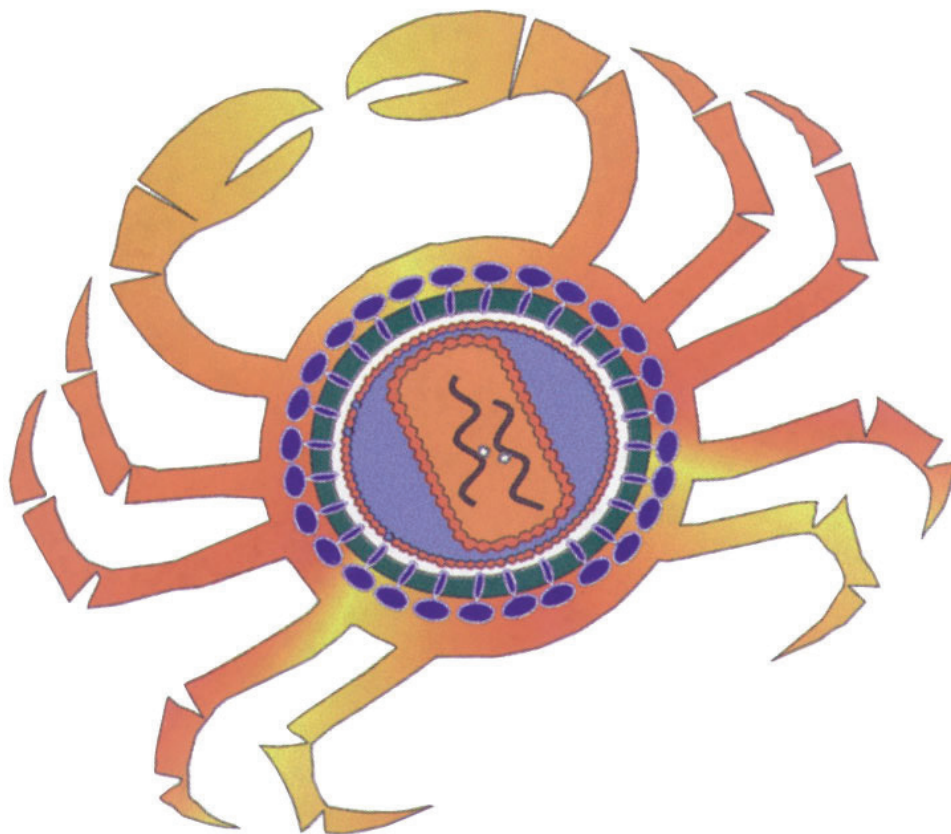# NIH > NATIONAL CANCER INSTITUTE

17th | International Conference on Malignancies in HIV/AIDS

October 21-22, 2019

NIH Campus
Bethesda, Maryland

PROGRAM

Day 1: October 21

8:00 a.m. – 8:15 a.m. **Day 1 Poster Setup**
Highlighted Posters (1-8) will stay up for the entire meeting.

8:15 a.m. – 8:20 a.m. **Welcome and Introduction**
Robert Yarchoan, M.D.
Director
Office of HIV and AIDS Malignancy
National Cancer Institute, NIH

8:20 a.m. – 8:30 a.m. **Opening Remarks**
Douglas R. Lowy, M.D.
Acting Director
National Cancer Institute, NIH

8:30 a.m. – 8:35 a.m. **Presentation of NCI Director's Career Achievement Award to**
Drs. Patrick S. Moore and Yuan Chang

8:35 a.m. – 9:00 a.m. **Plenary 1: 25 Years of KSHV Research**
Patrick S. Moore, M.D., M.P.H.
University of Pittsburgh

9:00 a.m. – 10:00 a.m. **Session 1: Kaposi's Sarcoma-Associated Herpesvirus (KSHV)**
Moderators: Paul M. Lieberman, Ph.D.
The Wistar Institute

Thomas S. Uldrick, M.D., M.S.
National Cancer Institute, NIH

9:00 a.m. – 9:15 a.m. ***O1. Functional Analysis of Human and Viral Circular RNAs During Kaposi's***
Sarcoma Herpesvirus Infection
Takanobu Tagawa, Ph.D.
National Cancer Institute, NIH

9:15 a.m. – 9:30 a.m. ***O2. KSHV Manipulates Host Iron Metabolism and Antioxidant Pathways to Promote***
Tumorigenesis and Resist Ferroptotic Cell Death
Ashlee V. Moses, Ph.D.
Oregon Health & Science University

9:30 a.m. – 9:45 a.m. ***O3. Induction of Kaposi's Sarcoma-Associated Herpesvirus-Encoded Thymidine***
Kinase (ORF21) by X-Box Binding Protein-1
Robert Yarchoan, M.D.
National Cancer Institute, NIH

9:45 a.m. – 10:00 a.m. ***O4. Characterizing Somatic Cellular Mutations in KS Tumors***
Warren Phipps, M.D., M.P.H.
Fred Hutchinson Cancer Research Center

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

10:30 a.m. – 12 noon	**Session 2: Human Papillomavirus and Associated Diseases** Moderators: Joel M. Palefsky, M.D., FRCP(C) University of California, San Francisco Mark H. Einstein, M.D., M.S. Rutgers University
10:30 a.m. – 11:00 a.m.	**P2. Alternative Outcomes of HPV Infection: Immune Control Versus Neoplastic Progression** John Doorbar, M.D. University of Cambridge
11:00 a.m. – 11:30 a.m.	**P3. Molecular Characteristics of Cervical Cancer in HIV+ and HIV- Ugandan Women** Daniela S. Gerhard, Ph.D. National Cancer Institute, NIH
11:30 a.m. – 11:45 a.m.	***O5. HIV Proteins Gp120 and Tat Induce an Epithelial–Mesenchymal Transition in HPV-Immortalized Anal and Cervical Epithelial Cells and Increase Their Migration and Invasion*** Sharof Tugizov, Ph.D., D.Sc., D.V.M. University of California, San Francisco
11:45 a.m. – 12 noon	***O6. Screening Tests for Anal High-Grade Squamous Intraepithelial Lesion Detection in U.S. Women Living With HIV*** Elizabeth Y. Chiao, M.D., M.P.H. Baylor College of Medicine
12 noon – 1:00 p.m.	**Lunch** (on your own)
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: HTLV-1 and Other Pathogens** Moderators: Ashlee V. Moses, Ph.D. Oregon Health & Science University Erle S. Robertson, Ph.D. University of Pennsylvania
2:00 p.m. – 2:30 p.m.	**P4. HTLV-1: New Strain** Genoveffa Franchini, M.D. National Cancer Institute, NIH
2:30 p.m. – 2:45 p.m.	***O7. Virus-like Vesicles as a Vaccine Platform for Kaposi's Sarcoma-Associated Herpesvirus*** Ting-Ting Wu, Ph.D. University of California, Los Angeles
2:45 p.m. – 3:00 p.m.	***O8. A CRISPR Screen Reveals Epigenetic Factors That Restrict B-Cell Epstein-Barr Virus Oncoprotein Expression*** Benjamin E. Gewurz, M.D., Ph.D. Harvard Medical School
3:00 p.m. – 3:30 p.m.	**Break and Poster Viewing**

3:30 p.m. – 5:30 p.m.	**Session 4: Prevention of HPV-Associated Cancers and Pathobiology of Lymphoma** Moderators*:* Elizabeth Y. Chiao, M.D., M.P.H. Baylor College of Medicine Teresa M. Darragh, M.D. University of California, San Francisco
3:30 p.m. – 4:00 p.m.	**P5. ANCHOR Trial Update** Joel M. Palefsky, M.D., FRCP(C) University of California, San Francisco
4:00 p.m. – 4:30 p.m.	**P6. Recent Trends in Anal Cancer Incidence: Implications for Prevention Using Disease Simulation Modeling** Ashish Deshmukh, Ph.D., M.P.H. University of Texas Health Science Center at Houston
4:30 p.m. – 5:00 p.m.	**P7. Evaluation of Cervical Images for Cancer Screening Using Artificial Intelligence Algorithms** Mark Schiffman, M.D., M.P.H. National Cancer Institute, NIH
5:00 p.m. – 5:15 p.m.	***O9. PD-L1+ B-Regulatory Cells Are Induced by Exposure to Factors That Are Elevated in HIV-1+ Subjects Who Develop AIDS-NHL*** Laura E. Martinez, Ph.D. University of California, Los Angeles
5:15 p.m. – 5:30 p.m.	***O10. Potential Alternative Survival Mechanisms in HIV-Associated Diffuse Large B-Cell Lymphoma (DLBCL) of Germinal Center (GCB) Origin*** Alanna Maguire, Ph.D., M.Sc. Mayo Clinic Arizona
5:30 p.m.	**End of Day 1**

Day 2: October 22

8:00 a.m. – 8:30 a.m.	**Poster Day 2 Setup and Viewing** **Highlighted Posters (1-8) will stay up for the entire meeting.**
8:30 a.m. – 8:45 a.m.	**Opening Comments** Robert Yarchoan, M.D. Office of HIV and AIDS Malignancy National Cancer Institute, NIH Geraldina Dominguez, Ph.D Office of HIV and AIDS Malignancy National Cancer Institute, NIH
8:45 a.m. – 9:45 a.m.	**Session 5: Cancer Treatment and Outcomes** Moderators: Richard F. Little, M.D. National Cancer Institute, NIH Richard F. Ambinder, M.D., Ph.D. Johns Hopkins University School of Medicine
8:45 a.m. – 9:15 a.m.	**P8. Cancer Outcomes in Patients With an Underlying HIV Infection:** Anna E. Coghill, Ph.D., M.P.H. Moffitt Cancer Center
9:15 a.m. – 9:45 a.m.	**P9. Cancer in People Living with HIV: Treatment Disparities and Opportunities** Gita Suneja, M.D., M.S.H.P. University of Utah
9:45 a.m. – 10:45 a.m.	**Roundtable: Cancer Treatment in the Era of cART** Moderator: Richard F. Little, National Cancer Institute Discussants: Richard F. Ambinder, Surbhi Grover, Lynda Dee, Thomas S. Uldrick, Elizabeth Y. Chiao, Jeff Taylor, and Eric A. Engels
10:45 a.m. – 11:15 a.m.	**Break and Poster Viewing**
11:15 a.m. – 12:15 p.m.	**Session 6: Epidemiology** Moderators: Eric A. Engels, M.D., M.P.H. National Cancer Institute, NIH Keith M. Sigel, M.D**.** Icahn School of Medicine at Mount Sinai
11:15 a.m. – 11:30 a.m.	*O11. Factors Associated With Treatment Completion and Treatment Response of Chemoradiation in HIV-Infected Patients in Botswana* Surbhi Grover, M.D., M.P.H. University of Pennsylvania
11:30 a.m. – 11:45 a.m.	*O12. Cancer-Attributable Mortality Among People With HIV in the United States During 2001-2015* Marie-Josèphe Horner, Ph.D. National Cancer Institute, NIH

11:45 a.m. – 12 noon	***O13. Kaposi's Sarcoma Incidence, Burden, and Prevalence Among Persons With HIV in the United States, 2000-2015***
	Sally Peprah, Ph.D.
	National Cancer Institute, NIH

12 noon – 12:15 p.m.	***O14. Cancer Immunotherapy Use and Effectiveness in Real-World Patients Living With HIV***
	Blythe J.S. Adamson, Ph.D, M.P.H.
	Flatiron Health

| 12:15 p.m. – 1:15 p.m. | **Lunch** (on your own) |

| 1:15 p.m. – 2:15 p.m. | **Day 2 Poster Viewing** (Presenters stand by their posters.) |

2:15 p.m. – 3:00 p.m.	**Session 7: Primary Effusion Lymphoma (PEL)**
	Moderators: Denise Whitby, Ph.D.
	Frederick National Laboratory for Cancer Research, NIH
	Thomas S. Uldrick, M.D., M.S.
	National Cancer Institute, NIH

2:15 p.m. – 2:45 p.m.	**P10. Primary Effusion Lymphoma: What Have We Learned From a Rare Disease**
	Ethel Cesarman, M.D., Ph.D.
	Weill Cornell Medical College

2:45 p.m. – 3:15 p.m.	**P11. Gene Essentially Landscape and Druggable Genetic Vulnerabilities of Primary Effusion Lymphoma**
	Eva Gottwein, Ph.D.
	Northwestern University

| 3:15 p.m. – 3:45 p.m. | **Break and Poster Viewing** |

3:45 p.m. – 5:30 p.m.	**Session 8: International Studies**
	Moderators: Charles Wood, Ph.D.
	University of Nebraska-Lincoln
	Erle S. Robertson, Ph.D.
	University of Pennsylvania Medical School

3:45 p.m. – 4:15 p.m.	**P12. Discerning Clinical and Biological Heterogeneity in Pediatric Kaposi Sarcoma**
	Nader K. El-Mallawany, M.D.
	Texas Children's Hospital/Baylor College of Medicine

4:15 p.m. – 4:30 p.m.	***O15. Suspected KSHV Inflammatory Cytokine Syndrome (KICS) in Participants With Mild or Moderate AIDS-KS Enrolled in A5264/AMC067 Is Associated With Inferior Survival***
	Scott V. Adams, Ph.D., M.P.H.
	Fred Hutchinson Cancer Research Center

4:30 p.m. – 4:45 p.m.	***O16. Treatment of Advanced AIDS-Associated Kaposi's Sarcoma (AIDS-KS) in Resource-Limited Settings: A Three-Arm, Randomized, Non-Inferiority Trial in Sub-Saharan Africa and Brazil (ACTG A5263/AMC066)***
	Susan E. Krown, M.D.
	AIDS Malignancy Consortium

4:45 p.m. – 5:00 p.m.	***O17. Poor Immune Cell Infiltration in the Endemic and Epidemic Kaposi's Sarcoma Microenvironment*** Salum J. Lidenge, Ph.D. University of Nebraska–Lincoln
5:00 p.m. – 5:15 p.m.	***O18. Rituximab for Diffuse Large B-cell Lymphoma in Malawi*** Mathew Painschab, M.D. The University of North Carolina at Chapel Hill
5:15 p.m. – 5:30 p.m.	***O19. Cervical Cancer Incidence in Women Living With HIV in South Africa, 2004-2014*** Tafadzwa Dhokotera, M.Sc. National Cancer Registry, National Health Laboratory Service, Johannesburg, South Africa
5:30 p.m.	**Meeting Adjourned**

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P1.   25 Years of KSHV: What Do We Do Now?

