immune status. Thus, the higher prevalence of oral HPV in HIV+ than HIV- individuals may be explained by a higher rate of acquisition or re-activation of oral HPV instead of differential clearance. The similar clearance of oral HPV in HIV+ and HIV- participants may also explain why a large increase in oropharyngeal cancer incidence has not been observed in HIV+ individuals.

O3. HIV Tat Increases HPV16 Infectivity Independant of Oral Keratinocyte Terminal Differentiation

William T. Seaman[1], Thatsanee Saladyant[1], Victoria Madden[2], Jennifer Webster-Cyriaque[1,3,4]

[1]Department of Dental Ecology, [2]Department of Pathology and Laboratory Medicine, [3]Department of Microbiology and Immunology, [4]School of Dentistry, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: HPV-associated oral malignacies and lesions have persisted and increased during the antiretroviral therapy era. These increases may not be solely attributed to immunodysfunction suggesting that HIV and/or other cellular factors may contribute to HPV-associated oral pathologies. Secreted HIV tat is readily taken up by HIV-uninfected cells and has been detected in saliva. These characteristics make tat a potential candidate for interactions in HPV-infected oral keratinocytes. We hypothesized that HIV tat promoted HPV pathogenesis in oral epithelial cells.

Methodology/Principal Findings: We describe a novel in vitro oral epithelial cell system utilizing the partially differentiated cell line, OKF6tert1, for the introduction of HPV 16 episomes obtained from clincal isolates by Cre-lox recombination. OKF6tert1 cells were permissive for HPV replication and displayed cellular consequences consistent with HPV infection including phospho-chk2, γ-H2AX and p53 modulation of DNA damage responses, E2 transactivation of the HPV LCR and E5 activation of a MAPK pathway. DNase resistant particles were detected by qPCR and visualized by transmission electron microscopy. While early (E6/E7) and late transcripts (E1^E4 and L1) were detected by RT qPCR, spliced L1 was only detected upon further OFK6tert1 differentiation. Detection of keratin 1 transcripts and involucrin crosslinking confirmed terminal differentiation. In the presence of HIV tat, differentiation was no longer required to generate spliced L1 message. Subsequent virions were significantly more infectious in de novo infection than those generated from partially differentiated cells not expressing HIV tat, as determined by HPV E7 IFA. While tat-associated transactivation and DNA damage were not critical to this process, tat facilitated post transcriptional maintenance of L1 mRNA levels. Deletion analysis determined that L1 nucleotides 5561 to 6820 were important to this process.

Conclusion/Significance: A novel monolayer system using immortalized oral cells supported permissive infection by HPV 16 clinical isolates. In this system, we demonstrated direct interaction between HIV tat and oral HPV, resulting in a more potent HPV infection. The HPV life cycle is tied to epithelial differentiation, however, in the presence of HIV tat, terminal differentiation was no longer required. In conclusion, the high rate of HPV-associated oral disease in the context of HIV may not only be tied to immune suppression, but to HIV-HPV interactions.

O4. Variation in Viral Gene Expression Distinguishes Two Subtypes of Kaposi Sarcoma

Dirk P. Dittmer, Kristen Tamburro, Mina Hosseinipour, Jie Xiong, Dan Namarika, Michael Nyirenda, Albert Mwafongo, Loreen Chiwoko, Deborah Kamwendo, Irving Hoffman, Sam Phiri

Department of Microbiology and Immunology, Department of Medicine, Lineberger Comprehensive Cancer Center, and Center for AIDS Research (CfAR) at The University of North Carolina at Chapel Hill, and UNC Project, Kamuzu Central Hospital, Lilongwe, Malawi

Kaposi Sarcoma (KS), caused by KS-associated herpesvirus (KSHV), is common among HIV-infected patients in the United States and globally. We conducted a comparative analysis of multiple patient populations, which develop KS today: (i) patients who developed KS because of ART failure; (ii) patients who developed KS despite successful long-term ART and complete HIV-suppression; and (iii) patients who developed KS as the AIDS presenting condition at the Lighthouse HIV clinic in Lilongwe Malawi with no history of chemo- or antiretroviral therapy (ART). Whole KSHV genome profiling clustered the patients into two groups: one with extremely restricted viral gene expression and one with evidence of substantial lytic gene transcription including the two viral kinases, which confer susceptibility to anti-retroviral drugs. Other biomarkers support this classification. This reinforces the idea of using anti-herpesvirus drugs as adjuvant to KS suppressive chemo or ART therapy. At the same time these data suggest that only a subset of patients will benefit and that gancilovir, cidofovir or AZT use should be coupled with kinase gene expression profiling.

This work was supported by funding from the National Cancer Institute to the AIDS Malignancy Consortium (CA121947) and the National Institute of Dental and Craniofacial Research (DE018304).

O5. Characterization of HHV-8 Gene Expression in Kaposi Sarcoma Tumors and Correlation With Clinical Presentation and Outcomes

Warren Phipps[1,6], Jackson Orem[9,10], Lilian Akello[9], Alex Bakenga[9], George Holoya[9], Siraji Obayo[9], Meei-Li Huang[2], Martin McIntosh[7], Timothy Rose[5,8], Gregory Bruce [8], Anna Wald[1,2,3,6], Larry Corey[1,2,6], Corey Casper[1,3,4,6]

Departments of [1]Medicine, [2]Laboratory Medicine, [3]Epidemiology and [4]Global Health, and [5]Pediatrics, University of Washington, Seattle, WA; [6]Vaccine and Infectious Disease Division, and [7]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA; [8]Seattle Children's Research Institute, Seattle, WA; [9]Uganda Cancer Institute, Kampala, Uganda; [10]Makerere University, College of Health Sciences, Kampala, Uganda

Background: In vitro work suggests that human herpesvirus-8 (HHV-8) produces several angiogenic and inflammatory gene products that contribute to KS development, but data on the expression of HHV-8 genes in vivo remain limited. We sought to comprehensively characterize HHV-8 gene expression in KS tumors of Ugandan adults and to correlate the expression of HHV-8 gene products with KS clinical presentation and outcomes.

Methods: KS biopsy specimens were obtained from treatment-naïve HIV-infected adults with histologically confirmed KS initiating therapy at the Uganda Cancer Institute. KS tumor biopsies were flash-frozen and stored in liquid nitrogen; HHV-8 mRNA gene transcripts were quantified in biopsy specimens using RNA-Seq.

Results: 34 participants contributed 46 KS biopsies. 7 (21%) participants were women, and the mean age was 32 years (range 18-56 years). The median baseline CD4 T-cell count was 191 cells/mm^3 (IQR 49, 237 cells/mm^3), and the median baseline plasma HIV-1 RNA level was 5.4 log10 copies/mL (IQR 4.9, 5.8 log10 copies/mL). The KS biopsies represented a range of tumor morphotypes, including 27 (58%) macular, 15 (33%) nodular, and 4 (9%) fungating lesions. All participants received treatment with ART and chemotherapy; 23 (68%) achieved a partial response, and 11 (32%) had progressive disease or died within the first 4 months of therapy. Based on the preliminary analyses completed to date, all biopsies had HHV-8 mRNA gene transcripts detected. Highly expressed transcripts in all samples included the known latent gene products T0.7/K12 (Kaposin), ORF71 (vFLIP), and ORF72 (vCYC), and the lytic gene products T1.1/Pan/K7 (vIAP), K4 (vCCL-2), K2 (vIL-6) and K8 (bZIP). Other highly expressed genes included the tegument-associated proteins, ORF11, ORF45, and ORF75. Minimal expression of herpesvirus core genes, with the exception of ORF57, was noted in all samples. Additional RNA-Seq data will be presented for the entire set of biopsies to further describe HHV-8 gene expression in KS tumors, and to evaluate the association between the expression of specific HHV-8 gene transcripts and KS morphotype, CD4 count, plasma HIV-1 RNA level, and KS response to treatment.

Conclusions: In this unique cohort of KS patients, KS tumors expressed high levels of both latent and lytic HHV-8 mRNA gene products, some of which may have important and unrecognized functions in the maintenance of viral infection or tumorigenesis. Further analysis will more fully characterize in vivo HHV-8 gene expression in KS tissue, and may provide insight into KS pathophysiology, clinical presentation, and treatment response.

O6. Prevalent High-Risk HPV Infection and Vaginal Microbiota in Nigerian Women

Eileen Dareng[1], Bing Ma[2,3], Ayo Famooto[1], Maryam Almujtaba[1], Sally Akarolo-Anthony[1,4], Ishak Lawal[5], Richard Offiong[5], Olayinka Olaniyan[6], Patrick Dakum[1], Cosette M. Wheeler[7], Doug Fadrosh[2], Honqiu Yang[2], Pawel Gajer[2,3], Rebecca M. Brotman[2,8], Jacques Ravel[2,3], Clement A. Adebamowo[1,4,8,9]

[1]Institute of Human Virology, Abuja, Nigeria; [2]Institute of Genome Sciences, [3]Department of Microbiology and Immunology, [8]Department of Epidemiology and Public Health, [9]Institute of Human Virology and Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD; [4]Department of Nutrition, Harvard School of Public Health, Boston, MA; [5]University of Abuja Teaching Hospital, Gwagwalada, Nigeria; [6]National Hospital, Abuja, Nigeria; [7]Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque, NM

Introduction: The microbiota is thought to play an important role in preventing colonization of the vagina by pathogenic organisms. Given the role of persistent high risk HPV (hrHPV) infection of the cervix as a necessary cause of cervical cancer, we hypothesized that in addition to already known risk factors, the bacterial species composition and abundance of the vaginal microbiota may represent cofactors in the etiology of hrHPV infection and cervical cancer.

Materials and Methods: 278 (151 HIV+ and 127 HIV-) women were enrolled between April 2012 and August 2012 in Nigeria. Questionnaires were used to collect demographics and information on risk factors of cervical cancer. Medical personnel collected mid-vaginal and exfoliated cervical cells samples from all participants. Vaginal bacterial composition and abundance (community state type, CST) were characterized by deep sequencing of barcoded 16S rRNA gene fragments (V4) on Illumina MiSeq platform and prevalent HPV was identified using the Roche Linear Array HPV Genotyping Test®. Multiple logistic regression was used to evaluate the association between CST of vaginal microbiota and HIV, as well as hrHPV; weighted UniFrac distances to compare the vaginal microbiota of individuals, and LDA (Linear Discriminant Analysis) effect size (LEfSe) algorithm to characterize the abundant phylotypes associated with prevalent hrHPV infection.

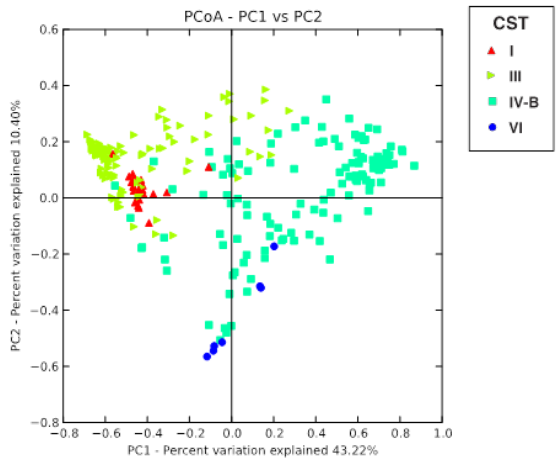


Figure 1. Weighted UniFrac principal coordinates analysis (PCoA) plot to compare sample distribution belonging to different CSTs.

Results: The prevalence of hrHPV infection was higher among HIV+ compared to HIV- women ($p<0.001$). Four CSTs were identified- CST IVB (lacking significant numbers of Lactobacillus) was the most prevalent and was found in 139 (50%) participants; followed by CST III (often dominated by *L. iners*) found in 109 (39.2%); CST I (often dominated by *L. crispatus*) in 22 (7.9%) and CST VI (dominated by members of the phylum Proteobacteria) in 8 (2.9%). A UniFrac analysis showed that all CSTs have distinct properties in terms of sample distance and distribution (see Figure 1). Using CST1 as the reference category, CST VI was significantly associated with HIV infection (OR 10.11, 95% CI 1.05 – 97.0, p=0.05). Overall, there was no significant association between CST and hrHPV, but subgroup analysis revealed an association between CST IVB and hrHPV in HIV- participants (multivariate OR=5.63,95% CI1.19 – 26.7,p=0.03). LefSe analysis on HIV- women revealed a strong association between hrHPV and the abundance of various vaginal bacterial taxa, particularly members of the family *Leptotrichiaceae* and *Prevotellaceae*, but also *Clostridiaceae* and *Peptostreptococcaceae.*

Conclusion: Our results suggest that the presence of a community dominated by members of the phylum Proteobacteria is associated with HIV infection; and among HIV- women, a low relative abundance of Lactobacillus is associated with prevalent hrHPV. Further research is needed to explore these relationships.

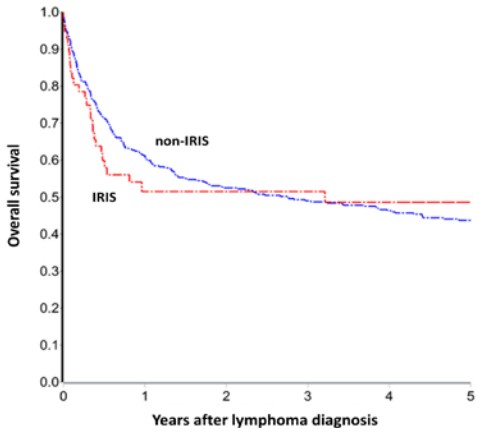
O7. Unmasking Lymphoma Immune Reconstitution Inflammatory Syndrome Among HIV-Infected Individuals in the Center for AIDS Research Network of Integrated Clinical Systems Cohort

Satish Gopal[1], Monita Patel[1], Chad Achenbach[2], Elizabeth Yanik[3], Greer Burkholder[4], Erin Reid[5], Benigno Rodriguez[6], Steven Deeks[7], Kenneth Mayer[8], Richard Moore[9], Mari Kitahata[10], Joseph Eron[1], Kristy Richards[1]

[1]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Northwestern University, Chicago, IL; [3]National Cancer Institute, National Institutes of Health, Bethesda, MD; [4]University of Alabama at Birmingham, Birmingham, AL; [5]University of California, San Diego, La Jolla, CA; [6]Case Western Reserve University, Cleveland, OH; [7]University of California, San Francisco, San Francisco, CA; [8]Fenway Health, Boston, MA; [9]Johns Hopkins University, Baltimore, MD; [10]University of Washington, Seattle, WA

Background: Cohort studies have demonstrated increased incidence of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) among HIV-infected individuals during the first 6 months after antiretroviral therapy (ART) initiation, perhaps due to unmasking immune reconstitution inflammatory syndrome (IRIS). Clinical characteristics and survival for unmasking lymphoma IRIS have not been described.

Methods: We studied lymphoma patients in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) from 1996 until 2011. Unmasking lymphoma IRIS was defined as HL or NHL occurring within 6 months after ART initiation accompanied by a ≥0.5 $\log_{10}$copies/mL reduction in HIV RNA between values taken prior to ART and at lymphoma diagnosis. Differences in presentation and survival were examined between lymphoma IRIS and non-IRIS cases.



IRIS=immune reconstitution inflammatory syndrome.

Figure 1. Overall survival for 482 HIV-infected adults in CNICS with lymphoma between 1996 and 2011, stratified by unmasking IRIS case status.

Results: Of 482 lymphoma patients, 56 (12%) met criteria for unmasking lymphoma IRIS. Of these, 12 (21%) had HL, 22 (39%) diffuse large B-cell lymphoma (DLBCL), 5 (9%) Burkitt lymphoma (BL), 10 (18%) primary central nervous system lymphoma (PCNSL), and 7 (13%) other NHL (Table 1). Median CD4 cell count at lymphoma diagnosis among IRIS cases was 173 cells/μL (IQR 73-302), and 48% had suppressed HIV RNA (<400 copies/mL). IRIS cases were overall similar to non-IRIS in histologic distribution and clinical characteristics, with the exception of more frequent hepatitis B/C co-infection (30% versus 19%, p=0.05), as well as lower HIV RNA at lymphoma diagnosis likely resulting from the IRIS case definition. Additionally, overall survival at five years was similar for IRIS (49%, 95% CI 37-64%) and non-IRIS (44%, 95% CI 39-50%), although increased early mortality was suggested among IRIS cases (Figure 1).

Conclusions: In a large HIV-associated lymphoma cohort in the United States, 12% of patients met a standardized unmasking lymphoma IRIS case definition. Detailed studies of lymphoma IRIS may help identify immunologic mechanisms of lymphoma control.

Acknowledgements
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O8. Kaposi Sarcoma Herpesvirus (KSHV) vFLIP Induces Systemic Endothelial Proliferation and a Proinflammatory Phenotype In Vivo

Gianna Ballon, Gunkut Akar, Ethel Cesarman

Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY

In vitro evidence suggests that vFLIP, a KSHV latent protein expressed in KS spindle cells, has an important role in the biology of KS. It is required for the in vitro spindling of endothelial cells and contributes to their proinflammatory phenotype. To evaluate the role of vFLIP in the pathogenesis of KS, we constructed a new mouse strain that allows for vFLIP expression in endothelial cells in an inducible manner upon administration of tamoxifen. This mice were obtained by crossing ROSA26.vFLIP knock-in mice (PMID: 21339646) with mice that express cre recombinase in an inducible and vascular specific fashion (Cdh5(PAC).creERT2). A cohort of nearly two hundred ROSA26.vFLIP;Cdh5(PAC).creERT2 mice have been generated and they have been followed for tumor development and pathological abnormalities. An abnormal proliferation of endothelial cells was found in several tissue types and organs (skeletal muscle, heart, pancreas, kidney, brown fat, perineuronal sites). These endothelial cells formed cordons of proliferating fusiform cells, reminiscent of the spindle cells found in KS lesions, express vFLIP, and retain the endothelial marker CD34. Thirty mice have also been subjected to submandibular bleeding to collect sera for qualitative and quantitative analyses of cytokines and exosomes. By using a quantitative flow cytometry based assay we found a profound perturbation in serum cytokines, which mimics certain aspects of virus-associated hemophagocytic syndrome (VAHS) (an extremely rare syndrome triggered by KSHV and reported in immunocompromised patients with multicentric Castleman's disease (MCD) and markedly elevated serum human interleukin-6 (IL-6) level) and KSHV inflammatory cytokine syndrome (KICS), a recently described clinical condition characterized by elevated KSHV viral loads, increased levels of viral IL-6 and IL-10 comparable to those seen in KSHV–MCD but lymphadenopathy is not prominent and the pathologic nodal changes of KSHV–MCD are absent. Noteworthy, we could assess the microenvironment of the proliferating, KSHV-expressing endothelial cells, and found an increased myeloid component, which contributes to cell heterogeneity as observed in KS. Ninety percent of the mice died from these abnormalities over a 12-month period of followup (P=0.0001). This mouse strain represents the first in vivo demonstration that vFLIP is capable of inducing endothelial proliferation and allows us to dissect the pathobiology of viral-associated vascular diseases. This model may be used to test therapy strategies targeting important aspects of the host tumor microenvironment.

O9. Human Herpesvirus 8 Infection Induces Polyfunctional B Lymphocytes Producing Cytokines and Chemokines That Drive Kaposi's Sarcoma

Emilee R. Knowlton[1], Giovanna Rappocciolo[1], Lauren M. Lepone[1], Sagar V. Nadgir[1], Arlene Bulotta[2], Stella J. Berendam[1], Jun Li[1], Todd A. Reinhart[1], Frank J. Jenkins[1,2], Charles R. Rinaldo[1,2]

[1]Department of Infectious Diseases and Microbiology, Graduate School of Public Health, [2]Department of Pathology, School of Medicine, University of Pittsburgh, Pittsburgh, PA

Background: An unsolved enigma of Kaposi's sarcoma (KS) is that human herpesvirus 8 (HHV-8) latency and lytic cycle encoded factors, while unique among human oncogenic viruses, are insufficient to cause KS. An emerging hypothesis of how HHV-8 causes KS is that virus-infected endothelial cells largely depend on an abnormal excess of exogenous, host cytokines and chemokines for their outgrowth. B cells are a major target of HHV-8 and could be a source of these immune mediators, yet there is little information on their infection and function in the development of KS.

Materials and Methods: Purified blood B cells and plasma from HHV-8/HIV-1 co-infected subjects with (cases) and without (controls) KS in the Multicenter AIDS Cohort Study (MACS) were directly assessed for HHV-8 lytic infection and production of immune mediators by PCR and flow cytometry. HHV-8 lytic ORF59 PF-8 protein expression and B cell phenotypes were measured by flow cytometry.

Results: HHV-8 lytic infection was evident in B cells of 60% of KS cases compared to 20% of controls. ORF59 PF-8 expression was found in 2.3% of B cells among cases compared to 0.65% of controls. Lytic infection resulted in elevated levels of IL-6, TNF-α, MIP-1α, MIP-1β, IL-8 and vascular endothelial growth factor (VEGF) in B cells of KS cases compared to controls. TNF-α, MIP-1α, VEGF and IL-8 were also enhanced in the serum of KS cases. Furthermore, HHV-8 infected cells among KS cases had a greater quantity and quality of polyfunctional B cells producing 3-to-5 combinations of IL-6, TNF-α, MIP-1α, MIP-1β and IL-8 (44%) than uninfected cells (29%) ($P<0.001$) as shown in Figure 1. The majority (60%) of HHV-8 infected B cells within cases and controls expressed the CD138 plasma cell terminal differentiation marker, while naïve and IgM memory B cells accounted for a smaller proportion. All HHV-8 infected B cell lineage subsets from cases and controls displayed greater polyfunctionality than uninfected B cell subsets.

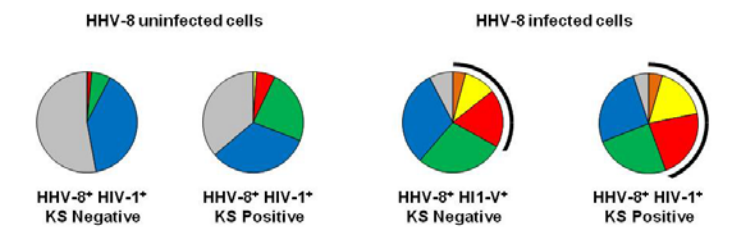

Figure 1: B cell-associated immune mediators are enhanced in KS
CD19⁺ cells were stained for ORF59 PF-8, TNF-α, IL-8, MIP-1α, IL-6 and MIP-1β. Total percentages of B cells expressing immune mediators within the HHV-8 uninfected (ORF59 PF-8^{neg}) and infected (ORF59 PF-8^{pos}) populations are shown (■5 ■4 ■3 ■2 ■1 ■0). Arcs represent combinations of 3-5 immune mediators (data are mean; 7 KS controls and 7 KS cases).

Conclusions: We show for the first time that HHV-8 lytic cycle infection occurs in naïve, IgM memory, and plasma cell populations of B cells of HHV-8/HIV-1 co-infected persons in association with production of polyfunctional immune mediators that could be centrally involved in the induction of KS.

O10. Kaposi Sarcoma-Associated Human Herpesvirus (KSHV) Latency-Associated Nuclear Antigen (LANA) Undergoes Cleavage by Caspases Following Exposure of Cells to Oxidative Stress

David A. Davis, Nicole E. Naiman, Victoria Wang, Robert F. Carey, Katharine S. Davidoff, Duosha Hu, Robert Yarchoan

HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Kaposi's sarcoma associated herpesvirus (KSHV), also known as human herpesevirus-8, is the causative agent of three malignancies: Kaposi sarcoma, primary effusion lymphoma (PEL) and multicentric Castlemen disease. The main latent gene, latency-associated nuclear antigen (LANA), has a variety of functions, including inhibition of p53 activity (with resultant protection against cell death) and tethering of KSHV episomes to host chromosomes. In this study, we demonstrate that LANA is upregulated and undergoes proteolytic processing to lower molecular weight forms following exposure to oxidative stress. Since oxidative stress can induce caspase-mediated apoptosis in many cell types and has also been reported to activate KSHV lytic activation, we explored the effects of oxidative stress on KSHV LANA. PEL cell lines exposed to hydrogen peroxide had an increase in LANA expression but also manifested processing to lower molecular weight forms of LANA as seen by Western blot. The increase in LANA was evident by both western blot and immunofluorescence analysis for LANA in BCBL-1 and BC-3 cells. A pan-caspase inhibitor (Z-VAD-FMK) inhibited cell death induced by H_2O_2 in PEL cells and also inhibited LANA processing as assessed by Western blot, suggesting that oxidative stress was inducing caspase cleavage of LANA. We screened the ability of different caspases to cleave a flag-tagged form of LANA in vitro. Caspases-1 and 3 efficiently cleaved LANA. Inhibitors of caspase-1 or caspase-3/7 inhibited cleavage of LANA in KSHV-infected cells in response to oxidative stress. Amino acid sequence analysis of LANA revealed the presence of several potential caspase cleavage sites. Peptides representing these sites were synthesized and exposed to caspases. Caspase cleavage analysis of peptides spanning certain potential cleavage sites revealed two regions (an N-terminal site and a C-terminal site) susceptible to capase-1 and 3 cleavage. These peptides were also able to inhibit caspase activity in a standard caspase activity assay, presumably through competitive inhibition. To confirm if these two sites were cleaved in full-length LANA we prepared flag-tagged LANA containing mutations at these two cleavage sites. LANA was no longer cleaved at the N-terminal site by caspase-3 and no longer cleaved at the C-terminal site by caspase-1. These data suggest that LANA may act as a caspase decoy during caspase activation in cells undergoing lytic activation following oxidative stress or inflammasome activation. This viral strategy may have evolved as a means for KSHV LANA to interfere with caspase-mediated apoptosis, thus thwarting a key cellular anti-viral mechanism. In addition, caspase cleavage of LANA may mediate a gain or loss of other LANA functions.

Acknowledgements

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O11. Regulation of Kaposi Sarcoma Herpesvirus (KSHV) Encoded Viral Interleukin 6 (vIL-6) by X-Box Binding Protein 1 (XBP-1)

Duosha Hu, Min Yang, Victoria Wang, Thomas Uldrick, Mark Polizzotto, David A. Davis, Ravindra Veeranna, Robert Yarchoan

HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative agent for Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and a subset of multicentric Castleman disease (MCD). KSHV-MCD is characterized by severe inflammatory symptoms caused in part by a KSHV interleukin-6 (vIL-6). vIL-6 is produced during lytic replication of KSHV, and also at a lower level during latent replication. Pathologically, KSHV-MCD is characterized by KSHV-infected plasmacytoid B cells in the marginal zones of affected lymph nodes; vIL-6 is expressed in these cells. B cells express high levels of spliced X-box-binding protein (XBP-1s) during differentiation in lymph nodes to plasma cells. XBP-1 is a transcription factor that mediates the unfolded protein response and B cell differentiation to plasma cells. It binds to XBP-1 response elements (XRE) on the promoter of specific genes. XBP-1s has been previously shown to activate KSHV RTA expression [see reference]. We hypothesized that in KSHV-MCD, a number of plasmablastoid B cells produce vIL-6 but not other lytic genes and that XBP-1s was responsible for this vIL-6 expression. In this study, sequence analysis of the promoter region of vIL-6 revealed several potential consensus XREs. Luciferase reporter assay experiments showed that spliced, but not unspliced, XBP-1 can activate the vIL-6 promoter. Site-directed mutagenesis revealed that much of the activity was mediated by one of these consensus XREs. The unfolded protein response can be induced by brefeldin A and tunicamycin; treatment of PEL cell lines with these agents led to an increase in XBP-1s RNA as assessed by RT-PCR as well as increased XBP-1s protein confirmed by western blot and immunofluorescence. In addition, these agents induced an increase of vIL-6 mRNA and protein respectively at concentrations that did not activate RTA. We also found that a greater number of plasmablastoid cells from KSHV-MCD lymph nodes expressed vIL-6 than ORF45, which is another lytic gene. Moreover, we found XBP-1 and vIL-6 were co-expressed in KSHV-MCD plasmablasts and PEL cells from patients. Taken together, these results suggest that XBP-1 can directly upregulate vIL-6 production by binding to XRE on its promoter. They suggest that XBP-1-can activate vIL-6 in plasmablastoid B cells without the need for KSHV lytic activation and that this is an important factor in the pathogenesis of KSHV-MCD. XBP-1-induced vIL-6 may also contribute to the pathogenesis of PEL as well as other KSHV-related disorders.

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

Reference
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J Gen Virol 2011 Feb;92(Pt 2):421-431.

O12. RNA-Independent Activation of RIG-I by Deamidation

Shanping He[1], Shanshan Song[1], Xiaojing He[2], Jun Zhao[1], Arlet Minassian[1], Zhiheng He[1], Yuqi Wang[1], Ebrahim Zandi[1], Jae U Jung[1], Xuewu Zhang[2], Pinghui Feng[1]

[1]Department of Molecular Microbiology and Immunology, University of Southern California, Los Angeles, CA; [2]Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX

Innate immunity is the first line of defense against viral infection. Central to the host immune response is the activation of pattern recognition receptors. Recent studies define RIG-I as a genuine RNA sensor. Upon binding to viral RNA, RIG-I dimerizes with its downstream adaptor MAVS and activates two closely-related kinase complexes—IKKalpha/IKKbeta/IKKgamma and IKKepsilon/TBK1. These kinase complexes, in turn, activate NFkappaB and interferon regulatory factors (IRFs) to up-regulate the gene expression of cytokines and interferons, thereby establishing potent antiviral immunity. We report here that herpesviral homologues of glutamine amidotransferase (designated vGAT) induce RIG-I deamidation and activation independent of RNA.

We previously reported that murine gamma herpesvirus 68 (gammaHV68), a model DNA virus for human tumorigenic Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein–Barr virus (EBV), hijacks MAVS and IKKbeta to enable viral infection. We reasoned that upstream virus-host interactions activate MAVS and IKKbeta. To identify viral activators, we screened a viral expression library and found that vGAT (previous known as ORF75c) was most potent to activate NFkappaB. Interestingly, vGAT specifically activated NFkappaB in a MAVS- and IKKbeta-dependent manner, without eliciting IFN signaling. To identify cellular proteins that interact with vGAT, we discovered that RIG-I was the most abundant vGAT-interacting partner. Genetic and biochemical data support that vGAT directly activated RIG-I.

These findings defined a virus-host interaction that activates MAVS and IKKbeta in gamma herpesvirus infection. Given that vGAT is a homologue of cellular GAT, we tested whether the enzyme activity of cellular GATs is necessary for vGAT-induced signaling. Indeed, a GAT inhibitor specifically diminished NFkappaB activation induced by vGAT, but not that by IKKbeta. Two-dimensional gel electrophoresis analysis indicated that vGAT expression reduced the charge of RIG-I. Mass spectrometry analysis identified three deamidated residues within RIG-I, one glutamine (Q^{10}) within the first CARD and two asparagines (N^{245} and N^{445}) within the ATPase domain. Surprisingly, $N^{245/445}D$ mutations reduced the ATP binding and ATPase activity of RIG-I helicase domains, suggesting a new means of RIG-I activation via deamidation. Indeed, deamidation of glutamine within the first CARD synergized with those of asparagines in the helicase domain in activating RIG-I in an RNA-independent manner. Finally, KSHV vGAT and KSHV infection induced RIG-I deamidation. Though vGAT shares homology with cellular counterparts, vGAT appears to possess no intrinsic activity. The identification of cellular GATs in RIG-I deamidation will be discussed. Taken together, our findings uncover a new means by which a cytosolic sensor is activated by an enzyme activity.

O13. KSHV-Dependent Activation of Platelet-Derived Growth Factor Receptor Signaling Is an Oncogenesis Driver and a Therapeutic Target in Kaposi's Sarcoma

Lucas Cavallin, Qi Ma, Sachin Gupta, Mani Kurian, Paola Locatelli, Paolo Romanelli, Pascal J. Goldschmidt-Clermont, Enrique A. Mesri

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

Kaposi's sarcoma (KS), an AIDS-defining cancer caused by the KSHV, is a vascular sarcoma characterized by intense angiogenesis and spindle cell proliferation. Both latent and lytic gene programs of KSHV participate in the angioproliferative response via autocrine and paracrine mechanisms (*paracrine oncogenesis).* Defining which are the critical host pathways subverted by viral infection to induce paracrine oncogenesis is essential to understand viral pathogenesis and to identify potential therapeutic targets. We set out to investigate in an unbiased manner which were the critical host responses activated by KSHV in the mECK36 model of KSHV-induced KS-like mouse tumors. To this end we used a receptor tyrosine kinase proteomic array. We found that KSHV induced tumors displayed a powerful and unique activation of the Platelet Derived Growth Factor (PDGF) receptor (PDGFR) tyrosine kinase signaling in a manner reminiscent of driver oncogenic signaling cascades. We found that both KSHV lytic infection and the vGPCR could activate secretion of PDGFR ligands PDGFA and PDGFB. Accordingly, IHC analysis of KSHV infected mouse tumors displayed prominent PDGFR phosphorylation, together with the expression of its ligands but only in areas co-localizing with KSHV infection. PDGFR activation induced c-myc and VEGF expression, angiogenesis and cell proliferation. Many lines of evidence support the candidacy of PDGFR as driver oncogenic signaling in KS: (1) Pharmacologic intervention with the PDGFR tyrosine kinase inhibitors Imatinib and Sunitinib inhibited tumorigenesis. (2) Constitutively active mutations in the PDGFR that also confer resistance to Imatinib can compensate for KSHV loss in mouse KS-like tumorigenesis. (3) Cytoplasmic tyrosine kinase domain-deleted dominant negative mutant to PDGFR that inhibit all forms of PDGFR signaling blocked tumorigenesis. (4) Analysis of human KS samples showed activation of PDGFR in areas of expression of its ligands and KSHV infection (KSHV LANA), indicating that the mechanisms of activation of PDGFR signaling operates also in human KS. This work identifies PDGFR signaling as oncogenic driver in KSHV-induced tumorigenesis and as a critical target for KS. It points to pharmaco-oncogenomic determinations related to PDGFR signaling status as key biomarkers in current AIDS-KS trials such as Imatinib/Gleevec. Moreover, as PDGF signaling is also an oncogenic driver of non-viral sarcomas, our work shows for the first time a oncogenic signaling overlap between virally and nonvirally induced sarcomas in the same manner that it is observed for other viral cancers.

O14. Using Proteomics to Understand Human Target Genes of KSHV MicroRNAs

Amelia M. Gallaher[1], Sudipto Das[2], Zhen Xiao[2], Thorkell Andresson[2], Philippe Kieffer-Kwon[1], Christine Happel[1], Joseph M. Ziegelbauer[1]

[1]HIV and AIDS Malignancy Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; [2]Laboratory of Proteomics and Analytical Technologies, Advanced Technology Program, SAIC-Frederick, Inc., NCI at Frederick, Frederick, MD

Kaposi's sarcoma-associated herpesvirus (KSHV) expresses unique microRNAs (miRNAs), but the targets and functions of these miRNAs are not completely understood. In order to identify human target genes of viral miRNAs, we measured protein expression changes caused by multiple KSHV miRNAs using pulsed stable labeling with amino acids in cell culture (pSILAC) [1] and mass spectrometry in primary endothelial cells. This led to the identification and validation of multiple human genes (ROCK2, GRB2, STAT3, AKAP9, TSPAN3) that are targeted by specific KSHV microRNAs and are repressed at the protein level, but not at the mRNA level. This is significant because these target genes would not be identified using mRNA expression profiling. Further analysis also identified that KSHV miRNAs can modulate activity or expression of upstream regulatory factors (ROCK2 and STAT3), resulting in suppressed activation of a protein involved in leukocyte recruitment (ICAM1) following lysophosphatidic acid treatment. In addition, modulation of other upstream regulatory factors by microRNAs resulted in a five-fold up-regulation of a pro-angiogenic protein (HIF1α), and up-regulation of a protein involved in stimulating angiogenesis (HMOX1). Other classes of genes that were repressed by KSHV miRNAs include translation factors, cytoskeleton genes, chromatin modifiers, and cell cycle regulators. This study [2] aids in our understanding of miRNA mechanisms of repression and miRNA contributions to viral pathogenesis.

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O15. KS-Detect: A Complete "Sample-In, Answer-Out" Solution to the Diagnosis of Kaposi's Sarcoma

Li Jiang[1], Gunkut Akar[2], Matthew Mancuso[1], David Erickson[1], Ethel Cesarman[2]

[1]Sibley School of Mechanical and Aerospace Engineering, Cornell University, Ithaca, NY; [2]Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY

Kaposi's sarcoma (KS) is difficult to distinguish from other angioproliferative diseases, particularly in Africa where access to trained pathologists is limited to a few hospitals and immunohistochemistry is frequently not available, and the cost of antibodies to KSHV LANA may be prohibitive. Multiple studies have shown that PCR based nucleic acid identification of Kaposi's sarcoma herpesvirus (KSHV/HHV-8) in skin biopsies represents the best method of performing an unambiguous diagnosis in the absence of immunohistochemistry. Biopsy based nucleic acid screening presents a number of challenges that cannot be addressed by existing detection technologies in limited resource settings. First, a field nurse must be able to extract the sample from the patient and process it in such a way so as to release the DNA without the use of traditional laboratory equipment like centrifuges. Secondly the amplification reaction must be carried out in an energy efficient way so that the amount of energy that can be stored in reasonably portable batteries does not significantly limit the number of tests that can be conducted. This is particularly important in places like Uganda where only a small fraction of the population has access to electricity and the supply is irregular even in large cities. Finally the results need to be interpreted in a quantitative fashion (beyond what can be done with the naked eye) without the need to engineer further specialized equipment. Ideally this system could also archive, transmit, and geo-locate the test and results to facilitate population level scientific studies. We have developed a "KS-Detect" system that can address many of these challenges. The system is comprised of a smartphone-assisted unpowered instrument and low-cost kits that will contain the lab-on-a-syringe and solar-thermal PCR chips. Our power consumption estimates, show that 160 independent diagnostic reactions can be conducted with this system before exhausting the battery of a standard iPhone. The different elements of this system have been developed. Extraction of biopsies using thermostable reagents not requiring refrigeration and a single boiling step has been performed. We have detected KSHV in down to 0.1% of infected PEL cells admixed with uninfected tumor cells, as well as transgenic mouse tails with one copy per cell and in actual skin and lymph node biopsies with KS using this extraction method. The first prototype solar-thermal PCR chips has been manufactured and tested successfully, and nanoparticle detection has been demonstrated. Progress towards implementation will be presented.

O16. Results of a Phase I Study of Lenalidomide in Patients With AIDS-Associated Kaposi Sarcoma (AMC 070)

Kelly Shimabukuro[1], *Page Moore*[2], *Erin Reid*[1]

[1]*University of California, San Diego, Moores Cancer Center; San Diego, CA;* [2]*University of Arkansas for Medical Sciences, Little Rock, AR*

Background: HIV-infected individuals have a high incidence of Kaposi sarcoma (KS), a virus induced endothelial tumor that arises in skin, mucosa, and viscera. When immunosuppression is reversed with highly active antiretroviral therapy (HAART), KS lesions often stabilize or regress suggesting that CD4 T cells are important in immunosurveillance. However, many patients treated with HAART develop or show persistent KS lesions and treatment with conventional anticancer therapy is not sufficient to eradicate disease. Lenalidomide is an IMiD™ compound with potent anti-angiogenic and immunomodulatory properties. Thalidomide, the parent analogue of lenalidomide, showed modest activity against HIV-associated KS. Lenalidomide has higher tumoricidal and immunomodulatory effects, including stimulation of apoptosis and enhanced NK cell cytotoxicity making it a promising candidate for KS therapy. The effects of lenalidomide on AIDS-associated KS have not been studied.

Methods: This is a multicenter, Phase I study, part of an ongoing Phase I/II study. Patients with HIV and newly diagnosed KS not requiring cytotoxic chemotherapy or KS refractory to standard chemotherapy were eligible for enrollment. Primary objective was to determine the maximum tolerated dose (MTD) of lenalidomide using a standard 3x3 dose escalation at four pre-specified doses (10mg/day, 15mg/day, 20mg/day, and 25mg/day given days 1-21 of a 28 day cycle). Subjects received six cycles, with treatment extended for up to six additional cycles if criteria for response were met. Dose limiting toxicity (DLT) was assessed in the first 28 days of treatment.

Results: Between September 2010 and September 2011, 15 patients were enrolled and completed at least one cycle of treatment. Median cycles were 6 (range 1-12). No DLT was seen at any dose level. Grade 3/4 toxicity seen after cycle 1 were: neutropenia (33.3%), hypophosphatemia (6.6%), lung infection (6.6%), and syncope (6.6%). Partial response (PR) was seen in 6 patients (40%), with 8 patients having stable disease (53%). Four of the 6 partial responses were seen at the highest dose level of 25mg/day.

Conclusion: Lenalidomide is well tolerated with recommended dose of 25mg daily for days 1-21 of each 28 day cycle. At least stable disease or better was seen in a majority of patients. These results suggest this regimen may be a promising alternative to cytotoxic chemotherapy. The Phase II portion of the trial is ongoing at this time with preliminary results assessing efficacy and response rates anticipated within the next year.

