NIH NATIONAL CANCER INSTITUTE

16th International Conference on Malignancies in HIV/AIDS

October 23-24, 2017

Lister Hill Center Auditorium
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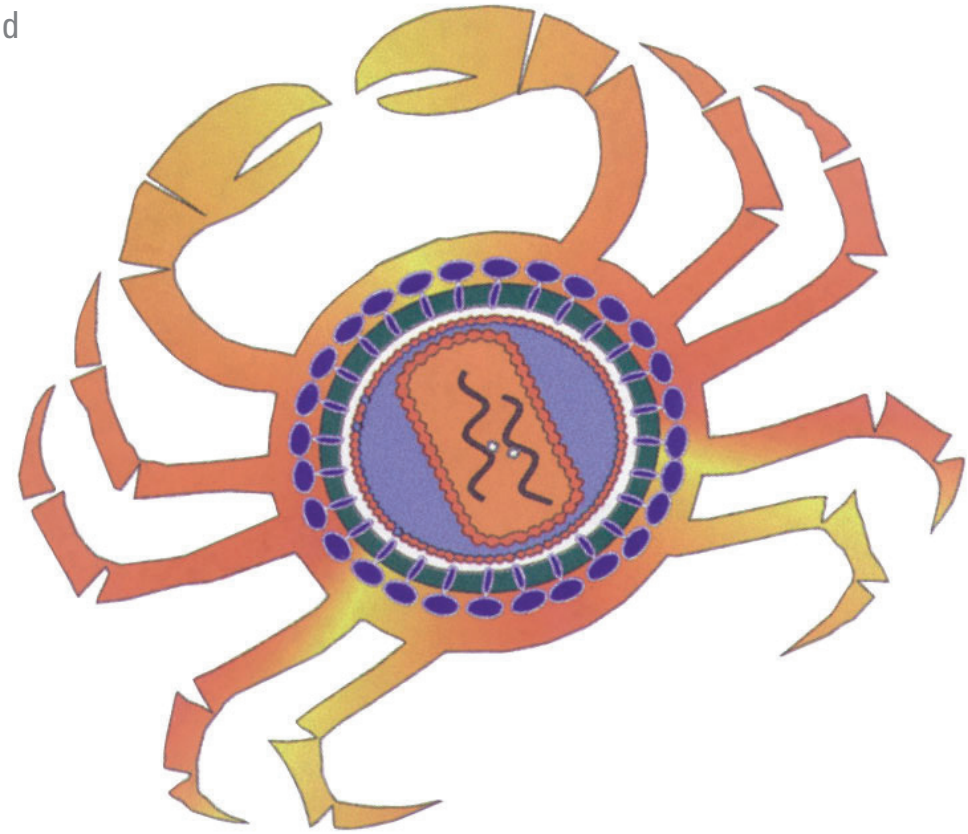
Bethesda, Maryland



Office of HIV and AIDS Malignancy | National Cancer Institute
National Institutes of Health | U.S. Department of Health and Human Services

PROGRAM

Day 1: October 23

7:45. a.m. - 5:30 p.m. **Registration**

8:00 a.m. - 8:30 a.m. **Day 1 Poster Setup**
Travel Awardee Posters will stay up for the entire meeting.

8:30 a.m. - 8:45 a.m. **Opening Remarks**
Geraldina Dominguez, Ph.D.
National Cancer Institute, NIH

8:45 a.m. - 9:00 a.m. **Welcome**
Robert Yarchoan, M.D.
National Cancer Institute, NIH

9:00 a.m. - 10:30 a.m. **Session 1: HPV and Cervical Cancer**
Moderators: Joel Palefsky, M.D.
University of California, San Francisco

Mark H. Einstein, M.D.
Rutgers University

9:00 a.m. - 9:30 a.m. ***P1. HPV/Vaccine Trial***
Douglas R. Lowy, M.D.
National Cancer Institute, NIH

9:30 a.m. - 10:00 a.m. ***P2. Cervical Cancer Control in Africa***
Hennie Botha, MBChB, M.Med, FCOG, Ph.D.
Stellenbosch University

10:00 a.m. - 10:30 a.m. ***P3. Molecular Carcinogenesis of Cervical Cancer: Beyond HPV***
Nicolas Wentzensen, M.D., Ph.D.
National Cancer Institute, NIH

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

11:00 a.m. - 12 noon **Session 2: Gene Therapy and Stem Cell Transplantation**
Moderator: Thomas S. Uldrick, M.D.
National Cancer Institute, NIH

11:00 a.m. - 11:30 a.m. ***P4. HIV Gene Therapy***
Hans-Peter Kiem, M.D., Ph.D.
Fred Hutchinson Cancer Research Center

11:30 a.m. - 12 noon ***P5. Hematopoietic Transplantation for Patients With HIV and Hematologic Malignancies***
Richard F. Ambinder, M.D., Ph.D.
Johns Hopkins University School of Medicine

12 noon - 1:00 p.m. **Lunch** (on your own or lunch boxes)

1:00 p.m. - 2:00 p.m. **Day 1 Poster Viewing** (Presenters stand by their posters.)

2:00 p.m. - 3:00 p.m. **Session 3: Epstein-Barr Virus and Rhesus Rhadinovirus**
Moderators: Ethel Cesarman, M.D., Ph.D.
Weill Cornell Medical College

Erle S. Robertson, Ph.D.
Perelman School of Medicine, University of Pennsylvania

2:00 p.m. - 2:15 p.m. ***O1. Development of an EBNA1 Inhibitor for the Treatment of HIV-Associated Epstein-Barr Virus-Driven Malignancies***
Troy E. Messick, Ph.D.
The Wistar Institute

2:15 p.m. - 2:30 p.m. ***O2. Tumor Epstein-Barr Virus Status Is Prognostic in Primary Effusion Lymphoma***
Kathryn Lurain, M.D.
National Cancer Institute, NIH

2:30 p.m. - 2:45 p.m. ***O3. Cell Receptor Activation Triggers Caspase-Mediated Cleavage of PIAS1 to Facilitate Epstein-Barr Virus Lytic Replication***
Renfeng Li, Ph.D.
Philips Institute for Oral Health Research

2:45 p.m. - 3:00 p.m. ***O4. Anti-IL-15-Mediated Depletion of NK Cells in Primary SIV Infection Does Not Alter SIV Replication but Accelerates Rhesus Rhadinovirus Pathogenesis***
Afam A. Okoye, Ph.D.
Oregon Health & Science University

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

3:30 p.m. - 5:45 p.m. **Session 4: KSHV and Kaposi Sarcoma**
Moderators: Dirk Dittmer, Ph.D.
The University of North Carolina at Chapel Hill

Paul M. Lieberman, Ph.D.
The Wistar Institute

3:30 p.m. - 4:00 p.m. ***P6. KSHV Targets Nuclear Export of mRNA to Regulate Host Gene Expression***
Ting-Ting Wu, Ph.D.
University of California, Los Angeles

4:00 p.m. - 4:15 p.m. ***O5. Manipulation of the Host Iron Regulon by Kaposi Sarcoma Herpesvirus (KSHV)***
Ashlee V. Moses, Ph.D.
Oregon Health & Science University

4:15 p.m. - 4:30 p.m. ***O6. Modulation of Cholesterol Pathway in KSHV Infection***
Anna Serquiña, M.D., Ph.D.
National Cancer Institute, NIH

4:30 p.m. - 4:45 p.m.	***O7. Portable Nucleic Acid Amplification Testing as a Means for Diagnosis of Kaposi Sarcoma in Africa*** Jeffrey N. Martin, M.D., M.P.H. University of California, San Francisco
4:45 p.m. - 5:00 p.m.	***O8* Kaposi Sarcoma-Associated Herpesvirus (KSHV) Seroprevalence and Antibody Levels in Relation to Haemoglobin and Malaria Among Individuals From Rural Uganda*** Angela Nalwoga, M.Sc. (Ph.D. candidate) MRC/UVRI Uganda Research Unit on AIDS
5:00 p.m. - 5:15 p.m.	***O9. T-cell Receptor Sequencing of Tumor-Infiltrating Lymphocytes in Kaposi Sarcoma Tumors Identifies Candidate Tumor-Reactive T-cell Responses*** Warren Phipps, M.D., M.PH. Fred Hutchinson Cancer Research Center
5:15 p.m. - 5:30 p.m.	***O10. Exploring the Function and Mechanism of Pomalidomide-Induced Increases in Immune Surface Markers in Primary Effusion Lymphoma Cells*** David A. Davis, Ph.D. National Cancer Institute, NIH
5:30 p.m. - 5:45 p.m.	***O11. AMC-070: Lenalidomide Is Safe and Effective in AIDS-Associated Kaposi Sarcoma*** Dirk Dittmer, Ph.D. The University of North Carolina at Chapel Hill
5:45 p.m.	**End of Day 1**

08* is a travel awardee.

Day 2: October 24

8:00 a.m. - 8:15 a.m. **Day 2 Poster Setup and Viewing**

8:15 a.m. - 8:30 a.m. **Welcome Day 2**
Geraldina Dominguez, Ph.D.
National Cancer Institute, NIH

8:30 a.m. - 10:00 a.m. **Session 5: Clinical Research and Trials**
Moderators: Lee Ratner, M.D., Ph.D.
Washington University School of Medicine in St. Louis

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

8:30 a.m. - 9:00 a.m. ***P7. Development of HIV-Specific T-Cell Therapy: Lessons From Epstein-Barr Virus***
Catherine Bollard, MBChB
Children's Research Institute

9:00 a.m. - 9:30 a.m. ***P8. As-Needed Versus Immediate Etoposide Chemotherapy in Combination With Antiretroviral Therapy for Mild or Moderate AIDS-Associated Kaposi Sarcoma in Resource-Limited Settings: A5264/AMC-067***
Thomas Campbell, M.D., Ph.D.
University of Colorado

9:30 a.m. - 9:45 a.m. ***O12. Cisplatin and Radiation Therapy in HIV-Infected Women With Locally Advanced Cervical Cancer in Sub-Saharan Africa (AMC-081)***
Mark H. Einstein, M.D., M.S.
Rutgers New Jersey Medical School

9:45 a.m. - 10:00 a.m. ***O13. Extracellular Vesicles Derived From HIV-Infected T Cells Promote Progression of Non-AIDS-Defining Cancers***
Ge Jin, Ph.D.
Case Western Reserve University

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

10:30 a.m. - 12 noon **Session 6: Epidemiology and Screening**
Moderators: Gypsyamber D'Souza. Ph.D.
Johns Hopkins Bloomberg School of Public Health

Elizabeth Chiao, M.D., M.P.H.
Baylor College of Medicine

10:30 a.m. - 11:00 a.m. ***P9. Projected Cancer Incidence and Burden in HIV-Infected Adults in the United States Through 2030***
Meredith S. Shiels, Ph.D.
National Cancer Institute, NIH

11:00 a.m. - 11:15 a.m. ***O14. Elevated Risk of First and Second Primary Cancers Among People With HIV***
Nancy A. Hessol, M.S.P.H.
University of California, San Francisco

11:15 a.m. - 11:30 a.m. ***O15. Lung Cancer Mortality Among People Living With HIV in the United States: Impact of Smoking and Smoking Cessation***
Krishna P. Reddy, M.D.
Massachusetts General Hospital

11:30 a.m. - 11:45 a.m. ***O16. Prevention and Early Detection of Cervical Cancer in Africa Through Community-Based Self-Administered Screening and Mobile Treatment Provision***
Miriam Nakalembe, MBChB, Ph.D.
Infectious Diseases Institute, Makerere University

11:45 a.m. - 12 noon ***O17. Persistent Anal HPV16/18 Infections as Predictors of High-Grade Anal Lesions in Older MSM***
Hilary K. Hsu, M.P.H.
University of California, Los Angeles

12 noon - 1:00 p.m. **Lunch** (on your own or lunch boxes)

1:00 p.m. - 2:00 p.m. **Day 2 Poster Viewing** (Presenters stand by their posters.)

2:00 p.m. - 3:30 p.m. **Session 7: Polyomaviruses and Immunotherapy**
Moderators: Thomas G. Gross, M.D., Ph.D.
National Cancer Institute, NIH

Corey Casper, M.D., M.P.H.
Fred Hutchinson Cancer Research Center

2:00 p.m. - 2:30 p.m. ***P10. BK Polyomavirus, APOBEC3B, and Cancer: Molecular Judo Gone Awry?***
Christopher Buck, Ph.D.
National Cancer Institute, NIH

2:30 p.m. - 3:00 p.m. ***P11. PD-L1 Inhibition and the Evolving Management of Merkel Cell Carcinoma***
Isaac F. Brownell, M.D., Ph.D.
National Cancer Institute, NIH

3:00 p.m. - 3:15 p.m. ***O18*. A Case Series of Nivolumab in Veterans With HIV Infection and Malignancy***
Elaine Chang, M.D.
Baylor College of Medicine

3:15 p.m. - 3:30 p.m. ***O19. AMS095: A Phase I Study of Ipilimumab (Ipi) and Nivolumab (Nivo) in Advanced HIV-Associated Solid Tumors (Preliminary Findings)***
Lakshmi N. Rajdev, M.D.
Albert Einstein College of Medicine and Montefiore Medical Center

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

4:00 p.m. - 5:25 p.m. **Session 8: Pathogen Host Interactions**

Moderators: Jennifer Webster-Cyriaque, Ph.D., D.D.S.
The University of North Carolina at Chapel Hill

Otoniel Martinez-Maza, Ph.D.
University of California, Los Angeles

4:00 p.m. - 4:20 p.m. ***P12. Epstein-Barr Virus and Malaria Profiles in African Burkitt Lymphoma: What Can We Learn From Array-Based Studies?***
Sam Mbulaiteye, M.D.
National Cancer Institute, NIH

4:20 p.m. - 4:35 p.m. ***O20. A Prospective Study of Serum Microbial Translocation and Inflammation-Associated Biomarkers and Risk of AIDS-Related Non-Hodgkin Lymphoma***
Marta Epeldegui, Ph.D.
University of California, Los Angeles

4:35 p.m. - 4:50 p.m. ***O21. Identifying Transcriptional and Prognostic Biomarkers of HIV-Associated Diffuse Large B-cell Lymphoma From Malawi***
Yuri Fedoriw, M.D.
The University of North Carolina at Chapel Hill

4:50 p.m. - 5:10 p.m. ***P13. KSHV and Co-infections***
Denise Whitby, Ph.D.
Frederick National Laboratory for Cancer Research, NIH

5:10 p.m. - 5:25 p.m. ***O22. Strategies to Improve Kaposi Sarcoma Outcomes in Zimbabwe: A Community-Based Clinical Trial of a Training Intervention for Improved Primary Care of AIDS-KS (SIKO study)***
Margaret Borok, M.D.
University of Zimbabwe College of Health Sciences

5:25 p.m. - 5:35 p.m. **Closing Comments**
Robert Yarchoan, M.D.
National Cancer Institute, NIH

5:35 p.m. **Meeting Adjourned**

019* is a travel awardee.

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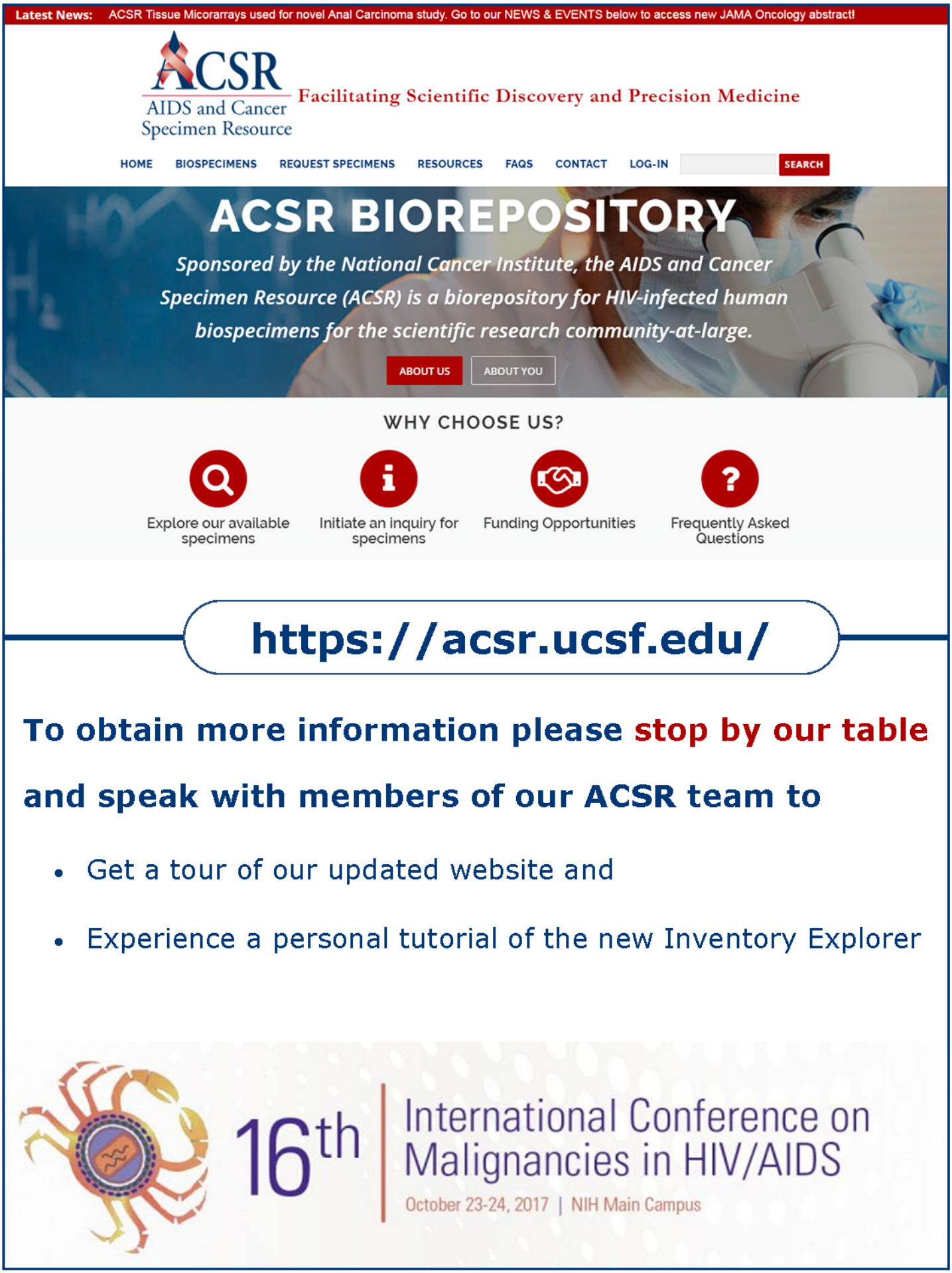
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PLENARY PRESENTATIONS

P1. HPV/Vaccine Trial

Douglas Lowy

Laboratory of Cellular Oncology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

HPV causes a range of epithelial cancers (1). Cervical cancer is the most important of them globally, as it accounts for ~90% of HPV-associated cancers worldwide (2). The main public health challenge for HPV-associated cancer lies in the developing world, where ~ 85% of cervical cancers occur and ~90% of the deaths from this cancer. Without additional interventions, it is projected that the annual number of cervical cancer deaths in the developing world will increase indefinitely, for example going from 206K in 2015 to 317K in 2030.

The HPV virus-like particle vaccines (Gardasil, Gardasil9 [Merck], and Cervarix [GlaxoSmithKline]) can potentially to eradicate HPV-associated cancer as a major worldwide public health problem, as they confer >90% vaccine efficacy (VE) in the primary prevention of new infections and disease caused by the HPV types targeted by the vaccines. The vaccines are most cost-effective if given prior to sexual debut, as the vast majority of oncogenic HPV infections are sexually transmitted. They are the first approved vaccines that target an infectious agent that induces local sexually transmitted disease. Fewer than 3% of eligible girls in the developing world had been vaccinated through 2015 (3).

The vaccines were originally approved for three doses, which is expensive – even with tiered pricing - and can pose logistical problems in many poor resource settings. Subsequently, they have been approved for two doses in young adolescents, based on immunobridging trials (4).

Post-hoc analyses of women in the Costa Rica Vaccine Trial (CVT) indicated that VE in women who received one or two doses of Cervarix was not inferior to VE against the intended three doses. Furthermore, the HPV16/18 antibody titers in the one dose women have been stable for 7 years, a finding without precedent for a protein-based subunit vaccine (5). We hypothesize that a single HPV vaccine dose may confer long-term protection in young adolescents and are testing it in an efficacy trial. It is a 4 arm, randomized controlled, non-inferiority trial in 20,000 12-16 year old girls that evaluates the efficacy and serum responses of two FDA-approved vaccines, Cervarix and Gardasil9, each of which is tested at one dose and two doses. If high efficacy is demonstrated for one dose of at least one of the vaccines, the evidence should be practice-changing. If a single vaccine dose were to cost $3, it would be possible to vaccinate an entire global female birth cohort (~60 million girls/year) for less than $200 million/year.

References

1. Lowy DR. 2016. HPV vaccination to prevent cervical cancer and other HPV-associated disease: from basic science to effective interventions. J Clin Invest 126:5-11.
2. Plummer M, et al. 2016. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health 4:e609-616.
3. Bruni L et al. 2016. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob Health 4:e453-463.
4. Iversen OE et al. 2016. Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women. JAMA 316:2411-2421.
5. Safaeian M et al. 2017. Durability of Protection Afforded by Fewer Doses of the HPV16/18 Vaccine: The CVT Trial. J Natl Cancer Inst in press.

P2. Cervical Cancer Control in Africa

M.H. Botha

D*epartment of Obstetrics and Gynaecology and Unit for Gynaecological Oncology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa*

Cervical cancer remains an important cause of morbidity and mortality in Africa. The incidence remains unacceptably high, cases are often diagnosed late and many have poor response to treatment. Treatment facilities, in particular advanced surgery and radiotherapy, are scarce and often under resourced. Determinants of the high cervical cancer rate and poor outcome of treatment include low number of health care workers (HCW) per capita, more HIV (human immunodeficiency virus) infections and competing health care needs. A lack of patient empowerment and knowledge leads to a low degree of health seeking behaviour.

The HIV epidemic in Africa complicates cancer control efforts. Co-infection with HIV and oncogenic HPV (human papilloma virus) leads to earlier cancer presentation, less effective treatment for pre-malignant lesions and higher morbidity and side-effects during treatment for advanced disease. HIV infected women host more strains of HPV for longer periods that HIV non-infected women. However, treatment with effective anti-retroviral HIV therapy (ARV) causes a time dependant reduction in HPV detection in line with immune reconstitution. Women on ARV also have better response to treatment of pre-malignant and malignant disease.

The uptake of HPV vaccination in national programs has been slow in Africa but there are notable exceptions like Rwanda, Botswana, Libya and South Africa. The successful introduction of a school based vaccination program is a momentous task, especially in settings where no adolescent, adult or school based vaccination programmes existed prior to the roll out. Education of HCW and the general public is crucial to the success, as no framework and culture for the immunisation of older youth and adult populations are established. Barriers include the challenges associated with administration of a 3-dose vaccine in a busy school calendar. A 2 dose schedule in young adolescents is equally effective and logistically much easier. Community based consent strategies which negated individual parental consent were introduced in Uganda, and parent opt-out strategies were used in Tanzania and Rwanda. The importance of grade-based, compared to age-based, eligibility criteria and completion of the vaccination series in one calendar year will improve uptake. HPV infection may increase HIV acquisition significantly. A theoretical possibility exist that HPV prevention through vaccination may, as an unintentional benefit, also reduce HIV transmission in at-risk populations.

Secondary prevention through screening has been shown to reduce cervical cancer significantly where comprehensive, population based, call-and-recall programs were introduced. In most countries in Africa the success of screening has been limited. Opportunistic screening will, at least for the foreseeable future, continue to be the norm. Self-sampling for HPV testing may be the ideal strategy in campaign-based, opportunistic programs where quick turnaround times are essential.

Linking health interventions achieve cost effective ways of disease prevention. By controlling HIV, the incidence of HPV related disease will, as a result, also be reduced. In addition, HIV treatment facilities are used to monitor cervical screening and treatment. Linking opportunistic screening of mothers to vaccination of their children is a potential way to increase disease awareness and screening uptake.

Treatment for advanced cancer may be complicated by concurrent HIV disease. HIV-positive patients with cervical carcinoma are less likely to complete chemo-radiotherapy and are more likely to experience hematologic toxicity.

P3. Molecular Carcinogenesis of Cervical Cancer: Beyond HPV

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Most cervical cancers are caused by persistent infections with one of a dozen carcinogenic human papillomaviruses (HPV). The cancer risk differs by HPV genotype, with HPV16 and HPV18 accounting for over 70% of all cervical cancers. HPVs are small circular double-stranded DNA viruses that encode for about 8 viral proteins. Two of these, E6 and E7, are potent oncoproteins that inhibit apoptosis by disabling p53 and activate the cell cycle by disrupting the pRB pathway. In addition, the viral oncogenes cause major chromosomal instability already at precancerous stages and may induce integration of the viral genome into the host cells. Despite these strong oncogenic features of HPV, only a small subset of HPV infections ever progress to precancer or cancer. Recent large scale genomic analyses, in part conducted through The Cancer Genome Atlas (TCGA) project, have revealed important somatic host alterations in cervical cancers that shed new light on the molecular carcinogenesis of cervical cancer. There is strong evidence that a large proportion of somatic mutations occurring in cervical cancers are related to the APOBEC mutation mechanism, which is thought to act in response to viral infections. Significantly mutated genes identified include PIK3CA, EP300, FBXW7, PTEN, HLA, ARID1A, KRAS and several others. Many characteristic copy number alterations have been described, most importantly amplification of 3q. Complementary studies in cervical precancers are now needed to establish the sequence of molecular events and the interplay between viral and host carcinogenic pathways. A better understanding of the molecular carcinogenesis may offer new tools to predict which infections and precancers will progress to cancer and may offer new targeted therapy approaches.

P4. HIV Gene Therapy

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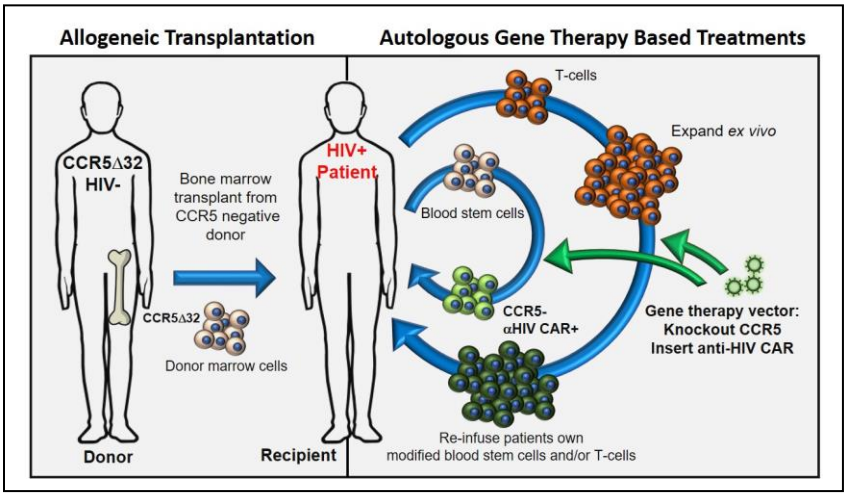
Despite the development of effective antiretroviral drugs, a sustained HIV cure has only been documented in one patient to date. In 2007, the "Berlin Patient" received a bone marrow transplant to treat his leukemia from a donor who was homozygous for a mutation in the CCR5 gene. This mutation, known as CCR5Δ32, prevents HIV replication by inhibiting the early stage of viral entry into cells, resulting in resistance to infection from the majority of HIV isolates. Over ten years after his last dose of antiretroviral therapy, the formerly HIV+ transplant recipient remains free of detectable replication-competent HIV. Multiple groups are now attempting to replicate this success, through the use of other CCR5-negative donor cell sources. Additionally, developments in the use of lentiviral vectors and targeted nucleases have opened the doors of precision medicine, and enabled new treatment methodologies using the patient's own cells to combat HIV infection through downregulation or targeted ablation of CCR5 expression. In addition to genetic protection strategies, cells can also be armed with anti HIV transgenes such as broadly neutralizing antibodies or chimeric antigen receptors directed against HIV. By combining gene therapy strategies to i) protect stem and T cells from HIV infection and ii) harness effective HIV-specific immunity, it might be possible to play both offense and defense against the virus. This would enable the immune system to immediately begin eliminating latently infected cells while waiting for new gene-modified and HIV resistant cells to mature from the bone marrow. In combination, targeted gene integration would allow for inserting the CAR T-cell gene cassette directly into the site of CCR5 disruption, delivering a single-step, one-two punch against the virus. In this presentation, I will review and discuss gene therapy-based anti HIV therapies, benefits, and challenges associated with this technology.



P5. Hematopoietic Transplantation for Patients With HIV and Hematologic Malignancies

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Beginning in the late 1980s, transplant-based approaches to the treatment of hematologic malignancies in patients with HIV have been explored. The initial experiences were notable for infectious and other complications. With the advent of antiretroviral therapy, autologous and allogeneic transplantation have been readdressed. A Bone Marrow Transplant Clinical Trials Network/AIDS Malignancy Study showed that patients with HIV and lymphoma undergoing autologous transplantation have outcomes comparable to matched controls. A subsequent trial from the same collaborators showed that fatal opportunistic infections and other non-relapse mortality was not seen at all in the first 100 days after allogeneic transplant in HIV patients with hematologic malignancies providing reassurance that allogeneic transplantation could also be safely carried out.

The report of the Berlin patient who received an allogeneic transplant from a CCR5delta32 homozygous donor and was cured of HIV stimulated interest in the use of HIV resistant donors. Because of the requirements for HLA matching and time delays while CCR5delta32 typing was carried out, very few patients have received such transplants. However, relaxed HLA-matching requirements with post-transplant cyclophosphamide as graft-versus-host disease prophylaxis and new policies that have led to routine CCR5delta32 typing in donors should profoundly change that equation and we can expect more transplantation with HIV-resistant donors in the immediate future.

P6. KSHV Targets Nuclear Export of mRNA to Regulate Host Gene Expression

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Manipulation of host gene expression allows a virus to control cellular functions, such as the antiviral response. Through coevolution with hosts, herpesviruses have acquired various strategies to evade the type I interferon responses. We identified that ORF10 of Kaposi's sarcoma-associated herpesvirus reduces the type I interferon receptor expression by inhibiting mRNA nuclear export. We hypothesized that KSHV ORF10 exploits RNA export pathway to control host gene expression. ORF10 interacts with RNA export factor (Rae1), and forms a complex with Nup98. Rae1 contributes to mRNA transport by interacting with Nup98 at the nuclear pore complex (NPC). The inhibitory effect of ORF10 on mRNA export is abolished by point mutations that disrupt the interaction with Rae1. Our preliminary results indicate that interaction of ORF10 with Rae1 allows ORF10 to gain access to the mRNA export machinery and interrupt its function at the NPC. Using a reporter assay and RNA sequencing, we found that the export inhibition of mRNAs by ORF10 is not global but selective. We identified a subset of cellular mRNAs whose RNA export is blocked by ORF10. Furthermore, we showed that the selectivity of ORF10's selectivity target is dictated by the 3' untranslated region (3'UTR) of the gene. Nevertheless, ORF10 reduces cytoplasmic RNA of ~20% of genes by > 50%, suggesting a host shutoff function of ORF10. KSHV lytic replication results in a widespread shutoff of host gene expression, and one major contributing gene to host shutoff is ORF37 (also known as SOX). Eliminating ORF10 expression from KSHV or knocking down Rae1 expression generate similar phenotypes: reduction in late gene expression and virion production. Thus, our results demonstrate that mRNA export inhibition by ORF10 has an unique biological role in viral replication that is distinct from the shutoff activity of ORF37. In conclusion, we uncovered a novel strategy by which KSHV manipulates host gene expression through inhibiting nuclear export of RNA. Regulation of gene expression is critical for successful viral replication and contributes to pathogenesis. An understanding of how KSHV regulates cellular processes through ORF10 may enable new therapeutic strategies against KSHV-related diseases.

P7. Development of HIV-Specific T-Cell Therapy: Lessons From Epstein-Barr Virus

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Adoptive T cell therapy using virus-specific T cells (VSTs) has been successful in boosting viral-specific immunity for the treatment of patients with EBV+ Lymphoma and for patients post-HSCT, effecting disease remissions and preventing viral reactivations of CMV and EBV. However, the therapeutic use of VSTs (non gene engineered) to boost HIV-specific T cell immunity in HIV+ patients has met with more modest success. Despite multiple attempts to eradicate HIV with allogeneic-HSCT, there is only one case of functional HIV cure. Hence, we hypothesized that broadly HIV-specific CD8 and CD4 T-cells (HXTCs) could be expanded from HIV+ individuals on ARVs, as well as HIV-negative adult and cord blood donors (dHXTC), employing a non-HLA restricted approach for the treatment of HIV+ individuals in the autologous or allogeneic settings. We adapted the manufacturing platform we had utilized successfully for the manufacture of EBV/LMP-specific T cells from patients with EBV+ lymphomas and expanded autologous HXTCs from HIV+ subjects under NCT02208167. To extend this approach to the allogeneic HSCT setting, we generated dHXTCs from HIV-naive adults and cord blood donors. Epitope mapping of both adult and cord dHXTC products revealed that products contained T cells recognizing unique epitopes not typically identified in HIV+ individuals, similar to our observations in the CMV setting, which may be critical in overcoming viral immune escape post-HSCT. In summary, building on our VST experiences for the treatment of patients with EBV+ lymphomas and viral infections post HSCT, we can now show that HIV-specific T cells can be expanded from HIV+ and HIV-negative donors for clinical use and may offer a unique T cell therapeutic for HIV cure as well as a platform for gene modification.

P8. As-Needed Versus Immediate Etoposide Chemotherapy in Combination With Antiretroviral Therapy for Mild or Moderate AIDS-Associated Kaposi Sarcoma in Resource-Limited Settings: A5264/AMC-067

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Background: Mild-to-moderate AIDS-associated Kaposi sarcoma (KS) often responds to antiretroviral therapy (ART) alone; the role of concomitant chemotherapy is unclear. WHO guidelines state that no randomized clinical trials or observational studies have been specifically designed to assess the value of adding chemotherapy to ART compared to ART alone, in mild to moderate KS, and that research is needed to assess if use of oral etoposide for chemotherapy is an effective therapy. A5264/AMC-067 was designed to address these knowledge gaps by evaluating the benefit of immediate addition of oral etoposide chemotherapy to antiretroviral therapy for the initial treatment of mild-to-moderate AIDS KS.

Methods: Chemotherapy-naïve, HIV-1-infected adults with mild-to-moderate KS who were initiating ART in Africa and South America were randomized 1:1 to initiate ART (TDF/FTC/EFV) alone (chemotherapy "As-Needed" arm) vs ART plus up to 8 cycles of oral ET (Immediate arm). Participants with KS progression on ART alone received ET as part of the As-Needed strategy. The primary outcome was ordinal: failure (composite of KS progression, initiation of non-study chemotherapy, lost-to-follow-up, and death), stable, and response at 48 weeks. Secondary outcomes included times to initial KS progression, suspected KS-associated immune reconstitution inflammatory syndrome (KS-IRIS), and KS response. A planned sample size of 234 per arm provided 90% power to conclude superiority of the Immediate Arm. At the third DSMB review for interim efficacy in March 2016, the board recommended closure of the study to further enrollment and follow-up due to futility in the primary outcome analysis.

Results: 190 participants were randomized (As-Needed=94, Immediate=96), the majority were men (71%) and African (93%); the median age was 34 years. 25 participants died (13%). Failure (53.8% vs 56.6%), Stable (16.3% vs 10.8%) and Response (30% vs 32.5%) at 48 weeks did not differ between arms (As-Needed vs Immediate) among those with Week 48 data potential (N=163, p=0.91). In the final multivariate model female sex (OR 0.45; 95%CI 0.21, 0.96) and lower neutrophil count [OR 0.36; 95%CI 0.16, 0.79) were associated with reduced odds of treatment failure while low albumin (OR 4.48; 95%CI 2.09, 9.58) and Karnofsky score <90 (OR 2.34; 95%CI 1.12, 4.88) were associated with higher odds of treatment failure. Times to KS progression (p=0.021), KS-IRIS (p=0.003), and KS response (p=0.003) favored the Immediate arm. Mortality, adverse events, CD4+ T-cell changes and HIV RNA suppression were similar at 48 weeks.

Conclusions: In HIV-infected individuals initiating ART with mild-to-moderate KS in low- and middle income countries, the addition of immediate oral etoposide failed to provide a clinically meaningful benefit at 48 weeks compared to the addition of chemotherapy if needed in the event of disease progression. Early clinical benefits of etoposide, including decreased incidence of KS-IRIS, faster time to KS treatment response and longer time to disease progression, were not sustained through week 48. Mortality was high and additional research is needed to define the optimal approaches to the initial management of mild-to-moderate KS in resource-limited settings.

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P9. Projected Cancer Incidence and Burden in HIV-Infected Adults in the United States Through 2030

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Background: People living with HIV (PLWH) have an elevated risk of certain cancer types. With modern antiretroviral therapy, the longevity of PLWH is increasing, the population is aging, and cancer rates are changing in the United States (U.S.). Understanding the future cancer burden among PLWH will inform the prioritization of cancer prevention, early detection, and treatment efforts. Here, we projected cancer incidence rates (IRs) and burden (i.e., number of new cases) among HIV-infected adults in the U.S. through 2030.

Methods: Data from the National Cancer Institute's HIV/AIDS Cancer Match Study (2000-2012) were used to project cancer rates and the Centers for Disease Control and Prevention's HIV Optimization and Prevention Economics model was used to project HIV prevalence estimates. Cancer rates and burden were projected among HIV-infected adults in the U.S. during 2013-2030 by age group for AIDS-defining cancers (Kaposi sarcoma [KS], non-Hodgkin lymphoma [NHL] and cervical cancer), and certain non-AIDS-defining cancers (Hodgkin lymphoma and cancers of the anus, liver, lung, breast, colon and prostate). All other cancers were combined into one group.

Results: The proportion of PLWH in the U.S. aged ≥65 years is projected to increase from 7.5% in 2006 to 21.4% in 2030. Based on significant declines during 2000-12, age-specific cancer incidence rates are projected to decrease across age-groups for NHL, cervical cancer, lung cancer and other cancers combined, and in some age-groups for KS, Hodgkin lymphoma and colon cancer. Prostate cancer rates are projected to increase, and rates of the remaining cancer sites are projected to remain constant. The estimated total cancer burden in PLWH is expected to decrease from 8090 cases in 2010 (2740 AIDS-defining cancers, 5340 non-AIDS-defining cancers) to 6690 cases in 2030 (720 AIDS-defining cancers, 5990 non-AIDS-defining cancers). In 2010, NHL (n=1490), KS (n=1130) and lung cancer (n=820) were estimated to be the most common cancers. However, in 2030, the most common cancers expected among PLWH will be prostate (n=1590), lung (n=1030), liver (n=480) and anal cancers (n=450).

Conclusions: If current trends in cancer incidence, HIV transmission, and survival continue, notable shifts in the cancer burden among PLWH will occur, with prostate and lung cancers expected to emerge as the most commonly diagnosed cancers in PLWH by 2030. Cancer will remain an important co-morbidity among PLWH, and expanded access to HIV therapies, and cancer prevention, screening and treatment are needed.

P10. BK Polyomavirus, APOBEC3B, and Cancer: Molecular Judo Gone Awry?

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BK polyomavirus (BKV) causes nephropathy in kidney transplant recipients. The virus has also been implicated as a possible cause of bladder and kidney cancers. Two kidney transplant recipients who developed BKV nephropathy followed by renal carcinoma both showed a swarm of BKV sequence variants encoding non-silent mutations in surface loops of the viral major coat protein. The appearance and disappearance of these mutations over time suggests intra-patient evolution of the virus. Some of the observed mutations conferred resistance to antibody-mediated neutralization. The mutations also modified the spectrum of receptor glycans the virus engages during the infectious entry process. Nearly all observed mutations are consistent with DNA damage caused by APOBEC3B, an antiviral cytosine deaminase. This is intriguing in light of a recent report showing that BKV induces APOBEC3B expression. The results indicate that polyomaviruses can employ APOBEC3B to acquire beneficial site-specific mutations, conceivably with carcinogenic consequences for the host.

P11. PD-L1 Inhibition and the Evolving Management of Merkel Cell Carcinoma

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Background: Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer that is associated with integrated Merkel cell polyomavirus (MCPyV) in 80% of cases. MCC incidence and relative mortality is elevated in immunocompromised populations. Until recently, no durable treatment options were available for patients with metastatic MCC. As an immunogenic cancer, MCC was hypothesized to be a candidate for immunotherapy. Avelumab is a human anti–programmed death-ligand 1 (PD-L1) IgG1 monoclonal antibody that effectively blocks programmed cell death protein 1 (PD-1) signaling, induces antibody-dependent cell-mediated cytotoxicity (ADCC), and possess a tolerable safety profile.

Methods: Patients with chemotherapy-resistant metastatic MCC were enrolled in JAVELIN Merkel 200 (NCT02155647), a phase 2, prospective, open-label, single-arm, international trial. Patients were not selected for tumor PD-L1 expression or Merkel cell polyomavirus (MCPyV) status. Eligible patients received avelumab 10 mg/kg Q2W until confirmed progression, unacceptable toxicity, or withdrawal. Tumors were assessed every 6 weeks (RECIST v1.1) by an independent review committee. Adverse events (AEs) were assessed by NCI CTCAE v4.0.

Results: A total of 88 patients were followed for a minimum of 12 months (median follow-up = 16.4 months). The confirmed objective response rate was 33.0% (95% CI, 23.3%-43.8%), with 10 patients achieving a complete response (11.4%). An estimated 74% of responses lasted ≥1 year, and 72.4% of responses were ongoing at the data cutoff (September 3, 2016). The median duration of response (DOR) was not yet reached (95% CI, 18.0 months-not estimable). Estimated 1-year progression free survival (PFS) and overall survival (OS) rates (Kaplan-Meier estimates) were 30% (95% CI, 21%-41%) and 52% (95% CI, 41%-62%), respectively. Median OS was 12.9 months (95% CI, 7.5-not estimable). Subgroup analyses suggested a higher probability of response in patients who received fewer prior lines of chemotherapy. Nonetheless, durable responses occurred irrespective of baseline factors, including tumor PD-L1 expression and MCPyV status. Drug-related AEs were generally mild and manageable with no grade 4 or 5 events.

Conclusions: PD-L1 blockade with avelumab demonstrated durable responses and favorable survival outcomes in patients with chemotherapy-resistant metastatic MCC. The therapy was generally well tolerated. Based on these studies, in March 2017 the U.S. Food and Drug Administration granted avelumab accelerated approval for the treatment of metastatic MCC.

P12. Epstein-Barr Virus and Malaria Profiles in African Burkitt Lymphoma: What Can We Learn From Array-Based Studies?

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Background: Epstein-Barr virus (EBV) and *Plasmodium falciparum* malaria infections are ubiquitous in parts of Africa and are causally linked to endemic Burkitt lymphoma (eBL), the commonest childhood cancer in Africa. However, the precise etiologic mechanism is unclear, partly because there is limited understanding of anti-EBV and anti-malaria antibody responses in children at risk of eBL. Immune responses to a handful of anti-EBV or anti-malaria antibodies have been characterized, and significant findings demonstrated only for IgG antibody against the EBV viral capsid antigen (VCA) and the *Pf* malaria whole schizont antigen. A complete understanding of the joint humoral responses against EBV and malaria could shed light on etiologic mechanisms underpinning these associations and reveal insights with translational applications for prevention and treatment of eBL.

Methods: We probed pre-treatment sera from 150 pediatric BL cases aged 0-15 years and 150 age, sex, and calendar-year matched controls from the NCI Ghana Burkitt Study (1965-1994) using an EBV microarray to measure IgG and IgA antibody responses against 199 distinct sequences representing 86 EBV proteins. Analyses were restricted to IgG and IgA antibody responses with an intra-class correlation coefficient (ICC) >70% and coefficient of variation (CV) <30%, with Bonferroni correction. Analysis of correlations between anti-EBV and anti-malaria antibodies were evaluated in the controls using existing data on IgG seroreactivity against the (*Pf* histidine rich protein 2 (HRP-II) and blood-stage malaria vaccine candidate SERA5 (SE36), which were previuosly shown to have positive and inverse associations, respectively, with eBL.