Patrick Moore and *Yuan Chang*

University of Pittsburgh, Pittsburgh, PA

One-quarter of a century ago, the virus causing Kaposi sarcoma was discovered. By 1994, KS had become synonymous with AIDS and, unlike any other cancer, was clearly capable of occurring as an epidemic. Simultaneously, revolutionary antiviral treatments accomplished something that few at the time thought possible— changing AIDS from being a death sentence to a chronic illness for most patients able to afford treatment. With effective antiretroviral therapy, KS rates in the United States are now at pre-HIV/AIDS levels. The science of KSHV has remained durable and fascinating. KSHV is a principal model for understanding cancer cell proliferation, particularly for its role in uncovering the interconnection between innate immunity and tumor suppression.

But for those without access to effective antiretroviral therapy and those living in hyperendemic portions of the globe, KS and related cancers remain unaddressed scourges. What needs to be done in the next 25 years of KSHV research to address diseases caused by this virus? Are they important enough for us to now be concerned about? Could KSHV come back again in the United States? Can we do something about it now?

P2.   Alternative Outcomes of HPV Infection: Immune Control Versus Neoplastic Progression

John Doorbar

University of Cambridge, Cambridge, UK

The high-risk (HR) papillomaviruses constitute one of the three evolutionary branches of Alpha papillomavirus, with the two remaining branches encompassing the low-risk HPVs that cause common and genital warts. During evolution, the high-risk papillomaviruses have acquired a number of additional molecular characteristics that are not shared by the low-risk types, which contribute to their ability to cause productive subclinical infections at a range of genital sites, and to cause neoplasia and cancer at the cervical transformation zone. High-risk HPV-associated cancer results from the deregulation of viral functions normally involved in the regulation of epithelial homeostasis and HPV genome amplification.

The cervical transformation zone is one of a number of vulnerable epithelial sites where HR HPV types cause cancer. Such sites lack a conventional epithelial organization, which at the cervix, allows the formation of a stratified epithelium from a previously columnar epithelium when a defensive epithelial barrier is required. This process of metaplasia, which involves a specialized cervical cell known as the 'reserve cell', can occur throughout a woman's life, and is thought to underlie the specific susceptibility of the cervix to HPV-associated cancer.

Although cervical cancer affects over half a million women per year, it is in fact a rare outcome of a very prevalent infection. For most women who become infected, disease clearance as a result of a cell-mediated immune response occurs within months or years. It is becoming apparent however, that disease clearance is not equivalent to the clearance of infection. Like many other viruses, papillomaviruses can cause chronic subclinical infections that are controlled by host immune-surveillance, with reactivation occurring following immune suppression. This hypothesis is supported by recent observation showing that the persistence of viral genomes in the epithelial basal layer requires the expression of a very limited subset of viral gene products, and that it is the suppression of the genes that drive disease pathogenesis that leads to disease clearance. These results explain many clinical observations, and have clear implications for the development of diagnostic and therapeutic strategies for disease management and treatment.

P3. Molecular Characteristics of Cervical Cancer in HIV+ and HIV- Ugandan Women

Alessia Gagliardi[1,13], Zusheng Zong[1,13], Vanessa Porter[1,12,13], Reanne Bowlby[1,13], Emma Titmuss[1,13], Constance Namirembe[2], Nicholas Griner[3], Hilary Allen[4], Jay Bowen[4], Simon Chan[1], Teresa M. Darragh[5], Mark H. Stoler, Thomas Wright, Patee Gesuwan[3], Maureen Dyer[6], Yussanne Ma[1], Karen L. Mungall[1], Carol Nakisige[2], Karen Novik[1], Jackson Orem[2], Martin Origa[2], HTMCP Cervical Working Group, Julie Gastier-Foster[4], Robert Yarchoan[7], Corey Casper[8], Gordon B. Mills[9], Janet S. Rader[10,13], Akinyemi Ojesina[11,13], Daniela S.Gerhard[3,13], Andrew J. Mungall[1,13], and Marco A. Marra[1,12,13]

[1]Canada's Michael Smith Genome Sciences Centre, Vancouver, BC, Canada; [2]Uganda Cancer Institute, Kampala, Uganda;[3]Office of Cancer Genomics, National Cancer Institute, NIH, Bethesda, MD; [4]Nationwide Children's Hospital, Columbus, OH; [5]Department of Pathology, University of California, San Francisco, San Francisco, CA; [6]Leidos Biomedical Research, Inc., Frederick, MD; [7]Office of HIV and AIDS Malignancies, National Cancer Institute, National Institutes of Health, Bethesda, MD; [8]Infectious Disease Research Institute, Seattle, WA; [9]Knight Cancer Institute, Oregon Health & Science University, Portland, OR; [10]Department of Obstetrics and Gynecology, Medical College of Wisconsin, Milwaukee, WI; [11]School of Public Health, University of Alabama, Birmingham, AL [12]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada; [13]These authors contributed equally to this work.

Introduction: NCI initiated the HIV+ Tumor Molecular Characterization Project (HTMCP) to gain insight into the genetic events driving HIV-associated cancers and to determine why certain cancers, but not others, have higher incidences in HIV-positive patients. Human papillomavirus (HPV) infection is required but not sufficient for cervical cancer development. According to UNAIDS women infected with HIV are 5 times more likely to develop cervical cancer than women not infected with HIV. Primary cervical cancer prevention strategies include both prevention of primary infection and secondary prevention with ablation of high-grade dysplastic lesions to prevent progression to invasive carcinoma. The use of HPV vaccines to inhibit persistent viral infection has shown to be effective but is not easily obtained in many low- and middle-income countries. Secondary prevention is rare because screening and follow-up ablations are not common.

Methods: HTMCP accrued 213 women with cervical cancer treated at the Uganda Cancer Institute in Kampala and neighboring hospitals. Tumor and blood samples were collected from 213 patients. The diagnosis was confirmed by central pathology review. While the age of onset of the disease was on average almost decade less in the HIV+ women versus HIV-, the difference was not statistically significant. We performed whole genome sequencing of tumor and normal DNA, RNA sequencing of the tumor in 123 cases and found by expression analysis that 5 of the tumors were endometrial. The rest of the study therefore used 118 cases for "discovery". A subset of those cases were also characterized for epigenetic alterations. Eighty-nine additional cases received targeted sequencing of 2735 genes and genomic regions.

Results and Conclusions: In the discovery cohort, we detected on average 311 coding mutations per tumor (range 30-2683). Twelve genes were found to be significantly mutated, of which PIK3CA was the most significantly mutated gene, as was reported in other cohorts. Strikingly, 87% of the cohort (101/118) had at least one mutation in a curated list of epigenetic modifier genes.

The somatic copy number alternations (sCNAs) in HIV+ and HIV- cases were broadly similar, yet there were notable differences. The sCNAs in HIV- cases were largely similar to those found in studies of Caucasian women. With respect to focal genomic alterations, and consistent with what was observed at the chromosome arm level, HIV+ cases exhibited a higher number of unique focal amplifications and deletions compared to the HIV- cases. The composition of this cohort allowed us to identify HPV clade specific molecular characteristics. Unsupervised clustering using DNA methylation data separated cervical cancer cases based on infection by HPV clades A9 and A7. Some of the epigenomic differences reported are also associated with the distinct expression profiles we observed when contrasting the cases separated by clade. Our study investigated the important relationship of HIV and HPV co-infection in the genomic landscapes of cervical cancers. in patients from Uganda. We found some genomic landscape differences between HIV+ and HIV- samples tumors in the genomic landscape and no differences in the epigenomic and transcriptomic landscapes.

P4.   HTLV-1: New Strain

Genoveffa Franchini

Animal Models and Retroviral Vaccines Section, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

While HTLV-1 is the only known retrovirus to directly cause cancer in humans, it has been relatively neglected since its discovery and its true prevalence worldwide remains unknown. HTLV-1A was isolated and characterized at the NIH in 1978 by Robert Gallo's group. In the early 1990s, we identified HTLV-1C, a variant first characterized from a Melanesian patient, but more later found also in indigenous Australian and New Caledonian populations. Both viruses cause T cell leukemia, Tropical Spastic Paraparesis/HTLV-1-associated myelopathy (TSP/HAM), and a wide range of inflammatory diseases. Recently, an extraordinarily high seroprevalence of HTLV-1C (up to 50%) has been recorded in the underserved Aboriginal communities in Australia. Interestingly, while HTLV-1A has been shown to cause subclinical respiratory manifestations, HTLV-1C infection is associated with high mortality at a young age (mid 40s) attributed to lung inflammation, bronchiectasis, and infectious diseases. By the age of 30, Aborigines of both sexes exhibit a 30-40% seroprevalence. The reason for the high seroprevalence of HTLV-1C is unclear but may result from traditional initiation rites involving repeated exposure to the blood of young males. In females, sexual intercourse is likely the predominant form of virus transmission. Although HTLV-1A and HTLV-1C share a high degree of similarity, the highest divergence is found in the pX region at the 3'end of the viral genome, particularly in the orf-1 gene. The development of clinical disease in individuals infected with HTLV-1A and HTLV-1C has been shown to be related to viral load. Therefore, understanding the complex kinetics, expression level, and function of the genes encoded in the 3'end of the HTLV-1 sub types will provide important insights into the virus host interaction, the host immune response and disease pathogenesis. This information can then be used to develop novel therapeutic approaches for the treatment of HTLV-1 infection.

P5.   ANCHOR Trial Update

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The incidence of anal cancer is increased among HIV-positive women and men who have sex with men (MSM), with an incidence of approximately 100/100,000 among the latter. The incidence of anal cancer has increased since the introduction of antiretroviral therapy, and it is now one of the most common cancers diagnosed in HIV-positive men and women. Anal and cervical cancer are very similar diseases, and each is preceded by a precursor, high-grade squamous intraepithelial lesions (HSIL). Despite the similarity to cervical cancer, where routine screening and treatment of the cervical HSIL has proven to be an effective secondary prevention approach, there is no routine screening for and treatment of anal HSIL. There are several barriers to implementation of an anal screening program, but one of the most important is the absence of high-quality clinical trial evidence that treating anal HSIL is effective in reducing the incidence of anal cancer. Consequently, there are no accepted standard of care guidelines for secondary prevention of anal cancer in high-risk populations, including those with HIV.

The main objective of the ANal Cancer/HSIL Outcomes Research (ANCHOR) study is therefore to determine the effectiveness of treating anal HSIL to reduce the incidence of anal cancer in HIV-positive men and women. Additional objectives include assessment of the safety of different treatments used in the HSIL treatment arm; to measure the impact of participation in ANCHOR on quality of life; and to collect clinical specimens and data to create a bank of well-annotated specimens that will enable correlative science focused on identification of host and viral factors important in pathogenesis of anal cancer and identification of novel biomarkers of progression from HSIL to cancer. We expect that biomarkers identified in this study will also be applicable to understanding pathogenesis and prognostication for HPV-related disease at other sites, such as the cervix and oral cavity. Thus the findings of this study will likely extend beyond anal cancer.

We will screen up to 17,385 HIV-positive men and women over the age of 35 years and enroll 5,058 with biopsy-proven anal HSIL at 17 sites around the United States. Participants are randomized to a treatment arm in which their HSIL will be removed to the greatest extent possible, or an active monitoring arm, in which they will be followed closely without intervention. Participants in both arms are followed every 6 months, or more often at the clinician's discretion, for up to 5 years after the last participant is recruited, and the incidence of cancer will be determined in both arms.

As of September 25, 8,500 men and women were screened and 3,420 were enrolled. 44% of ANCHOR participants are African-American and 23% identify as Latina or Latino. 17% of our participants are women. To date the study has had excellent retention with low drop-in and drop-out rates, and an excellent safety record. Development of the ANCHOR Health-Related Symptom Index (A-HRSI) is nearly complete and will soon be implemented in the study. The ANCHOR Specimen Bank continues to collect specimens and will be an excellent resource to address ANCHOR correlative science objectives and many other meritorious scientific questions. It is expected that the results of the ANCHOR Study will determine the standard of care for detection and treatment of anal HSIL in HIV-positive men and women in the U.S., and world-wide, as well and in HIV-negative men and women.