Acknowledgements
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O17. Antiretrovirals for Kaposi's Sarcoma (ARKS): A Randomized Trial of Protease Inhibitor-Based Antiretroviral Therapy for AIDS-Associated Kaposi's Sarcoma in Sub-Saharan Africa

Jeffrey Martin[1], Miriam Laker-Oketta[1,2], Victoria Walusana[3], Jackson Orem[3], Henry Wabinga[4], John Bennett[1], Adrienne Mocello[1], Megan Wenger[1], Toby Maurer[5], Peter Hunt[6], Andrew Kambugu[2], Edward Mbidde[2,7]

[1]Department of Epidemiology and Biostatistics, [5]Department of Dermatology, [6]Department of Medicine, University of California, San Francisco, San Francisco, CA; [2]Infectious Diseases Institute, Kampala, Uganda; [3]Uganda Cancer Institute, Entebbe, Uganda; [4]Department of Pathology, Makerere University, Kampala, Uganda; [7]Uganda Virus Research Institute, Entebbe, Uganda

Background: Combination antiretroviral therapy (ART) — including protease inhibitor (PI)-containing regimens — has long been known to decrease lesion burden in some patients with AIDS-associated Kaposi's sarcoma (KS), but exactly which ART component/mechanism is responsible is unknown. Among the potential explanations, PIs have been speculated to have direct anti-KS effects in humans based on their anti-angiogenesis and anti-KS effects *in* vitro and in KS animal models. We investigated the hypothesis that PI-containing ART is clinically superior to PI-sparing ART for the treatment of KS in sub-Saharan Africa, a region where initial ART choice is critical given chemotherapy inaccessibility.

Materials and Methods: We enrolled ART-naïve HIV-infected adults with KS in Uganda who had no urgent indications for chemotherapy/radiotherapy. KS was biopsy-confirmed with the exception of subjects who had only oral lesions which were not biopsy-amenable. Subjects were randomized to either PI-based (lopinavir/ritonavir plus emtricitabine/tenofovir) or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART (efavirenz plus emtricitabine/tenofovir) and observed every 4 weeks for 48 weeks for an indication for chemotherapy and overall survival. Chemotherapy was given free for those who developed an indication post-randomization.

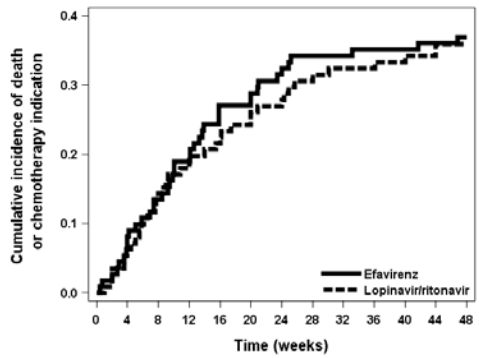

Figure 1. hazard ratio = 0.95; (95% CI: 0.62 to 1.5; p = 0.82).

Results: Among 224 subjects randomized (113 PI/111 NNRTI), 44% were women and median pre-treatment values were: 34 (IQR: 28-40) years old, 119 (IQR 24-265) CD4+ T-cells/mm3 and 222,323 (IQR 102,314-430,387) copies plasma HIV RNA/ml. Extent of KS was heterogeneous: 7.1% had oral lesions only, 24% had ≥50 skin lesions, and 71% were T1-stage. ART was well tolerated with only 7.1% in the PI arm and 8.1% in the NNRTI arm discontinuing their originally assigned drug class. There was no loss to followup from the perspective of vital status, and only 3 alive subjects were unavailable for clinical assessment at 48 weeks. A total of 36% of subjects experienced the primary composite outcome (indication for chemotherapy or death) by 48 weeks, but we found no evidence in intent-to-treat analysis for a difference between treatment groups (Figure1). Likewise, for mortality alone, 18% of subjects died by 48 weeks, but we found no treatment differences (Figure 2).

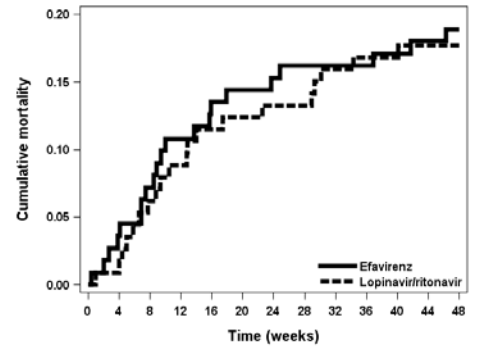

Figure 2. hazard ratio = 0.92; (95% CI: 0.50 to 1.7; p = 0.80.

Conclusions: Despite biological plausibility, we found no evidence that PI-containing ART was superior to NNRTI-based ART in terms of survival or need for chemotherapy among patients with AIDS-associated KS who did not initially have urgent chemotherapy indications. The high incidence of subsequent indications for chemotherapy and/or death indicates that ART alone for all comers with KS in sub-Saharan Africa is suboptimal and additional interventions are needed.

O18. Studies in Primary Cultures of Human Hepatocytes and Computer Simulations Provide Guidance for Dosing of Anticancer Drugs in Patients Treated With HAART Drugs

Raman Venkataramanan

School of Pharmacy and School of Medicine, University of Pittsburgh, Pittsburgh, PA

Patients with HIV are prone to AIDS defining and non-AIDS defining malignancies. In these patients antineoplastic therapy has to be used along with highly active antiretroviral therapy (HAART). HAART mediated inhibition of drug metabolizing enzymes, resulting in increased toxicity or induction of drug metabolizing enzymes leading to therapeutic failure are of major concern. We have utilized primary cultures of human hepatocytes to simulate in vivo interactions, and used computer simulations to predict the interactions.

Primary cultures of human hepatocytes are treated with various HAART drugs for a period of 4 days with ritonavir (10 μM), ketoconazole (1 μM), efavirenz (10 μM), rifampin (10 μM), Cobicistat (2.4 μM) or vehicle control (0.1% DMSO). On day 5, various anticancer drugs are added to the culture medium with the above agents for another 24-48 hr. The concentrations of anticancer drugs were measured in the samples (combined lysate and medium) using LC-MS/MS. The half life ($t_{1/2}$) and apparent intrinsic clearance (CLint, app) of anticancer drugs exposed to different HAART drugs were calculated and fold change in doses necessary to accomplish comparable drug exposure were predicted.

Our results suggest that, in order to achieve comparable drug exposure, the dose (400 mg twice daily) of nilotinib may have to be reduced (150-200 mg twice daily) or increased (800 mg twice daily), respectively, when ritonavir or efavirenz is co-administered; the dose (400 mg per day) of imatinib may have to be reduced (200 mg per day) or increased (400 mg twice daily), respectively, when ritonavir or efavirenz is co-administered; the dose of paclitaxel may have to be reduced by 4 folds or increased by 1.5 fold, respectively when cobicistat and nevirapine, is co-administered. The magnitude of changes predicted from hepatocyte studies are comparable to what is published for anticancer drugs interaction with ketoconazole and rifampin, providing confidence in the prediction of fold changes for anticancer drug and HAART drug interaction.

In addition it was possible to predict the magnitude of interaction for some of the anticancer drugs and HAART drugs using mechanistic PBPK modeling via computer simulations. Studies in primary cultures of human hepatocytes and computer modeling are valuable in predicting drug interactions involving anticancer drugs and HAART drugs and may inform drug dosing in confirmatory phase I trials in combination with HAART drugs through the Aids Malignancy Consortium (AMC).

O19. Differential Expression and Prognostic Utility of Immunophenotypic Markers in Diffuse Large B-Cell Lymphoma From Patients With and Without HIV Infection

Chun Chao[1], Michael J. Silverberg[2], Lanfang Xu[1], Otoniel Martínez-Maza[3], Donald I. Abrams[4,5], Hongbin D. Zha[6], Jonathan Said[7]

[1]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA; [2]Division of Research, Kaiser Permanente Northern California, Oakland, CA; [3]Departments of Obstetrics and Gynecology and Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA; [4]San Francisco General Hospital, [5]Department of Medicine, University of California, San Francisco, San Francisco, CA; [6]Los Angeles Medical Center, Kaiser Permanente Southern California, Los Angeles, CA; [7]Department of Pathology and Laboratory Medicine, School of Medicine, University of California, Los Angeles, Los Angeles, CA

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of HIV+ non-Hodgkin lymphoma [see reference]. Compared to HIV- DLBCL, HIV+ DLBCL often presents at an advanced disease stage, with extranodal involvement, and has an aggressive clinical course [see reference]. These differences suggest DLBCLs arise under the context of HIV infection are likely biologically different from those in the general population. Here we compared tumor marker expression and pathogenesis by HIV status.

Study Design: HIV+ DLBCL cases diagnosed between 1996-2007 within Kaiser Permanente (KP) California were identified. HIV- DLBCL cases were 1:1 matched to HIV+ cases by age, gender and race. Archived tumor specimens were retrieved for tissue microarray (TMA) construction. Immunohistochemistry staining was performed on TMA cores to analyze the expression of 25 B-cell oncogenic markers related to Epstein-Barr virus infection, cell cycle regulation, B-cell activation, and apoptosis regulation among others. Clinical data on international prognostic index (IPI) and mortality were collected from KP's medical records. The proportion of DLBCL tumors positively expressing each marker was calculated by HIV status. Differential expression of these markers was assessed by Fisher's exact test, and adjusted for multiple comparisons using Bonferroni's method. Bivariate and multivariable logistic regression adjusting for IPI, germinal center phenotype and DLBCL subtype were used to evaluate the prognostic significance of each tumor marker on 2-year mortality.

Results: Eighty HIV+ and 80 HIV- DLBCL cases were included. Mean age at DLBCL diagnosis was about 50 years in both groups. For the HIV+ cases, mean CD4 cell count at DLBCL diagnosis was 206 cells/mm^3. Expression of cMYC, BCL6, PKC-beta2, EBV, MUM1, and CD44 were significantly elevated in HIV+ tumors, compared to HIV- tumors, while expression of cyclin D2 and p27 were significantly elevated in HIV- tumors. In bivariate logistic regression, EBV [odds ratio (OR) = 4.44, 95% confidence interval 1.47-13.42] and IgM [OR=0.31 (0.12-0.81)] expression significantly predicted 2-year mortality in HIV+ but not in HIV- tumors. Both markers continue to predict mortality in multivariable models: OR =10.86 (2.00-58.91) and 0.19 (0.05-0.75) for EBV and IgM, respectively.

Conclusion: Several cell cycle and B-cell activation markers, such as cMYC and BCL6, may play a more predominant role in HIV-related lymphomagenesis. Tumor EBV and IgM status are also unique prognostic factors in HIV+ DLBCL and may have utility in clinical management of HIV+ DLBCL. These results suggest differences between HIV+ and HIV- DLBCL at the molecular level, which have implications on the development of novel therapeutics.

Acknowledgement
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O20. Targeting Sphingosine Kinase Induces Apoptosis and Regression of Virus-Associated Lymphoma In Vivo

Zhiqiang Qin[1], Lu Dai[2], Karlie Bonstaff[2], Can Senkal[4], Wenxue Wang[5], Tom Reske[2], Luis Del Valle[3], Christina Voelkel-Johnson[6], Erik Flemington[7], Besim Ogretmen[4], Charles D. Smith[5], Chris Parsons[1,2]

[1]Department of Microbiology/Immunology/Parasitology, [2]Department of Medicine, [3]Department of Pathology, Louisiana State University Health Sciences Center, New Orleans, LA; [4]Department of Biochemistry/Molecular Biology, [5]Department of Drug Discovery/Biomedical Sciences, [6]Department of Microbiology/Immunology, Hollings Cancer Center, Medical University of South Carolina, Charleston, SC; [7]Department of Microbiology, Tulane University School of Medicine, New Orleans, LA

Background and Specific Aims: Sphingosine kinase (SphK) is overexpressed by a variety of cancers, and its phosphorylation of sphingosine results in accumulation of sphingosine-1-phosphate (S1P) and activation of anti-apoptotic signal transduction. Existing data indicate a role for S1P in viral pathogenesis, but roles for SphK and S1P in virus-associated cancer progression have not been defined. The Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative agent of primary effusion lymphoma (PEL)—a rapidly progressive tumor arising in body cavities which incurs a median survival time of around 6 months with standard therapeutic approaches. ABC294640 is an orally bioavailable small molecule inhibitor of SphK under evaluation in early-phase clinical trials, although no preclinical or clinical data are available for this agent for hematologic or virus-associated malignancies. Therefore, we sought to determine whether ABC294640 displays inhibitory effects for HIV/KSHV$^+$ patient-derived PEL cells in vitro and in vivo, as well as potential mechanisms through which SphK regulates KSHV pathogenesis.

Methodology: Complementary in vitro assays were undertaken using RNAi and ABC294640 for targeting SphK1 and SphK2 in HIV/KSHV$^+$ patient-derived PEL cell lines. qRT-PCR and immunoblots were used to quantify KSHV gene expression and signal transduction, respectively; MTT assays and flow cytometry were used to assess metabolic activity and apoptosis; and mass spectrometry was used to quantify different bioactive sphingolipid intermediates associated with SphK activity. ABC294640 was used in a murine PEL xenograft model to assess the effects of SphK inhibition on KSHV$^+$ lymphoma progression in vivo.

Results and Conclusions: We find that targeting SphK induces caspase cleavage and apoptosis for KSHV$^+$ patient-derived PEL cells in the presence or absence of co-infection with the Epstein-Barr virus (EBV). Validating these results, we find that systemic administration of ABC294640 induces tumor regression in the PEL xenograft model. Complimentary ex vivo and in vitro analyses revealed that ABC294640 suppresses constitutive signal transduction associated with proliferation and survival of PEL cells, and increases intracellular accumulation of pro-apoptotic sphingolipid intermediates and KSHV lytic gene expression previously associated with cancer cell death. These results justify additional studies to identify mechanisms for SphK and S1P regulation of virus-associated PEL pathogenesis. Importantly, they also justify evaluation of ABC294640 in clinical trials as a single agent, or in combination with existing approaches, for the treatment of PEL and possibly other malignancies associated with oncogenic viruses.

O21. The HIV-1 Matrix Protein and AIDS-Related Lymphoma

Mark K. Lafferty[1], Lanea George[1], Lindsay Goicochea[2], Qing C. Chen[2], Robert C. Gallo[1], Joseph L. Bryant[1], Alfredo Garzino-Demo[1]

[1]Institute of Human Virology, [2]Department of Pathology, University of Maryland Medical Center, Baltimore, MD

Infection with human immunodeficiency virus-1 (HIV-1) is associated with an increased risk of non-Hodgkin lymphomas (NHLs). With the adoption of combination antiretroviral therapy (cART), NHLs have become the most frequent cause of AIDS-related mortality accounting for approximately a quarter of AIDS-related deaths. The overall incidence of NHLs have declined with the introduction of cART but not to the same degree as observed for other AIDS-defining illnesses and HIV+ individuals still have a 25 fold elevated risk of NHLs. The mechanisms responsible for the increased risk have not been fully elucidated but are thought to involve HIV-1 mediated impaired cellular immunity leading to chronic B cell activation and loss of control over opportunistic infections caused by oncogenic viruses. Interestingly, in the absence of both viral replication and impaired cellular immunity, 15% of HIV transgenic (Tg26) mice develop lymphoma. The Tg26 mouse model has a deletion in the HIV genome that spans the majority of the gag/pol region rendering the virus non-infectious due to both defects in the viral genome and non-permissivity of the host. Therefore, we hypothesize that HIV-1 proteins themselves may directly contribute to B cell lymphomagenesis. We characterized the lymphoma in the Tg26 mice as an early stage B cell lymphoma (CD19+CD93+CD43+CXCR4+CD21-CD23-IgM-IgD-) with enrichment in surrogate light chain (SLC) expression. Tg26 mice that develop lymphoma compared to asymptomatic Tg26 mice express elevated levels of HIV-1 proteins known to interact with B cells, p17, gp120, and nef. Our results indicate that recombination activating gene (RAG) 1 is upregulated in Tg26 mice that develop lymphoma and therefore may be a source of genomic instability. We are currently investigating the role of the HIV-1 matrix protein, p17. P17 is a structural protein that persists long-term in the lymph nodes of HIV-infected individuals in the absence of viral replication and activates intracellular signaling pathways via receptors that include CXCR1 and -2, which are present on B cells of HIV+ individuals.

O22. Characterizing Survival in the Absence of LMP1-Mediated NFκB Signaling in the Model of EBV-Driven AIDS Lymphoma

Alexander Price[1], *Pavel Nikitin*[1], *Luv Patel*[2], *Anthony Letai*[2], *Micah Luftig*[1]

[1]*Department of Molecular Genetics and Microbiology, Center for Virology, Duke University, Durham, NC;* [2]*Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA*

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

It has long been known that early after infection EBV expresses a set of latency-associated genes that mimic normal B-cell maturation and aid in immortalization of the infected B cell. In particular, Latent Membrane Protein 1 (LMP1) is a constitutively active version of the host CD40 receptor that signals chronically through the downstream NFκB pathway. This LMP1-induced NFκB signaling is absolutely critical for the generation and survival of LCLs. Indeed, inhibition of NFκB in LCLs induces apoptosis. As such, it was quite surprising when recent work from our laboratory identified a period early after infection where EBV-infected B-cells proliferated in the absence of LMP1 and were immune to apoptosis induced by NFκB inhibition.

To ascertain how these cells survive in the absence of LMP1-induced NFκB activation, we performed BH3 profiling to query the state of mitochondrial priming of apoptosis at different times post infection. These data support a model where uninfected B cells are characterized by active BCL-2, suggesting dependence on this anti-apoptotic molecule. As proliferation commences early after EBV infection, the cells are characterized by combined BCL-2 and MCL1 dependence. Finally, the resultant LCLs are characterized by BFL1/A1 dependence. Thus, EBV appears to promote survival at the mitochondria through different mechanisms through B-cell immortalization. Corroborating these results, we found that EBV-infected B cells were highly sensitive to ABT-737, a small-molecule inhibitor of BCL-2, BCL-xL, and BCL-w, if treated immediately after infection. However, proliferating B cells early after infection and LCLs were not. We are currently investigating the dependence of early-infected B cells and LCLs on MCL1 and BFL1 towards defining the mechanisms of survival at these key points during immortalization. Overall, these data aim to provide insight into how EBV prevents apoptosis and how this knowledge might be used to treat EBV-associated malignancies in the setting of HIV.

O23. Inflammatory Biomarkers and CT-Detected Lung Nodules: Potential Implications for Lung Cancer Screening of HIV-Infected Patients

Kristina Crothers[1], Keith Sigel[2], Juan Wisnivesky[2], Robert Dubrow[3], R. Scott Braithwaite[4], Amy Justice[5]

[1]Department of Medicine, University of Washington School of Medicine, Seattle, WA; [2]Department of Medicine, Mount Sinai School of Medicine, New York, NY; [3]Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT; [4]Departments of Medicine and Population Health, New York University School of Medicine, New York, NY; [5]VA CT Healthcare System and Department of Internal Medicine, Yale School of Medicine, New Haven, CT

Background: Lung cancer CT screening results in a mortality reduction in high-risk individuals, defined by age and smoking. However, additional criteria to improve detection of true positives and minimize false positives – primarily incidentally detected non-malignant nodules – are needed. Inflammatory biomarkers, particularly interleukin-6 (IL6) and D-dimer, have recently been associated with the incidence of cancers in HIV-infected persons, [see reference] raising the possibility that biomarkers could inform screening criteria for selection of high-risk individuals.

Methods: We determined the association between plasma levels of IL6, D-dimer and soluble CD14 (sCD14; a marker of monocyte activation) and CT findings in a cohort of 156 HIV-infected and 135 uninfected veterans without acute illness, enrolled 2009-2012, into a pulmonary sub-study of the Veterans Aging Cohort Study. All patients underwent a research chest CT scan; findings were abstracted from clinical interpretations and classified as positive per the National Lung Cancer Screening Trial (NLST) criteria. Clinical diagnoses (lung cancer, infections, inflammatory processes, or progression of CT findings within 6 months) were abstracted from the medical record. Biomarker levels were categorized as high (upper 25%ile) vs. not elevated. Associations between biomarker levels and outcomes were assessed using chi-squared tests, Fisher's exact tests or logistic regression.

Results: There was no significant difference by HIV in the proportion of CT scans classified as NLST-positive (29% of HIV-infected and 24% of uninfected, p=0.3). Among HIV-infected participants, those with a high sCD14 level were significantly more likely to have an NLST-positive scan (Table). In HIV-infected participants, CD4 count <200 cells/mm^3 was also an independent risk factor for an NLST-positive scan (OR 3.9, 95% CI 1.4-10.5, p=0.008). Considering clinical diagnoses following CT scans, 12% with high sCD14 compared to 6% with lower sCD14 (p=0.1) and 14% with high IL6 compared to 5% with lower IL6 (p=0.04) had a new pulmonary diagnosis or CT progression within 6 months. Overall, 4.1% of patients with a high sCD14 level had lung cancer diagnosed after CT compared to 0.4% of those with lower sCD14 levels (p=0.05), with no difference by IL6.

Conclusions: Of the inflammatory biomarkers measured, elevated levels of sCD14 were associated with an increased odds of incidentally-detected lung nodules among HIV-infected patients. Elevated sCD14 may correlate with screen-detected lung cancer and elevated IL6 with greater risk of subsequent pulmonary complications, but sample size was limited. Further evaluation is needed to determine whether inflammatory biomarkers can help identify high-risk individuals for lung cancer screening among HIV-infected patients.

AOR (95% CI, p-value) for NLST-positive chest CT scan according to baseline biomarker level		
Biomarker	**HIV Infected**	**HIV Uninfected**
High sCD14 level	3.3 (1.5-7.2, p=0.002)	0.8 (0.2-4.3, p=0.9)
High IL6 level	0.9 (0.40-2.1, p=0.9)	1.3 (0.5-3.7, p=0.6)
High D-dimer level	1.0 (0.5-2.3, p=0.9)	1.0 (0.4-2.8, p=0.9)
AOR = adjusted odds ratio; adjusted for pack-years of smoking, race/ethnicity and for HIV-infected patients, CD4 cell count <200 cells/mm^3; CI = Confidence interval		

Reference

O24. Applying the Methods of Causal Inference to HIV-Associated Malignancies: Estimation of the Impact of Antiretroviral Therapy on Kaposi's Sarcoma Incidence in East Africa via a Nested New User Cohort Analysis

Aggrey Semeere[1,2], Megan Wenger[2], Naftali Busakhala[3], Nathan Buziba[3], Mwebesa Bwana[4], Winnie Muyindike[4], Erin Amerson[2], Toby Maurer[2], Beverly Musick[5], Constantin Yiannoutsos[5], Robert Lukande[6], Barbara Castelnuovo[1], Andrew Kambugu[1], David Glidden[2], Eric Vittinghoff[2], Kara Wools-Kaloustian[5], Jeffrey Martin[2]

[1]Infectious Diseases Institute, Kampala, Uganda; [2]University of California, San Francisco, San Francisco, CA; [3]Moi University, Eldoret, Kenya; [4]Mbarara University of Science and Technology, Mbarara, Uganda; [5]Indiana University, Indianapolis, IN; [6]College of Health Sciences, Makerere University, Kampala, Uganda

Background: Antiretroviral therapy (ART) has undoubtedly reduced incidence of Kaposi's sarcoma (KS), but knowledge of the exact quantitative magnitude of reduction is needed to determine whether additional interventions are required to reduce excess KS risk. This is especially true in Africa where KS is among the most common malignancies. Recent methodologic advances reveal that the observational studies to date addressing whether ART reduces KS incidence have used conventional regression approaches to manage time-dependent confounding by CD4+ T cell count that fail to properly account for the mediating effects of CD4 count. Hence, heretofore we only have potentially biased estimates to base our understanding of the effect of ART on reducing KS incidence.

Methods: We studied HIV-infected adults at clinics in the East Africa International Epidemiologic Databases to Evaluate AIDs (IeDEA) consortium: Immune Suppression Syndrome Clinic in Mbarara, Uganda; Infectious Diseases Institute in Kampala; and AMPATH in Kenya. Among patients initially without KS followed from January 2004 to July 2012, we estimated the total causal effect of ART on KS incidence by employing a nested new user (NNU) cohort analysis to manage time-dependent confounding by CD4+ T-cell count without eliminating ART-mediated changes in CD4 count. The NNU analysis also adjusted for age, sex, and WHO-stage via pooled logistic regression which utilized inverse probability weights to account for possible informative censoring.

Results: We evaluated 159,036 patients (67% women), with a median age of 36 years (interquartile range (IQR): 30-43) and median CD4 count of 226 cells/mm^3 (IQR: 90-415). Median follow-up was 5.4 years (IQR: 3.6-6.9) during which 1326 incident KS diagnoses were made. In the unadjusted analysis, patients not on ART had higher KS incidence than those on ART (347 vs. 227/100,000 person-years). In adjusted analyses, compared to those not on ART, patients on ART had a 60% (95% CI: 50%-70%; $p<0.001$) reduction in KS incidence using conventional time-dependent proportional hazards regression, while in the NNU analysis there was an 80% (95% CI: 70%-90%; $p<0.001$) reduction. CD4 count modified the effect of ART in the NNU analysis; patients with the lowest CD4 counts had the greatest ART effect ($p<0.01$).

Conclusion: In East Africa, an area of high prevalence of both HIV and HHV-8, ART results in a substantial reduction in KS incidence. Studies investigating the effect of ART on HIV-associated malignancies will need to manage time-dependent confounding/mediation by CD4 count and will likely benefit by employing newer "causal" analytic approaches.

O25. Impact of Kaposi's Sarcoma on Survival Among HIV-Infected Adults in Africa in the Era of Antiretroviral Therapy

Stephen B. Asiimwe[1,2], Miriam Laker-Oketta[2,3], John Bennett[2], Adrienne Mocello[2], David Glidden[2], Jessica Haberer[5], Toby Maurer[6], Mwebesa Bwana1, Peter Hunt[7], David Bangsberg[5], Edward Mbidde[3,4], Jeffrey Martin[2]

[1]Department of Internal Medicine, Mbarara Regional Referral Hospital, Mbarara, Uganda; [2]Department of Epidemiology and Biostatistics, [6]Department of Dermatology, [7]Department of Medicine, University of California, San Francisco, San Francisco, CA; [3]Infectious Diseases Institute, Kampala, Uganda; [4]Uganda Virus Research Institute, Entebbe, Uganda; [5]Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Introduction: In sub-Saharan Africa, Kaposi's sarcoma (KS) remains one of the most common malignancies among HIV-infected adults. In resource-rich areas, we now know that survival after KS diagnosis has markedly improved, and, in fact, ART alone is often initiated for KS in absence of immediately life-threatening complications. In sub-Saharan Africa, ART alone is also often administered for persons with KS, but we know little of the effectiveness of this strategy.

Methods: We performed a cohort analysis of HIV-infected adults initiating ART in Uganda. Subjects with KS were from the Antiretrovirals for Kaposi's Sarcoma (ARKS) clinical trial, which enrolled ART-naïve patients with biopsy-confirmed KS, from throughout Uganda, who did not urgently require chemotherapy. The comparator group was subjects without KS from the Uganda AIDS Rural Treatment Outcomes (UARTO) Cohort, based in Mbarara, Uganda; these were consecutive patients initiating ART for indications other than KS. We aimed to perform comprehensive adjustment for confounders using a directed acyclic graph approach (Figure 1) and obtained measurements on all subjects using the same questionnaires and laboratory. Observation was from ART initiation to death, loss to followup, or administrative closure at 4 years.

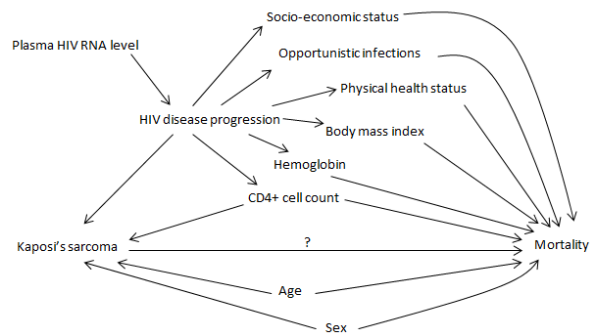

Figure 1. Directed acyclic graph (DAG) showing hypothesized causal relationship between KS and mortality, in addition to confounding.

Results: We evaluated 892 subjects (224 with KS/668 without). Median values for the combined population at the time of ART initiation were: age 34 years (IQR: 28-40), CD4+ T-cell count 155/mm^3 (IQR: 77-260), and plasma HIV RNA 141,828 copies/ml (IQR: 45,060–360,649). Subjects were observed for a median of 3.7 years (IQR 1.5-4.0) with 6.5% lost to follow up. In an unadjusted analysis, cumulative mortality at 4 years was 30% in the KS group compared with 6.7% in the non-KS group (Figure 2). After adjusting for the elements depicted in Figure 1, patients with KS had a 4.7-fold (95% CI: 2.5-8.9; p <0.001) higher rate of death in the first year after ART and a 2.5-fold higher rate (95% CI: 1.1-5.8; p = 0.032) thereafter.

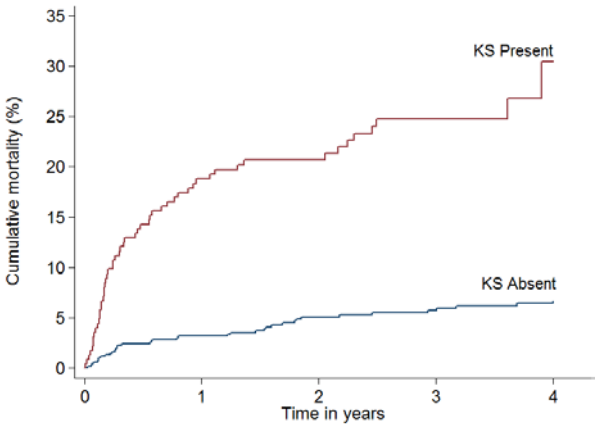

Figure 2. Mortality following ART initiation, by KS status.

Conclusion: Among HIV-infected adults newly initiating ART in Uganda, those with KS had substantially higher mortality than those without KS, indicating that treatment with ART alone for all comers with KS is suboptimal. The findings call for improved prognostic staging, increased access to potent chemotherapy, or development of new adjunctive therapy for KS in resource poor settings.

O26. Prevalence of HIV Infection Among U.S. Hodgkin Lymphoma Cases

Meredith S. Shiels[1], Erik Koritzinsky[1], Christina A. Clarke[2], Gita Suneja[3], Lindsay M. Morton[1], Eric A. Engels[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD; [2]Cancer Prevention Institute of California, Fremont, CA; [3]Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA

Background: Hodgkin Lymphoma (HL) is uncommon in the U.S. general population; however, HL risk is elevated in people with human immunodeficiency virus (HIV) infection. Thus, despite the low HIV prevalence in the U.S, the HIV epidemic may have contributed substantially to the general population burden of HL.

Methods: We used data from 14 U.S. cancer registries in the Surveillance, Epidemiology and End Results (SEER) Program that recorded HIV status of HL cases at diagnosis during 2000-2010. We computed the HIV prevalence in HL cases by demographic and tumor characteristics, the proportion of deaths among HL cases due to HIV, and 5-year overall and cause-specific mortality by HIV status.

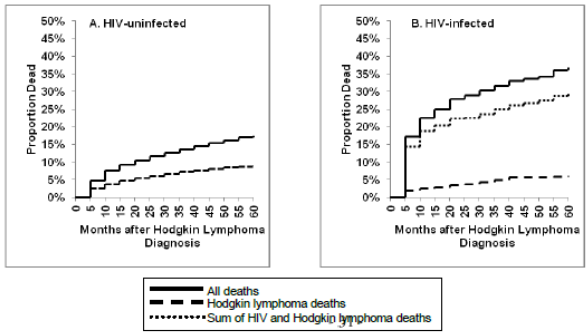

Figure 1. Five-year mortality among HIV-uninfected and HIV-infected Hodgkin lymphoma cases, 2000-2010.

Results: Of 22,355 HL cases in SEER, 848 (3.79%) were HIV-infected at diagnosis. HIV prevalence in HL cases was greater among males than females (6.0 vs. 1.2%). Among males, HIV prevalence was greatest among 40-59 year-olds (14.2%), non-Hispanic blacks (16.9%), Hispanics (9.9%), among cases of lymphocyte-depleted (15.1%) and mixed cellularity HL (10.5%), and among HL cases with "B" symptoms (9.13%). Patterns were similar among females, albeit with much lower prevalence. Eight percent of male and 1.5% of female HL cases died from HIV. Five-year mortality was two-fold higher in HIV-infected HL cases (36.9% vs. 17.5%). In contrast, the 5-year absolute risk of death due to HL was greater among HIV-uninfected HL cases compared to HIV-infected HL cases (9.0% vs. 6.2%, respectively).

Conclusions: In the U.S., a substantial proportion of lymphocyte-depleted and mixed cellularity HL cases, and HL cases among non-Hispanic black, Hispanic and middle-aged men are HIV-infected. Additionally, HIV is an important cause of death among HL cases. As the HIV-infected population in the U.S. continues to grow, the absolute number of HIV-infected HL cases will likely rise, resulting in an increasing proportion of general population HL cases who have HIV infection. Clinicians should be aware of the high prevalence of HIV in certain subgroups of HL patients, and routine HIV testing should be recommended for all patients presenting with HL.

O27. Risk of Non-Hodgkin Lymphoma Subtypes in People Infected With HIV During the HAART Era

Todd M. Gibson[1,2], Lindsay M. Morton[1], Meredith S. Shiels[1], Christina A. Clarke[3], Eric A. Engels[1]

[1]Division of Cancer Epidemiology and Genetics, [2]Cancer Prevention Fellowship Program, National Cancer Institute, National Institutes of Health, Bethesda, MD; [3]Cancer Prevention Institute of California, Fremont, CA

Background: HIV/AIDS-related immunodeficiency is strongly linked to increased risk of non-Hodgkin lymphoma (NHL), particularly the AIDS-defining NHL subtypes: diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL) and primary lymphomas arising in the central nervous system (CNS). However, risks of other NHL subtypes have not been well studied among HIV/AIDS patients in the HAART era, and few studies have separately examined risks in HIV-infected individuals prior to progression to AIDS.

Methods: We utilized linked HIV and cancer registry data from 7 states in the HIV/AIDS Cancer Match Study, restricted to people registered with HIV infection in 1996 or later (an era with widespread HAART availability). Incident cases of NHL were identified through linkage with cancer registries, and NHL subtypes were classified according to World Health Organization guidelines. For examination of risk in HIV-infected people (i.e., HIV-only), follow-up started at HIV registration and ended at the earliest of AIDS diagnosis, death, NHL diagnosis, or end of cancer registry followup. NHL cases diagnosed on the date of AIDS diagnosis were included in the HIV-only analysis, and we further included cases of AIDS-defining subtypes reported during the first three months after AIDS diagnosis to account for delayed reporting. For examination of risks following progression to AIDS, follow-up started at AIDS diagnosis and ended at the earliest of death, NHL diagnosis, or end of cancer registry follow-up. We separately determined incidence rates (IRs) in the HIV-only and AIDS periods, and used Poisson regression to examine relative risks between people with HIV-only and AIDS.

Results: We identified 455 cases of NHL among 111,320 people with HIV-only, and 1,027 cases of NHL among 97,522 people with AIDS. Incidence rates were highest for the AIDS-defining subtypes, whereas other subtypes were generally rare (see Table 1).

Table 1. Incidence Rates for NHL Subtypes Among People Registered With HIV

	HIV-only		AIDS	
NHL Subtype	**Cases**	**Incidence Rate***	**Cases**	**Incidence Rate***
Anaplastic large cell lymphoma	4	1.0	27	6.3
Burkitt lymphoma	80	19.3	103	23.9
CLL/SLL	8	1.9	7	1.6
Diffuse large B-cell lymphoma	201	48.6	514	119
Follicular lymphoma	9	2.2	15	3.5
Lymphoplasmacytic lymphoma	1	0.2	8	1.9
Mycosis fungoides/Sézary syndrome	2	0.5	3	0.7
Marginal zone lymphoma	11	2.7	11	2.6
Precursor lymphoblastic lymphoma	9	2.2	6	1.4
Peripheral T-cell lymphoma	3	0.7	19	4.4
NHL, not otherwise specified	125	30.2	304	70.5
Central nervous system lymphomas	40	9.7	180	41.7

* Incidence rate per 100,000 person-years

Risk was significantly increased for people with AIDS versus HIV-only for DLBCL (relative risk (RR)=2.5; 95% confidence interval (CI)=2.1-2.9), CNS lymphomas (RR=4.3; 95% CI=3.1-6.0), and T-cell lymphomas (anaplastic large cell: RR=6.5; 95% CI=2.5-21.9; peripheral T-cell: RR=4.4; 95% CI=2.1-25.8), but was similar for BL and other major B-cell lymphoma subtypes. Additional analyses will compare risks for NHL subtypes in HIV-infected people to the general population using standardized incidence ratios.

Conclusion: In the HAART era, NHL subtypes other than those already considered "AIDS-defining" remain uncommon. The more severe immunosuppression associated with progression to AIDS is associated with increased risks of DLBCL, CNS lymphoma, and T-cell lymphomas.

O28. Time Trends of Cancer Mortality Rates Among Men in the Veterans Aging Cohort Study

Janet P. Tate[1], Mark Trentalange[1], Lesley S. Park[2], Kristina Crothers[3], Robert Dubrow[2]

[1]Department of Internal Medicine, Yale School of Medicine, New Haven, CT; [2]Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT; [3]Division of Pulmonary and Critical Care Medicine, University of Washington School of Medicine, Seattle, WA

Background: We compared time trends of cancer mortality rates between demographically similar veterans with and without HIV infection across 14 years in the Veterans Aging Cohort Study Virtual Cohort (VACS).

Methods: HIV-infected veterans are entered into VACS when they begin care in the Veterans Health Administration (VHA) for HIV disease. HIV-uninfected veterans are matched 2:1 to infected veterans by age, sex, race/ethnicity, and VHA site. We obtained cause of death by linking VACS with the National Death Index (NDI). We restricted this analysis to men because VACS is 98% male. We calculated age- and race-ethnicity-standardized mortality rates by calendar period, using the entire cohort person-year distribution for the standard weights. We calculated standardized mortality rate ratios (MRR) comparing HIV-infected to HIV-uninfected. We examined cancer as the underlying cause of death and any mention of cancer on the death certificate, for all cancers combined, AIDS-defining cancers, non-AIDS-defining cancers, and specific cancer types.

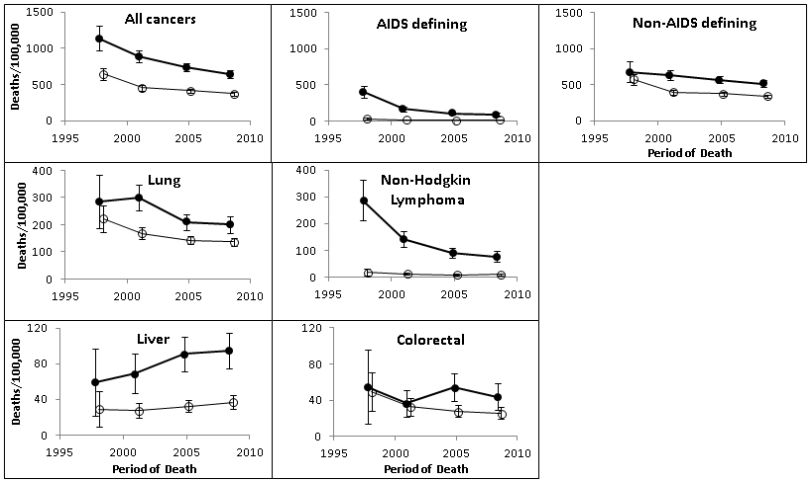

Figure 1. Age- and race-ethnicity-standardized "underlying cause" mortality rates (per 100,000 person-years) by calendar-year period (1996-1998, 1999-2002, 2003-2006, 2007-2009) and cancer group or specific cancer type for HIV-infected (●) and HIV-uninfected (o) veterans. The vertical bars represent 95% confidence intervals (some intervals are so tight that they are not readily visible.

Results: This analysis included 41,450 HIV-infected and 83,930 HIV-uninfected veterans who entered the cohort between October 1996 and December 2009 and were followed for death through 2009. The cohort was 47% black and 39% white. Median age at entry was 46 years. Of 27,195 deaths, 97% were successfully matched to NDI. All-cancer "underlying cause" mortality rates decreased over time among both HIV-infected and HIV-uninfected veterans (Figure 1); however, the MRR remained steady at about 1.75. Excess mortality for AIDS-defining-cancers among the HIV-infected remained high (MRR 9.1 in 2007-2009). The MRR for non-AIDS-defining cancers stabilized at about 1.5. For the four most frequent cancer types (lung, non-Hodgkin lymphoma, liver, colorectal), mortality rates were higher among the HIV-infected, but only liver cancer rates increased over time. When we divided colorectal cancer into colon and rectal cancer, elevated MRRs were restricted to rectal cancer. "Any-mention" MRRs were generally higher than "underlying cause" MRRs, with the all-cancer MRR remaining steady across periods at about 2.0. Excluding the first year of follow-up did not qualitatively change our results.

Conclusions: Cancer mortality rates overall decreased between 1996 and 2009, but liver cancer rates increased. MRRs comparing HIV-infected to HIV-uninfected remained elevated. This could result from elevated incidence among HIV-infected persons, which is known to occur for lung, non-Hodgkin lymphoma, liver, anal, and other cancers, or from poor survival among HIV-infected cancer patients. The elevated MRR for rectal cancer may be due to misclassification of anal cancer as rectal cancer.

Acknowledgement
This study is presented on behalf of the Veterans Aging Cohort Study.

O29. Epidemiologic Contributions to Recent Cancer Trends Among HIV-Infected People in the United States

Hilary A. Robbins, Meredith S. Shiels, Ruth M. Pfeiffer, Eric A. Engels

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: HIV-infected people have elevated risk for some cancers. Changing incidence of these cancers over time may reflect changes in three factors: HIV population demographic structure (e.g., age distribution), general population (background) cancer rates, and HIV-associated relative risks. We assessed the contributions of these factors to time trends in 10 cancers during 1996-2010.