Findings: The ICC/CV for the majority of EBV IgG (104/199) and IgA (108/199) markers on the EBV array were adequate. Levels of 31 IgG and 30 IgA anti-EBV antibodies were significantly different between eBL cases and age and sex-matched controls (P<0·00025); 28 of these markers showed concordant anti-EBV IgG and IgA responses. The odds ratios (OR) of association with eBL ranged from 2.5-31. For both IgG and IgA, the associations with eBL were weak to modest (OR= 2-5) for EBV VCA and EBV LMP-1. The associations were moderately strong (OR= 5-8) for EBV early protein BZLF1 (switches from latent infection to lytic infection) and very strong (OR=25-30) for BMRF1 (early antigen diffuse component, which is essential for lytic protein synthesis and lytic DNA replication, BHRF1 (which is a viral homolog of Bcl-2). More in-depth analyses are ongoing to characterize anti-EBV and anti-malaria humoral responses in this sample set.

Conclusions: Our study provides new epidemiological evidence of a broader repertoire of anti-EBV antibody responses associated with eBL using a novel EBV protein microarray to measure both IgG and IgA antibody responses. Ongoing analyses may shed new light on the interaction between anti-EBV and anti-malaria humoral responses in children at risk of eBL, clarify the etiologic mechanisms underpinning these associations, and suggest translational applications for prevention and treatment of eBL.

P13. KSHV and Co-infections

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Early epidemiological studies showed that prevalence of KSHV infection mirrors distribution of associated disease geographically and among AIDS risk groups. The high prevalence of KSHV infection in sub-Saharan Africa but not in populations of African descent in Europe or the Americas suggests that environmental co-factors may be important in KSHV transmission. Co-factors are also important in KS pathogenesis as most KSHV infected individuals will not develop disease. Chronic co-infections have the potential to affect both KSHV transmission and pathogenesis. The most important is HIV and evidence for its role in KS pathogenesis is substantial. Less is known about the role of HIV in KSHV transmission but studies suggest that HIV infection increases susceptibility to KSHV infection and also increases onward transmission. Case-control studies of KS in Uganda in the 1990s observed risk factors including contact with water, walking barefoot and owning pigs or goats suggestive of exposure to parasites[1, 2]. Our more recent KS case control study in Cameroon showed increased KS risk with walking barefoot and with not using insect nets[3]. In addition, our study of KSHV DNA detection in saliva and blood of Ugandan mothers and children showed an association with use of surface water[4]. More recently we have reported an association between KSHV prevalence and co-infection with malaria and hookworm in Ugandan mothers and children[5-7]. Our current studies in cohorts in Uganda and Kenya aim not only to further elucidate the associations observed between KSHV transmission and disease and parasitic co-infections but also to explore possible mechanisms. There are likely numerous other co-infections that impact KSHV biology and vice versa. EBV is another oncogenic gammaherpesvirus that shares many characteristics with KSHV and there is great potential for interaction between the two viruses. Both are shed in saliva and establish latent infections in B cells. There are an increasing number of studies examining the interaction between the two viruses in co-infected B cell lines *in vitro*. Our recent studies show that EBV is shed in saliva more frequently and at higher levels than KSHV, but subjects shedding high levels of KSHV often have no detectable EBV. This suggests that KSHV is able to interrupt EBV shedding possibly via a paracrine mechanism yet to be elucidated. Since malaria has long been recognized as a co-factor in EBV lymphomagenesis, the complexities of these multiple interactions will be challenging to unravel but such studies may yield rich rewards in terms of our understanding of viral oncology.

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ORAL PRESENTATIONS

O1. Development of an EBNA1 Inhibitor for the Treatment of HIV-Associated Epstein-Barr Virus-Driven Malignancies

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Background: HIV-infected individuals have twice the risk of developing cancer during their lifetimes as an uninfected person, despite the availability of cART. Epstein-Barr Virus (EBV)-associated cancers are among the most prevalent malignancies that occur in HIV$^+$ individuals. Currently, no pharmaceutical-based therapies exist that selectively target EBV-associated cancers. EBV, in its latent oncogenic form, is dependent on the continuous expression of Epstein-Barr Nuclear Antigen 1 (EBNA1), a multifunctional dimeric protein critical for viral genome replication, mitotic segregation, and viral gene expression. EBNA1 is unique with no structural analogs in the human proteome.

Methods: The aim of this program is to advance the development of a New Chemical Entity (NCE) for latent infection of EBV to treat EBV-associated cancer. We used structure-based drug design (70+ co-crystal structures) and medicinal chemistry Methods (2500+ compounds synthesized) to identify and develop a small molecule clinical candidate that selectively inhibits the DNA-binding activity of EBNA1 and inhibits EBV-associated tumor cell growth in four different mouse models of EBV-associated cancer.

Results: The clinical candidate inhibits EBNA1 function with nanomolar potency in biochemical assays and low micromolar activity in several cell-based assays. We demonstrate that EBNA1 inhibitors provide protection in 4 different xenograft models of EBV-driven tumor growth, including lymphoblastic B-cell lymphoma and patient-derived xenografts for nasopharyngeal carcinoma. Furthermore, RNA analysis experiments (by EBER-ISH and Nanostring-based technology) confirm in vivo target engagement by the elimination of EBV in treated tumor tissue. EBNA1 inhibitors are selective, showing little to no activity in an EBV-negative xenograft experiment. The clinical candidate has met industry-accepted criteria for drug suitability including in vitro ADME: physicochemical properties, metabolic stability, Cyp inhibition and induction, hERG, Ames genotoxicity and selectivity in broad-based screens. Pharmacokinetic studies indicate that the candidate is orally bioavailable, attaining high plasma levels with a relatively linear dose-exposure response in mouse, rat and dog. In 28-day repeat dose toxicity studies, we observe no toxicology findings that would preclude further development. The candidate exhibits a favorable predicted therapeutic index, possibly reflecting the lack of an endogenous target in uninfected cells. We have also performed salt selection, polymorph analysis and forced degradation studies and optimized the process chemistry for the synthesis of kilogram quantities of the API.

Conclusions: IND-enabling studies including safety pharmacology and toxicology and GMP manufacturing have begun with a projected IND filing in H1 2018. A first-in-human clinical trial could commence in 2018 depending on available funding.

O2. Tumor Epstein-Barr Virus Status Is Prognostic in Primary Effusion Lymphoma

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Background: Primary effusion lymphoma (PEL) is an aggressive HIV-associated B-cell non-Hodgkin lymphoma (NHL). Kaposi sarcoma-associated herpesvirus (KSHV) is the etiologic agent of PEL as well as Kaposi sarcoma (KS) and a plasmablastic form of multicentric Castleman disease (KSHV-MCD). In 70-90% of cases, PEL cells are co-infected with Epstein-Barr virus (EBV). With antiretroviral therapy (ART) and chemotherapy, median (med) overall survival (OS) is < 1 year. We previously showed PEL is associated with elevated interleukin (IL)-6 and that baseline immune factors including elevated IL-6, IgE and ferritin, are prognostic in PEL patients (pts) treated with curative intent. The role of EBV in PEL remains poorly understood. We evaluated the clinical characteristics and prognostic value of peripheral blood mononuclear cell (PBMC)-associated EBV viral load (VL) and tumor EBV status in pts with PEL.

Methods: We identified 20 patients diagnosed with PEL, including 19 who received ART and curative intent chemotherapy, as well as 19 KSHV-MCD and 28 HIV-associated lymphoma (HIV-L) pts. Tumor EBV status in PEL was evaluated by in situ hybridization against EBV-encoded small RNA (EBER). PBMC EBV and KSHV VL was evaluated by PCR for *pol* and *K6* respectively, normalized to *ERV3* (units, copies/10^6 PBMC). KSHV serostatus in HIV-L patients was determined by reactivity against K8.1 and/or LANA using a mulitplex assay. EBV VL in PEL, KSHV-MCD, and HIV-L were compared using two-tailed rank sum tests. Survival analyses evaluating cancer-specific mortality with Kaplan-Meier Methods and a two-sided log-rank test, as well as exploratory Cox modeling using backward selection, were performed.

Results: EBV VL in PEL (med=1,580; interquartile range (IQR)=35-4,333) was comparable to that in KSHV-MCD (med=488; IQR=1-1,692; p=0.09) and HIV-L (med 467; IQR=127-1592; p=0.25). KSHV VL in PEL (med=28,644; IQR=500-115,789) was comparable to KSHV-MCD (med=20,690; IQR=2,250-153,846; p=0.89), and elevated compared to HIV-L (med=0, p=<0.0001). 25% of HIV-L patients were KSHV seropositive, 6 of these 7 had a detectable but low KSHV VL (med=1; IQR=1-588). Med OS in 19 PEL pts who received chemotherapy was 22 months. 3-year cancer-specific survival was 47%. Med OS for EBER positive PEL was not reached, with 3-year OS of 64%. Med OS in EBER negative PEL was 10.4 months with no pts alive at 3 years (Figure 1, p=0.029 for comparison). Baseline EBV and KSHV VL were not prognostic (p=0.70, p=0.51). In Cox model analysis with backward elimination, EBER positivity was associated with a significantly decreased risk of death (HR=0.265; 95% CI: 0.076-0.931; p=0.038).

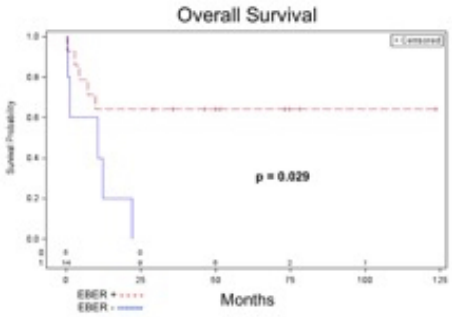

Figure 1. Cancer-specific survival in 19 patients with PEL (14 EBV positive and 5 EBV negative tumors) treated with ART and modified dose-adjusted EPOCH, including rituximab in 16 cases.

Conclusions: KSHV VL is useful in evaluating pts with suspected PEL. Neither baseline EBV nor KSHV VL are prognostic in PEL. With ART and chemotherapy, EBV-positive PEL has a significantly improved prognosis compared to EBV-negative PEL, with 64% probability of obtaining long-term remission.

O3. Cell Receptor Activation Triggers Caspase-Mediated Cleavage of PIAS1 to Facilitate Epstein-Barr Virus Lytic Replication

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Background: Epstein-Barr virus (EBV) in tumor cells is predominately in latent phase but the virus can undergo lytic reactivation in response to various stimuli. However, the cellular factors that control latency and lytic replication are poorly defined.

Methods: Using gene-knockout and reconstitution methods, we demonstrated that a cellular factor, PIAS1, restricts EBV lytic replication.

Results:
- We demonstrated that depletion of PIAS1 facilitates, while reconstitution of PIAS1 suppresses, EBV lytic reactivation.
- Strikingly, we showed that the cross-linking of B cell receptor (BCR), a physiologically relevant stimulus for EBV reactivation, triggers caspase-dependent cleavage of PIAS1.
- We demonstrated that caspase-3, -6 and -8 cleave PIAS1 at two evolutionarily conserved sites (D100 and D433) and that caspase inhibition abrogates EBV reactivation through preventing PIAS1 cleavage.
- We further demonstrated that a cleavage-resistant PIAS1 mutant strongly suppresses EBV replication upon BCR activation.
- Mechanistically, we showed that PIAS1 acts as a co-repressor for transcription factors critical for viral lytic gene expression and that caspase-mediated cleavage antagonizes the co-repressor function of PIAS1.

Conclusions: Our results establish PIAS1 as a critical regulator of EBV lytic replication and uncover a previously unappreciated mechanism by which EBV exploits apoptotic caspases to antagonize PIAS1-mediated restriction. These findings would have wide-ranging implications, especially in inspiring other researchers to further explore the emerging role of caspase activation and the subsequent cleavage of cellular or viral factors in the replication or reactivation of herpesviruses and, more broadly, other viruses.

O4. Anti-IL-15-mediated Depletion of NK Cells in Primary SIV Infection Does Not Alter SIV Replication but Accelerates Rhesus Rhadinovirus Pathogenesis

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Background: The common gamma-chain cytokine IL-15 plays an important role in enhancing the anti-viral effector activity of memory T and natural killer (NK) cells. However, IL-15 has also been implicated in driving the pathogenic hyperimmune activation that often characterizes progressive HIV/SIV infection. In nonhuman primates, IL-15 administration during primary SIV infection is associated with enhanced activation of $CD4^+$ memory T cells and higher post-peak virus replication set points. Thus, although IL-15 activity might provide benefit to an HIV/SIV infected host by supporting HIV/SIV-specific T and NK responses, it may also contribute to HIV/SIV pathogenesis and disease progression. In this study, we set out to determine the impact of IL-15 signaling blockade during primary SIVmac239 infection on SIV-specific immunity, virus replication kinetics and disease progression.

Methods: A total of 24 adult male rhesus macaques (RM), negative for MHC alleles associated with virological control (*Mamu* A*01/B*17/B*08) were selected and randomized into 3 groups of 8 RM each. Group 1 received 3 biweekly doses of a rhesusized anti-IL-15 monoclonal antibody (anti-IL-15 mAb) starting 6 weeks prior to SIV challenge. Group 2 received 3 biweekly doses of anti-IL-15 mAb starting 6 weeks before in addition to 4 biweekly doses after SIV challenge. Group 3 received a control-rhesusized monoclonal antibody with the same dosing schedule as Group 2.

Results: Anti-IL-15 mAb administration was efficient at neutralizing IL-15 signaling in vivo and caused a near complete depletion of NK cells in the blood and tissues. SIV-specific T cell responses, anti-SIV antibody titers and SIV replication kinetics were comparable between anti-IL-15 mAb treated animals vs. controls. Strikingly we observed a significantly higher proportion of anti-IL-15 mAb treated RM with rhesus rhadinovirus (RRV) reactivation (measured by RRV DNA in blood) as early as 6 weeks post-SIV infection. RRV is the simian homologue of the human Kaposi's sarcoma-associated herpesvirus and consequently, anti-IL-15 mAb treated RM had a higher incidence of hematological malignancies, including non-Hodgkins lymphoma at end-stage disease.

Conclusions: These data suggest that IL-15 activity may play a key role in mediating protection from RRV reactivation and tumor formation during progressive SIV infection either through the maintenance of NK cell homeostasis or by supporting T cell mediated immunity against RRV.

O5. Manipulation of the Host Iron Regulon by Kaposi Sarcoma Herpesvirus (KSHV)

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Iron is a critical element for the replication of diverse viruses but is also an important cofactor for the growth and proliferation of various cancers. KSHV-dependent neoplasms such as Kaposi sarcoma (KS) may therefore present an opportunity for which the manipulation of iron provides a two-pronged therapeutic approach. Further support for iron chelation as a treatment for KS comes from epidemiological data indicating that iron is a KS pathogenesis cofactor. Interestingly, infection-induced inflammation triggers the host acute phase response, which, among other things, alters iron homeostasis to limit iron availability during infection. It is therefore likely that KSHV faces a two-fold challenge; (a) virus-induced (e.g., vIL-6) inflammation reducing iron availability, and (b) "nutritional immunity" resulting from the host's own tightly regulated iron levels. To determine if KSHV manipulates the host iron regulon to facilitate infection and pathogenesis, we examined a panel of host iron-related gene products for changes in their expression after latent KSHV infection of lymphatic endothelial cells (LEC). We observed that infection of LEC with both BCBL- and recombinant BAC16-derived KSHV impacted the expression of nearly all the host iron genes tested. Based on results from immunoblot analyses, we categorized these changes based on direction and amplitude. Latent KSHV infection led to significant upregulation of the membrane associated ferric reductase STEAP3 and the iron transporters TRPML1 and ZIP14. The transferrin receptor 1 (TFRC), iron regulatory proteins 1 and 2 (IRP1/2), mitochondrial heme exporter FLVCR, HFE, and ferroportin (FPN) were upregulated to a lesser degree. With the exception of the divalent metal transporter DMT1, which was downregulated by the virus, these data suggest that KSHV-infected EC display an iron-acquisition phenotype. We next tested the expression of the iron gene panel for KSHV-dependent changes in the presence of excess iron or following iron depletion. While host iron gene expression changed predictably with respect to iron availability in mock-infected LEC, KSHV retained its ability to manipulate the iron regulon. We are currently examining the iron regulon in additional EC types and optimizing conditions to facilitate the testing of modern iron chelators with improved solubility profiles as potential therapeutic agents for KSHV-associated malignancy.

O6. Modulation of Cholesterol Pathway in KSHV Infection

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Background: Oxysterols are cholesterol derivatives emerging as a new class of signaling molecules. 25-hydroxycholesterol (25HC) is broadly antiviral (HIV-1, HCV, MHV68, among others) and CH25H (cholesterol-25-hydroxylase) converts cholesterol to 25HC and is interferon-inducible. Here, we hypothesize that KSHV counteracts this antiviral response by modulating the mevalonate/cholesterol pathway.

Methods: We utilize primary human vein endothelial cells (HUVEC) and infected iSLK (epithelial cell line) for these studies. To assay cholesterol, we use a modified Bligh-Dyer extraction method and directly measure cholesterol using the Amplex Red Cholesterol kit. Gene expression changes were measured using quantitative PCR and immunoblotting using the LI-COR system.

Results: From various screens, we found that KSHV viral miRNAs target enzymes in the mevalonate/cholesterol pathway. HMGCS1 (3-hydroxy-3-methylglutaryl-CoA synthase1), HMGCR (3-hydroxy-3-methylglutaryl-CoA reductase, rate-limiting step), and FDFT1 (farnesyl-diphosphate farnesyltransferase1, committed step in cholesterol branch) are repressed by multiple KSHV miRNAs. We transfected viral miRNA mimics in primary endothelial cells (HUVEC) and found cholesterol was reduced. However, depletion of HMGCS1 is not sufficient to decrease cholesterol. This suggests that multiple targets are needed to perturb this tightly-regulated pathway. We found that cholesterol levels were decreased in *de novo* infected HUVEC cells after 7 days. To confirm the role of viral miRNAs, we found that a mutant form of KSHV lacking 10 of the 12 miRNA genes had increased cholesterol compared to wild type infections. Since we hypothesized that KSHV is downregulating cholesterol to suppress the antiviral response by 25HC, we measured CH25H gene expression in *de novo* infection vs. long term infection. Consistently, CH25H mRNA increased in *de novo* infected HUVEC, but strongly suppressed in long-term latently infected cell lines. To confirm that 25HC is antiviral against KSHV, we added exogenous 25HC prior to *de novo* infection. We found that infection efficiency (as measured by latent gene LANA and lytic gene RTA expression) is suppressed in a dose-dependent manner by 25HC, while LANA promoter expression is unaffected. To further elucidate the mechanism of 25HC antiviral activity, we assayed different steps of the viral life cycle. Surprisingly, viral entry was not strongly inhibited by 25HC and no significant changes were detected in nuclear entry. We did find that 25HC treatment upregulated IL-6 expression by 20-fold and this activation of IL-6 was suppressed in infected cells. Current efforts are underway to understand how 25HC induces the innate immune response to counteract KSHV viral infection.

Conclusions: KSHV viral miRNAs target enzymes in the mevalonate pathway to modulate cholesterol in infected cells. This repression of cholesterol levels is useful to inhibit production of 25HC, which blocks KSHV infection at a post-entry step.

O7. Portable Nucleic Acid Amplification Testing as a Means for Diagnosis of Kaposi Sarcoma in Africa

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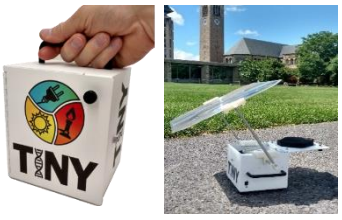
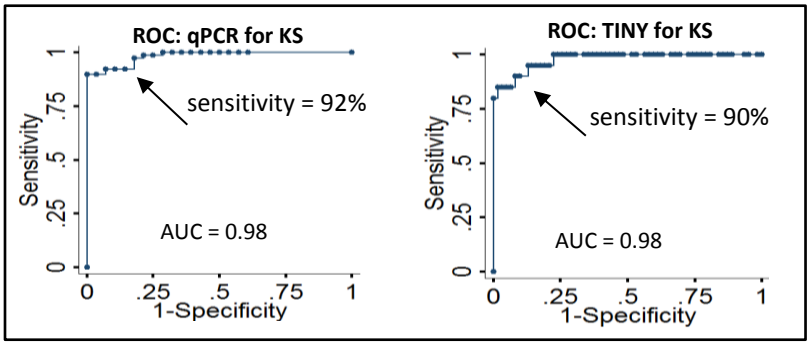
Background: Both the need for and problems associated with histopathologic diagnostic testing for Kaposi sarcoma (KS) in sub-Saharan Africa have been well chronicled. Accurate and timely pathology is needed both to facilitate early KS diagnosis — arguably the most compelling clinical issue related to KS in Africa — and to ensure that potentially toxic chemotherapy is only given to those who need it. Unfortunately, achieving optimal pathology services has been long limited by lack of personnel and equipment. Even where pathology is available, accuracy of KS diagnosis has often been sub-optimal. As an alternative to pathology, we hypothesized that quantification of KSHV DNA content in skin lesions can diagnose KS and that a low-cost portable nucleic acid amplification-based device can be developed.

Methods: We evaluated a consecutive sample of adults with clinically suspected KS referred to a skin biopsy service in Kampala, Uganda. Histopathologic evaluation of the 4 mm skin punch biopsies, including anti-LANA staining, was performed in Africa and in the US. Quantitative PCR (qPCR) for KSHV ORF 26, from extracted DNA from a portion of the biopsy, was performed under conventional controlled conditions. In addition, we developed a lightweight (1.1 kg) low-cost device called TINY (Tiny Isothermal Nucleic acid quantification system) that can perform loop-mediated isothermal amplification (LAMP) for ORF 26. Designed and produced at Cornell-Engineering, TINY runs on a variety of power sources, including solar. Using histopathology performed in the US as the gold standard, we determined the sensitivity & specificity of both qPCR and LAMP (as performed by TINY) for KS. Receiver operating characteristic (ROC) curves were used to assess various quantitative cutpoints and derive area under the curve (AUC).



TINY powered by sunlight

Results: We tested 116 adults with pigmented skin lesions, suspected by their primary care providers to be KS, who were referred for a skin biopsy. The median age was 34 years, 38% were women, and 98%were HIV-infected (of whom 81% were on antiretroviral therapy); 17% of lesions were macules, 75% plaques, and 8% nodules. Pathologic testing revealed that 79 were KS, 28 not KS and 9 were indeterminate. Using the 79 KS and 28 non-KS as gold standards, the AUC for qPCR for KS diagnosis was 0.98, and at the optimal cutpoint (6941 KSHV copies per 100,000 human cells), sensitivity was 92% and specificity 93%, with 93% of subjects correctly classified. Of the initial 82 specimens tested by TINY, sensitivity & specificity were comparable to qPCR (Figure).



Conclusions: In the context of East Africa, where KSHV infection is endemic, quantification of KSHV DNA content in skin lesions by PCR has both high sensitivity and specificity for the diagnosis of KS when compared to gold standard pathology. We have developed a portable low-cost device, which can run on multiple energy sources (including sunlight), that can perform isothermal nucleic acid amplification for KSHV that closely parallels the performance of qPCR performed in controlled laboratory conditions. This proof of concept and this prototype device are promising leads in the development of a point-of-care nucleic acid amplification-based diagnostic test for KS.

O8. Kaposi Sarcoma-Associated Herpesvirus (KSHV) Seroprevalence and Antibody Levels in Relation to Haemoglobin and Malaria Among Individuals From Rural Uganda[1]

Angela Nalwoga[1,2], Stephen Cose[1,2], Stephen Nash[2], Wendell Miley[3], Gershim Asiki[1], Sylvia Kushemererwa[1], Nazzarena Labo[3], Denise Whitby[3], Robert Newton[1,4]

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Kaposi sarcoma-associated herpesvirus (KSHV) is prevalent in rural Uganda, with a seroprevalence of over 90% in adults. Risk factors for high transmission of KSHV in rural areas leading to this high prevalence have not been well investigated. We examined the association between KSHV seroprevalence and antibody levels in relation to several risk factors in adults and children, including haemoglobin (Hb) levels, malaria parasitemia and socio-demographic factors in a rural Ugandan cohort.

KSHV seroprevalence was defined as seropositivity to either K8.1 or ORF73. KSHV IgG antibody responses to K8.1 (lytic) and ORF73 (latent) antigens were measured using ELISA among people from two consecutive General Population Cohort (GPC) surveys. Samples were collected from adults in 2014 and 2015 and from children (aged 1 - 17) in 2016. Malaria parasitemia was measured using Rapid Diagnostic Tests (RDTs). Hb levels were measured from capillary blood using the HemoCue Hb system. Socio-demographic data were collected by questionnaire. The association between KSHV seroprevalence and antibody levels with malaria parasitemia, Hb levels and socio-demographic factors was determined using regression analysis.

Among 4134 children, the mean age was 9 years, 50% were males, HIV prevalence was 1% and 18% had malaria parasitemia. Among 3288 adults, the mean age was 40 and the oldest person was 103, 39% were males and HIV prevalence was 9%. KSHV seroprevalence increased with age from 28% among 1 to 3 year olds to above 88% among adults aged 18 years and above. KSHV seropositive children aged 1 to 17 years were more likely to have malaria parasitemia than seronegative children (adjusted Odds Ratio (aOR) = 2.12, $p<0.0001$). Additionally, every unit (0.1g/dL) increase in Hb level was associated with a 7% reduced risk of being KSHV seropositive (aOR=0.93, $p=0.005$). Among adults, every unit increase in Hb levels was associated with reduced antibody levels to ORF73 (measured as optical density); the strength of the association was highest in the older age groups (adjusted regression coefficient of -0.20, p value<0.0001 in the 53 to 103 age group). A few other factors examined had an effect on seroprevalence of KSHV including age and HIV status.

KSHV seroprevalence is high in rural Uganda, there is an association between KSHV seroprevalence and malaria infection, even after adjusting for Hb levels. The association between KSHV seroprevalence and Hb levels was substantially reduced after adjustment for malaria, suggesting that the association with malaria cannot be explained by anaemia alone and merits further study.

[1]Travel Awardee

O9. T-cell Receptor Sequencing of Tumor-Infiltrating Lymphocytes in Kaposi Sarcoma Tumors Identifies Candidate Tumor-Reactive T-cell Responses

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Background: Kaposi sarcoma (KS) development is strongly associated with immune dysfunction in the context of HIV infection, but little is known about T-lymphocyte responses against KS tumor cells or human herpesvirus-8 (HHV-8), the viral cause of KS. A subset of patients with HIV-associated KS improve with initiation of antiretroviral therapy (ART) and restoration of immune function, suggesting that the adaptive immune system plays a role in mediating KS tumor regression. We hypothesize that superior response and survival in KS will be associated with the activation and expansion of tumor-reactive T-cells in KS tumors among patients treated with ART and chemotherapy. By comparing the composition and dynamics of the T-cell repertoire of tumor-infiltrating lymphocytes (TIL) in KS tumor samples from patients with and without favorable response to therapy, we aim to identify TIL characteristics associated with tumor regression and to identify the unique T-cell targets of that response. METHODS: High-throughput sequencing of the T-cell receptor β chain (TRB) locus was performed in TIL from 1-2 pre-treatment and 1-4 post-treatment KS tumors and in corresponding normal skin samples, which were obtained from HIV-infected adults with KS receiving care at the Uganda Cancer Institute in Kampala, Uganda. We compared the TRB repertoire observed in serially-collected tumors and in the corresponding normal skin samples to identify TRB sequences carried in candidate tumor-reactive T cells.

Results: TRB sequencing has been performed to date on 94 KS tumors and 23 corresponding normal skin samples obtained from 36 HIV-infected adults with KS who collectively demonstrated a range of treatment responses. Unique populations of T cells were identified in multiple pre- and post-treatment tumors in all subjects; however, many of these T-cell populations were not observed in the corresponding normal skin sample, suggesting the presence of KS-specific T cell responses. In three subjects who achieved durable complete response to treatment, response was associated with significant expansion in post-treatment tumor samples of a small number of T cell clones. One of these clones carried a TRB sequence of a previously reported CD8+ EBV-associated TRB, representing a “public” T-cell response shared by multiple individuals. Novel TRB sequences were also observed in multiple KS tumors from 2 or more subjects sharing specific MHC alleles. Based on sequencing to date, a subset of 9 subjects who share specific HLA-A alleles also share at least 5 candidate public tumor reactive TCRs, and a second cluster of 3 subjects share at least 3 candidate public TCRs. We compared these sequences to a library of TRB sequences derived from over 1000 individuals with a range of solid tumor and blood cancers, and found that several of these sequences are only identified in our in cohort of KS patients from Uganda. These novel sequences likely define a KS-specific T-cell response. TRB sequencing of additional KS tumors and normal skin samples is ongoing and will be presented.

Conclusions: Our results demonstrate the existence of putative KS- or HHV-8-specific T cell subsets within KS TIL that are (1) associated with favorable tumor response to therapy, and (2) identified by specific TRB sequences that are shared between multiple patients who share 1 or more HLA alleles. These data support the existence of public T-cell responses in KS TIL, which could have significant therapeutic value. Improved understanding of how cellular immune responses are associated with control of HHV-8 and KS tumor regression will provide important insights into KS biology, and may ultimately enhance KS staging approaches and lay the foundation for effective precision immunotherapy for KS.

O10. Exploring the Function and Mechanism of Pomalidomide-Induced Increases in Immune Surface Markers in Primary Effusion Lymphoma Cells

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Background: Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative agent of Kaposi sarcoma and two B-cell lymphomas, multicentric Castleman's disease and primary effusion lymphoma (PEL). Our group has recently shown that pomalidomide is clinically active in Kaposi sarcoma. Recently, our group demonstrated that pomalidomide can restore the surface expression of natural killer (NK) ligands ICAM-1 and B7-2 in latent PEL cells as well as increase MHC class I expression in lytic PEL cells. Here, we demonstrate that restoration of these markers leads to increased PEL cell killing by NK cells and investigate the mechanism by which pomalidomide restores surface expression markers.

Methods: KSHV-positive PEL lines, BCBL-1 and JSC-1, were treated with pomalidomide and later analyzed for surface expression markers by FACS. In addition, these cells were analyzed for NK-mediated cytotoxicity using YTS NK cells. We also developed a BCBL-1 cell line that acquired resistance to the cytotoxic effects of pomalidomide and evaluated the ability of pomalidomide to affect surface marker expression in these cells.

Results: Pomalidomide at 1 μM consistently restored ICAM-1 and B7-2 expression in BCBL-1 and JSC-1 cells. This led to an increased susceptibility of BCBL-1 cells to cell killing by YTS NK cells. JSC-1 cells were somewhat resistant to YTS cell killing, yet pomalidomide treatment slightly increased NK killing of JSC-1 cells. In order to better understand the mechanism by which pomalidomide affects these immune surface expression markers, a BCBL-1 cell line resistant to pomalidomide-induced killing at up to 10 μM was generated. These cells showed a more than 90% decrease in cereblon, an E3 ubiquitin ligase that is the protein target for pomalidomide. Examination of these cells by FACS demonstrated that the expression levels of the NK surface markers remained low and also no longer increased following pomalidomide treatment. This data suggests that upregulation of the NK surface markers, like the drug's cytotoxic effects, is likely occurring through cereblon. Effects downstream of the pomalidomide/cereblon interaction are currently being explored as possible mechanisms for restoration of these surface markers.

Conclusions: These data show that pomalidomide not only restores NK immune surface expression ligands in PEL cells but this also leads to increased NK killing by YTS NK cells. Furthermore, the data suggest that pomalidomide binding to cereblon is involved in the restoration of these NK ligands. We are currently investigating the downstream effects of the pomalidomide/cereblon interaction which result in MHC class I and NK surface marker restoration. By restoring NK ligand expression, pomalidomide may enable infected cells to be recognized and destroyed by NK cells and may provide an impetus for its use as a potential treatment for PEL or other KSHV-related cancers.

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O11. AMC-070: Lenalidomide Is Safe and Effective in AIDS-Associated Kaposi Sarcoma

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Background: Kaposi sarcoma (KS), an endothelial cell tumor associated with human-herpes virus-8 (HHV-8), remains among the most common malignancies occurring with HIV infection (AIDS-KS). When immunosuppression is reversed with antiretroviral therapy (ART), KS lesions often regress, highlighting the role of immunosurveillance. However, many patients treated with ART develop or have persistent KS and treatment with conventional anticancer therapy is typically insufficient to eradicate disease. Lenalidomide is an IMiD compound with potent anti-inflammatory, anti-angiogenic, and immunomodulatory properties, suggesting this agent would be active in treatment of AIDS-KS. This is a multicenter, phase I/II open label study in AIDS-KS patients with the primary objectives of determining the maximum tolerated dose (MTD) and clinical response rates for lenalidomide. Secondary objectives included estimating time to response and progression, and correlating response with the impact of lenalidomide on the following: T-lymphocyte subsets, NK cell function and number, HIV and HHV-8 copy number, as well as HHV-8 gene expression in KS tumor biopsies.

Methods: A phase I 3+3 design was used to identify the MTD to be used in the phase II portion. Phase I evaluated 4 pre-specified dose levels of lenalidomide (10, 15, 20 or 25 mg) taken orally daily on days 1-21 of a 28-day cycle. Subjects with at least partial response (PR) after cycle 6 were allowed to continue therapy up to a total of 12 cycles. Otherwise, subjects were to receive a maximum of 6 cycles. Key eligibility requirements were: biopsy-proven KS (either newly diagnosed or previously treated, but not warranting frontline chemotherapy); age $\geq$18 years; serologically documented HIV treated on a stable ART regimen $\geq$12 weeks with CD4 count >50/mm^3 and viral load <2,000 copies/ml; ECOG performance status <3; and adequate hematologic, hepatic and renal function.

Results: Thirty-eight subjects were enrolled from 14 AMC sites, 15 in phase I and 23 in phase II. All were male and the majority (68%) were Caucasian. The mean age of the participants was 47 years. Median baseline values included CD4 count 411 cells/mm^3 (range 122-799) and HIV viral load 44 (range <20-707). Nearly 76% of patients had received prior therapy for KS. MTD was not reached, as no DLTs occurred in phase I; the 25 mg dose level was chosen for phase II. The most frequently reported adverse events associated with lenalidomide across both phase I and II were neutropenia, fatigue, leukopenia and diarrhea. Four serious adverse events were considered at least possibly related: 1 moderate facial nerve disorder, 1 severe hypotension, and 2 severe lung infections. Of the 23 patients in the phase II portion, 19 were evaluable for response with 13 completing the maximum of 12 cycles, 3 discontinuing due to disease progression, and 2 due to adverse events. The overall and partial response rates were 58% [CI: 34-80%] with an additional 32% classified as stable disease for an overall disease control rate of 90%. The median time to response was 12.0 weeks [CI: 8-23]. Considering the additional 5 evaluable subjects treated at 25 mg level from phase I, the overall phase I+II PR rate at 25 mg level was 63% (CI: 41-81%). No responding subjects experienced progression of disease during follow-up (mean duration). No significant changes in T cell subsets or HIV viral copy numbers were found. Clinical response was associated with loss of HHV-8 transcription as expected. Assessment of the impact on NK cells & cytokines is ongoing and will be updated at the meeting.

Conclusions: Lenalidomide is active in a dose-dependent manner for AIDS-KS. The most common adverse events were manageable and consistent with known risks of lenalidomide. With 63% partial response rate and <10% discontinuation due to adverse events, the response and tolerability to lenalidomide found in this study compare favorably to other oral agents evaluated in KS.

O12. Cisplatin and Radiation Therapy in HIV-infected Women With Locally Advanced Cervical Cancer in Sub-Saharan Africa (AMC-081)

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Objectives: Numerous trials have shown improved survival when cisplatin was added to radiation therapy (RT) in women with locally advanced cervical cancer (LACC). None of these trials included HIV-infected women, for whom there was concern about treatment tolerance. This is a particular concern in SSA, where comorbidities are common. Our primary objective was to determine the feasibility and toxicity of administering chemoradiotherapy to HIV-infected women with LACC receiving concomitant antiretroviral therapy (ART).

Methods: HIV-infected women with LACC were enrolled in this prospective trial. Planned therapy included external beam RT (EBRT) and brachytherapy with curative intent at standard doses together with weekly cisplatin, 40mg/m^2, during EBRT and prescribed ART. The protocol allowed for dose delays and dose reductions of cisplatin.

Results: 41 women with LACC, mean age (SD) 44.2 (5.6) years, were enrolled in Harare, Zimbabwe (n=26) and Johannesburg, South Africa (n=15); 39 initiated treatment and were evaluable. FIGO stages were: IIA (1), IIB (29), IIIA (1), IIIB (10). Median CD4 counts and HIV viral load were 427 (range, 139–1204) and < 20 (range <20- 39900), respectively. Thirty seven of 39 women (95%) completed treatment per protocol, which in some cases required dose reductions or doses eliminated. A total of 228 cycles of chemotherapy were administered, most at the full dose (Table 1). Of the 36 participants who started at 40 mg/m^2, more than half were able to tolerate 4 or more doses (Table 2). GCSF was administered at the investigator's preference to 13 women. Two women with persistent hematologic toxicity did not complete treatment as per protocol.

Conclusions: Concomitant chemoradiotherapy in HIV-infected women with LACC on ART is well tolerated at standard doses. Dose delays and reductions were similar to those typically seen in HIV-uninfected women with LACC. Women who completed therapy continue to be followed for survival and correlative endpoints.

Table 1: Total cisplatin cycles given at full-prescribed dose for the 36 patients who started at 40 mg/m^2

# Cisplatin cycles given at full dose (40 mg/m^2)	N (% number of patients)
5-6	15 (42)
4	5 (14)
3	8 (22)
1-2	8 (22)

Table 2: Total cisplatin cycles completed for 39* patients undergoing concomitant chemo/EBRT

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cisplatin						
No dose modifications	39 (100)	30 (77)	31 (79)	24 (62)	17 (44)	13 (33)
Dose delayed	0	6 (15)	1 (3)	0	2 (5)	0
Dose reduced	0	2 (5)	7 (18)	12 (31)	11 (28)	14 (36)
Delayed & reduced	0	1 (3)	0	2 (5)	3 (8)	3 (8)
Drug discontinued/not administered	0	0	0	1(3)	6 (15)	9 (23)

*includes the 3 women starting at lower dose cisplatin

O13. Extracellular Vesicles Derived From HIV-Infected T Cells Promote Progression of Non-AIDS-Defining Cancers

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Background: Cancer is a major cause of mortality and morbidity in AIDS patients and in chronically HIV-infected people. In the era of antiretroviral therapy (ART), AIDS-defining cancers, including Kaposi's sarcoma, non-Hodgkin lymphoma and cervical cancer, have been dramatically reduced, while the incidence of non-AIDS-defining cancers (NADCs), such as head and neck squamous cell carcinoma (HNSCC) and lung cancer, has been increased. However, the mechanism underlying HIV-infected cells and the development and progression of NADCs remains largely unknown.

Methods: Extracellular vesicles (EVs) were isolated from culture supernatants of HIV-1-infected J1.1 and control Jurkat cells, plasma of HIV-positive individuals and sera of HIV-transgenic mice using the filtration/ultracentrifugation method. EVs were characterized by electron microscopy, immunoblotting with exosome markers CD63, CD9 and CD81 and acetylcholinesterase activities. HNSCC, non-small cell lung cancer (NSCLC) and mouse lung cancer cells were treated with EVs for cancer cell proliferation, migration, and invasion assays and EGFR/TLR3 signaling. The HIV trans-activation response (TAR) element RNA (TAR RNA) in EVs was detected using quantitative RT-PCR.

Results: HIV-positive and -negative T cells released EVs, which were enriched with exosomes, into culture media. EVs purified from HIV-infected T cells, but not those from control T cells, significantly stimulated proliferation, migration, and invasion of human HNSCC, NSCLC and murine lung cancer cells in vitro and growth of HNSCC xenografts in nude mice in vivo. EVs purified from plasma of HIV-positive individuals also induced HNSCC cell proliferation and migration. Serum EVs isolated from HIV-transgenic mice, but not those from normal controls, triggered human NSCLC cell proliferation and migration. Latently and actively HIV-infected T cells EVs promoted cancer cell growth at the same level. Cetuximab, an FDA approved monoclonal antibody to epidermal growth factor receptor (EGFR) for HNSCC and lung cancer therapy, blocked the tumor-promoting effects of HIV-infected T-cell EVs. HIV-infected T-cell EVs induced phosphorylation of the MAP kinase ERK1/2 through interaction with EGFR and the Toll-like Receptor 3 (TLR3) without inducing canonical phosphorylation of EGFR. However, EVs derived from cancer cell cultures were unable to induce HIV-1 transcription in the HIV activation reporter cell line. The TAR RNA, which exists in vast excess of any other HIV RNAs in EVs from HIV-infected T cells, enhanced cancer cell proliferation and stimulated expression of interferon-stimulated *IFIT1* and *IFNB* and the EGF-inducible human beta-defensin-3 (hBD-3) genes. In addition, The TAR RNA mutant with nucleotide replacements in the loop/bulge region failed to induce gene expression. Moreover, co-transfection of the TAR RNA aptamer R06 blocked induction of gene expression induced by the HIV TAR RNA.

Conclusions: HIV-infected T cells release EVs to promote growth and progression of NADCs through interaction with EGFR and TLR3. The HIV TAR RNA in HIV-infected T-cell EVs is critical for the tumor-promoting effects of HIV-infected T-cell EVs. Controlling biogenesis and release of the EVs and direct targeting of the TAR RNA may serve as an adjuvant for prevention and treatment of cancers in the HIV-infected population.

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O14. Elevated Risk of *First* and *Second* Primary Cancers Among People With HIV

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Background: HIV infection puts individuals at a higher risk of many *first* primary cancers relative to the general population. The use of antiretroviral therapy (ART) has led to a dramatic reduction in HIV-related mortality, increasing life expectancy in this population. However, ART does not fully restore health and, despite declines in the rates of Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL), cancer incidence remains elevated above population rates even in the era of effective ART. The combination of older age, immune perturbation, and prolonged exposure to carcinogens and oncogenic viral infections puts individuals treated with ART at a heightened risk of cancer. While the risks of *first* primary malignancies in people with HIV have been carefully studied, there is little information regarding risks of *second* primary malignancies. In this study, we aimed to determine which cancers are in excess as a *second* primary malignancy and if they differ from those in excess as a *first* primary malignancy.

Methods: This retrospective cohort study computer-linked the San Francisco HIV/AIDS surveillance registry data for adults diagnosed with HIV/AIDS from 1990–2010 with the California Cancer Registry data for the years 1985–2013 to identify adults (ages 16 and older) with primary cancers. The cancer registry provided data on cancer incidence and sequence (the order in which the cancers were diagnosed) as well as tumor type and behavior. Year at cancer diagnosis, age at cancer diagnosis, race, and sex-adjusted Standardized Incidence Ratios (SIRs) and Poisson 95% Confidence Intervals (CIs) were calculated using Surveillance Epidemiology and End Results (SEER) population data as the reference group. When calculating person-years at risk for the people in the HIV registry, we defined time zero as five years before the initial AIDS diagnosis or date of HIV diagnosis (whichever came first).

Results: Among the 22,623 adults with HIV, we identified 4,144 *first* primary cancers and 372 *second* primary cancers that occurred in 1985-2013. The majority of the 22,623 adults in the HIV/AIDS registry were male (94%), ages 25-44 at diagnosis (73%), white (63%), and reported men who have sex with men (MSM) as their risk group (70%). The *first* primary cancers were significantly elevated for all three AIDS-defining cancers: KS (SIR=126.9 CI=121.4-132.3), NHL (SIR=17.2 CI=16.1-18.4), and cervical cancer (SIR=8.0 CI=4.1-11.9). Significantly elevated SIRs were observed for the following *first* primary non-AIDS defining cancers: anal (SIR=46.7 CI=39.7-53.6), vulvar (SIR=13.3 CI=6.1-20.6), Hodgkin lymphoma (SIR=10.4 CI=8.4-12.5), eye and orbit (SIR=4.2 CI=1. 5-6.9), lip (SIR=3.8 CI=1.3-6.2), penile (SIR=3.7 CI=1.4-6.1), liver (SIR=3.0 CI=2.3-3.7), testicular (SIR=2.0 CI=1.4-2.6), tongue (SIR=1.9 CI=1.1-2.7) and lung (SIR=1.3 CI=1.1-1.6). Among all *second* primary cancers, the risks were significantly elevated for KS (SIR=28.0 CI=20.2-35.9), anal (SIR=17.0 CI=10.2-23.8), NHL (SIR=11.1 CI=9.3-12.8), Hodgkin lymphoma (SIR=5.4 CI=1.1-9.7), and liver (SIR=3.6 CI=1.4-5.8). Significantly lower *first* primary cancer SIRs were observed for pancreas (SIR=0.63 CI=0.29-0.97), colon (SIR=0.56 CI=0.37-0.76), and prostate (SIR=0.56 CI=0.46-0.66) and significantly lower *second* primary cancer SIRs were observed for prostate (SIR=0.56 CI=0.23-0.89) and kidney (SIR=0.43 CI=0.01-0.86).