P6.   Recent Trends in Anal Cancer Incidence: Implications for Prevention Using Disease Simulation Modeling

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Squamous cell carcinoma of the anus (SCCA) incidence is increasing rapidly in the United States (US). Over the past 15 years, incidence rates have nearly doubled among individuals aged ≥50 years with notable increases in regional (200% rise) and distant (300% rise) stage SCCA. Unfortunately, an increasing number of (nearly 30% in 2001 to 45% in 2016) onset cases are diagnosed at regional/distant stages, increasing the importance of prevention in the form of HPV vaccination and screening. Majority of persons at risk for SCCA are not age-eligible for HPV vaccination or have already been exposed to oncogenic HPV infection. Furthermore, limited resource availability, low prevalence of SCCA among the general population, and current uncertainties in harms vs benefits of screening may not justify the implementation of population-wide screening.

SCCA risk is markedly elevated among persons living with HIV (PLWH), especially among men who have sex with men (MSM), older individuals, and people with AIDS. SCCA shares biologic similarities with cervical cancer including an etiologic association with HPV infection and is preceded by high-grade squamous intraepithelial lesions (HSIL). Because HSIL detection through anal cytology has acceptable accuracy and persons with HSIL are at risk of progressing to SCCA, expert-opinion-based guidelines inferred from the cervical cancer screening literature recommend screening PLWH for SCCA. Yet, there is reluctance in its adoption because the optimal use and mortality benefits of screening are unclear.

This talk will review data necessary to inform a proposed disease simulation model (Simulation Model of Anal Cancer [SMAC]) that will determine age- and risk-based optimal SCCA screening algorithms (i.e., age to initiate/terminate screening in optimal frequency) in order to maximize screening benefits. Emphasis will be given towards recent trends in SCCA incidence, mortality, and survival (key long-term consequences of screening) among the general population and PLWH. An application of a disease simulation model will be covered demonstrating how age-based approach could optimize SCCA prevention as well as improve survival and quality of life in a cost-effective manner. Finally, future work will be outlined, including identification of risk-based approaches, consideration towards current uncertainties (e.g., HSIL to SCCA progression, HSIL treatment efficacy), and approaches to enhances the value of screening.

P7. **Evaluation of Cervical Images for Cancer Screening Using Artificial Intelligence Algorithms**

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Cervical cancer arises via a few well-defined steps: high-risk (HR) HPV infection, persistence (rather than usual immune control) strongly linked to precancer development, and invasion. HR HPV infection can be detected quickly and inexpensively now using increasingly useful HPV screening tests. HPV-negative women can be reassured of long-term low cervical cancer risk. But management of the many women testing HPV-positive is difficult. The target of cervical screening is to find and treat precancer, while avoiding overtreatment of HPV infections mainly due to clear. Visual inspection with acetic acid (VIA) is being used for both triage of HPV-positive women and primary screening, but it is highly inaccurate. Recently, we developed and validated a deep-learning based algorithm that is much more accurate than VIA in diagnosing precancer, and named it automated visual evaluation (AVE). This presentation will describe the excellent performance of AVE, and the promise of an inexpensive but accurate cervical screening strategy for low-resource settings that combines same-day HPV testing and AVE with novel treatments. A possible caution regarding reliance on this strategy in HIV-infected women will also be presented.

P8.   Cancer Outcomes in Patients With an Underlying HIV Infection

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Widespread administration of antiretroviral therapy has improved overall survival in people living with HIV (PLWH). An unintended correlate of this increased longevity is that a growing number of PLWH are developing solid-organ tumors that occur commonly in older age groups (e.g., breast cancer, prostate cancer). Cancer is now the leading cause of non-AIDS death, and the second leading cause of death overall, in the HIV population. This increasing cancer burden in PLWH includes malignancies not traditionally associated with HIV and has prompted research into the potential impact of HIV on cancer patient outcomes. Evidence from observational studies consistently suggests that PLWH experience poor overall and cancer-specific survival compared to HIV-uninfected individuals diagnosed with the same type and stage of cancer. The HIV-associated cancer survival deficit has been reported in elderly patients (Medicare), nationally-representative samples drawn from population- (HIV/AIDS Cancer Match) and hospital-based (National Cancer Database) US registries, as well as clinic populations in low and middle-income settings (Uganda, Botswana, and Brazil). Notably, cancer outcome disparities in PLWH persist after controlling for demographic (age, race) and clinical (cancer stage) risk factors. Results generated from the National Cancer Database, which included information on more than 14,000 PLWH and cancer, demonstrated elevated mortality for 13 different cancer types in patients with an underlying HIV infection, even after adjustment for receipt of health insurance and the type of health facility at which cancer treatment was administered. This argues against healthcare access as the sole driver of poor cancer patient outcomes in the setting of HIV. Most recently, Dr. Coghill and colleagues reported that poor disease-specific outcomes for prostate and breast cancer in elderly PLWH were not explained by differential cancer treatment patterns, including treatment delays and/or receipt of adjuvant therapy (Coghill, et. al., *JAMA Oncology* 2019). After adjustment for demographics, cancer stage, and detailed treatment annotation using the SEER-Medicare linked database, cancer-specific mortality was elevated in PLWH for prostate (HR=1.65; 95%CI 0.98-2.79; P=0.06) and breast cancer (HR=1.85; 95%CI 0.96-3.55; P=0.07). HIV-infected men with prostate cancer also experienced significantly higher rates of relapse/death after initial cancer therapy (HR=1.32; 95%CI 1.03-1.71; P=0.03), as did HIV-infected women with breast cancer (HR=1.63; 95%CI 1.09-2.43; P=0.02). Identifying factors that contribute to these poor cancer outcomes in PLWH, such as variation in the degree of immunosuppression or lack of access to newer cancer therapies, is increasingly important as the number of individuals diagnosed with both HIV and cancer continues to grow.

P9.   Cancer in People Living With HIV: Treatment Disparities and Opportunities

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Cancer is now the leading cause of non-AIDS death in the U.S. HIV population. People living with HIV (PLWHIV) are more likely to be diagnosed with certain cancers than the general population, and cancer survival is significantly worse in PLWHIV compared with uninfected people for several cancer types. PLWHIV are significantly less likely to receive cancer treatment compared with uninfected patients. Several large population-based studies initially documented this major treatment disparity, including data from the HIV/AIDS Cancer Match (HACM) Study and the National Cancer Database. These studies demonstrated that even after controlling for sociodemographic factors disproportionately affecting PLWHIV - like uninsurance/underinsurance and medical comorbidities - PLWHIV were still less likely to receive cancer treatment.

The currently available evidence suggests that PLWHIV and cancer should receive similar cancer treatment compared with uninfected patients. For non-Hodgkin lymphoma and anal cancer, there are high-quality studies with specific guidance on management of HIV-infected patients. For most other cancer types - especially non-AIDS-defining malignancies - there is a lack of high-quality data. The growing body of literature suggests that cancer treatment is generally safe and effective, particularly in patients with well-controlled HIV. Recently published management guidelines suggest that while adjustments in antiretroviral therapy may be needed to minimize drug-drug interactions and overlapping toxicities, cancer treatment should not be withheld due to HIV status alone.

Further studies in the field of cancer treatment disparities should aim to disentangle barriers to receipt of appropriate cancer care for PLWHIV. Ongoing studies in our observational research lab aim to understand the impact of HIV on cancer treatment decision-making for both clinicians and patients. Issues unique to HIV-infected cancer patients, such as multiple comorbidities and polypharmacy, can complicate cancer treatment decision-making. Knowledge gaps about cancer prognosis and toxicity of cancer treatment in HIV-infected patients further compounds the complexity.

The disparity in cancer treatment and survival is especially concerning given the near normal life expectancy of people living with HIV in the modern era of antiretroviral therapy. Evidence-based interventions are urgently needed to improve cancer treatment rates in this population.

P10. Primary Effusion Lymphoma: What Have We Learned From A Rare Disease

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It has been 25 years since the discovery of the Kaposi sarcoma herpesvirus (KSHV/HHV-8), in an AIDS related Kaposi sarcoma (KS) lesion. Evidence rapidly accumulated documenting that this virus is the causal agent of KS, being necessary, albeit not sufficient for this disease to develop. Soon after this discovery, viral sequences were also identified in a unique type of lymphoma, referred originally as body cavity based lymphoma (BCBL), which led to the designation of the first cell lines as BC or BCBL. Subsequently the term primary effusion lymphoma (PEL) was used, to differentiate from solid lymphomas in body cavities, such as EBV+ lymphomas that occur in association with pyothorax.

Interestingly, PEL had actually been described six years prior to the discovery of KSHV (Knowles, et al, Blood 1989). This report described three EBV+ cases with an indeterminate immunophenotype, two of which were lymphomatous effusions. While a B-cell lineage was demonstrated by immunoglobulin (Ig) gene rearrangement analysis, these lymphomas did not express B cell antigens. Subsequent studies recognized that these lymphomatous effusions occurred relatively frequently in HIV-infected individuals. However, they were thought of as unusual AIDS-related lymphomas, and it only became clear that they represent a quite distinct clinicopathologic entity with the recognition of the presence of KSHV within them.

While PEL is a rare tumor type, it has been critical to understanding many virological and pathogenic aspects of KSHV and its pathogenesis. While KS is a much more common malignancy than PEL, KS cell lines do not exist: cell lines previously thought to be KS lines lack KSHV. Therefore, PEL lines derived from patient specimens have been extensively used for in vitro and in vivo studies. These PEL cell lines allowed the first and prompt sequencing of KSHV genomes after the discovery of this virus, and served as a a tool for serological assays that provided evidence of causality of this virus and KS. These and other studies that have relied on PEL will be discussed.

P11. Gene Essentiality Landscape and Druggable Genetic Vulnerabilities of Primary Effusion Lymphoma

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Background: Primary effusion lymphoma (PEL) is a highly aggressive B cell cancer caused by Kaposi's sarcoma-associated herpesvirus. Our understanding of PEL is poor and therefore treatment strategies are lacking. We identified novel essential genes in PEL and performed experiments to establish their mechanisms of action and suitability as drug targets.

Methods: We conducted genome-wide CRISPR/Cas9 knock-out screens in a panel of eight PEL cell lines. Integration with data from unrelated cancers identified 210 genes as PEL-specific oncogenic dependencies. We also conducted validation and mechanistic experiments.

Results: Our data demonstrate requirements of PEL cell lines for MDM2, cyclin D2, cellular FLIP, MCL1, and the lymphoid transcription factor IRF4. Dependencies on cyclin D2, MCL1, and IRF4 render PEL cell lines highly sensitive to CDK4/6 or MCL1 inhibition and immunomodulatory drugs. Our functional investigation of IRF4 dependency in PEL places PEL into a group of hematologic malignancies where IRF4 serves as an oncogenic transcriptional master regulator that promotes cellular survival and proliferation. We show that IRF4 and its cellular and viral co-transcription factors function on PEL super-enhancers to drive expression of many essential survival genes, including IRF4 itself and MYC. We finally show that KSHV infection of PEL cell lines stimulates the high expression of IRF4 by autoregulatory positive feedback regulation.

Conclusions: In sum, our work identifies druggable oncogenic dependencies in PEL and shows that IRF4 functions as an oncogenic master transcription factor in PEL.

P12.   Discerning Clinical and Biological Heterogeneity in Pediatric Kaposi's Sarcoma

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Kaposi's sarcoma (KS) of childhood has been described in human herpesvirus-8/KS-associated herpesvirus (KSHV)-endemic regions of sub-Saharan Africa for over fifty years. More recently, as widespread HIV-infection has devastated the region, HIV-related pediatric KS has superimposed itself on endemic disease across the continent. KS is currently among the top three most common overall childhood malignancies in eastern and central Africa and is by far the most common HIV-related malignancy in children and adults alike. Childhood KS is clinically distinct from disease in adults, with unique characteristic features including frequent presentation with bulky lymphadenopathy, the absence of prototypical hyperpigmented cutaneous lesions, presence of severe cytopenias, and a fulminant disease course if untreated (with chemotherapy)—particularly in patients with lymphadenopathic KS. Distinct clinical phenotypes have surfaced among children with KS, each categorized by a unique profile of characteristic features and associated survival outcomes. On one hand, lymphadenopathic KS typically presents in younger children, is associated with a fulminant disease course and severe cytopenias on presentation, however responds favorably to mild/moderate chemotherapy plus antiretroviral therapy (ART) with excellent rates of long-term complete remission. On the other, woody edema KS exhibits an indolent disease course, typically occurs in teenagers, and although survival with partial remission and stable disease can be achieved with chemotherapy and ART, patients usually live with chronic disease. In stark contrast to both groups, children with visceral KS and/or disseminated skin/oral disease represent a sub-group with aggressive disease and high mortality risk, often experiencing disease relapse and progression. Ultimately, these divergent clinical phenotypes represent sub-categories of disease that likely have distinct biological phenomena driving them. One such biological distinction is the association of lytic-activation of KSHV and lymphadenopathic pediatric KS, a group of patients with a higher likelihood to present with KSHV viremia and consistently elevated interleukin-6 levels. Future studies may uncover other important biological associations, whether they are attributed to virologic mechanisms of oncogenesis driven by KSHV, underlying immunologic phenomena, genetic predisposition, or aberrant molecular pathways of the underlying malignant cells.