Methods: We applied Joinpoint and Poisson models to data from the U.S. HIV/AIDS Cancer Match Study to estimate annual percent changes (APCs) in incidence rates of AIDS-defining cancers (ADCs: Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer) and 7 non-AIDS-defining cancers (NADCs). We evaluated HIV-infected cancer trends with and without adjustment for demographics, trends in background rates, and trends in standardized incidence ratios (SIRs, to capture relative risk).

Results: Cancer rates among HIV-infected people rose over time for anal (APC 3.8%), liver (APC 8.5%), and prostate (APC 9.8%) cancers, but declined for KS (1996-2000: APC -29.3%; 2000-2010: APC -7.8%), NHL (1996-2003: APC -15.7%; 2003-2010: APC -5.5%), cervical cancer (APC -11.1%), Hodgkin lymphoma (HL, APC -4.0%), and lung cancer (APC -2.8%) (Table 1). Breast and colorectal cancer incidence did not change over time. Based on comparison of unadjusted and adjusted models, changing demographics contributed to trends for KS and breast, colorectal, liver, lung, and prostate cancers (all $p<0.01$). Trends in background rates contributed to HIV-infected trends for NHL and cervical, anal, breast, and colorectal cancers, and notably liver (APC 5.6%) and lung (APC -3.2%) cancers. SIRs declined for all three ADCs, HL (APC -3.2%), and lung cancer (APC -4.4%).

Table 1. Summary of Contributions to Cancer Trends Among HIV-Infected People, 1996-2010

Cancer and Calendar Period	Crude Time Trend	Summary of Contributions to Trends Among HIV-Infected People		
		Changes in HIV Demographics	Changes in General Population Incidence	Changes in the SIR
KS: 1996-2000	Decreasing	Yes	Not assessed	Yes
KS: 2000-2010	Decreasing	Yes	Not assessed	Yes
NHL: 1996-2003	Decreasing	No	No	Yes
NHL: 2003-2010	Decreasing	No	Yes	Yes
Cervix	Decreasing	No	Yes	Yes
Anus	Increasing	No	Yes	No
Breast	No change	Yes	Yes	No
Colorectum	No change	Yes	Yes	No
HL	Decreasing	No	No	Yes
Liver	Increasing	Yes	Yes	No
Lung	Decreasing	Yes	Yes	Yes
Prostate	Increasing	Yes	No	No

Conclusions: Demographic shifts influenced some cancer trends among HIV-infected individuals, notably intensifying increases over time in liver and prostate cancers while obscuring declines in lung cancer. For ADCs, declines were largely explained by falling relative risk (likely attributable, at least in part, to the effects of HAART). Changes in general population incidence contributed to trends for many NADCs.

O30. Cancer Treatment Disparities in HIV-Infected Individuals in the United States

Gita Suneja[1,2], Meredith Shiels[3], Rory Angulo[4], Glenn Copeland[5], Lou Gonsalves[6], Anne Hakenewerth[7], Kathryn Macomber[8], Sharon Melville[9], Eric Engels[3]

[1]Department of Radiation Oncology, [2]Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA; [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD; [4]HIV Surveillance Program, Connecticut Department of Public Health, Hartford, CT; [5]Michigan Department of Community Health, Lansing, MI; [6]Connecticut Tumor Registry, State of Connecticut Department of Public Health, Hartford, CT; [7]Texas Cancer Registry, Texas Department of State Health Services, Austin, TX; [8]Michigan Department of Community Health, Lansing, MI; [9]Texas Department of State Health Services, Temple, TX

Background: HIV-infected individuals with cancer have worse survival compared with uninfected counterparts. Proposed explanations include advanced stage at diagnosis, biologically aggressive disease, and death from AIDS-related causes. An additional explanation may be differences in cancer treatment; however, few studies have examined whether cancer treatment rates differ between HIV-infected and uninfected individuals.

Methods: We studied adults ≥18 years diagnosed with non-Hodgkin lymphoma, Hodgkin lymphoma, and cervical, lung, anal, prostate, colorectal, and breast cancers from 1996-2010 in Connecticut, Michigan, and Texas. HIV status was determined by linkage between state cancer and HIV registries. Cancer treatment was defined as chemotherapy, surgery, radiotherapy, or any combination during the first course of treatment. For each cancer type, we used logistic regression to assess the relationship between HIV status and cancer treatment, adjusted for clinical and demographic variables. For local stage diffuse large B-cell lymphoma (DLBCL), and cervical, non-small cell lung (NSCLC), colon, and breast cancers, we used logistic regression to assess the relationship between HIV status and standard-of-care treatment. We identified predictors of cancer treatment among HIV-infected cancer cases.

Results: We evaluated 3,045 HIV-infected and 1,087,648 uninfected cancer cases. A significantly higher proportion of HIV-infected cases with DLBCL, Hodgkin lymphoma, lung cancer, prostate cancer, and colorectal cancer did not receive cancer treatment, with adjusted OR (aOR) and 95%CI as follows: DLBCL 1.39, 1.17-1.65; lung cancer 1.55, 1.28-1.87; Hodgkin lymphoma 1.68, 1.26-2.24; prostate cancer 1.48, 1.08-2.02; and colorectal cancer 1.89, 1.15-3.09. HIV infection was also associated with lack of standard cancer treatment for local stage DLBCL (aOR 1.80, 1.34-2.43), NSCLC (1.87, 1.13-3.09), and colon cancer (4.44, 1.64-12.01). Among HIV-infected individuals, factors independently associated with lack of cancer treatment included low CD4 count (aOR 1.46, 1.17-1.81), male gender with injection drug use as mode of HIV exposure (aOR 1.58, 1.16-2.16), age ≥45 years (1.30, 1.04-1.63), black race (1.27, 1.01-1.59), and distant (1.40, 1.07-1.83) or unknown cancer stage (2.80, 2.02-3.88).

Conclusions: HIV-infected individuals are less likely to receive cancer treatment than uninfected people with the same cancers. Predictors of treatment include low CD4 count, male gender with injection drug use as HIV exposure, older age, black race, and distant or unknown cancer stage. Lack of cancer management guidelines specific for HIV-infected patients, exclusion of HIV-infected individuals from cancer clinical trials, and provider discomfort with dual disease management may contribute to the observed lack of treatment.

1. Changes of microRNA Expression Profiles in Kaposi's Sarcoma-Associated Virus-Infected Cells Under Hypoxia

Coralie Viollet-Djelassi[1,2], David A. Davis[1], Carme Camps[2], Martin Reczko[3], Francesco Pezzella[4], Ioannis Ragoussis[2,3,5], Robert Yarchoan[1]

[1]HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [2]Wellcome Trust Centre for Human Genetics, University of Oxford, UK; [3]Alexander Fleming Biomedical Sciences Research Center, Vari-Athens, Greece; [4]Nuffield Division of Clinical Laboratory Sciences, University of Oxford, John Radcliffe Hospital, Oxford, UK; [5]Genome Sciences, McGill University, Montreal, Quebec, Canada

Kaposi's sarcoma-associated herpesvirus (KSHV) is the cause of three cancers: Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman's disease. Hypoxia plays an important role in KSHV lifecycle as hypoxia-inducible factors (HIFs) are involved in the latent/lytic switch and KSHV infection can in turn enhance cellular levels of HIFs. Also, two KSHV-associated tumors tend to develop in settings of hypoxia; KS often occurs in the extremities and PEL exists in pleural effusions, which are hypoxic. Herpesviruses, including KSHV, can encode for microRNAs (miRNAs), and there is recent evidence that miRNA can contribute to cancer pathogenesis. With this background, we hypothesized that hypoxia and KSHV infection can alter cellular and viral miRNA expression profiles and that those changes play a role in cancer progression and viral pathogenesis.

To address this, we compared miRNA expression profiles of KSHV infected cells and non-infected cells under normoxia (21% O_2) and hypoxia (1% O_2) using qRT-PCR, Illumina small RNA sequencing, and total RNA deep sequencing. In SLKK cells (latently infected with KSHV), 112 mature human miRNAs and 4 viral miRNAs were differentially expressed in hypoxia compared to normoxia. hsa-miR-210 was one of the most upregulated cellular miRNA (+ 7.3 fold). Increased levels of miR-210 in hypoxia compared to normoxia were further validated by qRT-PCR in different KSHV-positive cell lines (BCBL1 and SLKK cells). Interestingly, the presence of KSHV alone was sufficient to increase miR-210, which was found significantly upregulated in infected normoxic SLKK cells compared to non-infected normoxic SLK cells. miR-K12-3-3p was the most significantly downregulated viral miRNA in hypoxic compared to normoxic infected cells (- 2.1 fold). Also, human miR-663b was downregulated to undetectable levels in hypoxia.

The expression patterns of mRNA and miRNAs were analyzed using Ingenuity Pathway Analysis (IPA). Canonical pathways including glycolysis, atherosclerosis signalling and coagulation system were found differentially regulated by hypoxia compared to normoxia in infected SLKK cells. The effect of the host-derived and virus-derived miRNAs on the expression patterns of both host and virus RNAs is being elucidated through integrated analysis in order to identify targets. The target mRNAs and respective proteins are being investigated in relation to KSHV–associated diseases and the hypoxic pathway.

The outcomes of the present study will aid our understanding of how KSHV uses the host RNA silencing machinery to its advantage and provides clues as to how this intersects with the use of the cell's response to hypoxia. This research was supported in part by the Intramural Research Program of the NCI, NIH, and by the Wellcome Trust.

2. Conserved and Divergent Susceptibility to Lytic Induction of EBV and HIV

An T. Phan, Samantha G. Fernandez, Kristin M. Keck, J.J.L. Miranda

Gladstone Institute of Virology and Immunology, San Francisco, CA

Background: Lytic induction therapy attempts to reactivate latent virus for consequent eradication of infected cells by lysis, immune response, or antiviral drugs. Such approaches are gaining clinical traction in the treatment of the Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV). Our laboratory has systematically classified small molecules with different mechanisms of action based on the ability to induce lytic replication in latent EBV and HIV.

Materials and Methods: We treated cell culture models of EBV and HIV latency with chromatin modifiers (SAHA, TSA, butyrate), global regulators of immune activation state (antibodies, TNF), cytotoxic chemotherapy drugs (doxorubicin, gemcitibine, prednisolone, bendamustine), or an activator of apoptosis (PAC-1). Lytic replication was monitored by reporter gene expression or staining of an immediate early gene product.

Results: (1) Classes of small molecules differ in the ability to reactivate EBV and HIV. Chromatin modifiers as well as global regulators of immune activation state induce both EBV and the HIV. Cytotoxic chemotherapy agents, on the other hand, only reactivate EBV. Activation of apoptosis does not disrupt latency in either virus. This suggests that shared mechanisms of maintaining latency in both EBV and HIV include chromatin control of viral promoters and host control of immune signaling. Reactivation through the DNA damage pathway, however, remains specific to EBV. (2) Cell lines permissive to one inducer are similarly permissive to other molecules. We further examined multiple EBV-infected cell lines and observed that lines more resistant to induction by one drug are also comparatively orthogonal to other drugs regardless of mechanism. This argues that resistance or susceptibility is determined by a common downstream bottleneck. (3) Bendamustine and prednisolone are newly identified as specifically capable of reactivating EBV but not HIV.

Conclusions: Small molecules may be classified into groups based on conserved or divergent mechanisms of reactivation against EBV and HIV. We therefore advocate selective choice of reagents for lytic induction therapy while treating EBV-associated cancers in AIDS survivors or attempting to purge the latent HIV reservoir during EBV coinfection. Care must be taken to avoid unintended reactivation.

3. EBV-Mediated B-Cell Transformation Is Suppressed by Oncogene-Induced Senescence Through the DNA Damage Response

Karyn McFadden, Amy Hafez, Pavel A. Nikitin, Micah A. Luftig

Department of Molecular Genetics and Microbiology, Duke University School of Medicine, Durham, NC

HIV/AIDS patients are 20-50 times more likely to develop Non-Hodgkin's lymphoma (NHL) than the general population and 80% of those afflicted will develop a high grade form of the lymphoma. AIDS-NHL is also strongly associated with co-infection by Epstein Barr virus (EBV), a gamma-herpes virus found ubiquitously within the adult population. In healthy individuals, EBV induced malignancies are kept largely in check by a strong cytotoxic T-cell response. Additionally, the DNA damage response (DDR) has recently emerged as an intrinsic pathway that suppresses EBV mediated transformation.

Upon EBV infection in vitro, B cells undergo a transient period of hyper-proliferation mimicking a germinal center reaction. This hyper-proliferation could lead to replicative stress and the formation of double-stranded DNA breaks resulting in genomic instability. However, this damage is sensed by a DDR kinase, ATM, which triggers a signaling cascade that ultimately results in the inhibition of EBV-mediated transformation [see reference].

In our recent work, we have expanded upon this initial observation by separating cells that undergo hyper-proliferation into populations that arrest and those that continue to proliferate. The arrested population cannot be re-stimulated to proliferate in vitro unlike the proliferating population which become immortalized LCLs. This population is enriched for markers of the DDR and appears to senesce following activation of a G1/S phase checkpoint. Additionally, the arrested population has a reduction in EBNA3C, an EBV latency protein that functions to suppress the cell cycle inhibitor p16 among other targets. Using this new system to characterize these early events after infection, we are beginning to uncover the effectors that mediate senescence in EBV infected cells. Overall, we are trying to understand the intrinsic pathways that cells use to suppress EBV-induced malignancies. Reactivation of such pathways may be a promising avenue for the treatment of AIDS-associated lymphomas.

Reference

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4. Epigenetic Differences in EBV Lytic Control Region Between EBV Latency Type I and III Cells

Fang Lu, Karen DiWispeleare, Paul M. Lieberman

The Wistar Institute, Philadelphia, PA

Epstein-Barr virus (EBV) can establish several different latency types with distinct latent gene expression programs, and corresponding differences in epigenetic marks on the viral genome. Modulation of epigenetic marks by drugs or shRNA can lead to changes in EBV gene expression including reactivation from latency. Here, we report that EBV latency type I cells (derived from Burkitt's Lymphoma) and type III in vitro immortalized lymphoblastoid cell line (LCLs) have markedly different responsiveness to lytic inducing agents, especially histone deacetylase inhibitors like sodium butyrate (NaB). To better understand the mechanisms controlling this difference, we investigated the epigenetic marks at the EBV lytic control region that regulates Zta and Rta immediate early (IE) gene transcription. Our results indicate that NaB-responsive cells (Mutu I) had higher levels of acetylated histone H3 (H3ac) and trimethylated H3K4 (H3K4me3) than non-responsive LCL when induced with NaB. Mutu I also had higher basal level of DNA methylation than LCL, while LCL showed higher basal level of H3K27me3 and NaB treatment did not change the histone H3K27me3 levels in both cell lines. We also found that shRNA depletion of EZH2, a catalytic subunit of polycomb repressive complex2 (PRC2), can de-repress gene expression of EBV IE protein Zta and EBV lytic reactivation in LCL, as well as Mutu I cells. Our study suggests that PRC2 mediates H3K27me3 at the EBV lytic control region, and plays a dominant role in repressing lytic reactivation in NaB non-responsive LCL. These studies have implication for treating different types of EBV lymphomas and carcinomas.

5. Episomal Persistence of KSHV Is Cell Type and Passage Dependent

Thomas Ellison[1], *Dean Kedes*[1,2]

[1]*Department of Microbiology, Immunology, and Cancer Biology,* [2]*Department of Medicine, Division of Infectious Diseases, University of Virginia, Charlottesville, VA*

Despite extensive investigation, our understanding of establishment and maintenance of latency by Kaposi's sarcoma-associated herpesvirus (KSHV) following experimental infection of cells in culture remains limited. Most current experimental systems rely upon the application of drug selection to retain KSHV over passage in culture. The recent discovery of a highly permissive primary cell system (rat mesenchymal precursor cells, MM [see reference]) that supports efficient infection by KSHV has enabled us to examine this interaction more systematically. In the absence of any drug selection, MM cells infected with the recombinant reporter virus rKSHV.219 rapidly lost GFP expression over passage, while retaining a high level of characteristic punctate LANA dots over more than 60 passages in culture as evaluated by imaging flow cytometry. In contrast, HeLa cells infected similarly with the reporter virus declined concomitantly in both punctate LANA dots and eGFP expression. Unexpectedly, MM cells infected at a later passage number from isolation (P36 vs. P7) and without selection displayed a dramatic spontaneous de-repression of the episomal GFP locus after 20 passages without any evidence of reactivation or horizontal spread in culture. These highly GFP+ MM.219 cells were sensitized to chemically induced reactivation, but rarely proceeded to late gene (K8.1) expression. These data are consistent with a model in which regional transcriptional activity within the viral episome is both cell type and passage dependent. Furthermore, these highly variable correlations between LANA dot and GFP signals underscore the potential insensitivity of GFP as a sole surrogate marker for recombinant KSHV infection in primary cells, especially in the absence of drug selection.

Reference

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6. HAART Drugs Alter the Metabolism of Paclitaxel in Primary Cultures of Human Hepatocytes

Imam H. Shaik[1], Robert A. Parise[2], Venkateswaran C. Pillai[1], Susan M. Christner[2], Jan H. Beumer, Raman[2] Venkataramanan[1]

[1]Department of Pharmaceutical Sciences and Department of Pathology, University of Pittsburgh, Pittsburgh, PA; [2]Molecular Therapeutics Drug Discovery program, University of Pittsburgh Cancer Institute, Pittsburgh, PA

Background: Paclitaxel, a tubulin depolymerization inhibitor is used for the treatment of many types of cancer and is metabolized by CYP2C8 and CYP3A4. As HIV patients live longer, the incidence of cancer has increased and patients with cancer and HIV require concomitant anti-retroviral (HAART) and anticancer therapy. HIV patients take nevirapine (a non-nucleoside reverse transcriptase inhibitor) and cobicistat (an enzyme inhibitor with no pharmacological activity) as part of HAART, which may expose them to drug interaction due to enzyme induction and inhibition properties of HAART components. Paclitaxel exposure is associated with both toxicity and efficacy and changes in exposure due to drug-drug interaction is expected to have clinical consequences. We studied the interactions of nevirapine, cobicistat, rifampin and ketoconazole on paclitaxel in human hepatocytes.

Methods: Hepatocytes were pretreated with vehicle (0.1% DMSO), nevirapine (26 μM), rifampin (10 μM), cobicistat (2.4 μM) or ketoconazole (10 μM) for 4 days. On the fifth day, paclitaxel (3.5 μM) was added and incubated for 24-48 h. Concentrations of paclitaxel and its major metabolites 6α-hydroxyl paclitaxel and 3-hydroxypaclitaxel were quantitated in combined lysate and medium samples using LC-MS/MS.

Results: The half-life ($t_{1/2}$) of paclitaxel was decreased from 25.5±9.5 to 18.2±15.4 and 10.2±1.7 h respectively, upon treatment with nevirapine and rifampin. The apparent intrinsic clearance (CLint,app) of paclitaxel was increased by 1.5-fold by nevirapine and 1.9-fold by rifampin. Cobicistat increased the $t_{1/2}$ of paclitaxel from 25.5 ±9.5 to 94.2±50.3, whereas ketoconazole did not alter the $t_{1/2}$. The paclitaxel CLint, app was decreased by 2.4-fold due to treatment with cobicistat whereas ketoconazole did not show any effect. The in vitro effects of ketoconazole is in line with clinical observations of the absence of an effect of ketoconazole on paclitaxel exposure. There are no clinical data on the effect of rifampin on paclitaxel. To achieve the desired drug exposure of paclitaxel in HIV patients on cobicistat and nevirapine, the paclitaxel dose may have to be reduced by at least 2-fold or increased by 1.5-fold, respectively. These observations may inform the starting doses of safety and pharmacokinetic clinical trials which will serve to validate our findings.

7. HAART Drugs, Ritonavir and Efavirenz, Alter the Metabolism of Anticancer Drug Imatinib in Primary Cultures of Human Hepatocytes

Venkateswaran Pillai, R.A. Parise, S.M. Christner, M.A. Rudek, J.H. Beumer, R. Venkataramanan

School of Pharmacy and University of Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, PA

Purpose: Patients with HIV are prone to AIDS defining and non-AIDS defining malignancies. In these patients antineoplastic therapy has to be used along with highly active antiretroviral therapy (HAART). A major concern is the complex drug interactions of HAART therapy as a result of their ability to inhibit or induce cytochrome P450, UGTs and uptake/efflux drug transporters. Our objective is to evaluate the potential interaction of HIV drugs ritonavir and efavirenz on the anticancer drug imatinib using primary cultures of human hepatocytes.

Methods: Two days after plating, hepatocytes were incubated with ritonavir (10 μM), ketoconazole (1 μM), efavirenz (10 μM), rifampin (10 μM) or vehicle control (0.1% DMSO) for 4 days. On day 5, imatinib (2.5 μM) was incubated with the above agents for another 24-48 h. The concentration of imatinib was measured in the collected samples (combined lysate and medium) using LC-MS. The half-life ($t_{1/2}$) and apparent intrinsic clearance ($CL_{int,app}$) of imatinib were calculated.

Results: The results are expressed as mean±S.D (n=3). Data were analyzed by non-parametric Friedman ANOVA followed by Dunn's multiple comparison test. The half-life (t½) of imatinib increased from 13.2±1.4 to 25.5±7.2 and 15.2±4.9 h respectively, upon treatment with ritonavir and ketoconazole. The $CL_{int,app}$ of imatinib was lowered 1.9-fold by ritonavir, and was not affected by ketoconazole. Efavirenz and rifampin decreased $t_{½}$ of imatinib from 14.5±3.1 to 8.2±2.8 and 5.1±0.9 h, respectively. The $CL_{int,app}$ of imatinib was increased 1.9-fold by efavirenz and 2.9-fold by rifampin.

Conclusions: Our results suggest that, in order to achieve comparable drug exposure, the clinically used dose (400 mg per day) of imatinib may have to be reduced (200 mg per day) or increased (400 mg twice daily), respectively, when ritonavir or efavirenz is co-administered. These results may inform confirmatory Phase I trials of imatinib in combination with HAART through the Aids Malignancy Consortium (AMC).

8. The Impact of Disrupting Rag-GTPase on KSHV Lytic Replication

Eric S. Pringle[1], Andrew M. Leidal[1], Craig McCormick[1]

[1]Department of Microbiology and Immunology, Dalhousie University, Halifax, Nova Scotia, Canada

Kaposi's sarcoma lesions are comprised of KSHV-infected spindle cells of endothelial origin. A small percentage of these cells undergo sporadic entry into lytic replication contributing to production of progeny virions as well as elaboration of a potent milieu of pro-inflammatory cytokines, both of host and viral origin. Given that ganciclovir treatment can lead to tumor reduction and the ability of vGPCR expressing endothelial cells to drive spindle proliferation in mouse models, lytic cells are likely essential for KS tumour survival and progression. The discovery that rapamycin and other rapalogues can also lead to KS regression and inhibit virus replication highlights the importance of the mTORC1 pathway to KSHV biology. For mTORC1 to be active, it must be localized to the lysosomal membrane by the Ragulator complex and small Rag-GTPase that are activated by intra-lysosomal amino acids. Lysosome bound mTORC1 can then be activated by Rheb-GTP. KSHV encodes at least three lytic proteins that stimulate signaling pathways that integrate on Rheb, ORF45, vGPCR, and K1. Fittingly, we and others have found that KSHV lytic replication features mTORC1 activation. However, it remains unclear by what means KSHV maintains Rag-GTPase activity. We hypothesised that it might also be possible to interrupt mTORC1 signaling in KSHV by disrupting the function of Rag-GTPases. Metformin, a biguanide compound used as an oral diabetes treatment, has recently been shown to disrupt mTORC1 kinase activity by the association of mTORC1 with lysosomes in a Rag-GTPase dependent manner. Here we show that metformin effectively restricts KSHV lytic replication and cytokine production, similar to virus replication in amino acid limiting environments. Metformin and other Rag-GTPase inhibiting compounds might represent a new class of KS therapeutic with a similar effect as rapalogues but with a distinct mechanism of action.

9. Influence of Poly(ADP-ribose) Polymerase (PARP1) on Methylation Pathway Enzymes in Human Papillomavirus Infection Relevant to HIV Infection

Kristofer Chua[1], Provabati Barman[1], David Elashoff[2], Diboro Kanabolo[1], Dorothy J. Wiley[1]

[1]Division of Translational Science, School of Nursing, [2]Biostatistics and Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA

Background: HPVs are a significant cause of human anogenital cancers worldwide; better understanding of the natural history of neoplasia may yield effective therapeutic targets. DNA-methyltransferases (DNMT) chemically modify cytosines, whether paired with guanine (CpG motif) or in CpA, CpT, and CpC motifs (non-CpGs). DNMT1 differentially affects CpGs. Poly(ADP-ribose) Polymerase (PARP1) modulates DNA repair pathways, chromatin architecture and gene expression; it directly down-regulates DNA methyltransferase 1 (DNMT1). Studies suggest PARP1 may modify Human papillomavirus Type 16 (HPV16) gene transcription as well. Our recent findings show focused methylated CpGs and non-CpGs in the HPV16 Long Control Region are more often associated with low-grade, not high-grade anal neoplasia. Thus, PARP1 and DNMT1 activity are of special interest and may be possible therapeutic targets in HPV16 infection.

Materials and Methods: HPV16-W12-episomal (W12E) cells and –uninfected oral keratinocytes (OK) were cultured using a standard protocol, grown to >80% confluence, and cells were treated for 24 hours with 3-aminobenzamide (3ABA) to inhibit PARP1. DNMT1 and HPV16-E2 –E6, and –E7 mRNA expression were evaluated using qPCR for (3ABA)-treated and –untreated cells. Estimates were normalized using GAPDH expression estimates. Descriptive analyses estimated the mRNA fold-change across cell types and across treatment groups for each outcome measure.

Results: In W12 cells, 3ABA-treatment decreased HPV16-E6 and –E7 mRNA expression 7% and 52%, respectively, i.e., treatment vs. not: for E6: dCt=0.78 {95% Confidence Interval: (0.77, 0.79)} vs. =0.67 (0.66, 0.68); for E7: dCt=2.74 (2.72, 2.75) vs. =2.13 (2.09, 2.16), respectively. However, E2-mRNA increased 21% with treatment, i.e., 3ABA-treated vs. untreated W12 cells, for E2: dCt=1.24 (1.22, 1.26) vs. =1.515, (1.51, 1.52). Albeit not statistically significant, data showed DMNT1-mRNA increase 4.4-fold with 3ABA-treatment in OK cells but decreased 38% over the untreated condition for HPV16-infected W12 cells (p-values>0.05).

Conclusions: PARP1 inhibition appears to more significantly affect HPV16 viral transcription than DNMT1 in W12 cells. Down-regulation of HPV16-E7 transcription appears more severe when compared to quantitative assessments of HPV16-E6 mRNA using quantitative PCR. However, HPV16-E2, a transcription repressor, is up-regulated when PARP1 is inhibited by 3ABA. Analyses showed DNMT1 mRNA was not statistically significantly changed with PARP1 inhibition.

10. Investigating the Role of KSHV miRNAs in Bypass of Oncogene-Induced Senescence

Natalie Sachrajda[1], Andrew M Leidal[1,2], J.M. Ziegelbauer, Craig McCormick[1]

[1]Department of Microbiology and Immunology, Dalhousie University, Halifax, Nova Scotia, Canada; [2]Department of Pathology, University of California, San Francisco, San Francisco, CA

Kaposi's sarcoma-associated herpesvirus (KSHV) is the infectious cause of Kaposi's sarcoma (KS), an AIDS-related cancer. KSHV has the ability to bypass a host anti-proliferative defence mechanism known as oncogene-induced senescence (OIS). OIS, a form of permanent cell-cycle arrest, is triggered by chronic oncogene expression and is being increasingly recognized as an important tumor suppressor mechanism in vivo. KSHV encodes 18 microRNAs (miRNAs) which are known to target tumor suppressor pathways and fine-tune host gene expression to create a local pro-tumor environment in KS tissue. Using an OIS-bypass screen, we identified two miRNAs that induced bypass of senescence. We are currently pursuing the mechanism by which these miRNAs bypass OIS by studying their effects on DNA damage responses, cell cycle regulation and autophagy, all of which are functionally implicated in OIS. We anticipate that our studies of viral control of OIS will advance our understanding of the fundamental mechanisms that govern OIS and how OIS can go awry in cancers that lack an underlying viral etiology.

11. The Kaposi's Sarcoma-Associated Herpesvirus ORF34 Protein Interacts With and Regulates the Hypoxia-Inducible Factor-2

Muzammel Haque, Konstantin Gus Kousoulas

Division of Biotechnology and Molecular Medicine, and Department of Pathobiological Sciences, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA

The hypoxia-inducible factors-1α (HIF-1α) and -2α (HIF-2α) are transcription factors which play important roles in the Kaposi's sarcoma-associated herpesvirus (KSHV) latent and lytic gene replication [1,2,8]. Both HIF-1α and HIF-2α are expressed in KS samples indicating that they play potentially important roles in the KSHV life cycle (3). HIF-1α and HIF-2α have similar structural and functional domains but have distinct transcriptional targets. Recently, several KSHV-encoded proteins have been shown to interact and affect the stability of HIF-1α [6,7]. Previously, we showed that the ORF34 promoter was strongly activated by HIF-2α acting through a functional hypoxia response element (HRE) located within the ORF34 promoter region [4]. Moreover, we showed that the KSHV ORF34 protein binds and causes HIF-1α degradation through the ubiquitin pathway [5]. In the present study, we show that the ORF34 protein interacts with HIF-2α. Specifically, immunoprecipitation of the ORF34 protein co-immunoprecipitated with the wild-type and the degradation-resistant form of HIF-2α. Additional co-immunoprecipitation experiments revealed that the carboxyl terminal portion of the ORF34 protein interacted strongly with the HIF-2α. Importantly, increasing amounts of ORF34 protein correlated with increased stability of the HIF-2α protein. The effect of ORF34 protein on HIF-2α dependent transcription is under investigation.

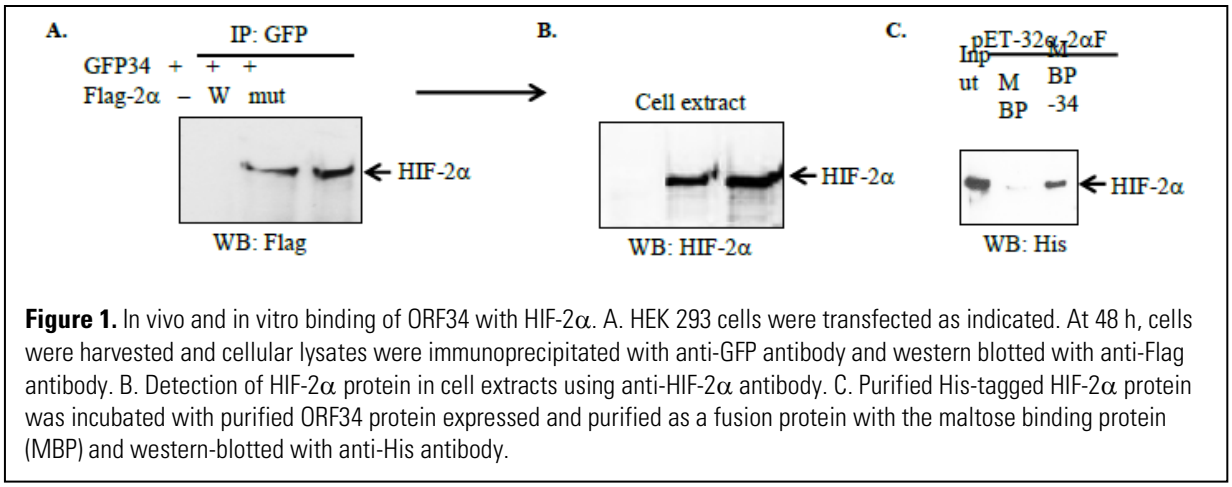

Figure 1. In vivo and in vitro binding of ORF34 with HIF-2α. A. HEK 293 cells were transfected as indicated. At 48 h, cells were harvested and cellular lysates were immunoprecipitated with anti-GFP antibody and western blotted with anti-Flag antibody. B. Detection of HIF-2α protein in cell extracts using anti-HIF-2α antibody. C. Purified His-tagged HIF-2α protein was incubated with purified ORF34 protein expressed and purified as a fusion protein with the maltose binding protein (MBP) and western-blotted with anti-His antibody.

Conclusion: This study shows that the KSHV ORF34 protein regulates HIF-1α and HIF-2α protein levels by different mechanisms.

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12. Kaposi's Sarcoma Tumor Evolution Is Characterized by Mast Cell-Driven Wound Remodeling

Christine A. King[1], Leona W. Ayers[2], David G. Nohle[2], David A. Kellough[2], Rosemary Rochford[1]

[1]Department of Microbiology and Immunology, SUNY Upstate Medical University, Syracuse, NY; [2]Department of Pathology, The Ohio State University, Columbus, OH

Background: Kaposi's sarcoma (KS) skin lesions involve chronic inflammation and abnormal vascular proliferation and are often described as wounds that fail to heal. Wound healing is a complex transition involving several temporally overlapping stages including inflammation, proliferation and remodeling. Wound healing involves multiple cell populations, the extracellular matrix and soluble mediators including cytokines and growth factors. Mast cells (MCs) and macrophages are key effector cells implicated in wound healing.

Materials and Methods: Paraffin embedded sections from KS lesions were obtained from the AIDS and Cancer Specimen Resource (ACSR/NCI). Skin lesions examined included patch, lymphangiomatous-like (LL-K), plaque and three stages of nodule development including very early nodule, intermediate nodule and maturing KS nodule. Tissue sections were stained for MC tryptase antibody (mouse monoclonal, clone AA1, DAKO, CA), KSHV lytic antibody 8.1 (mouse monoclonal, ORF K8.1a) and LANA-1 antibody (HHV8 mouse monoclonal, clone 13B10, NovoCastra/Leica) by immunohistochemistry (IHC). Stained slides were digitized at 20x resolution using ScanScope XT (Aperio,Vista, California). Regions of interest (ROI) were identified and the number of MCs was quantified using Tissue Studio 3.5 software (Definiens, Munich, Germany). A Definiens-based MC counting software algorithm was applied to each ROI.

Results: We observed prominent MC localization to vascular areas in association with all stages of KS lesions. Dual IHC for MC tryptase and LANA-1 antigens demonstrated that a subset of these cells expressed latent and lytic KSHV proteins and that latent antigen (LANA) was present in most KS tumor cells. In identifiable KS lesions, deposition of Type 1 collagen, a procollagen, encompassed the proliferation zone of all types of KS tumors and extended throughout the lesion. As the KS tumor matured, Type 1 collagen disappeared from the dense KS tumor mass along with diminished inflammatory cells, including MCs. Advanced KS tumors had a hyalinized appearance very different from the active, highly vascular, MC-rich KS lesions.

Conclusions: Our data clearly demonstrate that the stages of wound healing, including wound remodeling, underlie the evolution of the KS tumor and that major components of the evolving lesion, including MCs, are KSHV infected.

13. Mast Cells in Kaposi's Sarcoma – A Model for the Pathogenesis of KSHV-Driven Oncogenesis

Christine A. King[1], Leona W. Ayers[2], Julie A. Ritchie[1], Rosemary Rochford[1]

[1]Department of Microbiology and Immunology, SUNY Upstate Medical University, Syracuse, NY; [2]Department of Pathology, The Ohio State University, Columbus, OH

Background: KSHV, an oncogenic herpesvirus and etiologic agent of the endothelial cell neoplasm Kaposi's sarcoma (KS) is dependent upon both viral infection and chronic inflammation to produce lesions. Mast cells (MCs) are potent effectors of inflammation and fully permissive to KSHV. Infection in vitro with de novo viral gene expression is observed as early as 6h post-infection (p.i) and culminates in release of infectious progeny capable of establishing latent infection in primary human endothelial cells by 24 h p.i. [Ritchie 2012] We hypothesized that MCs are permissive for KSHV infection in vivo and contribute to KSHV-induced tumorigenesis.

Materials and Methods: Paraffin tissue sections of KS lesions from skin, lymph nodes, lung and GI were secured from the AIDS and Cancer Specimen Resource (ACSR/NCI). Tissue sections were stained with MC tryptase antibody (mouse monoclonal, clone AA1, DAKO, CA), histamine antibody (rabbit polyclonal, Lifespan), KSHV lytic antibody 8.1 (mouse monoclonal, ORF K8.1a) and LANA antibody (HHV8 mouse monoclonal, clone 13B10, NovoCastra/Leica) by immunohistochemistry (IHC). Stained slides were digitized at 20x resolution using ScanScope XT (Aperio, Vista, California). Regions of interest (ROI) were identified and MCs were quantified using Tissue Studio 3.5 software (Definiens, Munich, Germany). Definiens software algorithm to count MCs was applied to each ROI. Counts of MCs were compared to KS adjacent areas.

Results: We found that MCs were increased in association with KS tumor in all tissues examined. MCs were not evenly distributed throughout lesions; rather MC density was increased in vascular lesions and young lesions, greater at the periphery, highly associated with vessels while few MCs were observed within tight bundles of KS tumor cells (often degranulated). MCs exhibited extensive degranulation of cytoplasmic tryptase and histamine into early tumor expansion but disappeared as tumor matured. In lymph nodes with KS and Multicentric Castleman's Disease (MCD), MCs were associated with KS and vessels penetrating the node capsule but not with MCD follicles or KSHV infected plasmablasts. IHC staining demonstrated a sub-population of MCs within KS lesions that were positive for KSHV LANA. One infected MC was seen in contact with an infected plasmablast.

Conclusions: Human MCs, some latently infected with KSHV, are associated with KS in cutaneous, lymph node, lung and GI lesions in vivo where MCs accumulate at the vascular interface between healthy and malignant KS tissue, are a potential source of infectious virus and act as inflammatory drivers to maintain and advance lesions.

14. Novel Mechanism of KSHV Reactivation by Oral Bacterial Products

Janet Doolittle[1], RoShauna Rothwell[1], Deborah Granger[2], Brad Picott[1], Jennifer Webster-Cyriaque[1,3,4]

[1]Dental Research, School of Dentistry, [2]Department of Pharmacology, School of Medicine, [3]Department of Microbiology and Immunology, School of Medicine, [4]Department of Medicine, Lineberger Comprehensive Cancer Center, The University of North Carolina School of Medicine, Chapel Hill, NC

Background: Herpesviral sequences and bacterial infection co-occur at multiple sites, including the gut and the genitourinary tract. Recently, co-infections have been detected in the oral cavity, particularly in severe cases of periodontitis. The detection of replicating virus in these tissues has incited investigation of the relationship between bacterial infection and Kaposi Sarcoma-associated Herpesvirus (KSHV) reactivation.

Methods: Bacterial end products include short chain fatty acids (SCFAs), lipopolysaccharide (LPS), and lipoteichoic acid (LTA), among others, and are secreted by the oral bacterium *P. gingivalis* (PG), initiating viral reactivation from latency. Latently infected KSHV cell lines were incubated with crude spent media containing secreted components from PG or the known chemical inducers, TPA and sodium butyrate (NaB). Changes in gene expression upon viral reactivation by these three different inducers were assessed by microarray. Expression of selected genes was validated using qPCR. Enriched gene sets, determined using Gene Set Enrichment Analysis (GSEA), were compared to find similarities and differences. Induction of the hypoxia response was validated by luciferase assay using pGL2-HRE-luc in A293 cells.

Results: Our analysis revealed widespread inhibition of gene expression following KSHV reactivation. Directly comparing different the viral inducers, PG upregulates cancer-associated genes, while TPA upregulates genes involved in oxidative phosphorylation. In contrast to PG, NaB increases expression of genes involved in rRNA transcription. There were 206 gene sets significantly different between NaB and TPA treated cells, 17 between PG and TPA, and 2 between PG and NaB. Proteins involved in epigenetic modification were present in many gene sets enriched in response to PG treatment. In addition, hypoxia related genes were upregulated in TPA and PG spent media treated cells, but not in NaB treated cells. Hypoxia is a known inducer of KSHV reactivation. Induction of the hypoxia response in PG and TPA treated cells was confirmed by luciferase assay using a promoter containing hypoxia response elements.

Conclusions: TPA, NaB and PG spent media induce reactivation of KSHV through different mechanisms, with PG-induced reactivation being more similar to those of each chemical than the two chemicals are to each other. PG and TPA induce a hypoxic response in A293 cells, giving clues to the mechanism of reactivation of KSHV in the mouth. Oral bacteria facilitate viral pathogenesis and advance periodontal disease.

Acknowledgements
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15. Phosphoproteomic Analysis of KSHV-Infected Cells Reveals Diverse Roles of a Viral-Activated Cellular Kinase

Denis Avey, Fanxiu Zhu

Florida State University, Tallahassee, FL

Kaposi's sarcoma-associated herpesvirus (KSHV) is the etiological agent of primary effusion lymphoma, a subset of multicentric Castleman's disease, and Kaposi's sarcoma, the most common malignancy in HIV/AIDS patients. The pathogenesis of KSHV is intimately linked to its manipulation of cellular signaling pathways, including the extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase (MAPK) pathway. The aberrant stimulation of this pathway is induced by a wide variety of viruses and is a critical determinant in the progression of several diseases, including many human cancers. We have previously shown that KSHV ORF45 forms complexes with both ERK and p90 ribosomal S6 kinase (RSK, a major functional mediator of ERK MAPK signaling), and contributes to their sustained activation during KSHV lytic replication [1]. The activation of RSK by ORF45 is required for optimal KSHV progeny virion production, though the precise role of this activation throughout the viral life cycle is still unclear. We hypothesized that the activation of RSK by ORF45 causes differential phosphorylation of cellular and viral substrates, mediating downstream biological processes essential for efficient KSHV lytic replication. Accordingly, we observed widespread and significant differences in protein phosphorylation upon induction of lytic replication. Kinase inhibitor treatments confirmed that some of these changes are dependent on RSK activity. A phosphoproteomic screening identified several hundred proteins in KSHV-infected cells which exhibit differential phosphorylation upon lytic reactivation. Moreover, a comparison of the phosphoproteomic profiles of cells infected by either wild-type KSHV or a mutant deficient in RSK activation confirms that the phosphorylation of a subset of proteins is dependent on RSK activation by ORF45. These substrates are involved in the regulation of epigenetic modifications, transcription, and translation, among other processes. We confirmed our previous finding that eukaryotic translation initiation factor 4B (eIF4B) is phosphorylated at Ser422 in an ORF45/RSK-dependent manner during KSHV lytic replication [2]. Further characterization of the roles of ORF45-activated RSK during KSHV lytic replication will increase our understanding of the mechanisms by which KSHV manipulates host cell signaling pathways, and may be useful in the development of novel therapeutic options for the treatment of KSHV-related diseases.