Conclusions: This is one of the first studies to distinguish the risk of *first* versus *second* primary cancer among people living with HIV. While the types of cancers observed in excess as *second* primaries were similar to those as *first* primaries, the risk of certain *second* primary cancers were three or more times higher in people with HIV compared to the general population. Thus, cancer prevention, screening and treatment remain important considerations for people who survive a *first* primary cancer and are living and aging with HIV.

O15. Lung Cancer Mortality Among People Living With HIV in the United States: Impact of Smoking and Smoking Cessation

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Introduction: People living with HIV (PLWH) in the US face a high risk of lung cancer, both because >40% of PLWH smoke cigarettes and because HIV is an independent risk factor for lung cancer. We sought to project the cumulative lung cancer mortality by smoking exposure, and the number of lung cancer deaths expected, among PLWH in care in the US.

Methods: We used a validated Monte Carlo microsimulation model of HIV disease and treatment to project cumulative lung cancer mortality by age 80 among PLWH in care in the US according to age, sex, and smoking exposure, combining smoking status (current, former, or never) and intensity (heavy, moderate, or light, based on cigarettes per day). We stratified reported mortality rates attributable to lung cancer and to other non-AIDS-related causes by smoking exposure, and we accounted for an HIV-conferred independent risk of lung cancer (rate ratio 1.7, versus HIV-uninfected people). Lung cancer mortality risk ratios (versus never smokers) for male/female current moderate smokers were 23.6/24.2, and for those who quit at age 40 were 4.3/4.5. In sensitivity analysis, we accounted for non-adherence to antiretroviral therapy (ART), and for a range of HIV-conferred risks of death from lung cancer and from other non-AIDS-related diseases (e.g., cardiovascular disease). Additionally, we estimated the number of lung cancer deaths by age 80 if smoking habits did not change among PLWH aged 20-64 in care in the US (accounting for reported rates of non-adherence to ART).

Results: Among 40 year-old men with HIV, estimated cumulative lung cancer mortality for heavy/moderate/light smokers who continued to smoke was 28.9%/23.0%/18.8%, for those who quit smoking at age 40 was 7.9%/6.1%/4.3%, and for never smokers was 1.6%. Among women, the corresponding mortality for current smokers was 27.8%/20.9%/16.6%, for former smokers was 7.5%/5.2%/3.7%, and for never smokers was 1.2%. ART-adherent individuals who continued to smoke were 6-13 times more likely to die from lung cancer than from traditional AIDS-related causes, depending on sex and smoking intensity. For 40 year-old ART-adherent men who were current moderate smokers, the combined cumulative mortality from lung cancer and other non-AIDS-related causes – both of which were increased by smoking – was approximately 35 times that from AIDS-related causes; for women, it was approximately 27 times higher. Due to greater AIDS-related mortality risks, individuals with incomplete ART adherence had higher overall mortality but lower lung cancer mortality. Applying model projections to the ~644,200 PLWH aged 20-64 in care in the US (both smokers and non-smokers), 59,900 (9.3%) are expected to die from lung cancer if smoking habits do not change.

Conclusion: PLWH who adhere to ART but smoke are substantially more likely to die from lung cancer than from AIDS-related causes. Even when accounting for non-adherence to ART, nearly 1 in 10 PLWH initially linked to care in the US (combining both smokers and non-smokers) are expected to die from lung cancer if smoking habits do not change. Smoking cessation should be a priority in the care of PLWH.

O16. Prevention and Early Detection of Cervical Cancer in Africa Through Community-Based Self-Administered Screening and Mobile Treatment Provision

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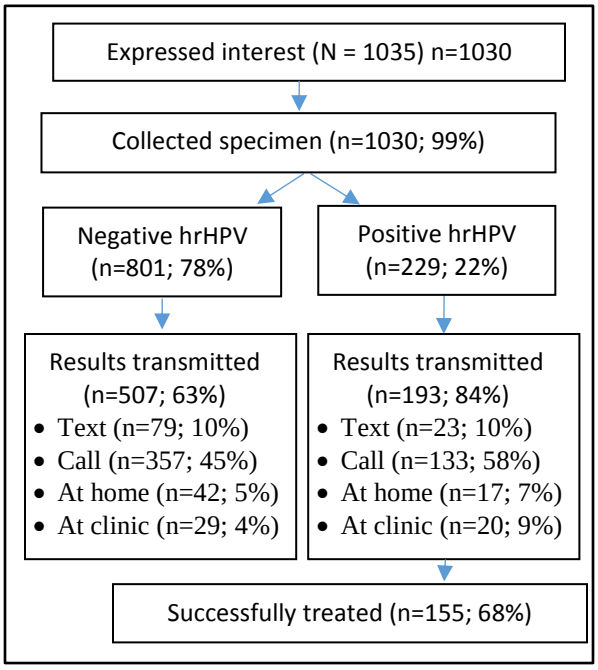
Background: Sub-Saharan Africa (SSA) bears the world's highest prevalence of high-risk HPV infection (hrHPV) and incidence of cervical cancer. To address the lack of screening and treatment that contributes to this burden, WHO recommends regions adopt simplified protocols in which screening is directly coupled with treatment. We developed and evaluated the feasibility of a lowcost community-based program featuring self-administered HPV screening and mobile treatment.

Methods: In a rural district in western Uganda, we first trained Village Health Team members (VHTs), also known as Community Health Workers, in a one-day session on the fundamental aspects of cervical cancer and its prevention. We then directed the VHTs to mobilize women to attend a one-day HPV screening fair at a central location in their respective communities. At the fair, the study team and VHTs provided instructions for self-collection of a vaginal sample for hrHPV testing. Notification of results was based on preference of phone call, text message, home visit or return clinic visit. Women could specify different notification options depending on their HPV result. In addition to their preferred method, hrHPV-positive women were called to confirm receipt of their results and informed about treatment availability and timing. Treatment was provided in mobile units near to women's homes. Prior to treatment, women underwent visual inspection with acetic acid to ensure they were candidates for cryotherapy, and had cervical biopsy for final cervical disease ascertainment.

Results: Between March 2016 and April 2017, 1035 women attended a health fair in one of 16 communities in rural Western Uganda and expressed interest in being screened; 1030 (99%) provided a self-collected vaginal sample. The median age of those screened was 34 years (IQR: 23-40). Almost 80% preferred to be contacted about their results by phone (67% call; 11% text); the remainder preferred coming to a clinic (12%) or a home visit (10%). Of the 229 found to be hrHPV-infected, 84% were reached with their results, 81% returned for a treatment visit, and 68% were treated. Of those notified of their results but not treated, 14 (7%) failed to return and 24 (12%) were ineligible because of pregnancy. Only 5 women required referral for LEEP.



Conclusion: In rural Uganda, a community-based screening program administered by VHT's and featuring self-collected vaginal swabs and mobile treatment was feasible, well attended, and well accepted. The findings support the concept of community-based mass HPV testing and treatment in Africa. Further optimization at each step of the program is needed to enhance cost-effectiveness and maximize population impact.

O17. Persistent Anal HPV16/18 Infections as Predictors of High-Grade Anal Lesions in Older MSM

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Background: Men who have sex with men (MSM) compose the highest risk group for anal cancer. High-grade squamous intraepithelial lesions, identified by anal biopsy and histology (hHSILs), are precursors for anal cancer, caused by persistent infection with high-risk human papillomaviruses (hrHPVs). There are 12 strongly carcinogenic hrHPVs (Group 1); these include HPV16 and 18, which account for up to 90% of anal cancers. There is no current standard approach to anal cancer screening, although experts recommend repeated screening using anal cytology. Cytology shows poor sensitivity when compared to biopsy to detect hHSIL, and HPV testing may be a viable screening alternative. The objective of this study is to compare the efficacy of anal cytology versus HPV testing to predict hHSIL in older MSM.

Methods: Participants are 183 U.S. MSM from the Anal Health Substudy (AHS), a nested cohort substudy of the Multicenter AIDS Cohort Study, who were followed for up to eight visits. A single Dacron swab was collected from the anal canal, and tested for cytology and 37 HPV types (Linear Array HPV DNA PCR assay). Following the AHS, men were assessed using the gold-standard: high-resolution anoscopy (HRA) with anal biopsy. Biopsies were classified as hHSIL or <hHSIL. Multivariable logistic regression models estimated odds ratios (ORs) and areas under the receiver-operating curve (AUCs) were calculated for five screening test strategies to predict hHSIL. Strategies compared were: having any abnormal cytology (abCyt) versus normal, persistent positivity (positive at two or more consecutive visits) for HPV types 16/18 (pHPV16/18+), and persistent positivity for Group 1 hrHPVs (pGroup 1+); two combined serial strategies were further assessed: abCyt & pHPV16/18+, and abCyt & pGroup 1+. Each model controlled for age, race, HIV, number of male receptive anal intercourse partners in the last two years, and smoking.

Results: Men were, on average, 59 (±8) years old; 58% (107/183) were HIV-infected, and 87% (159/183) were White, non-Hispanic. About 37% (67/193) had abCyt and 54% (98/183) had hHSIL. Persistently detectable HPVs were common, with 44% (80/183) testing pHPV16/18+ and 87% (159/183) testing pGroup 1+. On average, HIV-infected men were younger, more likely to have a lower CD4 count (<500 CD4 cells/mm^3), have abCyt, and test pHPV16/18+ (*p*-values<0.05). In adjusted multivariable models, abCyt alone had a 2.2-fold higher odds of hHSIL (95% CI 1.2, 4.2), pHPV16/18+ alone had 3.5-fold higher odds of hHSIL (1.8, 6.8), and pGroup 1+ alone was not associated with hHSIL (OR: 1.6 (0.6, 3.8)). When abCyt and pHPV16/18+ were combined in a model, positivity on both tests was associated with 3.3-fold higher odds of hHSIL (1.4, 7.6). When abCyt and pGroup 1+ were combined, positivity on both tests was associated with 2.1-fold higher odds of hHSIL (1.1, 4.1). Accuracy of individual test strategies, abCyt (AUC: 0.62), pHPV16/18+ (0.67), and pGroup 1+ (0.59), and combined strategies (AUCs: 0.62 & 0.63) were compared; no single strategy was significantly more accurate than another (*p*-values>0.05).

Conclusions: Results test suggest testing for persistent HPV16/18-positivity, even using commercially-available PCR Methods, may be an effective strategy for detecting hHSIL in older HIV-infected and -uninfected MSM. The high prevalence of hHSIL in this sample (54%) emphasizes an urgent need for a standard approach for screening. More research is needed to done.

O18. A Case Series of Nivolumab in Veterans With HIV Infection and Malignancy[2]

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Background: Cancer is now the leading cause of death among the HIV-infected U.S. population. Among non-HIV-infected patients with cancer, treatment with checkpoint inhibitors has become increasingly prevalent in the second-line and refractory setting, comprising a large segment of the rapidly evolving field of immunotherapy. Since 2015, nivolumab, an anti–PD-1 checkpoint inhibitor, has gained FDA approvals for non-small-cell-lung cancer (NSCLC), renal cell carcinoma (RCC), Hodgkin lymphoma (HL), melanoma, head and neck squamous cell carcinoma (SCC), and urothelial carcinoma, and is one of the most commonly used drugs in this class.

Most clinical trials highlighting checkpoint inhibitors have excluded HIV-infected patients. Currently, two phase I clinical trials are enrolling HIV-infected patients in anti–PD-1 trials, but there is still an urgent need for safety and efficacy data.

Methods: The primary objective of this was study was to characterize the HIV-infected veteran population receiving nivolumab and tolerance of the drug. We searched the Department of Veteran Affairs (VA) Corporate Data Warehouse (CDW) for all veterans nationwide who had received nivolumab between March 4, 2015, and July 26, 2017. Once these patients were identified, electronic medical records were reviewed through Compensation and Pension Records Interchange (CAPRI). Age, sex, geographic location, cancer type, number of doses of nivolumab received, previous cancer therapy, adverse effects, CD4 count, viral load, and response to therapy were extracted.

Results: As of 7/26/17, 16 HIV-infected patients were documented to have received nivolumab in the VA. The median age at nivolumab initiation was 65 (range, 47-85); all patients were male. Half (*n* = 8, 50%) received the drug for NSCLC. Two patients received it for HL and 2 patients for RCC. Four patients received it for off-label indications, including hepatocellular carcinoma (HCC) (*n* = 1), concomitant HCC and pancreatic adenocarcinoma (*n* = 1), small cell lung cancer (*n* = 1), and anal squamous cell carcinoma (*n* = 1). The median number of previous lines of therapy was 1 (range, 1-4). The median number of doses of nivolumab received was 5.5. The median baseline CD4 count was 304 cells/mm^3 (range, 63-915); 69% of patients had CD4 data within 3 months. Most patients (*n* = 11, 69%) had undetectable baseline HIV RNA viral loads. The majority (*n* = 9 of 14 with disease reassessment, 64%) of patients experienced progression of disease on nivolumab, while two patients (*n* = 2, 14%), had stable disease and one had partial response. Two patients (14%) had complete responses by positron emission tomography–computed tomography (PET-CT) scan. Both of these patients had HL, had received 4 prior lines of therapy, and continued on nivolumab therapy for at least 6 months. Four patients (27%) developed immune-related adverse events: 3 (20%) with pneumonitis, 1 of whom also developed rash, and 1 additional patient with hypothyroidism. No other adverse effects were noted.

Conclusion: Among all HIV-infected veterans with malignancy in the U.S., fewer than 20 patients have received nivolumab in the VA in the last two years. Based on this small retrospective case series, response rates were high in HL. The frequency of pneumonitis was higher than proportions reported in the literature (3-9%). Further studies need to address the safety of checkpoint inhibitors and its role in HIV-associated malignancies relative to traditional cytotoxic regimens.

[2]Travel Awardee

O19. AMS095: A Phase I Study of Ipilimumab (Ipi) and Nivolumab (Nivo) in Advanced HIV-Associated Solid Tumors (Preliminary Findings)

Lakshmi Rajdev[1], Missak Haigentz[1], Shelly Lensing[2], Howard Streicher[3], Richard F. Little[3], Dirk P. Dittmer[4], Mark H. Einstein[5], Elizabeth Chiao[6], Joseph A. Sparano[1], Ronald Miitsuyasu[7]. AIDS Malignancy Consortium

[1]Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY; [2]University of Arkansas for Medical Sciences Little Rock, AR; [3]Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD; [4]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Rutgers, The State University of New Jersey; [6]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX; [7]University of California, Los Angeles Care Center, Los Angeles, CA

Background: Although immune checkpoint blockade (ICB) using agents that target the priming phase (i.e. CTLA-4) and effector phase (e.g. PD-1, PD-L1) of host immunity, used individually or in combination, has emerged as an important new therapeutic strategy for a variety of cancers, little is known about the safety, tolerability and efficacy of ICB in patients (pts) with HIV infection and cancer.

Methods: AMC 095 (NCT02408861) is a multicenter, international (NCT02408861) phase I study of the PD-1 inhibitor, nivo alone or in combination with a CTLA-4 inhibitor, ipi, in 2 cohorts stratified by CD4 counts (Stratum 1: CD4 counts>200/uL and Stratum 2: CD4 count 100-200/uL) with additional expansion cohorts planned at the recommended phase II dose in pts with solid tumors, and classic Hodgkin's lymphoma. The primary study objective is to determine the safety and feasibility of the nivo alone and the nivo+ipi combination. Secondary objectives are to evaluate the effects of single agent nivo, and ipi+ nivo, on HIV replication and immune function (HIV viral load in plasma using conventional assay, CD4+, and CD8+ cells), and to obtain preliminary information regarding response.

Results: As of 7/27/17, 11 patients have been enrolled, 9 men and 2 women. Seven are white, 2 black, and 2 others. The cancer diagnoses of the enrollees are: Kaposi Sarcoma (KS) (2 pts), anal (2 pts), squamous cell carcinoma (scca) (3 pts):1 head and neck, 1 skin and 1 other, and other types of cancer.

Agent/Dose	Stratum	No. Treated	No. DLT	DLT Type
Dose Level 1 [DL1] Nivo 3 mg/kg q 2 wks	I-CD4 $\geq$ 200/uL	5	0	None
Dose Level 1 [DL1] Nivo 3 mg/kg q 2 wks	2-CD4 < 200 /uL	2	0	None
Dose Level 2 [DL2] Nivo 240 mg q 2 wks + Ipi 1 mg/kg q 6 wks	1-CD4 $\geq$ 200/uL	4	1	Grade 2 diarrhea requiring steroids
Total		11	1	

On Stratum 1 DL1, one pt (scca of skin) remains on treatment (48 weeks of therapy) and 2 others (gall bladder cancer and scca of tongue) received therapy for 28 and 36 weeks respectively.

Conclusion: Preliminary evidence suggests that nivolumab may be administered safely in HIV pts with CD4>200. The early evidence also suggests that nivolumab demonstrates clinical activity in HIV patients with solid tumors.
Funded by the National Cancer Institute Grant #UM1CA121947.

O20. A Prospective Study of Serum Microbial Translocation and Inflammation-Associated Biomarkers and Risk of AIDS-Related Non-Hodgkin Lymphoma

Marta Epeldeguil[1], Larry Magpantay[1], Yu Guo[1], Gordana Halec[1], William G. Cumberland[1], Priscilla K. Yen[1], Bernard Mactangay[2], Joseph B. Margolick[3], Anne F. Rositch[3], Steven Wolinsky, Otoniel Martinez-Maza[1], Shehnaz K. Hussain[5]

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Background: Chronic immune activation is a harbinger of AIDS-associated non-Hodgkin lymphoma (AIDS-NHL), yet the underlying basis remains unclear. Here we hypothesize that microbial translocation, the passage of microbial components from the gastrointestinal tract into the systemic circulation, is a source of systemic immune activation and inflammation in chronic HIV infection and may be an important contributor to AIDS-NHL.

Methods: We measured biomarkers of microbial translocation including bacterial receptors/antibodies, intestinal barrier proteins, macrophage activation-associated cytokines/chemokines and as well as inflammation biomarkers including soluble receptors in serum from 200 HIV-infected men from the Multicenter AIDS Cohort Study (MACS) prior to their AIDS-NHL diagnosis (mean=3.9 years; SD=1.6 years) and 200 controls. Controls were HIV-infected men who did not develop AIDS-NHL, matched to each case on the basis of their CD4 T cell count, prior antiretroviral drug use, and recruitment year into the cohort. Multiplex Luminex assays and ELISA were used to quantify 26 biomarkers in serum. We used multivariate conditional logistic regression to calculate odds ratios representing the risk of AIDS-NHL associated with log-transformed continuous biomarker levels, or quartiles of biomarker levels.

Results: Biomarkers of bacterial translocation and intestinal permeability were significantly increased in individuals with AIDS-NHL. Lipopolysaccharide-binding protein (LBP), fatty acid binding protein 2 (FABP2) and soluble CD14 had 1.6-, 2.9-, and 3.7-fold increases in risk for each unit increase on the natural log scale, respectively. Haptoglobin had a 2.1-fold increase and endotoxin-core antibody a 2.0-fold decrease risk for AIDS-NHL (4th versus 1st quartile). Biomarkers of macrophage activation were significantly increased in individuals with AIDS-NHL: B-cell activation factor (BAFF), IL18, monocyote chemoatractant protein-1 (MCP1), TNFα, and CCL17 had 2.2-, 2.0-, 1.6-, 2.8-, and 1.7-fold increases in risk for each unit increase on the natural log scale, respectively. Additionally, soluble receptors of cytokines involved in inflammation were elevated prior to AIDS-NHL diagnosis: sIL2Rα, sTNFRII and sIL6Rα were significantly associated with the overall AIDS-NHL risk and had 8.0-, 4.5- and 3.8-fold increases in risk for each unit increase on the natural log scale, respectively.

Conclusion: These data provide evidence for microbial translocation as a cause of the systemic immune activation in chronic HIV infection preceding AIDS-NHL development.

O21. Identifying Transcriptional and Prognostic Biomarkers of HIV-Associated Diffuse Large B-Cell Lymphoma From Malawi

Yuri Fedoriw[1], Nathan Montgomery[1], Tamiwe Tomoka[2], Bal Dhungel[2], Kristy Richards[3], Sara Selitsky[1], Joel Parker[1], Satish Gopal[1,2]

[1]The University of North Carolina, Chapel Hill, Chapel Hill, NC; [2]UNC Project-Malawi, Lilongwe, Malawi; [3]Cornell University, New York, NY

Background: Lymphoma incidence in sub-Saharan Africa (SSA) is increasing due to epidemic levels of HIV infection and population aging. Diffuse Large B-cell Lymphoma (DLBCL) is the most common lymphoma worldwide and in SSA, and is highly associated with HIV. Previous studies have identified at least two molecular subsets of HIV-negative DLBCL, one with an expression signature resembling germinal center B cells (GC), the other post-germinal center activated B cells (ABC). These cell-of-origin (COO) subtypes differ in their genetic alterations, signaling pathways, and outcomes. However, comprehensive phenotypic and molecular classification of HIV-associated DLBCL is incomplete. Such characterization may provide unprecedented and generalizable insight into lymphoma biology and inform prevention and treatment strategies regionally and worldwide. Here we describe profiling of HIV-associated DLBCL from the ongoing Kamuzu Central Hospital (KCH) Lymphoma Study prospective cohort to ultimately identify biological differences and clinically meaningful biomarkers of disease.

Methods: After primary diagnosis at KCH, tissue blocks were submitted to UNC for additional immunohistochemical assessment (IHC) and genomic classification. CD4, HIV RNA, and ART status were documented for all HIV+ patients, as well as lymphoma-related clinical and laboratory data. 116 adult cases (49 DLBCL) have been fully characterized in this manner, with approximately half of all lymphomas arising in HIV+ patients (n=59). Of the DLBCL samples, 36 (22 HIV+/14 HIV-) have undergone whole transcriptome sequencing with comparison to published expression data and correlation to clinical outcome and pathologic features. Enriched gene sets were determined using the z-statistic and the hallmark gene set, and differentially expressed (DE) genes were determined using DESeq2.

Results: Unsupervised hierarchical clustering of gene expression segregated DLBCL by HIV status ($p<0.00002$), indicating a strong contribution of HIV to expression phenotype. A total of 1,125 genes were DE between the clusters with an adjusted p-value of <0.05. The 4 HIV+ DLBCLs that clustered with HIV- cases were on ART longer than the HIV+ cases that clustered together (p=0.04). Gene set enrichment analysis identified significant differences related to WNT, MTOR, and p53 signaling pathways. While we have previously shown that clinical predictors are prognostic, there were no overall survival (OS) differences related to HIV status or gene expression cluster. HIV+ DLBCLs in our cohort have an expression COO signature and IHC profile shifted toward the GC subtype, compared to HIV- cases (p=0.02). However, COO subtype was not associated with significant OS differences among HIV+ or HIV- cases. Additional analyses have focused on identifying pathologic and molecular variables associated with outcomes in this cohort. Amongst all cases, increased relative expression of Human Endogenous Retrovirus (HERV) K113 was associated with inferior OS (p=0.02), and BCL2/MYC co-expression by IHC also showed a trend towards inferior OS in univariate analyses (p=0.06). When HIV+ cases were analyzed separately, both a gene expression-based proliferation signature (p=0.016) and IHC-based Ki-67 staining (p=0.046) were associated with inferior OS in HIV+DLBCL.

Conclusions: While the striking genetic heterogeneity of *de novo* DLBCL is known, similarly thorough studies of HIV-associated DLBCL are lacking. These studies are challenging to conduct, as prospective, single-center cohorts of HIV-associated lymphomas are uncommon in settings where HIV infection is less frequent. The KCH Lymphoma Study is a unique resource which addresses some of these obstacles. To date, we have identified transcriptional differences in DLBCL associated with HIV infection. As complete clinical outcome and laboratory information are available for all cases in our cohort, the study represents a first-of-its-kind analysis of HIV-associated DLBCL from SSA. The findings provide preliminary data to inform future basic and clinical investigations.

O22. Strategies to Improve Kaposi Sarcoma Outcomes in Zimbabwe: A Community-Based Clinical Trial of a Training Intervention for Improved Primary Dare of AIDS-KS (SIKO Study)

Margaret Borok[1], Samantha Mawhinney[2] Eric Simoes[2], Maxwell Matimba[1], Matthew Mulvahill[2], Camille Moore[2], Suzanne Fiorillo[2], Francis Jaji[1], Ivy Gudza[1], Thomas Campbell[2]

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Background: Zimbabwe is a predominantly rural country with approximately 80% of the population accessing medical care through a tiered system of local health centers. Over the past 5 years, antiretroviral therapy has been decentralized to primary care clinics staffed by generalist doctors and nurses. Little is known about how to improve Kaposi's sarcoma (KS) treatment outcomes in these settings.

Methods: A package of interventions designed to improve KS care in primary care settings by early detection and improved clinical management was evaluated in a randomized step-wedge cluster design. The package included a standardized clinical evaluation tool, palliative care integration, standardized KS treatment, and improved consultative services for rural clinicians. The interventions were implemented at 8 primary care sites (4 rural/4 urban) in Zimbabwe. All persons with suspected KS were eligible. Training modules incorporating KS recognition, particularly early KS, diagnosis and treatment, symptom control and palliative care were delivered during the intervention period at each site by a team of trained nurses and doctors experienced in KS patient care. The primary endpoint was the proportion with early stage (T0) KS versus advanced stage (T1) KS during the pre- and post-intervention periods.

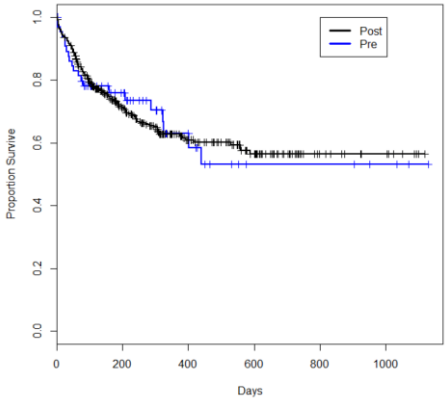

Figure 1. Unadjusted Kaplan-Meier plot of time to death for incident confirmed AIDS-KS in the SIKO study. Blue line shows survival prior to the training intervention; Black line is survival after the training intervention.

Results: Between February 2013 and January 2016, 1102 subjects (96% HIV+) with suspected KS were enrolled: 47%, 20% and 33% had incident (new), prevalent (previous) and false KS diagnoses, respectively, with 60%, 62% and 44% male; and 34%, 27% and 25% rural. For incident KS, median age (IQR) was 37 (32, 43). Adjusted odds (aOR) of early diagnosis among incident cases, within clinic, before and after the SIKO intervention, were 1.48 (0.63, 3.49; P=0.37); for false diagnosis aOR was 1.83 (1.16, 2.88; P=0.0096). Incident KS one-year mortality (95% CI) was 37% (32%, 42%), over twice the previously observed rate (16%) in the university-affiliated tertiary referral KS clinic. Adjusted hazard ratio for time to death was 1.36 (0.85, 2.20; P=0.20; Figure 1). In the first 90 days on study, and between 90 and 180 days there was a similar rate of return among the pre/post groups (HR 0.67, 0.38-1.21 p=0.19; HR 1.37, 0.79- 2.39, p=.26). After 180 days subjects enrolled post-intervention were more likely to return for care (HR 2.84, 1.47-5.48, p=0.0018).

Conclusions:

- The SIKO package of interventions increased both the number of new (incident) KS diagnoses but also increased the proportion of false KS diagnosis
- The SIKO interventions did not increase the proportion of early (T0) stage KS diagnoses at primary care sites in Zimbabwe
- KS mortality in decentralized primary care clinics in Zimbabwe was high and was not affected by the SIKO intervention
- The SIKO interventions increased the rate of return for a second visit after the KS diagnosis (improved retention in care)

HIGHLIGHTED POSTERS

These three posters were selected by the organizers for showcasing on both days of the ICMH.

1. Comparison of EBV and KSHV Seroprevalence in a Cohort of Children in Western Kenya With Differential Malaria Exposure

Katherine Sabourin[1], Ibrahim Daud[2], Peter O. Sumba[2], Nazzarena Labo[3], Wendell Miley[3], Denise Whitby[3], Rosemary Rochford[1]

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Background: Kaposi's sarcoma herpesvirus (KSHV) is associated with a number of human malignancies including Kaposi's sarcoma and primary effusion lymphoma. KSHV is endemic in many areas of sub-Saharan Africa including Kenya. Interestingly, the geographical distribution of KSHV seroprevalence is not uniform within the so-called KSHV belt suggesting difference in factors that promote transmission of the virus. A recent study found an association between malaria exposure and KSHV seropositivity (Trop Med Intl Health, 2015; 20: 665). In this study, we took advantage of samples from an existing cohort in Kenya where infants were followed through 3 years of age from 2 regions in Kenya with different malaria exposures: Kisumu District where malaria transmission is endemic and Nandi District where malaria transmission is limited. We also compared the seroprevalence of KSHV to EBV, another important childhood infection in sub-Saharan Africa.

Methods: Plasma from venous blood taken at 12, 18, 24, 30 and 36 months of age was analyzed for KSHV seroprevalence using ELISA to detect antibodies to ORF73 and K8.1 (n=132). Presence of antibodies to either ORF73 or K8.1 was used to indicate whether children were seropositive. EBV seroprevalence was determined by detection of antibodies to VCA and EBNA1. KSHV seroprevalence was also evaluated using a bead-based multiplex assay to detect a broader panel of KSHV antibodies (Plos Pathogen, 2014 10(3)e1004046). Adults from the same region were also assessed for KSHV seroprevalence by ELISA.

Results: By 3 years of age, KSHV seroprevalence was detected in 8 of 57 children from Kisumu District (14%) and in 3 of 75 children in Nandi (4%) by 36 months of age. Evaluation of the age of infection of the KSHV seropositive children found that 2 of 8 (25%) KSHV infected children from Kisumu were infected by 18 months of age, 5 (62%) by 30 months, and all 8 (100%) by 36 months. Whereas 1 (33%) KSHV positive child from Nandi was infected by 18 months of age and the remaining 2 children were infected by 36 months. Evaluation of bead-based multiplex data is ongoing. Seroprevalence of KSHV in both the Nandi and Kisumu adult communities were similar [44/62 (81%) and 140/184 (84%), respectively]. EBV seropositivity of all children in the study was detected by 16 months of age.

Conclusions: Several conclusions are suggested by these results. First, these studies confirm that Kenya has among the highest rates of KSHV seropositivity within sub-Saharan Africa. Second, children living in a malaria holoendemic region have a greater risk for infection with KSHV at an earlier age pointing to a potential role of malaria in enhancing KSHV transmission. Finally, although both EBV and KSHV are transmitted through saliva in endemic regions, EBV is transmitted much earlier in life than KSHV.

2. Raman Spectroscopy Distinguishes High-Grade Anal Intraepithelial Neoplasia (HGAIN) From Normal Tissue

Robert Oda[1,2], Natalie Kamada[3], So Yung Choi[4], Eunjung Lim[4], Anupam Misra[5], Tayro Acosta-Maeda[5], Jeffrey Killeen[6], Cris Milne[2], Melissa Agsalda-Garcia[2,3], Bruce Shiramizu[2,3]

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Background: Anal dysplasia is a potentially chronic disease that affects HIV-seropositive individuals for which regular screening is important for management of the condition. In light of this, proactive diagnosis of dysplasia is important for monitoring and management of the disease. Recently, Raman spectroscopy (RS) has emerged as a new and novel tool for the identification of cancerous tissue. RS utilizes Raman scatter to "fingerprint" chemical composition of cells or tissue through vibrational modes and gives insight into physical properties. RS uses monochromatic light and the inelastic scattered light generated from the sample is used to measure the Raman spectra. The goal of this study was to assess anal tissue using RS to identify potential markers for high grade anal intraepithelial neoplasia (HGAIN).

Methods: Anal biopsy specimens were obtained by high resolution anoscopy following informed consent and embedded in paraffin for pathological assessment. Sections of paraffin embedded tissue were mounted onto aluminum reflective slides and then deparaffinized in a wash gradient of xylene, 100% ethanol, 90% ethanol, 70% ethanol and deionized water. Slides were immersed in 0.9% NaCl saline solution before being visualized under a spectroscope. The specimen samples were then subjected to 40 point scan using a Raman microscope at a 50x magnification; scans were obtained at 15 accumulations with an exposure setting of 15 seconds per accumulation. Spectral data was processed in MATLAB and utilized an asymmetric least squares (AsLS) to baseline the spectral data. Principal component analysis (PCA) was applied to the data and principal component scores were plotted against each other for visual inspection. K-Nearest Neighboring (k-NN) analysis on the principal component scores was used for classification, using randomly selected 1/3 of the data as the training set, and the remaining 2/3 as the test set.

Results: Both normal and HGAIN pathology were identified from different anal biopsies. Raman fingerprints identified unique RS peaks which ranged from concentrations of DNA/proteins to various bond types and lengths. PCA was performed on AsLS baseline data and identified key variances in the tissue types which formed two distinct clusters that distinguished normal tissue from high grade lesions. The first three principal components covered 79.5% of all variance in the data. Analysis by k-Nearest Neighboring (kNN) was performed on the first 3 principal components and found 100% clinical accuracy, sensitivity, and specificity for both tissue types.

Conclusions: The RS fingerprints of the normal and HGAIN tissue demonstrated unique clustering and can potentially distinguish cancerous tissue from normal tissue. RS opens the door as a promising new tool that can be adapted for diagnosis for anal dysplasia and other HIV related co-morbidities. Supported in part by R21CA216830 and U54MD007584.

3. Advanced Stage of Hepatocellular Carcinoma Is Less Common Among HCV Infected in Both HIV Infected and Uninfected U.S. Veterans

J. Torgersen[1], D.M. Carbonari[1], M.J. Kallan[1], K. Mitchell-Richards[2], X. Zhang[3], K. D'Addeo[3,4], R. Mehta[3,4], L. Park[5], F. Kidwai-Khan[3,4], T. Taddei[3,4], A.C. Justice[3,4], V. Lo Re III[1]

[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]Greenwich Hospital, Greenwich, CT; [3]Yale School of Medicine, New Haven, CT; [4]Veterans Affairs Connecticut Healthcare System, West Haven, CT; [5]Stanford University School of Medicine, Stanford, CA

Background: The prevalence of hepatocellular carcinoma (HCC) has increased substantially among HIV infected patients (HIV+), driven primarily by chronic viral hepatitis coinfection. However, it remains unclear if HIV or chronic hepatitis C virus (HCV) infection are associated with more advanced stage of HCC at presentation. We evaluated the determinants of advanced HCC stage among a cohort of patients with pathologically-confirmed HCC.

Methods: We conducted a cross-sectional study of US Veterans with biopsy-proven HCC diagnosed between 2000 and 2016 in the Veterans Aging Cohort Study (VACS). Pathology reports of liver biopsy specimens were collected from the VA Corporate Data Warehouse (CDW). Demographic, clinical, and Background liver parenchymal tissue characteristics were compared by stage of HCC (American Joint Committee on Cancer [AJCC] Stage I-II versus Stage III-IV). Logistic regression was used to identify determinants of advanced HCC stage (AJCC stage III-IV). Hypothesized determinants of advanced HCC stage included HIV, hepatitis B virus (HBV) infection, HCV infection, level of alcohol consumption (not current; non-hazardous use; hazardous use), obesity, and diabetes. The potential for interaction between HIV infection and chronic HCV infection on stage of HCC was evaluated.

Results: A total of 226 Veterans with biopsy-proven HCC (99% male; 59% HIV+; 82% with chronic HCV infection) were identified. Advanced stage of disease was present in 89 (39%) participants and was more common among those without chronic HCV infection (p=0.01), but no difference was observed by HIV status (p=0.92). Chronic HCV infection was the only factor statistically significantly associated with stage of HCC after adjustment for covariates: patients with chronic HCV infection were less likely to be diagnosed with advanced stage of HCC when compared to those without chronic HCV infection (odds ratio, 0.34 [95% CI, 0.15-0.74]). This association remained after further adjusting for the presence of advanced hepatic fibrosis on tumor parenchyma. HIV, HBV infection, alcohol use, obesity, and diabetes were not associated with advanced stage of HCC at time of liver biopsy. There was no statistically significant interaction between chronic HCV infection and HIV status on stage of HCC.

Conclusion: Patients with chronic HCV infection were significantly less likely to have advanced stage of HCC at time of tissue diagnosis, which may reflect more frequent imaging among patients with chronic HCV infection. Further studies are needed to identify additional determinants of advanced stage HCC among individuals without chronic HCV infection.

DAY ONE POSTERS

The first three abstracts will be presented on both days. Abstracts 4-40 are on pages 55 to 91.

1. Comparison of EBV and KSHV Seroprevalence in a Cohort of Children in Western Kenya With Differential Malaria Exposure
2. Raman Spectroscopy Distinguishes High-Grade Anal Intraepithelial Neoplasia (HGAIN) From Normal Tissue
3. Advanced Stage of Hepatocellular Carcinoma Is Less Common Among HCV Infected in Both HIV Infected and Uninfected U.S. Veterans
4. 3D Genome Landscape of Epstein-Barr Virus Oncoproteins and Virus-Activated NF-κB in Lymphoblastoid Cells
5. A Neuroinvasive Murine Model of Epstein-Barr Virus-Associated Primary Central Nervous System Lymphoma
6. An Activating PI3Kδ Mutant Disrupts Epstein-Barr Virus Latency
7. Analysis of Small, Non-coding RNAs in Non-Human Primate Models of AIDS-Associated Malignancies
8. Regulation of B Cell Receptor Signaling by Viral microRNAs
9. Analysis of the Subcellular Localization of KicGAS (ORF52) of Kaposi's Sarcoma-Associated Herpesvirus (KSHV)
10. Anaplastic Large Cell Lymphoma in HIV+ Patients: Clinicopathologic Analysis
11. Androgen Receptor Activity in Prostate Tumors From HIV-Infected and HIV-Uninfected Men
12. Anti-KSHV and Anti-EBV IgA Antibodies in Saliva of HIV-Infected and Uninfected Cameroonians
13. Antiretroviral Therapy Reduces Human Herpesvirus-8 Replication in Oral Mucosa and Plasma Among Ugandan Adults With HIV Infection
14. Association of Serum Markers of Inflammation and Immune Activation With the Incidence of Non-AIDS-Defining Cancers in Men Living With HIV
15. Associations of Serum Inflammatory Biomarkers and Kaposi's Sarcoma in Men Who Have Sex With Men From 1984 to 2010
16. Autocrine Beta-adrenergic Signaling Drives Proliferation of Cells Transformed by KSHV and Suppresses Lytic Viral Replication
17. Biochemical Characterization of EBV Nuclear Antigen Regulation of Host Transcription Through the Notch Signaling Pathway and Implications for Rational Drug Design
18. Cancer-Specific HIV Nef Identified in Tumor Tissues From Patients With End-Stage Lymphoma
19. c-Myc Represses Transcription of the Epstein-Barr Virus Latent Membrane Protein 1 Early After Primary B Cell Infection
20. Distribution of HPV Subtypes Associated With Invasive Cervical Cancer in HIV-Infected and HIV-Uninfected Women From Botswana
21. EBV-Mediated B-Cell Transformation Is Suppressed by Oncogene-Induced Senescence Through Establishment of a Persistent DNA Damage Response

22. Epstein-Barr Virus Activation by Nelfinavir Is Linked to the JNK Pathway and Autophagy
23. Epstein-Barr Virus Promotes Apoptosis Resistance by Inducing a Germinal Center-Like Reaction in In Vitro Infected B Cells
24. HIV Status Is Associated With Enhanced Oncogenic Signaling in Diffuse Large B Cell Lymphoma
25. HPV-16 DNA Quantitation Distinguishes Cytology and Pathology Grades in Anal Dysplasia/Cancer
26. IFI16 Functions as a Major Epigenetic Modulator During KSHV Infection and Lytic Reactivation
27. KSHV Regulation of the microRNA Biogenesis Pathway
28. KSHV-Specific CD4 and CD8 T Cell Clones Reveal Effector Phenotype That Is Transferrable to Autologous T Cells
29. KSHV Viral Load and Human Interleukin-6 in Pediatric Kaposi Sarcoma—Evaluating the Role of Lytic Activation in Driving the Unique Clinical Features Seen in Endemic Regions
30. Pathogenic Oral Microbiomes Are Associated With EBV: How Bacterial Regulation of Euchromatin Leads to Epstein-Barr Virus Reactivation
31. Patient Biopsies From the Multinational Kaposi's Sarcoma Trial A5264/AMC067 Show Broad Variability in the Percentage of LANA+ cells and Only Rare Lytic Reactivation
32. Plasma Immunoglobulin E (IgE) Levels Are Associated With Kaposi's Sarcoma in HIV-Infected African Adults
33. Proteomic Analysis of Host Response to KSHV in HIV-Infected Patients With KSHV-Associated Diseases
34. Reprograming of T Cells by Ectopic CCR9 Expression Induces Preferential Trafficking to Gut Tissue
35. Targeting the mTOR Pathway as Therapy for Primary Effusion Lymphoma
36. The Nucleoside Analog 6-ethylthioinosine Induces AMP-Activated Protein Kinase Activity and Inhibits mTOR in Primary Effusion Lymphoma Cells
37. Unique Features of KSHV Infection in Tonsil-Derived Stromal Cells Uganda
38. Vaccine Development: A Highly Attenuated Recombinant Herpesvirus Induces the Generation of Memory Precursor Effector Cells
39. Whole Genome Sequence Analysis of KSHV and EBV From a Kaposi's Sarcoma (KS) Case-Control Study Conducted in Yaoundé, Cameroon
40. Immune Response Abnormalities in Epidemic and Endemic Kaposi's Sarcoma Patients

4. 3D Genome Landscape of Epstein-Barr Virus Oncoproteins and Virus-Activated NF-κB in Lymphoblastoid Cells

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Epstein-Barr Virus (EBV) encoded Nuclear Antigens (EBNAs) and virus activated NF-kB subunits mostly bind to enhancers in EBV transformed lymphoblastoid cells lines (LCLs). Using LCL 3D genome organization map that links EBV enhancers to promoters, we built the most comprehensive virus regulome. EBV regulome contained 1992 genes and enhancers directly linked to them. ~30% of genes essential for LCL growth were linked to EBV enhancers. CRISPR knock out of EBNA2 sites significantly reduced their target gene expression. Additional EBV super-enhancer (ESE) targets including MCL1, IRF4, and EBF were identified. MYC ESEs looping to MYC TSS was dependent on EBNAs. CRISPR deletions of MYC ESEs greatly reduced MYC expression and LCL growth. EBNA3A/3C altered CDKN2A/B spatial organization to suppress senescence. EZH2 inhibition decreased the looping at the CDKN2A/B loci and reduced LCL growth. This study defines the most comprehensive host-pathogen interactions on the spatial organization of chromatin during infection and cancer.

5. A Neuroinvasive Murine Model of Epstein-Barr Virus-Associated Primary Central Nervous System Lymphoma

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Background: Primary central nervous system lymphoma (PCNSL) is a primary intracranial tumor of B-cell origin that accounts for 1% of all lymphomas and 3-5% of primary brain tumors and is commonly, though not exclusively, observed in patients who are immunocompromised. HIV infection is the highest risk factor for PCNSL, which accounts for 15% of HIV-associated lymphomas. PCNSL has a reported incidence over 1000 times greater in the HIV positive population and the prognosis of PCNSL is better in non-HIV cases than in HIV-related cases. Although the advent of combination antiretroviral therapy (cART) has decreased the number of AIDS-related cases of PCNSLs, the mortality of CNS complications, including PCNSL, remains high in untreated HIV infected individuals and those unaware of their HIV status. In addition, it has been reported that the proportion of minority patients diagnosed with AIDS-related PCNSL has increased compared to the pre-cART era. EBV is associated with greater than 90% of PCNSLs in patients who are iatrogenically immunosuppressed and 100% of those who are infected with HIV. The development of effective vaccines and therapeutics for EBV-driven malignancies, including PCNSL, is hampered by the paucity of animal models for EBV pathogenesis and immune control, particularly in the CNS.

Methods: We have recovered a neuroinvasive, EBV+lymphoblastoid cell line (LCL; MUN14) from the brains of NSG-SCID mice implanted subcutaneously with EBV+ LCLs (M14). The neuroinvasive MUN14 line has now been serially passaged and neuroadapted through several rounds of peripheral engraftment and subsequent retrieval from the brains of NSG-SCID mice, guided by bioluminescent images obtained with the Xenogen IVIS imaging system.