O1.   Functional Analysis of Human and Viral Circular RNAs During Kaposi's Sarcoma Herpesvirus Infection

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Background: Circular RNAs are formed by back-splicing events, lack poly-A tails, and are more stable than mRNAs. We previously reported that upon Kaposi's sarcoma herpesvirus (KSHV) infection, the expression of hundreds of human circular RNAs are altered. A human circular RNA, hsa_circ_0001400, is upregulated upon KSHV infection and inhibits KSHV gene expression at a post-entry step. We and others also reported that KSHV expresses viral circular RNAs. Most of these viral circular RNAs are highly expressed during the lytic cycle. We found that some viral circular RNAs can alter cell growth kinetics. Functions and regulation of these human and viral circular RNAs are largely unknown in the context of KSHV infection.

Methods: We used gain- and loss-of-function experiments followed by RNA-sequencing to determine changes in gene expression caused by hsa_circ_0001400 upon de novo KSHV infection. Back-splicing is known to be regulated by certain RNA-binding proteins. To approach the mechanism by which KSHV induces circular RNA expressions, we inhibited specific RNA-binding proteins and determined the consequences on specific circular RNA expression that are induced by KSHV.

Previously, we screened for circular RNAs in infected cells *in vitro* and in lymph nodes from patients with KSHV infections. To investigate clinically relevant viral circular RNAs, we performed deep sequencing of exonuclease-treated, circular RNA-enriched RNAs from a lymph node of a patient with high expression of KSHV genes. Fractionation of cells was used to determine the subcellular localization of human and viral circular RNAs of interest.

Results: The human hsa_circ_0001400 broadly repressed KSHV gene expression. Surprisingly, hsa_circ_0001400 also repressed expression of dozens of interferon-stimulated genes, in addition to some genes that suggest the mechanism of how hsa_circ_0001400 inhibits KSHV infection. We found expression of different human circular RNAs that are induced by KSHV infection, are influenced by different RNA-binding proteins. Transcript levels of those circular RNAs and their linear counterparts, mRNAs, are counter-regulated by an RNA-binding protein indicating competitions between forward- and back-splicing.

Deep sequencing of patient samples identified new viral circular RNAs. Though human circular RNAs including hsa_circ_0001400 are often localized in cytoplasm, the localization of viral circular RNAs varied between areas, suggesting different localization mechanisms and functions among viral circular RNAs.

Conclusions: Specific cellular circular RNAs can regulate virus infection. Expression of human and viral circular RNAs vary between different cell types, infection status, and loci within cells. Understanding functions and mechanism of cellular and viral circular RNAs could lead to new strategies for inhibiting infection and cancerous cell growth.

O2. KSHV Manipulates Host Iron Metabolism and Antioxidant Pathways to Promote Tumorigenesis and Resist Ferroptotic Cell Death

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Background: Iron is an essential element for the growth and metabolism of normal cells. To support abnormal growth, tumor cells typically have a higher iron requirement that is satisfied through altered expression of proteins that regulate iron metabolism, including iron uptake, utilization, storage and export. While metabolically-active iron fuels cell growth, it also represents a hazard due to its detrimental redox activity and ability to activate ferroptosis, a ROS-reliant, iron-dependent form of regulated cell death. Ferroptosis is driven by an iron-catalyzed lethal lipid peroxidation that represents a failure of the cellular antioxidant system to detoxify lipid peroxides and restore redox homeostasis. Many tumor types resist the ferroptotic cascade via increased expression/activity of antioxidant pathways, most notably the system x_c^- /glutathione/GPX4 axis. The rationale for our study was to determine how KSHV manipulates cellular iron metabolism and antioxidant pathways to maintain high levels of tumor-promoting ROS while resisting ferroptosis.

Methods: Lymphatic endothelial cells (LEC) and LEC latently-infected with KSHV-BAC16 were used for the study. Expression of host genes implicated in iron metabolism, anti-peroxidant activity and regulation of ferroptosis was evaluated using RNA-seq, qPCR, immunoblotting, FACS and IFA. Cellular iron content was measured by ICP-MS. Markers of pro/antioxidant status (e.g., ROS, GSH) were measured via quantitative colorimetric assay. Susceptibility to ferroptosis was evaluated using selective inducers and inhibitors and measured via cell viability and lipid peroxidation assays.

Results: Our studies indicate that KSHV infection of LEC results in deregulation of host iron metabolism in order to promote iron acquisition and an iron-responsive growth phenotype. Exposure of LEC to exogenous iron also enhanced their susceptibility to *de novo* KSHV infection and increased the degree of lytic virus replication, likely as a result of increased expression of KSHV receptors and ROS levels respectively. However, while infected cells contain high levels of both iron and ROS, they do not succumb to ferroptosis. Our data indicate that KSHV-upregulation of system x_c^- (xCT) is central to the ability of infected LEC to escape ferroptosis, and that chemical inhibition of xCT with erastin leads to selective activation of lethal ferroptosis in infected, but not uninfected, LEC. Recent extension of this study to B cell systems suggests that KSHV manipulates iron metabolism genes and regulators of ferroptosis in both KSHV-permissive cell types.

Conclusions: We have identified a unique vulnerability in KSHV-infected cells that is brought about by the necessity to maintain a delicate pro/antioxidant balance in order to facilitate growth and survival. Our work suggests that selective induction of ferroptosis in KSHV-infected cells represents a promising anti-tumor strategy for KSHV-associated malignancies.

O3. Induction of Kaposi's Sarcoma-Associated Herpesvirus-Encoded Thymidine Kinase (ORF21) by X-Box Binding Protein-1

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Background: Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative agent of several diseases, including Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD). Like other herpesviruses, KSHV has latent and lytic gene expression programs. The lytic program is initiated by replication and transcription activator (RTA), but there is evidence that the thymidine kinase (TK) protein derived by ORF21 is also essential. Previously, we demonstrated that the viral protein derived from ORF21 could phosphorylate azidothymidine (AZT) and ganciclovir (GCV) and that ORF36 could phosphorylate GCV, leading to cell toxicity. We subsequently showed that AZT plus valganciclovir (a GCV prodrug) was effective in treating MCD; in retrospect, this was somewhat surprising since we showed that most MCD plasmablasts do not express the full lytic repertoire. For this reason, we explored the possibility that viral ORF21 and/or ORF36, which are both lytic proteins, may be upregulated in plasmablasts independent of full lytic replication. Our group and others have recently shown that some lytic genes of KSHV are directly activated by cellular proteins including hypoxia inducible factor 1 (HIF1) and X-box binding protein-1 spliced form (XBP-1s), which is highly expressed in maturing B cells in germinal centers. We showed that vIL-6 is upregulated by XBP-1s independent of full lytic replication and this may contribute to the pathogenesis of KSHV-MCD. Here, we hypothesized that XBP-1s may also directly activate ORF21 and/or ORF36 and if so, help explain the effectiveness of GCV/AZT in MCD.

Methods: Luciferase reporter constructs for KSHV ORF21 and ORF36 were developed to study the regulation of these promoters. Consensus XBP-1 response elements (XRE) identified in the promoters by sequence analysis were mutated by site-directed mutagenesis and utilized to study the effects of unspliced and spliced XBP-1 and other factors on the promoters. Binding of XBP-1s was done using chromatin immunoprecipitation assays and expression of relevant proteins studied by immunoblotting. Cytotoxicity assays were used to examine the ability of an XBP-1s inducer to enhance toxicity of PEL cells to AZT and GCV. RNAscope was used to study expression of XBP-1 and ORF21 in lymph nodes from patients with KSHV-MCD.

Results: XBP-1s activated the ORF21 promoter but not the ORF36 promoter. Activation of ORF21 was mediated primarily through two XBP-response elements (XRE) in the ORF21 promoter region. Mutation of these elements eliminated XBP-1s-induced up-regulation of the promoter, and chromatin immunoprecipitation studies provided evidence that XBP-1s can bind to both XREs. XBP-1s also substantially enhanced activation of ORF21 by RTA. Exposure of PEL cells to tunicamycin, a chemical inducer of XBP-1s, induced ORF21 within 4 hours, indicating that upregulation can occur independently of RTA. Tunicamycin-exposed PEL cells were also more susceptible to killing by zidovudine and ganciclovir. Finally, ORF21 expression in the lymph nodes of patients with KSHV-MCD was predominantly found in cells expressing XBP-1.

Conclusion: XBP-1s can directly upregulate KSHV ORF21 by binding to XRE on the promoter region and resulting enhanced phosphorylation of AZT and GCV may contribute to the utility of these drugs in treating KSHV-MCD and may, by enhancing lytic activation, also contribute to KSHV-MCD pathogenesis.

O4. Characterizing Somatic Cellular Mutations in KS Tumors

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Background: Kaposi sarcoma (KS) is considered an AIDS-defining malignancy; however, there is still debate about whether KS is a reactive process or a true clonal cancer. Several features of KS suggest that it may not develop from a transformation event that results in autonomously growing tumor cells, but instead represents a reactive process due to the combined effects of Kaposi sarcoma-associated herpesvirus (KSHV) and local or systemic inflammation. KS is a heterogeneous disease in terms of its histological, epidemiological and clinical features, and mounting evidence suggests that there may be different subtypes contributing to these various disease manifestations. Despite the large number of studies that have focused on understanding KSHV and the viral mechanisms of pathogenesis, the cellular genome of KS has not been systematically studied and remains largely unexplored. We hypothesize that previously unrecognized genetic alterations in some KS tumors may explain observed variation in KS presentation and response to therapy. To test this hypothesis, we assessed KS tumors for the presence of cellular mutations.

Methods: We performed whole exome sequencing on KS tumors and matched normal control skin from adults with HIV-associated KS receiving treatment at the Uganda Cancer Institute in Kampala, Uganda. Samples were mapped and analyzed using computational pipelines for DNA alterations. Consensus calls from five mutation callers (VarScan, SomaticSniper, Strelka, RADIA, and Muse) were used to identify single nucleotide variants (SNVs) and three mutation callers (VarScan, Strelka, Pindel) to identify insertion/deletions (InDels) in matched tumor-normal pairs. Technical artifacts and mutations outside the kit's coverage regions were removed. The variants were annotated using Oncotator. Genetic alterations were defined based on mutational burden, recurrent mutations with known or plausible biologic relevance, and clonality based on variant allele frequency (VAF).

Results: 31 KS tumors and matched normal skin samples have been sequenced and analyzed to date. Somatic cellular genetic alterations were present in all tumors, although the mutational burden was relatively low in most tumors, ranging from 1 to 103 mutations. However, 8 tumors appeared hypermutated compared to the other tumors, with over 200 independent mutations per sample. Recurrent mutations were observed in 2 or more samples, including mutations in potentially functionally relevant genes. Based on VAF, all tumors appeared to contain multiple independent clones with different alterations, but approximately one-third of the cases contained VAF clusters that indicate expansion of specific clonal populations. The majority (97%) of the mutations had a variant allele frequency of under 20%, suggesting that the potential tumor cell population represent a small fraction of cells in the lesions. Analysis of the relationship between tumor genomic alterations and KS clinical presentation and outcomes is ongoing.

Conclusions: These preliminary findings indicate that KS tumors carry a range of somatic cellular mutations, which may help explain the histologic and clinical heterogeneity of KS. The low mutational burden observed in a majority of samples suggests KSHV and other mechanisms are likely more important than clonal transformation in driving tumorigenesis. However, clonal populations are evident in some tumors, indicating that KS may exist as a range of polyclonal to monoclonal tumors. Mutations observed in functionally relevant genes may also alter cellular pathways and contribute to tumor development. These genomic alterations contribute to our understanding of the molecular mechanisms of KS pathogenesis and may ultimately serve as a basis for classifying specific KS subtypes and guide new therapeutic strategies.

O5. **HIV Proteins Gp120 and Tat Induce an Epithelial–Mesenchymal Transition in HPV-Immortalized Anal and Cervical Epithelial Cells and Increase Their Migration and Invasion**

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Background: The incidence of human papillomavirus (HPV)-associated anogenital epithelial neoplasia in human immunodeficiency virus (HIV)-infected individuals is substantially higher than that in HIV-negative individuals. HIV may increase the risk of HPV malignancy in epithelia by induction of an epithelial–mesenchymal transition (EMT) that leads to invasion of neoplastic cells.

Methods: HPV-16-immortalized anal AKC-2 and cervical CaSki cells were treated with HIV-1 envelope gp120 and transactivator tat proteins and their inactive forms. EMT induction was detected by mesenchymal morphology after Giemsa staining of cells. Expression of EMT markers was examined by Western blotting. The invasion activity of EMT cells was examined using collagen-coated Transwell inserts.

Results: HPV-16-immortalized anal AKC-2 and cervical CaSki cells were treated with HIV tat or gp120 proteins for 5-12 days. A spindle-like shape was acquired in 30-70% of cells. In these spindle-like cells, E-cadherin was downregulated, and vimentin was upregulated, indicating induction of the EMT phenotype. In contrast, nonactive gp120 and tat proteins did not alter cell morphology or expression of EMT markers. Transmigration of cells via collagen-coated membranes showed that tat and gp120-treated cells were 2-3 -fold more invasive than cells treated with inactive proteins.