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16. Pleural Effusions in Patients With Kaposi Sarcoma Are Associated With High Levels of Intracavitary IL6 and IL10 Suggesting That Intracavitary Inflammation Contributes to Disease Pathophysiology

Yuanbin Chen[1], Thomas S. Uldrick[2], Mark N. Polizzotto[2], Kathleen M. Wyvill[2], Karen Aleman[2], Seth M. Steinberg[3], Stefania Pittaluga[4], Vickie Marshall[5], Richard F. Little[2], Denise Whitby[5], Robert Yarchoan[2]

[1]Medical Oncology Branch, [2]HIV and AIDS Malignancy Branch, [3]Biostatistics and Data Management Section, and [4]Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [5]AIDS and Cancer Virus Program, SAIC-Frederick, National Cancer Institute, National Institutes of Health, Frederick, MD

Background: Patients with Kaposi sarcoma (KS) can develop pleural effusions. KS-associated herpesvirus (KSHV) can induce cytokine abnormalities, especially in IL-6 and IL-10, which contribute to symptoms in KSHV-associated multicentric Castleman disease (MCD) or KSHV-associated inflammatory cytokine syndrome (KICS). We hypothesize KS-associated pleural effusions are associated with localized cytokine abnormalities, and that many patients with KS-associated pleural effusions have KSHV-MCD or KICS.

Methods: Patients with KS and pleural effusions in whom concurrent primary effusion lymphoma had been excluded were identified and reviewed. Patients could have treated KSHV-MCD or lymphoma in remission. No effusion was attributable to concurrent untreated infection. Effusions were classified as chylous if effusion triglycerides >110 mg/dL. Paired serum and pleural effusion supernatants were evaluated for inflammatory cytokines. KSHV viral load (VL) was evaluated in blood and effusions. Differences between matched effusion and serum cytokines and KSHV VL were evaluated by Wilcoxon signed-rank test. Cytokines and KSHV VL between those with chylous and non-chylous effusions were compared by exact Wilcoxon rank-sum test. $p<0.01$ was considered significant, $0.01 < p < 0.05$ represented a trend. Survival was evaluated using Kaplan-Meier methods.

Results: *Patient characteristics:* 11 male patients, median (med) age 33 (23-45), documented pulmonary KS 4 (45%). All but one had a history KSHV-MCD (4) or KICS (6). Other conditions: lymphoma in remission (2), concurrent neuroendocrine tumor (1). Six had chylous effusions. Med CD4 55 cells/uL (7-402), HIV < 200 copies/mL (7), med c-reactive protein 44 mg/dL (0.7-62). *Cytokine results:* Pleural fluid IL-6, and IL-10 were significantly elevated compared to serum; pleural fluid IL-1b, TNF-a and KSHV VL elevations trended towards significance. Effusion IL-6 levels were ~2 log higher than those previously observed in serum of patients with symptomatic KSHV-MCD. Although based on very few cases, circulating KSHV PBMC (med 925 vs. 0 copies/10^6 PBMCs, p=0.046) and effusion IL-1b (med 15.3 vs. 1.9 pg/mL, p=0.032) exhibited trends toward greater values in non-chylous patients. *Overall survival:* Med survival was 64% after 5.5 months. Dividing cases according to chylous effusions or not, curves plateaued at 83% and 40% respectively.

Conclusions: KS-associated effusions contain very high levels of IL6. Intracavitary cytokine production may contribute to disease pathophysiology, especially in nonchylous effusions. Nonchylous effusions are generally associated with elevated circulating KSHV, effusion IL-1b, KSHV detected within these effusions (median 95,625 copies/10^6 PBMCs), and a high risk of death. Proteins not tested here, such as viral IL6, may also be important in KS-associated effusions.

17. Progressive Accumulation of Activated ERK2 Within Highly Stable ORF45-Containing Nuclear Complexes Promotes Lytic Gammaherpesvirus Infection

Evonne N. Woodson[1,2], Melissa S. Anderson[1,2], Matthew S. Loftus[1,2], Dean H. Kedes[1,2,3]

[1]Myles H. Thaler Center for AIDS and Human Retrovirus Research, [2]Department of Microbiology, Immunology, and Cancer Biology, [3]Department of Internal Medicine, University of Virginia Health Systems, Charlottesville, VA

Background: Earlier studies demonstrated that gammaherpesvirus infections result in the activation of mitogen activated protein kinases (MAPK) [1,2], including the extracellular signal-regulated kinases (ERK), ERK1 and 2. De novo infection with Rhesus monkey rhadinovirus (RRV), a close homolog of the human oncogenic pathogen, Kaposi's sarcoma-associated herpesvirus (KSHV), led to persistent activation of ERK2 and increased nuclear accumulation of pERK2 complexed with the RRV protein, ORF45 (R45) and cellular RSK. Using confocal microscopy, sequential pull-down assays and FRET analyses, we demonstrated that pERK2-R45 and pERK2-R45-RSK2 complexes were restricted to the nucleus and that pERK2 retained its ability to phosphorylate nuclear substrates. Further, even with pharmacologic inhibition of MEK, pERK2 but not pERK1, remained elevated during RRV infection, showing zero order decay and a half-life of 6-8 hours. Transfection of rhesus fibroblasts with R45 alone also led to the accumulation of nuclear pERK2 and addition of exogenous RSK augmented this effect. However, knockdown of RSK during bona fide RRV infection had little to no effect on pERK accumulation or virion production. The cytoplasmic pools of pERK showed no co-localization with either RSK or R45 but activation of pERK downstream targets in this compartment was evident throughout infection.

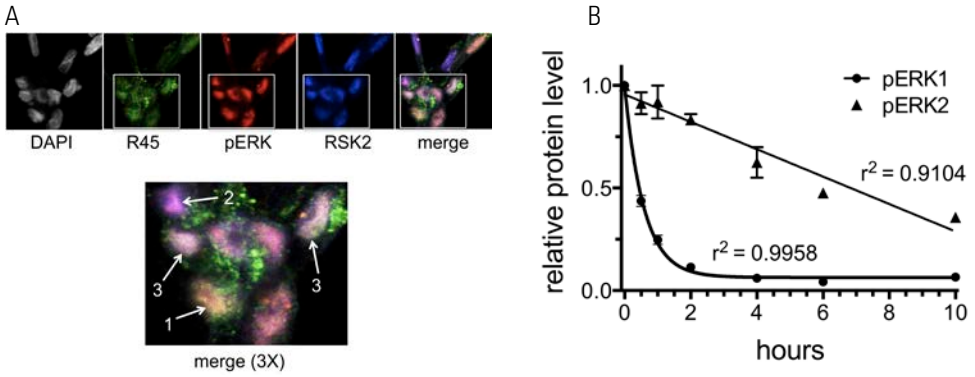

Figure 1. Activated ERK2 exists in highly stable complex with the viral protein, R45 and cellular RSK during de novo RRV infection. (A) RhF infected with RRV for 48h were fixed, permeabilized, and co-stained with the indicated antibodies. The images from columns 2 and 3 were merged manually to produce images in column 4. Areas of colocalization are indicated by white arrows. Bottom row: Infected RhF stained for all three proteins (R45, pERK, and RSK2). The inset in each single stained image, denoted by the white box, was merged to produce the overlay. An enlarged image (3X) of the triple overlay (bottom): 1. R45+pERK merge (yellow/orange), 2. pERK+pRSK2 (magenta), and 3. R45+pERK+pRSK2 (white). (B) Graphical representation of the decay of pERK1 and pERK2 in RRV-infected RhF (48h) following the addition of DMSO or the MEK inhibitor, U0126. Data are the mean of two independent experiments with error bars reflecting the range of the two values.

Conclusion: Together, these observations suggest a model in which R45 interacts with pERK2 to promote its nuclear accumulation, thereby promoting lytic viral gene expression, while also preserving persistent and robust activation of both nuclear and cytoplasmic ERK targets.

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18. Prospective Clinical, Virologic, and Immunologic Characterization of Kaposi Sarcoma Herpesvirus (KSHV) Inflammatory Cytokine Syndrome

Mark N. Polizzotto[1], Thomas S. Uldrick[1], Kathleen M. Wyvill[1], Karen Aleman[1], Vickie Marshall[2], Richard F. Little[1], Denise Whitby[2], Stefania Pittaluga[3], Seth M. Steinberg[4], Irini Sereti[5], Robert Yarchoan[1]

[1]HIV and AIDS Malignancy Branch, [3]Laboratory of Pathology, [4]Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [2]Viral Oncology Section, AIDS and Cancer Virus Program, Frederick National Cancer Laboratory; [5]HIV Pathogenesis Unit, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD

Background: Kaposi sarcoma herpesvirus (KSHV) is the causative agent of Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and a form of multicentric Castleman disease (KSHV-MCD), each associated with HIV. Recently a novel KSHV-associated syndrome distinct from KSHV-MCD was described [see reference]: KSHV inflammatory cytokine syndrome (KICS). We report characteristics of the first ten patients prospectively studied with KICS, separate from the original six cases, and compare them with HIV-infected controls.

Methods: We evaluated adults with at least two clinical abnormalities potentially due to KICS, including culture, biopsy and FDG-PET/CT to exclude alternate explanations such as KSHV-MCD. Those meeting the protocol case definition, including elevated CRP and KSHV viral load (VL), were followed. To better delineate any possible contribution of HIV to our findings we compared KICS patients with two control cohorts that were prospectively characterized: 20 HIV/KSHV-coinfected adults, and 20 HIV-infected adults not known to be KSHV-infected, each stratified by HIV suppression (10 with HIV VL <50copies/mL and 10 HIV VL>1000 in each). Comparisons were made by Wilcoxon rank-sum; given multiple comparisons $p<0.005$ was considered significant and $0.005<p<0.05$ trends.

Results: All 10 KICS subjects were HIV infected males; median (range) age 36 years (22-60); HIV VL 72 copies/mL (<50-74375; <50 in 5/10), CD4 88/μL (7-1308); KS in 10/10 and PEL in 2/10. Median number clinical abnormalities present 8 (6-11), worst symptom present CTC grade 3 (2-4). Symptoms included: gastrointestinal (present in 9/10); edema (9/10); respiratory (6/10); effusions (5/10); adenopathy (4/10); neurologic (3/10); fever (2/10). Laboratory abnormalities included anemia (present in 10/10, median hemoglobin 9.0g/dL, range 6.5-10.2); hypoalbuminemia (10/10, 2.4g/dL, 1.6-3.1); thrombocytopenia (6/10, 138×10^9/L, 27-371); leukopenia (4/10, 5.2K/μL, 2.5-13.9) and elevated CRP (10/10, 37.8g/dL, 4.9-185.0). None developed KSHV-MCD over 2 to 36 months; 5 died (3 KSHV-associated tumors, 2 other causes) while 5 remitted with various therapies. KICS patients compared with both HIV stratifications within each control group had more severe symptoms; lower hemoglobin and albumin; higher CRP; and elevated KSHV VL (1569 copies/10^6 PBMCs, 0-90909); human IL-6 (14.6pg/ml, 3.6-330.3); and IL-10 (36.5pg/ml, 4.6-2357.0); comparisons were significant or strong trends. Other cytokines (IFN-γ, TNF-α, IL-1 IL-8, IL-12) were not consistently different between KICS and control cohorts.

Conclusions: KICS subjects demonstrated diverse severe clinical abnormalities and a high rate of intercurrent KSHV-associated tumors. KSHV VL and an IL-6/IL-10 cytokine signature were elevated even compared with controls with unsuppressed HIV. KICS may be an important unrecognized cause of morbidity and mortality, including some symptoms previously ascribed to HIV. Characterization and exploration of KSHV-directed therapy continues.

Acknowledgements and Registration
This research was supported by the Intramural Research Program of the National Cancer Institute. This study is registered as NCT01419561.

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19. Quality Assurance for HPV-Related Laboratory Diagnoses Within an International Clinical Trial in the NIH-NIAID Division of AIDS Clinical Trial Network

Catherine C. Godfrey, Vikrant V. Sahasrabuddhe, Pamela M. Michelow, Mandana Godard, Katie Lammersen, Janice Darden, Scott Evans, Robert W. Coombs, Timothy Wilkin, Cynthia S. Firnhaber

National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: There is a fundamental tension in international clinical trials between central review of entry diagnostic evaluations and the use of the local standard of care laboratory diagnosis [1]. Central diagnosis minimizes)site to site variation. Strategy trials assess the effect of an intervention in the clinical setting and rely on local laboratories for entry diagnoses [2]. External quality assurance (EQA) is an accepted methodology for ensuring comparability of clinical laboratory diagnoses in the clinical setting. There are no reports of use and deployment of an EQA methodology for the ascertainment of entry criteria and endpoint evaluation in cervical cancer prevention clinical trials for HIV-infected populations in international resource limited environments.

Methods: ACTG 5282 is an ongoing multicenter randomized Phase II strategy trial comparing screening with HPV testing to a cytology based strategy in HIV infected women. (NCT01315353). The study will screen 700 HIV+ women at ACTG sites in South Africa, Botswana, Malawi, Zimbabwe, Zambia, India, Haiti, and Peru to compare cumulative incident CIN2+ rates. A comprehensive EQA program was established and comprised cytology review through a standard cytology proficiency package, histology review by an independent pathologist and a virology panel validated by the NIH/NIAID/DAIDS-sponsored Virology Quality Assurance (VQA) Program. Prestudy and on-study evaluations are reported.

Results: Seven laboratories and 17 pathologists from clinical sites participated in the pre-study evaluation. 10/17 participants were less than fully successful in a commercial cytology proficiency program; with remediation all were successful. Pre-study assessment of site-prepared clinical material in cytology revealed 71% good agreement between the central reader and the local laboratory. (90% CI 42-98). In 28/35 histological evaluations (80%) there was concordance between the local and central reviewer. Nine of 35 (26%) histological specimens had significant issues with sample collection including cautery artifact and missing the transformation zone. Specimen processing was a significant issue. All laboratories were fully successful with virology panels. Of pathologists and laboratories supporting enrolling sites, 6/13 were less than fully successful with the commercial scheme in the subsequent year. Five of six on-study evaluations were initiated for enrolling sites with 2/5 successful cytology submissions and 2/4 successful histology submissions. All sites had successful VQA panels.

Conclusions: Clinical trials evaluating HPV and cervical cancer prevention efforts for HIV-infected women in resource limited settings need to incorporate sustained efforts for quality assurance of cytopathology and histopathology endpoints. These efforts may also result in improved proficiency in pathology reporting in these settings.

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20. Quantitative High-Resolution Genetics of Hepatitis C Virus

Hangfei Qi[1], C. Anders Olson[1], Nicholas C. Wu[1], Ruian Ke[2], Claude Loverdo[2], Roland Remenyi[1], Virginia Chu[1], Shawna Truong[1], Laith Q. Al-Mawsawi[1], Ting-Ting Wu[1], James O. Lloyd-Smith[2], Ren Sun[1]

Department of Molecular and Medical Pharmacology; [2]Department of Ecology and Evolutionary Biology. University of California, Los Angeles, Los Angeles, CA

The establishment of HCV replicon and infectious systems has enabled study of viral replication mechanisms and facilitated high-throughput screening of small-molecule inhibitors. Identification of many new classes of antiviral agents raised the demands on defining mechanism of drug actions. To address this, we have developed a high-resolution genetic profiling platform to simultaneously quantify the effects of all possible single amino acid mutations in the targeted protein on replication fitness and sensitivity to a given inhibitor.

To systematically define the interactions between NS5A and its inhibitor Daclatasvir, we constructed a saturation mutant library; each position was engineered into all 20 possible amino acids, in the drug-targeted region (Domain IA of NS5A). The abundance of each mutant virus, in the presence and absence of the drug, was determined by high-throughput sequencing. Quantitative analysis of the increase or decrease of the replication fitness and drug sensitivity for each mutant revealed a comprehensive insight into the amino acids governing drug-protein interactions, which are all clustered to the surface of the dimer. Moreover, the fitness and drug-sensitivity profile also provide a comprehensive reference of the genetic barrier for drug-resistance, which can be utilized to predict clinical outcomes using mathematical models. This in-depth analysis of NS5A function and its evolutionary space may facilitate the development of second-generation drugs with higher genetic barriers for drug-resistance, and also can inform the patient-specific use of Daclatasvir based on viral variant spectra from patients.

We also applied this method to define the virus-host interactions in high resolution. We have previously identified a region of the Core protein involved in anti-IFN function using 15bp insertional mutagenesis. We mutated each position of the region to all possible 20 amino acids and look for mutants that are diminished specifically in the presence of IFN-α. We were able to determine the impact of each amino acid substitution regarding the replication fitness and anti-IFN function, adding our understanding the underlying mechanism.

Overall, this quantitative high-resolution genetics approach is a combination of forward and reverse genetics. It can be done at whole genome scale as we have achieved with the HIV genome. It enables simultaneous monitoring the abundance of every mutation, either positively or negatively selected in a given condition, and determining the phenotypic effects of each genetic modification in parallel. This approach will be generally applicable to studying other virus-host interactions or virus-drug interactions.

21. Tilmanocept, a Labeled Ligand for Macrophage Mannose Receptor (CD206), May Allow Imaging of Kaposi's Sarcoma Spindle Cells and Tumor-Associated Macrophages

Michael S. McGrath[1,2], *Leanne C. Huysentruyt*[2], *Rongzhen Zhang*[2]

[1]*AIDS and Cancer Specimen Resource, San Francisco, CA;* [2]*Department of Medicine, Hematology-Oncology, University of California, San Francisco, San Francisco, CA*

Background: Kaposi's sarcoma (KS) not only affects skin but in more advanced disease involves a variety of visceral tissues including lymph nodes. Attempts to confirm KS involvement in tissues other than skin have generally been problematic outside the use of tumor biopsies. Tilmanocept, a technetium labeled ligand for macrophage mannose receptor (CD206) approved for use in identifying cancer involved sentinel lymph nodes may allow KS specific tumor imaging if sufficient numbers of cells within KS tumors express CD206. The goal of the current study was to characterize macrophage antigen expression in a large number of KS tissues to determine whether Tilmanocept might be useful for KS tumor imaging.

Materials and Methods: A KS tissue microarray (TMA) was obtained from the AIDS and Cancer Specimen Resource (ACSR). Fluorescence tagged Tilmanocept was obtained from Navidea (Dublin, Ohio). All KS tissues were stained with macrophage specific markers: CD68, MAC387 (M1), CD163 (M2) and CD206. Fluorescence tagged Tilmanocept was also used to identify CD206 in the TMA. KS diagnosis was confirmed by H&E stain and detection of HHV8 latent antigen (LANA) within tumor cells.

Results: The current study confirmed the presence of CD206 on tumor-associated macrophages (TAMs) as well as a majority of KS tumor cells in 66 evaluable cases. Most TAMs in KS were identified with the M2 specific anti-CD163 antibody whereas the M1 anti-MAC387 antibody identified a smaller subset of cells. Both antibodies primarily identify recent blood monocyte derived migrants. The pan macrophage-CD68 antibody also identified a large number of TAMs in more than 90% of tumors. KS tumor spindle cells in general expressed macrophage antigens; however; the most prevalent antigen for both KS tumor spindle cells and TAMs was the CD206 molecule. A parallel study with fluorescence labeled Tilmanocept showed in a confocal microscopic evaluation that both KS tumor spindle cells as well as TAMs were recognized by this new imaging agent.

Conclusions: KS pathogenesis appears to involve an ongoing replenishment of TAMs from recent blood derived monocytes that express either M1 (MAC-387) or M2 (CD163) antigens. This study also confirmed a previous observation [see reference] that both TAMs and KS tumor cells express the CD206 macrophage mannose receptor. Tilmanocept, a labeled ligand for CD206, may allow effective imaging of KS involved nodes and other visceral sites of disease.

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22. Viability Study of PBMC Specimens Shipped From Africa to the United States in Liquid Nitrogen Vapor Shippers

Leanne C. Huysentruyt[1], Nicholas Cu[1], Ronald Honrada[1], Debra L. Garcia[1], Peter W. Hunt[2], Jeffery N. Martin[2], Michael S. McGrath[1]

[1]AIDS and Cancer Specimen Resource, San Francisco, CA; [2]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA

Background: Specimens under the custodianship of the AIDS and Cancer Specimen Resource (ACSR), an NCI-funded biorepository, are subject to viability testing as part of its quality control program. In collaboration with Dr. Jeffrey Martin, the ACSR conducted a study to test the long-term viability of PBMC specimens shipped from Africa to the United States.

Materials and Methods: Blood specimens from clinical studies conducted in Uganda were collected, processed and stored as PBMCs in liquid nitrogen (LN2) until transferred to the ACSR. PBMC specimens (10x10^6 cells/mL) were prepared for shipment in Uganda and sent to the United States via World Courier in LN2-cooled MVE Vapor Shippers. Upon arrival, ACSR stored PBMCs in LN2-vapor phase Thermo Fisher CryoPlus LN2 freezers for long-term storage. For the purpose of this study, PBMC viability was assayed using the trypan blue exclusion method.

Results: PBMCs that were processed in 2008 arrived at the ACSR in two LN2-vapor shippers with varying levels of LN2 remaining in each. One shipper had excess LN2-liquid visible in the tank while the other contained only LN2-vapor. Representative PBMCs were tested 5 months after receipt to determine if there were any differences in viability between tanks. The LN2-liquid group (n=4), had 89.1+/-2.8% (SEM) viability with (11.0+/-2.8)x10^6 viable cells remaining. The LN2-vapor group (n=8) had 72.6+/-3.1% viability with (5.1+/-0.5)x10^6 viable cells, both values significantly lower than the LN2-liquid group (p=0.006, p=0.01, respectively). The viability of these specimens was retested 37 months later (~58 months after initial processing) to compare the effects of LN2-liquid versus LN2-vapor over time. Aliquots from the LN2-liquid group had significantly higher viability (66.7+/-3.7% versus 10.6+/-2.2%; p=0.0001) and recovery [(3.83+/-0.5)x10^6 versus (5.45+/-1.3)x10^5; p=0.0001] when compared to those from the LN2-vapor group.

Conclusions: The viability of frozen PBMCs shipped from Africa was better maintained over time in the LN2-liquid group, suggesting that when overfilled with LN2, the shippers maintained appropriately low temperatures ensuring long-term viability as compared to PBMCs shipped in vapor phase LN2 shippers. Results indicate that viability and recovery of PBMCs are directly influenced by the adherence to manufacturer's guidelines. Per manufacturer's specifications, LN2 shippers provide only 40% of specimen hold time when shipped on its side or 10% hold time when placed upside down. These findings highlight the importance of maintaining and monitoring appropriate shipping conditions and temperatures to achieve optimal viability.

23. Abnormal Kappa/Lambda Free Light Chain Ratios and the Impact of Antiretroviral Therapy (ART) in HIV-Infected Men of the Multicenter AIDS Cohort Study (MACS)

Elizabeth Crabb Breen[1], Gerson Melendez[1], Richard Olmstead[1], Ronald J. Fecek[2], Jay H. Bream[3], Joseph Margolick[3], Nikolas Wada[4], Roger Detels[5]

[1]Cousins Center for Psychoneuroimmunology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA; [2]Department of Infectious Diseases and Microbiology, University of Pittsburgh, Pittsburgh, PA; [3]Department of Molecular Microbiology and Immunology, [4]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [5]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA

Background: Multiple myeloma (MM), a non-AIDS-defining malignancy of immunoglobulin (Ig)-secreting B cells, has an increased incidence among HIV-infected (HIV+) persons. Monoclonal gammopathy of undetermined significance (MGUS) and/or an abnormal ratio of kappa and lambda Ig free light chains (K/L ratio) in serum have been shown to precede MM. Increased prevalence of MGUS and abnormal K/L ratios in HIV+ men prior to the initiation of potent ART has been reported in the MACS, a longitudinal study of untreated and treated HIV infection in men who have sex with men in the U.S. However, it is not known if ART affects the prevalence of abnormal K/L ratios, or if the prevalence of abnormal K/L ratios is related to HIV-associated immune activation.

Materials and Methods: Serum K/L ratios were determined in 267 HIV+ MACS men who had samples available approximately two years (range 1.5-2.5 years) before and after the first study visit at which highly active ART use was reported. Serum concentrations of 24 markers of immune activation and inflammation were measured pre- and post-ART (BAFF/Blys, CXCL13, sCD14, sCD27, sgp130, sIL2Rα, sIL6R, sTNFR2, IL1β, IL2, IL6, IL8, IL10, IL12p70, GM-CSF, IFN-γ, TNF-α, eotaxin, IP-10, MIP-1β, MCP-1, MCP-4, TARC, CRP).

Results: The prevalence of an abnormal K/L ratio (<0.26 or >1.65) decreased significantly from pre- (60/267, 22%) to post-ART (27/267, 11%) (Table 1, p<0.001). Overall, 55% of men (147/267) achieved viral suppression (<50 copies/ml plasma HIV RNA) at the post-ART visit. The prevalence of an abnormal K/L ratio post-ART was not significantly different between men with successful viral suppression (12/147, 8%) and men who failed to suppress (15/120, 13%). Successful viral suppression was associated with a decrease in serum levels of some biomarkers, including sCD27, sIL2Rα, IL10, and IP-10.

Table 1.

		Post-ART	
		Normal K/L (n=240)	Abnormal K/L (n=27)
Pre-ART	Normal K/L (n=207)	199	8
	Abnormal K/L (n=60)	41	19

Conclusions: In some HIV+ men, abnormal K/L ratios normalize following the initiation of ART. However, the presence of an abnormal K/L ratio post-ART does not appear to be related to the success or failure of HIV suppression. Treated HIV+ individuals with abnormal K/L ratios may be at particular risk for future development of multiple myeloma. Additional studies are planned utilizing the unique longitudinal resources of the MACS to characterize the stability of K/L ratios and of MGUS, and their relationships to HIV suppression and immune activation over the course of long term HIV infection.

Acknowledgements

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24. Breast Milk as a Potential Source of Epstein-Barr Virus (EBV) Transmission Among African Infants

Ibrahim I. Daud[1,2,3], Sidney Ogolla[2,4], Peter O. Sumba[2], Elizabeth A. Bukusi[5], Zipporah Ng'ang'a[3], Arlene C. Dent[6], Rosemary Rochford[1]

[1]SUNY Upstate Medical University, Syracuse, NY; [2]Center for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya; [3]Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya; [4]Maseno University, Kisumu, Kenya; [5]Center for Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenyal; [6]Case Western Reserve University, Cleveland, OH

Background: Infection with Epstein-Barr virus (EBV) early in life and repeated malaria exposures have been proposed as risk factors for endemic Burkitt lymphoma (eBL). We have previously reported that there is a significantly earlier age of primary EBV infection in infants from Kisumu, a malaria holoendemic region of Kenya compared to infants from Nandi, an area with little malaria transmission [see reference]. Strikingly, 35.3% of children in Kisumu were infected before 6 months of age.

Methods: In this study, we followed a cohort of infants from birth through 12 months of age and analyzed whether exposure to maternal breast milk could be a source of infectious virus. We quantified EBV DNA levels in breast milk and infant's blood in samples collected prospectively from 98 mother-child pairs at 6, 10, 14 and 18 weeks after delivery.

Results: We found that the prevalence of EBV DNA in breast milk was significantly higher at 6 weeks and decreased sequentially till 18 weeks (6 weeks 77% [66/87]; 10 weeks 58% [52/90]; 14weeks 31% [28/89]; 18weeks 24% [16/68]; Chi 53.1, P < .0001). Similarly, median EBV load in breast milk was significantly higher at 6 weeks than that of the subsequent visits (6 weeks, median virus load, 2,874 copies/mL, range 218-263,400 copies/mL; 10 weeks median virus load, 813 range 66-10,044 copies/mL; 14 weeks, median virus load, 565 copies/mL, range 68-8,184 copies/mL; 18 weeks, median virus load, 284, range 134-2,256 copies/mL, P< .0001). To confirm if there was infectious virus in the breast milk, a subset of samples were treated with DNAse prior to DNA extraction. We observed that samples were DNAse resistant suggesting that virus DNA was encapsidated. We next exposed PBMC to 100µl of breast-milk supernatant and observed evidence of viral transformation (e.g., blast formation, clumping and proliferation). The prevalence of EBV DNA in children was 97% (66/68) at 6 weeks if the mother had EBV DNA in breast milk.

Conclusion: Taken together this suggests that breast milk contains infectious EBV and is a potential source of viral transmission.

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25. Cancer Burden Among HIV-Positive Persons in Nigeria: Preliminary Findings From the Nigerian AIDS-Cancer Match Study

Sally N. Akarolo-Anthony[1,2], Luigino Dal Maso[3], Festus Igbinoba[4], Sam M. Mbulaiteye[5], Clement A. Adebamowo[1,6]

[1]Office of Strategic Information and Research, Institute of Human Virology, Abuja, Nigeria; [2]Department of Nutrition, Harvard School of Public Health, Boston, MA; [3]Epidemiology and Biostatistics Unit, Aviano Cancer Center, IRCCS, Aviano, Italy; [4]Abuja Cancer Registry, National Hospital Abuja, Nigeria; [5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD; [6]Institute of Human Virology and Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD

Background: Although Nigeria has a large HIV epidemic, the impact of HIV on cancer in Nigerians is unknown.

Materials and Methods: We conducted a registry linkage using a probabilistic matching algorithm among a cohort of 18,965 HIV positive persons registered between 2005 and 2012 at health facilities where the Institute of Human Virology Nigeria (IHVN) provides HIV prevention and treatment services. Their data was linked to data from 2009 to 2012 in the Abuja Cancer Registry. Match files with first name, last name, sex, date of birth and unique identification numbers were provided by each registry and used for the linkage analysis. We describe demographic characteristics of the HIV clients and compute Standardized Incidence Ratios (SIRs) to evaluate the association of various cancers with HIV infection.

Results: Between 2006 and 2012, 17,826 persons living with HIV (PLWA) were registered. Their median age (Interquartile range (IQR)) was 33 (27-40) years; 41% (7,246/17,826) were men and 59% (10,580/17,826) were women. From 2009 to 2012, 2,029 clients with invasive cancers were registered at the Abuja Cancer Registry. The median age (IQR) of the cancer clients was 45 (35-68) years. Among PLWA, 39 cancer cases were identified, 69% (27/39) were incident cancers and 31% (12/39) were prevalent cancers. The SIR (95% CI) for the ADCs were 5.7 (4.1, 7.2) and 2.0 (0.4, 3.5), for Kaposi Sarcoma (KS) and Cervical Cancer (CC) respectively (Table 1). There was no other statistically significant increased risk of other cancers among PLWA.

Table 1: Spectrum of Observed Cancers and Standardized Incidence Ratios for HIV-Infected Persons

Cancer type	ICD Code	Morphology Code	N (%)		Incidence/100,000 person-years
		Crude Rate		SIR (95% CI)	
		AIDS-defining cancers			
Kaposi sarcoma	C46	9140	8 (21)	4.9	5.7 (4.1, 7.2)
Cervical cancer	C53	8070	8 (21)	7.8	2.0 (0.4, 3.5)
		Non-AIDS-defining cancers			
Anus	C21	8010	1 (2)	0.6	0.3 (0, 17.8)
Liver	C22	8170, 8174	3 (8)	1.8	0.5 (0, 5.1)
Other non-epithelial skin	C44	8070	3 (8)	1.8	4.0 (0, 8.5)
Breast	C50	8010, 8521	9 (23)	8.8	1.6 (0.2, 3.0)
Ovary	C56	8010, 8310	2 (5)	2.0	3.6 (0, 20.1)
Prostate	C61	8010	1 (2)	0.6	0.4 (0, 16.9)
Eye	C69	8052	1 (2)	0.6	1.5 (0, 18.1)
Other, non-specified		8001	3 (8)	1.8	0.5 (0, 4.7)

Conclusions: Consistent with the findings from other studies, the risk of KS but not CC or non-Hodgkin's lymphoma, was significantly increased among HIV-positive persons, compared to the general population.

26. Cancer Incidence in HIV-Infected Versus HIV-Uninfected Veterans: Comparison of Cancer Registry and ICD-9 Code Diagnoses

Lesley S. Park[1], Janet P. Tate[2], Robert Dubrow[1]

[1]Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT; [2]Department of Internal Medicine, Yale School of Medicine, New Haven, CT

Background: The Veterans Aging Cohort Study (VACS) has followed HIV-infected and demographically-matched HIV-uninfected veterans since 1996. VACS has two data sources on cancer incidence: Veterans Affairs (VA) Central Cancer Registry (VACCR) and International Classification of Diseases, Ninth Revision (ICD-9) codes from VA encounters. Compared to gold standard chart review, both sources had approximately 85% sensitivity; however, VACCR had higher positive predictive value (94% versus 61%). We compared cancer incidence by HIV status using VACCR versus ICD-9 data. We hypothesized that the data sources would lead to different conclusions.

Materials and Methods: Each analysis was conducted for all cancers combined and specific cancer types, comparing VACCR versus ICD-9 code data by HIV status. We calculated age-, sex-, race/ethnicity-, and calendar-period-standardized incidence rates (IR) per 100,000 person-years using the entire cohort distribution for the standard weights, IR ratios (IRR), and 95% confidence intervals (95% CI). We secondarily examined effects of missed cases due to healthcare utilization outside the VA in Medicare/Medicaid encounters, which were linked to VACS. Finally, we calculated standardized incidence ratios (SIR) to compare VACS rates to SEER rates.

Table 1. Observed Number of First Primary Cancer Cases, SIRs, and 95% CIs

		VACCR			ICD-9		
Cancer type	**HIV status**	**Observed # cases**	**SIR**	**(95% CI)**	**Observed # cases**	**SIR**	**(95% CI)**
All first primary cancers†	+	2421	1.72	(1.65, 1.79)	4282	3.35	(3.25, 3.45)
	–	3194	0.87	(0.84, 0.90)	5525	1.62	(1.58, 1.67)
Oral cavity & pharynx	+	120	1.96	(1.64, 2.35)	286	4.71	(4.19, 5.29)
	–	227	1.48	(1.30, 1.68)	427	2.79	(2.53, 3.06)
Colorectal	+	124	0.76	(0.64, 0.90)	376	2.31	(2.09, 2.56)
	–	264	0.62	(0.55, 0.70)	471	1.12	(1.02, 1.23)
Anal	+	149	23.05	(19.63, 27.07)	281	43.56	(38.75, 48.96)
	–	13	0.82	(0.48, 1.42)	33	2.09	(1.49, 2.94)
Liver	+	173	3.80	(3.28, 4.41)	272	5.98	(5.31, 6.74)
	–	139	1.18	(1.00, 1.39)	259	2.20	(1.95, 2.48)
Lung	+	445	2.06	(1.88, 2.26)	647	3.02	(2.79, 3.26)
	–	614	1.09	(1.01, 1.18)	894	1.59	(1.49, 1.70)
Prostate	+	396	0.69	(0.63, 0.77)	588	1.05	(0.97, 1.14)
	–	1085	0.73	(0.68, 0.77)	1555	1.07	(1.02, 1.12)
Hodgkin lymphoma	+	75	8.24	(6.57, 10.33)	136	14.97	(12.65, 17.71)
	–	20	0.93	(0.60, 1.44)	49	2.29	(1.73, 3.02)
Non-Hodgkin lymphoma	+	315	4.69	(4.20, 5.23)	627	9.42	(8.71, 10.19)
	–	113	0.67	(0.55, 0.80)	229	1.36	(1.19, 1.54)
Kaposi sarcoma	+	227	28.07	(24.65, 31.97)	528	65.92	(60.53, 71.79)
	–	1	0.05	(0.01, 0.39)	7	0.38	(0.18, 0.81)

† Subjects may have more than one primary cancer; the "all first primary cancers" analysis only includes the first incident cancer.

Results: There were 6,010 VACCR and 13,386 ICD-9 incident cancer diagnoses among 124,936 veterans. For all cancers combined, incidence was twice as high using ICD-9 codes (IR_{HIV+}=2,120, IR_{HIV-}=1,087) compared to VACCR (IR_{HIV+}=1,103, IR_{HIV-}=571). However, the IRR for HIV-infected compared to HIV-uninfected was approximately two, regardless of the data source (VACCR IRR = 1.93, 95% CI: 1.82, 2.05; ICD-9 IRR = 1.95, 95% CI: 1.86, 2.05). For

specific cancer types, most IRRs were in the same direction, of similar magnitude, and of similar statistical significance, regardless of data source. HIV-infected subjects were more likely than HIV-uninfected subjects to access Medicare/Medicaid; IRRs increased when we added Medicare/Medicaid ICD-9 codes to VACS ICD-9 codes. SIRs based on ICD-9 codes were higher than SIRs based on VACCR and were greater than 1.0 for almost every cancer type (Table 1). The all-cancer VACCR SIR for the HIV-uninfected was less than 1.0, suggesting that VACCR may miss cases.

Conclusions: Both data sources yielded similar IRR estimates for the effect of HIV. Adding Medicare/Medicaid data resulted in higher IRRs, suggesting VACS results were biased towards the null, meaning the effect of HIV is greater than the VACS data show. Elevated cancer risk among the HIV-infected is consistent with other studies. ICD-9 codes may be useful for estimating rate ratios, but should be avoided when estimating incidence or SIRs.

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27. Cancer in HIV-Infected Children: Record Linkage Study in South Africa

Julia Bohlius[1], Nicky Maxwell[2], Rosalind Wainwright[3], Janet Poole[4], Alan Davidson[5], Cristina Stefan[6], Matthias Egger[1]

[1]University of Bern, Switzerland; [2]University of Cape Town, South Africa; [3]Chris Hani Baragwanath Academic Hospital, South Africa; [4]Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand, South Africa; [5]Red Cross Children's Hospital and the University of Cape Town, South Africa; [6]Tygerberg Hospital and Stellenbosch University, South Africa

Background: HIV-infected children are at increased risk of developing cancer. However, most incidence analyses are stemming from Europe and the USA [1-4]. We identified the prevalence and incidence of cancer in HIV-infected children in antiretroviral therapy (ART) programs in South Africa.

Methods: We linked records of patients aged ≤16 years from five ART programs (Harriet Shezi and Rahima Moosa in Johannesburg; Khayelitsha, Red Cross and Tygerberg in Cape Town) to the records of the four corresponding paediatric oncology units (Baragwanath and Charlotte Maxeke in Johannesburg; Red Cross and Tygerberg in Cape Town). Records were linked based on folder numbers, names, birth date and sex. We calculated prevalence at enrollment, incidence rates and hazard ratios (HR) from Cox regression adjusted for ART (time-updated), sex, age, clinical stage and year.

Results: Data of 13,074 HIV-infected children were included in the analysis of prevalence and 12,303 children (33,089 person years) in the incidence analysis. A total of 73 cancers were identified: 11 cancer cases were recorded in the ART programs only, 50 in the oncology files only, and 12 were recorded in both datasets. Forty-eight children (0.4%) presented with a prevalent cancer and 25 children developed cancer after enrollment into ART program for an incidence rate of 76 per 100,000 person-years. Most cancers were AIDS-defining: 22 prevalent and 10 incident Kaposi sarcoma, 20 prevalent and 9 incident non-Hodgkin lymphoma. HRs were 8.18 (95% CI 2.05-32.73) comparing age >10 with <3 years, 1.04 (95% CI 0.44-2.45) comparing boys and girls, and 2.02 (95% CI 0.45-9.05) comparing advanced with less advanced HIV/AIDS stage (see Table 1).

Table 1. The Risk of Developing Cancer Among HIV-Infected Children in South Africa: Results From Univariable and Multivariable Analyses

		Univariable analyses	***Multivariable analyses***
		Hazard ratio (95% CI)	*Hazard ratio (95% CI)*
Time-updated ART	*Not on ART*	*1*	*1*
	On ART	*0.54 (0.19 - 1.54)*	*0.59 (0.18 - 1.89)*
Gender	*Female*	*1*	*1*
	Male	*0.94 (0.43 - 2.06)*	*1.04 (0.44 - 2.45)*
Age at enrollment into ART program [years]	*<3 years*	*1*	*1*
	3 to 5 years	*4.51 (1.43 – 14.25)*	*3.90 (1.09 – 13.99)*
	5 to 10 years	*3.49 (1.19 –10.24)*	*3.43 (1.06 – 11.08)*
	>10 years	*7.69 (2.25 – 26.31)*	*8.18 (2.05 – 32.73)*
Advanced stage HIV/AIDS disease*	*No*	*1*	*1*
	Yes	*1.09 (0.32 – 3.73)*	*2.02 (0.45 – 9.05)*
Calendar year of enrollment into ART program	*Before 2005*	*1*	*1*
	In or after 2005	*0.47 (0.20 – 1.14)*	*0.41 (0.15 – 1.07)*

All models are stratified by cohort; multivariable analyses are adjusted for time-updated ART, gender, age and calendar year at enrollment into ART program, HIV/AIDS stage. ART: antiretroviral therapy; CI: confidence interval. *WHO 2005 surveillance definition.

Conclusion: The incidence of cancer in HIV-infected children is high but ascertainment of cancers in ART programs is incomplete.