Results: We have characterized the neuroinvasive and brain tumor growth phenotype of the neuroadapted MUN14 line compared to the parental EBV+LCL (M14) in NSG-SCID mice by following the growth and distribution of these cells (both GFP+ and firefly luciferase+) after site specific engraftment. Neuroinvasion (the ability of EBV+LCLs to invade the CNS) was assessed after engraftment via peripheral routes (intracardiac, intravenous, or subcutaneous); EBV-mediated brain tumor growth was compared by direct injection of neuroadapted MUN14s or M14s directly in the brain *via* the intracranial route. In mice that are implanted with the MUN14 cell line *via* peripheral routes, we observed increased neuroinvasion (*i.e.* fewer days before CNS infiltration), increased CNS growth rates, and more rapid clinical progression compared to mice engrafted with the parental M14 line. Molecular characterization of neuroinvasive EBV-associated B-cell lymphoma is underway for both cellular and viral changes.

Conclusions: We have established a robust murine model of PCNSL with high rates of neuroinvasion, reliable establishment of EBV+ B-cell tumors in the brain, and clinical and pathological correlates with PCNSL. An animal model for PCNSL will provide an important tool for identifying viral and cellular determinants of neuroinvasion and CNS tumor growth and for testing novel therapeutic agents in the CNS.

6. An Activating PI3Kδ Mutant Disrupts Epstein-Barr Virus Latency

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Background: Epstein-Barr virus (EBV) is a human gammaherpes virus that is present in most of the adult population and is responsible for several lymphoproliferative diseases. Stimulation of the B cell receptor (BCR) pathway, of which PI3Kδ is a member, has been shown to be an activator of EBV. Dominant-activating mutations in PI3Kδ have been implicated in T cell senescence and human immunodeficiency (1). With PI3Kδ playing a role in the BCR pathway, we set out to determine if an activating mutation might affect the EBV lifecycle.

Methods: The Akata Burkitt lymphoma cell line and an engineered derivative cell line (BX1) carrying a recombinant EBV that constitutively expresses a green fluorescent protein (GFP) were used. Cells were nucleofected with a doxycycline-inducible pTRIPZ plasmid containing wild type and mutant PI3Kδ. Quantitative PCR was performed to measure DNA viral load and reverse-transcribed RNA levels. Flow cytometry was used to detect and quantify cells expressing GFP and RFP. Immunoblotting and immunofluorescence were performed to detect PI3Kδ phosphorylation and EBV ZTA.

Results: BCR stimulation with anti-IgG resulted in increased phosphorylation of PI3Kδ and ZTA expression as seen by immunoblot, qRT-PCR and immunofluorescence, as well as an increase in viral genomes by qPCR. Phosphorylation of PI3Kδ and lytic activation of EBV ZTA by anti-IgG was blocked by idelalisib, a PI3Kδ inhibitor, as seen by immunoblot, qRT-PCR and immunofluorescence, and blocked the increase of viral genomes as seen by qPCR. Finally, nucleofecting cells with a vector containing an activating mutation in PI3Kδ and inducing the vector with doxycycline activates BX1 EBV as seen by flow cytometry, while wild type did not.

Conclusions: Elevated levels of EBV have been reported in patients with activating mutations in PI3Kδ, likely due to a lack of T cell activity against EBV-positive cells. An additional explanation is that the activating mutant PI3Kδ results in increased BCR pathway signaling, reactivating virus in B cells. Our results confirm that PI3Kδ is involved in reactivation of EBV via the BCR pathway and support that expression of a dominant-activating PI3Kδ activates EBV *in-vitro*. Further work on patient specimens harboring dominant-activating mutations in PI3Kδ would help determine if there is clinical significance in these findings.

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7. Analysis of Small, Non-coding RNAs in Non-Human Primate Models of AIDS-Associated Malignancies

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Background: Cellular and molecular factors contributing to increased cancer development in HIV-infected individuals, particularly in the context of aging, are complex and still unclear. Simian immunodeficiency virus (SIV) infection of nonhuman primates (NHP) recapitulates multiple aspects of HIV pathogenesis, including the development of AIDS-related malignancies. Our preliminary molecular and immunopathological analyses of lymphomas from juvenile and adult SIV-infected RM showed that several of these tumors are positive for simian oncogenic gamma-herpesviruses—namely, rhesus macaque rhadinovirus (RRV) and rhesus lymphocryptovirus (rLCV). Both these viruses express stable, non-coding regulatory microRNAs (miRNAs) that, in combination with specific cellular miRNAs, can aid as biomarkers in differentiating disease states. In this project, we detect and monitor longitudinal changes in peripheral viral and cellular miRNA expression patterns in RM models of AIDS-related malignancies with a longer-term goal of identifying intersecting molecular and immunological events that lead to increased cancer risk.

Methods: Young adult RM (4-6 years old), immunologically deficient young adult RM (treated with rhesusized anti-IL-15 mAb), and aged (>17 yr) RM (naturally infected with g-herpesviruses) were experimentally inoculated with SIVmac329. Blood (plasma and PBMCs) and tissue samples were collected in the weeks prior to and post SIV challenge. Plasma-associated small ncRNAs were isolated at multiple select time points and levels of miR-16, miR-17, miR-21, miR-146a, and miR-155 were assayed by qRT-PCR. Viral loads were monitored in parallel. In another cohort of pathogen-free RM experimentally infected with RRV, circulating g-herpesvirus miRNA levels were monitored by qRT-PCR. Next generation sequencing analysis to comprehensively profile longitudinal changes in viral and host circulating miRNAs in these cohorts is ongoing.

Results: For many miRNAs, peripheral levels remain fairly stable pre-and post-SIV challenge, with relative minor fluctuations. Notably, at 14 days' post SIV infection, inflammation-associated oncogenic miRNAs (miR-155 and miR-17) were significantly increased in aged RM but surprisingly not in younger adult RM or IL15-depleted RM. These changes concurred with peak SIV loads, low CD4+ and CD8+ T cell counts, and differences in B cell subsets. Examination of cell-associated and cell-free miRNAs in a small cohort of RRV-inoculated RM showed that multiple RRV miRNAs were readily detectable four weeks' post-infection, coinciding with the establishment of latent infection.

Conclusion: These studies improve our understanding of peripheral viral and cellular miRNA expression patterns in vivo in RM and identify some of the major miRNA fluctuations that can occur following SIV challenge. Work is currently ongoing to integrate the complex molecular and immunological changes observed in these cohorts to define factors leading to the induction and progression of SIV-associated cancer in this model.

8. Regulation of B Cell Receptor Signaling by Viral microRNAs

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Background: MicroRNAs are key post-transcriptional regulators in health and disease. During viral infection, these small molecules govern many stochastic processes that facilitate cell state transitions, immunological responses, and decisions driving viral persistence and/or leading to oncogenic transformation. Through the mapping of miRNA interactomes in gamma-herpesvirus infection models, several studies demonstrate that miRNAs and their targets play essential roles in multiple aspects of viral life cycles, including manipulation of signaling pathways and successful navigation of anti-viral responses. In this study, we examined some of the miRNA-mediated molecular interactions that govern the balance between Epstein-Barr virus (EBV) latency and lytic reactivation, focusing specifically on virally-encoded miRNAs that alter B cell receptor (BCR) signaling.

Methods: 14 individual EBV miRNAs were screened in NF-kB and AP1 reporter cells in the presence of anti-IgM to identify potential disruptors of BCR signaling. To determine miRNA targets, photo-activatable ribonucleoside-enhanced cross-linking and immunoprecipitation (PAR-CLIP) analysis was performed on three latency III EBV+ AIDS-associated diffuse large B cell lymphoma (DLBCL) cell lines and also on Burkitt's lymphoma cells stimulated with anti-IgM to induce lytic reactivation. 3'UTR interactions, determined through subsequent bioinformatics and pathway analysis of the CLIP-seq data, were selected for validation by luciferase reporter assays. Targets related to BCR signaling were additionally confirmed by western blot analysis to monitor protein knockdown in the presence of the viral miRNAs. Decoy inhibitors were used in EBV+ BL cells to define specific viral miRNAs controlling BCR-mediated lytic reactivation. shRNAs directed against individual EBV miRNA targets were used in parallel experiments to mechanistically dissect miRNA-associated phenotypes.

Results: Our functional screens identified five EBV miRNAs that when ectopically expressed significantly reduced BCR-mediated NF-kB or AP1 activation. Temporal expression of BCR-responsive genes was also disrupted by EBV miRNAs. Congruent with these observations, inhibition of the endogenous EBV miRNA activity in EBV+ BL cells enhanced BCR-stimulated lytic reactivation. To gain insight into the molecular mechanisms by which EBV miRNAs influence BCR signaling, we performed PAR-CLIP analysis and identified >65 EBV miRNA targets associated with BCR signaling; these included core NF-kB components (CHUK, IKBKB), members of the Grb2 signalsome, and members of the MALT1 signaling complex. shRNAs to several of these targets could phenocopy EBV miRNA effects.

Conclusions: Our studies demonstrate that EBV miRNAs control the latent/lytic switch, in part, through inhibition of host signaling adaptor molecules situated downstream of BCR. Multiple BCR components are targeted by EBV miRNAs, and functionally, the viral miRNAs reduce BCR-mediated transcriptional activation, consequently influencing the transcriptional environment in infected host cells. Our data support a model whereby viral miRNAs actively dampen signals from external reactivation stimuli during persistent infection, thus playing a key role in maintaining a cellular environment conducive to latency. Ongoing studies are focused on dissecting additional relevant and critical miRNA interactions involved in g-herpesvirus infection.

9. Analysis of the Subcellular Localization of KicGAS (ORF52) of Kaposi's Sarcoma-Associated Herpesvirus (KSHV)

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To date, the Kaposi's sarcoma (KS) remains one of the most common AIDS-associated malignancies. As causative agent to KS, the Kaposi's sarcoma-associated herpes virus (KSHV) belongs to gammaherpesvirnae, which is also responsible for Primary Effusion Lymphoma (PEL) and Multicentric Castleman's Disease (MCD). ORF52 of KSHV is a small (131aa), basically charged, gammaherpesvirus-specific protein, and present abundantly in the tegument layer of virions. We recently found that ORF52 directly inhibits cGAMP synthase (cGAS), the principal cytosolic DNA sensor. ORF52 represents the first viral inhibitor of cGAS and is therefore also known as KicGAS (KSHV inhibitor of cGAS). Because both cGAS and KicGAS are mostly localized in the cytoplasm, we assumed the cytoplasmic localization of KicGAS is important for its inhibition of cGAS, but the mechanisms that govern KicGAS subcellular localization remained unknown. We therefore analyzed the subcellular localizations of KicGAS and its homologues of other related gammaherpesviruses. We found that ORF52 of KSHV, RRV, and MHV68 are mostly cytoplasmic localized but the EBV homologue (BRLF2) is surprisingly nuclear restricted. Interestingly, KicGAS cytoplasmic localization was largely unaffected by the treatment of leptomycin B (LMB), a anticancer drug that inhibits CRM1/exportin1-mediated nuclear export whereas RRV and MHV ORF52 relocated into nucleus upon LMB treatment. Analyses of a series of truncation and deletion mutants of KicGAS suggested the region near the 20th aa controls its localization. Further analyses revealed a classical PKI-class Nuclear Exporting Signal (NES).

Ongoing studies will determine the roles of the identified NES in cGAS inhibition and KSHV viral production.

10. Anaplastic Large Cell Lymphoma in HIV+ Patients: Clinicopathologic Analysis

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Background: Anaplastic large cell lymphoma (ALCL) may be ALK positive or ALK-negative. ALCL, ALK+ contain an *ALK* gene rearrangement (*ALK*-R) resulting in ALK protein expression.[1,2] ALCL, ALK negative consist of 3 genetic subgroups that associate with prognosis: (1) *DUSP22/IRF*-R (30%; good prognosis, similar to ALCL, ALK+) (2) *TP63*-R (8%; poor prognosis) and (3) no *DUSP22*-R, *TP63*-R *or ALK*-R, i.e. triple negative (TN; 60%; intermediate prognosis).[3] Mature T-cell non-Hodgkin lymphomas (TNHLs) in HIV+ individuals are rare, accounting for <5% of HIV-associated lymphomas. A significant percentage (~20%) of the HIV+ TNHLs are ALCL,[4-7] which are considered to be aggressive in HIV+ patients (median survival 5 months; 2 year overall survival 21%). Although a few HIV+ ALCLs are ALK protein positive, HIV+ ALCLs with an *ALK*-R are exceedingly rare.[4,5] Due to their rarity, HIV+ ALCLs are incompletely characterized. We evaluated the clinicopathologic features of HIV+ ALCLs, including FISH for genetic status.

Methods: Six HIV+ males and 1 female (age 33-63yrs; median 43 yrs) diagnosed with ALCL between 1990 – 2017 were studied. Clinical information was obtained from the medical record or the submitting institution. Where available, previous immunophenotypic and molecular results, including EBER ISH, LANA IHC and HTLV-1 PCR (these to exclude viral infection as a cause of CD30 expression), were reviewed. Where material was available, immunostaining for ALK protein and FISH for *ALK*-R, *DUSP22*-R and *TP63*-R was performed.

Results: At diagnosis 6 patients were on ART and 40% had a CD4 counts >200/mm3. Initial biopsy sites were: lymph node (3), skin (2), eyelid (1), peri-rectal tissue (1) with 3 patients having localized, 3 patients having disseminated and 1 unknown extent of disease. All ALCLs tested were CD30 and CD4 positive and CD20, CD8, LANA and EBER negative. CD2, CD5, CD7 and CD3 were expressed in 75%, 75%, 50% and 43% of cases, respectively. In 40% of tested cases ALK protein was positive. FISH analysis showed that 1/3 was *ALK*-R, however no *DUSP22*-R or *TP63*-R cases were identified. Where known, the patients were treated with chemotherapy with or without radiation and/or stem cell transplant. 2 patients have gone into remission and are alive 42 and 48 months from diagnosis; 3 have died 5,6 and 7 months after diagnosis and 2 patients have been lost to follow-up. Neither CD4 count nor ALK status correlated with outcome.

Conclusions: Although HIV+ ALCL, ALK+, is considered very rare in the literature, 40% of our cases express the ALK protein and/or are *ALK*-R. While some HIV+ patients with ALCL have aggressive disease, including one of our patients with an ALK+ lesion, others, including our 2 ALCL, ALK negative cases, if treated appropriately, have long-term survival.

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11. Androgen Receptor Activity in Prostate Tumors From HIV-Infected and HIV-Uninfected Men

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Background: Although androgens are required for prostate tumor growth, circulating levels of testosterone are not associated with development of prostate cancer. However, men with low testosterone who develop prostate cancer have tumors that are more aggressive, perhaps because tumors are already partially hormone refractory. Men with HIV more frequently experience hypogonadism compared with uninfected individuals and may be prone to develop more aggressive prostate tumors. We therefore hypothesized that androgen receptor activity is dysregulated in prostate tumors of men infected with HIV.

Methods: We selected 9 HIV-infected prostate cancer cases and 15 HIV-uninfected cases from among men included in the Uro-Onc Database (UODB) at the University of California, San Francisco for whom whole transcriptome gene expression profiling data was available from biopsy specimens as part of standard care. We evaluated the scores from three published signatures[1-3] related to androgen receptor activity with respect to HIV status using t-tests.

Results: Differential AR activity, as evidenced by the Sharma et al. 16-gene signature[1], the only signature derived from an analysis of AR binding sites in human prostate tissue, was significantly associated with HIV status **(Figure 1)**. HIV-infected men had more aggressive tumors based on previous analyses of the signature with respect to prostate cancer-specific survival in two independent clinical datasets. Mean scores for both of the in vitro-derived signatures, the Kumar et al. signature[3] (p=0.12) and the Faisal et al signature[2] (p=0.09), were also higher among HIV-infected men compared to HIV-uninfected men.

Conclusions: Our preliminary data suggest that AR activity may be altered in HIV-infected men with prostate cancer. Additional analyses among a larger validation sample of prostate cancer cases will investigate whether associations are independent of clinical and tumor characteristics, and evaluate the role of circulating androgen levels as mediating factors. These findings could inform prostate cancer management for HIV-infected men, as well as provide more general insight into the role of testosterone deficiency on prostate tumor development.

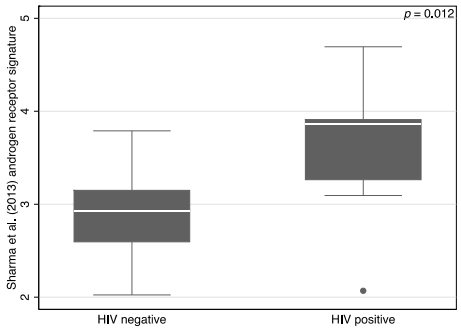

Figure 1. Expression of confirmed human AR target genes (Sharma et al. 16-gene signature) in prostate tumors from HIV-uninfected (n=15) and HIV-infected (n=9) men.

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12. Anti-KSHV and Anti-EBV IgA Antibodies in Saliva of HIV-Infected and Uninfected Cameroonians

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Background: In certain areas of sub-Saharan Africa (SSA), EBV infection is ubiquitous, KHSV infection very prevalent; and HIV infection generalized. Both KSHV and EBV are causal factors for malignancies common in SSA: Kaposi's Sarcoma (KS), Burkitt's lymphoma and other AIDS related non-Hodgkin's lymphomas (AR-NHL). Systemic humoral responses to KHSV have been extensively studied, however, antibody responses at mucosal surfaces in the oral cavities have not; in contrast, anti-EBV salivary antibodies are being actively investigated, albeit primarily in the context of another EBV associated malignancy, nasopharyngeal carcinoma. Because both EBV and KSHV are shed in and transmitted by saliva, it is imperative to understand mucosal immunity to both viruses, and the correlates of viral control in the oral cavity.

Methods: We developed a bead-based multiplex assay that measures IgA responses against 63 KSHV-encoded proteins, the well-studied EBV antigens EBNA and VCA, as well as a control antigen. Reactivity was measured by Median Fluorescence Intensity (MFI) and was log10 transformed. We tested archival saliva from 176 individuals recruited as controls in a previous KS case-control study, and investigated the relationship between anti KSHV and anti EBV saliva IgA and socio-demographic covariates, HIV infection, serum anti KSHV IgG measured via ELISAs and KSHV viral load (VL) in PBMCs and saliva measured by quantitative real time PCR. In univariate analyses, quantitative variables were evaluated with Pearson's correlation with correction for multiple comparisons; group differences were estimated with T-test; multivariate analyses utilized linear regression models.

Results: We examined samples from 176 individuals, selected to represent a linear, wide distribution of saliva KSHV VL. Median age was 38 years (interquartile interval, IQR, 32-47); 99 (56%) were men, 118 (67%) were HIV infected, 42(24%) had detectable KSHV VL in PBMCs, in those individuals, PBMC VL was however low (median, 2.2 logs, IQR 1.9-2.7). By design, 148 (84%) had a detectable KSHV VL in saliva (med 3.6 logs, IQR: 2.7-4.5). Proportion of responders over threshold was widely variable by antigen from below 3% to 61% (mean 18%); proportion for frequently studied antigens were: KSHV K8.1, 14%, KSHV ORF73 25%, EBNA, 3%, VCA 20%. Overall, IgA responses to KSHV antigen did not vary by HIV infection, but varied significantly by sex (M:2.53 logs, 95% confidence interval -95% CI- 2.52-2.55, F:2.49, 95%CI 2.47-2.5); the converse was true for EBV antigens (HIV+2.3, 95% CI 2.1-2.4 vs HIV-2.0, 95% CI 1.9-2.1). Responses to KSHV, but not to EBV were lower in individuals with detectable KSHV VL in saliva (2.51, 95% CI 2.50-2.52 vs 2.54, 95% CI 2.54-2.57). Saliva IgA did not correlate with age, with KSHV VL in saliva or PBMCs, nor with anti KSHV K8.1 serum IgG, however saliva IgA were modestly but significantly correlated with anti KSHV ORF73 serum IgG ($r=-0.1$, $p<0.0001$). In multivariate analysis, controlling for age, sex, HIV, detectable saliva KSHV VL, anti KSHV IgA were not independently associated with any factors, while anti KSHV IgA were higher in HIV infected individuals.

Conclusions: In a proportion of KSHV infected Cameroonians, anti KSHV and anti EBV salivary IgA were detectable; the proportion varied by antigen but was generally small. Individuals with detectable saliva KSHV VL and males tended to have lower anti KSHV IgA, while anti EBV IgA were higher in HIV infected persons.

13. Antiretroviral Therapy Reduces Human Herpesvirus-8 Replication in Oral Mucosa and Plasma Among Ugandan Adults With HIV Infection

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Background: Antiretroviral therapy (ART) may inhibit human herpesvirus-8 (HHV-8) replication through several mechanisms, including a direct drug effect or through suppression of HIV and restoration of host immunity. We sought to determine the effect of ART initiation on HHV-8 replication among Ugandan adults.

Methods: In 2012-2015 we conducted a prospective study of persons co-infected with HIV and HHV-8, without Kaposi sarcoma, and ART naïve, in Kampala, Uganda. Infection with HHV-8 was defined as ≥3 oral swabs or ≥1 plasma sample with HHV-8 DNA detected by polymerase chain reaction (PCR). Participants provided weekly blood samples and collected home oral swabs before and after initiating ART for up to 2 years. HHV-8 DNA was quantified in samples by PCR. Mixed effects models tested for associations of ART, sex, age, baseline CD4 count and HIV-1 RNA level with HHV-8 shedding.

Results: Of 140 enrolled participants, 36% were men; median age was 31 years (range 20-56). At baseline, median CD4 T-cell count was 277 cells/mm3 (range 56-487) and median plasma HIV-1 RNA was 4.9 log10 copies/mL (range 2.6-6.3). During the study, 114 participants started ART with non-nucleoside reverse transcriptase inhibitor-based regimens.

9305 oral swabs and 1293 plasma samples were collected. Before ART, HHV-8 was detected in 69% (1391/2004) oral swabs and 35% (147/419) plasma samples. After ART initiation, HHV-8 was detected in 45% (3275/7301) oral swabs and 27% (240/874) plasma samples. Compared to pre-ART, reduction of oral HHV-8 replication was greater in months 4-24 after ART initiation (RR=0.5, 95% CI 0.4-0.6, p<0.001) than in months 0-4 (RR=0.8, 95% CI 0.7-0.9, p<0.001). Older age was associated with a reduction in frequency of oral HHV-8 shedding (RR=0.8 per 10 years older, 95% CI 0.7-1.0), while higher rates were observed in men (RR=1.7, 95% CI 1.3-2.2) and those with higher baseline CD4 (RR=1.1 per 100 unit increase, 95% CI 1.0-1.3). ART was also associated with reduction of plasma HHV-8 detection in months 4-24 (RR=0.6, 95% CI 0.4-0.7, p<0.001) but not in months 0-4 (p=0.72).

Conclusions: ART significantly reduces oral and plasma HHV-8 replication in adults with HIV, which may have implications for decreasing HHV-8 transmission and preventing KS. The greater reductions in HHV-8 rates observed after 4 months of therapy suggest the primary mechanism of ART effect on HHV-8 is indirect through HIV suppression or improved host immune function.

14. Association of Serum Markers of Inflammation and Immune Activation With the Incidence of Non-AIDS-Defining Cancers in Men Living With HIV

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Background: The introduction of HAART in the mid 1990's led to a dramatic increase in life expectancy of people living with HIV (PLWH), and a decline in mortality attributable to AIDS-defining malignancies. However, the incidence of non-AIDS defining cancers (NADCs) has increased in PLWH, and is currently higher than in the general population. One possible explanation is that some NADCs may be promoted by the state of persistent inflammation and immune activation from HIV in PLWH. The objective of this study was to examine the relationship of serologic markers of inflammation and immune activation with NADCs among participants enrolled in the Multicenter AIDS Cohort Study (MACS).

Methods: We conducted this cross-sectional analysis using data from 1533 HIV-infected men in the MACS who had 24 inflammation/immune activation markers tested in longitudinal serum samples obtained between 1984 and 2009. All men who developed an AIDS-defining cancer were excluded. Our study population included 73 men who developed a NADC and had serum markers tested within 2 years before cancer diagnosis, and a comparison group of 1460 men who remained cancer-free throughout follow-up. For the comparison group we selected the last MACS visit at which serum marker data were obtained. The 24 pro- and anti-inflammatory and immune activation molecules included IL-1β, IL-6, sIL6r, IL-8, TNF-α, sTNF-R2, CRP, eotaxin, MCP-1, MCP-4, MIP-1, TARC, GM-CSF, IFN-γ, IP-10, IL-2, sIL-2Rα, IL-10, IL-12p70, BAFF, BLC/BCA-1, sCD14, sCD27, and gp130. We examined the association of the markers with overall NADC incidence, and separately for five NADC subgroups: a) NADCs with a known viral etiology, b) NADCs without a known viral etiology, c) prostate cancer, d) anal cancer, and e) GI cancers. The marker values were log-transformed and then compared using multiple linear regression models to adjust for MACS site, age, race, education, smoking history, BMI, current CD4 cell count, HIV RNA level, viral hepatitis infection, cumulative HAART exposure, prior AIDS diagnosis, and calendar year.

Results: Men who developed a NADC were significantly older than the controls (median 52.4 vs. 46.6 yrs, respectively; $p<0.01$), and had significantly higher smoking exposure and less cumulative HAART exposure. Levels of IL-6, TNF-α, CRP and IFN-γ were significantly elevated in the NADC group compared to cancer-free participants. CRP, IFN-γ, TARC, BLC/BCA-1 and BAFF were each significantly elevated in participants with virus-related cancers, but only CRP was significantly elevated in participants with viral-unrelated cancers. No marker was significantly elevated in men with prostate cancers, sIL6r was the only maker significantly elevated in men with anal cancer, and CRP was the only marker elevated in men with a GI cancer.

Conclusions: Consistent with other cancers, increased inflammation (IL-6, TNF-α, CRP) precedes the incidence of NADCs among PLWH, as well as increased cellular immune responses (IFN-γ); for NADCs with a known viral etiology, increased T and B cell activation may also contribute. The cross-sectional design of this study, however, limits our ability to draw conclusions about whether the association between increases in serum markers and NADC incidence is due to HIV-related immune dysregulation, production of factors by developing tumors or tumor microenvironment, or inflammation and/or immune responses stemming from coinfection with other oncogenic viruses. Further research is needed to examine the presence of viral coinfection together with longitudinal immune marker data and markers of HIV disease progression, to further explore whether inflammation and/or inappropriate immune activation due to HIV infection explains the elevated risk of NADCs among PLWH, and whether effective HIV therapy lowers this risk.

15. Associations of Serum Inflammatory Biomarkers and Kaposi's Sarcoma in Men Who Have Sex With Men From 1984 to 2010

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Background: AIDS related Kaposi's sarcoma (AIDS-KS) continues to be a source of significant morbidity and mortality among the HIV infected population, despite the advent of HAART with 7.5 cases per 1000 person-years occurring in the United States[1]. This study investigated the association of serum biomarkers of inflammation and immune activation prior to AIDS-KS development.

Methods: Data were collected by the Multicenter AIDS Cohort Study (MACS) between 1984 and 2010 for the longitudinal cohort of 1500 men who have sex with men in the ARRA1 sub-study. Levels for 25 biomarkers were tested in serum from 10,000 visits. Biomarkers include: eotaxin, GM-CSF, IFN-γ, IL-12p70, IL-1β, IL2, BAFF, sCD14, IL-6, sGP130, sIL-2Rα, BLC-BCA1, CD27, sTNFR-2, IL-8, IL-8 Pro, IL-6, sCRP, IP-10, MCP-1, MCP-4, MIP 1β, TARC and TNF-α. Each biomarker's levels were log transformed and compared between those who developed AIDS-KS and those who did not. Three different Cox proportional hazards models were developed for each natural log transformed biomarker. (1) unadjusted, (2) adjusted for age at the last visit, time on HAART and race/ethnicity and (3) fully adjusted for HBV co-infection, HCV co-infections, race/ethnicity, age at last visit, education, smoking and time on HAART. These models were run for all visits and for the visits one year prior to diagnosis or censoring.

Results: At the visits one year prior to censoring or AIDS-KS diagnosis, GM-CSF, IL-6, IL-12p70, MIP1 β and BAFF were each statistically significantly lower among cases than those without AIDS-KS. Other biomarkers were elevated among AIDS-KS cases including: sIL-2Rα, IP-10, MCP-1, sTNF-R2, and sCD14. In the fully adjusted model, across all study visits, sIL-2Rα (HR= 4.24, p=<.0001), sIL-6R (HR=2.40, p=.0093), IL-10 (HR= 1.61, p=<.0001), IP-10 (HR= 2.53, p=<.0001), MCP-1 (HR=3.79, p=.0001), MIP 1β (HR=.60, p=.0034), sTNFR-2 (HR=3.61, p=<.0001), BAFF (HR=2.59, p=<.0001), sCD14 (HR=3.88, p=.0065)and CD27 (HR=2.32, p=.0004) were found to be statistically significantly associated with risk of AIDS-KS. At one year prior to diagnosis or censoring in the fully adjusted model, sIL-2Rα (HR= 2.47, p=.0013), IP-10 (HR=1.81, p=.0045), IL-10 (HR= 1.48, p=.0007), MCP-1 (HR=2.75, p=.0168), sTNFR-2 (HR=2.24, p .0069), BAFF (HR=1.65, p=.0330), and CD27 (HR=1.76, p=.0437) were statistically significant.

Conclusions: While the majority of the biomarkers had differences in their overall averages, in the final year before diagnosis only five were significantly lower and 5 were significantly higher than levels found in those who did not develop AIDS-KS. Six of these were also statistically significant predictors for AIDS-KS in the Cox proportional hazards models. All of these increased the hazard ratio of developing AIDS-KS indicating that increased levels of these markers may predictive of AIDS-KS development.

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16. Autocrine Beta-adrenergic Signaling Drives Proliferation of Cells Transformed by KSHV and Suppresses Lytic Viral Replication

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Background: Kaposi sarcoma (KS) and primary effusion lymphomas (PEL) are tumors associated with immune suppression in HIV-positive individuals infected with KS herpesvirus (KSHV). Both tumors are difficult to treat, particularly in resource-limited settings. Therefore, we have sought out generic medications with in vitro activity against these neoplasias that may improve the treatment response of patients with KS and PEL in a variety of economic settings.

Methods: We assessed the effect of the generic "beta blocker" propranolol using an established in vitro models of KS as well as PEL cell lines. Proliferation of cells was assessed by measurement of XTT metabolism as well as flow cytometry of cells stained with BrdU and 7-AAD in the presence or absence of drugs, including the beta adrenergic antagonists propranolol, metoprolol, or ICI118,551 (non-selective, beta-1-selective, and beta-2-selective, respectively); the STAT3 inhibitor 5,15-DPP; or the CDK6 inhibitor PD-0332991. Expression of the beta-1 and beta-2 receptors on model cells was measured by flow cytometry. RT-PCR was used to demonstrate expression of the enzymes required for synthesis of catecholamines. Secretion of the catecholamines norepinephrine and epinephrine by KSHV-infected cells was measured with a commercially-available ELISA. Cell viability following treatment with bleomycin with or without propranolol was measured by XTT metabolism. Finally, efficacy of propranolol with or without ganciclovir was assessed using NOD/SCID mice engrafted with the PEL cell line BCBL-1.

Results: Proliferation of KSHV-infected endothelial cells and PEL cells was reduced and viral lytic gene expression was increased by all three beta adrenergic antagonists tested. In both cell types KSHV-infected cells secreted norepinephrine and epinephrine and expressed the betaadrenergic receptors through which these catecholamines signal. Bleomycin and propranolol demonstrated synergistic killing of both lymphatic and vascular endothelial cells transformed by KSHV. The proliferative defect seen in PEL cells was associated with STAT3 and CDK6 activity. Daily administration of propranolol along to NOD/SCID mice bearing BCBL-1 cells in the peritoneum resulted in decreased solid tumor formation and de-repressed expression of viral lytic genes. Co-administration of propranolol and ganciclovir resulted in a statistically significant survival benefit over control animals. CONCLUSIONS Our data demonstrate that the generic drug propranolol has activity against two KSHV-associated malignancies and suggest that autocrine beta-adrenergic signaling contributes to cancer cell proliferation and maintenance of latency. Reduction of proliferation with concomitant lytic induction provides an opportunity for cytotoxic anti-tumor drug treatment. Further evaluation of beta-adrenergic antagonists for the treatment of KSHV-associated neoplasias is therefore warranted.

17. Biochemical Characterization of EBV Nuclear Antigen Regulation of Host Transcription Through the Notch Signaling Pathway and Implications for Rational Drug Design

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Background: Epstein-Barr virus (EBV) is one of the most prevalent and persistent oncogenic viral infectious agents, with over 90% of humans infected from childhood and adolescence for the duration of their lives. Typically, EBV infection is asymptomatic because a cytotoxic T-cell response suppresses active EBV infection and the virus assumes restricted latency. In immunocompromised patients, however, the host immune system may no longer be able to adequately control EBV infection of B-cell lymphocytes, permitting EBV to enter less restricted latency. This can result in uncontrolled cellular proliferation, leading to EBV-associated malignancies such as Burkitt's and several other B-cell lymphomas. EBV-associated malignancies contribute to 1.8% of all cancer deaths worldwide.

EBV proteins mediate oncogenesis, in part, by co-opting the host Notch signaling pathway, an important developmental pathway involved in B cell maturation. Of the nine viral latency proteins, four—EBNA2, 3A, 3B, and 3C—bind to and modulate the activity of the downstream DNA binding component of the Notch signaling pathway, the host transcription factor RBPJ, which normally activates transcription from the binding of the cleaved intracellular domain of host NOTCH1 during active Notch signaling. The interactions of EBNA2, EBNA3A, and EBNA3C with RBPJ are critical for establishment of cell growth during latent EBV infection and are required for *in vitro* EBV transformation of B cells into lymphoblastoid cell lines (LCLs).

Despite the importance of EBNA-RBPJ interactions for EBV replication and oncogenesis, the interface between RBPJ and the EBNAs has been poorly characterized because of technical challenges in obtaining soluble EBNA protein for study. The present study overcomes these technical challenges to structurally characterize the EBNA proteins and biochemically identify their interactions with rationally mutated RBPJ. We propose a molecular model by which RBPJ interacts with its four viral-binding partners, the EBNAs, and its host-binding partner, intracellular NOTCH1, at unique and overlapping sites. The resulting high-resolution map of RBPJ's binding interfaces can guide future rational design of therapeutics that inhibit virus-RBPJ binding without disrupting host-RBPJ interactions.

Methods: Human RBPJ, EBNA, and NOTCH1 constructs were recombinantly expressed using *E. coli* and purified using nickel affinity, ion exchange, hydrophobic interaction, and gel filtration chromatography. Protein-protein interactions were biochemically characterized using co-precipitation and fluorescence anisotropy. Structural information will result from x-ray crystallography.

Results: The wild-type RBPJ construct has been shown to bind both the EBNA2 and NOTCH1 constructs by fluorescence anisotropy. In contrast, single site-specific mutants of RBPJ have been shown to selectively disrupt RBPJ binding to EBNA2 and NOTCH1. Further, a novel purification strategy of the EBNA3 constructs has been demonstrated to yield soluble EBNA3 for further biochemical and structural characterization, thereby overcoming the major technical hurdle for characterizing the EBNA3 proteins.

Conclusions: Preliminary data are consistent with the literature and our proposed model that RBPJ interacts with its binding partners at unique and overlapping sites. The novel strategy to purify the EBNA3 constructs has generated sufficient quantities of protein for binding characterization using fluorescence anisotropy and structural characterization using x-ray crystallography. The goal is for these data is to generate a high-resolution map of RBPJ's interactions with its binding partners, enabling future rational design of drugs to treat EBV-associated cancers.

18. Cancer-Specific HIV Nef Identified in Tumor Tissues From Patients With End-Stage Lymphoma

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Background: AIDS-related lymphoma (ARL) is a disease process wherein HIV-infected and activated tumor associated macrophages (TAMS) are found within B-cell lymphomas. The HIV Nef protein is a flexible and multifunctional protein that is required for pathogenicity of the virus. Numerous functions of the Nef protein have been associated with TAMs, where it plays a role in regulating function and promoting their survival. Furthermore, HIV-infected macrophages form small virological synapses that extend into B-cells in the presence of Nef. These synapse nanotubes then exclusively transport Nef from macrophages into B-cells, evading protective virus-specific immunoglobin responses and interfering with the production of certain classes of antibodies in B-cells. Nef maintains a high degree of genetic variation among intra- and inter-host isolates; however, while several functional Nef domains have been identified, their importance in ARL has not yet been discerned. In an earlier study, we reported that specific Nef protein three-dimensional structures were associated with viruses isolated from ARL tumor tissues from two patients. In the current study, we used a novel machine-learning approach, applied to 1,698 sequences derived from 31 subjects and 25 types of anatomical tissues, to determine if it was possible to classify Nef sequences as from ARL(+) or ARL(-) cases based on structural or functional domains of the protein.

Methods: 1,698 unique Nef sequences were downloaded from public data resources, translated and aligned. For 23 subjects, the primary pathology of the subjects at death, other than HIV infection, was known. 71 different features describing various physicochemical characteristics of amino acids were identified from the available literature and resources. These features were grouped into six major classes: amino acid size, shape or structure (n=24), polarity (n=6), composition (n=5), hydrophobicity (n=25), and miscellaneous other features such as those associated with HPLC and pKa (n=8). All features were calculated for the complete Nef protein and 10 specific functional domains in separate analyses. A total set of 71 features calculated for 11 total regions, or 781 total features. A standard regression analysis was used to determine that 153 of the 781 features individually maximized class separation between Nef sequences derived from brain and non-brain tissues. These 153 features were then provided as input in the development of evolved neural networks sub-selecting 10 at a time as input to the models. The set of all sequences with known tumor or non-tumor origin was divided randomly into training (n=1019 sequences), testing (n=509 sequences), and validation (n=170 sequences). The process of generating training and testing sets was repeated three times with random assortments of the sequence data to avoid sampling bias. The best neural network was assayed for performance on the training, testing, and validation sets. A binary discriminating threshold was determined to maximize classification accuracy of the two classes ARL and non-ARL virus. This threshold was fixed prior to use with any testing or validation samples. In this way, the neural network output (ZAPP score) could be compared to the threshold for the purpose of binning sequences into one or the other class.

Results: Nef sequences from ARL (+) subjects were classified correctly at >90%, indicated that there are underlying physicochemical differences between Nef derived from patients with ARL as compared to other populations, particularly subjects with neurological disease.

Conclusions: The study suggests that there is a HIV Nef-associated contribution to ARL pathogenesis. The approach elucidated structure-function properties of brain and tumor Nefs that were not discernable by viewing sequence information alone. This machine learning approach applied to a much larger set of data, could generate predictors for HIV associated disease such as ARL and provide potential new drug targets.

19. c-Myc Represses Transcription of the Epstein-Barr Virus Latent Membrane Protein 1 Early After Primary B Cell Infection

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Background: Epstein-Barr Virus (EBV) is a large herpesvirus that is almost ubiquitous within the human population with >95% of people harboring a latent EBV infection in resting memory B cells. Primary EBV infection can result in infectious mononucleosis, but is normally controlled by $CD8^+$ T cells. In immune compromised individuals, such as HIV-infected patients, latent EBV can promote uncontrolled B-cell proliferation leading to diffuse large B-cell lymphomas. This disease can be modeled by *de novo* infection of primary human B cells with EBV, which leads to their immortalization into lymphoblastoid cell lines (LCLs). The major viral oncoprotein, Latent Membrane Protein 1 (LMP1), is required for immortalization. Our lab has demonstrated that LMP1, surprisingly, does not reach LCL expression levels until ~21 days following primary B-cell infection. Given the rapid proliferation of early-infected B cells and the important role of c-Myc as a driver of proliferation, we investigated the role of c-Myc in regulating LMP1 expression.

Methods: Lymphocytes from healthy human blood donors were isolated using a histopaque density gradient. Cells were stained with the proliferation tracking dye CellTrace Violet (CTV) before being infected with EBV B95-8 strain. To study early proliferation, B cells were either sorted to purity from PBMCs based upon CD19 expression and CTV prolife ($CD19^+/CTV^{low}$) on day 7 post infection or treated in bulk. To study times late post-infection, EBV infected B cells were cultured for >35 days to generate pure lymphoblastoid cell lines (LCLs). 4-thiouridine metabolic labeling of nascent mRNA was used to profile transcription rates as well as ChIP-PCR to interrogate promoter occupancy. Western blot and RT-qPCR analysis was used to determine changes in gene expression and protein abundance.

Results: We found that the change in LMP1 mRNA expression from day 7 to LCL was due to a ~25-fold increase in transcription rate with a 2-fold increase in half-life resulting in a 50-fold increase in LMP1 mRNA abundance. This effect was specific to the LMP1/2A bi-directional promoter (LMP1p) as we did not observe a significant change in the transcription rate of viral EBNA transcripts from the C promoter. The LMP1p was similarly occupied by the viral EBNA2 transcription factor at early versus late times post infection, but displayed increased H3K9Ac, indicative of active promoters. The chromatin insulator CTCF, necessary for LMP1 expression in LCLs, displayed similar LMP1 promoter occupancy early versus late implying that the change in LMP1 transcription was not due to a change in chromatin looping. We found that an EBV-infected Burkitt's lymphoma cell line expressing high levels of endogenous c-MYC displayed significantly lower levels of LMP1 transcription relative to an LCL. Using an LCL system with conditional EBNA2 and c-Myc expression, we found that c-Myc over-expression suppressed LMP1 transcription. Finally, c-Myc inhibition via the BET inhibitors JQ1 and OTX015 caused an increase in LMP1 mRNA levels in early-infected B cells suggesting a physiological role for c-Myc in LMP1 repression.

Conclusions: This study shows that the transition from EBV-infected primary B cells to immortalized LCLs proceeds through a period of c-Myc mediated repression of LMP1. While LMP1 is necessary for immortalization and LCL survival via signaling through NF□B, the interplay between c-Myc and LMP1 must be tightly regulated to promote cellular survival. However, the physiological reason to maintain low LMP1 levels early after infection remains unknown. As it is known that NF□B signaling enhances antigen presentation, LMP1-expressing B cells are prime targets for $CD8^+$ T cells. Thus, high levels of c-Myc after EBV infection may serve as a mechanism for immune evasion via reduced antigen presentation. This would allow infected cells to transition into the resting memory B cell compartment, the ultimate reservoir for latent EBV-infected B cells *in vivo*. However, in the absence of T-cell pressure, as in HIV-infected patients, the transition to high LMP1-expressing LCL-like cells can drive lymphomagenesis. Understanding the interplay between c-Myc and LMP1 can lead to a better understanding of how EBV^+ lymphomas develop within immune-compromised hosts. This can ultimately lead to the development of better prognostic biomarkers and new therapeutic rationale for EBV-associated lymphomas in HIV/AIDS patients.

20. Distribution of HPV Subtypes Associated With Invasive Cervical Cancer in HIV-Infected and HIV-Uninfected Women From Botswana

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Background: Cervical cancer is the fourth most common cancer in women worldwide and a leading cause of cancer in Botswana. Human papillomavirus (HPV) is the primary causative agent. In general, women with HIV are at a higher risk of persistent HPV infection leading to cervical cancer. However, distribution of HPV subtypes by HIV status is not well known in invasive cervical cancer in Botswana.

Objective: To define the prevalence and distribution of HPV genotypes by HIV status among women with cervical cancer from Botswana.

Methods: The DNA was extracted from formalin-fixed, paraffin-embedded samples (10 µm section) of 134 cervical cancer specimens. HPV genotyping was performed through Abbott Real-Time PCR. For samples with low DNA yield, we designed a double nested-PCR approach (using consensus SB01/02 primer pair followed by MY011/09 primers and therefore GP5/6 primers) and the final 150bp PCR products were subjected to direct DNA sequencing to determine HPV subtypes. Statistical comparisons were done through likelihood ratio chi-square and logistic regression analyses.

Results: Of the 134 women, 94 were HIV-infected and 40 were HIV-infected. Median age of all patient was 49 years (range: 29–84) and most patients presented with stages II (49%) and III (34%) disease. The HPV-high risk (*HR)* types identified alone or in combination with other subtypes were HPV-*16* (80%), -*18* (28%), -*45* (4%), -*33* (3%) -*56* (0.7%) and the rest were other HPV-*HR* (8%), which it was not possible to further determine. Eighty nine (89%) of HIV-infected, 73% of HIV-uninfected and overall 84% of all patients had HPV-*16*, -*18* or both. HIV-uninfected subjects were likely to be HPV-*45* carriers (*P*=0.058). About 33% of HIV-infected subjects had more than one HPV subtype and 30% of HIV-uninfected had more than one HPV subtype. The age group distribution of the participants was not significantly associated with overall HPV-*HR* prevalences. There was also no significant correlation between cancer stage and HPV-*HR* genotypes. However HPV-*33* was seen to be more common in cancer stage I (*P*=0.063).