Conclusions: HIV-1 gp120 and tat proteins in HPV-immortalized anal and cervical epithelial cells induced the EMT phenotype, which led to increased invasion of cells via collagen membranes. Thus, HIV proteins gp120 and that may accelerate the HPV neoplastic process in HIV- and HPV-coinfected individuals.

O6. Screening Tests for Anal High-Grade Squamous Intraepithelial Lesion Detection in U.S. Women Living With HIV

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Background: Compared to HIV-negative women, women living with HIV (WLHIV) have >10-fold higher risk for anal squamous cell carcinoma (a-SCCA). Experts suggest strategies developed for cervical cancer screening may prevent cancer by detecting anal histological High-Grade Squamous Intraepithelial Lesion (hHSIL) for treatment. Currently, there is no consensus on anal hHSIL screening strategies.

Methods: Between 2014 and 2016, 276 HIV-infected adult females were recruited at 12 U.S. AIDS Malignancy Consortium (AMC) clinical-trials sites to evaluate hHSIL prevalence and test screening strategies. Participants completed a detailed questionnaire, underwent anal assessments including high-risk human papillomavirus (hrHPV) testing, using hrHPV-HC2™ and hrHPV-APTIMA™, anal cytology (anal-cyt) and concurrent high-resolution anoscopy, where >2 biopsies were obtained. Screening test characteristics for predicting hHSIL, validated by central pathology, were estimated: sensitivity (SN), specificity (SP), positive predictive value (PPV) and false-omission rate. Paired analyses compared SN and SP for hrHPV single tests to anal-cyt, alone.

Results: 83% (229/276) of women showed complete sociodemographic, test and biopsy data (analysis sample). SN for ASC-H/HSIL cytology was 27% for hHSIL was significantly (SS) lower than other screening strategies (all p<0.001), but SP of 97% (all p<0.001) and PPV of 76% (all p<0.001) were highest. Anal-cyt, >ASC-US, hrHPV-HC2, and -APTIMA SN estimates were high, individually, but differed little from one another (83%, 77%, and 75%, respectively, p-values>0.2). SP was higher for hrHPV-APTIMA than anal-cyt (67% vs. 50%, p<0.001), however, HC2 was not (67% vs. 61%, p=0.064). Anal-cyt (>ASC-US), hrHPV-APTIMA, and –HC2, PPV and false-omission rates were low, respectively (Table).

Conclusions: Anal hrHPV testing demonstrated similar SN for anal-cyt, >ASC-US, to predict anal hHSIL. Although SN was similar between cytology and hr HPV tests, the SP was significantly higher for hrHPV-APTIMA compared to cytology. Thus, anal hrHPV testing may be an important alternative or adjunctive strategy to anal cytology for anal hHSIL screening among WLHIV.

Table: Comparison of Test Characteristics for Performance of Individual Anal Cancer Screening Test Strategies for Predicting Anal Histological HSIL (hHSIL) in 229 HIV-infected Women

Test Strategy	hHSIL+ N (%)	SN (95% CI)		SP (95% CI)		PPV (95% CI)		False Omission Rate (95% CI)	
anal-cyt									
>ASC-US**	135 (59%)	83%	(71%, 92%)	50%	(42%, 57%)	37%	(29%, 46%)	11%	(5%, 19%)
ASC-H/HSIL***	21 (9%)	27%	(16%, 40%)	97%	(93%, 99%)	76%	(53%, 92%)	21%	(16%, 27%)
APTIMA	102 (45%)	77%	(64%, 87%)	67%	(59%, 74%)	45%	(35%, 55%)	11%	(6%, 18%)
HC2	118 (52%)	75%	(62%, 85%)	61%	(53%, 68%)	41%	(31%, 50%)	13%	(7%, 20%)

* Based on observed prevalence of 26% anal hHSIL, *Atypical squamous cells- Undetermined Significance (ASCUS), ***Atypical squamous cells-high grade features (ASC-H)/High grade squamous intraepithelial lesions (HSIL)

O7. Virus-like Vesicles as a Vaccine Platform for Kaposi's Sarcoma-Associated Herpesvirus

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Background: Kaposi Sarcoma-associated Herpesvirus (KSHV) is linked to several devastating diseases such as Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. Both prophylactic and therapeutic KSHV vaccines would be beneficial for those at high risks of being immunocompromised and those living in endemic HIV areas, especially in Africa where resources are limited.

Methods: Infected cells produce and release membrane vesicles that resemble virions but do not contain a complete set of viral components required for infectivity. KSHV-infected cells produce a large amount of such non-infectious virus like vesicles (VLVs). We hypothesize that these KSHV-envelope encompassing particles (KEEPs) will constitute ideal antigens for a vaccine without the safety risk of a live virus. To test this hypothesis, it is critical to separate KEEPs from infectious virions. Our laboratory generated a viral mutant that only produces KEEPs that lack capsids and viral genomes. This strategy exploits a mutation that blocks capsid maturation to prevent the production of infectious virions but not KEEPs. We aimed to assess the immunogenicity of KEEPs.

Results: In a preliminary immunization study, injections of KEEP without adjuvants elicited KSHV-specific humoral immunity. The KEEP immune serum reacted with the surface of cells expressing KSHV lytic proteins. In addition, it neutralized KSHV and inhibited infection of target cells. Currently, we are investigating whether inclusion of adjuvants increases the immunogenicity of KEEPs.

Conclusions: KEEP provides a novel vaccine platform for KSHV. The efficacy and utility of KEEP as a vaccine can be further improved by incorporating additional antigens to elicit cellular immunity that targets KSHV latent proteins.

O8. A CRISPR Screen Reveals Epigenetic Factors That Restrict B-Cell Epstein-Barr Virus Oncoprotein Expression

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Background: To accomplish the remarkable task of lifelong infection, Epstein-Barr virus (EBV) switches between four viral genome latency programs to navigate the B-cell compartment and evade immune responses. EBV expresses combinations of eight EBV nuclear antigen (EBNA) and latent membrane proteins (LMP) to reach the memory B cell compartment, the site of viral persistence. Upon memory cell differentiation and in most EBV+ Burkitt lymphomas (BL), all but one viral antigen is repressed for immunoevasion. De-repression of EBV latency antigens could sensitize EBV+ BL to immunotherapy approaches directed against EBNA and LMP antigens. Yet, host epigenetic machinery that governs these important aspects of EBV oncoprotein silencing remain to be characterized by systematic genetic analysis. While evidence has accumulated that methylation silences viral latency promoters including in BL, the exact mechanisms of initiation or maintenance of silencing remain largely unknown. Additional roles of histone modification have not yet been systematically analyzed.

Methods: To gain insights into host epigenetic mechanisms that silence EBV latent antigens, we performed a genome-wide CRISPR/Cas9 screen in MUTU I cells established from an African BL tumor. The Brunello library, comprised of 76,000 lentiviruses that each encode a single guide RNA was used for a loss-of-function screen. Top screen hits were validated in multiple BL and by cDNA rescue. RNAseq was performed to identify genome-wide effects of screen hit knockout on host and viral mRNA expression.

Results: The ubiquitin ligase UHRF1 and its DNA methyltransferase partner DNMT1 were critical for restriction of EBNA and LMP expression. All UHRF1 reader and writer domains were necessary for silencing, and DNMT3B was identified as an upstream viral genome CpG methylation initiator. Polycomb repressive complex I exerted a further layer of control over LMP expression, suggesting a second mechanism for latency program switching. UHRF1, DNMT1 and DNMT3B are upregulated in human tonsil germinal center B-cells, providing a molecular link between B-cell state and EBV latency program.

Conclusions: These results suggest how B-cell state regulates EBV gene expression on the path to persistent infection and suggests targets for novel immunotherapy approaches.

O9. PD-L1[+] B-Regulatory Cells Are Induced by Exposure to Factors That Are Elevated in HIV-1^{+} Subjects Who Develop AIDS-NHL

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Background: Human Immunodeficiency Virus (HIV-1) infection continues to be a major global public health concern. Despite the introduction of combination anti-retroviral treatment (cART), HIV-infected individuals have an elevated risk for developing non-Hodgkin lymphoma (NHL), accounting for 20-30% of AIDS-related deaths in high resource countries. Chronic HIV-1 infection leads to the progressive loss of T-cell immune function, polyclonal B-cell activation, and microbial translocation (i.e. LPS endotoxin). We previously showed that B-cell activation precedes the development of AIDS-related NHL (ARL), as characterized by elevated levels of several cytokines (IL-6, IL-10, CXCL13, TNFα, and IP-10) and B-cell activation molecules (sCD23, sCD27, sCD30, κ and λ-immunoglobulin free-light-chains). We also found that B-regulatory cells (Bregs) (CD19^{+}CD24^{+}CD38^{+}), which also express programmed death-ligand 1 (PD-L1) and secrete IL-10, are significantly elevated in peripheral blood of HIV-1^{+} subjects who develop ARL. Furthermore, B-cells treated with CD40L^{+} HIV-1 virions leads to the induction of Activation Induced Cytidine Deaminase (AICDA) and CD10 expression, which are also elevated preceding the development of ARL. We, therefore, hypothesize that CD40L^{+} HIV-1 virions, inflammatory cytokines (IFNα), and/or LPS can induce a Breg-like cell phenotype expressing PD-L1 that may be representative of pre-tumor cells. Furthermore, we hypothesize that these Breg-like cells and NHL tumor cells secrete PD-L1 expressing exosomes. PD-L1 exosomes have been recently shown to be prognostic markers in melanoma patients.

Methods: B-cells were isolated from PBMCs from healthy donors. Cells were stimulated with human anti-CD40 (1 μg/ml), IFNα (100 U/ml), LPS (1 U/ml) or CD40L^{+} HIV-1 virions for 48 hours. Cells were then stained for flow cytometry to assess the expression of CD19, PD-L1, and the transferrin receptor CD71. To begin to investigate the role of PD-L1 expressing exosomes, exosomes were isolated from B-cell culture supernatants of NHL and ARL cell lines 2F7 and Ramos. Exosomes were then evaluated for the expression of tetraspanin proteins and exosome markers CD9, CD63, and CD81, and for the surface expression of PD-L1 by flow cytometry.

Results: We found that B-cell stimulation with IFNα, CD40L^{+} HIV-1 virions, or LPS induces a Breg-like cell phenotype with significant increased expression of PD-L1. Stimulation with anti-CD40 + LPS or CD40L^{+}

HIV-1 virions + LPS increased the expression of both PD-L1 and CD71 on Bregs. Exosomes isolated from 2F7 and Ramos showed a significantly higher percentage of CD81-expressing exosomes as compared to CD9^{+} and CD63^{+} exosomes. Furthermore, 10% of CD81^{+} exosomes expressed PD-L1 on the surface of exosomes isolated from 2F7 cells, while 40% of CD81^{+} exosomes from Ramos cells expressed PD-L1.

Conclusions: B-reg like cells express PD-L1, which may represent a pre-tumor cell population. ARL cell lines secrete exosomes containing PD-L1, which can potentially modulate CD4^{+} and CD8^{+} T-cell function. Investigating the molecular mechanisms governing PD-L1^{+} Breg cell activation will yield new avenues of discovery and understanding of how pre-tumor B-cells arise, how they contribute to immune activation and/or exhaustion during chronic HIV-1 infection, and to the development of ARL.

O10. Potential Alternative Survival Mechanisms in HIV-Associated Diffuse Large B-Cell Lymphoma (DLBCL) of Germinal Center (GCB) Origin

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Introduction: DLBCL is more aggressive in HIV infected individuals compared to the general population. The molecular pathology driving the enhanced aggressive nature of HIV associated [HIV(+)] DLBCL, however, is poorly understood. Previously, we demonstrated that HIV(+) GCB DLBCL tumors are more proliferative, with enhanced genomic stability and increased expression of DNA repair genes compared to their HIV(-) counterparts (**Maguire et al, Int J Cancer,2019**). In this study, we examined known DLBCL negative prognostic markers such as **BCL2** and, given the immune compromised nature of HIV (+) patients, we also assessed whether specific immunological signaling pathways that may work in conjunction with, or independently of, increased DNA repair, were altered in HIV(+) GCB DLBCL tumors.

Methods: A total of 40 cases, including 19 HIV(+) GCB-DLBCL cases from the AIDS and Cancer Specimen Resource Network (https://acsr.ucsf.edu/) and 21 HIV(-) GCB DLBCL institutional cases were included in this study. H&Es were reviewed by a hematopathologist to validate diagnosis and determine tumor content. Samples were macrodissected up to minimal tumor content by area of ≥60%. Protein expression was assessed by IHC on 5 μm FFPE sections. Two 10 μm FFPE sections per sample were DNA/RNA extracted. DNA was used for copy number variant (CNV) analysis using Agilent array CGH. RNA was used to perform DLBCL subtyping using the Lymph2Cx assay (**Scott et al, Blood, 2014**) and gene expression profiling using the NanoString PanCancer Pathways and PanCancer Immune Profiling panels.