28. The Use of Computerized Record Linkage for Cancer Ascertainment in a South African HIV Cohort

Mazvita Sengayi[1,2], Adrian Spoerri[3], Danuta Kielkowski[1], Julia Bohlius[3], Christie Cloete[4], Tamaryn Crankshaw[4], Janet Giddy[4]

[1]National Cancer Registry, National Health Laboratory Service, Johannesburg, South Africa; [2]Graduate School for Cellular and Biomedical Sciences, University of Bern, Switzerland; [3]Institute of Social and Preventive Medicine, University of Bern, Switzerland; [4]McCord Hospital, Durban, South Africa

Background: Despite the high HIV burden, few studies have evaluated cancer risk in HIV-infected people in South Africa. Data collected in HIV cohorts are often incomplete with respect to cancer diagnoses. To improve cancer ascertainment, we conducted a probabilistic record linkage of the National Cancer Registry (NCR) data with the Sinikithemba HIV cohort at McCord Hospital in KwaZulu-Natal (KZN) province, South Africa.

Methods: We linked the records of all adult (aged ≥ 16 years) patients on antiretroviral treatment (ART) enrolled at the Sinikithemba HIV clinic from January 2004 to December 2011 with the cancer records of the public laboratories in KZN province. G-link software was used for data linkage. Linkage variables were names, date of birth and gender.

Results: A total of 8742 records of HIV-positive patients on ART were linked with 36817 cancer records. We identified 357 cancer cases occurring in 338 patients in the linkage. Median age at cancer diagnosis was 36 years and most patients were female (213; 63%). Fifty-two percent (187) of all cancers were diagnosed prior to ART initiation. The five most frequent cancers in men were Kaposi's sarcoma (71; 55%), non-Hodgkin's lymphoma (9; 7%) oro-pharyngeal (6; 4.6%), conjunctiva (6; 4.6%) and oesophagus (5; 3.9%).The five most frequent cancers in women were Kaposi's sarcoma (75; 32.9%), cervix (58; 25.4%), breast (17;7.5%), conjunctiva (15; 6.6%) and non-Hodgkin's lymphoma (11; 4.8%).

Conclusions: Probabilistic record linkage is a valuable tool for cancer diagnosis ascertainment in HIV cohorts in resource-constrained settings and may reveal the full spectrum of HIV-related cancers. AIDS-defining cancers still account for the majority of cancers occurring in HIV-positive people in the South African ART era, with women and young people most affected.

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29. Lymphomas in HIV-Positive Children in South Africa

D.C. Stefan[1], G.P. De Bruin[1], D. Stones[2]

[1]Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; [2] Departments of Paediatrics and Child Health, Universitas Hospital and University of the Free State, Bloemfontein, South Africa

Background: The AIDS epidemic has contributed to an increase of the incidence of lymphomas, especially in sub-Saharan Africa. There is very little literature regarding the description of the clinical features as well as precise guidelines for the management of these hematological malignancies in children.

Materials and Methods: This is a retrospective analysis of data of HIV-positive children diagnosed with lymphomas at several pediatric oncology centers in South Africa over a 5 year period (2006-2010).

Results: There were 456 cases of lymphomas diagnosed between 2006 and 2010. Most children presented with non-Hodgkin lymphomas (163). Age at diagnosis ranged from 17 days to 15.6 years. Out of 456 cases of lymphomas more than 15% (73 patients) were diagnosed in children infected with HIV. More than 80% presented with advanced disease. Most patients received antiretroviral therapy and most patients followed standard lymphoma protocols. Nearly one third had co-existing pathology, mostly tuberculosis. Overall survival of lymphomas for 2 centers was 60% and 68% and below 50% (46%) for the HIV-infected children.

Conclusions: The study still shows a high incidence of lymphomas in HIV-positive children. The survival remains low mainly due to advanced disease and association with co morbidities and toxicity of the treatment. An increased awareness program associated with a better coverage of ARVs and adapted protocols might improve the outcome of the HIV-positive children diagnosed with lymphomas.

30. CD4 Count and HIV Viral Load as Predictors of Kaposi Sarcoma Risk: The Role of Lag in Marker Measurement

Robert Dubrow[1], Li Qin[1], Haiqun Lin[1], Keri N. Althoff[2], Chad J. Achenbach[3], Gypsyamber D'Souza[2], Eric A. Engels[4], Nancy A. Hessol[5], Amy C. Justice[1], Wendy A. Leyden[6], Sharada P. Modur[2], Richard D. Moore[2], Romain S. Neugebauer[6], Michael J. Silverberg[6]

[1]Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, IL; [4]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD; [5]Department of Clinical Pharmacy and Medicine, University of California, San Francisco, San Francisco, CA; [6]Division of Research, Kaiser Permanente Northern California, Oakland, CA

Background: Among HIV-infected persons, CD4 count and HIV RNA levels each predict Kaposi sarcoma (KS) risk. However, the optimal time point in the past (i.e., lag) of marker measurement for risk prediction is not well established. We examined this research question among patients in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

Methods: This analysis included 15 NA-ACCORD cohorts with KS diagnoses validated by chart review or cancer registry linkage. Cohort-specific observation time ranged from 1984 to 2009. CD4 count and HIV RNA values were imputed at 30-day intervals, based on assumption of a linear change between observed values. In eight separate Cox models, we examined the relationship between KS risk and CD4 count and HIV RNA, respectively, imputed at 6, 12, and 24 month lags as well as at baseline (i.e., entry date into cohort, which represents the longest possible lag). We also mutually adjusted CD4 count and HIV RNA in the same model for each of the 16 lag time combinations. Each model was adjusted for the baseline covariates sex, age, race/ethnicity, cohort, calendar-period of enrollment, HIV transmission group, and any use of antiretroviral therapy. We used Akaike's information criterion (AIC) to assess relative model fit (lower AIC indicates better fit, with a difference of 10 conventionally considered meaningful). To enable comparison of models in exactly the same cohort of individuals, we excluded the first 24 months of observation time.

Table 1. CD4 count and HIV RNA hazard ratios and 95% confidence intervals as a function of lag

Variable	6 months	12 months	24 month	Baseline	Best mutually-adjusted[a]
CD4 count (cells/µl)[b]					
350 – 499	2.3 (1.5-3.5)	2.0 (1.4-2.8)	2.7 (2.0-3.5)	1.4 (1.1-1.7)	2.0 (1.3-3.0)
200 – 349	5.1 (3.5-7.4)	4.4 (3.3-6.0)	5.0 (3.8-6.5)	1.7 (1.3-2.2)	3.6 (2.5-5.3)
100 – 199	13.2 (9.1-19.1)	10.5 (7.7-14.3)	8.3 (6.3-11.1)	2.1 (1.5-2.8)	7.5 (5.1-11.1)
50 – 99	28.5 (19.5-41.6)	21.1 (15.2-29.4)	13.7 (9.8-19.3)	3.0 (2.0-4.3)	14.4 (9.7-21.5)
<50	44.5 (31.4-63.0)	26.7 (19.5-36.5)	13.7 (9.6-19.5)	1.4 (0.9-2.2)	20.4 (14.0-29.7)
AIC	10,711	10,947	11,279	11,674	–
HIV RNA (copies/ml)[c]					
500 – 9,999	1.3 (0.8-2.2)	1.2 (0.7-1.9)	1.3 (0.8-2.0)	2.1 (1.2-3.5)	1.1 (0.7-1.9)
10,000 – 99,999	6.2 (4.3-9.0)	6.0 (4.3-8.6)	6.2 (4.4-8.7)	3.8 (2.3-6.2)	3.6 (2.5-5.1)
≥100,000	21.7 (15.3-30.8)	19.5 (14.0-27.4)	15.8 (11.3-22.1)	4.1 (2.4-6.7)	6.4 (4.4-9.3)
AIC	10,847	10,769	10,837	11,661	10,543

[a]CD4 count with 6 month lag and HIV RNA with 6 month lag; [b]reference: CD4≥500; [c]reference: HIV RNA<500

Results: We followed 53,604 individuals among whom 642 incident KS cases were diagnosed. At baseline, the cohort was 83% male, 45% white, 37% black, 30% men who have sex with men, 27% other/unknown HIV transmission group, and 47% antiretroviral therapy naïve; mean age was 40 years. Median follow-up was 6.1 years. In separate models, the best predictors of KS risk were CD4 with 6 month lag and HIV RNA with 12 month lag (Table 1). However, the best mutually adjusted model was CD4 with 6 month lag and HIV RNA with 6 month lag, with both variables remaining highly significant (Table 1).

Conclusions: CD4 count and HIV RNA with 6 month lags were the best independent predictors of KS risk. We plan to perform sensitivity analyses related to the method of marker imputation, to examine other CD4 and HIV RNA measures such as trajectory and duration below a given threshold, and to consider the role of antiretroviral therapy.

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31. Characteristics of HIV-Associated Cancer Cases in the Largest Clinical System Serving HIV+ Men and Women in Bronx, New York

Missak Haigentz[1], Juan Lin[2], Xiaonan Xue[2], Mindy Ginsberg[2], Uriel Felsen[1], Marina Shcherba[1], David Hanna[2], Linda Fisher[3], Julie Chung[3], Kevin Wilson[3], Kathryn Anastos[1,2], Howard D. Strickler[2]

[1]Department of Medicine, [2]Department of Epidemiology and Population Health, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY; [3]Health Information Management Department, Montefiore Medical Center, Bronx, NY

Background: Despite increasing evidence of an excess of non-AIDS defining cancers (non-ADCs) in HIV+ patients, the spectrum of tumor types and characteristics of HIV+ cancer cases is only partially understood. We studied 13 years of data at Montefiore Medical Center – Einstein (MMC-E), the largest clinical system in Bronx, NY, a predominantly minority population with 1-2% HIV prevalence.

Methods: All invasive cancers diagnosed 1/1/2000 – 12/31/2012 at MMC-E were identified through the Cancer Registry and linked to the HIV Integrated database (HIDR), which contains electronic medical records of all HIV+ patients at MMC-E.

Results: The dataset included 14,936 HIV+ persons during the 13-year interval studied, with 58% men and 42% women. Of these, 40% were Black, 42% White Hispanic, 18% White non-Hispanic, and 14% self-identified as MSM and 17% reported IDU. Among 42,967 cancers diagnosed at MMC-E, a total of 935 cancer cases were HIV+, of which 363 (39%) were ADCs and 572 non-ADCs (61%), affecting 2% and 3% of HIV+ persons, respectively. The median age at initial cancer diagnosis was 44 and 52 years for ADCs and non-ADCs, respectively ($p<0.001$). The most common ADC was non-Hodgkin's lymphoma (N=238; median CD4=133), followed by Kaposi's sarcoma (N=92; CD4=80), and cervical cancer (N=24; CD4=213). The most common non-ADCs were lung (N=93; CD4=252), liver (N=70; CD4=325), head and neck (HNC; N=47; CD4=240), prostate (N=42; CD4=437), breast (N=40; CD4=559), anal (N=37; CD4=196) and Hodgkin's lymphoma (N=35; CD4=136). Among more notable observations: HPV-associated HNC (N=21; CD4=197) had non-significantly lower CD4 than non-HPV-associated HNC (N=27; CD4=255) and were significantly more likely than non-HPV-associated HNC to involve non-MSM (74% versus 36%;$p=0.03$); among anal cancers cases, 31% were MSM (vs. 19% among all cancers; $P<0.05$), whereas 59% involved other men (non-MSM) and 10% women; 39% of liver cancers versus 18% of other cancer cases reported IDU ($P<0.001$).

Conclusions: Approximately 5% of HIV+ persons were diagnosed with cancer during a 13 year period, of which more than half were non-ADCs. Among common non-ADCs the lowest CD4s were among Hodgkin's lymphoma and anal cancer, whereas breast and liver cancer cases had the highest CD4s. Interestingly, while IDU was a risk factor for liver cancer and MSM for anal cancer, the majority of these tumors were not in these risk groups, nor were most HPV-associated HNC among a high risk group for HPV. These results have implications to screening and prevention, and point to the importance to clinical cohort data of this type.

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32. Comorbidities: A Potential Barrier to Enrolling HIV-Infected Lung Cancer Patients in Therapeutic Clinical Trials

Jeannette Y. Lee[1], Page C. Moore[1], Matthew A. Steliga[2]

Departments of Biostatistics[1] and Surgery[2], University of Arkansas for Medical Sciences, Little Rock, AR

Background: Lung cancer among HIV-infected individuals is increasing with time. Although clinical trials are the optimal approach to evaluating new therapeutic approaches for lung cancer, comorbidities may limit participation by HIV-infected persons. This study investigated the prevalence of comorbidities among HIV-infected non-small cell lung cancer (NSCLC) cases.

Materials and Methods: The basis for this study was the SEER-Medicare database which links Medicare claims data with patients identified through cancer registries as part of the Surveillance Epidemiology and End Results (SEER) program (www.seer.cancer.gov). This study includes patients who were diagnosed with NSCLC between 1998 and 2007, qualified for Medicare based on age and were 65 years of age or older at the time of lung cancer diagnosis. HIV patients were identified based on the databases of Medicare claims for health care services given between 1998 and 2009. Fisher's exact test was used to compare HIV and nonHIV patients with respect to demographic characteristics and the proportion with comorbidities. Logistic regression analyses adjusted for age, race and gender were used to compare HIV infected and uninfected patients with respect the prevalence of comorbidities. Odds ratios (ORs) were estimated using their point estimates and Wald's 95% confidence intervals (CIs).

Results: This study included 111,219 patients: 174 with HIV and 111,045 without HIV. In comparison to those without HIV, HIV patients were more likely to be men (68% vs 52%, P<0.001), from minority populations (41% vs 13%, P<0.001), between 65 and 74 years of age (61% vs 50%, P=0.004). HIV status was not associated with stage of disease at diagnosis. Comorbidities occurred in 73.6% of HIV patients and 51.5% of nonHIV patients (P<0.001). The most common conditions for both HIV and nonHIV patients were COPD, diabetes mellitus and congestive heart failure, all of which occurred more frequently among HIV patients (Table 1).

Table 1.

Comorbidity	Prevalence HIV (%)	Prevalence Non-HIV (%)	OR (95% CI), P-value*
COPD	53.45	37.22	2.02 (1.50, 2.72), P<0.001
Diabetes mellitus	29.31	14.40	2.12 (1.52, 2.94), P<0.001
Congestive heart failure	18.97	9.96	2.13 (1.48, 3.18), P<0.001

In comparison to non-HIV patients, HIV positive patients were also more likely to have cerebrovascular disease, dementia, peptic ulcer disease, renal disease and liver disease. HIV status was not associated with myocardial infarction or peripheral vascular disease.

Conclusions: The higher prevalence of comorbidities among HIV infected NSCLC patients suggests that clinical trial strategies for this patient population must be tailored to address this issue.

33. A Comprehensive Household-Based Cohort Study of Primary Epstein-Barr Virus (EBV) Infection in Ugandan Infants

Soren Gantt[1], Jackson Orem[4], Elizabeth Krantz[2], Stacy Selke[2,3], Meei-Li Huang[2,3], Annet Nakaganda[4], Peace Imani[2], Zaam Nalule[4], Anna Wald[2,3], Larry Corey[2], Corey Casper[2,3]

[1]University of British Columbia, Vancouver, British Columbia, Canada; [2]Fred Hutchinson Cancer Research Center, Seattle, WA; [3]University of Washington, Seattle, WA; [4]Uganda Cancer Institute, Kampala, Uganda

Background: EBV infection is nearly universal by 3 years of age in Uganda, where endemic Burkitt lymphoma is the most common childhood malignancy. Most knowledge about primary EBV infection comes from studies of young adults in resource-rich settings. Relatively little is known about the virologic, immunologic or clinical aspects of early childhood EBV infection.

Materials and Methods: We established a prospective cohort in Kampala, Uganda, called the Primary Herpesvirus Infection in Children Study (PHICS). Pregnant women, their newborn infants, and all other children <7 years old in the home (secondary children) were included. At weekly home visits, a clinician collected detailed clinical and behavioral data, and obtained an oral swab from each subject. Quantitative EBV PCR was performed on all oral swabs and an area-under-the-curve (AUC) was calculated to represent the level of viral shedding by mothers and secondary children in the 28 days prior to each visit. Behaviors were also defined for the 28 days prior to each visit. Primary infection in infants was defined by ≥2 consecutive oral swabs with ≥3.5 log copies of EBV per ml by PCR. Cumulative incidence was calculated using the Kaplan-Meier method, and associations between EBV acquisition in infants and exposures were tested using Cox regression.

Results: Thirty-two households, consisting of 32 mothers, 32 infants, and 49 secondary children were followed for a median of 57 weeks from birth. Seventeen mothers, 4 secondary children, and none of the infants were HIV-infected. A total of 4993 oral swabs were collected, of which 2967 (59.4%) were positive for EBV. HIV-infected mothers and secondary children showed a trend toward higher oral EBV AUCs versus those without HIV ($p=0.07$). Primary EBV infection was documented in 19 infants (cumulative incidence of 47.4% at 12 months), and was associated with persistent high-level oral shedding and frequent viremia. Maternal HIV infection was associated with EBV acquisition (HR 6.7, $p<0.001$). Intensity of EBV oral shedding by household contacts in the previous 4 weeks, sex of the infant, breastfeeding, or reported saliva-sharing behaviors, was not associated with EBV acquisition when adjusting for maternal HIV status.

Conclusions: EBV is acquired before one year of age in nearly half of Ugandan infants, and is strongly associated with maternal HIV infection independent of household exposure to saliva or the practice of breastfeeding. Additional work is ongoing to characterize the clinical manifestations and virus-specific cellular and humoral immune responses during primary EBV infection.

34. Delayed Diagnosis of HIV-Associated Kaposi Sarcoma in Uganda: A Qualitative Analysis

Erin Amerson[1], Amy Forrestel[1], Lisa Butler[2,3], Miriam Laker-Oketta[2,4], Mwebesa Bwana[5], Toby Maurer[1], Jeffrey Martin[2]

[1]Department of Dermatology, [2]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA; [3]Department of Medicine, Division of General Pediatrics, Boston Children's Hospital and Harvard Medical School, Boston, MA; [4]Infectious Diseases Institute, Kampala, Uganda; [5] Mbarara University of Science and Technology, Mbarara, Uganda

Background: In East Africa, HIV-associated Kaposi sarcoma (KS) has high incidence, morbidity and mortality. Despite visible skin lesions, patients with KS often do not obtain formal diagnosis until they develop advanced disease. We sought to identify reasons for this delay.

Methods: In this first phase of a mixed-methods study, we conducted semi-structured interviews with HIV-infected Ugandan adults recently diagnosed with advanced KS, defined as bulky or ulcerated lesions, oral lesions interfering with chewing or swallowing, edema causing functional impairment, or symptoms suggestive of gastrointestinal or pulmonary involvement. Subjects were identified from clinics throughout Uganda as part of a recruiting network for a trial for non-advanced KS. Two coders independently evaluated the interview transcripts using thematic analysis. A theoretical model of delays to care proposed by Ulett's adaptation of Andersen's behavioral model of health services use was used to organize the themes [see reference].

Results: Seventeen subjects were interviewed (82% men). The median time from first noticing lesions to receiving a KS diagnosis at a facility capable of administering antiretroviral therapy was 7 months (interquartile range 4 to 18 months). A variety of reasons for delay in diagnosis were provided, which fell into 3 categories: patient-related, contextual environment, and health care system-related. The most common patient-related issues included initial lack of self-concern over symptoms (65%), preliminary use of traditional medicine (58%), and stigma (41%). Logistical issues related to the patient's contextual environment included cost of transport to medical facilities (82%) and job or household responsibilities (29%). After deciding to seek biomedical treatment, 76% experienced misdiagnosis or miscommunication by health care workers; 47% cited difficulties with medical clinic schedules, with facilities only open certain days, long wait times, or being asked to return another day without being seen by a provider. Subjects also mentioned cost of doctors' fees or tests (35%), difficulties in achieving contact with appropriately trained medical providers (29%), insensitive treatment by medical staff (24%), and difficulty navigating the referral process (24%). No subject had heard of KS prior to his/her diagnosis.

Excerpts from patients with advanced-stage KS during interviews regarding reasons for delayed diagnosis

I took long to go to the hospital due to fear. Others were saying it is "Etalo", which the Baganda use to trap people. It is said that in case you went to the hospital and they inject you – that the swollen leg bursts and you die. So, I feared to go to the hospital. *(Interview 7001)*	*The major hindrance was that patients are so many, and there is no doctor. By the time you get into the treatment room, they tell you that it's past time and tell you to come back later. Yet, you have nowhere to sleep. The following day you come so early in the morning, and if you chanced to meet the doctor he will also tell you to come back for results later. It's so disgusting – wasting money on to and fro without treatment. I gave up and decided to go back to the village, so that if I am to die let me die.* *(Interview 7003)*	*To make matters worse, during that time I had just divorced with my wife and she had abandoned all the children to me… So I had many sources of pain: no money for hospital; and no money to cater for the family, which would generate disgust and hatred to the whole world. That's how I remained without treatment.* *(Interview 7007)*

Conclusions: A range of reasons—originating from the affected patient, the health care system, and the contextual environment—contribute to delayed diagnosis of KS in Uganda. While a larger quantitative study is being performed to estimate attributable risk of each determinant, the present data indicate that a multi-pronged intervention will be needed to promote earlier KS detection in the region.

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35. Developing Clinical Strength-of-Evidence Approach to Define HIV-Associated Malignancies for Cancer Registration in Kenya

Anne Korir[1], Nathan Mauti[1*], Pamela Moats[2], Matthew J. Gurka[2], Geoffrey Mutuma[1], Christine Metheny[2], Peter M. Mwamba[3], Peter O. Oyiro[3], Melanie Fisher[2], Leona W. Ayers[4], Rosemary Rochford[5], Walter O. Mwanda[3], Scot C. Remick[2]*

[1]Kenya Medical Research Institute, Nairobi Cancer Registry, Nairobi, Kenya; [2]West Virginia University School of Medicine, Morgantown, WV; [3]University of Nairobi Institute of Tropical and Infectious Diseases, University of Nairobi College of Health Sciences, and Kenyatta National Hospital, Nairobi, Kenya; [4]The Ohio State University College of Medicine, Columbus, OH; [5]SUNY Upstate Medical University, Syracuse, NY

Background: Sub-Saharan Africa cancer registries are beset by an increasing cancer burden further exacerbated by the AIDS epidemic where there are limited capabilities for cancer-AIDS match co-registration. We undertook a pilot study based on a *"strength-of-evidence"* approach using clinical data that is abstracted at the time of cancer registration for purposes of linking cancer diagnosis to AIDS diagnosis.

Methods/Findings: The standard Nairobi Cancer Registry form was modified for registrars to abstract the following clinical data from medical records regarding HIV infection/AIDS in a hierarchal approach at time of cancer registration from highest-to-lowest strength-of-evidence: (1) documentation of positive HIV serology; (2) antiretroviral drug prescription; (3) CD4+ lymphocyte count; and (4) WHO HIV clinical stage or immune suppression syndrome (ISS), which is Kenyan terminology for AIDS. Between August 1 and October 31, 2011, a total of 1,200 cancer cases were registered. Of these, 171 cases (14.3%) met clinical strength-of-evidence criteria for association with HIV infection/AIDS; 69% (118 cases were tumor types with known HIV association – Kaposi's sarcoma, cervical cancer, non-Hodgkin's and Hodgkin's lymphoma, and conjunctiva carcinoma) and 31% (53) were consistent with non-AIDS defining cancers. Verifiable positive HIV serology was identified in 47 (27%) cases for an absolute seroprevalence rate of 4% among the cancer-registered cases with an upper boundary of 14% among those meeting at least one of strength-of-evidence criteria. The application of this approach to analysis of the Kisumu Cancer Registry will be presented.

Conclusions/Significance: This pilot demonstration of a hierarchal, clinical strength-of-evidence approach for cancer-AIDS registration in Kenya establishes feasibility, is readily adaptable, pragmatic, and does not require additional resources for critically under staffed cancer registries. Cancer is an emerging public health challenge, and African nations need to develop well-designed population-based studies in order to better define the impact and spectrum of malignant disease in the backdrop of HIV infection.

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*Contributed equally to this project

36. Effect of HIV on Enrollment in Oncology Care in Botswana

Carolyn A. Brown[1,2], Scott Dryden-Peterson[1,3,4], Gita Suneja[5,6], Memory Nsingo-Bvochora[6], Kamal Verma[7], Zola Musimar[7], Mukendi Kayembe[8], Heluf Medhin[9], Matthew Boyer[1,11], Mompati Mmalane[1], Timothy Rebbeck[12], Shahin Lockman[1,3,4]

[1]Botswana Harvard AIDS Institute, Gaborone, Botswana; [2] John's Hopkins Bloomberg School of Public Health, Baltimore, MD; [3] Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA; [4]Harvard School of Public Health, Boston, MA; [5]Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA; [6]Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA; [7]Department of Oncology, Gaborone Private Hospital, Gaborone, Botswana; [8]Department of Oncology, Princess Marina Hospital, Gaborone, Botswana; [9]Anatomic Pathology, National Health Laboratory, Gaborone, Botswana; [10]Department of Public Health, Ministry of Health, Gaborone, Botswana; [11]Joan C. Edwards School of Medicine, Marshall University, Huntington, WV; [12]Department of Epidemiology, University of Pennsylvania, Philadelphia, PA

Background: Timely initiation of oncologic care and treatment can improve patient outcomes. In countries with high HIV prevalence and robust HIV treatment programs, frequent, scheduled contact with the medical system may yield better access to cancer care among persons with HIV (compared to HIV-uninfected individuals). We sought to understand the impact of HIV status and socioeconomic factors on timeliness of receipt of specialized oncology treatment and cancer stage at presentation in Botswana, a country with an adult HIV prevalence of 23.4% [see reference].

Methods: We performed a retrospective analysis of patients with new cancers enrolling in the Botswana Prospective Cancer Cohort between October 2010 and June 2013. On presentation for specialized oncology care, consenting patients were interviewed and medical records abstracted. Due to differing referral patterns, cases of Kaposi's sarcoma were excluded from this analysis. Associations between known HIV infection and log-transformed time to presentation (symptom onset to first clinical evaluation and first clinical evaluation to enrollment in oncology care) were assessed using generalize linear models. Factors associated with advanced oncologic stage at presentation were assessed using logistic regression (with backward model selection). Study design did not enable assessment of patients not accessing oncology care.

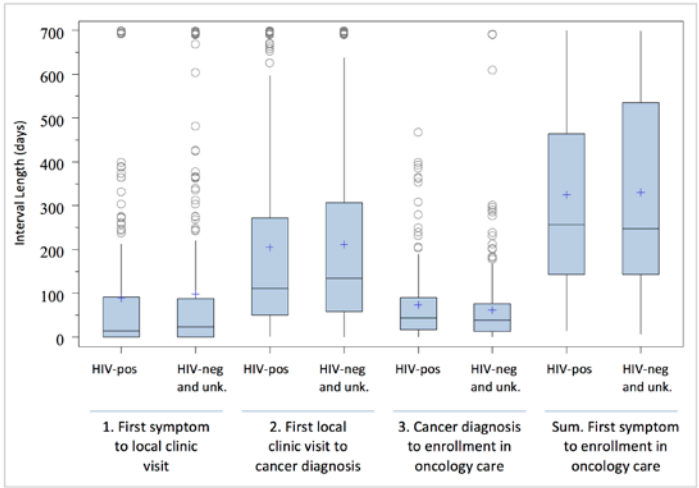

Figure 1. Intervals in accessing specialized oncology care by known HIV status. Box plots display median and interquartile range. Mean noted by cross. For display purposes, outliers truncated at 700 days.

Results: A total of 451 patients were included in the analysis, including 181 (40.1%) HIV-infected, 198 (43.9%) HIV-uninfected, and 72 (16.0%) with unknown HIV status. Patients with known HIV infection were younger and had higher incomes and education, but were less likely to be married or use traditional medicine. There were no significant differences in the median duration from onset of cancer symptoms and enrollment in specialized care between individuals with known HIV infection and those without known HIV infection, 256 (interquartile range [IQR] 143-464) and 247 days (IQR 143-535), respectively (P=0.77, Figure 1). In multivariable analysis, cancer site (P=0.016), education beyond primary school (P<0.001) and utilization of traditional healers (P=0.026) was associated with decreased time to presentation. Advanced stage at presentation was significantly associated with pain as initial symptom (adjusted

odds ratio [aOR] 1.86, 95% confidence interval [95%CI] 1.06-3.27), living without electricity (aOR 2.15, 95%CI 1.31-3.53), and cancer site (P<0.001), but not with known HIV infection.

Conclusions: Among patients needing specialized oncology care in Botswana, substantial delays were encountered, irrespective of HIV status. Identification of barriers to treatment referral and initiation are critical to improve cancer outcomes in Botswana.

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37. HIV Infection and Mortality Among Patients With Cancer in Botswana

Scott Dryden-Peterson[1,2,3], Gita Suneja[4,5], Zola Musimar[6], Memory Nsingo-Bvochora[7], Heluf Medhin[8], Kamal Verma[6], Mukendi Kayembe[9], Carolyn Brown[1,10], Matthew Boyer[1,11], Mompati Mmalane[1], Timothy Rebbeck[12], Shahin Lockman[1,2,3]

[1]Botswana Harvard AIDS Institute, Gaborone, Botswana; [2]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA; [3]Harvard School of Public Health, Boston, MA; [4]Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA; [5]Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA; [6]Department of Oncology, Princess Marina Hospital, Gaborone, Botswana; [7]Department of Oncology, Gaborone Private Hospital, Gaborone, Botswana; [8]Department of Public Health, Ministry of Health, Gaborone, Botswana; [9]Anatomic Pathology, National Health Laboratory, Gaborone, Botswana; [10]John's Hopkins Bloomberg School of Public Health, Baltimore, MD; [11]Joan C. Edwards School of Medicine, Marshall University, Huntington, WV; [12]Department of Epidemiology, University of Pennsylvania, Philadelphia, PA

Background: Since the availability of combination antiretroviral therapy (ART), survival for HIV-infected patients with cancer has been similar to HIV-uninfected patients in high-income countries. However, little is known about the survival of patients with HIV and cancer in sub-Saharan Africa where most HIV infections occur. Available evidence from two retrospective studies in Uganda suggest that HIV-infected patients may experience inferior outcomes [1,2]. We sought to prospectively evaluate the role of concurrent HIV-infection on survival of patients diagnosed with malignancy in a country with high HIV treatment coverage.

Methods: We have enrolled to the Botswana Prospective Cancer Cohort sequential patients presenting for oncologic care in Gaborone, Botswana. Patient interviews and record abstraction are performed at baseline to assess risk factors, including HIV status and CD4 cell count, cancer stage, and treatment plan. Patients are followed every 3 months for treatment outcome. The current analysis includes new cases of cancer enrolled from October 2010 to June 2013. Patients of unknown HIV status (no negative test within 6 months) who declined HIV testing were analyzed as HIV-uninfected. Association between HIV-infection and all-cause mortality was assessed using the logrank test and a Cox proportional hazards model adjusting for age, cancer site, sex, and cancer stage.

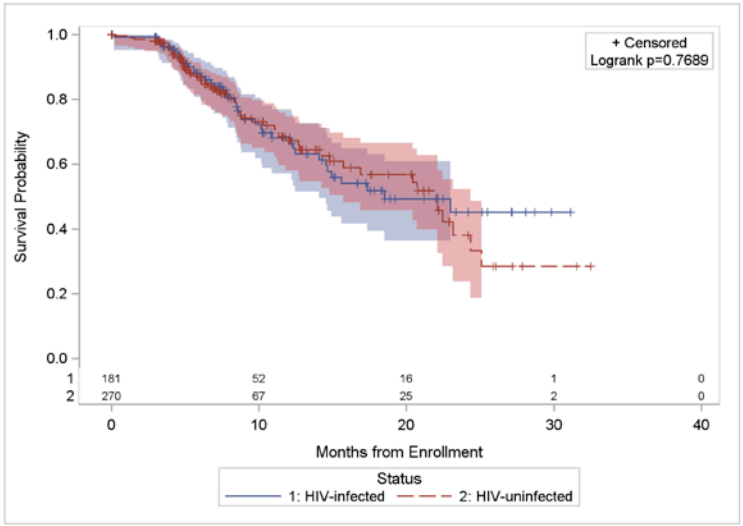

Figure 1. Survival by HIV status for all patients, excluding Kaposi's sarcoma. Shaded bands indicate 95% confidence limits.

Results: A total of 568 patients with a new cancer diagnosis were enrolled, including 294 (51.8%) HIV-infected, 201 (35.4%) HIV-uninfected, and 73 (12.9%) with unknown HIV status. The majority (61.4%) were female and lifetime non-smokers (64.3%). Among HIV-infected patients median CD4 count was 309 cells/μL (interquartile range 167-473 cells/μL) and most HIV infected patients (77.6%) were receiving ART. HIV-infected patients were younger than HIV-uninfected patients (median age 41.5 and 61.7 years, respectively, P<0.001). For survival analysis, the 117 patients with Kaposi's sarcoma were excluded due to collinearity with HIV-infection. After a median follow-up of 5.8 months, 101 (22.3%) patients have died— 41 (22.7%) HIV-infected and 60 (22.2 %) HIV-uninfected. Survival was not

significantly different between HIV-infected and HIV-uninfected patients with cancer, median 18.5 and 22.1 months respectively (Figure 1, P = 0.77). In adjusted multivariable models, there were no significant differences in the risk of death by HIV status. Findings were unchanged when patients with unknown HIV status were excluded.

Conclusions: The prevalence of HIV infection among patients seeking oncology care in Botswana is high. In the setting of a mature antiretroviral treatment program with high treatment coverage, HIV-infection was not associated with increased mortality. Longer follow-up is needed.

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38. Elevated Risks for Alcohol-Related Cancers in a Cohort of 2,770 Recipients of Liver Transplant

Pierluca Piselli[1], Giovanni Battista Vizzini[2], Augusto Lauro[3], Umberto Baccarani[4], Patrizia Burra[5], Maria Rendina[6], Massimo Rossi[7], Giuseppe Tisone[8], Giuseppe Maria Ettorre[9], Fausto Zamboni[10], Diego Serraino[11]

[1]INMI "L. Spallanzani" IRCCS, Roma, Italy; [2]ISMETT, Palermo, Italy; [3]Policlinico "S. Orsola-Malpighi" Bologna, Italy; [4]Policlinico Univ. Udine, Italy; [5]Policlinico Univ. Padova, Italy; [6]Policlinico Univ. Bari, Italy; [7]Policlinico "Umberto I", Roma, Italy; [8]Policlinico "Tor Vergata", Roma Italy; [9]POIT San Camillo-Forlanini - INMI "L. Spallanzani, Italy; [10]Azienda Ospedaliera "Brotzu", Cagliari, Italy; [11]IRCCS Centro di Riferimento Oncologico, Aviano, Italy

Background: Iatrogenic immunosuppression after organ transplantation is associated with a 2-4 fold higher risk of developing a neoplastic disease. Much of such excess risk is attributable to infection with oncogenic viruses, but individual life style factors may also play a relevant role. The aim of this study was to assess the role of alcohol abuse on the risk of developing de novo cancers after liver transplantation (LT).

Materials and Methods: Data were from a clinical-based, retrospective, cohort of 2,770 individuals (74.7% men, median age 56 years) who underwent, between 1990 and 2010, LT in nine Italian centers. At transplant, information was collected on socio-demographic characteristics, life style habits, liver disease and transplant-related variables. Follow-up visits were scheduled every six months: cancer diagnoses (histologically documented) and vital status were ascertained through clinical chart and, when possible, by means of a record linkage with population-based cancer registries. Person-years (PYs) at risk for cancer were computed from date of transplant to whichever came first among date of cancer diagnosis, date of death or date of last follow-up. The number of cancers diagnosed among LT recipients was compared with that expected in the general population matched by sex, age, area of residence and calendar period. SIR and 95%CIs were computed accordingly.

Results: In 740 (26.7%) of the 2770 LT recipients, alcohol abuse was the cause of liver disease. The median time of follow-up was 4.7 years (IQR: 2.3-8.9), and 186 cancers were diagnosed in 16364PYs of observation (non-melanoma skin cancers excluded). Table 1 reports SIR and 95%CIs for cancers with at least five observed cases, according to history of alcohol abuse. A 1.5-fold elevated risk was documented for all cancers in the whole cohort, with SIR=2.3 among LT recipients with a history of alcohol abuse and SIR=1.3 in those without. All cancers strongly related with alcohol consumption showed significantly elevated SIRs only among LT recipients with history of alcohol abuse (e.g., esophagus: SIR=24.0 and SIR=2.9 in alcoholics and non alcoholics, respectively; head&neck cancers: SIR=11.4 and 2.2 in alcoholics and non-alcoholics, respectively) (Table 1). SIR for KS or PTLD did not differ in magnitude by history of alcohol consumption.

Table 1. Standardized Incidence Ratios (SIR) and 95% Confidence Intervals for Selected Cancer Sites, by History of Alcohol Abuse, Italy, 1990-2010

		History of alcohol abuse		
Cancer site	**No° of cases**	**No**	**Yes**	**Total**
		SIR (95%CI)	**SIR (95%CI)**	**SIR (95%CI)**
Kaposi sarcoma (KS)	14	48.6 (23-89)	58.0 (15.8-148)	51.0 (27-86)
Post Transplant Lymphoproliferative Disorders (PTLD)	36	4.2 (2.8-6.0)	3.0 (1.2-6.1)	3.9 (2.7-5.4)
Oral cavity	15	2.0 (0.6-5.0)	13.2 (6.6-24)	5.2 (2.9-8.6)
Head & neck	33	2.2 (1.1-4.0)	11.4 (7.2-17)	4.8 (3.3-6.8)
Tongue	6	1.9 (0.0-10.5)	23.2 (7.5-54)	8.0 (3.0-18)
Larynx	17	2.7 (1.0-5.9)	12.7 (6.3-23)	5.5 (3.2-8.8)
Esophagus	9	2.9 (0.4-10.3)	24 (9.6-50)	9.1 (4.1-17.2)
Lung	25	1.1 (0.6-1.9)	2.2 (1.0-4.0)	1.4 (0.9-2.1)
Colorectal	22	1.5 (0.9-2.3)	1.0 (0.3-2.4)	1.3 (0.8-2.0)
All non melanoma skin cancers excluded	186	1.3 (1.1-1.5)	2.3 (1.8-2.9)	1.5 (1.3-1.8)

Conclusions: Findings from this cohort of LT recipients indicate a strong role of alcohol abuse in determining the risk of de novo cancers after LT. Immunosuppression does not seem to influence the risk of developing alcohol-related cancers in individuals with a history of heavy alcohol consumption.

Acknowledgements
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39. Engaging Traditional Health Practitioners in the Early Detection of Kaposi's Sarcoma in Uganda

Lisa M. Butler[1,2,3], Miriam O. Laker-Oketta[1,4], Philippa Kadama-Makanga[4], Joseph Baguma[5], Jeffrey N. Martin[1]

[1]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA; [2]Department of Medicine, Division of General Pediatrics, Boston Children's Hospital, Boston, MA; [3]Department of Pediatrics, Harvard Medical School, Boston, MA; [4]Infectious Diseases Institute, Kampala, Uganda; [5]Traditional and Modern Health Practitioners Together Against AIDS (THETA), Kampala, Uganda

Background: In sub-Saharan Africa, Kaposi's sarcoma (KS) is the most commonly reported HIV-associated malignancy among adults, but many patients are not diagnosed until advanced disease has developed. In Uganda, we have recently learned that delayed diagnosis of KS at biomedical facilities is frequently preceded by patient's consulting with traditional health practitioners (THPs), which in many cases prolongs time without correct diagnosis. We hypothesized that, with the proper relationship building, THPs can be taught about KS and engaged to promote early diagnosis in the community.

Methods: In partnership with THETA, a non-governmental organization devoted to promoting collaboration between traditional and biomedical practitioners, we attempted to contact all THPs in three rural districts in western Uganda. Identification was via pre-existing lists and respondent-driven referral. THPs were offered free two-day training on KS, led by biomedical providers and THETA staff. The only incentive was transport reimbursement. A pre- and post-training assessment of KS-related knowledge was administered, and follow-up sessions were held at 6 months to obtain feedback.

Results: Between January 2012 and June 2013, 758 THPs participated in training and completed pre- and post-training assessments. The median age was 47 years (IQR 37-58), 54% were women, and specializations included herbalists (58%), traditional birth attendants (25%), diviners (8%), spiritualists (14%), and bone setters (4%). Prior to training, only 22% of THPs correctly identified a picture of KS as cancer, and only 13% had heard of the condition KS. Understanding of the biomedical details of KS was equally poor (Table 1). At the end of training, THP understanding of KS was substantially improved in most areas (Table 1), including 95% knowing that KS could cause a variety of other symptoms besides skin lesions (e.g., edema).

Table 1. Responses to Pre- and Post-Training Questions Regarding KS Among Traditional Health Practitioners in Rural Uganda. Percentages Refer to Fraction Answering the Question Correctly.

	Pre-Training	Post-Training
KS is a type of cancer	7%	89%
KS is caused by a virus	0.92%	4.0%
A biopsy is required for best diagnosis of KS	3.8%	79%
Without treatment, an HIV-infected patient with KS would likely die	7.5%	85%

In follow-up sessions several months later, THPs generally reported feeling more confident in their ability to suspect KS and make referrals to biomedical facilities. Challenges included patient refusal of referrals due to distrust of biomedical facilities or holding belief in the predominance of THPs to provide a cure.

Conclusions: With only nominal incentive, THPs in Uganda were eager to attend training regarding KS. Prior to training, THP knowledge about KS was very low, but a two-day training was able to impart a working knowledge about the recognition and management of KS to the majority of attendees. In rural sub-Saharan Africa, where HIV and KS prevalence are high and health care access limited, THPs offer considerable promise to facilitate early diagnosis of KS.