Conclusion: In our cohort of cervical cancer patients, more HIV-infected patients present with HPV-*16/18* subtypes compared to HIV-uninfected patients. Although HPV-*16/18* accounts for most cervical cancers in Botswana, other HPV-*HR* subtyples are assoicated with a signficant number of cervical cancers as well. Close to a third of pateints have more than one HPV subtype in the tumor tissue.

21. EBV-Mediated B-Cell Transformation Is Suppressed by Oncogene-Induced Senescence Through Establishment of a Persistent DNA Damage Response

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Background: Epstein-Barr virus (EBV) is an oncogenic γ-herpesvirus that is associated with B cell lymphomas, particularly in HIV-infected, immunocompromised patients. Approximately half of all cases of AIDS related lymphomas, including AIDS Non-Hodgkin's Lymphomas (AIDS NHL), are associated with EBV. This viral infection is ubiquitous in the human population and healthy individuals control the infection by a strong cytotoxic T-cell response.

Early after EBV infection *in vitro*, primary human B cells undergo a transient period of hyper-proliferation, which results in replicative stress and formation of double stranded DNA breaks. This DNA damage is sensed by a DNA damage response (DDR) kinase, ATM, which triggers a signaling cascade ultimately resulting in cell cycle arrest and the inhibition of EBV-mediated transformation. In our recent studies, we found that early arrested EBV-infected B cells exhibit a metabolic imbalance characterized by decreased oxidative phosphorylation activity and low dNTP nucleotide pools. Furthermore, we reported that supplementation of growth media of early EBV-infected B cells with exogenous nucleosides can not only enhance transformation of B cells, but also reduce the level of activated DDR foci present early after infection.

Cellular senescence due to oncogene activation often results in activation of a persistent DDR, characterized by DNA damage occurring at irreparable genomic sites, such as telomeres. Recent work from the Masucci group suggests that persistent DDR foci, including telomere dysfunction-induced foci (TIFs) and ALT-associated PML nuclear bodies (APBs) are present early after EBV infection. We therefore sought to characterize the persistent DDR foci that exist in the specific subpopulation of EBV-infected B cells that undergo cellular arrest.

Methods: In this study, we applied a unique double staining method to isolate EBV-infected primary human B cells that initially proliferate and then arrest from cells that continue to proliferate and become immortalized. The arrested population was sorted and examined by immunofluorescence and IF-Telomere FISH to examine the localization of DNA damage. Further, proliferation and transformation assays were performed to determine factors associated with establishing senescence.

Results: We found that the arrested subpopulation of EBV-infected B cells exhibited an increase in both the presence of PML NBs and the localization of PML NBs to DNA damage foci, including γH2AX and 53BP1. Additionally, we observed an increase of hallmarks of persistent DDR present in the arrested cells as compared to LCLs, which include ALT-associated PML NBs and telomere dysfunction-induced foci. Importantly, we found that treatment with danazol, a drug used to treat telomere diseases and increases telomerase reverse transcriptase expression, significantly increased proliferation of early EBV-infected B cells and enhanced transformation, thus permitting early infected cells to overcome cellular senescence.

Conclusions: In a model of immune-suppression associated EBV-induced B-cell proliferation, we observed the presence of hallmarks of persistent DDR foci early after EBV infection specifically in the arrested subpopulation of B cells. Additionally, we found that danazol, a drug used to treat telomere diseases, can facilitate EBV-infected B cells to overcome the early aberrant proliferation-induced cellular arrest and ultimately enhance transformation of B cells. These data describe the innate tumor suppressor responses important to control the earliest events of EBV-mediated B-cell immortalization in the immune-suppressed, such as those infected with HIV.

22. Epstein-Barr Virus Activation by Nelfinavir Is Linked to the JNK Pathway and Autophagy

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Background: Latent infection of Epstain-Barr Virus (EBV), which can be reactivated by various cellular mechanisms, is associated with a variety of malignancies. ER stress can activate the EBV, as shown by previous studies using bortezomib[1]. Nelfinavir is an HIV protease inhibitor that has been shown to induce ER stress in various cancer cell lines[2]. However, the specific mechanism of nelfinavir on virus activation has not been explored. Based on a report that ER stress activates the c-Jun N-terminal kinase (JNK) signaling pathway and autophagy[3], we investigated whether these pathways are involved in nelfinavir-induced EBV activation.

Methods: The Akata Burkitt lymphoma cell line and an engineered derivative cell line (BX1) carrying a recombinant EBV that constitutively expresses a green fluorescent protein (GFP) were used. Cells were treated with varying doses of nelfinavir and the JNK inhibitor SP600125 at 20μM. Chloroquine (10μM) or 3-methyladenine (5mM) was used for autophagy inhibitions. Fluorescence microscopy was used to determine the number of lytic cells expressing GFP. Quantitative PCR was performed to measure DNA viral load and reverse-transcribed RNA levels.

Results: Nelfinavir treatment in Akata cells induced EBV lytic gene expression in a dose-dependent manner as assessed by increased EBV Zta RNA levels and GFP expression in BX1 Akata cells. The JNK inhibitor SP600125 blocked lytic expression. Inhibiting early steps of autophagy by 3-methyladenine blocked nelfinavir-induced EBV activation, while inhibiting late steps of autophagy by chloroquine did not.

Conclusions: These results suggest that the JNK signaling pathway mediates EBV induction by nelfinavir and that the early steps of autophagy play an important role in this process. Further studies will help clarify the mechanism involved in the pathway and provide insight into the effect of nelfinavir *in vivo*.

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23. Epstein-Barr Virus Promotes Apoptosis Resistance by Inducing a Germinal Center-Like Reaction in In Vitro Infected B Cells

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Epstein-Barr virus (EBV) is a highly prevalent pathogen that manipulates apoptosis to establish latent infection in immune-competent hosts and to ensure tumor survival in immune-compromised individuals. Primary infection takes place in the oral cavity, where viral entry induces naïve B cells to undergo the germinal center (GC) reaction to gain access to the long-lived memory B cell compartment. Because apoptosis eliminates several cells during the GC reaction, the "Germinal Center Model" for latency establishment posits that viral expression is temporally regulated to mimic the various stages of B cell maturation to overcome the apoptotic barrier. Consequently, apoptotic regulation is critical for the survival of EBV-infected B cells *in vivo.* While some findings suggest that EBV can bypass the GC by directly infecting memory B cells, we have observed that *in vitro* infection of naïve and memory B cells mimics several aspects of GC B cells, indicating that a GC-like reaction is inherent to the viral life cycle. Using BH3 profiling, we found that both human GC B cells and early-infected B cells depend upon MCL-1 to regulate apoptosis at the mitochondria. Consequently, human GC B cells and early-infected B cells are resistant to ABT-737, a chemotherapeutic that activates intrinsic apoptosis by inhibiting BCL-2, BCL-XL, and BCL-W. In addition to MCL-1, GC-levels of CD38 expression were also observed in early-infected B cells, as well as the upregulation of several markers associated with B-cell maturation, such as PAX5, IRF4, BLIMP1, and XBP1. These levels of CD38 expression were absent in mitogen-stimulated proliferating B cells, suggesting a virus-specific effect. However, in early-infected B cells, there is a significant downregulation of BCL-6, which is necessary for the GC reaction, and CXCR4, indicating that some aspects of the GC are adverse for EBV outgrowth. These findings show that, to an extent, GC mimicry is important in EBV outgrowth *in vitro*, with the notable exception of BCL-6. The role of MCL-1 in mediating survival in not just EBV-infected B cells but also in normal GC B cells make it an especially interesting candidate to target in EBV-associated malignancies and GC-derived lymphomas.

24. HIV Status Is Associated With Enhanced Oncogenic Signaling in Diffuse Large B Cell Lymphoma

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Background: In the post-ART era, Diffuse Large B cell Lymphoma (DLBCL) is up to 17-fold more likely to occur in HIV positive (+) individuals compared to HIV negative (-) individuals and tends to follow a more aggressive clinical course. Moreover, the vast majority of HIV(+) patients frequently present at advanced stages with high tumor burdens with poor prognosis. The molecular pathology underpinning the clinical features of DLBCL in HIV(+) patients relative to the general population is poorly understood; however, it is suspected to depend on decreased host immune surveillance and alternative mechanisms of tumorigenesis. In this study, we sought to identify the differences in gene expression between HIV(+) and HIV(-) DLBCL cohorts that may contribute to the unique features of HIV(+) DLBCL.

Methods: Gene expression profiling (GEP) was performed on a total of 70 DLBCL cases, 31 HIV(+) obtained from AIDS Cancer Specimen Resource (https://acsr.ucsf.edu/) and 39 HIV(-) institutional cases. All cases were reviewed by a hematopathologist to determine tumor content and cases with less than 70% tumor content were macro-dissected. RNA was extracted from 4x 5µm formalin fixed, paraffin embedded (FFPE) sections using the Qiagen AllPrep DNA/RNA FFPE Kit and quantified using a NanoDrop. Digital GEP was performed using customized NanoString GEP panel targeting over 1300 genes including nine HIV-1 viral genes.

Results: The NanoString Lymph2Cx assay, which subtypes DLBCL by cell of origin (COO), showed that 74% (23/31) of HIV(+) cases were of Germinal Center B cell (GCB), 13% (4/31) were Activated B cell (ABC) and 13% (4/31) were Unclassifiable (UNC). In comparison, 54% (21/39) of HIV(-) cases were GCB, 31% (12/39) were ABC and 15% (6/39) were UNC. Although no association with COO subtype was found, when the data was re-analyzed within the GCB subtype alone, stratification by HIV status was observed. In particular, reduced expression of genes associated with immune regulation was observed in HIV(+) GCB cases compared to HIV(-) GCB cases. In contrast, expression of genes associated with cell cycle regulation and homologous recombination (the predominate double stranded DNA repair pathway employed during the cell cycle), were higher in HIV(+) cases compared to HIV(-) GCB cases. Intriguingly, low, but measurable, expression of HIV-1 genes was observed in approximately 30% of HIV(+) cases but not in HIV(-) cases.

Conclusions: Within the GCB subtype, marked differences in gene expression are associated with HIV status. We also identified detectable levels of HIV gene expression within the HIV(+) cohort. Overall, the data suggest that the aggressive nature of DLBCL in HIV(+) patients may, in part, be mediated by enhanced cell proliferation potentiated by aberrant DNA repair that may be further compounded by intra-tumoral, HIV-infected immune cells such as T-cells or histiocytes.

25. HPV-16 DNA Quantitation Distinguishes Cytology and Pathology Grades in Anal Dysplasia/Cancer

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Background: There have been increasing trends in anal dysplasia/cancer particularly among those infected with HIV. Due to these increasing incidence rates, HIV-positive individuals are encouraged to undergo routine anal dysplasia screening using anal cytology with a follow-up high resolution anoscopy (HRA), the current gold standard, if the anal cytology is abnormal. However, variability in anal cytology sensitivity and specificity possibly due to sampling could influence if and when follow-up HRA is performed. The objective of this study was to include HPV-16 DNA quantitation in the screening algorithm since HPV-16 is the most prevalent high-risk HPV type and accounts for the majority of anal cancers.

Methods: Anal cytology specimens were obtained from 75 HIV-positive patients enrolled in the Hawaii Center for AIDS RMATRIX Pilot Project RM004 and used for anal cytology and HPV-16 detection. Abnormal anal cytology results were reported as atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells but cannot exclude high-grade (ASC-H), low-grade squamous intraepithelial lesions (LSIL), or high-grade squamous intraepithelial lesions (HSIL). Biopsy results obtained from an HRA were available from 18 patients who provided consent. Abnormal biopsy results were reported as low-grade anal intraepithelial neoplasia (LGAIN) and high-grade anal intraepithelial neoplasia (HGAIN). For HPV-16 detection, DNA was extracted and assayed for the E6 oncogenic region and *β-globin* using quantitative real-time PCR to determine HPV-16 copies per cell. HPV-16 DNA copy numbers obtained from patients were compared based on anal cytology and biopsy grades using Kruskal-Wallis test. Receiver operating characteristic (ROC) analysis was used to select the choice of a cut-off point for HPV-16 copy number and to evaluate the productivity ability of high-grade HRA.

Results: Of the 75 anal cytology specimens, 31 were Negative and 44 were Abnormal (18 ASCUS, 2 ASC-H, 15 LSIL, and 9 HSIL). HPV-16 copy numbers were significantly different according to anal cytology grade (p=0.001) with the following means (±SD): Negative (45±217), ASCUS (108±312), ASC-H (89±126), LSIL (484±1397), and HSIL (4406±11010). For the 18 patients that underwent HRA, biopsy grades are as follows: 4 Negative, 9 LGAIN, and 5 HGAIN. Additionally, HPV-16 copy numbers were also significantly different according to HRA grades (p=0.009) with the following means (±SD): Negative (59±118), LGAIN (88±183) and HGAIN (7410±14648). It was determined that an HPV-16 copy number greater than or equal to 65 predicted a high-grade HRA (p=0.04) with a sensitivity=1, specificity=0.843 and area under the ROC curve (AUC)=0.920.

Conclusions: Significantly higher HPV-16 copy numbers corresponding to higher anal cytology and HRA grades were observed suggesting the importance of HPV burden on disease stage. Furthermore, it was determined that HPV-16 copy numbers greater than or equal to 65 can distinguish high-grade disease from the other grades. Together this supports the potential use of HPV quantitation with anal cytology in anal dysplasia screening. This modified algorithm requires further evaluation to determine who should undergo HRA. Supported in part by U54MD007584.

26. IFI16 Functions as a Major Epigenetic Modulator During KSHV Infection and Lytic Reactivation

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Background: KSHV (HHV-8) is associated with AIDS related Kaposi's sarcoma and primary effusion lymphoma. KSHV hijacks multiple cellular proteins and pathways to establish lifelong latency in infected hosts, and latency is associated with KSHV malignancies. It is well known that KSHV uses the repertoire of host epigenetic mechanisms to orchestrate its gene regulations. We have previously shown that Interferon-γ inducible protein 16 (IFI16), a host nuclear innate immune DNA sensor, plays an important role in the maintenance of KSHV latency [J Virol. 2016 Sep 12;90(19):8822-41]. In addition, studies from our laboratory and others have suggested that IFI16 acts as an antiviral restriction factor against lytic replication of a number of DNA viruses, by inhibiting either viral-DNA replication (HCMV and HPV) or transcription (HSV-1, HCMV and HPV) through epigenetic modifications of the viral epigenome. However till date, no specific epigenetic function of IFI16 has been identified to support this claim.

Methods: We thus hypothesized that IFI16 mediates epigenetic modifications of the KSHV episome in some way that leads to its heterochromatinization and/or maintenance of its heterochromatic form. To this end, we first attempted to decipher if IFI16 is associated with any histone methyltransferases (MTase) activity that leads to its observed transcriptional silencing function. We used both de novo infection and latency models of KSHV to validate our findings.

Results: Co-immunoprecipitation and His-tag pulldown experiments revealed that IFI16 is able to pull-down an MTase that can specifically transfer methyl groups from S-adenosylmethionine (SAM) to H3. Knockdown of IFI16 followed by ChIP analysis in latently infected B cells confirmed that IFI16 plays an important role in recruiting a H3-MTase that specifically methylates at H3K9 leading to heterochromatinization of the KSHV genome. During de novo infection of endothelial cells, CRISPR mediated knockout of IFI16 limited the recruitment of H3K9-me3 and RNA polymerase II on both latent and lytic KSHV promoters leading to a dysregulation in the latency establishment process.

Conclusions: Thus, we have identified a previously unknown function of IFI16 that leads to epigenetic silencing of the KSHV genome via recruitment of the silencing mark, H3K9-me3 on the KSHV genome. Presently studies are underway to identify the associated H3K9 MTase enzyme and decipher further mechanistic details of this novel role of IFI16 in herpes viral life cycle.

27. KSHV Regulation of the microRNA Biogenesis Pathway

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Background: MicroRNAs (miRNAs) are small RNAs that regulate gene expression posttranscriptionally. Kaposi's sarcoma-associated herpesvirus (KSHV) expresses 12 pre-miRNAs during latency that are converted into mature miRNAs. It was assumed that viral miRNAs could not be specifically targeted for inhibition by host factors. However, the recent discovery that monocyte chemoattractant protein induced protein (MCPIP1) can cleave miRNA precursor molecules raised the possibility that the host could inhibit biogenesis of viral miRNAs in the context of inflammatory signals. If MCPIP1 could inhibit biogenesis of viral miRNAs, then we hypothesized that KSHV may benefit from repression of MCPIP1.

Methods: We analyzed gene expression changes induced 48 hours after KSHV infection in primary endothelial cells. In order to assess the role of MCPIP1 mediated degradation of viral pre-miRNA, we used a combination of assays in primary HUVECs measuring miRNAs at various steps of biogenesis or a cell-free system. To demonstrate the importance of pre-miRNA sequences in MCPIP-mediated degradation, we have made point mutations in specific locations of the stem-loops structures of pre-miRNAs.

Results: We observed that upon KSHV infection the miRNA biogenesis inhibitor, MCPIP1, was repressed and pro-biogenesis factors (Dicer, TRBP1, and TRBP2) were increased in expression. MCPIP1 can degrade the majority of KSHV miRNA precursors, but a specific KSHV miRNA, miR-K6-5p, which is resistant to MCPIP1 degradation, can directly target the MCPIP1 transcript and decrease MCPIP1 expression. Results from seven different human and viral pre-miRNAs showed a wide range of degradation for MCPIP1-mediated degradation in cell-free assays. Mutations in key locations of pre-miRNA can inhibit MCPIP-mediated degradation. MCPIP1 is also repressed upon infection with EBV and purified MCPIP1 can also cleave two of three EBV pre-miRNAs that we have tested. In a KSHV patient-derived cell line, repression of MCPIP1 increased production of KSHV miRNAs. Recently, we found that MCPIP1 expression caused a decrease in expression of the lytic switch gene, RTA. We are further investigating the consequences of MCPIP1 expression on viral replication.

Conclusions: Together, the data suggests that herpesvirus infections can promote biogenesis of their viral miRNAs by inhibiting a host factor that represses miRNA biogenesis and promoting expression of host factors that promote miRNA biogenesis.

28. KSHV-Specific CD4 and CD8 T Cell Clones Reveal Effector Phenotype That Is Transferrable to Autologous T Cells

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Background: Information on the type, breadth, and magnitude of cell mediated KSHV responses is lacking. In another study, we analyzed KSHV seropositive, but otherwise healthy donors and patients with KSHV related disease, for T-cell responses to 82 KSHV ORFs by ELISpot**.** To gain a deeper understanding of the responses seen, we isolated clonal populations of KSHV specific T-cells from donors identified as positive in the ELISpot assay for further study. Isolation of antigen specific T-cell clones is labor intensive and time consuming yielding a product with a finite lifespan and utility for investigation. To circumvent this, we molecularly cloned the TCR from several KSHV specific clones and inserted them into a retroviral vector. With this vector, we are able to confer KSHV specificity to fresh T-cells providing a potentially limitless supply of effector cells for study. To capture TCR specificities of interest and produce specific T cells for addition studies, we molecularly cloned and sequenced TCR genes from KSHV-specific T-cell clones and transduced them into other HLA-restriction matched T cells for further in-depth studies.

Methods: KSHV antigen specific T-cell clones were isolated from donor PBMC by first flow cytometry-based sorting of T cells for IFN-g responses to KSHV peptides using an IFN-g capture antibody capture system (see below), followed by limited dilution cloning. T-cell clones were analyzed for effector responses to presented KSHV peptides, intracellular cytokine staining (ICS) for induction of IFN-g and MIP-1b, and CD107a degranulation. TCR genes (both α and β chains) from T-cell clones with multiple effector responses were isolated, sequenced and transferred to bulk autologous T cells using a retroviral vector with a truncated (non-signaling) NGFR reporter as a transduction marker. Transfer of antigen specificity to the transductants was confirmed by ICS.

Results: Donor R2 yielded four $CD4^+$ T cell clones (R2c1, R2c29, R2c33, R2c39) responding to ORF37, peptide 49, that exhibited 3 distinct clonotypes. Clones R2c33 and R2c39 share the same α and β CDR3 sequences, while clones R2c1 and R2c29 had unique α and β CDR3 sequences. All four exhibited a response consistent with a CD4+ effector phenotype (IFNγ and MIP1β detected by ICS and degranulation measured by CD107a capture) when stimulated with ORF-37 peptide 49 Transfer of cloned TCRs from R2c1, R2c29, and R2c33 to unselected fresh CD4+ T cells from R2 conferred specificity to ORF37 peptide 49. HLA sequencing and MHC blockade experiments confirmed HLA class II restriction based on either DP*04:02 or 15:01; DQA*05 or 01:02; or DQB*13:05 or15:03 haplotypes**.**

Conclusions: This extensive molecular immunology approach facilitates the detailed characterization of T-cell responses to KSHV and will further our understanding of the role of cellular immunity in KSHV biology and, potentially, disease.

29. KSHV Viral Load and Human Interleukin-6 in Pediatric Kaposi Sarcoma—Evaluating the Role of Lytic Activation in Driving the Unique Clinical Features Seen in Endemic Regions

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Background: Kaposi sarcoma (KS) is among the most common childhood malignancies in central and eastern Africa. Clinical features unique to pediatric KS include lymphadenopathy and peripheral blood cytopenias, demonstrating clinical overlap with KS-associated herpesvirus (KSHV) lymphoproliferative disorders. Based on the established role of lytic activation in KSHV-associated lymphoproliferation, we explored potential overlap in KSHV-driven biology in children with KS.

Methods: We performed a prospective observational pilot study of the clinical and virologic characteristics of KS diagnosed in HIV-infected children and adolescents in Lilongwe, Malawi. Plasma samples were collected to evaluate KSHV viral load (VL) and circulating human interleukin-6 (hIL-6) levels. Quantitative KSHV DNA was measured using a real-time quantitative polymerase chain reaction assay using the LANA78 primers. hIL-6 levels were quantified using standard ELISA kits. Clinical features and treatment response were documented. Patients received treatment according to institutional standard of care combining chemotherapy and anti-retroviral therapy (ART).

Results: There were 25 patients enrolled between June 2013 and August 2015. Biopsy confirmation was obtained in 22 (88%). There were 10 females (40%) and the median age was 6.4 years (range 1.7−17). Lymphadenopathy was the most common site of KS involvement (64%), followed by skin and oral mucosa (44% each), woody edema (12%), and pulmonary (8%). Based on TIS staging criteria, 20% were T_1. Nearly half of the patients (48%) were on ART at KS diagnosis, 27% had a severe suppression of the CD4 count at baseline (I_1), 22% had a suppressed baseline HIV VL, and 8% presented with a concurrent opportunistic illness (S_1). Baseline median laboratory data included hemoglobin 9.9 g/dL (range 4.8−12.5), platelet count 317 x 10^9/L (range 7−729), CD4 count 482 cells/mm^3 (range 2−2,013), and HIV VL 92,289 copies/mL (range suppressed−2,163,000). Overall, 18 patients (72%) were alive with median follow-up of 19.5 months (range 6−26); 17 were in complete remission. Baseline plasma KSHV VL and hIL-6 levels were analyzed in 18/25 patients (72%) at time of KS diagnosis, with follow-up studies being performed at time of clinical remission of KS in 10 patients at median time 6.5 months (range 4−8) after KS diagnosis. KSHV VL was detectable at baseline in 12/18 (67%) compared to 2/10 (20%) in remission. Baseline KSHV VL measured < 1,000 copies/mL in 6 patients, between 1,000-10,000 in 4, and two children had levels of 17,037 and 656,164 respectively. Among patients with detectable baseline KSHV VL, 11/12 (92%) had KS lymphadenopathy and the median age was 4.3 years; for patients with undetectable baseline KSHV VL, 1/6 (17%) had KS lymphadenopathy and the median age was 12.8 years. Patients presenting with woody edema had undetectable baseline KSHV VL. Median baseline hIL-6 level was 8.53 pg/mL (range 4.31−28.33) compared with median hIL-6 level in remission of 5.85 pg/mL (range 3.81−9.66). Median baseline hIL-6 for four patients initially presenting with platelet count < 50 x 10^9/L was 17.45 pg/mL (range 12.71−28.33). For patients with hIL-6 level > 10pg/mL, 6/7 (86%) had KS lymphadenopathy, compared to 6/11 (55%) patients with hIL-6 level < 10pg/mL.

Conclusions: Detectable KSHV VL and elevated hIL-6 levels were present in the majority of pediatric KS patients. Lymph node involvement in childhood KS appears to be associated with detectable KSHV VL and higher levels of hIL-6. Lytic activation of KSHV and the associated elevation of IL-6 may contribute to the unique clinical manifestations of pediatric KS in KSHV endemic regions of Africa.

30. Pathogenic Oral Microbiomes Are Associated With EBV: How Bacterial Regulation of Euchromatin Leads to Epstein-Barr Virus Reactivation

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Background: Epstein-Barr virus (EBV) is a gamma herpesvirus important to AIDS-associated malignancies and is associated with several human oral and gastric cancers. Lytic reactivation from latency contributes to EBV spread. Determining in vivo mechanisms of viral reactivation is essential to combat EBV-associated disease. Increased EBV detection in the oral cavity is correlated with periodontitis severity, suggesting that bacterial pathogens contribute to viral reactivation. This study sought to determine in vivo mechanisms underlying bacteria-mediated reactivation of the EBV lytic cycle.

Methods: Oral microbiome analysis was performed on 10 HIV+ subjects at baseline and 12 months post-intervention. In vitro heterochromatin assays were performed using bacterial spent media (BSM) obtained from either pathogenic anaerobic bacteria (*F. nucleatum* [Fn] and *P. gingivalis* [Pg]) associated with periodontitis or oral commensal bacteria (*S. Sanguinis* [Ss]). BSM was used to treat the latently-infected EBV+ human gastric carcinoma cell line, AGS-EBV. ChIP and reporter assays were performed to assess transcriptional activation of EBV lytic promoters. Biochemical and biophysical experiments (time course, dose response, heat sensitivity) characterized viral reactivation following BSM cell treatment. Lytic viral proteins were detected by immunoblots after treatment. Inhibitors of p38, erk1/2, PKC, PI3K, and NF-kappaB were used to determine if these pathways were involved in lytic reactivation. Epigenetic marks associated with regulation of gene expression were analyzed by immunoblot and ChIP. Intracellular viral DNA levels following activation of lytic viral gene expression were assessed by qPCR.

Results: Dental treatment of oral bacterial infections reduced mean EBV VL from 3596 co/mL to 309 co/mL. Bacteria highly correlated with elevated EBV VL were Porphyromonas/Parabacteriodes, Abiltrophia, and Flavobacteriales. Post treatment, increased host-compatible genera (Bifidobacteria, Streptococcus, Neisseria, and Veillonella) were detected. Bifidobacteria, an anti-tumor immunity promoter, was negatively correlated with EBV VL (rgr coef -0.2, p=0.02). Late log phase Pg/Fn BSM were superior to mid log phase for viral activation, the effect was titratable, and Pg strains (capsulated vs. noncapsulated) did not differ in EBV reactivation ability. MALDI TOF and LCMSMS analyses of pathogen BSM, commensal BSM, and NaB detected distinct metabolic and ion chromatogram spectra. Purified Pg LPS did not enhance EBV gene expression. DNase treatment did not diminish EBV reactivation, suggesting that bacterial PAMP activation was not important. BSM–mediated viral reactivation was distinct from NaB. Some BSM products associated with viral reactivation were heat stable. In vivo heterochromatin assays show that Pg and Fn relieved repressed chromatin while the commensal Ss and media (WC) maintained closed chromatin. Pathogen BSM increased global expression of activating epigenetic modifications, total H3Ac, H3K9Ac, H3K27Ac and H3K4me3, the commensal Ss did not, and only Pg increased H3S10p. Pg-mediated activating epigenetic modifications and EBV R expression was NFkappaB-driven. Targeted MAPK, JNK, PI3K, and PKC pharmacologic inhibition did not decrease expression. Heat stable Pg and Fn products demonstrated erk1/2-dependent expression of EBV Z, EBVR, and H3K27ac. Erk1/2 inhibition did not change bacteria mediated H3K9ac, H3S10p and H3K4me3 expression. Lentiviral knockdown of ASH2L, a SETD1 lysine methyltransferase component, decreased Pg mediated H3K4me3 expression and decreased EBV R and Z expression, while the scrambled shRNA did not. In ChIP assays, Pg enhanced H3K27ac occupancy 8 fold on the BRLF1 promoter and 18 fold on the BZLF1 promoter while Fn, and Ss did not. Pathogens that activated of lytic EBV gene expression, increased EBV DNA levels by 5 fold.

Conclusions: Decreased EBV VL by dental manipulation of the pathogenic microbiome and the ability of pathogen BSM to induce EBV gene expression suggested that bacterial end products reactivate the EBV lytic cycle. H3 acetylation/methylation suggests that epigenetic factors induced by the interaction of bacterial end products with latently-infected cells are involved in regulating lytic reactivation. Erk1/2 and NF-kappa B were critical to epigenetic marks that drive EBV lytic reactivation. We conclude that anaerobic pathogens induce EBV lytic reactivation, contributing to the spread of viral infection and increase the risk of EBV-associated neoplasms.

31. Patient Biopsies From the Multinational Kaposi's Sarcoma Trial A5264/AMC067 Show Broad Variability in the Percentage of LANA+ cells and Only Rare Lytic Reactivation

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Background: The percentage of KS tumor cells infected with KSHV as assessed by immunohistochemistry (IHC) for latency-associated nuclear antigen (LANA) is variable. Little is known regarding the clinical significance of this variability. Also, there are scant data regarding expression of lytic proteins in patient biopsies. Lytic replication is emerging as a therapeutic target and lytic viral genes may exert paracrine oncogenic functions. This study was performed to assess variability in the number of LANA+ KS tumor cells and to assess the prevalence of lytic protein+ cells in ACTG and AMC clinical trial A5264/AMC067**.** This trial enrolled chemotherapy-naïve adults with mild to moderate AIDS-KS that were initiating ART with or without immediate oral etoposide at 10 sites in Africa and South America.

Methods: An external quality assurance program included central laboratory assessment of pre-treatment diagnostic biopsies performed at clinical trials sites in Brazil, Kenya, Malawi, Peru, South Africa, Uganda and Zimbabwe (NCT01352117/A5264/AMC062). IHC was performed on 188 KS skin biopsies for LANA and for the K8.1 lytic protein. Computer quantitative image analysis was performed to quantitate the percentage of LANA+ KS tumor cells by assessing only areas involved by histologic KS. K8.1 IHC slides were assessed manually.

Results: LANA expression was used as an inclusion criterion and observed in KS tumor cells in all the patient biopsies. The percentage of LANA+ cells varied from 0.5% - 94.0% (mean 27.2%) according to computer image analysis. Almost half of the cases (45%) had less than 20% LANA positive cells in the area involved by histologic KS, while only 4% had more than 80% LANA+ cells in the lesional area. Expression of the K8.1 lytic protein was observed in KS tumor cells in 10.6% (18/169) of cases, of which 8 showed numerous positive cells and 10 showed only 1-2 positive cells. K8.1 expression correlated with lytic morphology (with features of necrosis including nuclear shrinking and chromatin condensation) in individual positive cells.

Conclusions: LANA expression is always present, but in a highly variable percentage of tumor cells in mild to moderate KS. Expression of the K8.1 lytic protein was observed in only 10% of biopsies and typically in only rare cells. This latter data suggests limited potential for therapy targeted toward KSHV-replication or associated cell lysis. Assessment of the correlation between percent LANA+ KS cells, K8.1 expression, tumor morphotype (plaque v. nodule), CD4 counts, HIV viral load and clinical outcomes is ongoing and will be presented.

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32. Plasma Immunoglobulin E (IgE) Levels Are Associated With Kaposi's Sarcoma in HIV-Infected African Adults

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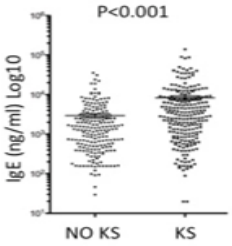
Background: The mechanisms by which the development of Kaposi's sarcoma (KS) is fostered by an inflammatory environment are not fully understood. This is particularly relevant in sub-Saharan Africa where KSHV is endemic and host co-infection with other pathogens — with their potential attendant inflammation — is common. One such co-infection example is the high prevalence of parasitic infections in Africa. To address this, we sought to understand whether Immunoglobulin E (IgE), a marker of parasitic infections and an activator of pro-inflammatory innate immune cells including eosinophils, basophils and mast cells, may have a role in the etiology or pathogenesis of KS.

Methods: In a cross-sectional study of untreated HIV-infected adults in Uganda, we compared individuals with newly diagnosed KS to persons who were KSHV antibody-positive but without KS. KSHV antibody was measured by immunofluorescence assay and EIA, KSHV plasma DNA by PCR for ORF25, and plasma IgE by EIA (Bioscience).

Results: We studied 224 participants with KS and 192 without KS; the median age was 34y and 48% were men. In an unadjusted analysis, those with KS had a higher median plasma IgE level (2995 ng/ml; interquartile range: 983-8100) than those without KS (1272; IQR: 472-2936), p<0.001. After adjusting for age, sex, CD4+ T cell count, and plasma HIV RNA levels, there was a dose-response relationship between plasma IgE level and occurrence of KS. Persons in the highest quartile of IgE levels had a 3-fold greater odds of having KS than those with levels in the lowest quartile, p=0.001. In participants with KS, the number of anatomic skin sites with KS lesions was associated with plasma IgE levels; those with highest quartile of affected anatomic sites had mean IgE levels 1.5 times (95% CI: 1.0-2.1) greater than those in the lowest quartile (least number of affected sites), after adjusting for age, sex, CD4 count and HIV RNA levels. Higher eosinophil counts were also associated with higher plasma IgE levels (dose-response relationship, p<0.001 for trend).

Conclusion: In HIV-infected Africans with concurrent KSHV infection, higher plasma IgE levels are associated with KS, independent of age, sex, CD4 count, and plasma HIV RNA. In individuals with KS, the extent of KS is associated with higher IgE levels. These findings suggest that IgE-driven inflammation may play a role in the etiology or pathogenesis of KS.



	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	P value	Odds Ratio* (95% CI)	P value
IgE, quartiles, ng/ml				
20-656	Ref.		Ref.	
657-1962	1.1 (0.65-2.0)	0.67	1.1 (0.56-2.0)	0.85
1963-5559	2.0 (1.1-3.4)	0.02	1.7 (0.91-3.2)	0.09
6000-140480	4.3 (2.4-7.7)	<0.001	3.0 (1.6-5.8)	0.001

*Odds ratio adjusted for sex, age, CD4 count, and plasma HIV RNA

33. Proteomic Analysis of Host Response to KSHV in HIV-Infected Patients With KSHV-Associated Diseases

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Background: We developed a multiplex assay to detect IgG recognizing most KHSV encoded proteins and showed that humoral response to KSHV is heterogeneous in patients with KSHV-associated malignancies. Moreover, we found that those with HIV had reactivity to a broader range of antigens and more intense reactivity than HIV-uninfected individuals. However, patients (pts) with HIV and KSHV-associated malignancies are quite heterogeneous and present across a wide range of CD4+ T-cell counts. In the case of multicentric Castleman disease (KSHV-MCD) and KSHV-inflammatory cytokine syndrome (KICS), interleukin (IL)-6 and IL-10 dysregulation may also affect humeral responses. The effects of these HIV- and KSHV-related factors on anti-KSHV antibody response is poorly understood. We evaluated factors associated with the breadth and intensity of antibody responses in a heterogeneous population of patients with KSHV-associated diseases, including Kaposi sarcoma (KS), KSHV-MCD, primary effusion lymphoma (PEL) and KICS.

Methods: Pts with KSHV-associated malignancies were identified from the HIV & AIDS Malignancy Branch clinic. Sera collected at time of therapy initiation were evaluated using a bead-based multiplex luminex assay that measures IgG responses against 67 KSHV-encoded proteins. Comparison of strength (mean fluorescence intensity, MFI) and breadth of reactivity against KSHV antigens were evaluated in univariate and multivariate analyses that included age, sex, CD4+ and CD8+ T-cell counts, CD19+ B-cell counts and HIV viral load (VL). Differences and ratios in responses against specific KSHV-antigens were evaluated by ANOVA and moderated t-test with Benjamini-Hochberg correction for multiple comparisons, as well as multivariate linear regression models.

Results: We examined sera from 82 pts with HIV and KSHV-associated diseases, including 65 with KS, 34 with KSHV-MCD, 17 with PEL and 10 with KICS (some pts had more than one KSHV-associated disease). Median (med) age was 44 (inter-quartile interval (IQR) 38-55); 78 were men; 4 were women; med CD4+ T-cell count was 224 (IQR 93-456); and 63% had undetectable HIV viral load. Pts with KS had responses against the greatest number of KSHV-antigens. Differences in patterns of reactivity between diseases were noted for several lytic (K8.1, ORF38, ORF63, ORF65,) and latent (ORF73, K10p5) antigens in univariate analysis. Patients with KS had significantly higher reactivity against K8.1 than KICS (fold change (FC)=5) and PEL pts (FC=3.5) and significantly higher reactivity against ORF73 than MCD (FC=5.4) In multivariate analyses, decreased combined reactivity was noted in KSHV-MCD (p=0.001), PEL (p=0.002) and KICS (p=0.04). Increased HIV viral load was associated with lower reactivity (p=0.05). CD4+ T-cell count was not independently associated with reactivity.

Conclusions: Amongst KSHV-associated diseases, KS is associated with the broadest and most intense humoral response. Antibody response to KSHV may be hampered by uncontrolled HIV- and KSHV-associated inflammation, as seen in the setting of KSHV-MCD, KICS and PEL. While responses to individual antigens do not appear specific for any KSHV-associated disease, differences were noted between groups that may provide insight into disease pathogenesis.

34. Reprograming of T Cells by Ectopic CCR9 Expression Induces Preferential Trafficking to Gut Tissue

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Adoptive cell immunotherapy holds great promise for the elimination of malignant or virus-infected cells, however, challenges still exist in the targeting of effector cells to specific sites. In humans and non-human primates, the development of AIDS is accompanied by a disruption of the gut-associated lymphoid tissue owing to a massive depletion of CD4+ T cells upon viral infection which results in significant pathology. To target future immunotherapeutic T cells to the gut, we evaluated the ability of ectopic expression of a gut-specific homing protein, CCR9, in adoptive transfer experiments. *In vitro*, transduction of PBMC-derived T cells with a retroviral CCR9 expression vector induced specific responses to its cognate ligand, CCL25, ERK phosphorylation and chemotaxis. Upon infusion into rhesus macaques, CCR9 engineered T cells were preferentially found in the gut, but not in rectal tissue, consistent with the expected homing of endogenous CCR9 T cells. Interestingly, the infused cells found in the gut were predominantly central memory T cells (CD28+ CD95+). Thin section confocal microscopy observed CCR9 transductants colocalized with lymphoid aggregates in the gut. Importantly, engineered CCR9 T cells specifically persisted only in the gut, suggested a potential for long-term engraftment. Taken altogether, our results strongly support the feasibility of engineering antitumor and antiviral T cells to traffic to specific anatomical sites for optimal immunotherapeutic effect.

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35. Targeting the mTOR Pathway as Therapy for Primary Effusion Lymphoma

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Primary effusion lymphoma (PEL) is caused by Kaposi's Sarcoma-associated Herpes Virus (KSHV). PEL has a poor prognosis with a median survival time shorter than six months. PEL has an aberrantly activated mTOR pathway, making mTOR a potential target for anticancer drugs. We previously reported that rapamycin, an allosteric inhibitor of mTORC1, decreases proliferation and induces G1 arrest in PEL and Kaposi Sarcoma. However, rapamycin resistance develops over time. MLN0128 is an ATP-competitive inhibitor of mTOR kinase, which is capable of inhibiting both mTORC1 and mTORC2, and has entered phase I/II clinical trials for other malignancies. In this study, we tested the efficacy of MLN0128 against PEL in culture and *in vivo*.

Our results demonstrated that MLN0128 has a greater effect on inhibiting proliferation than rapamycin. Colony formation assays showed that treatment of 100 nM MLN0128 completely inhibited colony formation of PEL. MLN0128 has a ~30 nM EC_{50} values across several PEL cell lines, as measured by Cell Titer Glo Assay. Rapamycin similarly has low EC_{50} values for PEL, but rapamycin is a cytostatic drug that only inhibits PEL growth. Flow cytometric detection with annexin V/propidium iodine showed that MLN0128 induces apoptosis of PEL, whereas rapamycin induced G1 arrest. Moreover, using western blots we determined that MLN0128 inhibited phosphorylation of mTORC1 (S6 and 4E-BP1) and mTORC2 (NDGR1 and AKT) targets. Rapamycin by comparison inhibited the phosphorylation of S6, but not of 4EBP1 or mTORC2 targets. This may be the molecular mechanism for the differential phenotype and potentially increased efficacy of MLN0128 in the clinic. Mice injected with luciferase-tagged PEL and treated with 1-3 mg/kg of MLN0128, showed a reduced effusion volume and lower levels of IL-6 than the vehicle group. Exposing PEL to rapamycin for extended periods of time generated rapamycin resistant clones. The resistant clones had an EC_{50} to rapamycin 10 times higher than the parental cell line. Flow cytometric detection showed that MLN0128 induced apoptosis of rapamycin-resistant PEL clones.

Our *in vitro* and *in vivo* results suggested that MLN0128 might offer a new approach to the treatment of PEL and Kaposi Sarcoma. Also, the mTORC inhibitor MLN0128 is active against chemotherapy and rapamycin resistant PEL.

36. The Nucleoside Analog 6-ethylthioinosine Induces AMP-Activated Protein Kinase Activity and Inhibits mTOR in Primary Effusion Lymphoma Cells

Jouliana Sadek[1], Utthara Nayar[1], Jonathan Reichel[1], Jennifer Totonchy[1], Herman Van Besien[1], Shizuko Sei[2], Robert H. Shoemaker[3], J. David Warren[1], Olivier Elemento[1], Kenneth M. Kaye[4], Ethel Cesarman[1]

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Background: Primary effusion lymphoma (PEL) is an aggressive B cell malignancy with plasmacytic differentiation. PEL is frequently resistant to conventional chemotherapy and carries an extremely poor prognosis with a median survival time of less than 6 months. We have previously reported the discovery of a novel nucleoside analog 6-ethylthioinosine (6-ETI) as a potent and selective inhibitor of PEL with IC50 in the low nanomolar range and a remarkable anti-tumor response in a PEL xenograft mouse model. Investigating 6-ETI's mechanism of cell death, we found that 6-ETI induced necrosis and ATP depletion accompanied by S-phase arrest and inhibition of DNA synthesis. We showed that 6-ETI is a pro-drug that gets activated through phosphorylation by adenosine kinase (ADK) phosphorylation. RNA-seq analysis of drug-resistant resistant clones revealed inactivating alterations of ADK as the mechanism of resistance. Furthermore, we reported ADK overexpression in primary PEL specimens and PEL cell lines, while other lymphomas do not express ADK, which correlates with 6-ETI cytotoxicity and explains its exquisite selectivity.

Methods: To interrogate the role of ADK in the sensitivity of PEL cell lines to 6-ETI, we tested the effect of ADK inhibition, both pharmacological and genetic, on PEL viability by treating cells with specific ADK inhibitors and knocking out ADK expression using CRISPR/ CAS9 system.

We also evaluated the effect of 6-ETI treatment on AMP-activated protein kinase (AMPK) and the downstream mammalian target of rapamycin (mTOR) pathway signaling to further characterize 6-ETI mechanism of action. We also assessed the therapeutic potential of combining 6-ETI with PI3K inhibitors since PEL cells have aberrantly activated PI3K/mTOR pathway.

Results: We found that inhibiting ADK activity prior to 6-ETI treatment or knocking out ADK expression using CRISPR/Cas9 in BC1 PEL cell line rendered cells resistant to treatment with 6-ETI indicating that ADK is necessary to confer sensitivity to 6-ETI. Assessment of the specific signaling pathways that are perturbed by treatment revealed that 6-ETI activates AMPK and inhibits mTOR downstream signaling in sensitive, but not resistant cell lines. In addition, we observed synergy between the pan class I PI3K inhibitor BKM120 and 6-ETI treatment in inducing toxicity in primary effusion lymphoma cell lines.