Results: A total of 126/740 genes on the PanCancer and 110/579 genes on the PanCancer Immune panels were differentially expressed between the HIV(+) and HIV(-) cohorts at $p \leq 0.05$. Of these, 61/126 and 10/110 were significantly increased, while 65/126 and 100/110 were significantly decreased in the HIV(+) cohort. Of the 10 immune related genes upregulated, the transferrin receptor gene (**TRFC/CD71**), with a fold increase of 3.9, was the most significantly increased gene in the HIV(+) cohort (p=0.002, FDR=0.0025). As expected, losses in both adaptive and innate immune signaling were observed, as well as reduced expression of **BCL2** pro-apoptotic genes, including **BCL2** itself. Although CNV analysis revealed both cohorts to be predominately diploid at the **BCL2** locus, when aberrations did occur, they were exclusively losses/deletions in the HIV(+) cohort and exclusively gains/amplifications in the HIV(-) cohort. These results were highly concordant with **BCL2** protein expression; where cases with losses/deletions had low **BCL2** expression, while those with gains/amplifications had high **BCL2** expression. In addition, the HIV(+) cohort was also found to be significantly more proliferative by **Ki67** staining (p=0.008). Indeed, an inverse relationship was found between the proliferation marker **Ki67** and **BCL2** by IHC in samples with **BCL2** gene aberrations.

Conclusions: The immune related **TRFC/CD71** gene is commonly expressed on aggressive B-cell lymphomas, and is a known mediator of iron uptake which has been shown to be necessary for, and positively regulates, T and B cell proliferation. Here we show that HIV(+) GCB DLBCL tumors have increased expression of **TRFC/CD71** and the proliferation marker **Ki67** at the mRNA and protein level respectively. This is in line with our previous findings that HIV(+) GCB DLBCL tumors have increased and reduced expression of genes associated with promoting and inhibiting proliferation respectively. These findings alongside reduced expression of **BCL2**, a known negative prognostic marker in DLBCL, suggests a reduced dependence on the pro-survival effects of **BCL2** and a switch to a mechanism that depends on preventing both cycle inhibition and the induction of apoptosis.

O11. Factors Associated With Treatment Completion and Treatment Response of Chemoradiation in HIV-Infected Patients in Botswana (Ipabalele Study-1 U54 CA190158-01)

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Background: Cervical cancer (CC) is the leading cause of cancer-related death among women in Sub-Saharan Africa. Additionally, women living with HIV (WLHIV) are more likely to have persistent HPV infection that increases risk for CC. More than 1/3 of adult women in Botswana are infected with HIV, and a widespread ART (antiretroviral therapy) program has increased life expectancy and reduced mortality due to AIDS-related infections. Cure for locally invasive CC is achieved with chemoradiation therapy (CRT). While some studies suggest that concurrent HIV infection may be associated with decreased survival; in Botswana, HIV has not been shown to have an impact on overall survival or acute toxicities among those who initiated CRT.[1] It is not well documented what factors contribute to completion of CRT among WLHIV. Additionally, it is not known what influence HIV plays in the response to CRT.

Methods: Patients with histologically confirmed cervical cancer were prospectively enrolled between Jan 2015-June 2019 to Ipabalele study at the only radiation oncology facility in Botswana.

A cohort of 180 HIV-infected women were included in analysis. Patient records were reviewed for clinical factors including treatment completion, associated treatment toxicities, and squamous cell carcinoma antigen (SCCAg) levels <2.2ng/ml as a response at the end of treatment.

Results: 180 HIV-infected women with diagnosed cervical cancer were followed for a period of 3 months post-treatment. Mean$\pm$SD age of cohort was 44$\pm$9 years old (range 22-71 years old). Baseline mean$\pm$SD CD4 count was 484$\pm$247 cells/μL and mean$\pm$SD CD4 at end of treatment was 110$\pm$100 cells/μL with an average change of -381 cells/μL. 97% (176/180) patients were ART at the time of diagnosis for mean of 7 years (range 0-19). 59% of women (n=106) completed all treatment (external beam radiation >45Gy and brachytherapy >20Gy and >4 cycles of chemotherapy). 65% (78/121) had a response as measured by normalization in SCCAg levels (<2.2 ng/ml) at the end of treatment. At three-month follow-up, similar proportions (64%, 32/50) showed SCCAg normalization). Factors that had a significant influence on treatment incompletion included increased age (p=0.05), and lower baseline albumin (p=0.05). Change in CD4 at the end of treatment or at 3 months was not associated with treatment response. After adjusting for external radiation dose, brachytherapy dose, and chemo given, only time on ART at the initiation of CRT was a significant factor in predicting SSCAg treatment response. Patients who did not achieve response at 3 months had less total time on ART than patients who achieved SCCAg response at 3 months (mean$\pm$SD: 4$\pm$4 years vs. 8$\pm$6 years) and odds for SCCAg nonresponse was decreased by 15.6% for each additional year of ART (OR = 0.844, 95% CI 0.741 – 0.962, P=0.01)

Conclusions: In this study, HIV infected women with diagnosed cervical cancer who completed CRT were followed for three months. Factors associated with treatment incompletion included increased age and lower baseline albumin while factors associated with treatment response as measured by presence of SSCAg included time on ART. Longer follow-up will be needed to correlate SCCAg response to survival.

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[1] Grover S, Bvochora-Nsingo M, Yeager A, et al. Impact of Human Immunodeficiency Virus Infection on Survival and Acute Toxicities From Chemoradiation Therapy for Cervical Cancer Patients in a Limited-Resource Setting. Int J Radiat Oncol Biol Phys. 2018 May 1;101(1):201-210.

O12. **Cancer-Attributable Mortality Among People With HIV in the United States During 2001-2015**

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Background: Cancer mortality is an emerging public health concern for HIV populations. The main challenge to accurately measuring cancer mortality, especially among people with multiple comorbidities, is misclassification of causes of death. To address this issue, prior studies have used a standardized protocol to adjudicate causes of death among people with HIV. In contrast, this study uses a statistical approach to parse deaths attributable to cancer and other causes. The population attributable risk approach uses cancer diagnoses and their association with overall mortality to estimate a population-attributable fraction (PAF) of cancer-related deaths. We characterized cancer-attributable deaths across demographic and risk groups in the HIV/AIDS Cancer Match (HACM) Study, a population-based cohort study of HIV-infected people across the entire HIV care continuum in the United States.

Methods: The HACM study includes HIV-infected people identified through routine public health surveillance at the state level. Cancer is ascertained through linkage to population-based cancer registries. Vital status is provided from state and national sources at the time of the linkage. The current study population comprised 510,657 HIV-infected subjects followed during 2001-2015 in 10 regions. Cox regression models were used to estimate hazard ratios (HR) for the association between cancer diagnosis and overall mortality, adjusted for time-varying AIDS status, sex, race/ethnicity (White, Black, Hispanic, other), transmission risk group (men-who-have-sex-with-men [MSM], injection drug use [IDU], MSM/IDU, heterosexual, other/unknown), and attained calendar year (2001-2005, 2006-2010, 2011-2015). Cancer was treated as a time-dependent variable; incident and prevalent cancers were included. Attained age was used as the timescale. Population attributable fraction (PAF) was calculated as $p_d \bullet [(HR-1)/HR]$, where p_d is the proportion of deaths preceded by cancer. Cancer attributable mortality rate was estimated as the product of PAF and overall mortality rate.

Results: A total of 32,009 prevalent and incident cancers were diagnosed in the cohort, and 103,480 deaths occurred over 3.6 million person-years (median follow-up=6.7 years); 17.5% of deaths were preceded by cancer. Overall, 14.5% (95%CI 14.1-14.8%) of deaths were attributable to cancer with an estimated cancer-attributable mortality rate of 415 per 100,000 person-years. Non-AIDS defining cancers collectively contributed more to mortality than AIDS-defining cancers (9.2% vs. 5.0% of deaths). Individual cancer sites contributing the largest fraction of deaths were non-Hodgkin lymphoma (3.5%), lung cancer (2.4%), Kaposi sarcoma (1.3%), liver cancer (1.1%), and anal cancer (0.6%). The fraction of deaths attributable to cancer increased from 12.6% in 2001-2005 to 17.1% in 2011-2015, but the cancer attributable mortality rate declined from 484 in 2001-2005 to 314 per 100,000 person-years in 2011-2015. The cancer-attributable mortality and PAF of cancer deaths increased across age groups. Among ≥60 year-olds, 19.0% of deaths were attributed to cancer versus 11.4% among 20-39 year-olds.

Conclusion: With large declines in overall mortality rates and in deaths from AIDS-related causes, cancer represents a growing fraction of all deaths. One in 7 deaths in the HIV population during 2001-2015 was attributable to cancer. Moreover, the fraction of deaths attributed to non-AIDS defining cancers collectively surpasses that of AIDS-defining cancers. The proportion of deaths due to non-AIDS defining cancers will likely rise as the HIV population ages. Estimates of cancer mortality are informative for public health planning and cancer control programs supporting people with HIV.

O13. Kaposi's Sarcoma Incidence, Burden, and Prevalence Among Persons With HIV in the United States, 2000-2015

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Background: The introduction of antiretroviral therapy (ART) resulted in a significant reduction in rates of Kaposi sarcoma (KS) in the United States; however, KS rates remain highly elevated among persons with HIV compared to the general population. In the current ART era, it remains unclear if KS trends have varied significantly across all age, race/ethnicity and HIV risk-groups. Additionally, the current number of incident KS cases and prevalence of KS among persons with HIV has not been quantified. Therefore, this study described recent temporal trends in the incidence of KS over a 16-year period, estimated the current burden of new cases and estimated prevalence of KS, by selected demographic and HIV transmission groups, among persons with HIV.

Methods: KS incidence rates were estimated with data from the HIV/AIDS Cancer Match (HACM) study, a data linkage study of HIV and cancer registries in 9 states, Puerto Rico and Washington, D.C. Using adjusted Poisson regression models, we estimated temporal trends in KS incidence rates by demographic and HIV transmission groups. Standardized incidence ratios (SIRs) were estimated as the observed number of KS cases relative to the number of cases expected based on general population rates. In addition, we applied KS incidence rates and prevalence estimates from HACM to CDC HIV surveillance data on the number of persons living with HIV, to estimate the incident number of KS cases (2008-2015) and the 2015 prevalence of KS in the United States

Results: Between 2000 and 2015, 2,820 persons were diagnosed with KS during 4,227,818 person-years of follow-up in the HACM Study. Seventy-two percent of persons diagnosed with KS were between the ages of 30 and 49 years, 93% male, 26% white, 48% black and 70% were men who have sex with men (MSM). KS rates were highest among 30-39-year-olds, and incidence rates declined significantly with age. KS incidence was also significantly higher among males, non-Hispanic Blacks, Hispanics, MSM and those with a recent HIV diagnosis. KS rates were elevated 459-fold (95% CI: 441.7, 475.7) in persons with HIV compared to the general population and rates declined from 110.9 per 100,000 person years in 2000 to 51.6 per 100,000 in 2015 at an annual percentage change (APC) of -6% per a year. KS rates declined significantly across all age (APC range -8, -4%/year), race/ethnicity (range -7, -5%/year) and HIV-risk groups with the steepest decline of -9% per a year (95% CI: -12, -5,) observed among male and female injection drug users. During 2008-2015, an estimated 5469 KS cases were diagnosed in the United States (95% CI: 5152, 5726), declining from 722 new KS cases in 2008 to 645 new cases in 2015. At the end of our period in 2015, 0.25% of the persons living with HIV in the United States had a diagnosis of KS within the prior 5 years, resulting in 2421 prevalent KS cases.

Conclusions: A consistent gradual decline in the incidence of KS has occurred among persons with HIV in the United States during the current ART era. This decrease is uniform across both demographic and key HIV-risk groups, though rates remain elevated relative to the general population and the number of persons with HIV with a prior KS diagnosis in 2015 is notable. Taken together, our findings suggest that, if current efforts to control HIV in the United States through early initiation of ART, linkage to and retention in care are sustained, rates of incident KS might continue to decline among persons with HIV.

O14. Cancer Immunotherapy Use and Effectiveness in Real-World Patients Living With HIV

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Background: Patients with HIV are commonly excluded from clinical trials of immunotherapy to treat cancer. Clinical adoption of checkpoint inhibitor therapy after US Food and Drug Administration (FDA) approval is unknown in this population. We aimed to 1) describe the real-world uptake of checkpoint inhibitors (anti-CTLA-4, anti-PD-1, or anti-PD-L1) among cancer patients with HIV and 2) compare overall survival (OS) by HIV-infection status of lung cancer patients using these agents.

Methods: The retrospective cohort study included patients diagnosed with advanced non-small cell lung cancer (NSCLC) or any of 13 other cancers who initiated systemic cancer therapy between January 1, 2013 and January 31, 2019. The data source was a de-identified nationwide electronic health record (EHR)-derived database from Flatiron Health. HIV status was obtained using a previously described algorithm (ISPOR 2019), with positive cases confirmed. The probability of any checkpoint inhibitor treatment (i.e., nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and ipilimumab) in any line of therapy was compared by HIV status using multivariable logistic regression adjusted for age, race, gender, practice type, and cancer type. Overall survival for advanced NSCLC patients administered checkpoint inhibitors was compared between HIV+ and HIV- patients using unadjusted, adjusted, and propensity score matched analyses.