40. Genetic Variation in Immunoglobulin Gene Diversification Pathways and Activation-Induced Cytosine Deaminase Expression Predisposes to HIV-Associated Non-Hodgkin Lymphoma

Shehnaz K. Hussain[1,2], Zuo-Feng Zhang[1,2], Roger Detels[1], Charles Rabkin[3], Jeremy Martinson[4], Steven Wolinsky[5], Lisa P. Jacobson[6], Priya Duggal[6], Jay H. Bream[7], Otoniel Martínez-Maza[1,2,8-10]

[1]Department of Epidemiology, UCLA Fielding School of Public Health, [2]Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA; [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD; [4]Department of Pathology, School of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; [5]Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL; Department of Epidemiology[6] and Molecular Microbiology and Immunology[7], Johns Hopkins University, Baltimore, MD; [8]Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, CA; [9]Department of Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA; [10]UCLA AIDS Institute, Los Angeles, CA

Introduction: Immunoglobulin gene diversification depends on the actions of the highly regulated DNA-mutating enzyme activation-induced cytidine deaminase (AICDA) and subsequent low-fidelity DNA repair via two germinal center reactions: class switch recombination (CSR) and somatic hypermutation (SHM). Aberrant AICDA activity and defective DNA repair have been implicated in the formation of point mutations and translocations of oncogenes associated with non-Hodgkin lymphoma (NHL). We sought to determine whether AICDA expression or variation in DNA repair genes associated with CSR and SHM predisposes to NHL among HIV-infected men in the Multicenter AIDS Cohort Study.

Methods: We selected 269 tagSNPs in 29 candidate gene regions using HAPMAP genotype data and NIEHS Environmental Genome Project resequencing data from individuals of European descent, with an $r^2 \geq 0.80$ to delineate bins of correlated SNPs. Genomic DNA was extracted from peripheral blood cell pellets for 183 NHL cases and 533 HIV-infected controls matched on baseline date, race, HIV-infected follow-up time, and CD4+ T lymphocyte count. Genotyping was performed using a custom Illumina GoldenGate® assay. AICDA expression was measured with the Luminex platform using the Panomics QuantiGene Plex 2.0 system on viably frozen B cells from a subset of 145 NHL cases with sample availability between 3 and 6 years prior to NHL diagnosis, and 145 HIV-infected matched controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random effects multivariate logistic regression models for each tagSNP (additive model) and AICDA expression (detectable versus undetectable) adjusting for age, HIV load, prior AIDS, and HAART. Gene-based association tests were performed with likelihood ratio tests comparing models with and without terms for all SNPs within a gene.

Results: AICDA mRNA was detected in 8.3% of cases and 2.8% of controls, OR=3.67, 95% CI=1.02–13.1. SNP and gene-based tests showed promising associations between NHL and two genes important for repair of double strand breaks: XRCC5 (non-homologous end joining) and ATM (DNA damage sensor). The most strongly associated tagSNPs within these genes were rs41296769 (XRCC5), OR=3.19, 95% CI=1.14-7.24, and rs1800889 (ATM), OR=0.37, 95% CI=0.18-0.76. Gene-based tests included 23 tagSNPs for XRCC5 ($p=0.0006$), and 11 tagSNPs for ATM ($p=0.0897$). Additional genes with notable tagSNP-NHL associations ($p<0.05$) included APEX1, APEX2, MLH1, MSH3, POLM, and UNG.

Conclusions: Detectable AICDA expression was observed preceding an HIV-associated NHL diagnosis, and variation in several genes involved in the repair/promotion of AICDA-induced lesions was associated with NHL risk.

41. High Prevalence of HPV in Non-Anal Sites of HIV-Seropositive Individuals With Anal Squamous Intraepithelial Lesions

Eleanore Chuang[1,2], Eunjung Lim[3], Cris Milne[2], Xumei Zhu[4], Melissa Agsalda[2], Jeffrey Killeen[5], Marc Goodman[6], Bruce Shiramizu[1,2]

[1]Department of Tropical Medicine, Medical Microbiology and Pharmacology, [2]Hawaii Center of AIDS, [3]RMATRIX, Research Design and Biostatistics, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI; [4]Cancer Center, University of Hawaii, Honolulu, HI; [5]Department of Pathology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI; [6]Cancer Prevention and Genetics, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Human papillomaviruses (HPV) are associated with ano-genital and head/neck cancers. Because human immunodeficiency virus type 1 (HIV)-infected individuals are at risk for HPV-associated anal cancer other non-anal sites may also be at risk for HPV. The objective of the study was to assess HPV from non-anal sites from individuals with anal squamous intraepithelial lesions (ASIL).

Materials and Methods: Anal cytology specimens, oral washes, and swabs from cervix, penile head/shaft/foreskin and scrotum were obtained as per guidelines approved by the local institutional review board. Anal cytologies (ASIL or negative) and HPV genotypes were assessed including high-risk (oncogenic) genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). Of the seven specimens, analyses were limited to male anal, oral, penile head/shaft and scrotum due to specimen availability for HPV amplification (+ or -), HPV genotyping, and HPV 16/18. Specimens were scored 1 for a positive result or 0 for a negative result based on a single criterion. The sum of five specimen scores provided a cumulative score for each patient on a scale of 0 to 5. To assess bivariate association for HPV risk, chi-square or Fisher's exact tests were used for categorical variables (e.g. gender, race) and Wilcoxon nonparametric tests were used for continuous variables (e.g. HPV amplification, HPV genotyping, and HPV 16/18) using SigmaPlot 11.0.

Results: There were 46 participants (37 males, 9 females); 20 Whites, 26 non-Whites (7 Native Hawaiians, 9 Asians, 5 Native Americans, 4 African Americans, 1 Hispanic). Males had higher risk of ASIL than females (RR=11.7); however only 1 female had ASIL. Native Hawaiians had lower odds than non-Native Hawaiians of having ASIL (RR=0.7); Asians had lower odds than non-Asians (RR=0.8); but overall non-Whites had equal odds compared to Whites (RR=1.0); none were statistically significant. HPV data from only male patients were compared for ASIL since there was only 1 female ASIL. All analyses demonstrated significance in the 5 cumulative scores compared to anal cytology: 1) +/- HPV, p=0.017; 2) HPV genotype, p=0.025; 3) HPV 16/18, p=0.045.

Conclusions: Individuals with ASIL compared to those with normal anal cytologies were more likely to be positive for HPV, positive HPV genotyping, and positive HPV 16/18. Because of the risk of anal cancer associated with some HPV subtypes, the implications of an combined effect of HPV in non-anal sites with ASIL warrant further study.

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42. HIV- Associated Plasmablastic Lymphoma: No Longer an Oral Cavity Presenting Malignancy

Shabnam Seydafkan[1], Shahrzad Ehdaievand[1], Clifford Gunthel[2], Marina Mosunjac[1], Minh Ly Nguyen[2]

[1]Emory University School of Medicine, Department of Pathology, [2]Emory University School of Medicine, Department of Medicine, Division of Infectious Diseases, Atlanta, GA

Background: Plasmablastic lymphoma (PBL), an aggressive B-cell lymphoma, is a rare malignancy occurring primarily in the oral cavity and in association with human immunodeficiency virus (HIV) infection. We present a clinicopathologic review of PBL cases in an inner city hospital.

Materials and Methods: This is a retrospective review of all plasmablastic lymphoma cases identified from pathological records from January 2004 to June (or July?) 2013 at an inner city hospital .Electronic patient's files were used for extraction of demographic data, HIV status, HIV-associated risk factors, laboratory data, PET imaging scan results, pathology reports and flow cytometry reports. Pathology slides with immunohistochemistry stains were reviewed.

Results: Of the 15 patients diagnosed with PBL over the 10 year period, there were 14 men and 1 woman with an average age of 43.4 years (range: 26-63 years). Two (12.5%) patients were HIV negative. The majority (66.7%) presented with extraoral disease (anus/colon/rectum (5), inguinal node (3), stomach (2), penis (1) lungs (1)). The most common HIV –associated risk factor was men having sex with men (40%). There were 4 (26.7%) with HIV and Hepatitis C coinfections. The average CD4 cell count at PBL diagnosis was 176.3 cells/mm3 (range: 23-485), and 9 (81.8%) had an undetectable viral load (less than 400 copies/mL at the time of PBL diagnosis). Among the 2 HIV-patients, PBL presented as an oral cavity/gingiva lesion in one, and a neck mass in the other. Among THE 12 patients with available Pet scans, 81.85 had evidence of metastatic disease. Immunohistochemical studies showed the following: CD138+ (100% , Cd20+(44%) and Cd45+(37%).

Conclusion: Over the past 10 years, the majority of PBL (81%) presented as an extraoral lesion in our institution, with the most common site being in the anorectal area, making diagnosis of PBL challenging. In those cases, an appropriate immunohistochemical pattern with plasma cell and B cell markers should help the diagnosis.

43. Improving Cervical Cancer Prevention Among HIV-Infected Women Using Novel HPV-Based Biomarker Assays: Design and Implementation of a Multicentric Study in India

Vikrant V. Sahasrabuddhe[1], Nicolas Wentzensen[1], Arati Mane[2], Ramesh S. Paranjape[2], Sanjay M. Mehendale[3], for the NCI-ICMR "Intramural-to-India" HIV-Cervical Cancer Study Protocol Team

[1]National Cancer Institute, National Institutes of Health, Bethesda, MD; [2]National AIDS Research Institute, Indian Council of Medical Research, Pune, Maharashtra, India; [3]National Institute of Epidemiology, Indian Council of Medical Research, Chennai, Tamil Nadu, India

Background: While HPV DNA testing is a highly sensitive screening method, it cannot differentiate between the majority of benign infections and few persistent infections linked to cervical precancer. Given the high prevalence of carcinogenic HPV DNA and higher risk for cervical precancer/cancer among HIV-infected women, there is a substantial need for screening tests that are both adequately sensitive as well as specific, so as to maximize detection while reducing false-positive referrals.

Objectives and Study Design: Through a U.S.-India collaborative partnership, an observational study protocol is currently underway for evaluating clinical performance of novel HPV-based biomarker assays to detect cervical precancers among HIV-infected women in India. The NCI intramural Division of Cancer Epidemiology and Genetics (DCEG) has partnered with Indian Council of Medical Research (ICMR) institutes: National Institute of Epidemiology (NIE) and National AIDS Research Institute (NARI). Consenting HIV-infected women, $\geq$18 years, non-pregnant, and with no history of treatment for cervical pre-cancer/cancer are offered enrollment at clinical recruitment sites linked to HIV/AIDS clinics in the cities of Pune, Belgaum, and Chennai. Along with standardized approaches to cervical sample collection, enrolled women undergo colposcopy and multiple biopsies of acetowhite lesions. Biomarker assays [including (i) immunocytostaining by $p16^{INK4a}$/Ki-67 (cellular markers associated with oncogenic transformation following persistent carcinogenic HPV infection), (ii) testing for HPV E6/E7 mRNA (expressed during progression of transient to transforming HPV infection), and (iii) HPV DNA genotyping] are being conducted on cervical specimens that are collected and stored locally, batch shipped monthly to central laboratories [NARI and Tata Memorial Hospital (TMH) in Mumbai] and analyzed in a blinded fashion. All histology endpoints are confirmed by two independent pathologists locally, along with central review for adjudication of discordant results. Colposcopy images with localization of colposcopic lesion and location of biopsy sites by lesion severity are uploaded to a central database and reviewed concurrently for quality control purposes.

Implementation and Results: Enrollment of the first 53 women (target n=1000) into the study has been completed successfully. Initial HPV genotyping results showed a 23% (95%CI: 13%-35%) prevalence of carcinogenic HPV. Updated enrollment statistics with HPV data, cytology results, and CD4 counts will be presented at the time of the 14th ICMAOI meeting.

Conclusion: This study will permit validation of collection, transport, storage, implementation protocols, and field efficacy for biomarker assays, describe their sensitivity and specificity with reasonable precision for a wide range of prevalence of precancer, and provide a resource for studies of HIV-HPV coinfection.

44. Indoleamine 2,3-dioxygenase (IDO) Activity as a Determinant of AIDS-Associated Kaposi's Sarcoma in Africa

Helen Byakwaga[1,2], Peter W. Hunt[2], Miriam Laker-Oketta[2,3], Dave V. Glidden[2], Yong Huang[2], Mwebesa Bwana[1,2], A. Rain Mocello[2], John Bennett[2], Victoria Walusansa[4], David R. Bangsberg[5], Edward Mbidde[3,6], Jeffrey N. Martin[2]

[1]Mbarara University of Science and Technology, Mbarara, Uganda; [2]University of California, San Francisco, CA; [3]Infectious Diseases Institute, Kampala, Uganda; [4]Uganda Cancer Institute, Kampala, Uganda; [5]Massachusetts General Hospital, Center for Global Health, Harvard Medical School, Boston, MA; [6]Uganda Virus Research Institute, Entebbe, Uganda

Background: Other than human herpesvirus 8 (HHV-8) and CD4+ T cell lymphopenia, the mechanisms responsible for Kaposi's sarcoma (KS) are poorly understood. This is the case both in resource-rich areas, and in resource-poor hyperendemic areas such as sub-Saharan Africa. Additional mechanisms must exist in Africa given how relatively few HIV-infected patients develop KS despite high prevalence of both HHV-8 infection and low CD4+ T cell count. One recently explored pathway of HIV pathogenesis involves induction of the enzyme indoleamine 2,3-dioxygenase (IDO) in monocytes/dendritic cells, which catabolizes tryptophan into kynurenine and several other immunologically active metabolites that suppress T cell proliferation. We investigated whether IDO may have a role in the etiology of KS.

Materials and Methods: In a case-control design, cases were HIV-infected adults, sampled throughout Uganda, with biopsy-confirmed KS and no urgent indications for chemotherapy; they were being seen in preparation for the Antiretrovirals for Kaposi's Sarcoma (ARKS) clinical trial. Controls without KS were derived from the Uganda Rural AIDS Treatment Outcomes (UARTO) cohort, a consecutive sample of HIV-infected adults starting antiretroviral therapy (ART) in southwestern Uganda. Measurements for both cases and controls used the same instruments, and all biological tests were performed in the same laboratories on samples obtained prior to ART. IDO activity was assessed by the ratio of plasma kynurenine to tryptophan levels (K:T), measured by liquid chromatography tandem mass spectrometry.

Results: We studied 631 subjects: 222 KS cases and 409 non-KS controls (Table). Cases had a wide spectrum of mucocutaneous KS ranging from oral lesions only to widespread cutaneous dissemination. In multivariable regression, KS was independently associated with K:T but in a non-linear relationship. There was no effect of K:T among those in the lower three quartiles but subjects with the highest quartile of K:T (i.e., highest values) had a 64% reduction in the odds of KS (Table). The relationship between K:T and KS was present at all levels of CD4+ T cell count ($p = 0.44$ for interaction). KS was also independently associated with lower CD4+ T cell counts, higher plasma HIV RNA levels, and men.

Conclusions: Higher IDO activity, as evidenced by higher plasma K:T ratio, was protective against the occurrence of KS. This relationship is independent of both plasma HIV RNA level and CD4+ T cell count. The findings are consistent with the hypothesis that lymphocyte proliferation is necessary for the development of KS, which is compatible with the inflammatory nature of KS lesions.

Table 1.

Participant Characteristics			Multivariable Logistic Regression for KS	
KS (n=222)	**No KS** (n=409)		**Odds Ratio (95% CI)**	***p value***
		Sex		
Men	56%		32%	Ref
Women	44%	68%	0.41 (0.28-0.60)	<0.001
Age in years	34 (28-40)a	35 (29-40)	0.83 (0.65-1.05)	0.11
		CD4+ T cell count/mm^3		
<50	35%		16%	Ref
51-100	11%	18%	0.27 (0.15-0.49)	<0.001
101-200	23%	41%	0.32 (0.20-0.53)	<0.001
201-350	18%	21%	0.49 (0.28-0.84)	0.009
>350	13%	3%	2.36 (1.08-5.16)	0.031
HIV RNA, log10 copies/ml	5.3 (5.0-5.6)a	5.1 (4.6-5.6)	2.00b (1.45-2.74)	<0.001
		Kynurenine:Tryptophan (K:T) ratio, by quartile		
0.034-0.089 (lowest)	27%		24%	Ref
0.090-0.120	28%	23%	0.94 (0.57-1.56)	0.82
0.121-0.179	29%	23%	0.89 (0.53-1.48)	0.64
0.180-1.369 (highest)	16%	30%	0.36 (0.21-0.64)	<0.001

a median (IQR); b 2-fold increase in odds of KS per log10 increase in HIV RNA

45. Is HHV-8 More Common Among HIV-Infected People? Systematic Review and Meta-Analysis

Eliane Rohner[1], Natascha Wyss[1], Zully Faralli[1], Sam M. Mbulaiteye[2], Matthias Egger[1], Urban Novak[3], Marcel Zwahlen[1], Julia Bohlius[1]

[1]Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland; [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; [3]Department of Medical Oncology, University Hospital Bern, Switzerland

Background: Infection with human herpesvirus 8 (HHV-8) is a necessary cause of Kaposi sarcoma (KS). HIV-infection is a risk factor for KS; however, it is unclear whether HIV is associated with HHV-8-infection.

Methods: We systematically searched Medline and Embase without language restrictions until December 2012. We included cross-sectional studies of HIV-infected and HIV-uninfected adults from the same source population. We pooled confounder-adjusted odds ratios (OR) of the association between HHV-8 and HIV seropositivity using random-effects meta-analysis and explored sources of heterogeneity in meta-regression. The final model included the variables risk group (low risk heterosexuals, pregnant women, high risk heterosexuals and men having sex with men (MSM)) and region (HHV-8 endemic versus non-endemic).

Results: We screened 2,760 hits for eligibility and included 23 studies with 32,318 participants using 12 different HHV-8 testing strategies. Thirteen studies were conducted in Africa, 3 in South America, 3 in North America, 3 in Europe, and 1 in Asia. Studies conducted in Africa mainly included low risk heterosexuals and pregnant women (11 out of 13). Studies outside Africa were mainly conducted in adults at increased risk for sexually and parenterally transmitted infections (8 out of 10). HHV-8 test positivity was higher in HIV-infected than in HIV-uninfected adults (OR 1.73, 95% CI 1.41-2.13), with substantial heterogeneity between studies (I^2 =85.3%, p<0.001). Part of the heterogeneity (30.3%) was explained by the HHV-8 endemicity of a region (p-value for interaction=0.022) and different risk behaviors of study participants (p=0.027). There was little evidence for an association between HHV-8 and HIV in low risk heterosexual populations in endemic regions (OR 1.16, 95% CI 0.87-1.55). The association was stronger in high risk heterosexual populations (OR 1.93, 95% CI 1.43-2.61) and MSM (OR 2.28, 95%CI 1.14-4.58) in non-endemic regions, and in pregnant women in endemic regions (2.31, 95%CI 1.25-4.29), see Figure 1.

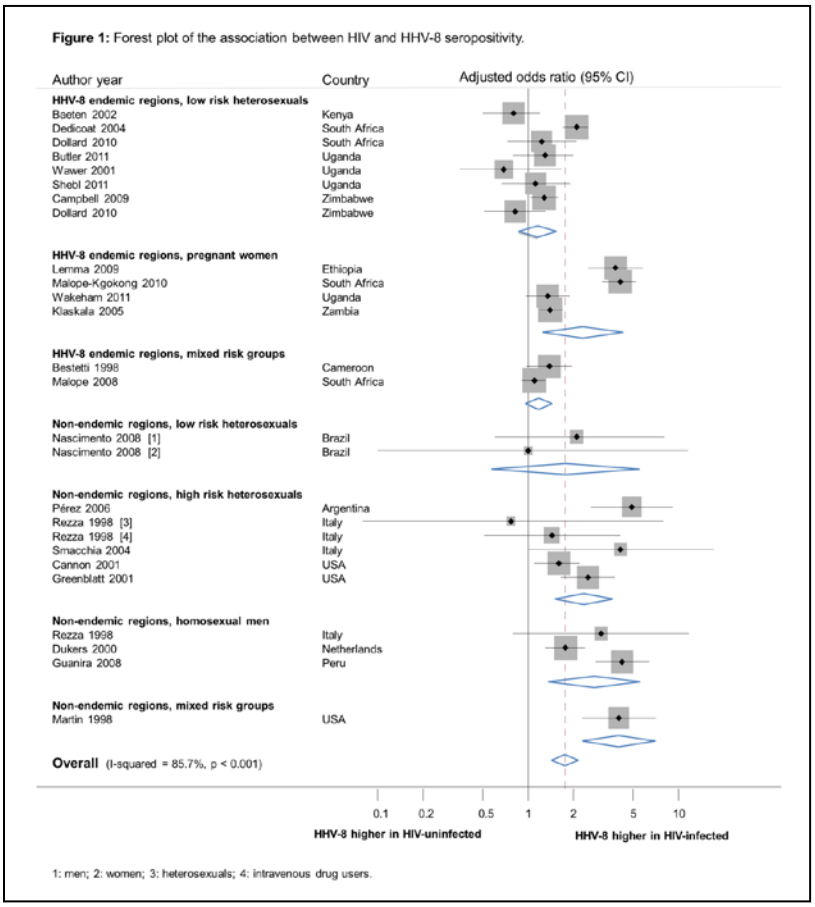

Figure 1: Forest plot of the association between HIV and HHV-8 seropositivity.

Conclusions: We found a higher HHV-8 seroprevalence in HIV-infected than in HIV-uninfected adults. This association was more pronounced in regions where HHV-8 is not endemic compared to endemic regions. Our results indicate that it may not be HIV-infection per se that increases the risk of HHV-8 co-infection but that the two infections share common routes of transmission, i.e. high-risk sexual behaviors. The association between HIV and HHV-8 in pregnant women from endemic regions is unclear. Future studies should be prospective and establish the sequence of infection with the two viruses.

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46. Low Level of Kaposi's Sarcoma-Specific Knowledge and Screening Practices Among Clinicians in Uganda

Miriam Laker-Oketta[1,2], Megan Wenger[2], Lisa Butler[2,3,4], Philippa Makanga[1], Toby Maurer[2], Edward Mbidde[5], Jeffrey Martin[2]

[1]Infectious Diseases Institute, Kampala, Uganda; [2]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA; [3]Department of Medicine, Division of General Pediatrics, Boston Children's Hospital, Boston, MA; [4]Department of Pediatrics, Harvard Medical School, Boston, MA; [5]Uganda Virus Research Institute, Entebbe, Uganda

Background: Although Kaposi's sarcoma (KS) remains one of the most commonly diagnosed malignancies in sub-Saharan Africa, diagnosis is often made in advanced stages when available interventions are ineffective. Health care provider knowledge about KS and screening practices may be among the reasons for delayed diagnosis, but little is known about this in Africa. Low levels of KS-specific knowledge and screening practices might be especially prevalent in resource-limited areas, where lower-level medical cadres are the front-line providers, facilities are remote, and daily patient workload is high.

Methods: From January 2012 to July 2013, we assessed, via a structured questionnaire, knowledge about KS among all health care providers working at government facilities in three rural districts in western Uganda (Kiboga, Kyankwanzi and Hoima). Questions covered KS epidemiology, clinical presentation, diagnosis and management. Prior to the assessment of the health care workers, we also interviewed patients at the HIV clinics of these facilities as they were exiting the clinic. These exit interviews covered aspects of the providers' history taking and physical examination.

Results: In the three districts, we surveyed 379 health care workers from 84 facilities (one hospital, 4 health center (HC) IV, 33 HC III, 43 HC II and 3 other facilities). The median age was 29 years (IQR 25-39), 71% were women, and 1.1% were medical officers (physician), 10% clinical officers, 54% nurses, 22% nurse assistants, 7.5% laboratory technicians and 5.4% other cadres. The few physicians reflect their limited number in these districts. In general, there was a low level of accurate knowledge about KS (Table 1). Overall, among all health workers, the following had perfect scores: 8% of workers on questions regarding KS disease classification, 17% on KS lesion morphology, 0% on KS symptoms, 55% on KS diagnosis, and 12% on KS treatment. Among the provider types with appreciable sample size, clinical officers had the best performance.

Table 1. Knowledge Regarding KS Among Health Care Workers, by Provider Type, in Rural Uganda. Values Refer to Median Score (Interquartile Range) per Group, with 100% Being Maximum Score per Topic.

	Medical Officer	Clinical Officer	Nurse	Nurse Assistant	Laboratory Staff
Topic	**(N = 4)**	**(N = 33)**	**(N = 188)**	**(N = 64)**	**(N = 26)**
Classification of KS[a]	100% (50%-100%)	0% (0%-50%)	0% (0%-0%)	0% (0%-0%)	0 % (0%-50%)
Morphology of KS[b]	100% (67%-100%)	33% (0%-100%)	0% (0%-33%)	0% (0%-0%)	0% (0%-33%)
Symptoms of KS[c]	40% (40%-60%)	0% (0%-25%)	0% (0%-0%)	0% (0%-0%)	0% (0%-0%)
Diagnosis of KS[d]	75%	82%	54%	40%	62%
Treatment for KS[e]	88% (60%-100%)	60% (20%-60%)	20% (20%-60%)	20% (0%-20%)	20% (0%-20%)

[a] 4 item survey
[b] 3 item survey
[c] 8 item survey
[d] Single item survey - % refers to fraction answering correctly
[e] 5 item survey

A total of 1747 patients were interviewed following encounters at the respective HIV clinics. They reported that their providers rarely asked about skin problems or examined their skin or mouth (Table 2).

Table 2. Practices of Health Workers, as Reported by Patients, in HIV Clinics in Rural Uganda. %'s Refer to Affirmative Responses.

Provider Practice	Hospital	Health Center Level IV	Health Center Level III	Health Center Level II
	(N = 445)	(N = 751)	(N = 475)	(N = 76)
Asked about skin	13%	12%	16%	9.2%
Examined mouth	8.3%	8.0%	12%	4.0%
Examined upper body skin	2.0%	3.4%	2.8%	0%
Examined lower body skin	2.8%	2.0%	2.3%	4.0%

Conclusion: In a setting from rural Uganda, health workers have very low level of KS knowledge and are generally not screening for KS. Although not investigated directly, these provider factors may contribute to delayed diagnosis of KS. Given the public health relevance of KS in the region, there is an urgent need for clinician training in KS epidemiology, diagnosis and management.

47. Participant-Reported Outcomes From an Intervention to Increase the Capacity of AIDS Service Organizations to Refer Clients to AMC Trials

Jack E. Burkhalter[1], John Guidry[2], Andrea Gillespie[1], Julie Kumar[1], Mark Kornegay[2], Ingmar Gorman[1], Erica Lubetkin[3], Ariela Noy[4]

[1]Department of Psychiatry and Behavioral Sciences, [4]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Gay Men's Health Crisis, Community Health and Research, New York, NY; [3]Department of Community Health and Social Medicine, Sophie Davis School of Biomedical Education, The City College of New York, New York, NY

Background: The AIDS Malignancy Consortium (AMC) confronts challenges to recruiting for cancer trials that parallels the national challenge [1]. In 2011, the AMC Behavioral Research Working Group was formed to develop and evaluate behaviorally-based interventions to increase recruitment to AMC trials. Community-based AIDS service organizations are at the frontlines and have regular client contact, representing an important conduit for education about and referral to AMC trials [2]. Presented is a study aiming to increase community referrals of HIV+ clients to the AMC.

Materials and Methods: A collaboration of investigators from Memorial Sloan-Kettering Cancer Center, The City College of New York, and community partner Gay Men's Health Crisis, and a Community Advisory Board developed an educational intervention targeted to New York City area community-based AIDS service organizations (ASOs). The intervention comprised a 1.5 hour in-person, interactive, skill-building workshop to educate and train ASO staff about cancer within HIV/AIDS, clinical research, and AMC referral, followed one month later by a 0.5 hour teleconference booster session. N=17 ASOs were recruited and n=246 of their staff participated. ASO staff completed assessments pre- and post-workshop and final outcomes one month after the booster session. ASOs received $250 payments. Participant-reported outcomes are presented.

Results: Staff participants were 71% female, 45% African-American, 33% Hispanic, and were on average 39 years old. Awareness of the AMC was very low. Analyses of intervention impact showed improvement in knowledge of, and attitudes about, clinical research ($p<.001$), increases in self-efficacy and intention to educate and refer HIV+ clients to the AMC ($p<.001$), and improved skill to make referrals ($p<.001$). N=15 ASOs (89%) and n=136 (51.9%) staff supplied final outcome data. N=18 staff (13.2%) from 6 ASOs (40%) reported making a total of 68 AMC referrals, with a mean of 11.3 (SD=11.3) referrals/site. N=10 (7.4%) participants reported that they or their agency had initiated a program to educate clients about the AMC. The most common reasons for not making referrals were that AMC trials were not relevant to their client base (28%), and lack of an opportunity to make a referral (25%).

Conclusions: An educational training workshop targeting the staff of community-based AIDS service organizations significantly improved participant-reported measures of knowledge, attitudes, self-efficacy, and intentions and skills to educate and refer clients to the AMC. These data show that a brief intervention with follow-up has potential to change ASO staff practices to include active referral of clients to cancer clinical trials. Future work will focus on examining referral barriers and capturing data on received community referrals.

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48. Pitfalls of Practicing Cancer Epidemiology in Resource-Limited Settings: The Case of Survival After a Diagnosis of Kaposi's Sarcoma in Sub-Saharan Africa

Esther Freeman[1], Aggrey Semeere[2,3], Megan Wenger[3], Mwebesa Bwana[4], F. Chite Asirwa[5], Naftali Busakhala[6], Emmanuel Oga[7], Michael Odutola[7], Vivian Kwaghe[8], Antoine Jaquet[9], Habakkuk Azinyui Yumo[10], Jean Claude Dusingize[11], Kathryn Anastos[12], Donald Hoover[13], Francois Dabis[9], Constantin Yiannoutsos[5], Kara Wools-Kaloustian[5], Jeffrey Martin[3]

[1]Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; [2]Infectious Diseases Institute, Kampala, Uganda;[3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA; [4]Immune Suppression Syndrome Clinic, Mbarara University, Uganda; [5]Indiana University School of Medicine, Indiana; [6]AMPATH, Moi University, Kenya; [7]Institute of Human Virology Nigeria; [8]University of Abuja Teaching Hospital, Nigeria; [9]INSERM U897 & ISPED, Université Bordeaux, France; [10]R4D International, Yaounde, Cameroon; [11]Regional Alliance for Sustainable Development, Kigali, Rwanda; [12]Department of Medicine, Albert Einstein College of Medicine/Montefiore Medical Center; [13]Department of Statistics, Rutgers University

Background: Survival after diagnosis is one of the most fundamental parameters in cancer epidemiology. In resource-rich settings, ambient clinical databases and municipal data (e.g., death registries) combine to make survival estimation in real-world populations relatively straightforward. In resource-poor settings, it is less clear how well we can determine cancer-specific survival with ambient data. We addressed this issue for Kaposi's sarcoma (KS), the most common HIV-associated malignancy in sub-Saharan Africa. Survival following a KS diagnosis has improved in resource-rich settings with the advent of antiretroviral therapy (ART), but, despite increasing ART availability, little is known about contemporary KS survival in sub-Saharan Africa.

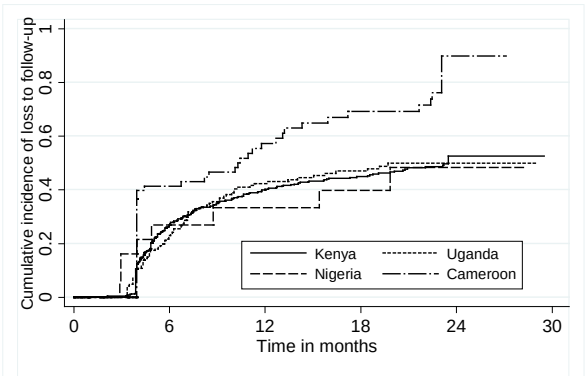

Figure 1. Cumulative incidence of loss to follow-up after diagnosis of KS in four sub-Saharan countries.

Methods: We analyzed data from HIV-infected adults diagnosed with KS from January 2009 to July 2013 who were cared for at clinics participating in the East, West, and Central Africa International Epidemiologic Databases to Evaluate AIDS (IeDEA) Consortia. Patients were followed from KS diagnosis until death, loss to follow-up, or database closure. Attempts at survival estimation were made using the Kaplan-Meier technique. To calculate incidence of loss to follow-up (defined as unknown vital status within the 3 months prior to database closure), we employed the cumulative incidence approach with death as a competing event.

Results: We evaluated 939 adults with KS; 41% were women and the median age was 35 years (IQR: 30-41) and median CD4+T cell count 154/mm^3 (IQR: 51-300) at time of diagnosis. There were 677 cases from 26 clinics in the AMPATH network in Kenya, 172 from Uganda, 23 from Nigeria, and 67 from 3 clinics in Cameroon. Nominally, 22% of patients were estimated to be dead by 2 years (range 17%-28% across sites) but this estimate was clouded by 51% cumulative lost to follow-up by 2 years (range across sites 40% to 76%; Figure). With no functional regional or national death registry, the vital status among the lost is unknown. After adjustment for site in proportional hazards regression, age <30 years (hazard ratio (HR) 1.32, 95% CI 1.01-1.74), male sex (HR 1.35, 95%CI 1.09-1.66), and CD4 count $\leq$50 (HR 1.44, 95% CI 1.02-2.04) were independently associated with loss to follow-up.

Conclusions: With half of all patients with KS lost to follow-up by the end of two years, we could not accurately estimate survival. Until we either generally strengthen data systems or implement cancer-specific enhancements to derive more accurate estimates (e.g., tracking of the lost in the community, as is the planned next step for these sites), insights from cancer epidemiology will be severely limited in sub-Saharan Africa.

49. Preliminary Impact of an Anal Dysplasia Clinic to Identify Invasive Squamous Cell Carcinoma of the Anus (SCCA) in HIV-Infected Men

Lacey Siekas[1], David Aboulafia[2,3]

[1]Virginia Mason Medical Center , Department of Gastroenterology, Seattle, WA; [2]Virginia Mason Medical Center, Department of Hematology/Oncology; [3]Division of Hematology, University of Washington, Seattle, WA

Clinical Background: We performed a retrospective chart review of cases of invasive SCCA identified through the Virginia Mason Medical Center tumor board registry from November 2007 through August 2013 using histology codes (80703-80753). Nine cases of SCCA were identified in HIV-infected individuals. These were analyzed to determine whether they had been examined in our anal dysplasia clinic with high resolution anoscopy (HRA) preceding their diagnosis of invasive SCCA. A total of 5 cases fulfilled this criterion; representing 1.1% of the 455 HIV-infected persons screened to date within the dysplasia clinic. Preceding their diagnosis, 3 in the HRA group had symptoms of pain and bleeding. Within the non-HRA group, all SCCA cases presented with symptoms (3 having anal pain and one with back pain). One individual from the HRA clinic was diagnosed with invasive SCCA by HRA-directed biopsy, the others by directed surgical biopsy following HRA-identified abnormalities. Cases not seen in the HRA clinic underwent diagnostic biopsies either by general surgery or interventional radiology. Median time of follow up between preceding HRA and diagnosis of SCCA was 13 months (range, 1-36 months). Among HRA screened individuals 3 patients had T_1 lesions and 2 patients had T_2 lesions. In the non-HRA group, 3 patients had T2 lesions and 1 patient had $T_0N_xM_1$ disease. One patient in the HRA group was later diagnosed with recurrent and metastatic SCCA 55 months after his diagnosis of $T_1N_0M_0$ SCCA. He was non-compliant with follow-up HRA recommendations and died 17 months later from progressive cancer. Among the non-HRA group, 2 patients died of progressive cancer. Their median survival was 15.5 months. All 9 patients were men who have sex with men and 8 were on highly active anti-retroviral therapy (HAART). Only 1 patient had a history of non-compliance with HAART. Among the HRA screened cases the median CD4 + T lymphocyte count nadir prior to SCCA diagnosis was 16 cells/mm^3 (range, 5-40 cells/mm^3); at time of anal cancer diagnosis their median CD4+ count was 285 cells/mm^3 (range, 160-375 cells/mm^3). The 6 surviving men remain disease with a median follow up of 28.5 months (range, 1-56 months).

Table 1.

	Number of cases	Median age (range) in years	Median duration of HIV infection in years at time of diagnosis (range)	Median CD4 + counts (range) at time of diagnosis (cells/mm^3)	Median HIV viral load results at diagnosis (copies/mL)
Seen in HRA clinic prior to SCCA	5	48 (43-53)	18 (13-24)	285 (160-375)	87 (<40-87)
Not seen in HRA clinic prior to SCCA	4	48 (43-51)	15 (6-21)	362 (139-550)	20844 (<40-41643)

Conclusion: In patients with long-standing HIV-infection, invasive SCCA was identified at an earlier stage in those who were adherent to dysplasia screening recommendations in comparison to those identified through surgical referral. All patients on long-standing HAART had significant immune reconstitution at time of cancer diagnosis.

50. Prevalence and Incidence of Genital Warts Among Women in Abuja, Nigeria

Ayo Famooto[1], Eileen Dareng[1], Patrick Dakum[1,2], Olayinka Olaniyan[3], Richard Offiong[4], Clement Adebamowo[1,2,3,5]

[1]Institute of Human Virology, Abuja, Nigeria; [2]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD; [3]National Hospital, Abuja, Nigeria; [4]University of Abuja Teaching Hospital, Gwagwalada, Nigeria; [5]Institute of Human Virology and Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD

Introduction: Relatively few studies have been conducted to characterize genital warts in sub-Saharan Africa (SSA). Most studies done so far were on high risk populations such as sex workers. Even fewer studies have been conducted to elucidate the HPV types associated with genital warts in SSA. Our goal in this present study is to determine the prevalence and incidence of genital warts, associated risk factors as well as the HPV types associated with genital warts in HIV+ and HIV- women in Nigeria.

Materials and Methods: 852 participants were recruited into a prospective cohort study and followed up at 6 monthly intervals, from women attending cervical cancer screening clinics in 2 hospitals in Nigeria- National Hospital Abuja and University of Abuja Teaching Hospital between April 2012 and August 2013. Trained nurses conducted pelvic examinations and documented findings. Digital images of the cervix were taken and reviewed by a consultant gynecologist for quality assurance. First follow up visit data was available for 242 participants and used to calculate incidence. In a subset of 278 women, baseline results for cervical HPV DNA were available .A logistic regression model was used to identify risk factors associated with prevalent genital warts.

Results: The point prevalence of genital warts at baseline was 2.7% (23/852). The baseline prevalence rates were significantly higher among HIV+ women than HIV- women (OR 6.32, 95% CI 2.05 – 25.82, p = 0.0002). Among women who returned for follow up, incidence risk was 1.67% (4/239, 3 women had being diagnosed with genital warts at baseline and were no longer at risk during the follow up period). Incident genital warts was associated with HIV status, although this association was not significant (Incident risk ratio 3.23, 95% CI 0.34-30.66, p=0.28). Risk factors for prevalent genital warts identified were HIV infection, abnormal cervical morphology using visual inspection with acetic acid/Lugol's iodine and inconsistent use of condoms during sexual intercourse (see Table 1). 3.2% (9/278) of the participants with baseline HPV DNA results had prevalent warts and hrHPV was detected in 55.6% (5/9) with types 51, 52, 56, 58, and 59 (25%, 12.5, 25%, 25%, 12.5 respectively- 2 participants had multiple hrHPVinfections). lrHPV was detected in 55.6 %(5/9) and the types present were 6, 11, 54, 61, 62, 66, 69, 81, 83, and 84 (with multiple low-risk infections occurring in 4 individuals). Of the 5 individuals infected with hrHPV, 4 were co-infected with lrHPV.

Conclusion: Genital warts are common among the population sampled. Several participants with genital warts had multiple low risk and high risk HPV infections. Further research is needed to guide policies on effective prevention and control of genital warts.

Table 1. Univariate and Multivariate Assessment of Factors Associated With Prevalent Genital Warts in 852 Women in Abuja, Nigeria

Characteristic	Prevalent Genital Warts Absent N= 829	Prevalent Genital Warts Present N=23	P Value‡	Multivariate OR∞ (95% CI)	P Value
HIV Status[a]					
HIV Seronegative	487 (99.2)	4 (0.8)		1.0	
HIV+ CD4 > 200cells/µl	290 (95.7)	13 (4.3)	<0.000	5.6 (1.7,18.2)	0.004
HIV+ CD4 ≤ 200 cells/µl	30 (88.2)	4 (11.8)	1	8.4 (1.7,41.4)	0.009
Mean age (years)	37.6	34. 4	0.06	1.0 (0.9, 1.0)	0.38
Education[a]					
No formal education	11 (91.7)	1 (8.3)			
Koranic school	2 (100.0)	0 (0.0)	0.76		
Vocational school	2 (100.0)	0 (0.0)			
≤12 years	286 (97.0)	9 (3.0)			
>12 years	526 (97.6)	13 (2.4)			
Mean age at first sex (years)	20.1	19.9	0.79		
Smoking[a]					
Never smoked 100 sticks	815 (97.3)	23 (2.7)	0.54		
Ever smoked 100 sticks	13 (100.0)	0 (100.0)			
History of pregnancy[a]					
Never been pregnant	69 (97.2)	2 (2.8)	0.95		
Ever been pregnant	759 (97.3)	21 (2.7)			
Cervical status					
VIA/VILI -	797 (98.0)	16 (2.0)	<0.000	1.0	<0.001
VIA/VILI+	32 (82.1)	7 (17.9)	1	13.4 (4.5, 40.1)	
Condom use with partner[a]					
Never/Sometimes	719 (97.8)	16 (2.2)	0.02	1.0	0.19
Always	107 (93.9)	7 (6.1)		2.1 (0.7, 6,1)	
Vaginal douching[a]					
Never douched	320 (98.2)	6 (1.8)	0.22		
Ever douched	508 (96.8)	17 (3.2)			
Genital Ulceration					
Absent	826 (97.3)	23 (2.7)	0.77		
Present	3 (100.0)	0 (0.0)			
Number of sexual partners in past year[a]					
None	76 (97.4)	2 (2.6)			
1–2 partners	730 (97.2)	21 (2.8)	0.85		
>2 partners	11 (100)	0 (0)			
Self- report of STD diagnosis in past 3 months					
Bacterial vaginosis	14	0			
Candidiasis	8	0			
Trichomonas vaginalis	0	0			
Herpes infection	1	0			
Chlamydia	8	0			
Pelvic inflammatory disease	11	0			

∞Variables included in the model were age, hiv status/CD4 count, consistent use of condom and cervical morphology as determined by visual inspection with acetic acid/Lugol's iodine.