Conclusions: Herein, we report the discovery and characterization of a new nucleoside analog, 6-ethylthioinosine (6-ETI) as an effective therapeutic for the treatment of PEL and other ADK-expressing cancers and identified ADK overexpression as a biomarker for 6-ETI sensitivity. Our data demonstrates that the sensitivity to 6-ETI treatment is associated with the activation of AMPK activity and the inhibition of the mTOR pathway and suggests that the potential combination of 6-ETI with PI3K/mTOR inhibitors could represent a promising treatment for PEL patients.

37. Unique Features of KSHV Infection in Tonsil-Derived Stromal Cells Uganda

Jennifer Totonchy[12], Jessica Osborn[2], Ayana Morales[3], Ethel Cesarman[2]

[1]Chapman University School of Pharmacy, Biomedical and Pharmaceutical Sciences, Irvine, TX; [2]Weill Cornell Medical College, Pathology and Laboratory Medicine, New York, NY; [3]Weill Cornell Medical College, Infectious Diseases, New York, NY

Background: Much of the research conducted in KSHV suggests that a significant source of KSHV infection occurs via asymptomatic oral shedding in the mouth, detected in saliva. It is though that in addition to oral epithelial cells, a main source of KSHV infection can be from oropharyngeal lymph node tissues such as the tonsil, a mucosa associated lymphoid tissue. The role of the oral lymphoid tissue microenvironment in KSHV pathogenesis remains to fully characterized and may represent the initial site for virus replication in a new human host. It is known that KSHV may infect a variety of different cells including endothelial cells, B lymphocytes, and fibroblasts. Furthermore, gingival fibroblasts and periodontal ligament fibroblasts have been shown to be susceptible to KSHV infection (Dai L. et al 2012) and demonstrate a tumor associated fibroblast phenotype similar to that seen in non- viral malignancies. Primary cells from human tonsil specimens were studied to explore their susceptibility to KSHV infection and understand their ability to contribute to viral spread within tonsil tissue.

Methods: Primary tonsil derived stromal cells or fibroblast reticular cells (tFRC) were isolated and cultured. Primary human umbilical vein endothelial cells (HUVEC) and tFRC were infected with wild type BAC16 KSHV and live cell imaging was performed. Cells were harvested for Western blot, nuclear and cytoplasmic lysates prepared. Real-time quantitative PCR was performed and RNA quantified using Qubit assay. Flow cytometry of infected pHUVEC and tFRC was performed to assess for percentage of GFP+ cells. Immunoflourescence assay (IFA) was performed to assess for DAPI and LANA.

Transfer of infection from infected tFRC stained with APC dye to uninfected FRC was assessed and compared to transfer of infection amongst HUVEC. HUVEC and fibroblasts were dyed, and then infected with BAC16 KSHV. At 3 days post-infection, these cells were sorted for a pure population of Dye+GFP+ cells and co-cultured them with uninfected non-dyed cells. Flow cytometry was performed, looking for GFP+/dye negative (newly infected cells) at 24, 48 and 72hours post-coculture. In a follow up experiment, infected FRC were co-cultured with B lymphocytes, after which flow cytometry was performed to assess for newly infected B lymphocytes.

Results: In this study we demonstrate that tonsil- derived fibroblast reticular cells are susceptible to KSHV infection, however exhibit several unique features compared to endothelial cell cultures. Infected tFRC reveal uncharacteristic distribution of LANA protein at early times post- infection, and demonstrate delayed establishment of latency and periodic spontaneous reactivation. tFRC are resistant to reactivation with chemical induction with TPA. KSHV infection amongst tFRC is stable over time, but virus appears to spread poorly within tFRC cultures demonstrated both by live cell imaging as well as using a dye/flow cytometry. Intriguingly, tFRC are able to transfer KSHV infection to primary B lymphocytes.

Conclusion: Taken together, this data suggests that tFRC may represent a site for persistent KSHV infection, hence a latent reservoir that feed into the infected B cell reservoir.

38. Vaccine Development: A Highly Attenuated Recombinant Herpesvirus Induces the Generation of Memory Precursor Effector Cells

Gurpreet Brar[1], Nisar Farhat[1], Alisa Sukhina[1], Yong Hoon Kim[1], Tiffany Hsu[1], Sara Shu[1], Marcia A. Blackman[2], Ren Sun[1], Ting-Ting Wu[1]

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Background: Shaping the viral specific T cell repertoire requires the consolidation of multiple signals, including clearance of the antigens, epitope recognition on MHC, and inflammatory cytokines.

The immune system generates short lived cells (SLEC) and memory precursor effector cells (MPEC) in response to infection. Once the infection has been cleared, SLEC undergo apoptosis while MPEC become long lasting memory cells[1]. The viral specific T cell populations generated during KSHV and EBV infection are unable to clear the gammaherpesvirus infections that can develop into cancers and malignancies, which manifest predominantly in immunocompromised populations including AIDS and transplant patients. In this study, we design a vaccine to drive the generation of MPEC to protect against gammaherpesvirus latent infection.

Method: Using murine herpesvirus 68 (MHV-68), we generated a recombinant herpesvirus containing loss of function mutations in 4 interferon antagonist genes, and K3, a viral gene responsible for downregulating MHC I. The major latency locus containing ORF73 (LANA) is replaced with a cassette constitutively expressing RTA using a PGK promoter. We assessed the cellular immune response generated 1 and 2 months post vaccination with the recombinant virus. Tetramer staining in combination with T cell phenotyping, and intracellular staining were assessed using flow cytometry. Adoptive T cell transfers into naïve mice, prior to WT virus challenge, suggests the generation of MPEC mediated protection against WT herpesvirus challenge.

Results: In order to generate potent long-term memory T cells, a vaccine needs to modulate the innate immune response to favor the generation of MPEC over SLEC. Removal of viral type I interferon antagonist genes generates a recombinant virus that is highly attenuated *in vivo*. This form of attenuation results in a short interval of antigen production while concurrently inducing inflammatory and immunomodulatory cytokines such as IFNβ, TNFα and IL-12. The recombinant virus confers protection against long-term latency when administered as a vaccine. Immunization generates a large population of KLRG^{low}CD127^{high} viral specific MPEC which are fated to become long term memory T cells.

Conclusion: The recombinant virus is unable to persist in the host and shows no detectable signs of replication *in vivo*. Despite the attenuated replication, the virus is able to generate a robust T cell memory response that is phenotypically and functionally distinct from the T cell population generated by the WT persistent virus. We demonstrate that by guiding the immune response to generate a larger MPEC population, a highly attenuated vaccine can elicit long term antiviral memory.

Reference

Joshi, N. S. et al. Inflammation Directs Memory Precursor and Short-Lived Effector CD8+ T Cell Fates via the Graded Expression of T-bet Transcription Factor. *Immunity* **27,** 281–295 (2007).

39. Whole Genome Sequence Analysis of KSHV and EBV From a Kaposi's Sarcoma (KS) Case-Control Study Conducted in Yaoundé, Cameroon

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Background: Until recently, KSHV and EBV genotype analysis was performed using known variable gene regions, representing a small fraction of the total viral genome, including the KSHV K1/K15 and EBV EBNA 2/3 genes which are used to subtype viral strains. In sub-Saharan Africa, where both KSHV and EBV are endemic, their associated viral cancers are a significant public health problem. The contribution of sequence variations, outside those regions routinely analyzed, contributing to viral transmission or disease pathogenesis, are currently understudied.

Methods: Whole genome sequence analysis of KSHV and EBV was conducted in 49 DNA samples selected from a large KS case-control study nested within the IeDEA Central Africa cohort. DNA from matched whole blood and saliva for 173 case and 988 control subjects were tested by qPCR for KSHV and EBV viral load. Selection for whole genome sequencing was made using KSHV raw viral load results >4,000 copies. All samples were sequenced using the SureSelect^{XT} target enrichment system for Illumina (version B.3, Agilent Technologies). Selective capture of KSHV and EBV DNA was performed using custom overlapping 120mer biotinylated RNA baits spanning both viral genomes excluding the repeat regions. Sequence reads were mapped to GK18 (AF148805), ZM004 (KT271453), ZM128 (KT271467), and HHV-8 type M (U75698) reference genomes using BWAMEM after removal of low quality bases and adapter trimming (BBDuk). Reads that did not align to KSHV were extracted and aligned to both EBV Type 1 (NC007605) and Type 2 (NC009334) reference genomes using BWA MEM.

Results: Of the 49 samples sequenced, full length KSHV genomes were obtained from 19 KS case and 21 control subjects. Five regions of KSHV repetitive sequence in or close to K4.2, K7, K12, ORF73, and K15 were unresolved constituting approximately 6% of total viral genome. EBV sequences were obtained from 11 KS cases and 11 controls. Phylogenetic analysis of the KSHV K1 gene indicated all samples were A5 or B subtypes commonly observed in Africa, while EBV clustered with both EBV 1 and 2 subtypes. Of note, one sample from a KS case had a deletion of the KSHV K1 gene region that was confirmed in separate sequencing runs using DNA from matched whole blood and saliva. Another saliva sample from a KS case has sequences suggestive of dual infection with two different KSHV strains. Analyses identifying sequence variations in both KSHV and EBV whole genome alignments are currently ongoing.

Conclusions: We have successfully obtained full length KSHV genome sequences from 40 KS case and control subjects from Cameroon. This study is the first comparing whole KSHV viral genome sequences between KS cases and controls in the same region allowing analyses of virus diversity and the possible association of sequence variation with disease risk. In addition, EBV genomes were obtained from 22 subjects.

40. Immune Response Abnormalities in Epidemic and Endemic Kaposi's Sarcoma Patients

Salum J. Lidenge[1,2,5], For Yue Tso[5], Eun Hee Kwon[5], Danielle M. Shea[5], John N. Richards[1], Veenu Minhas[3], Gleb Haynatzki[4], Julius Mwaiselage[1,2], Charles Wood[5], John T. West[5]

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Background: Mechanisms underlying Kaposi's sarcoma (KS) development are unclear. The high incidence of KS in HIV-1$^+$ individuals implicates immune dysregulation in epidemic KS (EpKS) development. However, immune responses in African endemic KS (EnKS) are uncharacterized. To compare innate and adaptive immune responses in EpKS and EnKS, we recruited histologicallyconfirmed Tanzanian KS patients, as well as non-cancer controls.

Methods: KSHV and HIV-1 nucleic acids were detected by PCR in PBMC, plasma, buccal, and tumor lysates. KSHV-specific and neutralizing antibody (nAb) responses were quantified. Levels of more than 14 cytokines/chemokines, and T-cell differentiation subsets and checkpoint inhibitory molecules were also quantified. The Mann-Whitney U-test was used to assess median differences between groups. All tests were 2-tailed and *P*-values <0.05 were considered significant.

Results: KSHV DNA was more frequently detected in EpKS patients. While all EpKS and some EnKS patients mounted nAb responses, the EpKS patients had higher nAb prevalence and titer when compared to EnKS patients (P=0.001). Levels of the cytokines IP-10 and IL-10 were higher in EpKS versus EnKS patients (P=0.006 and P=0.005, respectively), whereas, IL-4 was lower in EpKS versus EnKS patients (P=0.004). Surprisingly, the levels of all 14 cytokines/chemokines measured were comparable between EnKS patients and HIV-1$^-$ controls. CD4$^+$ and CD8$^+$ T-cells differentiation subsets were similar between EpKS and EnKS. Naïve and effector T-cells were depleted in both KS forms, and central memory T-cells were elevated.

Conclusions: This study represents the first in-depth comparison of innate and adaptive immune parameters between African endemic and epidemic KS patients from the same region. The detection of similar abnormalities in T-cell subsets in both EpKS and EnKS, suggests that KSHV is inducing cellular immunity alterations and HIV-1 co-infection is exacerbating and accelerating KSHV pathogenesis and KS development. These alterations clearly can occur in the absence of HIV-1 infection as well as when HIV-1 disease is effectively mitigated through ART.

Keywords: Kaposi's sarcoma, epidemic, endemic, Tanzania, immune response, HIV-1, KSHV.

DAY TWO POSTERS

The first three abstracts will be presented on both days. Abstracts 41-77 are on pages 95 to 131.

1. Comparison of EBV and KSHV Seroprevalence in a Cohort of Children in Western Kenya With Differential Malaria Exposure
2. Raman Spectroscopy Distinguishes High-Grade Anal Intraepithelial Neoplasia (HGAIN) From Normal Tissue
3. Advanced Stage of Hepatocellular Carcinoma Is Less Common Among HCV Infected in Both HIV Infected and Uninfected U.S. Veterans

41. A Newly Established Prospective Cohort in the ART Era of Community-Based Newly Diagnosed HIV-Related Kaposi Sarcoma in Africa
42. AMC-063: Pilot Study of Bortezomib Exploiting an Oncolytic Viral Strategy in AIDS-Associated Kaposi Sarcoma
43. Assessing HIV Eligibility in CTEP-Sponsored Trials
44. Barriers to Early Presentation of Breast Cancer Among Women in Johannesburg, South Africa
45. Breast Cancer in HIV-Positive Women in an Urban Hospital in the South
46. Cancer Risk in Older People Living With Human Immunodeficiency Virus Infection in the United States
47. Cancers Averted Among HIV-Infected Adults During the Modern ART Era
48. Comparison of Anal Cytology, HPV Test Findings, and Historical Cytology Results to Predict Anal Histological High-Grade Squamous Intraepithelial Lesions
49. Comparison of Prostate-Specific Antigen at Initial Diagnosis of Prostate Adenocarcinoma in HIV+ Versus Uninfected Patients in the Veterans Aging Cohort Study (VACS)
50. Delay in South African AIDS Lymphoma Diagnosis
51. Developing Media to Promote Community Awareness of Early Detection of Kaposi's Sarcoma in Africa
52. Effect of Storage Duration on Signal Expression Fitness of microRNAs Derivative From Archival Formalin-Fixed Paraffin Embedded (FFPE) Tissue: Advancing Fit-For-Purpose Studies in the AIDS and Cancer Specimen Resource (ACSR)
53. Feasibility of Using Rapid Case Ascertainment to Evaluate Kaposi Sarcoma in Africa
54. High Cancer Burden Among Antiretroviral Therapy Users in the Malawi HIV-Cancer Match Study: An Observational Cohort Study
55. High Mortality Among HIV-Associated Head and Neck Cancers
56. HIV-Associated Differences in Stage at Presentation and Survival After Diagnosis for U.S. Cancer Patients
57. Impact of Protease Inhibitors-Based Regimens on Incidence of HIV-Associated Kaposi Sarcoma: A Systematic Review of Literature
58. Incidence and Clearance of Anal HPV Infections in the Multicenter AIDS Cohort Study
59. Incidence of Cancer Mortality in Hospitalized HIV-Infected Adults in Nigeria

60. Kaposi Sarcoma Herpesvirus Shedding in Saliva of Patients With KSHV-Associated Malignancies
61. Low Prevalence of KSHV DNA in Female Genital Fluid: Findings From Zimbabwean Women and Systematic Review of the Literature of KSHV Shedding in Body Fluids and Mucous Membrane Surfaces
62. Malignant Neoplasms in HIV-Infected Patients of St. Petersburg
63. Molecular Pathology of Cancers Among HIV Cameroonian Patients
64. Patient and Treatment Characteristics by HIV of Women With Cervical Cancer Enrolled in UPenn-University of Botswana U54 Project 3
65. Patterns of Repeated Anal Cytology Testing Among HIV-Positive and HIV-Negative Men Who Have Sex With Men
66. Personalized Lung Cancer Screening for HIV-Infected Individuals Using VACS Index: A Simulation Study
67. Short-Term Outcomes for Lung Cancer Resection Surgery in HIV Infection
68. Quality Approach to Tissue Microarray Construction From the AIDS and Cancer Specimen Resource
69. Portable Confocal Microscopy as a Diagnostic Tool for Kaposi's Sarcoma in Africa
70. Real-World Use of ART and Chemotherapy for Kaposi's Sarcoma in a Large Community-Based HIV Health Care Network in Kenya
71. Risk of Non-AIDS-Defining Cancers Among Veterans With Well-Controlled HIV Infection
72. Prevalence and Determinants of High-Risk Human Papillomavirus mRNA Detected Through Community-Based Cervical Cancer Screening in Uganda
73. Rituximab in Malawi: Early Results From a Phase II Clinical Trial
74. Spectrum of HIV-Related Cancers in Pre- and Post-HAART Era, Indian Study
75. The Impact of HIV Infection on Squamous Cell Carcinoma (SCC) Antigen levels in Patients With Advanced Cervical Cancer Treated With (Chemo-) Radiotherapy in Botswana
76. The Networking CancerVIH Group on AIDS Malignancies: Epidemiological Data and Guidelines for an Optimal Practice in Oncology and Immunology Field
77. Training Community Health Workers About Early Detection of Kaposi's Sarcoma: A Comparison of Expert-Led Versus Community Health Worker Supervisor-Led Approaches

41. A Newly Established Prospective Cohort in the ART Era of Community-Based Newly Diagnosed HIV-Related Kaposi Sarcoma in Africa

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Background: Most of our understanding of the contemporary disease course of HIV-related KS in sub- Saharan Africa comes either from data from the pre-ART era, extrapolation from resource-rich settings, collections of patients with KS derived from tertiary care settings, or clinical trial populations. Furthermore, outside of the clinical trials, most studies are plagued by high rates of losses to follow-up. Collectively, these limited data have precluded our knowledge of current real-world outcomes following diagnosis of KS in the community in Africa and factors that determine prognosis. In particular, apart from survival, there is almost no information on patient-centered outcomes. To address our limitations in knowledge, we designed a prospective cohort study of KS in the contemporary era.

Methods: HIV-infected adults with a recent diagnosis of KS are identified from HIV primary care clinics in East Africa that are participating in rapid case ascertainment (RCA) programs for KS. Coupling with clinics participating in RCA allows for near-complete representative sampling of newly diagnosed cases of KS in the primary care population. Biopsy confirmation for KS is performed unless the only available lesions are not deemed safe for biopsy. At the first study encounter, measurements are made via medical record review, questionnaires, physical exam including detailed assessment of KS, and collection of biological specimens for real-time testing and archival storage. Participants are then longitudinally followed with medical record review and brief in-person evaluation every 16 weeks. The objectives of follow-up are to understand survival, health care utilization, and patient-centered outcomes, particularly quality of life. As much as possible, the study seeks to document the ambient disease course without altering it. To achieve complete ascertainment of survival and patient- centered outcomes, we employ well- established processes to track patients in the community if they fail to return to their health care facilities (i.e., physical tracing to their residences).

Measurement/Procedure	Baseline	Follow-up
Sociodemographic and contact information	x	x
Narrative timeline: first lesion to KS diagnosis	x	
KS lesion assessment	x	
HIV-specific and KS-specific therapy	x	x
Quality of life: general, skin-specific, edema-specific	x	x
Medical record review	x	x
Specimen collection: blood, saliva, biopsy	x	

Results: Initial recruitment has been performed in the primary care clinics of the AMPATH network in western Kenya. Among the 74 initial participants enrolled with newly diagnosed KS, 45% are women, the median (IQR) age is 38 (32-43) years, hemoglobin 11 (9-12) g/dl, CD4 count 342 (118-480) cells/mm3, and 46% had undetectable plasma HIV RNA. Of the potentially evaluable visits, for week 16 follow-up, 75% of participants completed the visit, 12% died prior to the visit, and 13% not known to be dead did not complete the visit. At week 32 follow-up, 81% completed the visit and 19% died prior. Nearly 13% of these outcomes were derived from physically searching for the patient in the community. For 4 of 7 deaths, we were able to interview family members and/or review time-of-death medical records. Conclusions: We have established a prospective cohort of HIV-infected adults with newly diagnosed KS in East Africa. The primary care-based sampling allows for representative inferences regarding individuals diagnosed with KS in the community. In addition to survival, whose ascertainment is enhanced by active tracking of patients who become lost, follow-up is focused on brief assessments emphasizing quality-of-life measurement in several domains. Preliminary findings are notable for a near complete ascertainment of vital status; 7 deaths among the first 74 patients denotes the seriousness of the prognosis. Finally, a cohort such as this brings forth heretofore rarely undiscussed ethical issues — relevant to the longitudinal study of any malignancy in a resource-limiting setting — regarding what is appropriate for researchers from resource-rich regions to investigate if state-of-the art treatment is not being provided or clinically accessible to participants.

42. AMC-063: Pilot Study of Bortezomib Exploiting an Oncolytic Viral Strategy in AIDS-Associated Kaposi Sarcoma

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Background: Still among the most common malignancies in persons living with HIV, AIDS-related Kaposi sarcoma (KS) is often incompletely controlled, requiring serial therapies in affected individuals. Human herpes virus (HHV8) induces transformation of endothelial cells comprising KS, where it then resides in a predominately latent state. Bortezomib, a proteasome inhibitor initially approved for multiple myeloma, is a potent inducer of HHV8 lytic activation. Lytic activation of latent HHV8 infecting KS is hypothesized to be beneficial both for direct tumor cell lysis, as well as induction of cytotoxic immune responses by viral lytic gene products. Furthermore, both HHV8 and HIV hijack the ubiquitin-proteasome pathway, evading important innate host defense mechanisms by targeting critical protective host proteins for proteasomal degradation, including p53 and antiretroviral cytadine deaminase, APOBEC3G. Proteasome inhibition would be expected to restore such defenses and, indeed, was found in preclinical studies to impair HIV infectivity. Through restoration of host tumor suppressor and antiviral function, increased immune recognition and viral oncolysis, bortezomib is hypothesized to have multi-faceted activity in KS. This is a multicenter pilot study with the primary objective of determining the maximum tolerated dose (MTD) of bortezomib in AIDS-KS. Secondary objectives included estimating the impact of bortezomib on KS response rates, and HHV8 and HIV viral loads (VL).

Methods: A 3+3 dose escalation design was used to determine the MTD of single-agent bortezomib. Key inclusion criteria included biopsy proven KS relapsed or refractory to frontline chemotherapy, age $\geq$18 years, serologically documented HIV treated on a stable ART regimen $\geq$12 weeks, and adequate hematologic, renal and hepatic function. Key exclusions were symptomatic visceral KS, concurrent active opportunistic infection, and grade 3-4 peripheral neuropathy. There was no minimum CD4 count or maximum HIV VL requirement. Bortezomib was administered intravenously on days 1, 8, and 15 of each 28-day cycle at one of 4 doses: 0.75, 1, 1.2, or 1.6 mg/m^2 for a maximum of 8 cycles.

Results: Seventeen subjects were enrolled from six sites within the AMC. Median CD4 count was 376/mm^3 (156-963). No dose limiting toxicities (DLTs) occurred; 8 subjects were treated at the highest dose level. The only serious adverse event attributed as possibly related to bortezomib was one subject with grade 3 vomiting. The most common mild to moderate adverse events included diarrhea (53%), fatigue (53%) and nausea (41%). Among the 15 subjects evaluable for response, partial response (PR) occurred in 9 (60%) with the remainder having stable disease for an overall disease control rate of 100%. The median time to response was 2.1 months (range 1.9 to 2.8) and none of the subjects with PR relapsed (median follow-up 2.8 months, range 1.9 to 18.5). Of 7 subjects treated at the highest dose and evaluable for HHV8 VL during cycle 1, 5 had increased HHV8 VL at some point during the cycle compared with baseline. In 13 subjects evaluable for changes in HIV VL through cycle 1, 8 had decreases (five were >1 log), while 5 had increases (2 > 1 log).

Conclusion: Single agent bortezomib is well tolerated without occurrence of DLTs at the highest tested dose and demonstrates activity in AIDS-KS. The 60% PR rate is remarkable given the dose-finding nature of the study in a relapsed/refractory population. Impact on PBMC HHV8 VL was not dramatic, but there was a trend toward increased VL during cycle 1 at the highest studied dose, consistent with HHV8 lytic activation; additional studies comparing lytic gene expression within tumor biopsies pre- and post-treatment are planned. Single copy HIV VL testing demonstrated a downward trend as hypothesized during cycle 1 in over half of evaluable subjects.

43. Assessing HIV Eligibility in CTEP-Sponsored Trials

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Background: Since the introduction of highly active antiretroviral therapy (HAART) in 1996, the life expectancy of people with HIV is now comparable to that of the general population. Increased longevity has led to a shift in the age distribution in this population and therefore has had significant implications for cancer risk and total burden of cancer cases. In fact, cancer is now the leading cause of mortality among HIV-infected persons where HAART is widely available.

Considering the increased burden, throughout the past ten years, the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI) has been making a concerted effort to include patients with HIV into their clinical trials. We recently undertook an effort to evaluate our progress and success at achieving our goal across the program.

Methods: CTEP protocols that were approved between 1 January 2013 and 31 January 2016 were reviewed for HIV patient eligibility. Trials that excluded people with HIV were further investigated to identify scientific justification provided in the protocol.

Results: A total of 225 protocols were approved and reviewed for HIV patient eligibility. The majority of trials were Phase I (27%) and Phase II trials (42%). People living with HIV were excluded from 46% of approved trials within the CTEP portfolio. The most common justification for exclusion was antiretroviral medications may have pharmacokinetic interactions with the study agent. Another common justification was stated as “these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy”. Many protocols also justified exclusion because conditions such as uncontrolled infection (including HIV), in the opinion of the treating physician, would make the protocol unreasonably hazardous to the patient.

Conclusions: Many of the reasons listed for excluding people living with HIV in the CTEP portfolio were antiquated and these trials were not able to provide clear and compelling grounds that show exclusion is necessary. The potential for pharmacokinetic interactions is not unique to anti-HIV therapy and none of the protocols provided scientific evidence to support this claim. Healthy HIV-positive patients that are included in cancer clinical trials should be treated using the same standards as other patients with co-morbidities, and anti-retroviral therapy should be considered a concomitant medication. Moving forward, CTEP trials need to follow the guidelines provided for protocol authors and will require protocols to provide proper scientific justification if HIV-infected individuals need to be excluded from the trial.

44. Barriers to Early Presentation of Breast Cancer Among Women in Johannesburg, South Africa

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Background: The incidence of breast cancer is rising in South Africa (SA), where HIV prevalence is high and most breast cancer patients are diagnosed at a late stage. We studied patient and provider factors associated with stage at diagnosis among women seen at the tertiary Chris Hani Baragwanath Academic Hospital in Soweto, Johannesburg, in 2015-2016.

Methods: Using a questionnaire developed and validated for local conditions, we collected data on patient and health system barriers to early-stage diagnosis, as well as socio-demographic, lifestyle and clinical information. We compared patients diagnosed in early stages (0-II) and patients diagnosed in late stages (III-IV) with respect to those factors. We used Student's t-test and the Wilcoxon rank-sum test to evaluate differences between groups in means and medians, respectively, for continuous variables and Pearson chi-square tests and Fisher exact tests for categorical variables. We then developed multivariable logistic regression models to identify factors independently associated with late stage at diagnosis.

Results: Among 499 women in our sample, 243 (49%) were diagnosed at an early stage and 256 (51%) at a late stage. Factors inversely associated with late stage at diagnosis were education through or beyond high school (odds ratio (OR) 0.59, 95% confidence interval (CI) 0.36-0.99), receiving treatment for hypertension (OR 0.58, 95%CI 0.36-0.94), and greater knowledge/awareness of breast cancer (OR 0.84, (95%CI 0.75-0.95). Self-reported delays >3 month from first recognition of breast symptoms to accessing the health system (OR 2.84, 95%CI 1.71-4.71), having had more than 1 visit within the health system referral network (OR 2.72, 95%CI 1.47-5.04 for 2 visits, and OR 1.78, 95%CL 1.10-2.86 for ≥3 visits), and triple-negative molecular subtype (OR 2.75, 95% CI 1.15-5.99) were associated with late stage at diagnosis. Overall, 22.6% of patients were HIV-infected, but in the full model, HIV status was not associated with late stage at diagnosis.

Conclusions: Lack of education and lack of specific knowledge about breast cancer among patients, and inefficiencies in the health care system were associated with late diagnosis. Sustained community and health worker education programs may promote more timely referral for definitive diagnosis and treatment and improve breast cancer survival.

45. Breast Cancer in HIV-Positive Women in an Urban Hospital in the South

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Background: Potent and more tolerable antiretroviral therapy (ART) has allowed widespread use, improved longevity and decreased incidence of AIDS-related malignancies with HIV/AIDS (PLWHA), but increased incidence of non-AIDS-related cancers, such as breast cancer (BC). Little is reported about BC in HIV positive patients. We report our experience with BC cancer in our cohort of HIV-infected women in a Health System in the South.

Methods: This is a retrospective descriptive single center chart review of HIV+ women who were diagnosed with BC during 8/1/2014 to 7/31/2017 period. The Grady Health System provides care to a large patients' population in the city of Atlanta, GA.

Results: During the 3-year period, 14 HIV+ women were diagnosed with breast cancer. We divided them in those in care and not in care as determined by undetectable viral load at the time of BC diagnosis (BCDx)

Table 1 displays the characteristics of the 2 groups

Characteristics	**Women with UVL at BCDx (N=6)**	**Women with DVL at BC Dx (N=8)**	**P value (ttest)**
Age at BCDx-median(IQR)	59(54,63)	51(47,56.5)	0.54
Race: African-American	5 (83.3%)	8 (100%)	
CD4 at BCDx	676(502,874)	357(145,505)	0.33
BC detected by Self exam Mammogram	 1 5	 6 2	
Hormonal status ER+/PR+ HER2+	 6/5 1	 4/3 0	
Stage of BC DCIS Stage1A Stage 2A/2B Stage 3B Stage 4	 1 2 1/1 1 0	 1 1 1/1 2 2	
Therapy Surgery Radiation Chemotherapy Hormone/HER2-inhibitor	 5 2 1 4	 6 4 4 4	
Months of follow up	16 (10,27)	24,6 (8.94,29.04)	0.78
Death	1 (16%)	2 (25%)	
ART changed due to drug interaction with chemotherapy	1	0	

Conclusion: In the new era of ART with patients living longer and developing non-AIDS related cancer, HIV providers and oncologists will need to familiarize with the potential drug-to- drug interactions of ART and chemotherapy, in order to provide optimal care to the HIV-infected patients.

46. Cancer Risk in Older People Living With Human Immunodeficiency Virus Infection in the United States

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Background*:* Cancer risk is increased in people living with HIV (PLWH) due to HIV-induced immunosuppression, co-infections with oncogenic viruses, and high prevalence of behavioral risk factors for cancer such as smoking. Improved survival due to highly active antiretroviral therapy (HAART) has led to an aging of PLWH. Few previous studies could evaluate cancer risk in older PLWH as this population has historically been too small to target. Herein, we evaluated the cancer risk in older (age≥50 years) PLWH.

Methods*:* We included data from the HIV/AIDS Cancer Match Study (1996-2012) which links information from 9 population-based HIV and cancer registries using a probabilistic algorithm. We evaluated the risk of AIDS-defining cancers (ADCs) [Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), cervical cancer] and certain non-AIDS-defining cancers (NADCs) [Hodgkin lymphoma, and cervix, anus, lung, liver, oral cavity/pharynx, breast, prostate, and colon cancers] in older PLWH compared to the general population by calculating the standardized incidence ratios (SIRs) and excess absolute risks (EARs). Cancer risk according to attained age, AIDS diagnosis, and time since HIV diagnosis was estimated using Poisson regression.

Results: We included 183,542 older PLWH who contributed 928,194 person-years of follow-up. During the follow-up, 10,371 cancers were diagnosed, of which 1,647 (15.9%) were ADCs, 5,798 (55.9%) were selected NADCs, and 2,926 (28.2%) were other cancers. Risk was significantly increased for KS (SIR=103.3), NHL (SIR=3.1), Hodgkin lymphoma (SIR=7.6), and cervix (SIR=2.0), anus (SIR=14.0), lung (SIR=1.7), and liver (SIR=2.9) cancers, and reduced for breast (SIR=0.5), prostate (SIR=0.5), and colon (SIR=0.6) cancers. SIRs declined with age for all cancers; however, EARs increased with age for anal, lung, liver, and oral cavity/pharyngeal cancers. Among PLWH, incidence of KS declined with age (p-trend=0.0014) whereas the incidence of lung, prostate, and colon cancers increased with age (p-trend<0.0001). Older PLWH with a prior AIDS diagnosis had an increased incidence of KS (adjusted incidence rate ratio [aIRR]=1.86, NHLs (aIRR=1.74), anal (aIRR=2.66), lung (aIRR=1.37), and oral cavity/pharyngeal (aIRR=1.67) cancers, and Hodgkin lymphoma (aIRR=2.19) compared to those who were not previously diagnosed with AIDS. Cancer incidence was highest for most cancers within the first 5 years after HIV diagnosis and aIRRs decreased with increasing time since HIV diagnosis for KS, NHL, lung cancer, and Hodgkin lymphoma (p-trend <0.05).

Conclusions: Risk of ADCs and certain NADCs remains elevated in older PLWH compared to the general population. However, the SIRs for cancers decrease with age, suggesting that the combined effect of aging and HIV does not further amplify the relative risk of cancers. Despite lower relative risks, the EARs are higher for some NADCs among older PLWH leading to a greater number of excess cancers in this group. Cancer risk was also highest within the first 5 years after HIV diagnosis for most cancers, underscoring the importance of early HIV diagnosis, rapid initiation of HAART after HIV diagnosis, and cancer risk factor mitigation among older PLWH.

47. Cancers Averted Among HIV-Infected Adults During the Modern ART Era

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Background: People living with HIV (PLWH) are at an increased risk of developing several cancers. Since 1996, the availability of modern highly active antiretroviral therapy (HAART) has improved immune function, and reduced the risk of certain cancers known to occur in excess among PLWH. Here, we quantified the number of cancer cases averted in the U.S. HIV-positive population during 2008-12 due to declining cancer incidence rates over time.

Methods: We utilized cancer incidence data (2001-2012) collected from the U.S. HIV/AIDS Cancer Match Study for anal, cervical, liver and lung cancers, Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and cancer overall. Using Poisson regression, we estimated site-specific cancer incidence rates among PLWH stratified by age-group, race/ethnicity, sex, risk group, and calendar year. The number of PLWH in the U.S. was obtained for the same strata using data from the Centers for Disease Control and Prevention's National HIV Surveillance System for the years 2008-2012. We estimated the actual cancer burden by multiplying contemporaneous cancer incidence rates and counts of PLWH. To estimate the number of cancers averted during 2008-12, we subtracted the observed number of cancers from the number of cancers expected if 2001 rates had persisted throughout 2012. Finally, we calculated the number of remaining excess cancer cases by subtracting the number of cancers that would have occurred if general population incidence rates were acting in the PLWH population from the observed number of cancers.

Results: Among PLWH, overall cancer rates were 35% lower during 2010-2012 compared to 2001-2003 ($p<0.0001$). During 2001-2012, nearly all site-specific cancer rates declined, except liver cancer rates, which remained stable over time. The largest declines in rates (all $p <0.0001$) were observed for cervical cancer (61% decline), NHL (54%) and KS (49%). During 2008-2012, 36,674 cancer cases were estimated to have occurred among PLWH in the US. We estimated that had cancer rates remained stable since 2001, an additional 21,473 cancer cases would have occurred during 2008-12, including 8802 additional cases of NHL, 4263 cases of KS, 2617 lung cancers, 911 cervical cancers, and 459 HLs. While substantial progress has been made in reducing cancer burden among PLWH, 19,697 cancers occurred during 2008-2012 in excess of what would be expected based on general population rates. The largest numbers of excess cases were observed for NHL (n = 5591), KS (n = 4060), anal cancer (n = 2774), and lung cancers (n = 2006).

Conclusions: In the U.S., substantial progress has been made in preventing cancer among PLWH given the observed declining rates and estimated large number of cancer cases averted. This progress is likely due to the success of HAART, restoring immunity, and preventing the development of some cancers. However, the large number of excess cancers that remain highlight opportunities for further cancer prevention control initiatives targeted to PLWH, particularly tobacco cessation, alcohol reduction and human papillomavirus vaccine programs

48. Comparison of Anal Cytology, HPV Test Findings, and Historical Cytology Results to Predict Anal Histological High-Grade Squamous Intraepithelial Lesions

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Background: The diagnostic accuracy of repeated Dacron anal cytology tests is important to clinicians, payers, and patients. Twelve high-risk human papillomaviruses are evaluated by experts as Group 1 carcinogens (Group1/hrHPVs).

Methods: Data for 157 HIV-infected and 115 -uninfected men (n=272) who have sex with men (MSM) were tested during a randomized clinical trial of anal cytology and high-threshold HPV tests to predict anal histological high-grade squamous intraepithelial lesions (hHSIL) evaluated at one study visit where all men received High-Resolution Anoscopy (HRA) examinations. Anal cytology and HPV testing were evaluated from a single Dacron swab specimen, using a protocol that required multiple randomly-ordered swab specimens. Cytology results were classified as Atypical Squamous Cells of Unknown Significance or more severe (≥ASCUS), no intraepithelial lesions (NIL), or *unsatisfactory* for evaluation. Group1/hrHPV-DNA and –mRNA were assessed by two signal-amplification assays using residual liquid-based cytology samples. Historical (anal) Dacron cytology findings were gathered from two sources: medical records for community participants and cytology performed between 2010 and 2014, as part of a large multicenter longitudinal study, the Multicenter AIDS Cohort Study (MACS). Concurrent cytology, HPV, and histology laboratory analyses were performed by a single CLIA-certified laboratory, while historical cytology specimens were not. HRA-guided biopsy findings formed the outcome, hHSIL vs. <hHSIL. Analyses adjusted for the effects of historical cytology, sociodemographic, HIV-infection, and sexual-behavior characteristics and swab-randomization order. Adjusted multivariable logistic regression analyses assessed associations between current and historical cytology and hrHPV assays to predict hHSIL, and areas under Receiver-Operating Curves (AUCs) were compared to evaluate differences between models.

Results: On average, men were 55 (σ=12) years old, White (73%), and former or current smokers (77%). Nearly 42% were HIV-uninfected, with 39% and 19% of HIV-infected men showing ≥500 or <500 CD4-T-lymphocytes/mm^3, respectively. Fewer than half of the men reported receptive anal intercourse partners during the two years prior to the exam, with 28%, 19%, and 4% reporting 1, 2, or ≥3, respectively, and 58% reporting none. Cytology showing NIL, ≥ASCUS, or unsatisfactory were near-equally distributed: 35%, 35%, and 30%. Nearly 55% of subjects had ≥1 historical cytology specimens, of whom 56% (84/150) had ≥1 NIL finding. Concurrent and historical cytology characteristics and receptive anal intercourse partnerships were strongly associated with hHSIL (p<0.005). The prevalence of hrHPV-DNA and –mRNA positivity at the HRA visit was 58% and 57%, respectively. Fully-adjusted models showed the diagnostic accuracy of synchronously drawn HPV and cytology findings differed, with cytology showing lower accuracy than either the hrHPV-DNA or –mRNA test: 0.69, vs. 0.75 (p=0.04), 0.79, (p=0.002), respectively. When fully adjusted models for current and historical cytology findings were evaluated together and compared to those that evaluated the current cytology alone, hrHPV-DNA, or –mRNA assays alone, repeated cytology improved the models little and both cytology findings were lower than hrHPV-mRNA testing: 0.70 (ref), 0.69 (0.26), 0.75 (0.10), 0.79 (p=0.0085), respectively. The hrHPV-mRNA assay modestly better predicted hHSIL over hrHPV-DNA testing (p=0.05).

Conclusions: A single hrHPV-mRNA test may more accurately predict hHSIL than a single cytology or hrHPV-DNA test finding. Multiple cytology findings over time may not improve accuracy of cytology over a single measure. More research is needed.

49. Comparison of Prostate-Specific Antigen at Initial Diagnosis of Prostate Adenocarcinoma in HIV+ Versus Uninfected Patients in the Veterans Aging Cohort Study (VACS)

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Background*:* Serum prostate-specific antigen (PSA) is utilized for the screening, prognosis and monitoring of prostate adenocarcinoma. Patients with higher PSA at diagnosis are considered to have higher risk disease with a higher propensity to metastasize. The purpose of our study was to compare the PSA at time of initial biopsy and diagnosis of prostate adenocarcinoma in HIV–infected (HIV+) compared to uninfected patients in the modern combination antiretroviral therapy (ART) era.

Methods: VACS is a multi-institutional cohort of HIV+ and uninfected patients matched 2:1 on age, race, sex, and clinical site. We linked the VA Central Data Warehouse oncology database (VA-CDW) to identify patients diagnosed with prostate cancer. Laboratory tests for total prostate specific antigen (PSA) were identified from October 1999 through May 2017. Trends of PSA tests completed by each VA laboratory were reviewed to ensure nearly complete identification of all relevant PSA tests, and test results were standardized. The PSA result closest to the date of biopsy (or date of diagnosis if there was no CPT and ICD-9 procedure codes for biopsy) within a 180 day window was utilized for analysis. If no PSA was found within 180 days prior to biopsy, a PSA value within 90 days post-biopsy/diagnosis was utilized. A univariate analysis was performed comparing PSA in HIV+ vs uninfected patients. PSAs were then categorized according to established risk models for localized prostate cancer.

Results: There were 3,518 incident prostate cancer cases (908 HIV+, 2,610 uninfected). PSA was unknown in 189 cases (47 HIV+, 142 uninfected), which were excluded, leaving 3,186 (91% of all recorded cases) in the analytic sample. Average age (61 years old) and distribution of race/ethnicity (two-thirds non-Hispanic black) were similar between the HIV+ and uninfected groups. PSA values of >20ng/mL were found more frequently among HIV+ patients (15% vs 10%, Table 1). Lower PSA values <4.0ng/mL, 4.0-10.0 ng/mL and 10.0-20.0 ng/mL were similarly distributed by HIV status.

Table 1: Distribution of PSA by HIV status

	HIV+ N=828		**Uninfected N=2,363**		
Serum PSA (ng/mL)	**N**	**(%)**	**N**	**(%)**	**p-value**
<4.0	99	12%	315	13%	0.0004
4.0-10.0	497	60%	1522	64%	
10.0-20.0	109	13%	298	13%	
>20.0	123	15%	228	10%	

Conclusions: HIV+ patients present with prostate adenocarcinoma with higher serum PSA at biopsy which may either connote more aggressive disease or delayed diagnosis. Future studies will examine relationship of stage at diagnosis, Gleason score, HIV viral load, and CD4 count.

50. Delay in South African AIDS Lymphoma Diagnosis

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Background: We set out to evaluate the time from admission to a tertiary hospital with constitutional symptoms and/or lymphadenopathy to confirmed diagnosis of lymphoma in HIV-infected patients followed at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, South Africa. Medical procedures that patients underwent during their work-up and prior to a final lymphoma diagnosis were noted.

Methods: A chart review of HIV-associated lymphomas diagnosed at CHBAH between January 13th, 2017 to July 19th, 2017 was performed. As we were unable to confirm when South African patients first went to a clinic with symptoms, date of referral to the hospital for admission was used as a surrogate. Time from presentation to the hospital with symptoms until a confirmed diagnosis of lymphoma was made was calculated. A total of 44 patients were diagnosed with HIV-associated lymphoma at CHBAH during this time period, of which 35 patients were available to be screened as part of a prospective collection and 25 patients gave consent for medical record review.

Results: Of the 25 patients from CHBAH, 14 (56%) were women. The average age was 42 years (IQR 38-45). The majority of patients (56%) had simultaneous diagnosis of HIV and lymphoma. Average CD4 count was 225 x 10^6/l (IQR 69-296) of whom 16 (64%) patients were receiving antiretroviral therapy (ART) and 6/16 had undetectable viral loads at time of lymphoma diagnosis. Peripheral lymph node biopsy was the predominant site of pathological confirmation at 40%, followed by an abdominal/pelvic site at 28%, maxillary/nasal biopsy at 20%, Lung at 8%, and Bone marrow at 4%. The distribution of lymphoma patients were DLBCL 17/25 (68%), 2 of which were MYC+, 3/25 (12%) classical Hodgkin lymphoma, 5/25 (20%) Plasmablastic lymphoma. Burkitt lymphoma patients were among the 44 HIV-associated lymphoma patients diagnosed during this time period, but none of them are included in this cohort of 25 patients. Over 90% of the HIV-associated lymphomas were of advanced stage (21 stage IV, 2 stage III, 2 stage II).

Among the 25 patients, delay from first presentation to the hospital could be ascertained for 16 patients. The calculated delay for these 16 patients until lymphoma diagnosis was 14.9 weeks (3.7 months) with a range from 4 weeks to 51 weeks. Forty-four percent (11/25) of CHBAH patients had at least 1 prior biopsy or cytology specimen taken before their diagnosis was made. Among 11 patients at CHBAH with a prior non-diagnostic biopsy before their lymphoma diagnosis, there was an average 2.3-month delay. Abdominal/pelvic site of diagnostic biopsy was associated with a 5.5-month (N=5) delay at CHBAH.