Results: Among 112,761 cancer patients, 304 were identified as HIV+. The HIV+ patients were more likely to be younger, male, and black than HIV- patients. The frequency of real-world treatment with checkpoint inhibitors was 14.8% among HIV+ patients and 20.4% among HIV- patients with adjusted odds ratio of 0.73 (p = 0.09). For patients with advanced NSCLC, in the unadjusted analysis, median OS of HIV- patients administered checkpoint inhibitors (n = 12,073) was 10 months (95% CI: 9.7 - 10.4); the median OS of HIV+ NSCLC patients administered checkpoint inhibitors (n = 19) was 13.5 months (95% CI: 6.9 - NA). After adjusting for age, practice type, race, therapy line number, and stage at diagnosis, the hazard ratio (HR) of OS for NSCLC patients using checkpoint inhibitors was 0.89 (95% CI: 0.48-1.66) for HIV+ vs. HIV-. In the propensity score matched analysis, the overall survival of NSCLC patients administered checkpoint inhibitors was similar comparing HIV+ (n = 19) to matched HIV- (n = 209) patients (HR for death for HIV+: 0.77; 95% CI: 0.44-1.36).

Conclusions: Our findings indicate that the use of FDA-approved checkpoint inhibitors among HIV+ patients with cancer is comparable to the HIV- population, even in the context of limited clinical evidence for the HIV+ subgroup. There was no evidence that the effectiveness of checkpoint inhibitors differed by HIV status among patients with advanced NSCLC. Results align with recent initiatives to broaden cancer therapy clinical trial inclusion criteria to allow for more generalizable prospective data, as recommended by the National Cancer Institute Cancer Therapy Evaluation Program and American Society of Clinical Oncology-Friends of Cancer Research HIV Working Group, and support the recent FDA Draft Guidance for Industry regarding cancer clinical trial eligibility criteria for patients with HIV.

O15. Suspected KSHV Inflammatory Cytokine Syndrome (KICS) in Participants With Mild or Moderate AIDS-KS Enrolled in A5264/AMC067 Is Associated With Inferior Survival

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Background: AIDS-related Kaposi sarcoma (AIDS-KS) remains a significant cause of morbidity and mortality in resource-limited settings. A KS herpesvirus (KSHV) inflammatory cytokine syndrome (KICS) has been proposed to describe interleukin-6 mediated systemic inflammation in KSHV-infected patients without a pathological diagnosis of multicentric Castleman disease. A working definition of KICS includes certain clinical symptoms, laboratory and radiographic abnormalities, and elevated KSHV viral load. KICS is associated with high mortality, however its prevalence in KS patients in resource limited settings, especially in those with mild or moderate KS, is unknown. We hypothesized that applying the working definition of KICS may identify HIV and KSHV co-infected populations at high risk of death.

Methods: Between November 2011 and March 2016, clinical trial A5264/AMC-067 randomized HIV infected adults with mild to moderate KS and who were ART and chemotherapy naïve to receive ART alone (chemotherapy as-needed arm) or ART plus etoposide (ET) (immediate arm). Participants were followed for 48 weeks for the primary survival analyses. We conducted a retrospective analysis evaluating the prognostic value of KICS signs and symptoms in participants of A5264/AMC-067. Clinical symptoms [fever, fatigue (grade >1), edema, cachexia, respiratory symptoms, gastrointestinal symptoms, arthralgia/myalgia, altered mental state, and neuropathy] and chest X-ray or laboratory abnormalities [anemia, thrombocytopenia, hypoalbuminemia, hyponatremia, lymphadenopathy, and effusion], were graded using DAIDS v.1 criteria. KSHV viral load was not assessed. *Suspected* KICS was defined by the presence of ≥1 KICS clinical symptom, and ≥ KICS laboratory or X-ray abnormality. A 3 point KICS score of progressive disease severity was calculated for each participant: 0) does not meet suspected KICS criteria; 1) symptoms grade 1 only and ≥1 lab/radiographic abnormalities (any grade); 2), one or more symptoms grade ≥2 and ≥1 lab/radiographic abnormalities (any grade); 3) one or more symptoms grade ≥2 and ≥1 lab/radiographic abnormalities grade ≥2. We used Kaplan-Meier methods to estimate overall survival (OS) at 1 year from enrolment, and Cox regression analysis, adjusting for age, sex, continent, study arm and KS T, I, and S stage to estimate hazard ratios with 95% confidence intervals (95% CIs).

Results: Analysis included 190 participants. Median age was 34 years, 136 (71%) were male. 93% were enrolled at African sites and 7% in South America. 94 (50%) met suspected KICS criteria (KICS score >0); 62 (33%) with KICS score 1, 17 (9%) with KICS score 2, and 15 (8%) with KICS score 3. Edema was the symptom most commonly grade ≥2 (15% of cohort). Hypoalbuminemia was the commonest lab abnormality (17% grade 1, 19% grade ≥2). KICS prevalence did not differ significantly by age, sex, or continent of clinical site. Nineteen deaths were observed. 1-year OS (95%CI) was 96% (89-98%) in participants with KICS score 0, 90% (80-95%) with KICS score 1, 88% (61-97%) with KICS score 3, and 53% (25-74%) with KICS score 3 (log-rank P <0.001). Participants with KICS (any score) had a higher hazard of death, HR 4.2 (1.4-12.6). Risk of death increased with increasing KICS score. (KICS score 1, HR (95%CI), 2.4 (0.7-8.5); KICS score 2, HR (95% CI), 3.0 (0.55-16.4); KICS score 3, HR (95% CI), 15.3 (4.5-53). Adjustment for age, sex, KS stage, clinical site, continent, study arm, CD4 count, or CD4/CD8 ratio did not substantially change results. Association of suspected KICS with death was attenuated with adjustment for albumin, a component of KICS score, but remained significant for KICS score 3 v 0, HR (95%CI), 6.9 (1.6-29.2).

Conclusions: Participants with suspected KICS had an increased risk of death related to the severity of symptoms. Suspected KICS Score 3, found in 8% of mild to moderate KS patients in A5264/AMC-067, was associated with a 15-fold increase in one-year morality. Suspected KICS Score 3 retained prognostic value after correcting for ACTG TIS staging criteria. Suspected KICS can be identified from clinical symptoms and basic laboratory and radiographic procedures and may be a useful tool for identifying KS patients with an increased risk of death. KSHV viral load evaluation is ongoing to further define KICS in A5264/AMC-067.

O16. Treatment of Advanced AIDS-Associated Kaposi's Sarcoma (AIDS-KS) in Resource-Limited Settings: A Three-Arm, Randomized, Non-Inferiority Trial in Sub-Saharan Africa and Brazil (ACTG A5263/AMC066)

Susan Krown[1], Carlee Moser[2], Patrick MacPhail[3], Roy Matining[2], Catherine Godfrey[4], Stephanie Caruso[5], Mina C. Hosseinipour[6], Wadzanai Samaneka[7], Mulinda Nyirenda[8], Naftali Busakhala[9], Fred Okuku[10], Josphat Kosgei[11], Brenda Hoagland[12], Noluthando Mwelase[3], Vincent Oliver[13], Henriette Burger[14], Rosie Mngqibisa[15], Mostafa Nokta[16], Thomas Campbell[17], and Margaret Borok[18], for the A5263/AMC066 Team

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Background: Effective management of advanced AIDS-KS requires treatment with a combination of antiretroviral therapy (ART) and chemotherapy. In high-resource countries, the preferred chemotherapeutic agents are pegylated liposomal doxorubicin and paclitaxel (PTX). Because of higher cost and low availability, these drugs are rarely used in countries with limited resources where AIDS-KS is most common. In low- and middle-income countries, a widely available, relatively inexpensive regimen of bleomycin and vincristine (BV) is commonly used to treat AIDS-KS, but optimal treatment regimens have not been systematically evaluated in these settings.

Methods: Participants with advanced AIDS-KS, were randomized (1:1:1) to receive ART (EFV, FTC, TDF) with one of three open-label chemotherapy regimens: BV (BV+ART) or an easily-administered regimen of oral etoposide (ET+ART) (the investigational arms), or PTX (PTX+ART) (the active control). The primary outcome was progression-free survival (PFS) at week 48, which was used to evaluate if BV+ART and/or ET+ART was non-inferior (NI) to PTX+ART, using a 15% NI margin. Secondary outcomes, evaluating superiority of PTX+ART, included evaluations of death, KS progression, tumor response rates, safety, CD4+ T-cell count recovery and HIV viremia suppression.

Results: 334 participants enrolled between October 2013 and March 2018, when the DSMB recommended study closure; the ET+ART arm closed 2 years prior, in March 2016 per DSMB recommendation. Week 48 PFS rates were higher in the PTX+ART arm compared to both investigational arms. Absolute differences and 95% confidence intervals (CIs) were -30% (-52%, -8%) for the comparison with ET+ART and -20% (-33%, -7%) for the comparison with BV+ART, but both CIs overlapped the NI margin. Recipients of PTX+ART showed superior outcomes with respect to response rate (odds ratio (95% CI): 0.3 (0.1, 0.7) and 0.8 (0.5, 1.3) compared to ET+ART and BV+ART, respectively), response duration, and the composite of death or progression by week 48 (difference (95% CI): 25 (2, 48) and 20 (8, 33) compared to ET+ART and BV+ART, respectively).

	Complete+Partial Response (%)	Median Response Duration (weeks)	Death by Week 48 (%)	Progression or Death by Week 48 (%)
ET+ART	31	24	26	72
PTX+ART (Mar '16)	58	54	11	47
BV+ART	60	59	19	53
PTX+ART (Mar '18)	65	87	10	33

The most common AEs of neutropenia, low serum albumin, weight loss, and anemia were similar across treatment arms. CD4 counts increased progressively; ≥87% achieved HIV VL < 200 copies/ml.

Conclusion: PTX+ART was superior to both oral ET+ART and BV+ART, supporting its use to treat advanced AIDS-KS in resource-limited settings.

O17. Poor Immune Cell Infiltration in the Endemic and Epidemic Kaposi's Sarcoma Microenvironment

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Background: In sarcomas, tumor infiltrating immune cells (TIIC) are known to be associated with good prognosis. Unfortunately, in Kaposi's sarcoma (KS), prognostic markers are lacking and the role of TIIC is not known. The high incidence of KS in the HIV-1+ infected, transplant recipients and the elderly, mechanistically implicates immune dysregulation and immune suppression in tumorigenesis. Nevertheless, whether TIIC, by their absence, presence, or dysfunction, play a primary role in KS has not been fully investigated, especially in comparison of African endemic-KS (EnKS) to epidemic (EpKS).

Methods: We have utilized a combination of immunohistochemistry (IHC) and multi-color immunofluorescence (IF) imaging to investigate relationships between TIIC and KSHV infected cells in 14 EnKS and EpKS tumor biopsies. Using three-color IF, immune cell-surface lineage specific markers were co-stained with both KSHV latency associated nuclear antigen (LANA) and a nuclear dye to assess co-localization of TIIC and KSHV-infected cells in tumor tissue. We have tested for tumor infiltration of T-cells (CD8 and CD4), B-cells (CD19), Macrophages (CD68/CD163), Monocytes (CD14), and NK-cells (CD56). Each lineage marker was assessed and quantified in regions of the same tissue devoid of KSHV LANA and where infection was readily detected. The endothelial cell marker, CD34 was also evaluated to confirm the lineage of KSHV infected cells. Assessment of normal skin from a non-KS individual was conducted to control for normal levels of immune cell infiltration. Matched uninvolved skin was used in comparison to tumor when possible. A two-tailed Mann-Whitney U-test was used to assess median differences between regions where P-value <0.05 was considered significant.

Results: The KSHV infected (LANA positive) cells in the KS tumors uniformly expressed CD34 consistent with an endothelial origin. Despite the nodular presentation of sampled KS lesions, the 'spindle' cells exhibited variable levels of KSHV infection, as indicated by low, medium and high LANA expression. While CD8 T-cells were detected in the KS biopsies, the distribution was sparse in the LANA positive region of the tumor; whereas there were significantly more CD8 T-cells in areas devoid of LANA. (P<0.05). Conversely, there appeared to be more CD68+ macrophages in the LANA positive regions. (P<0.05). Few CD19 B-cells were detected in regions distinct from those expressing LANA. Similarly, CD14 monocytes were rare and showed no co-localization with LANA. CD56 NK-cells and CD4 T-cells were not evident in most of the KS biopsies. While a few CD8 and CD4 T-cells, CD19, CD14 and CD68 were randomly distributed, CD56 and KSHV LANA were not detected in the normal skin tissue.

Conclusions: While both EnKS and EpKS biopsies contain CD8 T-cells, the distribution is biased towards the LANA negative regions of the biopsies instead of colocalizing with KSHV antigen. The colocalization of macrophages with KSHV Ag require further characterization to investigate the type of macrophage and whether they are supporting or inhibiting tumor growth. Overall, there is a dearth of TIIC in EnKS and EpKS tumors.

O18. Rituximab for Diffuse Large B-Cell Lymphoma in Malawi

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Background: There are no prospective data for rituximab in low-income countries (LICs) in sub-Saharan Africa (SSA). Rituximab improves survival for diffuse large B-cell lymphoma (DLBCL) in high-income countries (HICs), including for HIV+ patients if CD4 ≥50 cells/µL. However, rituximab is usually unavailable in SSA, where HIV+ DLBCL occurs most frequently worldwide, and where hematopoietic growth factors are not routinely available and infectious complications differ from HICs. High-quality data from the region are needed to guide clinicians and policymakers in SSA.