‡ Pearson's chi square was calculated for categoriczl variables.

[a] 24 HIV positive cases did not have CD4 results available. 4 participants did not have information on educational status. 1 participant did not have smoking history, pregnancy history and vaginal douching data available, 3 participants did not have condom use history data. 12 participants did not have number of sex partners in past year.

51. Rates of Cancer Gene Alterations in HIV-Infected Non-Small Cell Lung Cancer Patients

Keith Sigel[1], Carlie Sigel[2], Juan Wisnivesky[1], Kristina Crothers[3], Mary Beth Beasley[4]

[1]Department of Medicine, [4]Department of Pathology, Mount Sinai School of Medicine, New York, NY; [2]Department of Pathology, Memorial Sloan-Kettering Hospital, New York, NY; [3]Department of Medicine, University of Washington School of Medicine, Seattle, WA

Background: The presence of genetic alterations in EGFR, KRAS and ALK in non-small cell lung cancers (NSCLC) can impact treatment decisions and may be associated with lung cancer outcomes. HIV infection has been associated with an independent increase in the risk of NSCLC as well as poor lung cancer prognosis.[1, 2] HIV infection has been shown to modulate EGFR and upregulate expression in some cancer types.[3] To our knowledge the genetic profile of lung cancers from HIV-infected patients has not been reported.

Methods: Using clinical databases at Memorial Sloan-Kettering Cancer Center (MSKCC) and the Mount Sinai Hospital, we identified 25 patients with HIV infection, lung adenocarcinoma, and clinical genotyping data. We then matched each case to 4-5 control patients from the MSKCC database by age, sex, Asian versus non-Asian race, and smoking history (never smoked, former smoker, and current smoker). Median age was compared by HIV status using the Wilcoxon test. Demographics, smoking exposure, cancer stage, and rates of KRAS and EGFR mutations were then compared by HIV status using conditional logistic regression to account for matching.

Results: HIV-infected patients were more likely to be of Hispanic ethnicity (Table 1; 24% vs 6%; p<0.001) but were otherwise no different by matching characteristics. Stage at cancer diagnosis did not differ by HIV status (p=0.6). No EGFR mutations were observed among HIV-infected patients, compared to 5 (5%) among HIV uninfected patients, but the difference was not significant (p=0.3). Rates of KRAS mutations were similar (32% vs 38%; p=0.6) when comparing HIV-infected to uninfected NSCLC cases. No ALK rearrangements were detected in tumors from HIV-infected patients.

Table 1. Cohort Characteristics by HIV Status

	HIV+ (n=25)	HIV- (n=103)	P-value
Age, median (IQR)	58 (55-64)	59 (54-66)	0.9
Male, n, %	17 (68)	71 (69)	0.9
Race/ethnicity, n, %			
White	8 (32)	66 (64)	--
Black	11 (44)	31 (30)	0.9
Hispanic	6 (24)	6 (6)	0.001
Smoking Status, n, %			
Former Smoker	8 (32)	39 (38)	--
Current Smoker	17 (68)	64 (62)	0.9
Cancer Stage			
I-IIIA	12 (46)	50 (28)	--
IIIB-IV	13 (54)	53 (52)	0.6
Presence of *KRAS* Mutation	8 (32)	39 (38)	0.6
Presence of *EGFR* Mutation	0 (0)	5 (5)	0.3
Presence of *ALK* Rearrangement	0/12 (0)	--	

IQR: Interquartile range

Conclusions: HIV-infected patients had similar rates of *EGFR* and *KRAS* mutations in lung adenocarcinomas when compared to similar HIV-uninfected patients.

52. Role of p53 in HIV Infection and Related Cancers

Buonaguro Franco M., Tornesello Maria Lina, Buonaguro Luigi

Department of Experimental Oncology, Istituto Naz. Tumori – IRRCS "Fondazione G. Pascale," Napoli, Italy

In order to evaluate the role of p53 in HIV and related cancers a literature survey has been performed along with a biomolecular study on a subset of Italian liver cancers. Mutations within the p53 DNA binding domain, besides reducing its oncosuppressor activity, often determine gain of function with pleiotropic, unexpected results. In particular mutations in Exon7 have been related to higher replication of the HIV virus and frequently identified in HIV-related opportunistic cancers (OC). The p53 role in HIV infection has been associated to p53 A273H mutants able to activate HIV-LTR driven transcription and promote HIV replication. The HIV-LTR region containing Sp1-binding sites would be relevant, given that p53 mutants interact with DNA-bound Sp1 and subsequently increase transcription from Sp1-dependent promoters [1]. Moreover interference with p53 expression inhibits HIV-replication supporting the role of p53 in HIV replication. P53 mutants have been identified with high frequency also in HIV-related cancers (see Table 1), in particular liver cancers infected with hepatotropic viruses, but also squamous cancers of ano-genital and oropharyngeal tract positive for HPVs, as well as EBV-related Burkitt lymphomas. BL biopsies and most cell lines show p53 mutations, in alternative mutations of the MDM2 or ARF proteins involved in p53 modulations. HHV8-associated Kaposi's Sarcoma and PEL, instead, do not have p53 mutations, but show viral-related p53 inactivation. A further support to the carcinogenic role of p53 mutants is given by the higher incidence of most OC in regions at high exposure of Aflatoxin B_1 (AFB_1). Such mycotoxin, in fact, induces at high frequency several p53 mutations, which have been prevalently associated to HBV-related HCC. In Gambia a 3.8 relative risk increase of cirrhosis development in subjects with the R249Ser p53 mutation in serum and a synergistic interaction between AFB1 intake and HBV infection has been shown. Moreover AFB_1 would contribute to OC for its immune suppressive activity and the induction of mitotic recombination events.

Table 1. TP53 Mutations in HIV-1-Associated Opportunistic Cancers

Opportunistic Cancers	Viral Agents	Frequency in HIV Infection	P53 Changes	% p53 Mutations	References
Hepatocellular carcinoma ***	HBV/HCV	+++	B-Catenin-related inactivation & Several mutations	>25%	Kuniholm MH et al., Env Health Pers 2008 Tornesello ML, et al. Genomics, 2013
Cervical cancer	HPVs	++	HPVs E6-related ubiquitination & Several mutations	13.3% SCC-5.9% ACC	Lechner MS et al., The EMBO journal 1992 Tornesello ML et al. Gynecol Oncol., 2013
Oropharingeal cancer	HPV16	++	HPV16 E6-related ubiquitination & Several mutations	>50%	Lechner MS et al.,1992 Perri F et al. Annals of Oncol. 2013
Burkitt lymphoma	EBV	+++	Several mutations	41%	Newcomb EW Leuk Lymphoma 1995
Kaposi's sarcoma	HHV8	+++	LANA-related ubiquitination Rare-p53 mutants	---	Cai Q et al. PLoS Pathogens 2012. Katano H et al., Cancer. 2001

*** 3.8 higher relative risk of HCC in subjects with AFB_1-related mutations in serum
Kuniholm MH et al., *Environ Health Perspect* 2008

In Italy, as most Western countries characterized by a modest/assent AFB_1 exposure, p53 mutations show a much lower relevance in HCC with a 33.3% mutation frequency equivalent to and mutually exclusive from those present in the Exon3 of *CTNNB1* gene, a p53-repressor [2], without any significant specificity for HBV and HCV-related HCC. The modest p53 mutation level in Western general population could contribute to the low transmission rate and replication titer of HIV as well as to the lower frequency of OC, which are weakly associated to the immunodeficiency.

Acknowledgements
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53. Serum Markers of Inflammation and Immune Activation and Subsequent Risk of Cutaneous Squamous Cell Carcinoma in the Multicenter AIDS Cohort Study

Shehnaz K. Hussain[1,2], Dorothy Wiley[3], Amber D'Souza[4], Emilee Knowlton[5], Steven Wolinsky[6], Jay H. Bream[7], Zuo-Feng Zhang[1,2], Roger Detels[1], Otoniel Martínez-Maza[1,2,8,9,10]

[1]Department of Epidemiology, University of California, Los Angeles, CA; [2]Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA; [3]School of Nursing, University of California, Los Angeles, CA; [4]Department of Epidemiology, Johns Hopkins University, Baltimore, MD; [5]Department of Infectious Diseases and Microbiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA; [6]Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL; [7]Department of Molecular Microbiology and Immunology, Johns Hopkins University, Baltimore, MD; [8]Department of Obstetrics and Gynecology, David Geffen School of Medicine, Los Angeles, CA; [9]Department of Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine, Los Angeles, CA; [10]UCLA AIDS Institute, Los Angeles, CA

Introduction: Cutaneous squamous cell carcinoma (skin SCC) risk is increased more than 2-fold among HIV-infected adults and is one of the most commonly diagnosed non-AIDS defining cancers, yet risk factors are poorly understood. HIV infection contributes to a potentially tumor-permissive immune environment characterized by chronic immune suppression and chronic immune activation. Our prior work shows increased age, higher HIV load, and lower CD4+ T lymphocyte count are associated with increased skin SCC risk, possibly related to decreased immunologic competence. We sought to determine whether serum markers of inflammation and immune activation predispose individuals to development of skin SCC.

Methods: Sera from 39 HIV-infected and 18 HIV-uninfected cases from the Multicenter AIDS Cohort Study were tested for levels of inflammation and immune activation molecules (sCD14, sTNFRSF8 [sCD30], CRP, CSF2 [GMCSF], CXCL10[IP10], IFNG, IL1B, IL2, sIL2RA, IL4, IL5, IL6, sIL6R, sIL6ST [sGP130/sCD130], IL8, IL10, IL12, TNFA, sTNFRSF1B [sTNFR2], and sTNFRSF13C [sBAFF-R]) at three time points (0-1, 3-5, and 8-10 years) preceding a pathology-confirmed skin SCC diagnosis. Up to three controls were individually matched to each case on HIV status, follow-up time, race, study site, and HAART use and duration. Odds ratios (ORs) and 95% confidence intervals were obtained from age-adjusted conditional logistic regression models for the association between one log unit increase in marker levels and skin SCC.

Results: Serum levels of sTNFRSF8, CXCL10, sIL2RA, sIL6R, IL10, and TNFRSF13C were significantly elevated among HIV-infected skin SCC cases compared to controls, with the strongest associations observed at the 0-1 year time point for all markers (OR =1.7 to 3.1) except for TNFRSF13C, which was only associated with skin SCC at the 8-10 year time point (OR=8.6). No markers were significantly elevated among HIV-uninfected skin SCC cases compared to controls, and most ORs hovered around the null. Higher serum levels of IL1B were associated with a significant reduced risk of skin SCC in both HIV-infected and -uninfected subjects, and consistently across the three time points (OR=0.7 to 0.8).

Conclusions: Several markers of inflammation and immune activation are elevated immediately preceding a skin SCC diagnosis among HIV-infected men. However, higher levels of IL1B, a pro-inflammatory cytokine important in host defense against microorganisms, were associated with a significantly reduced risk of skin SCC.

54. Task-Shifting and Skin Punch for the Histologic Diagnosis of Kaposi's Sarcoma: A Public Health Solution to a Public Health Problem

Miriam Laker-Oketta[1,2], Megan Wenger[2], Aggrey Semeere[1], Barbara Castelnuovo[1], Andrew Kambugu[1], Robert Lukande[3], F. Chite Asirwa[4], Naftali Busakhala[5], Nathan Buziba[5], Kara Wools-Kaloustian[4], Constantin Yiannoutsos[4],Mwebesa Bwana[6], Winnie Muyindike[6], Erin Amerson[2], Edward Mbidde[1], Toby Mauer[2], Jeffrey Martin[2]

[1]Infectious Diseases Institute, Kampala, Uganda; [2]University of California, San Francisco, San Francisco, CA; [3]Makerere University, Kampala, Uganda; [4]Indiana University, Indianapolis, IN; [5]Moi University, Eldoret, Kenya; [6]Mbarara University of Science and Technology, Mbarara, Uganda

Background: In sub-Saharan Africa, despite increasing ART availability, Kaposi's sarcoma (KS) remains one of the most common malignancies. Most KS diagnosis is on clinical grounds, contributing to both overdiagnosis and — all too commonly — diagnostic delay. Where biopsy is available, it has traditionally been excisional and performed by surgeons. This results in additional appointments in different facilities, follow up visits for suture removal, and often prohibitive patient costs at each step; all these impediments contribute to low biopsy utilization. We hypothesized that a simpler approach — skin punch biopsy — could make histologic diagnosis more accessible.

Methods: We introduced skin punch biopsy to the Infectious Diseases Institute (IDI) in Kampala, Uganda, in 2007, and, then again in2008, to municipal HIV Clinics in Mbarara, Uganda and AMPATH in Kenya. Equipment and brief training were provided at each site. The procedure consists of local anesthesia with lidocaine-epinephrine followed by use of a disposable 4 mm cylindrical punch blade to obtain specimen. Hemostasis is facilitated by Gelfoam®, a clot promoter. Patients remove the dressing after 4 days.

Results: A total of 2801 biopsies have been performed (Figure); 15% have been performed by physicians, 12% by clinical officers, 61% by nurses, and 11% by a laboratory technologist, pharmacy technician or phlebotomist. The procedure has been well tolerated. In a consecutive sample of biopsies performed at one site, hemostasis was achieved by pressure alone in 12.7% of biopsies, Gelfoam in 87%, and suture in 0.3%, including patients with low platelet counts (4.4% had platelet count <50,000/µl). Although training was offered to all clinicians with the potential for each to perform his/her own procedure, biopsy provision evolved to be limited to high volume service teams which, at two of the sites, has resulted in having at least one practitioner on call for same day procedures. At the IDI, the biopsy service has evolved into a national referral service. In Mbarara, it is now a regional referral service, while in AMPATH, biopsy teams now cover the entire >100,000 patient network.

Conclusion: After only minimal training and provision of disposable and inexpensive equipment, HIV/AIDS clinics in East Africa can rapidly integrate same day skin punch biopsy for KS into their practices. With the skin punch approach, task shifting for KSdiagnosis occurred not only from surgeon to non-surgeon but also from physician to non-physician, thereby greatly increasing access. Skin punch biopsy should be part of any HIV clinic's essential equipment/procedures.

55. Update on the Cancer Profile in HIV Patients From a Reference Center in Argentina

Valeria Irene Fink[1,2], Yotam Arens[3], Silvina Figurelli[4], Hugo Concetti[4], Daniel Lewi[5], María Pía Coppola[5], Diego Zurita[6], Rene Bun[7], Laura Svidler[7], Gisela Presencia[7], María Eugenia Socias[1], Carina Cesar[1], Patricia Patterson[1], María Inés Figueroa[1], Eduardo Rodríguez[8], María Laura Fischer[9], Héctor Pérez[2], Catherine McGowan[10], Omar Sued[1], Pedro Cahn[1,2]

[1]Clinical Research, Fundación Huésped, Buenos Aires, Argentina; [2]Infectious Diseases, [4]Pathology, [5]Oncology, [6]Gynecology, [7]Proctology, [8]Dermatology, [9]Hematology, Hospital Fernández, Buenos Aires, Argentina; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [10]Vanderbilt University School of Medicine, Nashville, TN

Introduction: The profile of cancer in HIV patients has changed with the widespread use of HAART. Data about cancer and HIV in Latin America are scarce. Hospital Fernandez Infectious Diseases Unit is a public HIV reference center in Argentina with more than 4,000 HIV-positive patients in follow-up.

Materials and Methods: Retrospective data collection on cancers diagnosed in HIV- infected patients between January 2004 and December 2012 was performed. Demographic, HIV andcancer data were collected.

Results: Three hundred and forty two cancers were diagnosed in 336 patients. Most frequent cancers were Kaposi sarcoma (KS) (35.4%), Non-Hodgkin's lymphoma (NHL) (26.4%), Hodgkin's lymphoma (7.3%), anal (5.3%), cervix (5.2%), skin (4.4%) and lung (3.8%). Sixty nine patients (20.5%) had their cancer diagnosis concomitant orwithin six months of the HIV diagnosis (35 were KS and 19 were NHL). Table 1 shows the characteristics of AIDS and non-AIDS-defining cancers. AIDS-defining cancers corresponded to 68.5% of the total cancers studied in the period 2004-2006, 56.6% in the period 2007-2009 and 69% in the period 2010 to 2012.

Table 1. Characteristics of AIDS and Non-AIDS-Defining Cancers

	AIDS-Defining Cancers (n=226)	Non-AIDS Defining Cancers (n=115)	p
Female, n (%)	47 (21%)	35 (30.4%)	0.052
Age at diagnosis, median (IQR) (years)	37.6 (32.7-45.3)	43.9 (36.7-53.3)	0.001
Time from HIV diagnosis, median (IQR) (years)	2.6 (0.2-7.62)	7.7 (2.5-13.3)	<0.0001
CD4 at cancer diagnosis, median (IQR) (cells/µl)	85.5 (30.5-224.8)	225 (103-446)	0.001

Conclusions: Opportunistic cancers are still the most frequent tumors. Patients with non-AIDS-defining cancers were older, had a longer time since HIV diagnosis, and had a higher CD4 cell count. Late HIV diagnosis continues to be a problem in our population. Access to early HIV diagnosis should be granted.

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Author Index

Aboulafia, D 49
Abrams, D O19
Achenbach, C O7, 30
Adebamowo, C O6, 25, 50
Agsalda, M 41
Akar, G O8, O15
Akarolo-Anthony, S O6, 25
Akello, L O5
Aleman, K 16
Al-Mawsawi, L 20
Almujtaba, M O6
Althoff, K 30
Amerson, E O24, 34, 54
Anastos, K 31, 48
Anderson, M 17
Andresson, T O14
Angulo, R O30
Arens, Y 55
Asiimwe, S O25
Asirwa, F 48, 54
Avey, D 15
Ayers, L 12, 13, 35
Baccarani, U 38
Baguma, J 39
Bakenga, A O5
Ballon, G O8
Bangsberg, D O25, 44
Barman, P 9
Beachler, D O2
Beasley, M 51
Bennett, J O17, O25, 44
Berendam, S O9
Beumer, J 6,7
Bohlius, J 27, 28, 45
Bonstaff, K O20
Boyer, M 36, 37
Braithwaite, R O23
Bream, J 23, 40, 53
Breen, E 23
Brotman, R O6
Brown, C 36, 37
Bruce, G O5
Bryant, J O21
Bukusi, E 24
Bulotta, A O9
Bun, R 55
Buonaguro F, ... 52
Buonaguro L 52
Burk, R O2
Burkhalter, J 47
Burkholder, G O7
Burra, P 38
Busakhala, N O24, 54
Butler, L 34, 39, 46
Buziba, N O24, 54
Bwana, M O24, O25, 34, 44, 48, 54
Byakwaga, H 44
Cahn, P 55
Camps, C 1
Carey, R O10, 33
Casper, C O5, 33
Castelnuovo, B O24, 54
Cavallin, L O13
Cesar, C 55
Cesarman, E O8, O15
Chao, C O19
Chaturvedi, A P9
Chen, PJ P7
Chen, Q O21
Chen, Y 16
Chiwoko, L O4
Christner, S 6, 7
Chu, V 20
Chua, K 9
Chuang, E 41
Chung, J 31
Clarke, C O26, O27
Cloete, C 28, 55
Coghill, A P5
Concetti, ... H 55
Coombs, R 19
Copeland, G O30
Coppola, M 55
Corey, L O5
Cranston, R O2
Crankshaw, T 28, 55
Crothers, K O23, O28, 51
Cu, N 22
Dabis, F 48
Dai, L O21
Dakum, P O6, 50
Dal Maso, L 25
Darden, J 19
Dareng, E O6, 50
Das, S O14
Daud, I 24

Davidoff, K O10
Davidson, A 27
Davis, D O10, O11, 1
De Bruin, G 29
Deeks, S O7
Del Valle, L O20
Dent, A 24
Detels, R 23, 40, 53
Dittmer, D O4
DiWispeleare, K 4
Doolittle, J 14
Dryden-Peterson, S 36, 37
D'Souza, G O2, 30, 53
Dubrow, D O23, O28, 26, 30
Duggal, P 40
Dusingize, JC 48
Egger, M 27, 45
Ehdaievand, S 42
Elashoff, D 9
Ellison, T 5
Engels, E O26, O27, O29, O30, 30
Erickson, D O15
Eron, J O7
Ettorre, GM 38
Evans, E 19
Fadrosh, D O6
Famooto, A O6, 50
Faralli, Z 45
Fecek, R 23
Felsen, U 31
Feng, P O12
Fernandez, ... F 2
Figueroa, M 55
Figurelli, S 55
Fink, V 55
Firnhaber, C 19
Fischer, M 55
Fisher, L 31
Fisher, M 35
Flemington, E O20
Forrestel, A 34
Freeman, E 48
Gajer, P O6
Gallaher, A O14
Gallo, R O21
Gantt, S 33
Garcia, D 22
Garzino-Demo, A O21
George, L O21
Gibson, T O27
Giddy, J 28, 55
Gillespie, A 47
Gillison, M O2
Ginsberg, M 31
Glidden, D O24, O25, 44
Godard, M 19
Godfrey, C 19
Goicochea, L O21
Goldschmidt-Clermont, P O13
Gonsalves, L O30
Goodman, M 41
Gopal, S O7
Gorman, I 47
Granger, D 14
Greenspan, D O1
Guidry, J 47
Gunthel, C 42
Gupta, S O13
Gurka, M 35
Haberer, H O25
Hafez, A 3
Haigentz, M 31
Hakenewerth, A O30
Hanna, D 31
Happel, C O14
Haque, M 11
He, S O12
He, X O12
He, Z O12
Henrich, T P3
Herrera, R O1
Hessol, N 30
Hoffman, I O4
Holoya, G O5
Honrada, R 22
Hoover, D 48
Hosseinipour, M O4
Hu, D O10, O11
Huang, ML O5, 33
Huang, Y 44
Hunt, P O17, O25, 22, 44
Hussain, S 40, 53
Huysentruyt, L 21, 22
Igbinoba, F 25
Imani, P 33
Jacobson, L 40
Jaquet, A 48
Jenkins, F O9
Jiang, L O15
Jung, J O12
Justice, J O23, 30
Kadama-Makanga, P 39

Kambugu, A O17, O24, 54
Kamwendo, D O4
Kanabolo, D 9
Kayembe, M 36, 37
Ke, R 20
Keck, K 2
Kedes, D 5, 17
Kellough, D 12
Kieffer-Kwon, P O14
Kielkowski, D 28, 55
Killeen, J 41
King, C 12, 13
Kitahata, M O7
Knowlton, E O9, 53
Korir, A 35
Koritzinsky, E O26
Kornegay, M. 47
Kousoulas, K 11
Krantz, E 33
Kumar, J 47
Kurian, M O13
Kuritzkes, D P3
Kwaghe, V 48
Lafferty, M O21
Laker-Oketta, M O17, O25, 34, 39, 44, 54
Lammersen, K 19
Lauro, A 38
Lawal, I O6
Lee, J 32
Leidal, A 8, 10
Lemon, S P6
Lepone, L O9
Letai, A O22
Lewi, L 55
Leyden, W 30
Li, J O9
Lieberman, P 4
Lim, E 41
Lin, H 30
Lin, J 31
Little, R 16, 18
Lloyd-Smith, J 20
Locatelli, P O13
Lockman S, ... 36, 37
Loftus, M 17
Loverdo, C 20
Lu, F 4
Lubetkin, E 47
Luftig, M O22, 3
Lukande, R O24, 54
Ma, B O6
Ma, Q O13
Macomber, K O30
Madden, V O3
Makanga, P 46
Mancuso, M O15
Mane, A 43
Margolick, J O2, 23
Marshall, V 16, 18
Martin, J O17, O24, O25, 22, 34, 39, 54
Martínez-Maza, O P8, O19, 40, 53
Martinson, J 40
Maurer, T O17, O24, O25, 34, 54
Mauti, N 35
Maxwell, N 27
Mayer, K O7
Mbidde, E O17, O25, 54
Mbulaiteye, S 25, 45
McCormick, C 8, 10
McFadden, K 3
McGowan, C 55
McGrath, M 21, 22
McIntosh, M O5
Medhin, H 36, 37
Mehendale, S 43
Melendez, G 23
Melville, S O30
Mesri, E O13
Metheny, C 35
Michelow, P 19
Milne, C 41
Minassian, A O12
Minkoff, H O2
Miranda, J 2
Mmalane, M 36, 37
Moats, P 35
Mocello, A O17, O25, 44
Modur, S 30
Moore, P 32
Moore, R O7, O16, 30
Morton, L O26, O27
Mosunjac, M 42
Musick, B O24
Musimar, Z 36, 37
Mutuma, G 35
Muyindike, W O24, 54
Mwafongo, A O4
Mwamba, P 35
Mwanda, W 35
Nadgir, S O9
Naiman, N O10
Nakaganda, A 33

Nalule, Z 33
Namarika, D O4
Neugebauer, R 30
Ng'ang'a, Z 24
Nguyen ML 42
Nikitin, P O22, 3
Nohle, D 12
Novak, U 45
Noy, A 47
Nsingo-Bvochora, M 36, 37
Nyirenda, M O4
Obayo, S O5
Odutola, M 48
Offiong, R O6, 50
Oga, E 48
Ogolla, S 24
Ogretmen, B O20
Olaniyan, O O6, 50
Olmstead, R 23
Olson, C O17, 20
Orem, J O5 33
Oyiro, ... 35
Palefsky, J P2, O1
Paranjape, R 43
Parise, R 6, 7
Park, L O28, 26
Parsons, C O20
Patel, L O22
Patel, M O7
Patterson, P 55
Pérez, H 55
Pezzella, F 1
Pfeiffer, R O29
Phan, A 2
Phipps, W O5
Phiri, S O4
Picott, B 14
Pillai, V 6, 7
Piselli, P 38
Pittaluga, S 16, 18
Poole, J 27
Polizzotto, M O11, 16, 18
Presencia, G 55
Price, A O22
Pringle, E 8
Rabkin, C 40
Qi, H 20
Qin, L 30
Qin, Z O20
Ragoussis, I 1
Rappocciolo, G O9
Ravel, R O6
Rebbeck, T 36, 37
Reczko, M 1
Reddy, S O2
Reid, E O7, O16
Reinhart, T O9
Remenyi, R 20
Remick, S 35
Rendina, M 38
Reske, T O20
Richards, K O7
Rinaldo, C O9
Ritchie, K 13
Robbins, R O29
Rochford, R 12, 13, 24, 35
Roden, R P1
Rodriguez, B O7
Rodríguez, E 55
Rohner, E 45
Romanelli, P O13
Rose, T O5
Rossi, M 38
Rothwell, R 14
Rudek, M 7
Sachrajda, N 10
Sahasrabuddhe, V 19, 43
Said, J O20
Saladyant,T O3
Seaman, W O3
Selke, S 33
Semeere, A O24, 48, 54
Sengayi, M 28, 55
Senkal, C O20
Sereti, I 18
Serraino, D P4, 38
Seydafkan, S 42
Shaik, I 6
Shcherba, M 31
Shiels, M O26, O27, O29, O30
Shimabukuro, K O16
Shiramizu, B 41
Siekas, L 49
Sigel, C 51
Sigel, K O23, 51
Silverberg, M O19, 30
Smith, C O20
Socias, M 55
Song, S O12
Spoerri, A 28. 55
Stefan, C 27, 29
Steinberg, S 16, 18

Steliga, M 32
Stones, D 29
Strickler, H O2, 31
Sued, O 55
Sugar, E O2
Sumba, P 24
Sun, R 20
Suneja, G O26, O30, 36, 37
Svidler, ... 55
Tamburro, K O4
Tate, J O28, 26
Tisone, G 38
Tornesello, M 52
Trentalange, M O28
Truong, S 20
Tugizov, S O1
Uldrick, T O11, 16, 18
Veeranna, R O11
Veluppilar, P O1
Venkataramanan R O18, 6, 7
Verma, K 36, 37
Viollet-Djelassi, C 1
Vittinghoff, E O24
Vizzini, G 38
Voelkel-Johnson, C O20
Wabinga, H O17
Wada, N 23
Wainwright, R 27
Wald, A O5, 33
Walusana, V O17, 44
Wang, V O10, O11
Wang, W O20
Wang, Y O12
Weber, K O2
Webster-Cyriaque, J O3, 14
Wenger, M O17, O24, 46, 48, 54
Wentzensen, N 43
Wheeler, C O6
Whitby, D 16, 18
Wiley, D O2, 9, 53
Wilkin, T 19
Wilson, K 31
Wisnivesky, J O23, 51
Wolinsky, S 40, 53
Wools-Kaloustian, K O24, 48, 54
Woodson, E 17
Wu, N 20
Wu, T-T 20
Wyss, N 45
Wyvill, K 16, 18
Xiao, Z O14
Xiong, J O4
Xu, L O19
Xue, X 31
Yang, H O6
Yang, M O11
Yanik, E O7
Yarchoan, R O10, O11, 1, 16, 18
Yiannoutsos, C O24, 48, 54
Yumo, H 48
Zamboni, F 38
Zandi, E O12
Zha, H O19
Zhang, R 21
Zhang, X O12
Zhang, ZF 40, 53
Zhao, J O12
Zhu, F 15
Zhu, X 41
Ziegelbauer, J O14
Zurita, D 55
Zwahlen, M 45

Clement A. Adebamowo, M.D., D.Sc.
Associate Professor
Department of Epidemiology and Public Health
Institute of Human Virology
Greenebaum Cancer Center
School of Medicine
University of Maryland
Suite 460
725 West Lombard Street
Baltimore, MD 21201
(410) 736-8919
cadebamowo@som.umaryland.edu

David A. Adeyemi, M.D., M.P.H.
Coordinator, Research
Department of Strategic Information, Research and Training
Institute of Human Virology
Pent House, Maina Courts
252 Herbert Macaulay Way
Central Business District
Abuja, Nigeria 00234
+2348035654717
david.crownsworth@gmail.com

Sally N. Akarolo-Anthony
Doctoral Candidate
School of Public Health
Harvard University
677 Huntington Avenue
Boston, MA 02115
(443) 985-7112
sna094@mail.harvard.edu

Karen Aleman, R.N.
HIV AIDS Malignancy Branch
National Cancer Institute
National Institutes of Health
872 Holly Drive, South
Annapolis, MD 21409
(410) 757-2148
(301) 402-7552 Fax
alemank@mail.nih.gov

Keri N. Althoff, Ph.D.
Assistant Professor
Bloomberg School of Public Health
Johns Hopkins University
Room E7142
615 North Wolfe Street
Baltimore, MD 21231
(410) 614-4914
kalthoff@jhsph.edu

Richard F. Ambinder, M.D., Ph.D.
Director
Division of Hematologic Malignancies
Professor of Oncology
School of Medicine
Johns Hopkins University
Bunting-Blaustein Building, Room 390
1650 Orleans Street
Baltimore, MD 21231
(410) 955-8839
(410) 955-0960 Fax
ambindri@jhmi.edu

Kathryn Anastos, M.D.
Professor of Medicine, Epidemiology and Population Health
Division of General and Internal Medicine
Department of Medicine
Montefiore Medical Center and Albert Einstein College of Medicine
Second Floor
3311 Bainbridge Avenue
Bronx, NY 10467
(718) 515-2593
(718) 547-0584 Fax
kanastos@montefiore.org

Stephen B. Asiimwe, M.D.
Postdoctoral Fellow
Department of Epidemiology and Biostatistics
Department of Internal Medicine
Mbarara Regional Referral Hospital
University of California, San Francisco
Apartment 617
525 Nelson Rising Lane
San Francisco, CA 94158
(415) 815-7336
asiimwesteve@gmail.com

Denis R. Avey
Department of Cell and Molecular Biology
Florida State University
1908 Monticello Drive
Tallahassee, FL 32303
(239) 634-0824
dra06c@fsu.edu

Gianna Ballon, M.D.
Department of Pathology and Laboratory Medicine
Weill Cornell Medical College
Cornell University
Room C406
1300 York Avenue
New York, NY 10021
(212) 746-6948
(212) 746-4483 Fax
gib2004@med.cornell.edu

Stefan K. Barta, M.D., M.S.
Assistant Professor
Albert-Einstein College of Medicine
Montefiore Medical Center
Hofheimer 100
111 East 210th Street
Bronx, NY 10467
(917) 912-8112
sbarta@montefiore.org

Daniel C. Beachler, M.S.P.H.
Doctoral Student
Department of Epidemiology
Bloomberg School of Public Health
Johns Hopkins University
Apartment 3B
1024 Chesapeake Drive
Havre de Grace, MD 21078
(717) 514-5540
danbeachler@gmail.com

Steven Becker, Ph.D.
National Institutes of Health
Apartment 201
10851 Amherst Avenue
Silver Spring, MD 20902
(240) 276-6790
steven.becker@nih.gov

Kishor Bhatia, Ph.D., FRCPath
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 20892-2440
(301) 496-4995
(301) 480-4137 Fax
bhatiak@mail.nih.gov

Donald G. Blair, Ph.D.
Chief
Cancer Etiology Branch
Division of Cancer Biology
National Cancer Institute
National Institutes of Health
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-6190
blaird@mail.nih.gov

Nkegoum Blaise, M.D.
Assistant Professor
Department of Pathology and Oncology
University Hospital Center
Melen-Yaounde
Yaounde, Cameroon 2787
002 (379) 999-0292
nkegoum@yahoo.fr

Julia Bohlius, Ph.D., M.S.P.H.
Research Fellow
Institute of Social and Preventive Medicine
University of Bern
Finkenhubelweg 11
Bern, 3012
Switzerland
004 (131) 631-3523
jbohlius@ispm.unibe.ch

Adam Bossert
Research Fellow
National Institute of Allergy and Infectious Diseases
National Institutes of Health
40 Convent Drive
9000 Rockville Pike
Bethesda, MD 20892
(301) 594-8237
adam.bossert@nih.gov

Maria T. Botello-Harbaum, Ed.D., M.S.
AIDS Malignancy Consortium
EMMES Corporation
Suite 700
401 North Washington Street
Rockville, MD 20850
(301) 251-1161
mbotello-harbaum@emmes.com

Paige Bracci, Ph.D.
University of California, San Francisco
Suite 280
3333 California Street
San Francisco, CA 94118
(415) 476-3354
paige.bracci@ucsf.edu

Elizabeth Crabb Breen, Ph.D.
Associate Professor
David Geffen School of Medicine
University of California, Los Angeles
Cousins Center for PNI
300 MP, 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.
Fogarty International Center
National Institutes of Health
Building 31, Room B2-C39
31 Center Drive
Bethesda, MD 20892
(301) 496-1415
jackie.officer@nih.gov

Anissa J. Brown, Ph.D.
Program Analyst
Office of AIDS Research
Office of the Director
National Institutes of Health
5635 Fishers Lane
Suite 4000
Bethesda, MD 20892
(301) 594-7019
(301) 480-5247 Fax
brownani@mail.nih.gov

Carolyn Brown
Botswana Harvard AIDS Institute
Bloomberg School of Public Health
Johns Hopkins University
2904 Elliott Street
Baltimore, MD 21224
(269) 744-7234
carolyn.brown.a@gmail.com

Wei Bu, Ph.D.
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Building 50, Room 6128
Bethesda, MD 20892
(201) 496-7676
buw@mail.nih.gov

Chris Buck, Ph.D.
Investigator
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
(301) 594-7060
buckc@mail.nih.gov

Jack E. Burkhalter, Ph.D.
Assistant Attending Psychologist
Department of Psychiatry and Behavioral Sciences, Behavioral Sciences Service
Memorial Sloan-Kettering Cancer Center
Seventh Floor
641 Lexington Avenue
New York, NY 10044
(646) 888-0040
(212) 888-2584 Fax
burkhalj@mskcc.org

Naftali W, Busakhala, M.D.
Professor
AIDS Malignancy Consortium School of Medicine
Moi University
P.O. Box 4606-30100
Eldoret, Kenya 30100
25 (472) 151-7566
25 (453) 203-0786 Fax
nbusakhala@yahoo.com

Shalanda A. Bynum, Ph.D., M.P.H.
Assistant Professor
Department of Preventive Medicine and Biometrics
Division of Social and Behavioral Sciences
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814
(301) 295-1585
shalanda.bynum@usuhs.edu

Diana Campbell
Graduate Student
Graduate School of Public Health
University of Pittsburgh
130 DeSoto Street
Pittsburgh, PA 15261
(412) 400-0593
dmc111@pitt.edu

Virginia Carroll, Ph.D.
Postdoctoral Fellow
Institute of Human Virology
School of Medicine
University of Maryland
725 West Lombard Street
Baltimore, MD 21201
(410) 706-4664
vicarroll@ihv.umaryland.edu

Corey Casper, M.D., M.P.H.
Associate Member
Vaccine and Infectious Disease Division
Fred Hutchinson Cancer Research Center
Associate Professor of Medicine, Epidemiology and Global Health
University of Washington
Medical Director of Infection Control
Seattle Cancer Care Alliance
MS M1-B140
1100 Fairview Avenue, North
Seattle, WA 98109
(206) 667-4600
(206) 667-1965 Fax
ccasper@fhcrc.org

Jessica Castilho, M.D., M.P.H.
Clinical Fellow
Division of Infectious Diseases
School of Medicine
Vanderbilt University
A2200 Medical Center North
1161 21st Avenue, South
Nashville, TN 37232
(615) 322-2035
jessica.castilho@vanderbilt.edu

Mary Allegra Cermak, M.A.
AIDS Clinical Trials Group Community Coordinator
Social & Scientific Systems, Inc.
8757 Georgia Avenue
Silver Spring, MD 20910
(301) 628-3312
acermak@s-3.com

Ethel Cesarman, M.D., Ph.D.
Professor, 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

Chun R. Chao, Ph.D.
Research Scientist
Department of Research and Evaluation
Kaiser Permanente, Southern California
Second Floor
100 South Los Robles Avenue
Pasadena, CA 91101
(626) 564-3797
(626) 564-3409 Fax
chun.r.chao@kp.org

Anil K. Chaturvedi, Ph.D.
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Room 6E238
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-7193
chaturva@mail.nih.gov

Pei-Jer Chen, M.D., Ph.D.
Director
Department of Medical Research
National Taiwan University Hospital
No.7, Zhongshan S. Road
Zhongzheng District
Taipei, Taiwan 10002
88 (622) 312-3456
peijerchen@ntu.edu.tw

Yuanbin Chen, M.D.
Medical Oncology Branch
National Cancer Institute
National Institutes of Health
Building 37, Room 5002
37 Convent Drive
Bethesda, MD 20892
(301) 496-8823
yuanbin.chen@nih.gov

Rebecca Chornock
Medical Student
Drexel University
Hormonal and Reproductive Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
415 Bostwick Lane
Gaithersburg, MD 20878
(301) 915-5047
rchornock@gmail.com

Kristofer Chua
Staff Research Associate
School of Nursing
University of California, Los Angeles
2821 Maricopa Street
Torrance, CA 90503
(310) 626-7931
kchua@sonnet.ucla.edu

William Clark, M.S.
Biologist
National Cancer Institute
National Institutes of Health
9609 Medical Center Drive
West Tower, Room 7W-354
Bethesda, MD 20892-9750
(240) 276-6407
clarkw2@mail.nih.gov

Anna E. Coghill, Ph.D., M.P.H.
National Cancer Institute
National Institutes of Health
Apartment 3
2568 University Place, NW
Washington, DC 20009
(240) 276-7184
anna.coghill@nih.gov

Kristina Crothers, M.D.
Associate Professor
Harborview Medical Center
Division of Pulmonary and Critical Care Medicine
Department of Internal Medicine
School of Medicine
University of Washington
325 Ninth Avenue
P.O. Box 359762
Seattle, WA 98104
(206) 744-9870
kcrothers@medicine.washington.edu

Eileen Dareng, M.D., M.P.H.
Senior Program Analyst, Research Coordinator, Data Center Manager
Department of Strategic Information, Research and Training
Institute of Human Virology
Plot 252, Herbert Macaulay Way
Central Business District
Abuja, Nigeria 93960
234 (803) 294-2394
eobe@ihvnigeria.org

Ibrahim I. Daud, M.S.
Fogarty Doctoral Fellow
SUNY Upstate Medical University
Kenya Medical Research Institute
Centre for Global Health Research
KEMRI/CDC Centre, Kisian, Off Kisumu Busia Highway
Kisumu, Kenya 40100
25 (472) 648-7199
Ibrayed@yahoo.com

David A. Davis, Ph.D.
HIV and AIDS Malignancy Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
(301) 402-3630
dadavis@helix.nih.gov

Gerhard P. de Bruin, M.D.
Junior Consultant
Pediatric Intensive Care Unit
Department of Health
Western Cape Government
Room 49, C3A, Gold Lane, Third Floor
Tygerberg Hospital, Francie van Zijl Drive, Parow
Cape Town, South Africa 7505
(921) 938-4538
gpdebruin@yahoo.co.uk