Conclusions: Lengthy delays from referral to the hospital with symptoms suggestive of lymphoma and ultimate diagnosis were observed among the HIV-infected patients diagnosed with lymphoma at CHBAH in Soweto, South Africa. These delays are a likely contributor to the advanced stage at diagnosis seen within this population. It is important to note that the reported delay for HIV-associated lymphomas diagnosed at CHBAH likely under-estimates the true delay that incorporates symptom onset and initial presentation to a primary care clinic. Additionally, significant delays were seen in patients requiring more than 1 diagnostic procedure and those ultimately diagnosed through an abdominal/pelvic biopsy. These findings highlight the need for prioritization of non-diagnostic or suggestive biopsies for referral to Hematology and definitive diagnosis. Education, both in the HIV-population and the medical community, for symptoms of aggressive lymphomas and appropriate diagnostic triage are needed. Strategies to detect markers of lymphoma in either non- diagnostic tissue specimens or blood could prove to be very useful in addressing the delays associated with invasive and repeat biopsies.

51. Developing Media to Promote Community Awareness of Early Detection of Kaposi's Sarcoma in Africa

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Background: Despite its overtly cutaneous presentation and the possibility of remission when antiretroviral therapy alone is used to treat early stage disease, most cases of Kaposi's sarcoma (KS) in Africa are diagnosed too late for effective treatment. Training health workers about early recognition of KS can increase knowledge, but this can only be clinically impactful if providers actually encounter early KS (i.e., if patients with early KS present to care). Indeed, recent work from Zimbabwe showed that facility-based KS training failed to increase early KS diagnosis, a finding that is unsurprising given the general public's lack of knowledge about KS and the importance of early detection. We hypothesized that educating affected populations about KS is critical in making progress in early detection and that enhanced community awareness about KS can be achieved through exposure to common media.

Methods: To craft a culturally appropriate educational theme regarding detection of KS and develop media, we employed community-engaged research to learn about health-related behavior in the context of skin disease. We interacted with KS survivors, HIV-infected patients, facility-based and community health workers, traditional healers, and media professionals. We tested our media (comics, radio plays, and a short film) among adults in markets in rural Uganda. Participants were randomized to exposure to 1 of the 3 media, and we evaluated them for change in knowledge and attitudes concerning KS using pre- and posttests featuring KS photographs.

Results: In comics, 90 second radio play, and a 10 minute film, we developed a 3-part theme aimed to the general public: "Look" meaning to regularly examine one's skin/mouth; "Show" referring to bringing to the the attention of a health worker any skin changes; and "Test" denoting to remind providers about skin biopsy for definitive diagnosis. Among 240 participants exposed to the media, the median age was 30 yrs, 50% were women, 6% HIV-infected and 60% literate. Exposure to the media resulted in increases in the ability to recognize/name KS, awareness that anyone is at risk or KS, and knowledge of how to prevent KS from becoming a substantial problem.

%'s reflect correct responses. All posttest changes are p <0.05 unless noted by *	Comics (n=80)		Film (n=79)		Radio plays (n=81)		All participants (N=240)	
Question (Correct Response)	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
What do you think this condition is? (*Kaposi's sarcoma*)	1.3%	40%	0%	49%	2.5%	53%	1.3%	48%
Who is at risk for this condition? (*All people and/or HIV-infected*)	40%	43%*	27%	54%	37%	54%	35%	50%
Would you consider yourself to be at risk? (*Yes*)	68%	80%	62%	78%	65%	73%	65%	77%
How would you prevent this condition from becoming a problem for you? (*Examine skin & present to health care provider*)	46%	81%	49%	82%	43%	77%	46%	80%

Conclusion: Featuring a theme of "Look", "Show", and "Test", we developed media (comics, radio plays, and a film) aimed for the general community in Africa about early detection of KS. Exposure to these media resulted in increases in knowledge and change in attitudes concerning KS among community members. Although the increases in KS-related knowledge were not large, they may be as much as can be expected from a single exposure. Optimal outcomes will likely require multiple exposures and facilitated discussions. The media elements are freely available online, and affected areas may consider their use as is. Formal efficacy testing will require community trials and KS stage-at-diagnosis outcomes.

52. Effect of Storage Duration on Signal Expression Fitness of microRNAs Derivative From Archival Formalin-Fixed Paraffin Embedded (FFPE) Tissue: Advancing Fit-For-Purpose Studies in the AIDS and Cancer Specimen Resource (ACSR)

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Background: Contemporary genomic approaches have greatly increased the demand from biorepositories such as the AIDS and Cancer Specimen Resource (ACSR) for derivatives from archived formalin-fixed paraffin-embedded (FFPE) tissue. As with many types of biobanked samples, the requirements for using FFPE derivatives in contemporary genomic platforms were not known when the tissues were banked, a particularly critical issue for nucleic acids derivatives, which are tightly cross-linked into the FFPE matrix. As determined by our previous Fit-for-Purpose study in the ACSR, the small non-coding RNAs (microRNAs or miRNAs) are among the most "fit" genomic derivatives from archival FFPE, even after twenty or more years of storage. The objective of the current study was to confirm the fitness of miRNA derivatives from our previous study by assessing the performance of miRNA derived from "Older" and "Newer" FFPE blocks in an end point assay such as a multiplex miRNA assay. More specifically, we sought to determine if storage duration affected signal expression in a stock multiplex immune miRNA panel, by comparing the normalized signal expression of miRNAs derived from "Older" and "Newer" FFPE in the ACSR.

Methods: FFPE blocks were stratified by storage duration in the ACSR into 11-year intervals as "Older" FFPE (1990-2001) or "Newer" FFPE (2002-2015) and then randomly sampled. Small non-coding RNAs were extracted from a single 10 µm FFPE section from each block, and the purity and concentration of these derivatives assessed on a 2100 BioAnalyzer using the Small RNA kit. The miRNA derivatives were then interrogated on an Abcam® Firefly™ multiplex stock immunology panel to determine the relative quantitation of normalized signal expression against 68 miRNAs, spike-in miRNAs controls, miRNA normalization controls, and other miRNA quality control parameters. Student's t-test was used to determine if normalized signal expression levels of miRNAs were significantly different between the "Older" and "Newer" FFPE blocks, with multiple testing corrected by the Benjamini Hochberg (BH) method. The relative quantification of signal expression between the "Older" and "Newer" FFPE blocks was also analyzed using the 2-ΔΔCt method. Both "Older" and "Newer" FFPE blocks were then assigned to an Ordinal Fitness Category based on the overall quality of their miRNA signal expression as follows: "High Quality miRNA Derivatives", "Good Quality miRNA Derivatives", "Medium Quality miRNA Derivatives" and "Poor Quality miRNA Derivatives" or a "Bad FFPE Block". The distribution of miRNA derivatives into these Ordinal Fitness Categories was then tested between "Older" and "Newer "blocks using a Likelihood Ratio Chi-Square test.

Results: After BH multiple test correction, no single miRNA was observed to have a significantly lower normalized signal expression level due storage duration. However, ten percent (N = 4) failed to have any signal expression to miRNAs and were classified as Poor Quality miRNA Derivatives" or a "Bad FFPE Block." The distribution of "Bad Blocks" was not significantly ($p < 0.05$) greater among the "Older" FFPE than the "Newer" FFPE as determined by a Likelihood Ratio Chi-Square test ($P = 0.13$).

Conclusions: At approximately 20–22 nucleotides in length, miRNAs are less prone to the common forms of degradation and modification in the FFPE matrix than other nucleic acid derivatives. Here, normalized signal expression levels to any single miRNAs were not significantly different in the "Older" FFPE compared to the "newer" FFPE. However, ten percent (n =4) of the miRNA derivative from FFPE bocks in the study failed to generate any signal expression to miRNAs and, as such, were considered "Poor Quality miRNA Derivatives" or "Bad FFPE Blocks." The frequency of "Bad FFPE Blocks" among the "Older" FFPE was not significantly different than the frequency of "Bad FFPE Blocks" among the "Newer" FFPE. The current study used several novel quality assurance metrics to show that miRNA from archived FFPE tissue blocks, even after twenty or more years of storage, remains a valuable resource for contemporary genomic platforms.

53. Feasibility of Using Rapid Case Ascertainment to Evaluate Kaposi Sarcoma in Africa

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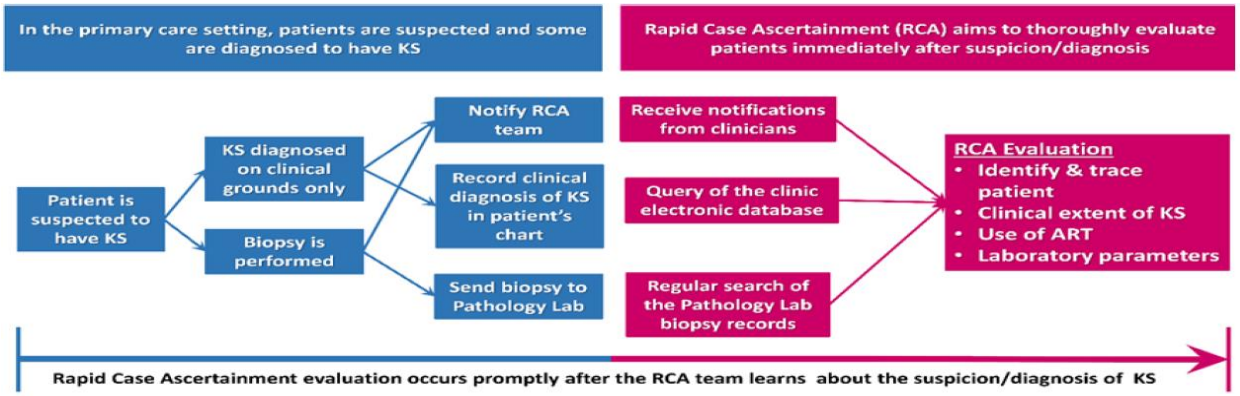
Background: Questions abound concerning HIV-related Kaposi's sarcoma (KS) in sub-Saharan Africa in the current era. Why do some patients develop KS and others do not? What percentage is diagnosed with advanced KS, thus representing failure of early detection? How many HIV-infected patients are using antiretroviral therapy (ART) and develop KS despite an undetectable HIV viral load? What are the biochemical determinants of prognosis? Addressing these questions requires detailed characterization of patients with KS immediately upon diagnosis and prior to what may be a swift change in KS disease stage, death, or loss-to-follow-up. This expeditious evaluation — common in resource-rich settings — is called Rapid Case Ascertainment (RCA). We describe the feasibility of RCA for KS in Africa.

Results: From July 2016 to March 2017, we identified 89 patients with apparent new KS. Clinical notification yielded 84% of the cases, EMR query 9%, and pathology lab review 6. 8%. Of the 88, 19 were ineligible for RCA upon further review: 13 had prior KS, 5 did not have KS histologically, and 1 originated outside AMPATH. Of the 69 patients who were eligible, RCA was performed among 36% by 14 days, 54% by 30 days, and 62% by 90 days. Reasons for failing to perform RCA included death prior to reaching the patient (4), insufficient locator information (5), and logistical breakdown due to a local strike (8). Among 43 patients for whom RCA was done, median age was 39 eyars, 52% were women, and 70% had been prescribed ART. Clinically, 85% had T1 stage. Median CD4 count was 351 cells/mm^3, and 50% had undetectable viral load.



Conclusion: In a primary care network in East Africa, an RCA approach to identify patients with newly diagnosed KS was able to find the majority shortly after diagnosis. A substantial fraction of cases have advanced KS at diagnosis and have developed KS despite ART. By addressing the identified logistical challenges, it should be possible to further optimize RCA to evaluate even a higher fraction in a shorter time. The feasibility of performing RCA for KS has implications for the study of all HIV-associated cancer.

Characteristic	KS Cases (n=43)
Age at diagnosis , years	39 (32,43)*
Female gender	52%
Source of information	
Clinician notification	84%
Histopathology laboratory	9.0%
Electronic medical records	6.8%
ACTG clinical staging	
T1 stage	86%
I1 stage	32%
S1 stage	65%
CD4+ T-cells , cells/mm^3	351 (185,484)*
Viral load categories, cps/ml	
undetectable (<40)	50%
40-1,000	21%
>1,000	28%
Hemoglobin, g/dl	11 (9.4,13)*
ART in use	70%

*median (interquartile range)

54. High Cancer Burden Among Antiretroviral Therapy Users in the Malawi HIV-Cancer Match Study: An Observational Cohort Study

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Background: With improved antiretroviral therapy (ART) access in sub-Saharan Africa, epidemiologic data are needed to characterize potential changes in the cancer burden in HIV-infected populations. The Malawi HIV-Cancer Match Study specifically aims to characterize cancer incidence patterns among ART initiators in Malawi, where HIV prevalence is 9% and ART coverage has reached 67% among guideline-eligible HIV patients, using a current threshold for ART eligibility of 500 CD4 cells/μL.

Methods: In this observational, retrospective cohort study, we used probabilistic algorithms to link cancer cases from the population-based cancer registry with electronic medical records supporting ART delivery in the country's two largest HIV cohorts, Lighthouse Trust (LT; 2007-2010) and Queen Elizabeth Central Hospital (QECH; 2000-2010). Incidence rates (IR) and 95% confidence intervals were calculated non-parametrically among naïve ART initiators separately by each cohort, sex, individual cancer sites, early versus late incidence periods, and WHO stage at ART clinic enrollment.

Results: We identified 4,346 cancers among 28,576 new ART users. Patients tended to initiate ART at advanced WHO stage (LT stage III/IV: 55%; QECH stage III/ IV: 66%); median age at ART initiation was 33 years (IQR: 16-49 years). Between 5%-18% of patients had prevalent malignancies, which were predominantly AIDS-defining cancers. Kaposi sarcoma (KS) incidence had the highest IR (347 to 1204 per 100,000 person-years), followed by cervical cancer (IR: 39 to 108). Non-Hodgkin lymphoma was detected at a low rate in our study (IR: 1.8 to 1.9). KS incidence was greatest during the early period of 4-24 months after ART initiation. Non-AIDS defining cancers (NADC) represent an emerging burden, accounting for 2-15% of the total cancer case load. At QECH, the highest incidence rates of NADC were for cancers of the esophagus (13.7), breast (12.9), female reproductive cancers (9.9), eye/conjunctiva (8.5). At LH, the highest incidence rate of NADC was for bladder cancer (7.9), esophagus (2.2), eye/conjunctiva (1.9).

Conclusions: Cancer IR among Malawian ART users are not mirroring patterns occurring in high-income countries. A range of non-AIDS defining cancers are afflicting HIV populations, though at lower rates than expected, and are eclipsed by the high burden of KS and cervical cancer. Observed cancer incidence rates in our study vary in magnitude across cohorts and demonstrate heterogeneity of record linkage results that may be obtained from real-world, routine clinical databases used for HIV care in sub-Saharan Africa. Our results represent a range of the measurable cancer burden, rather than a single point estimate. Population-based resources are important for the region, even with the acknowledged infrastructure and diagnostic challenges in low-income countries. Understanding cancer incidence patterns during the contemporary era of African ART delivery will provide a strong foundation for evidence-based cancer control policies in countries with high HIV prevalence and a high proportion of infection-related cancers.

55. High Mortality Among HIV-Associated Head and Neck Cancers

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Background: Since the introduction of HAART, the number of deaths among HIV patients due to non-AIDS defining malignancies, such as head and neck cancer (HNC), has been rising. In addition, given high rates of HPV co-infection, the impact of HIV+ status in HPV-associated HNC individuals deserves specific focus. This study aims to characterize the demographics, HIV disease status, lifestyle factors, and cancer presentation of a cohort of HIV-infected, HNC patients in order to inform prevention, treatment, and prognostication of these patients.

Methods: Retrospective chart review was performed on 39 patients from Yale-New Haven Hospital with HIV and HNC between 2001 and 2016, identified from the Yale Cancer Registry and medical record review. If not previously done, p16 staining was performed on archived tumor tissue to determine HPV prevalence.

Results: Of our HIV-HNC cases, 79% were male and the median age at cancer diagnosis was 55 years (range 43-73 years). The majority of individuals had a history of tobacco use (87% past/current smokers at time of cancer diagnosis), with a median of 40 pack-years. A significant proportion of the cohort also had a past/current history of alcohol use (70%) and substance use (75%). The vast majority of patients were on anti-retroviral therapy at the time of cancer diagnosis (78%), with a median CD4 count of 399 (range 11-1264), and 86% having an undetectable viral load. The locations of HIV-HNC were as follows: oropharynx (38%), larynx (28%), oral cavity (23%), nasopharynx (5%), and hypopharynx (5%). There was a high proportion of advanced stage cancer (53% Stage IV). Among those with 5-year follow-up (N=23), 5-year mortality was 65%. Among the specimens with HPV testing (N=27), 48% of the tumors were HPV+. The 5-year mortality of HPV+ tumors was 80% while that of HPV- tumors was 60%. Also of note, 13% of patients were diagnosed between 2001-2005, 37% were diagnosed between 2006-2010, and 50% were diagnosed between 2011-2016.

Conclusions: Despite well-controlled HIV at the time of HNC diagnosis, the majority of patients presented with advanced cancer and high rates of 5-year mortality (65%) compared to the general population (<40%). Preliminary information on HIV-HPV co-infection demonstrates HPV+ tumors are associated with a high rate of 5-year mortality and poor prognosis, substantially higher than in the general population where HPV-associated HNC generally confers improved prognosis. In addition, this study demonstrates a greater than three-fold increase in the diagnosis of HNC among HIV+ individuals over 15 years, emphasizing the growing burden of this disease and the need for further research into the pathogenesis, diagnosis, and treatment of HIV-HNC, to provide a better understanding of both increased incidence and poor prognosis.

56. HIV-Associated Differences in Stage at Presentation and Survival After Diagnosis for U.S. Cancer Patients

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Background: People living with HIV (PLWH) are at increased risk for developing several cancers, but less is known about how HIV impacts the rate of cancer progression to advanced disease or death relative to HIV-uninfected cancer patients. Our previous work suggests that stage at diagnosis is shifted toward more advanced disease for certain cancers in the context of HIV, and that HIV-infected cancer patients experience higher overall mortality following diagnosis compared to non-PLWH. The stage shift among PLWH could be due to more aggressive tumors or late diagnosis, and the survival deficit may be attributable to HIV-related differences in tumor characteristics or access to cancer care. However, previous studies did not have information on patient health insurance status, a potentially important variable given that access to care could influence the poorer outcomes observed in HIV-infected cancer patients. Here, we examined the differences in stage distribution and overall survival between PLWH and non-PLWH following a cancer diagnosis after controlling for health insurance.

Methods: We compared the distribution of cancer stage at presentation and all-cause mortality after diagnosis between 8, 587 PLWH and 7,349,659 non-PLWH in the US diagnosed with non-AIDS-defining cancers (oral cavity/pharynx/larynx, stomach, colorectum, anus, liver, pancreas, lung, female breast, cervix, prostate, bladder, kidney, thyroid, and melanoma) using data from the National Cancer Database (2004-2014). Polytomous logistic regression and Cox proportional hazards regression were used to evaluate the association between HIV and advanced stage or overall survival after a cancer diagnosis, respectively. Models were adjusted for age, sex, race, health insurance, year of cancer diagnosis, median household income (zip code), type of treatment facility, and cancer stage (survival analysis only).

Findings: PLWH were more likely than non-PLWH to be uninsured (7.6% vs. 3.3%) and less likely to have private health insurance (26.9% vs. 44.2%; $p<0.0001$). Compared to non-PLWH, the odds of being diagnosed with a stage IV cancer (compared to stage I), after accounting for health insurance and other confounders, were elevated in PLWH for melanoma and cancers of the stomach, liver, pancreas, lung, and thyroid (OR range: 1.17-1.94) but significantly lower for cancers of the anus (OR=0.53; 95%CI 0.39-0.71). Further, PLWH experienced worse overall survival after a cancer diagnosis compared to HIV-uninfected cancer patients after accounting for traditional prognostic factors (cancer stage) and receipt of health insurance, with hazard ratios ranging from 1.30 (95%CI 1.19-1.43) for liver cancer to 2.29 (95%CI 1.92-2.73) for female breast cancer. Notably, the effect of HIV on both stage and survival was largely the same after restricting to patients with private health insurance.

Conclusion: Melanomas and cancers of the stomach, liver, pancreas, lung, and thyroid are more likely to be diagnosed at later stages in PLWH, even after accounting for health insurance. HIV was also associated with increased all-cause mortality following a cancer diagnosis after adjusting for cancer stage and health insurance. This suggests that the HIV-related survival deficit in cancer patients is not due solely to differences in tumor characteristics (stage) or access to private health insurance. Although elevated mortality in HIV-infected cancer patients may reflect in part deaths from AIDS, the survival deficit could also represent inadequate cancer treatment or an association between HIV-related immunosuppression and cancer progression.

57. Impact of Protease Inhibitors-Based Regimens on Incidence of HIV-Associated Kaposi Sarcoma: A Systematic Review of Literature

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Background: HIV-positive patients are at increased risk for developing acquired immunodeficiency syndrome (AIDS) defining cancers (ADC) such as Kaposi sarcoma (KS), with KS the most common malignancy in HIV patients and causing significant morbidity and mortality. Experimental studies have shown that protease inhibitors (PI) have direct effects on angiogenesis and tumor growth with KS; however, the findings of epidemiological studies evaluating the association between PI use and risk of incident KS are mixed. We performed the first systematic review to critically evaluate and synthesize these study results.

Methods: We followed PRISMA guidelines for the conduct and reporting of systematic reviews. We performed structured keyword searches in PubMed to identify eligible original epidemiological research reports in peer-reviewed medical journals published in English and French languages before June 2017. We also performed ancestry searches of bibliographies of included studies to identify any missed studies. Eligible studies reported use of PI and risk of incident KS in HIV-infected cohorts aged 18 and older compared to a parallel HIV-infected cohort on non-nucleotide reverse transcriptase inhibitor (NNRTI) or not receiving active anti-retroviral therapy (ART). We excluded publications that included HIV patients who received antiretroviral therapy other than ART (i.e., mono- or dual therapy). Two clinicians independently performed keyword searches, reviewed studies for eligibility, and abstracted data. Disagreements among reviewers were resolved by consensus with a third senior clinician author.

Results: We identified 867 citations using PubMed keyword searches and ancestry searches. Among the 90 full citations reviewed, a total of 8 articles were eligible for inclusion in our review. All eight included studies were cohort studies (7 retrospective and 1 prospective) with sample sizes ranging from 8640 to 109,461. 7 out of 8 studies were performed in Western countries, with the 8th study including patients from both Western countries (~85%) and from Africa (~15%). 5 out of 8 studies compared the relative risk of incident KS in HIV patients on PI based regimen to HIV patients not receiving any ART, with study disease specific relative risk estimates ranging from 0.47-0.93, all statistically significant. 3 other studies compared relative risk of incident KS in HIV patients on PI based regimens to HIV patients on NNRTI based regimens, with disease specific relative risk estimates ranging from 0.53-0.87, with 2 out of 3 studies reaching statistical significance. Only 2 studies evaluated the effect of boosted PI on incidence of KS, with mixed results reported. One study demonstrated a protective effect of boosted PI on risk of incident KS when used more than two years in veterans in the U.S. (adjusted incidence rate ratio = 0.79, 95% CI: 0.69-0.90, $p<0.001$); while the other study found increased risk of incident KS among individuals who used PIs for 2-5 years in a multicentered study done across several countries.

Conclusion: Our systematic review suggests standard PI based regimens are associated with modest to moderate reduction of incidence of KS in HIV infected patients. However, given heterogeneity across study populations and designs, we were unable to pool results. Additional research is necessary to evaluate conflicting results on the boosted PI regimens on KS risk, and to also evaluate if PIs are similarly associated with reduced KS risk in non-western populations with higher Background prevalence of human herpes virus (HHV8).

58. Incidence and Clearance of Anal HPV Infections in the Multicenter AIDS Cohort Study

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Background: Human papillomaviruses (HPVs) commonly infect anal epithelium. Twelve high-risk (hr) Group 1 HPVs are strongly carcinogenic, 13 Group 2 hrHPVs are weakly carcinogenic, and 16 lower-risk (lr) HPV types commonly evaluated are not carcinogenic. Group 1 HPV types 16 and 18 cause 80-90% of anal cancers. Men who have sex with men (MSM) are disproportionally affected by anal cancer, for which no standard of care for screening or treatment exists. The objective of this study is to characterize incidence and clearance of anal HPV infections in a large cohort of HIV-infected and –uninfected MSM.

Methods: Periodic anal HPV testing was performed for 1,259 U.S. MSM as part of the Anal Health Substudy (AHS), a nested longitudinal substudy of the Multicenter AIDS Cohort Study. A single Dacron swab was collected at multiple visits and tested for 37 Group 1 and 2 hrHPVs and lrHPVs types using the Linear Array HPV DNA PCR assay. HIV-stratified type-specific and (HPV) group-specific crude incidence and clearance rates and rate ratios (RRs) were calculated. A HPV positive visit that followed a type-specific negative test visit defined incidence; and a type-specific negative visit that followed a HPV positive test visit defined clearance.

Results: At baseline, men were, on average, 55 (±9) years old; 73.8% were White, non-Hispanic, 18.0% were Black, non-Hispanic, and 8.2% reported another race group. Half the men were HIV-infected (n=610), and in comparison to HIV-uninfected men, were younger, more likely non-White, and more sexually active (p-values<0.001). Data collected for 4,253 visits averaged to 3.4 (2-7) visits per man, spanning 26.9 (4.1-45.5) months of follow-up time, on average.

At baseline, most men (79.6%) tested positive (+) for one or more anal HPVs. HPV16 and 18 infections were common, with 25.2% of men testing positive for one or both. Approximately 46.5% tested positive for another Group 1 hrHPV, 34.9% were Group 2+, and 60.2% were lrHPV+.

Incident infections were common, occurring in 35 men per 1,000 person-months (pm) for 872 men. Specifically, 108 men had incident HPV16 infection (4/1,000 pm), 68 had HPV18 (2.2/1,000 pm), 514 had other Group 1 (18.3/1,000 pm), 402 had Group 2 (13.8/1,000 pm), and 628 had lrHPV (23.3/ 1,000 pm). HIV-infected men conferred a 1.7-fold and 2-fold higher risk for HPV16 and 18 incidences, respectively, compared to HIV-uninfected men. Similarly, incidence rates were higher in HIV-infected men than –uninfected men for 25 other Group 1, Group 2, and lrHPV types of the remaining 35 HPV types (RRs: 1.7-5.6, p-values<0.05).

HPV clearance occurred frequently. A total of 897 men, 53.4 per 1,000 pm, cleared one or more infections. Over the study period, 19.6 men per 1,000 pm cleared HPV16 and 31.5 men per 1,000 pm cleared HPV18. By group, 65.3 men per 1,000 pm cleared at least one other Group 1 infection, 45.2 men per 1,000 pm cleared Group 2 hrHPVs, and 45.1 men per 1,000 pm cleared lrHPVs. HIV-infected men had a 27% higher clearance for any HPV (p<0.05) than -uninfected men, but when assessed by type, only HPV61 yielded a significant difference (RR: 1.9, p<0.05).

Conclusions: Using PCR, anal HPV DNA is commonly detected in older HIV-infected and –uninfected MSM. HPV incidence remains high, higher yet in HIV-infected men, but clearance is also common in all men. Data suggests there remains risk for ongoing exposure to hrHPV infections as MSM age, highlighting the disproportionate lifelong risk for anal cancer that MSM experience.

59. Incidence of Cancer Mortality in Hospitalized HIV-Infected Adults in Nigeria

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Background: Cancers contribute to morbidity and mortality in patients living with HIV (PLHA). In addition to AIDS-associated cancers, non-AIDS cancers are not uncommon among PLHA. Incidence data on cancer mortality in hospitalized patients are scare in sub-Saharan Africa. We wanted to determine the incidence of mortality among PLHA hospitalized with cancer diagnosis in Jos, north central Nigeria.

Methods: We documented episodes of hospitalization among adult PLHA receiving HIV care and treatment at the Jos University Teaching Hospital, Nigeria over a 3-year period. HIV disease characteristics at the time of hospitalization as well as specific cancer diagnosis confirmed by biopsy were noted. We used Kaplan-Meier analysis to assess survival and calculated incidence rates (IR) of mortality for specific cancers using STATA version 13.1

Results: There were 590 episodes of hospitalization for 583 patients. Mean age at the time of admission was 34±9 years and 379 (64.9%) were females. Median CD4 count at admission was 113cells/mm^3, (IQR: 46-244), 66 911.3%) were on second-line ART and 24.6% were virologically suppressed (<400copies/ml). Forty (6.8%) cancer cases were seen, contributing a total of 18,739 total person-time. The median time to event was 297 days (IQR: 100-763). There were 29 (72.5%) cases of Kaposi sarcoma, 3 (7.5%) cases each of anal and intraocular cancers, 2 (5.0%) cases of colorectal cancer and 1 (2.5%) of NHL, PLCC and soft tissue sarcoma. NHL had the highest IR for mortality at 23.8/1000 PYs. This was followed by colorectal Ca, with an IR of 8.1/1000PYs. IR was 0.6/1000PYs for Kaposi sarcoma, 0.5/1000PYs for intraocular cancer and 0.4/1000PYs for anal cancer. The probability of survival differed significantly by cancer type (LogRank P<0.001) [Figure 1].

Conclusion: We found very high IR for mortality among PLHA with NHL. Adequate resources for the effective management of HNL and cancers in general are needed to optimize the gains of ART programs in resource-limited settings like ours.

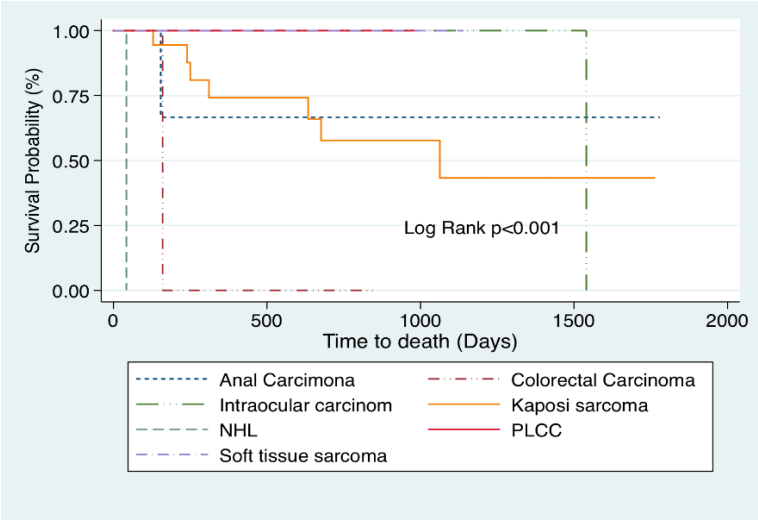

Figure 1. Kaplan-Meier survival plot of cancers among hospitalized PLHA in Jos, Nigeria

60. Kaposi Sarcoma Herpesvirus Shedding in Saliva of Patients With KSHV-Associated Malignancies

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Background: Kaposi Sarcoma (KS) Herpesvirus (KSHV) is the etiologic agent of 3 KSHV associated malignancies or proliferative disorders (KAMP): KS, KSHV-associated multicentric Castleman disease (MCD) and primary effusion lymphoma (PEL). KSHV can be shed in saliva of KSHV seropositive people with no KAMP, and saliva exchange is a mode of KSHV transmission. Little is known about KSHV in saliva of KAMP patients (pts). KSHV detection in peripheral blood mononuclear cells (PBMC) is uncommon in healthy individuals, but may be seen in some KAMP pts. The relationship between PBMCs and saliva KSHV in KAMP is unknown**.** We evaluated patterns of and risk factors for KSHV shedding in saliva of KAMP pts, as well as correlation between oral and PBMC-associated KSHV viral load (VL) in this population.

Methods: Pts with KAMP attending HAMB clinic from 2000-2016 with ≥3 available saliva specimens were included. Saliva was collected using a mouthwash based protocol and pelleted**.** KSHV VL was evaluated by quantitative real time polymerase chain-reaction (PCR) for KSHV *K6*. VL was normalized to *ERV3* copy number as determined by PCR (copies/10^6 cells). Clinical correlations included demographics, KAMP categorization, as well as CD4+ and HIV VL values when obtained within the same month as saliva KSHV VL measurements. Pts were classified as never, variable or always shedders if KSHV VL was not detected in any; in some but not all and in all samples respectively. Correlations between blood and saliva KSHV VL were determined by calculating Pearson's coefficient. Clinical associations with blood and saliva KSHV VL were evaluated in uni and multivariate analysis using nonparametric Methods and longitudinal models.

Results: We examined 1555 saliva and 1202 PBMC samples in 126 pts, who might have ≥1 diagnosis: 82% had KS (including documented oral KS, 10%), 10% PEL and 30% MCD. At baseline, median (med) age was 44 years (y), 98% were male, 93% HIV infected, 37% had undetectable HIV VL, and 60% had < 200 copies/mL, med CD4+ T cell count was 304 cells/uL (interquartile range [IQR] 179-455). Med saliva samples per patient was 12 (IQR 7-19), med follow up 2.8 years (IQR 1-5.6). Most patients (67%) were variable shedders, 26% never shedders and 7% always shedders. Med shedding frequency was 18% (IQR 0-47%). KSHV VL was generally low in saliva (med 33 copies, IQR 0-3000) and PBMC (med 71, IQR 1-1789) Pts with oral KS tended to shed more than those without (47%, IQR 20-62 vs 13%, 0-40%, p=0.07), but also tended to have less controlled HIV infection. Controlling for age, sex, HIV VL <200, and CD4 count, pts with classic KS (cKS) shed KSHV more frequently than HIV+ pts with any KAMP (61% IQR 38-93% vs 15% IQR 0-40%, p=0.002). Oral shedding decreased with increasing CD4 counts (p=0.02) and increased with increasing HIV VL (p=0.004). Age, sex or type of KAMP did not significantly affect oral KSHV VL in HIV infected patients. When both PBMCs and saliva samples were collected on the same day, KSHV VL was detected only in saliva in 22% of the cases, only in PBMCs in 38% of the cases, and in both in 40% of the cases. Correlation between VL saliva and PBMC was modest (r=0.35 p<0.001). HIV VL correlated with KSHV VL in PBMC (r=0.19, p<0.001), but not in saliva (r=0.03, p=0.3).

Conclusions: HIV+ pts with KAMP do not shed KSHV in the saliva often. In these pts with generally well-controlled HIV, KSHV was detected in the saliva 15% of the time points, and KSHV oral shedding decreased with control of HIV viremia and increasing CD4 T-cell counts. However, KSHV is more frequently detected in saliva of pts with oral involvement of KS. KSHV VL may be a useful diagnostic and research biomarker in this setting, although HIV control may be an important confounding factor. In contrast to HIV-associated KAMP, KSHV shedding in cKS was more common, suggesting immunologic defects affecting control of KSHV, absent HIV infection, may manifest in both oral shedding and tumorigenesis. While elevated PBMC-associated KSHV VL is common in untreated PEL and KSHV-MCD, these patients did not shed KSHV in saliva more than KS patients. VL in PBMC and saliva were not tightly correlated. B-cell lymphoproliferation and associated KSHV PBMC VL in these diseases may be controlled by different factors than those that control shedding in saliva.

61. Low Prevalence of KSHV DNA in Female Genital Fluid: Findings From Zimbabwean Women and Systematic Review of the Literature of KSHV Shedding in Body Fluids and Mucous Membrane Surfaces

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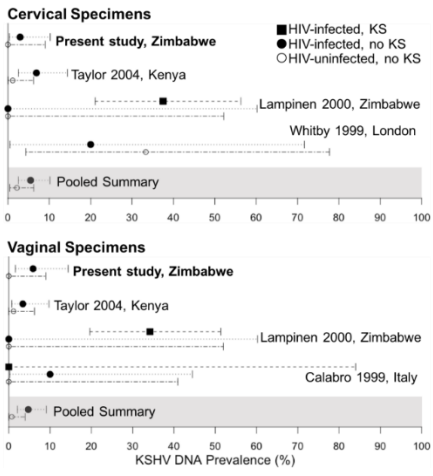
Background: KSHV infection is endemic among adults in most of sub-Saharan Africa, but exact routes of KSHV transmission are not understood. For example, sexual transmission has been proposed by some studies but not others. Knowledge of KSHV transmission mechanisms would ideally be derived from direct epidemiologic studies of person-to-person spread, but these are difficult to perform. Hence, another valuable source of clues are clinical virologic studies that examine which body fluids harbor KSHV and hence are biologically plausible to facilitate transmission. As a means to study potential sexual transmission of KSHV, we comprehensively examined conventionally accessible body fluids from African women for the presence of KSHV and systematically reviewed the published literature for similar data.

Methods: In a cross-sectional study, we selected a stratified sample of HIV-infected and HIV-uninfected women of reproductive age who were participating in two different HIV-associated cohort studies in Harare, Zimbabwe. KSHV infection status was determined by presence of anti-KSHV antibodies as measured by an induced IFA and EIA's for ORF65 and K8.1, performed at the CDC. Presence of KSHV DNA in various body fluids was assessed by PCR for KSHV ORF 25, an assay with sensitivity of under 5 copies, also performed at the CDC. In addition to the present empiric work, a systematic search of PubMed, Web of Science and EMBASE retrieved all articles published from 1995 - 2017 measuring KSHV DNA in any body fluid or mucous membrane surface among KSHV-antibody-positive individuals.

Results: Among 611 women (411 untreated HIV-infected and 200 HIV-uninfected), 108 (18%) were KSHV antibody-positive (68 HIV-infected and 40 HIV-uninfected). Among the 108, median age was 30 yrs (IQR 27-34) overall, and median CD4+ T cell count 218 cells/mm^3 (IQR 156-372) in the HIV-infected. Among the KSHV antibody-positive, detection of KSHV DNA was common in the different components of saliva but rare on vaginal and cervical surfaces (Table). In saliva, KSHV DNA detection was independently associated with age; the oldest quartile (34-48 yrs) was 2.1 times more likely (95% CI: 0.99 to 4.6, p=0.05) to shed KSHV DNA than the youngest (19-27 yrs). HIV-infected women had DNA detected more commonly, but this was not significant. A total of 29 prior studies reported on KSHV DNA in at least 1 body fluid/mucous membrane surface. Across all studies, saliva is the fluid which harbors KSHV most commonly. Female genital fluid has been studied much less often (Figure), but prior work supports our finding of very low DNA prevalence.

	Prevalence of KSHV DNA among KSHV antibody-positive women (N = 108)		
Specimen type	HIV-infected	HIV-uninfected	Age-adjusted PR (95%-CI)*
Saliva supernatant	26%	20%	1.2 (0.56--2.6)
Saliva cellular pellet	35%	21%	1.5 (0.72--3.1)
Saliva combined	37%	20%	1.6 (0.78--3.3)
Blood	21%	10%	1.8 (0.60--5.2)
Vaginal swab	6%	0%	--
Ectocervical swab	3%	0%	--
Endocervical swab	0%	0%	--

*prevalence ratio comparing HIV-infected to HIV-uninfected (reference)



Conclusion: Among KSHV-infected Zimbabwean women, KSHV DNA was commonly found in saliva but rarely detected in a comprehensive sampling of vaginal and cervical surfaces. Low prevalence of KSHV DNA in female genital fluids in our study sample is consistent with prior work from Africa but extends the inference to a larger and more representative population. Our findings, combined with prior data showing low KSHV prevalence in semen, argue against conventional penile-vaginal intercourse being an important contributor to KSHV transmission in Africa. Instead, research efforts should focus on the role of saliva in KSHV spread.

62. Malignant Neoplasms in HIV-Infected Patients of St. Petersburg

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Goal: Research the prevalence of malignant neoplasms (MNs) in HIV, evaluate clinical characteristics of the disease's course, including overall survival.

Methods: Retrospective analysis of 473 HIV-infected patients of St. Petersburg diagnosed with MNs during 2006-2015.

Results: Average age of patients – 37 years; males prevailed – 66.8%. In 111 patients, MNs was diagnosed simultaneously or within the first three months from identifying the infection (23.5%). Median survival was 2 years 8 months; in 53% – over 5 years.

Median duration of HIV prior to MNs was 8 years. In 80% MNs were diagnosed at advanced stages.

36 patients were infected with HIV due to homosexual contacts; later on, 23 developed Kaposi sarcoma whereas 9 – hemoblastosis. Upon diagnosis, 8% of patients were active drug users.

88 patients were receiving antiretroviral therapy (ART) during >6 months prior to MN; 33 had suppressed HIV activity. Subsequently, ART was given to 246 patients of whom 68 discontinued therapy. HIV RNA <50 copies/mL – in seven patients; median CD4 count – 93 cells/μL; <200 cells/μL – in 200 patients.

Malignant lymphomas were encountered in 47.5% (non-Hodgkin – 163, Hodgkin – 62), Kaposi sarcoma – 56; lung cancer – 34; cervical cancer – 26; head and neck squamous cell cancer – 19; glioblastoma – 17; colon cancer – 15; breast cancer – 15; other MNs – 66 cases.

Complicated MNs were found in 337 patients; 3 or more complications (cachexy, bleeding, ascitis, hydrothorax, pain) – in 234 patients.

57.3% of patients had the conditions limiting cancer treatment; 58 had CD4 <50 cells/μL.

One-year overall survival from MN diagnosis was 40%; five-year survival – 19%. Opportunistic infections involving the brain (20%) and the lungs (17%) worsened five-year survival whereas HIV duration before MN diagnosis, CD4 counts, HIV RNA, co-infections, hepatitis B and C did not make any impact on five-year survival. Initiating ART after MN diagnosis improved five-year survival (49%).

Conclusions: Over one half of all tumors in the study arm (51.8%) are HIV-associated malignancies. A proportion of Hodgkin lymphoma, lung cancer, head and neck squamous cancer, glioblastoma and stomach cancer – most common malignancies not associated with HIV– increases.

63. Molecular Pathology of Cancers Among HIV Cameroonian Patients

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Background: Molecular techniques for cancer diagnosis is an evolving field with direct application on targeted and new drugs. Unfortunately, in low income countries, these techniques and these drugs are not available.

Aim: The aim of our study was to classify our cancers using new WHO classification of malignant diseases.

Material and Methods: Between 2011 and 2017, cancers diagnosed amongst HIV Cameroonian patients in our hospital were send to Paris, France (AVICENNE Hospital, Pr ANTOINE Martin), and Germany for molecular techniques including immunohistochemestry, FISH, and Pyrosequencing. All samples were processed prospectively and free of charge through this International collaboration.

The diagnosis of cancer in our institution was always true, but the classification was always wrong or unavailable. We have to mention that our hospital is the oldest University Hospital in the country and no other pathology laboratory offers better experience of cancer diagnosis.

Results: 26 cancers patients with HIV were included in this series.

Among these:

- 12 had lymphomas (2 nodular sclerosis ,2 mixed cellularity, Hodgkin lymphoma, 1 nodular lymphocyte–predominant HL, 3 gastric MALT Lymphomas, 2 Extranodal NK/T-cell lymphoma, nasal type and 2 atypical Burkitt's lymphoma)
- 6 early stage Kaposi's sarcoma confirmed by the presence of HHV8 in tumours cells by immunohistochemestry
- 3 Triple negative breast cancer
- 2 colon cancer (MLH1 and MLH3)
- 3 soft tissue sarcomas

No patient of this series received targeted treatment because of the price and the availability of the drugs. 3 patients even died before we received the diagnosis from Paris.

Conclusion: Molecular diagnosis of cancer and targeted drugs are necessary through international collaboration and should be introduced in low income countries.

64. Patient and Treatment Characteristics by HIV of Women With Cervical Cancer Enrolled in UPenn-University of Botswana U54 Project 3

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Background: Cervical cancer, an AIDS defining neoplasm, is the leading cause of cancer related mortality among women in sub-Saharan Africa including Botswana. Development and progression to cervical cancer requires chronic HPV infection. HIV infection is known to accelerate this progression. The burden of disease is greatest in Africa and increasing rapidly despite wide usage of antiretroviral therapy (ART). With this Background, we wanted to explore the role of immune status and reconstitution on toxicities and outcomes of cervical cancer patients treated with chemoradiation (CRT) through the U54 consortia grant.

Methods: Women with cervical cancer with or without HIV infection initiating radical CRT in Botswana were enrolled in a prospective observational cohort study from December 2016 –June 2017. Blood and tissue have been collected in these patients to assess immune markers before and after treatment.

Results: Of 78 women with cervical cancer enrolled during the study period, 77% (60/78) women were HIV-infected. 68% of women with cervical cancer at presentation were in the age group of 40-59 years. 23.3% (14/60) of HIV-infected women were in the age group of 24-39 compared to 5.6 %(1/18) of HIV-uninfected. 65% (39/60) of HIV-infected women were single compared to 50 %(9/18) of HIV-uninfected women. Seventy eight percent of all participants (61/78) had stage II/III cervical cancer. Median CD4 count in HIV-infected was 519 cells/ul. 98.3% (59/60) of all HIV-infected patients were on anti-retroviral treatment (ART) at the time of curative cervical cancer treatment initiation. We found no significant difference in baseline laboratory values between HIV-infected and HIV-uninfected women. Although median haemoglobin at baseline was 11.5 g/dL in HIV-infected vs. 12.4 g/dL in HIV-uninfected. In regards to cancer treatment, over 95% of all patients completed prescribed external beam dose, all patients completed prescribed brachytherapy dose and 65% of patients in both groups received 4 or more cycles of concurrent chemotherapy.

Conclusions: HIV infected women with cervical cancer present at a younger age than HIV-uninfected women. HIV status had no effect on stage, baseline laboratory values and treatment characteristics in our cohort so far. Further analysis of immune markers will be done to assess role of immune status and reconstitution on treatment outcomes for cervical cancer in HIV-infected and HIV-uninfected women.

65. Patterns of Repeated Anal Cytology Testing Among HIV-Positive and HIV-Negative Men Who Have Sex With Men

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Background: Men who have sex with men (MSM) are at increased risk for anal cancer. In cervical cancer screening, patterns of repeated cytology are used to identify low- and high-risk women, but little is known about these patterns for anal cytology among MSM.

Methods: We analyzed data from MSM in the Multicenter AIDS Cohort Study (MACS) who were offered anal cytology testing annually (HIV-positive, n=708) or every 2 years (HIV-negative, n=796) for 4 years. After excluding men with anal dysplasia treatment during testing, at least 2 valid cytology results were available for 474 HIV-negative and 502 HIV-positive MSM, and at least 3 results for 328 HIV-positive MSM. We used inverse probability weighting to address possible selection bias.

Results: Following a single negative cytology, the frequency of the next cytology remaining negative was lower among HIV-positive MSM with CD4≥500 (74%) or CD4<500 (68%) than HIV-negative MSM (83%) ($p<0.001$). Alternatively, after a single abnormal cytology, the frequency of the next cytology remaining abnormal was highest among HIV-positive MSM with CD4<500 (70%) compared to CD4≥500 (53%) or HIV-negative MSM (46%) ($p=0.003$). Among HIV-positive MSM, 37-38% had 3 consecutive negative results, while the proportion with 3 consecutive abnormal results was larger among CD4<500 (22%) than CD4≥500 (10%) ($p=0.008$).

Conclusions: Many HIV-positive MSM have consistently negative anal cytology over a four-year period. Following abnormal anal cytology, a repeated cytology is commonly negative in HIV-negative or immunocompetent HIV-positive men, while persistent cytological abnormality is more likely among HIV-positive men with CD4<500.

66. Personalized Lung Cancer Screening for HIV-Infected Individuals Using VACS Index: A Simulation Study

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Background: Lung cancer is the leading cause of non-AIDS defining cancer (NADC) deaths among HIV infected (HIV+) individuals. While both the U.S. Preventive Services Task Force (USPSTF) and the U.S. Centers for Medicare & Medicaid Services (CMS) endorsed lung cancer screening with computed tomography (CT) for the general population, the benefits and harms associated with lung cancer screening are unclear for HIV+ smokers. In this study, we integrated the Veterans Aging Cohort Study (VACS) Index, a widely validated and well-calibrated risk index for HIV+ individuals, into the Lung Cancer Policy Model (LCPM) to determine the optimal lung cancer screening strategy for HIV+ patients.

Methods: We developed a version of the LCPM tailored to HIV+ individuals (LCPM-HIV) using data from the literature and patient data from VACS. We then used the LCPM-HIV to estimate the life-years gained, the number of CT exams performed to screen HIV+ individuals, and postoperative deaths with different VACS index scores and smoking status. The VACS index is a well-established risk index for predicting all-cause mortality among HIV+ individuals, including clinical predictors such as age, CD4 count, HIV-1 RNA, hemoglobin, platelets, aspartate and alanine transaminase (AST and ALT), creatinine, and viral hepatitis C infection. Higher VACS index scores indicate higher all-cause mortality rates. In this study, we compared health outcomes of a scenario with no screening implemented to outcomes of a screening scenario using eligibility criteria established by the CMS (55-77 years of age and ≥30 pack-year smoking history, ≤15 years since quitting). We also varied the VACS index scores of HIV+ patients to estimate the impact on screening outcomes.

Results: For HIV+ current smokers with VACS index scores between 0-20, starting lung screening at age 55 can provide 0.02 life-years gained using CMS recommendations (Table 1). Quitting smoking at age 55 will increase the life-years gained to 0.05 because former smokers have longer life expectancy. Current HIV+ smokers with VACS index scores above 40 have negligible life-years gained from screening. Meanwhile, former smokers have no life-years gained when their VACS index score is above 61. Across the entire VACS index range, the average numbers of screening CT exams per person range from 2.8 to 8.0 and 4.4 to 11.0 for current and former smokers, respectively. The numbers of postoperative deaths per 100,000 patients are between 118-154 for current smokers and 89-137 for former smokers. In addition to increasing life-years gained, quitting smoking reduces the risk of dying from surgery.

Table 1. Estimated Health Outcomes of HIV+ Patients Associated with Lung Cancer Screening

	Current				Former (quit at age 55)			
VACS Index	0-20	21-40	41-60	>61	0-20	21-40	41-60	>61
Life-years gained	0.02	0.01	0.00	0.00	0.05	0.03	0.02	0.00
# of screening CT exams per person	8.0	6.1	4.5	2.8	11.0	9.3	7.2	4.4
Postoperative deaths per 100K	118	127	148	154	89	94	118	137

Conclusions: Results from our simulation model demonstrate a threshold VACS index score above which lung cancer screening with CT does not provide any benefit to the HIV+ population. Quitting smoking will increase the benefits and reduce the harms from screening, due to a combination of longer life-expectancy among HIV+ patients and reduced operative mortality risk.

67. Short-Term Outcomes for Lung Cancer Resection Surgery in HIV Infection

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Background: Lung cancer is the leading cause of cancer death in HIV infected (HIV+) persons. Outcomes are worse compared to the general population. Less aggressive treatment of lung cancer in HIV+ patients is one of the reasons, and is in part due to perceptions of higher rates of treatment complications in this group, despite very limited data on lung cancer treatment outcomes in HIV+ persons to support this assertion. We identified HIV+ lung cancer patients from a national cohort undergoing surgical lung resection and uninfected comparators to determine the rates and risk factors of major surgical complications.

Methods: We linked clinical and cancer data from the Veterans Aging Cohort Study (VACS) to surgical outcomes from the Veterans Affairs Surgical Quality Improvement Project (VASQIP) database to identify 424 patients (151 HIV+, 273 uninfected) with pathologically confirmed lung cancer, who underwent either lobectomy, limited resection or pneumonectomy within the VA system between 2000-2016. We collected data on baseline characteristics, including HIV-related laboratory data at the time of surgery. From VASQIP, we identified outcomes including major 30-day surgical complications and 30-, and 180-day mortality. We then compared rates of 15 key short-term adverse outcomes by HIV status, and among HIV+ patients we compared characteristics for patients with and without major complications.

Results: Patients did not differ by HIV status in age (mean 60 years), sex, race/ethnicity, prevalence of chronic conditions (chronic obstructive pulmonary disease, congestive heart failure, diabetes), surgical risk class, functional status impairment, year of surgery/cancer diagnosis, cancer stage or histologic subtype. Surgical approach also did not differ by HIV status (70% lobectomy, 19% limited resection, 11% pneumonectomy). Reoperation and pneumonia were the most frequent 30-day complications for HIV+ patients and the frequency of complications did not differ by HIV status for any complication (select complications shown in Table 1). 30-day mortality was 2% for HIV+ patients and did not differ by HIV status (p=0.9); 180-day mortality trended higher for HIV+ patients however (11% versus 6%; p=0.07). There were no significant predictors of post-operative complications for HIV+ patients.

Conclusions: In a nationwide ART-era cohort of HIV+ and uninfected lung cancer patients undergoing surgical lung resection, short-term outcomes following surgery did not differ by HIV status. Concerns regarding short-term surgical complications should not influence treatment decisions for HIV+ patients with lung cancer.

Table 1. 30-Day Complication Rate for Lung Cancer Surgery by HIV Status

Complication	**HIV+** (n=151)	**HIV-** (n=273)	**p-value**
Death, n (%)	3 (2.0)	6 (2.2)	0.9
Pneumonia, n (%)	16 (10.6)	23 (8.4)	0.5
Reoperation, n (%)	13 (8.6)	26 (9.5)	0.8
Sepsis, n (%)	4 (2.7)	5 (1.8)	0.6
Reintubation, n (%)	9 (6.0)	24 (8.8)	0.3
Myocardial Infarction, n (%)	1 (0.7)	1 (0.4)	0.7

68. Quality Approach to Tissue Microarray Construction From the AIDS and Cancer Specimen Resource

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Background: Tissue Microarrays (TMAs) are used to conserve precious tissue resources and control immunohistochemistry (IHC) costs and variation across a sample set. The creation and quality assurance associated with TMA construction has not been standardized. We present a series of steps and standards that provide a quality product allowing the end-user confidence in the results. Herein, we outline 2 processes for construction of TMAs and essential quality control measures developed by the AIDS Cancer Specimen Resource Network's Science and Technology Core.

Methods: The thickness and tissue area of the paraffin blocks are first assessed to determine if there is adequate tissue for TMA construction. Next, the Core pathologist reviews each H&E slide and circles areas of tumor and non-tumor. The circled slides and blocks are documented by scanning on a copy machine. The core size is dependent upon the tissue area, tumor type, and the desired representation of tissue architecture. Before beginning construction, the placement of tissue cores and orientation of the TMA is detailed in a map, which organizes the workflow. This map should be developed asymmetrically to give a defined orientation without ambiguity for the block and cut slides. The TMA should contain no more than 40 cases for ease of scoring, allowing for placement away from the edge of the block, and distribution throughout the entire block. Orientation and control tissues should be included. The "Recipient Block Method" works best for the TMA technologist who has limited experience, as well as for thin donor blocks. The recipient block (Quick-Ray, Sakura Finetek) is made by pouring melted paraffin into the mold with the correct core size, then cooled. After deposition of the donor cores into the newly created recipient block, it is placed on a glass slide, heated, and then gently pressed to seat the cores and level the surface. An alternate method is the "Tape Method". No stacking of cores is done with this method; therefore the donor block tissue should be at least 5mm thick. A piece of double-sided tape is applied to the floor of the stainless steel block mold. The cores are taken from the donor block, and carefully positioned upright on the tape. A tissue cassette is placed upon the stainless steel mold and melted paraffin is poured slowly and steadily through the grid, and left undisturbed for 20 minutes so as to not disturb the cores, then the block is placed in the refrigerator for another 30 minutes, then the block and tape are removed from the steel mold.

Results: Using these Methods, we have created >20 well-organized TMAs for the ACSR that are ready for the Quality Control process. Thirty unstained sections are made, with H&Es performed on sections 15 and 30 and reviewed for tumor presence (to determine accuracy of the punch). Protein quality is assessed by performing IHC for pancytokeratin, and/or CD20, and/or LANA. mRNA quality is assessed using U6 in situ hybridization. All QC results are recorded and are part of the scoring map for reference when experimental work is performed. The H&Es and IHC/ISH slides are scanned with the Aperio system (Leica) and uploaded to the ACSR website where investigators can review the available materials. Storage conditions for unstained slides include 40 C, desiccant, and nitrogen atmosphere.

Conclusions: These TMA construction Methods and quality assurance allow the ACSR Science and Technology Core to inexpensively create valuable resources to benefit the HIV research community.

69. Portable Confocal Microscopy as a Diagnostic Tool for Kaposi's Sarcoma in Africa

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Background: AIDS-related Kaposi's sarcoma (KS) is one of the most commonly reported malignancies in HIV infected adults. In sub-Saharan Africa, survival after a KS diagnosis is unacceptably poor with one year mortality up to 46%, even with increased use of antiretroviral therapy (ART). Key among the reasons for poor survival is late diagnosis, with 69%-86% of KS patients diagnosed with advanced (T1) stage KS. In resource-poor settings, histopathologic diagnosis is not always available and is impeded by lack of trained pathologists and equipment. Therefore, there is a need for alternative diagnostic approaches. Reflectance confocal microscopy (RCM) is an optical technology that can visualize cellular details of the skin at point of care without taking biopsy. Previously, RCM has not been utilized in resource-poor settings due in part to its high cost. Our aim was to develop a low-cost smartphone portable confocal microscope for use among patients suspected to have KS in resource-poor settings.

Methods: We developed a low-cost smartphone confocal microscopy device that uses an inexpensive LED light source (Panel A). This lightweight device images the skin through a series of lenses and displays it on a smartphone screen in real-time. The device can be used both *in vivo* on intact skin (Panel B) and *ex vivo* on skin that has been biopsied. Among patients with suspected KS referred for a biopsy in Kampala, Uganda , we performed *in vivo* imaging at three depths of 125, 175, and 225 µm to evaluate cellular features in the epidermis and deeper in the dermis. For *ex vivo* imaging, the skin biopsy was placed in 1% acetic acid for 5 minutes to enhance the nuclear contrast of the confocal images.

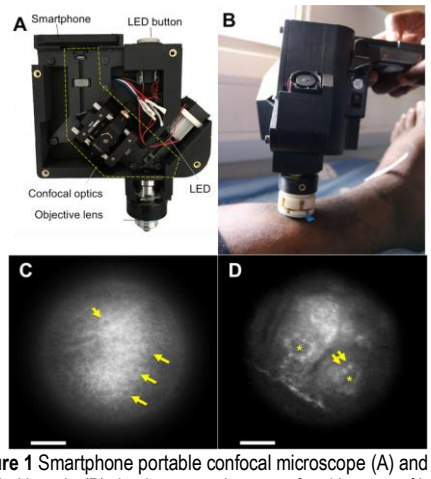

Figure 1 Smartphone portable confocal microscope (A) and its use in Uganda (B); *in vivo* smartphone confocal images of human skin (C and D). Epidermis image (C) visualizes numerous cell nuclei (dark circles pointed by arrows). At dermal-epidermal junction (D), dermal papillae (asterisks) are delineated by circular arrangements of melanocytes (bright dots pointed by arrows). Scale bar = 100 µm.

Results: 130 patients with suspected KS had both *in vivo* and *ex vivo* images taken of lesional skin with the portable confocal microscope. The device cost 10-20 times less than a full-size confocal microscope. Imaging took <15 minutes to complete. The device achieved high lateral resolution of 1 µm and axial resolution of 5 µm. *In vivo* confocal images visualized characteristic cellular features of skin, including the honeycomb pattern of keratinocytes, bright scatter from melanocytes, and dark oval areas corresponding to dermal papillae (Panels C and D). Previously unreported, *in vivo* imaging was limited due to light scattering noted in Fitzpatrick skin type 5 and 6 darker skin tones, limiting the best quality images to the epidermis and the dermoepidermal junction. *Ex vivo* imaging, in contrast, was able to visualize cellular nuclei in both the dermis and the epidermis.

Conclusions: We developed a low cost portable confocal microscope for use in resource-limited settings, which was able to detect cellular features of skin similar to those expected from traditional dermatopathology. We report for the first time the challenge of *in vivo* confocal microscopy in darker skin individuals due to limited penetration of light into the dermis, an obstacle that can be theoretically overcome by using a longer wavelength. *Ex vivo* confocal microscopy performed on skin biopsy samples shows promise as a possible tool for rapid point-of-care diagnosis of KS.

70. Real-World Use of ART and Chemotherapy for Kaposi's Sarcoma in a Large Community-Based HIV Health Care Network in Kenya

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Background: Kaposi's sarcoma (KS) is one of the most common HIV-associated malignancies in sub-Saharan Africa. KS survival has improved largely due to antiretroviral therapy (ART). In resource-rich settings, survival has also benefited from chemotherapy. Little is known, however, about chemotherapy epidemiology of KS in resource-limited regions. We sought to determine the prevalence of indications for chemotherapy amongst patients with newly diagnosed HIV-associated KS, penetration of chemotherapy, and regimens used in a large community-based health care network in East Africa.

Methods: We identified all patients newly diagnosed with HIV-related KS from 2009-2012 in the 26-clinic AMPATH network in Kenya, a member of East Africa IeDEA. Through chart review, we ascertained disease severity at diagnosis and KS-specific treatment. Indications for chemotherapy were considered AIDS Clinical Trial Group (ACTG) T1 stage and/or "severe" disease defined by WHO KS treatment guidelines (which includes functional disability due to disease and/or symptoms from visceral KS).

Results: Of 674 patients diagnosed with KS, charts were available for 599 (89%); 61% were men, median age was 35 years, and median CD4 at KS diagnosis was 184 cells/µl. At diagnosis, of 476 patients with evaluable ACTG T stage, 72% were T1 stage. The most common T1 indication was tumor-related edema (254 of 345), although 30% had more than one T1 indication. Of 354 patients with evaluable WHO KS treatment guideline staging, 27% had documented "severe" disease. Overall, of the 583 patients with evaluable KS diagnosis date, by six months after diagnosis, 45% were already on/had started ART alone, and 46% had started ART plus chemotherapy (Table 1). In the 261 treated with ART alone, 93 (36%) subsequently became LTFU over the 6-month period, and 22 (8%) died, effectively precluding subsequent chemotherapy.

Table 1: KS treatment at six months after diagnosis	N= 583
ART alone	261 (45%)
ART plus chemotherapy	270 (46%)
Chemotherapy alone	5 (1%)
Death prior to therapy initiation	4 (1%)
Loss to follow-up prior to therapy initiation	33 (6%)

Among all patients, 49% received chemotherapy of any kind within 2 years of KS diagnosis. Of those receiving chemotherapy, median time to first chemotherapy was 28 days (IQR 4-57 days). Restricting to patients with a chemotherapy indication, for patients with T1 disease, 57% received chemotherapy; for patients with WHO "severe" disease, 59% received chemotherapy by the end of two years. Initial regimens were bleomycin-vincristine (78%), adriamycin-bleomycin-vincristine (10%), etoposide (7%), gemcitabine (3%), and vincristine (1%).

Conclusions: A substantial fraction of patients with KS in East Africa are diagnosed at advanced disease stage. For patients with apparent chemotherapy indications, nearly half did not receive chemotherapy; prospective work is needed to understand why (e.g., poor access, inability to tolerate therapy, sufficient response to ART alone, or patient preference). Liposomal anthracyclines, which are often first-line in resource-rich settings, are very expensive in this setting, and were not used as first line. These findings highlight challenges in East Africa in cancer care.

71. Risk of Non-AIDS-Defining Cancers Among Veterans With Well-Controlled HIV Infection

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Background: The introduction of combined antiretroviral therapy has revolutionized HIV-infection management, resulting in improved outcomes and survival for HIV-infected individuals. However, as individuals with HIV are living longer and aging, their risk of mortality from cancer has increased. We aimed to examine risk of non-AIDS-defining cancers in a large contemporary cohort of patients with well-controlled HIV infection during the antiretroviral therapy era.

Methods: This was a retrospective cohort study from a total of 121 facilities in the Veterans Health Administration. Veteran patients with HIV diagnosis between 1 October 1999 and 31 December 2016 were included and followed until cancer diagnosis, death or 12/31/2016. Non-AIDS-defining cancers were identified using the VA Clinical Cancer Registry, and included esophageal, stomach, lung, head and neck, colorectal, prostate, liver, anal, oropharyngeal, and Hodgkin lymphoma. We compared the incidence rate of all non-AIDS-defining cancers combined in veterans with HIV with those in a matched cohort (4:1 matched on age, sex, and date of HIV-matched diagnosis) of veterans without HIV infection. We also report incidence rates separately for esophageal, stomach, lung, and prostate cancers.

Results: We identified 46,765 patients with HIV infection who met our study eligibility criteria. Most were men (96.9% of follow-up time) and aged 40 to 59 years at HIV infection (65.7%). Further, African Americans (48.2%) and whites (40.9%) were the two largest race/ethnicity groups. During 430,595 person-years of follow-up, 4020 patients develop a non-AIDS-defining cancer (all cancers combined), yielding an incidence rate of 9.34 per 1,000 person-years (95% confidence interval [CI] 9.05-9.63). Incidence rates were highest among persons aged >70 years and Asians. The incidence rate of all NADCs combined was almost 5-fold higher among the HIV cohort relative to the non-HIV cohort (incidence rate, 1.96 per 1,000 person-years). Among HIV-infected patients, risk of esophageal, stomach, lung and prostate cancer were 2.93-fold (0.17 vs. 0.06 per 1,000 person-years), 2.86-fold (0.12 vs. 0.04 per 1,000 person-years), 4.64-fold (2.22 vs. 0.48 per 1,000 person-years), and 3.52-fold (2.71 vs. 0.75 per 1,000 person-years) higher relative to the non-HIV cohort, respectively.

Conclusions: People with HIV infection are at increased risk for developing common non-AIDS-defining cancers compared to age-matched controls in the antiretroviral therapy era. Further research is needed to understand the reasons for this increased risk.

72. Prevalence and Determinants of High-Risk Human Papillomavirus mRNA Detected Through Community-Based Cervical Cancer Screening in Uganda

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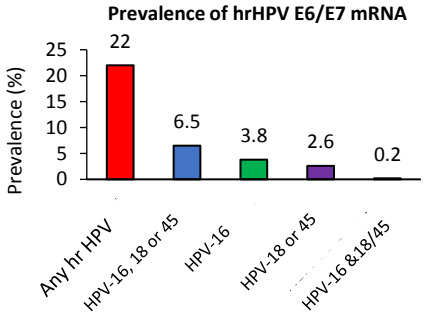
Background: Infection with high-risk human papillomavirus (hrHPV) is a prominent cause of cervical dysplasia and cervical cancer. Sub-Saharan Africa bears the world's highest prevalence of hrHPV and cervical cancer incidence. Most of the data available in Africa on the prevalence of hrHPV has been based on HPV DNA tests. There are few studies evaluating the prevalence and associated determinants for the presence of hrHPV E6/E7 RNA in cervical-vaginal specimens, a finding that may more accurately reflect women's cervical cancer risk.

Methods: Women from 16 communities in the Kiboga district of rural western Uganda were mobilised by local Village Health Team members to attend community-based HPV screening fairs in walking distance from their residences. At these fairs, the women provided a self-collected vaginal sample, which was tested for E6/E7 mRNA from any of 14 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68) as measured in a non-differentiating assay using the APTIMA® platform. Specimens were also tested for the specific presence of E6/E7 mRNA from the most oncogenic HPV types (16 and 18/45). Participants who tested positive for any hrHPV E6/E7 mRNA were subsequently offered Visual Inspection with Acetic Acid and cervical biopsy at a mobile treatment unit, brought to their village, in order to determine true disease status and appropriate therapy.

Results: Between March 2016 and April 2017, 1030 participants provided a vaginal sample during 16 health fairs. The median age was 34 years (IQR 28-40), most of them were married (81%), and the majority had only primary level education (76%) with non-professional employment (89%). HIV prevalence was 13%. Most women (94%) had never been screened for cervical cancer. Prevalence of any hrHPV E6/E7 mRNA was 22% (n=229); HPV-16 was found in 3.8% and HPV-18/45 in positivity remained significantly associated with any hrHPV infection (Table). Among the 144 hrHPV mRNA positive women who underwent a pre-treatment biopsy, 139 had adequate biopsies taken. Among these biopsies, 13 women had cervical intraepithelial neoplasia 2 or greater (CIN2+), resulting in the presence of any hrHPV mRNA detection having positive predictive value (PPV) of 9.3% (95% CI: 6-16). The PPV for CIN2+ associated with detection of HPV-16 or HPV-18/45 E6/E7 mRNA was only slightly higher, 12% and 19%, respectively.



2.6% (Figure). Only two (0.2%) participants tested positive for both HPV 16 and 18/45. Age, parity, marital status and HIV seropositivity were associated with presence of any hrHPV E6/E7 mRNA in unadjusted analyses. When adjusted for age, marital status, parity, current pregnancy, and HIV serostatus, only age, pregnancy and HIV-

Characteristic	Unadjusted	Adjusted
Age, per additional yr	0.97 (0.96-0.99)*	0.96 (0.94-0.98)
Pregnancy		
Not pregnant	Ref.	Ref.
Pregnant	1.4 (0.95-1.9)	1.4 (1.0-2.0)
HIV status		
HIV-uninfected	Ref.	Ref.
HIV-infected	1.9 (1.5-2.5)	2.1 (1.6-2.7)

* denotes prevalence ratio and 95% confidence interval

Conclusion: In a community-based sample of young women from Uganda, the prevalence of E6/E7 mRNA from any hrHPV type is high. In contrast, the prevalence of E6/E7 mRNA from the most oncogenic HPV types (16, 18, 45) was substantially lower, which in part explains the low PPV for CIN2+ that we observed for detection of E6/E7 mRNA from any hrHPV. The findings emphasize the need for identifying more specific screening approaches for cervical dysplasia/cancer as well as the importance of long-term follow-up amongst women who are found to harbor hrHPV but who do not have significant cervical disease.

73. Rituximab in Malawi: Early Results From a Phase II Clinical Trial

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Background: Rituximab improves survival for diffuse large B-cell lymphoma (DLBCL), including HIV+ patients if CD4 ≥50 cells/μL. Due to cost and limited infusion capacity, it is usually unavailable in sub-Saharan Africa (SSA), where HIV+ DLBCL occurs most frequently worldwide. This is likely the 1st prospective description of rituximab safety, feasibility, and efficacy in SSA, where hematopoietic growth factors are not routinely available and infectious complications differ from high-income countries.

Methods: We are conducting a non-randomized phase II clinical trial of up to 6 cycles of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for DLBCL in Lilongwe (NCT02660710), using the Indian biosimilar, to assess safety, feasibility, and efficacy. Eligible patients are 18-60 years of age with performance status (PS) ≤2, and new DLBCL diagnosis rendered locally using immunohistochemistry and telepathology. HIV+ and HIV- patients are eligible. Adequate bone marrow, renal, and hepatic function are required, and CD4 ≥100 cells/μL for HIV+ patients. Although initially an exclusion criterion, protocol amendment in April 2017 allowed hepatitis B surface antigen-positivity (HBsAg+) if HIV+ and receiving tenofovir-lamivudine as antiretroviral therapy (ART). Treatment monitoring and dose adjustment are standardized, hematopoietic growth factors are not available, and supportive care is per protocol. All patients receive premedication to prevent hypersensitivity, and rituximab is administered using simplified infusion protocols. All HIV+ patients receive ART concurrently with chemotherapy, typically with tenofovir-lamivudine-efavirenz as per Malawi guidelines.

Results: From 8/1/2016 to 7/31/2017, we screened 21 patients with 9 (43%, 7 HIV+, 2 HIV-) enrolled and treated with RCHOP. Reasons for screening failure were: non-DLBCL (6 including 5 plasmablastic & 1 peripheral T-cell lymphoma); CD4 <100 cells/μL (3); PS >2 (1); and HBsAg+ (2). Median age was 49 years (range 23-55), and 5 (56%) were female. 3 (33%) were stage III/IV, median lactate dehydrogenase was 432 IU/L (range 373-979), median PS 0 (range 0-2), median age-adjusted international prognostic index (aaIPI) 1 (range 0-3), and median tumor bulk 82 cm^2 (range 25-240) measured as sum of product diameters for ≤6 palpable target lesions. Among 7 HIV+ patients, 5 (71%) were on ART for a median 18 months before enrollment (range 1-107) with median CD4 272 cells/μL (range 145-844) and 3 (38%) with suppressed HIV RNA. As of 7/31/2017, all patients were alive with 6 having completed treatment on protocol after a median 4.5 RCHOP cycles (range 2-6). 7 patients were in protocol-defined complete response (CR) and 2 partial response (PR). Reasons for treatment cessation before 6 cycles were neutropenia per protocol in 2 patients and social reasons in 1. Outcomes compare favorably with historical CHOP-treated patients who would been eligible for the trial. 5 patients (56%) experienced grade 3/4 neutropenia. Other grade 3/4 toxicities were grade 4 sepsis in 1 patient which resolved with appropriate antibiotics, grade 3 hyperkalemia, and grade 3 hyperglycemia in a patient newly diagnosed with diabetes coincident with study participation. No hypersensitivity occurred nor hepatitis in 1 HIV+/HBsAg+ patient. In addition, 3 HIV+ multicentric Castleman disease (MCD) patients, including 1 with hemophagocytic lymphohistiocytosis, received rituximab +/- etoposide through compassionate use exemption granted by Malawi regulatory authorities, for severe relapsed/refractory disease after 2 prior chemotherapy lines and no therapeutic alternatives. All MCD patients completed treatment and are doing well, although 1 experienced mild worsening of concurrent Kaposi sarcoma requiring paclitaxel.

Conclusions: In early experience, rituximab was safe, feasible, and effective for selected DLBCL patients and relapsed/refractory HIV+ MCD in Malawi. As anticipated, neutropenia was common without growth factors, leading to reduced cytotoxic cumulative dose and dose intensity. Enrollment and follow-up continue toward target accrual of 40 patients followed 5 years from RCHOP initiation.

74. Spectrum of HIV-Related Cancers in Pre- and Post-HAART Era, Indian Study

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Introduction: With the availability of combined antiretroviral therapy and treatment of opportunistic infections there is an increased life expectancy of HIV positive patients and hence an increase in chronic diseases inclusive of cancers is expected. Malignancies account for more than one-third of the causes of death among HIV infected patients. Government of India launched the free ART programme in 2004 .We studied the spectrum of HIV related cancers in the pre and post HAART era, at a tertiary referral cancer centre in India.

Materials and Methods: We used the gender and age-specific proportions of each cancer site of the year 2008 that was recorded in the Hospital Cancer Registry at Tata Memorial Hospital, to estimate an expected number of various cancer sites among HIV positive cancer patients during the period 2001-2006 (pre HAART era) and 2007-2015 (post HAART era) respectively . The observed number of site specific cancer cases was divided by the expected number to obtain proportional incidence ratio (PIR). An increased PIR means that proportion of cancer for a particular cancer site is more in HIV positive cancer cases compared to that expected from the data of hospital based cancer registry. The standard error of the PIR was estimated to compute 95% CI.

Observations: There were 511 patients with HIV related cancers in pre HAART era and 758 patients in the post HAART period .74.5% patients were diagnosed to have HIV at the time of cancer diagnosis in pre HAART era as compared to 54.5% in the post HAART era . The CD4 counts were < 200cell/cumm in 36.7% NHL in the post HAART era as compared to 63.3% in the pre HAART era .There were more ADC as compared to NADC in both the pre (51.1%)and post HAART era (56.34%) respectively.

Conclusions: In the post HAART era higher proportion of HIV related cancers were diagnosed in patients already in routine clinical care for HIV. All the cancers with increased PIR are infection related cancers. AIDS defining cancers continue to be the frequent cancers among PLWHA in India .There is a need for early detection of HIV infection and more widespread ART coverage in India.

Cancer site	PIR(95%CI)			
	Males		Females	
	PRE HAART	POST HAART	PRE HAART	POST HAART
AIDS defining cancers(ADC)				
NHL	6.4(5.4-7.6)	9.16(7.96-10.54)	6.7(4.9-.3)	8.18(6.42-10.44)
Cervical cancer	-	-	3.3(2.7-4.1)	4.28(3.67-4.99)
Non AIDS defining cancers (NADC)				
Anal canal	5.81(2.91-11.63)	4.25(2.21-8.17)	2.15(0.30-15.25)	3.37(1.27-8.99)
Vulva	-	-	3.27(0.46-23.23)	4.58(1.72-12.20)
Penis	2.01(0.84-4.83)	1.66(1.47-4.80)	-	-
Hodgkin's disease	1.37(0.74-2.54)	1.44(0.77-2.68)	2.50(0.80-7.74)	2.76(1.32-5.79)
Conjunctival cancer	1.15(0.16-8.18))	4.75(1.19-19.01)	-	14.27(3.57-57.08)

75. The Impact of HIV Infection on Squamous Cell Carcinoma (SCC) Antigen levels in Patients With Advanced Cervical Cancer Treated With (Chemo-) Radiotherapy in Botswana

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Background: There is a high burden of cervical cancer among HIV-infected women in sub-Saharan Africa. However, due to resource constraints, assessment of treatment response at the end of treatment is limited in low and middle countries. Several studies have investigated a wide range of potential tumor markers that could be used as monitoring tools of treatment response and outcomes in cervical cancer in the HIV-uninfected patients. Change in squamous cell carcinoma antigen (SCC-Ag) from before to end of treatment or during follow up has been associated with response to treatment as well as early detection of disease recurrence in HIV-uninfected patients. However, the relationship between SCC-Ag levels in patients with HIV infection has not been clearly elaborated. Our hypothesis is that HIV infection has an impact on the SCC-Ag levels, therefore the purpose of the present study was to determine SCC-Ag levels of HIV-infected and HIV-uninfected patients with locally advanced cervical cancer that were treated with definitive radiotherapy.

Methods: Seventy-eight patients who presented with cervical cancer who were receiving definitive radiotherapy at the Department of Radiation Oncology at GPH in Gaborone, Botswana were studied. Baseline patient and tumor related characteristics including but not limited to diagnosis staging, HIV status, Viral load and CD4 count as well as treatment related information were collected. The serum SCC-Ag levels were measured prior to treatment, at the end of treatment and 12 weeks post treatment completion.

Results: Out of the 78 patients studied, 60 (76.9%) were HIV infected and 18 (23.1%) were HIV uninfected. Only 88.5% (75.4% HIV infected and 24.6% HIV uninfected) and 56.4% (72.7% HIV infected and 27.3% HIV uninfected) had end of treatment and 12 weeks post treatment data respectively, available for analysis. We explored the relationship between SCC-Ag levels and HIV status at the three time points. Even though the data suggests a decrease in serum level of SCC-Ag from baseline to end of treatment in the HIV infected patients compared to HIV uninfected patients, there was no significant difference ($p = 0.275$ and 0.1808, respectively) between the two groups. However, the data shows a statistically significant difference ($p = 0.0304$) in the serum level of SCC-Ag between the HIV-infected (M = 0.70; IQR = 0.00-1.20) and HIV-uninfected (M = 0.00; IQR = 0.00-0.00) patients at 12 weeks post treatment completion.

Conclusions: We observed statistically significant differences among the HIV-infected and HIV-uninfected were at 12 weeks post treatment completion; however a larger sample size is required to support this difference. In future analysis, we will correlate clinical responses changes in SCC-Ag after treatment and overall survival, which will guide quality of care in this population in Botswana.

76. The Networking CancerVIH Group on AIDS Malignancies: Epidemiological Data and Guidelines for an Optimal Practice in Oncology and Immunology Field

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In France, the number of people living with HIV is estimated at 152 000[1] and the overall incidence of cancers in this population is estimated at 14 ‰[2], cancer being the leading cause of death (36% of deaths[3]). The incidence of the number of people living with HIV and cancer would therefore be more than 2,000 per year. The primary aim of the CancerVIH network is to provide access for all patients to the multidisciplinary skills necessary for optimal diagnosis and follow-up care. In May 2014, a National Pluridisciplinary Consultation Meeting (RCP "ONCOVIH") was set up, accessible via a web-conference system to all practitioners in France, including DROM-COM. This RCP takes place twice a month and brings together cancer specialists (medical oncologists, radiation therapists, hematologists), specialists in HIV infection (infectious diseases, internists, virologists, immunologists) and pharmacologists. One of the primary concerns of this RCP is to ensure that antiretroviral treatments and anti-cancer treatments are not interacted. 69 RCPs have already occurred: 369 patients were presented (41 in 2014, 85 in 2015, 144 in 2016 and 99 in July 31, 2017 with a constant increase in the number of patients presented each year). 62 patients were presented several times (2 to 5 times) for a total of 457 records submitted since 2014. The CancerVIH network participates in the drafting of recommendations for the screening, diagnosis and follow-up of people infected with HIV and cancer at the national level, in particular through the involvement of the Scientific Council of CancerVIH in the drafting and proofreading the Cancer chapter of the Morlat report[4] and also at the European level with the drafting and publication of guidelines for care[5]. In 2017, the CancerVIH network will set up a database accessible via an online platform. This platform should make it possible, through a facilitated presentation in RCP, to increase the number of patients in the database (in order to get closer to national representation) and thus to collect epidemiological data on people living with HIV and Cancer. Some data are already available, notably thanks to the 369 patients already presented: The CancerVIH network also aims to provide people living with HIV and cancer with access to therapeutic innovation, including new immunotherapy molecules. Immuno-virological monitoring[6] has been drafted and published, enabling HIV-infected people to be treated with anti-PD1 or anti-PD-L1 while monitoring the effect of these new molecules on HIV reservoir. A national cohort will also be established (ANRS CO24 ONCOVIHAC) which will include people living with HIV treated with an immune check-point inhibitor. Already CancerVIH group has set some data regarding tolerance and efficacy when using immunotherapy that will be presented at the meeting.

	2014 [95% CI]	2015 [95% CI]	2016 [95% CI]	31/07/2017 [95% CI]	Total [95
PATIENTS	41 [39,0-43,0]	85 [80,8-89,3]	144 [136,8-151,2]	99 [94,1-104,0]	369 [350,5
SEX Men	30 [28,5-31,5]	62 [58,9-65,1]	111 [105,5-116,6]	75 [71,3-78,6]	278 [264,1
Women	10 [9,5-10,5]	21 [20,0-22,05]	32 [31,0-33,6]	24 [22,8-25,2]	87 [82,7-
Transgender		1	1		2 [1,9-2
AGE between 21 and 60 years old	32 [30,4-33,6]	61 [58,0-64,1]	104 [98,8-109,2]	71 [67,5-74,6]	268 [254,6
≥ 61 years old	7 [6,7-7,4]	24 [22,8-25,2]	39 [37,1-41,0]	28 [26,6-29,4]	98 [93,1-1
CLASSANT-SIDA CANCERS	8 [7,6-8,4]	43 [40,9-42,2]	64 [60,8-67,2]	40 [38-42]	155 [147,3
Lung	4 [3,8-4,2]	14 [13,3-14,7]	44 [41,8-46,2]	24 [22,8-25,2]	86 [81,7-
Kaposi	4 [3,8-4,2]	26 [24,7-27,3]	20 [19-21]	15 [14,3-15,8]	65 [61,8-
Cervix		3 [2,9-3,2]		1	4 [3,8-4
NO CLASSANT-SIDA CANCERS	33 [31,4-34,7]	42 [39,9-44,1]	80 [76-84]	59 [56,1-62,0]	214 [203,3
NHL	11 [10,5-11,6]	7 [6,7-7,4]	17 [16,2-17,9]	12 [11,4-12,6]	47 [44,7-
Anal canal	6 [5,7-6,3]	5 [4,8-5,3]	11 [10,5-11,6]	4 [3,8-4,2]	26 [24,7-
Head and neck	2 [1,9-2,1]	7 [6,7-7,4]	8 [7,6-8,4]	7 [6,7-7,4]	24 [22,8-
Breast	3 [2,9-3,2]	1	9 [8,6-9,5]	3 [2,9-3,2]	16 [15,2-
Liver	1			6 [5,7-6,3]	7 [6,7-1
Pancreas	2 [1,9-2,1]	1	4 [3,8-4,2]	3 [2,9-3,2]	10 [9,5-1
Hodgkin…		2 [1,9-2,1]	3 [2,9-3,2]	2 [1,9-2,1]	7 [6,7-1
HIV DIAGNOSTIC Conc. cancer diagn.	4 [3,8-4,2]	6 [5,7-6,3]	15 [14,3-15,8]	8 [7,6-8,4]	33 [31,4-
< 5 ans	10 [9,5-10,5]	15 [14,3-15,8]	22 [20,9-23,1]	14 [13,3-14,7]	61 [58,0-
Betw. 6 and 10 years	4 [3,8-4,2]	14 [13,3-14,7]	14 [13,3-14,7]	10 [9,5-10,5]	42 [39,9-
Betw. 11 and 20 years	8 [7,6-8,4]	23 [21,9-24,2]	46 [43,7-48,3]	18 [17,1-18,9]	95 [90,3-
Betw. 21 and 30 years	11 [10,5-11,6]	24 [22,8-25,2]	41 [39,0-43,1]	33 [31,4-34,7]	109 [103,4
> 30 years	1	3 [2,9-3,2]	12 [11,4-12,6]	6 [5,7-6,3]	22 [20,9-
CD4 NADIR MEDIAN (/MM³)	62 [58,9-65,1]	107 [101,7-112,4]	155 [147,3-162,8]	142 [134,9-149,1]	125 [118,8

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77. Training Community Health Workers About Early Detection of Kaposi's Sarcoma: A Comparison of Expert-Led Versus Community Health Worker Supervisor-Led Approaches

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Background: Late diagnosis of KS remains rife in sub-Saharan Africa despite the possibility for remission when antiretroviral therapy for HIV is initiated when KS is still mild/moderate. Although multifactorial in origin, late presentation of KS is largely due to scant knowledge of KS in the community — only 7% of HIV-infected patients in a survey had ever heard of KS. It can be argued that actively promoting community awareness about KS is more important now than ever as KS incidence is, in general, declining and fewer persons (and providers) will encounter and learn about KS passively. In resource-limited settings, community health workers (CHWs) have been trained to promote timely diagnosis of several diseases in the community. Utilizing CHWs to promote early detection of KS should be feasible given the cutaneous presentation of KS. Indeed, in Uganda, we earlier showed that expert-led training of CHWs resulted in increases in their KS-related knowledge. We set out to determine whether training CHWs using their regular supervisors would result in comparable increases in knowledge.

Methods: Between 2012 and 2015, a group of experts (research physicians and KS-experienced research nurses) provided a one-day training, using a standardized manual, to CHWs in western Uganda about early detection of KS. Training emphasized a three-part theme: "Ask", meaning inquire about patients' skin; "Look", referring to examining the skin and mouth for suspicious lesions; and "Test", meaning to refer all suspicious skin lesions to facilities where skin punch biopsy can be done. In 2016, we trained supervisors of CHWs (typically primary care nurses) in the aforementioned region in a two-day session. Day 1 focused on KS epidemiology, presentation, examination, diagnosis, and treatment for higher-level health professionals. Day 2 focused on practical skills for delivering training about KS to CHWs. Within 4 months after the training, each supervisor trained a group of his/her CHWs using the same manual that was used in the earlier expert-led sessions. Baseline KS-related knowledge and change in knowledge amongst the CHWs was assessed using structured questions in a pre-and posttest format respectively.

Results: A total of 228 CHWs received training about KS from a group of 3 experts, and 492 CHWs were trained by their CHW supervisors (30 different supervisors). Pre-training assessment found that only 38% of the CHWs had ever heard about KS, and only 13% were able to recognize KS from photographs (Table). The post-training evaluation showed that the CHWs trained by their supervisors demonstrated change in KS-related knowledge comparable to those trained by expert trainers.

%'s reflect correct responses stated in parentheses.
*All posttest changes are $p < 0.05$ compared to pre-test unless noted

	Expert-led Training (n=228)		CHW Supervisor-led Training (n=492)	
Question (Correct Response)	**Pretest**	**Posttest**	**Pretest**	**Posttes**
Have you ever seen a person with this condition--KS photo? *(Yes)*	75%	-	60%	-
What do you think this condition is? *(Kaposi's sarcoma)*	23%	-	8.3%	-
Have you ever heard about KS? *(Yes)*	17%		48%	-
What is the best way to diagnose it? *(Perform a biopsy)*	43%	91%	57%	92%
How would you treat a patient with it? (*Send to a health facility)*	13%	98%	46%	92%
What would happen if an HIV-infected person with Kaposi's sarcoma is not treated *(He will likely die)*	79%	94%	85%	88%*
HIV gives an opportunity for Kaposi's sarcoma to develop *(Yes)*	-	96%	-	91%

Conclusion: Using a well-developed training manual in a 1-day session, CHW supervisors in Uganda successfully taught their CHWs about early detection of KS. The CHWs trained by their supervisors obtained knowledge about KS to a similar degree as those trained by experts. To promote early detection of KS in the face of its declining incidence, training CHWs in KS identification may be the vital link given their ubiquitous nature in sub-Saharan Africa and their often first-line presence as health workers. Training CHWs using their assigned community-based supervisors should result in more CHWs trained, continuous training, and cost-efficient capacity-building within an already existing structure.

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