Paolo De Paoli, M.D.
Scientific Director
Centro di Riferimento Oncologico
National Cancer Institute
Via Gallini 2
Aviano, Italy 33081
39 (043) 465-9282
dirscienti@cro.it

Dirk P. Dittmer, Ph.D.
Professor
Program in Global Oncology
Department of Microbiology and Immunology
Lineberger Comprehensive Cancer Center
Center for AIDS Research
Carolina Center for Genome Sciences
The University of North Carolina at Chapel Hill
Mary Ellen Jones Building, Room 715
CB 7290
Chapel Hill, NC 27599-7290
(919) 966-7960
(919) 962-8103 Fax
dirkdittmer@me.com

Geraldina Dominguez, Ph.D.
Program Director
Office of HIV and AIDS Malignancy
National Cancer Institute
National Institutes of Health
Building 31, Room 3A-33
31 Center Drive
Bethesda, MD 20892-2440
(301) 496-4995
domingug@mail.nih.gov

Scott Dryden-Peterson, M.D.
Instructor
Botswana Harvard AIDS Institute
Harvard Medical School
Harvard School of Public Health
Brigham and Women's Hospital
PBB-B4
75 Francis Street
Boston, MA 02115
(617) 435-2479
scott_peterson@post.harvard.edu

Amber D'Souza, Ph.D.
Associate Professor
School of Public Health
Johns Hopkins University
Suite E6132
615 North Wolfe Street
Baltimore, MD 21205
(410) 502-2583
demorgan@jhsph.edu

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

Robert W. Eisinger, Ph.D.
Director, Scientific and Program Operations and Therapeutics Research Coordinator
Office of AIDS Research
National Institutes of Health
Suite 4000
5635 Fishers Lane
Bethesda, MD 20892
(301) 496-0358
be4y@nih.gov

Nader K. El-Mallawany, M.D.
Assistant Professor of Pediatrics
Division of Hematology, Oncology, and Stem Cell Transplant
New York Medical College
Room 7B
249 East 118th Street
New York, NY 10035
(917) 592-4640
nader_kim@nymc.edu

Benjamin Emmanuel, M.P.H.
Ph.D. Student
University of Maryland, Baltimore
Apartment A
4418 LaPlata Avenue
Baltimore, MD 21211
(630) 344-2016
ben.emmanuel@umaryland.edu

Eric A. Engels, M.D., M.P.H.
Senior Investigator
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Executive Plaza South, Suite 7076
6120 Executive Boulevard
Bethesda, MD 20892
(301) 496-8115
(301) 402-0817 Fax
engelse@exchange.nih.gov

Marta Epeldegui, Ph.D.
Assistant Project Scientist
David Geffen School of Medicine
University of California, Los Angeles
BSRB 173
650 Charles E. Young Drive, South
Los Angeles, CA 90095
(310) 206-6846
mepel@ucla.edu

Luis A. Espinoza, Ph.D., M.S.
Scientific Review Officer
Center for Cancer Research
National Cancer Institute
National Institutes of Health
6701 Rockledge Drive
Bethesda, MD 20892
(301) 435-0952
espinozala@csr.nih.gov

Oluranti A. Famooto
Institute of Human Virology
Plot 252, Herbert Macaulay Way
Central Business District
Abuja, Nigeria 900001
234 (803) 071-2744
olani_ayo@yahoo.com

Pinghui Feng, Ph.D.
Human and Animal Virology
Department of Molecular Microbiology and Immunology
Keck School of Medicine
University of Southern California
NTT 6428A
1441 Eastlake Avenue
Los Angeles, CA 90033
(323) 865-0657
(323) 865-0778 Fax
pinghuif@usc.edu

Valeria I. Fink, M.D.
Fundación Huésped
Pasaje Peluffo 3932
Buenos Aires, 1202
Argentina
(114) 981-7777
valeria.fink@huesped.org.ar

Marcia Firmani, Ph.D., M.P.H.
Program Director and Assistant Professor, Medical Laboratory Sciences
School of Medicine and Health Sciences
Department of Clinical Research and Leadership
Department of Microbiology, Immunology and Tropical Medicine
Department of Pathology
The George Washington University
Suite 5065
2100-W Pennsylvania Avenue, NW
Washington, DC 20037
(202) 994-8338
firmanim@gwu.edu

Esther Freeman, M.D., Ph.D.
Instructor
Harvard Medical School
Department of Dermatology
Massachusetts General Hospital
Suite 200
50 Staniford Street
Boston, MA 02114
(617) 875-2658
esther.freeman@gmail.com

Robert Freund, Ph.D.
Chief
AIDS and AIDS Related Research Integrated Review Group
Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive
Bethesda, MD 20892
(301) 435-1050
freundr@csr.nih.gov

Soren Gantt, M.D., Ph.D.
Associate Professor
Department of Pediatrics
Division of Infectious Diseases
University of British Columbia
Child and Family Research Institute
Room A5-144
950 West 28th Avenue
Vancouver, British Columbia V5Z 4H4
Canada
(604) 875-2151
sgantt@cfri.ca

Debra L. Garcia, M.P.H.
Operations Director
AIDS and Cancer Specimen Resource
University of California, San Francisco
Building 3, Room 207
1001 Potrero Avenue
San Francisco, CA 94110
(415) 206-5268
(415) 206-3765 Fax
dgarcia@acsr.ucsf.edu

Alfredo Garzino Demo, Ph.D.
Associate Professor
Institute of Human Virology, and Department of Microbiology and Immunology
School of Medicine
University of Maryland
725 West Lombard Street
Baltimore, MD 21201
(410) 706-4689
agarz001@umaryland.edu

Daniela S. Gerhard, Ph.D.
Director
Office of Cancer Genomics
Center for Cancer Genomics
National Cancer Institute
National Institutes of Health
Building 31, Room 10A-07
31 Center Drive
Bethesda, MD 20892
(301) 451-8027
gerhardd@mail.nih.gov

Todd M. Gibson, Ph.D.
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Executive Plaza South, Room 7091
6120 Executive Boulevard
Bethesda, MD 20892
(301) 594-7653
gibsontm@mail.nih.gov

Catherine Godfrey, M.D.
National Institute of Allergy and Infectious Diseases
National Institutes of Health
6700B Rockledge Drive
Bethesda, MD 20892
(301) 496-1540
cgodfrey@niaid.nih.gov

Satish Gopal, M.D.
Clinical Assistant Professor
Center for Infectious Diseases
School of Medicine
The University of North Carolina at Chapel Hill
UNC Project-Malawi
Private Bag A-104
Lilongwe, Malawi
26 (588) 288-9597
gopal@med.unc.edu

Daphnee Guillaume, M.P.H., CHES
Research Associate
Uniformed Services University of the Health Sciences
Apartment 24
12642 Grey Eagle Court
Germantown, MD 20874
(301) 295-3735
dguillau@mail.usf.edu

Kailash Gupta, Ph.D.
Program Officer
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
6700 Rockledge Drive
Bethesda, MD 20892
(301) 435-3724
kgupta@niaid.nih.gov

Amy Hafez, M.S.
Graduate Student
Duke University
Apartment 1436
2616 Erwin Road
Durham, NC 27705
(443) 783-8346
ayh5@duke.edu

Missak Haigentz, M.D.
Associate Professor of Clinical Medicine
Albert Einstein College of Medicine
Montefiore Medical Center
Hofheimer Building, Room 100
111 East 210th Street
Bronx, NY 10467
(718) 920-4826
(718) 798-7474 Fax
mhaigent@montefiore.org

F. Gray Handley, M.S.P.H.
Associate Director for International Research Affairs
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Room 5226
6610 Rockledge Drive
Bethesda, MD 20892
(301) 594-6128
gray.handley@nih.gov

Christine Happel, Ph.D.
Postdoctoral Fellow
HIV and AIDS Malignancy Branch
National Cancer Institute
National Institutes of Health
Building 10
10 Center Drive
Bethesda, MD 20892
(301) 402-3624
happelc@mail.nih.gov

Muzammel Haque, Ph.D., M.S.
Assistant Professor
Division of Biotechnology and Molecular Medicine
Department of Pathobiological Sciences
School of Veterinary Medicine
Louisiana State University
H.D. Wilson Hall, Room 137
Baton Rouge, LA 70803
(225) 578-9120
mhaque2@lsu.edu

Rohan Hazra, M.D.
Medical Officer
Maternal and Pediatric Infectious Disease Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Room 4B11
6100 Executive Boulevard
Bethesda, MD 20892
(301) 435-6868
hazrar@mail.nih.gov

Nicholas Homa
Graduate Student
Department of Molecular Genetics and Microbiology
Duke University
24 Lansgate Court
Durham, NC 27713
(484) 201-4804
njh16@duke.edu

James Hoxie, M.D.
Professor of Medicine
Director
Penn Center for AIDS Research
Professor
Department of Medicine
Division of Hematology and Oncology
University of Pennsylvania
522G Johnson Pavilion
3610 Hamilton Walk
Philadelphia, PA 19104
(215) 746-2754
nagdeman@mail.med.upenn.edu

Duosha Hu, M.D., Ph.D.
Visiting Fellow
HIV and AIDS Malignancy Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Building 10, Room 5A-24
9000 Rockville Pike
Bethesda, MD 20892
(301) 402-3630
hud2@mail.nih.gov

Rebecca Liddell Huppi, Ph.D.
Program Director
Office of HIV and AIDS Malignancy
National Cancer Institute
National Institutes of Health
Building 31, Room 3A-33
31 Center Drive
Bethesda, MD 20892-2440
(301) 496-4995
(301) 480-4137 Fax
liddellr@exchange.nih.gov

Shehnaz K. Hussain, Ph.D., M.S.
Assistant Professor
Department of Epidemiology
Fielding School of Public Health
University of California, Los Angeles
Box 951772
650 Charles E. Young Drive, South
Los Angeles, CA 90095
(310) 825-8165
skhussain@ucla.edu

Denise Jenkins, M.B.A.
AIDS Malignancy Program Specialist
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

Evonne N. Johnson-Woodson, Ph.D.
Myles H. Thaler Center for AIDS and Human Retrovirus Research
Department of Microbiology, Immunology, and Cancer Biology
University of Virginia
Unit 8
1048 Saint Charles Avenue, NE
Atlanta, GA 30306
(757) 517-5319
enj8y@virginia.edu

Dean Kedes, M.D., Ph.D.
Associate Professor
School of Medicine
University of Virginia
P.O. Box 800734
1340 Jefferson Park Avenue
Charlottesville, VA 22908
(434) 243-2758
kedes@virginia.edu

Ravie Kem, Pharm.D.
Senior Clinical Research Pharmacist
Cancer Therapy Evaluation Program
National Cancer Institute
National Institutes of Health
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-6575
kemr@mail.nih.gov

Elliott D. Kieff, M.D., Ph.D.
Harriet Ryan Albee Professor of Microbiology and Molecular Genetics
Harvard Medical School
Director, Infectious Diseases
Brigham and Women's Hospital
181 Longwood Avenue
Boston, MA 02115
(617) 525-4252
(617) 525-4257 Fax
ekieff@rics.bwh.harvard.edu

Christine A. King, Ph.D., M.S.
Research Assistant Professor
Department of Microbiology and Immunology
SUNY Upstate Medical University
2117 Weiskotten Hall
750 East Adams Street
Syracuse, NY 13210
(315) 464-5465
kingch@upstate.edu

Emilee R. Knowlton, Ph.D.
Postdoctoral Scholar
Department of Infectious Diseases and Microbiology
Graduate School of Public Health
University of Pittsburgh
620 Parran Hall
130 DeSoto Street
Pittsburgh, PA 15261
(740) 629-4269
erk21@pitt.edu

Aimee Kreimer, Ph.D.
Investigator
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Room 6-E104
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-7102
kreimera@mail.nih.gov

Susan E. Krown, M.D.
Vice-Chair for International Activities
AIDS Malignancy Consortium
Memorial Sloan-Kettering Cancer Center
Apartment 9D
160 Riverside Drive
New York, NY 10024
(212) 362-4550
krowns@mskcc.org

Daniel R. Kuritzkes, M.D.
Chief
Division of Infectious Diseases
Professor of Medicine
Harvard Medical School
Brigham and Women's Hospital
Room 449
65 Landsdowne Street
Cambridge, MA 02139
(617) 768-8398
dkuritzkes@partners.org

Edward L. Kyle
Biologist
Research Analysis and Evaluation Branch
Division of Extramural Activities
National Cancer Institute
National Institutes of Health
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-6424
kylee@exchange.nih.gov

Mark Lafferty, Ph.D.
Postdoctoral Fellow
Institute of Human Virology
School of Medicine
University of Maryland
Room S607
725 West Lombard Street
Baltimore, MD 21201
(410) 706-4664
mlafferty@ihv.umaryland.edu

Miriam O. Laker-Oketta, M.D., M.S.
Clinical Research Fellow
Department of Epidemiology and Biostatistics
University of California, San Francisco
Apartment 905
1560 Third Street
San Francisco, CA 94158
(415) 412-5322
drmiriaml@yahoo.co.uk

Jennifer Lam
Ph.D. Candidate
Global Disease Epidemiology and Control Program
Bloomberg School of Public Health
Johns Hopkins University
Room 10E
500 West University Parkway
Baltimore, MD 21210
(510) 499-6057
jelam@jhsph.edu

Jeannette Lee, Ph.D.
Professor
Department of Biostatistics
University of Arkansas for Medical Sciences
Room 781
4301 West Markham
Little Rock, AR 72205
(501) 526-6712
jylee@uams.edu

Stanley M. Lemon, M.D.
Professor of Medicine
Center for Infectious Diseases
School of Medicine
The University of North Carolina at Chapel Hill
Second Floor
130 Mason Farm Road
Chapel Hill, NC 27599-7030
(919) 843-1848
(919) 966-6714 Fax
smlemon@med.unc.edu

Alexandra M. Levine, M.D., MACP
Chief Medical Officer
Payson Professor of Medicine
Professor of Hematology/HCT
City of Hope National Medical Center
1500 East Duarte Road
Duarte, CA 91010
(626) 471-7213
(626) 471-7200 Fax
alevine@coh.org

Paul H. Levine, M.D., FACP
Research Professor
Department of Biochemistry and Molecular Biology
The George Washington University
4816 Montgomery Lane
Bethesda, MD 20814
(301) 469-7394
paulhlevine@earthlink.net

Renfeng Li, Ph.D.
Viral Oncology Program
Johns Hopkins University
CRB1, Room 316
1650 Orleans Street
Baltimore, MD 21287
(443) 652-2980
rli13@jhmi.edu

Richard F. Little, M.D., M.P.H.
Senior Investigator
Head, Hematologic and AIDS-Related Malignancies and Hematopoietic Stem Cell Transplantation
Clinical Investigations Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Executive Plaza North, Room 7025
MSC 7436
6130 Executive Boulevard
Bethesda, MD 20892
(301) 496-2522
(301) 402-0557 Fax
littler@mail.nih.gov

Xiaoyan Liu, Ph.D.
HIV and AIDS Malignancy Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
(240) 899-4512
hzliuxiaoyan@126.com

Fang Lu, Ph.D.
Associate Staff Scientist
The Wistar Institute
3601 Spruce Street
Philadelphia, PA 19104
(215) 898-9523
fanglu@wistar.org

Joseph Lubega, M.D.
Postdoctoral Fellow
Pediatric Hematology-Oncology
Baylor College of Medicine
Apartment 667
7510 Brompton Street
Houston, TX 77025
(862) 235-7376
lubega@bcm.edu

Micah Luftig, Ph.D.
Assistant Professor
Department of Molecular Genetics and Microbiology
Duke University Medical Center
Box 3054, CARL 424
213 Research Drive
Durham, NC 27710
(919) 668-3091
micah.luftig@duke.edu

Trinh Ly, M.D.
Therapeutics Research Program
Collaborative Clinical Research Branch
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Room 5108
6700B Rockledge Drive
Bethesda, MD 20892
(301) 402-2297
tly@niaid.nih.gov

Cynthia Mahlangu, F.N.P.
Research Nurse and Outreach Manager
Department of Health
WITS Health Consortium, Confession Wellness Clinic
Chiawelo Ext 2
3002 East Nefefe Street
P.O. Box 761 Jabulani Mall PO Kwaxuma 1868
Soweto Johannesburg, South Africa 1868
(084) 238-8410
confession.wellness@gmail.com

Laura A. Mamo, Ph.D.
Associate Professor
Health Equity Institute
San Francisco State University
1600 Holloway
San Francisco, CA 94142
(202) 302-7035
lmamo@sfsu.edu

Susan Marriott, Ph.D.
Professor and Leader
Scientific Working Group on AIDS Related Malignancies
Department of Molecular Virology and Microbiology
Baylor College of Medicine
One Baylor Plaza
Houston, TX 77025
(713) 798-4440
sjm.bcm@gmail.com

Vickie Marshall, M.S.
Research Associate III
Viral Oncology Section
AIDS and Cancer Virus Program
Frederick National Laboratory for Cancer Research
SAIC-Frederick, Inc.
Building 535, Room 428
P.O. Box B
Frederick, MD 21702
(301) 846-5828
marshallv1@mail.nih.gov

Jeffrey N. Martin, M.D., M.P.H.
Professor, Epidemiology and Biostatistics
University of California, San Francisco
Suite 5700
185 Berry Street
San Francisco, CA 94107
(415) 514-8010
(415) 514-8150 Fax
martin@psg.ucsf.edu

Otoniel Martinez-Maza, Ph.D.
Professor
Departments of Obstetrics and Gynecology, Microbiology, Immunology and Molecular Genetics, and Epidemiology
David Geffen School of Medicine
School of Public Health,
UCLA AIDS Institute and Jonsson Comprehensive Cancer Center
University of California, Los Angeles
BSRB 173
615 Charles Young Drive
Los Angeles, CA 90095
(310) 825-2542
(310) 206-5387 Fax
omartinez@mednet.ucla.edu

Toby Maurer, M.D.
Department of Dermatology
School of Medicine
University of California, San Francisco
50 Ravenwood Drive
San Francisco, CA 94127
(415) 206-8680
maurert@derm.ucsf.edu

Sam M. Mbulaiteye, M.D.
Principal Investigator
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Executive Plaza South, Suite 7080
6120 Executive Boulevard
Bethesda, MD 20892-7248
(301) 594-7825
(301) 402-0817 Fax
mbulaits@mail.nih.gov

Renicha McCree, Ph.D., M.Ed., M.P.H.
Cancer Prevention Fellow
Division of Cancer Prevention
National Cancer Institute
National Institutes of Health
Room 2W-160
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-6663
renicha.mccree@nih.gov

Jeanne McDermott, Ph.D., M.P.H.
Program Officer
Fogarty International Center
National Institutes of Health
Building 31, Room B2C-39
31 Center Drive
Bethesda, MD 20892
(301) 496-1492
jeanne.mcdermott@nih.gov

Michael S. McGrath, M.D., Ph.D.
Principal Investigator
AIDS and Cancer Specimen Resource
University of California, San Francisco
Building 3, Room 207
1001 Potrero Avenue
San Francisco, CA 94110
(415) 206-8204
mike.mcgrath@ucsf.edu

Enrique A. Mesri, Ph.D.
Associate Professor and Graduate Program Director
Department of Microbiology and Immunology
Director
Miami CFAR AIDS Malignancies Program
Miller School of Medicine
Sylvester Comprehensive Cancer Center
University of Miami
PAP Building, Suite 09B
1550 NW 10th Avenue
Miami, FL 33136
(305) 243-5659
(305) 243-8309 Fax
emesri@med.miami.edu

Marissa Mika, M.P.H.
Doctoral Candidate
History and Sociology of Science
University of Pennsylvania
303 Cohen Hall
249 South 36th Street
Philadelphia, PA 19104
(650) 930-6768
mmika@sas.upenn.edu

Wendell Miley, M.S.
Research Associate III
Viral Oncology Section
AIDS and Cancer Virus Program
National Cancer Institute
National Institutes of Health
SAIC-Frederick, Inc.
P.O. Box B
Frederick, MD 21702
(301) 846-1887
mileyw@mail.nih.gov

Paolo Miotti, M.D.
Office of AIDS Research
National Institutes of Health
5635 Fishers Lane
Bethesda, MD 20892
(301) 435-7699
pm122m@nih.gov

J.J. Miranda, Ph.D.
Assistant Investigator and Assistant Professor
Gladstone Institute of Virology and Immunology
Department of Cellular and Molecular Pharmacology
University of California, San Francisco
1650 Owens Street
San Francisco, CA 94122
(415) 734-4861
jj.miranda@gladstone.ucsf.edu

Suraj Mishra
IRTA Postbaccalaureate
HIV and AIDS Malignancy Branch
National Cancer Institute
National Institutes of Health
Apartment 403
4301 North Henderson Road
Arlington, VA 22203
(804) 386-6288
suraj.mishra@nih.gov

Ronald Mitsuyasu, M.D., FACP
Professor of Medicine
Group Chair
AIDS Malignancy Consortium
Director
Center for Clinical AIDS Research and Education
Department of Medicine and CARE Center
UCLA AIDS Institute
UCLA Jonsson Comprehensive Cancer Center
University of California, Los Angeles
UCLA CARE Center
Suite 980
9911 West Pico Boulevard
Los Angeles, CA 90035
(310) 557-1891
(310) 557-1899 Fax
rmitsuya@mednet.ucla.edu

Eduardo Montalvo, Ph.D.
Scientific Review Officer
Center for Scientific Review
National Institutes of Health
Building II
6701 Rockledge Drive
Bethesda, MD 20892
(301) 435-1168
(301) 594-6363 Fax
montalve@csr.nih.gov

Shaheen B. Mowla, Ph.D.
Department of Clinical Laboratory Sciences
Division of Haematology
University of Cape Town
Faculty of Health Sciences, 6.10 Chris Barnard
Anzio Road, Observatory
Cape Town, South Africa 7925
2 (721) 406-6560
shaheen.mowla@uct.ac.za

David Muddiman, Ph.D.
Distinguished Professor of Chemistry
Director and Founder
W.M. Keck Fourier Transform Mass Spectrometry Laboratory
Department of Chemistry
North Carolina State University
Box 8204
2620 Yarbrough Drive
Raleigh, NC 27695
(919) 515-7607
dcmuddim@ncsu.edu

Minh Ly T. Nguyen, M.D.
Assistant Professor of Medicine
Grady Health Systems School of Medicine
Emory University
2424 Coralwood Drive
Decatur, GA 30033
(404) 993-6999
mnguye3@emory.edu

Ariela Noy, M.D.
Hemotologist and Medical Oncologist
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10065
(212) 639-7423
noya@mskcc.org

Emmanuel A. Oga, M.D.
University of Maryland, Baltimore
Unit 306
929 North Wolfe Street
Baltimore, MD 21205
(443) 453-3407
eoga@umaryland.edu

Joel Palefsky, M.D., FRCP(C)
Professor
Department of Medicine
University of California, San Francisco
Box 0126
M-1203
505 Parnassus
San Francisco, CA 94118
(415) 476-1574
(415) 476-0986 Fax
joelp@medicine.ucsf.edu

Lesley S. Park, M.P.H.
Doctoral Candidate
Department of Chronic Disease Epidemiology
Center for Interdisciplinary Research on AIDS
School of Public Health
Yale University
Apartment 402
80 Howe Street
New Haven, CT 06511
(703) 835-1987
lesley.park@yale.edu

Chris H. Parsons, M.D.
Associate Professor
Director, HIV Malignancies Program
Department of Medicine
Louisiana Cancer Research Center
Louisiana State University Health Sciences Center
1509 Melody Drive
Metairie, LA 70002
(843) 822-3884
cpars1@lsuhsc.edu

Hannah Peavy, M.D.
Medical Officer
Division of Lung Diseases
Lung Biology and Disease Branch
Program Director, AIDS/TB
National Heart, Lung, and Blood Institute
National Institutes of Health
6701 Rockledge Drive
Bethesda, MD 20892
(301) 435-0222
peavyh@nhlbi.nih.gov

Warren Phipps, M.D., M.P.H.
Acting Instructor
Vaccine and Infectious Disease Division
University of Washington/Fred Hutchinson Cancer Research Center
1100 Fairview Avenue, North
Seattle, WA 98109
(206) 667-4600
(206) 667-1965 Fax
wtphipps@fhcrc.org

David Phung, M.D.
Diagnostic Radiologist
Presbyterian Medical Center
Suite B32
5350 San Mateo Boulevard
Albuquerque, NM 87109
(571) 309-3519
dp.vieclam@gmail.com

Prasanth Pillai, D.O.
Helen Devos Children's Hospital
100 Michigan Street, NE
Grand Rapids, MI 49503
(734) 717-7024
prasanth.pillai.do@gmail.com

Pierluca Piselli, Sc.D., M.P.H
Department of Epidemiology
National Institute for Infectious Diseases "L. Spallanzani"
Via Portuense 292
Rome, Italy 00173
39 (065) 517-0900
pierluca.piselli@inmi.it

Mark Polizzotto, M.D.
Assistant Clinical Investigator
HIV and AIDS Malignancy Branch
National Cancer Institute
National Institutes of Health
Building 10, Room 6N-110
9000 Rockville Pike
Bethesda, MD 20892
(301) 693-4969
mark.polizzotto@nih.gov

Alexander Price
Graduate Student
Luftig Laboratory
Duke University
CARL 423
Durham, NC 27705
(919) 668-3123
(509) 308-5435 Fax

Eric S. Pringle, M.S.
Department of Microbiology and Immunology
Dalhousie University
Tupeer Building, Room 7F
5850 College Street
Halifax, Nova Scotia B3H 3A2
Canada
(902) 412-7252
eric.pringle@dal.ca

Asimah Rafi, Ph.D.
Technical Resources International
Suite 650
6500 Rock Spring Drive
Bethesda, MD 20817
(301) 897-1712
arafi@tech-res.com

Bridgett Rahim-Williams, Ph.D.
Senior Research Fellow and Assistant Professor
National Institute on Minority Health and Health Disparities
National Institutes of Health
Building 3, Room 5W-11A
3 Center Drive
Bethesda, MD 20892
(727) 642-6860
bridgett.rahim-williams@nih.gov

Giovanna Rappocciolo, Ph.D.
Research Assistant Professor
Department of Infectious Diseases and Microbiology
University of Pittsburgh
604 Parran Hall
130 De Soto Street
Pittsburgh, PA 15261
(412) 606-9890
giovanna@pitt.edu

Elizabeth L. Read-Connole, Ph.D.
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
5478 Rider Place
San Diego, CA 92130
(858) 353-1984
egreid@ucsd.edu

Jennifer R. Rider, Sc.D.
Assistant Professor of Medicine
Channing Division of Network Medicine
Department of Medicine
School of Medicine
Harvard University
Ninth Floor
677 Huntington Avenue
Boston, MA 02115
(617) 432-3040
rider@hsph.harvard.edu

Charles R. Rinaldo, Ph.D.
Chairman and Professor
Department of Infectious Diseases and Microbiology
University of Pittsburgh
A419C Crabtree Hall, GSPH
130 DeSoto Street
Pittsburgh, PA 15261
(412) 624-3928
rinaldo@pitt.edu

Hilary A. Robbins, M.S.P.H.
Post-Baccalaureate Fellow
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Room 6-E228
9069 Medical Center Drive
Bethesda, MD 20892
(240) 276-7187
hilary.robbins@nih.gov

Rosemary Rochford, Ph.D.
Professor and Vice President for Research
SUNY Upstate Medical University
750 East Adams Street
Syracuse, NY 13210
(315) 464-4515
rochforr@upstate.edu

Richard Roden, Ph.D.
Professor
Johns Hopkins University
1550 Orleans Street
Baltimore, MD 21287
(410) 502-5161
roden@jhmi.edu

Isaac R. Rodriguez-Chavez, Ph.D.
Director
AIDS and Immunosuppression Program
Integrative Biology and Infectious Diseases Branch
National Institute of Dental and Craniofacial Research
National Institutes of Health
Room 614
6701 Democracy Boulevard
Bethesda, MD 20892
(301) 594-7985
(301) 480-8319 Fax
isaac@mail.nih.gov

Eliane Rohner, M.D.
Scientific Assistant
Institute of Social and Preventive Medicine
University of Bern
Niesenweg 6
Bern, Switzerland 3012
4 (131) 631-3518
erohner@ispm.unibe.ch

Romin Roshan
Research Associate II
AIDS and Cancer Virus Program
SAIC-Frederick, Inc.
Unit 1C
2500 Hemingway Drive
Frederick, MD 21702
(301) 846-7622
romin.roshan@nih.gov

Ro S. Rothwell, Ph.D., CCRP
Clinical Protocol Specialist
EMMES Corporation
Suite 700
401 North Washington Street
Rockville, MD 20850
(301) 251-1161, ext. 2752
(301) 576-3924 Fax
rrothwell@emmes.com

Michelle Rudek, Pharm.D.
Associate Professor of Oncology
Director
Analytical Pharmacology Core Laboratory
Johns Hopkins University
Sidney Kimmel Comprehensive Cancer Center
Room 1M52
1650 Orleans Street
Baltimore, MD 21287
(410) 614-6321
(410) 614-8397 Fax
mrudek2@jhmi.edu

Natalie Sachrajda
Dalhousie University
5850 College Street
Halifax, Nova Scotia B3H 4R2
Canada
(902) 440-0597
nt609576@dal.ca

Mahboobeh Safaeian, Ph.D.
Investigator
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Room 6E224
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-7185
safaeianm@mail.nih.gov

Vikrant Sahasrabuddhe, D.P.H., M.D., M.P.H.
Associate Investigator
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Room 7E230
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-7332
(240) 276-7838 Fax
vikrant.sahasrabuddhe@nih.gov

Maria Said, M.D., M.H.S.
Program Officer
Division of International Training and Research
Fogarty International Center
National Institutes of Health
Building 31
31 Center Drive
Bethesda, MD 20842
(301) 496-1653
maria.said@nih.gov

Johann W. Schneider, M.D.
Professor
Division of Anatomical Pathology
Department of Pathology
Faculty of Medicine and Health Sciences
Stellenbosch University
National Health Laboratory Service
Tygerberg Hospital
Stellenbosch University
P.O. Box 19063
Tygerberg, South Africa 7505
2 (721) 938-4041
jws2@sun.ac.za

Arnold M. Schwartz, M.D., Ph.D., FACCP, FCAP
Professor of Pathology
The George Washington University
Kaiser Building, Fifth Floor
2100-W Pennsylvania Avenue, NW
Washington, DC 20037
(202) 994-8804
(202) 994-2618 Fax
arnies@gwu.edu

Aggrey S. Semeere, M.D.
Physician/Research Fellow
Infectious Diseases Institute
University of California, San Francisco
185 Berry Street
San Francisco, CA 94107
(818) 497-4089
asemeere@gmail.com

Anna Serquiña, M.D., Ph.D.
Postdoctoral Fellow
HIV and AIDS Malignancy Branch
National Cancer Institute
National Institutes of Health
Building 10, Room 5A-21
Bethesda, MD 20892
(301) 402-3624
anna.serquina@nih.gov

Diego Serraino, M.D.
Epidemiology and Biostatistic Unit
IRCCS Centro di Riferimento Oncologico
Via F. Gallini, 2
Aviano, Italy 33084
39 (043) 465-9354
serrainod@cro.it

Shabnam Seydafkan, M.D.
Postdoctoral Research Fellow
Emory University
4203 Briarcliff Gables Circle
Atlanta, GA 30329
(404) 731-4146
seydafkan_sh@yahoo.com

Hasnaa Shafik, M.D., Ph.D.
Program Director
Office of Cancer Centers
National Cancer Institute
National Institutes of Health
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-5622
shafikh@mail.nih.gov

Gerald B. Sharp, D.P.H.
Epidemiologist
Basic Science Program
Epidemiology Branch
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Room 4103
6700B Rockledge Drive
Bethesda, MD 20892
(301) 451-2573
gsharp@niaid.nih.gov

Meredith S. Shiels, Ph.D., M.S.
Research Fellow
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Room 6E-218
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-7182
shielsms@mail.nih.gov

Kelly Shimabukuro, M.D.
Assistant Professor of Medicine
Division of Hematology-Oncology
University of California, San Diego
3855 Health Sciences Drive
La Jolla, CA 92093
(858) 822-3115
(858) 822-6186 Fax
kshimabukuro@ucsd.edu

Bruce Shiramizu, M.D.
Professor
Hawaii Center for AIDS
Cancer Center
Department of Tropical Medicine, Medical Microbiology, and Pharmacology
University of Hawaii
BSB 325AA
651 Ilalo Street
Honolulu, HI 96813
(808) 692-1677
(808) 692-1984 Fax
bshirami@hawaii.edu

Keith M. Sigel, M.D., M.P.H.
Assistant Professor of Medicine
Division of General Internal Medicine
Department of Medicine
School of Medicine
Mount Sinai Hospital
Box 1087
1 Gustave Levy Place
New York, NY 10029
(646) 283-8329
(917) 210-4057 Fax
keith.sigel@mssm.edu

Sylvia Silver, D.A.
Director
East Coast AIDS and Cancer Specimen Resource
Professor of Pathology
The George Washington University
School of Medicine and Health Sciences
2300 I Street, NW
Washington DC 20037
(202) 994-2945
(202) 994-5056 Fax
ssilver@gwu.edu

Michael J. Silverberg, Ph.D., M.P.H.
Research Scientist
Division of Research
Kaiser Permanente
Fifth Floor
2000 Broadway
Oakland, CA 94612
(510) 891-3801
(510) 891-3508 Fax
michael.j.silverberg@kp.org

Edgar Simard, Ph.D.
Senior Epidemiologist
Surveillance Research Program
American Cancer Society
250 Williams Street
Atlanta, GA 30303
(404) 417-5935
edgar.simard@cancer.org

Barbara Sina, Ph.D.
Fogarty International Center
National Cancer Institute
National Institutes of Health
Building 31, Room B2C-39
31 Center Drive
Bethesda, MD 20892
(301) 402-9467
sinab@mail.nih.gov

Jean D'Amour Sinayobye, M.D., M.S.
Equity in Access to Care and Treatment
WE - ACTx, HIV/AIDS Specialized Clinic
Clinical Epidemiologist in Regional Alliance for Sustainable Development, RASD, RWANDA
WE-ACTx
P.O. Box 5141
Dorona House, Avenue Kalisimbi
Kigali, Rwanda N/A
250 (078) 887-2581
sinayobyed@gmail.com

Dinah Singer, Ph.D.
Director
Division of Cancer Biology
National Cancer Institute
National Institutes of Health
Room 6W-442
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-6180
singerd@mail.nih.gov

Cheryl C. Solomon, M.S.
Co-Infections and Malignancies Subcommittee of the ACTG
Clinical Research and Bioscience
Social & Scientific Systems, Inc.
8757 Georgia Avenue
Silver Spring, MD 20910
(301) 628-3327
csolomon@s-3.com

Daniela C. Stefan, Ph.D.
Professor and Head
Pediatric Hematology Oncology
Tygerberg Hospital
Stellenbosch University
73 Tafelberg Road Kendrige
Cape Town, WA 7550
2 (782) 451-8228
cs@sun.ac.za

Megan Stine, Ph.D.
Scientific Program Manager
National Cancer Institute
National Institutes of Health
Building 31, Room 10A-07
31 Center Drive
Bethesda, MD 20892
(301) 451-3860
megan.stine@nih.gov

Robert M. Strother, M.D.
Medical Oncologist
Canterbury District Health Board
5 Veolas Road
Lyttleton, New Zealand 46202
6 (427) 703-3247
matthew.strother@health.cdhb.nz

Ren Sun, Ph.D.
Professor
University of California, Los Angeles
Factor Building, Room 10-155
650 Charles E. Young Drive, South
Los Angeles, CA 90095
(310) 794-5557
rsun@mednet.ucla.edu

Gita Suneja, M.D.
Instructor, Radiation Oncology
University of Pennsylvania
Room 416
777 South Broad Street
Philadelphia, PA 19147
(267) 207-5499
suneja@uphs.upenn.edu

Jeff Taylor
Patient Advocate
AIDS Treatment Activists Coalition
AIDS Malignancy Consortium
850 Spencer Drive
Palm Springs, CA 92262
(760) 835-1926
jefftaylorps@gmail.com

Sharof M. Tugizov, Ph.D., D.Sc.
Professor
Department of Medicine
Department of Orofacial Sciences
University of California, San Francisco
Room S420
513 Parnassus Avenue
San Francisco, CA 94143
(415) 514-3177
sharof.tugizov@ucsf.edu

Thomas Uldrick, M.D.
Staff Clinician
Retroviral Disease Section
HIV and AIDS Malignancy Branch
National Cancer Institute
National Institutes of Health
Building 10, Room 6N-106
10 Center Drive
Bethesda, MD 20892
(301) 402-6296
uldrickts@mail.nih.gov

Alicia L. Vargas
Statistician
DC Cancer Registry
Department of Health
Third Floor
899 North Capitol Street, NE
Washington, DC 20002
(202) 724-7703
alicia.vargas@dc.gov

Sundar Venkatachalam, Ph.D.
Program Director
Epithelial Cell Regulation and Transformation Program
Integrative Biology and Infectious Diseases Branch
National Institute of Dental and Craniofacial Research
National Institutes of Health
6701 Democracy Boulevard
Bethesda, MD 20892
(301) 594-4812
sundarv@nih.gov

Raman Venkataramanan, Ph.D.
Professor, Pharmaceutical Sciences
School of Pharmacy
University of Pittsburgh
718 Salk Hall
Pittsburgh, PA 15261
(412) 648-8547
(412) 648-7671 Fax
rv@pitt.edu

Mukesh Verma, Ph.D.
Branch Chief
Division of Cancer Control and Population Sciences
National Cancer Institute
National Institutes of Health
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-6889
vermam@mail.nih.gov

Coralie Viollet-Djelassi, M.S.
Fellow
HIV and AIDS Malignancy Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Building 10, Room 5A-25
9000 Rockville Pike
Bethesda, MD 20892
(301) 402-3630
coralie.viollet-djelassi@nih.gov

William Wachsman, M.D., Ph.D.
Professor of Medicine
Division of Hematology-Oncology
Moores Cancer Center
University of California, San Diego
3350 La Jolla Village
San Diego, CA 92161
(858) 552-8585
(858) 552-7416 Fax
wwachsman@ucsd.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 HIII, NC 27599
(919) 966-8911
cyriaquj@dentistry.unc.edu

Robert S. Wehbie, M.D., Ph.D., FACP
Hematology Oncologist
Rex Cancer Center of Wakefield
The University of North Carolina at Chapel Hill
Suite 102
11200 Governor Manly Way
Raleigh, NC 27614
(919) 570-7550
saliba@med.unc.edu

Megan Wenger, M.P.H.
Department of Epidemiology and Biostatistics
University of California, San Francisco
Lobby 5, Suite 5700
185 Berry Street
San Francisco, CA 94107
(415) 514-8016
mwenger@psg.ucsf.edu

Nicolas Wentzensen, M.D., Ph.D., M.S.
Hormonal and Reproductive Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Room 7-E114
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-7303
wentzenn@mail.nih.gov

Denise Whitby, Ph.D.
Senior Scientist and Principal Investigator
Viral Oncology Section
AIDS and Cancer Virus Program
SAIC-Frederick, Inc.
NCI-Frederick
P.O. Box B
Frederick, MD 21701
(301) 846-1714
(301) 846-7119 Fax
whitbyd@mail.nih.gov

Makeda J. Williams, Ph.D., M.P.H., CHES
International Program Officer
Center for Global Health
National Cancer Institute
National Institutes of Health
Executive Plaza North, Suite 100
6130 Executive Boulevard
Bethesda, MD 20892
(301) 451-1445
(301) 496-3954 Fax
willimak@mail.nih.gov

Tyrone V. Wilson
Division of Extramural Activities
National Cancer Institute
National Institutes of Health
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-6403
wilsonty@mail.nih.gov

Ida Wong-Sefidan, M.D.
Department of Hematology/Oncology
University of California, San Diego
3855 Health Sciences Drive
La Jolla, CA 92093
(858) 822-6583
icwong@ucsd.edu

T-C Wu, M.D., Ph.D.
Departments of Pathology, Oncology, Obstetrics and Gynecology, and Molecular Microbiology and Immunology
School of Medicine
Johns Hopkins University
Cancer Research Building II, Room 309
1550 Orleans Street
Baltimore, MD 21231
(410) 614-3899
(443) 287-4295 Fax
twu1@jhmi.edu

Elizabeth L. Yanik, Ph.D., M.S.
Postdoctoral Fellow
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
9609 Medical Center Drive
Bethesda, MD 20892
(240) 276-7781
elizabeth.yanik@nih.gov

Robert Yarchoan, M.D.
Director
Office of HIV and AIDS Malignancy
National Cancer Institute
Chief
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) 496-0328
(301) 480-5955 Fax
robert.yarchoan@nih.gov

Hao Zhang, M.D.
Program Officer
Drug Development and Clinical Sciences Branch
Therapeutics Research Program
Division of Acquired Immunodeficiency Syndrome
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Room 5153
6700B Rockledge Drive
Bethesda, MD 20892
(301) 451-2191
(301) 453-0928 Fax
hazhang@niaid.nih.gov

Li Zhang, M.D.
Medical Officer
Laboratory for Integrative Neuroscience
National Institutes of Health
5625 Fishers Lane
Bethesda, MD 20892
(301) 443-3755
lzhang@mail.nih.gov

Joseph M. Ziegelbauer, Ph.D.
Head
Viral MicroRNA Section
National Cancer Institute
HIV and AIDS Malignancy Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Building 10, Room 6N-110
Bethesda, MD 20892
(301) 594-6634
ziegelbauerjm@mail.nih.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA
NIH
National Institutes of Health
NATIONAL CANCER INSTITUTE