Methods: We are completing a single-arm phase 2 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 telepathology and immunohistochemistry. 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). Monitoring, administration, dose adjustment, and supportive care are per protocol, and hematopoietic growth factors are not available. All HIV+ patients receive ART concurrently with chemotherapy, typically with tenofovir-lamivudine-efavirenz as per Malawi guidelines.

Results: From 8/1/2016 to 7/31/2019, we screened 75 patients with 39 (52%, 29 HIV+, 10 HIV-) enrolled and treated with RCHOP. Reasons for screening failure were: non-DLBCL (16: 7 plasmablastic, 5 Burkitt, 3 T-cell lymphoma, 1 primary effusion lymphoma); CD4 <100 cells/µL (11); PS >2 (3); HBsAg+ (2); death during screening (2); absconded during screening (1); and platelets <100x10³/µL (1). Among screened patients confirmed to have DLBCL, 66% were enrolled. Median age was 44 years (range 22-58), and 17 (44%) were female. Stage III/IV was present in 23 (59%), median lactate dehydrogenase (LDH) was 537 IU/L (range 27-2480, laboratory upper limit 250 IU/L), median PS 1 (range 0-2), median age-adjusted international prognostic index (aaIPI) 2 (range 0-3), and median tumor bulk was 195 cm² (range 16-436) measured as sum of product diameters for ≤6 palpable target lesions. Among 29 HIV+ patients (74%), median CD4 was 208 cells/µL (range 102-1551) and 22 (76%) had suppressed HIV RNA, with 24 (83%) having been on ART for a median 37 months before enrollment (range 5-132). As of 7/31/2019, 34 (87%) patients had completed RCHOP per protocol after a median 6 cycles (range 2-6), with no loss to follow-up and median follow-up 16 months (range 4-36) among patients still alive. Estimated Kaplan-Meier 1-year overall survival (OS) was 70% (95% CI 50-83%) and 1-year progression-free survival (PFS) was 58% (95% CI 38-73%). Among 34 patients who completed RCHOP per protocol, 25 (74%) experienced grade 3/4 neutropenia, 5 (15%) febrile neutropenia, 14 (41%) other grade 3/4 toxicities, and 2 (6%) died from treatment-related complications.

Conclusions: In early experience, rituximab was feasible and effective for high-risk DLBCL patients under routine program conditions in Malawi. Important toxicities occurred, but these were identified and managed, leading to low treatment-related mortality and high 1-year OS compared to other published studies from SSA for this population. Patient follow-up continues, and formal comparison to historical cohorts receiving CHOP without rituximab and cost-effectiveness analyses are planned. Larger regional studies may be appropriate incorporating rituximab together with setting-appropriate chemotherapy strategies, to define curative approaches that best optimize safety and efficacy in SSA.

O19.   Cervical Cancer Incidence in Women Living With HIV in South Africa, 2004-2014

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Introduction: Women living with HIV have a high prevalence of high risk Human Papilloma Virus (HPV) subtypes and decreased clearance of HPV infection leading to a more persistent HPV infections.[1] This results in HIV positive women being at a high risk of developing cervical cancer (CC). As of 2014, the age standardized incidence rate (ASR) of CC incidence for the general population was 23 / 100 000 women according to the South African National Cancer Registry (NCR).[2] However, data on CC incidence in HIV positive women at a national level is limited in South Africa. We created a national cohort of women diagnosed with HIV in order to evaluate CC incidence in this group.

Methods: The national HIV cancer cohort used routinely collected HIV records from the National Health Laboratory Service in South Africa and was linked to cancer records from the NCR from 2004-2014. The HIV records included HIV diagnostic tests, CD4 counts and HIV RNA viral loads whilst the cancer records included ICD-O-3 codes. Privacy preserving probabilistic record linkage was used to identify records belonging to the same person. We calculated the overall crude incidence rates (IR) in HIV positive women for the entire study period. We calculated crude incidence rate using the total analysis time and age specific incidence rates of CC per 100 000 person-years (pyrs). Our analysis was restricted to women who were at least 16 years of age at their last HIV test.

Results: There were 3 291 059 females with a median age of 32 years (Interquartile Range (IQR): 25-39) at entry into the cohort. The median CD4 count at baseline was 313 cells/µl (IQR: 178-484). The cumulative analysis time was 8 666 229 pyrs and we identified 9 321 incident CCs during the study period. Approximately one third (31%, n=2 864) of all CC cases were in 30-39 year age group and one third (37%, n=3 441) in the 40-49 year age group. The overall crude incidence rate (IR) of CC amongst women diagnosed with HIV was 108/100 000 pyrs (95% Confidence Interval (CI) 105-109). The IR of CC increased with age from 5.4 (95% CI 2.3-13) in 16-19-year age group to 412 (95% CI 343-496) per 100 000 pyrs in the 70-79 year age group (see Table). The limitation of our cohort is that we only included individuals with more than two tests; this may have caused selection bias and an overestimation of CC incidence rate.

Table 1: Age-Specific Incidence Rates of Cervical Cancer per 100 000 Person Years for Women Living With HIV for the Period 2004-2014

Age category	Cervical cancer cases	Person-years	ASIR (95% CI)
16-19	5	93 000	5.4 (2.3-13.0)
20-29	485	1 700 000	28.5 (26.1-31.1)
30-39	2864	3 550 000	80.7 (77.8-83.7)
40-49	3441	2 200 000	156 (151-162)
50-59	1883	877 000	215 (205-225)
60-69	520	215 000	242 (222-264)
70-79	113	27 000	412 (343-496)
80-89	10	3 000	297 (160-553)

Conclusion: There is a steep rise in CC incidence by age with an early onset of CC observed particularly in the 40-49 year age groups. There is need for intensified implementation of primary and secondary CC prevention strategies across all age groups within this key population of HIV positive women.

HIGHLIGHTED POSTERS

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

1. Modulation of vFLIP-Induced NF- κB Signaling in Primary Effusion Lymphoma Using NEMO Coiled Coil Mimics

Jouliana Sadek[1], Michael G. Wuo[2], David Rooklin[2], Arthur Haunstein[3], Seong Ho Hong[2], Archana Gautam[5], Hao Wu[3], Yingkai Zhang[2,4], Paramjit S. Arora[2], and Ethel Cesarman[1]

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Background: Kaposi's sarcoma-associated herpesvirus-encoded viral FLICE inhibitory protein (vFLIP) constitutively activates the NF-κB pathway in primary effusion lymphoma (PEL) by binding to NEMO, the modulatory subunit of the I kappa B kinase (IKK) complex, thus playing a major role in PEL tumorigenesis. NEMO serves as a key fulcrum in the NF-κB signaling pathway by coupling the upstream signals to IKK complex catalytic subunits through its elongated coiled coil motif. We have previously reported that si-RNA mediated inhibition of vFLIP expression can significantly decrease NF-κB activity and induce apoptosis in PEL cell lines. In addition, transgenic expression of vFLIP in B cells induces lymphomas in mice. These observations support the role of vFLIP as a viral oncogene and indicate that targeting this oncoprotein is a viable therapeutic approach for the treatment of KSHV-associated diseases. vFLIP interacts with the coiled coil region of NEMO, but the topological complexity of this scaffolding protein has limited inhibitor design.

Methods: We undertook a comprehensive effort to block the interaction between vFLIP and NEMO by screening small molecule libraries and rationally designing α-helical secondary and tertiary structure mimics of NEMO. We characterized a series of these NEMO mimics using biophysical and biochemical assays including circular dichroism and TR-FRET assays. We then examined the ability of these mimics to modulate NF-κB signaling, disrupt the target complex and induce cell death using NF-κB reporter assays, coimmunoprecipitation and western blotting, and cell viability assays respectively. In addition, we used fluorescence polarization assay to determine the binding of the lead compound CHD3^{NEMO} to vFLIP and used live confocal microscopy to show that FITC-labeled CHD3^{NEMO} is able to enter cells through an active transport mechanism. We also investigated the anti-tumor activity of CHD3^{NEMO} in a PEL xenograft model.

Results: We observed that only a tertiary protein structure mimic of NEMO (CHD3^{NEMO}) is necessary for potent and selective inhibition. The rationally designed NEMO mimic (CHD3^{NEMO}) binds vFLIP directly (kd =240nM), disrupts the target complex accompanied by proteasomal-mediated degradation of both vFLIP and NEMO and suppression of NF-κB transcriptional activity. The reduction in vFLIP expression and disruption of its downstream interactions promotes cell death, preferentially in vFLIP expressing PEL cell lines. We also demonstrated that CHD3^{NEMO} delayed tumor growth in a PEL xenograft mouse model and attenuated NF-κB signaling _in vivo_, making this compound the first-in-class helical tertiary structure mimic that targets an intracellular protein-protein interaction in cellular and animal models.

Conclusion: Taken together**,** this data supports that targeting recalcitrant tertiary complex epitopes, such as those involving vFLIP/NEMO interaction complex, can be achieved using a mimicking approach with coiled coil mimetics, and that this novel strategy may be useful to treat KSHV-associated diseases. Furthermore, this NEMO mimic can be used as a tool to investigate other functions of vFLIP and the nexus of the signalosome complex stability in regulating NF-κB signaling.

2. Identification of the Kaposi's Sarcoma Progenitor as a PDGFRA(+)/Sca-1(+) Mesenchymal Stem Cell: A De Novo KSHV-Infection to Tumorigenesis Model

Julian Naipauer[1,2], Santas Rosario[1], Sachin Gupta[1], Courtney Premer[3], Omayra Mendez[1], Mariana Schlesinger[1], Virginia Ponzinibbio[1,2], Jain Vaibhav[4], Lauren Gay[4], Renne Rolf[4], Ho Lam Chan[5], Lluis Morey[5], Daria Salyakina[1], Martin Abba[,2,6], Sion Williams[1,2], Joshua M. Hare[3], Pascal J Goldschmidt-Clermont[1], and <u>*Enrique A. Mesri*</u>*[1,]*

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Background: Kaposi's sarcoma (KS) is an AIDS-defining cancer caused by Kaposi's sarcoma herpesvirus (KSHV). Pending questions on KS are its cellular ontology, the molecular mechanisms of viral oncogenesis and the specific environmental conditions leading to viral oncogenesis. Since 1) sarcomas are cancers of mesenchymal origin 2) we identified PDGFRA as a predominant oncogenic signaling triggered by KSHV in AIDS-KS (Cavallin et al PLOS Pathogens July 2018 2018 Jul 9;14(7), 3) PDGFRA is an oncogenic driver of many non-viral sarcomas and 4) PDGFRA is a key phenotypic and functional mesenchymal stem cell marker; we tested whether PDGFRA(+) mesenchymal stem cell can be KS progenitor cells and we sought to identify environmental conditions in which KSHV infection of MSCs would lead to tumorigenesis.

Methods: We infected PDGFRA(+)/SCA-1(+) and PDGFRA(-)/SCA-1(+) murine or human mesenchymal stem cells (MSCs) with rKSHV219 and we tested the effect of incubation in MSC media or in media containing angiogenic growth factors (KS-like media) in tumorigenesis (murine cells) or in cell proliferation (human cells).

Results: We found an upregulation of the KSHV oncogenic lytic program leading to tumorigenicity; only when PDGFRA(+) MSCs were grown in a pro-angiogenic KS-like environment. RNAseq and ChIP-seq analysis showed that KSHV-infected MSCs in KS-like environment display a de-repressed KSHV epigenome that allows for expression of oncogenic KSHV lytic genes. KSHV lytic induction with an HDAC inhibitor (SAHA/Vorinostat) to mimic KSHV in vivo lytic switch. KSHV-infected MSCs grown in MSC media, which are not tumorigenic massively-upregulated KSHV lytic genes, stopped proliferating and showed senescence features. In contrast, KSHV-infected MSCs in KS-like environment, that are tumorigenic, did not further enhanced KSHV lytic gene expression neither displayed senescence features after SAHA treatment. Moreover, these cells continue proliferating even in the presence of p53 and p21 upregulation with concomitant PDGFRA and AKT activation, suggesting that infected PDGFRA(+) MSCs grown in KS-like environment are epigenetically adapted to overcome KSHV lytic-driven oncogene-induced senescence through PDGFRA signaling activation. Inhibition of PDGFR signaling during KSHV lytic reactivation blocks cell proliferation and induce senescence, validating PDGFRA signaling as an oncogenesis pathway that sustains infected cell survival and proliferation. Experiments in KSHV-infected PDGFRA(+) human MSCs (hMSCs) that are natural and productive targets of KSHV infection showed that infected hMSC grown in MSC media are productively infected and do not proliferate while productively infected hMSCs grown in KS-like conditions continue to proliferate through a PDGFRA-mediated mechanisms, thus confirming the results and the clinical relevance of the murine systems.

Conclusion: PDGFRA defines a population of MSC Kaposi's sarcoma progenitors by enabling KSHV oncogenesis in a KS-like environment. We designed a novel model of de novo KSHV infection and tumorigenesis, creating a very robust platform to identify KSHV oncogenic pathways and their relationship with cellular lineages and extracellular growth environments.

3. Utility of Cerebral Spinal Fluid KSHV Viral Load in Primary Effusion Lymphoma

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Background: The peripheral blood mononuclear cell (PBMC)-associated KSHV viral load (VL) is elevated in patients with primary effusion lymphoma (PEL), KSHV-associated multicentric Castleman disease (MCD), and KSHV-associated inflammatory cytokine syndrome (KICS). More than 80% of PEL is co-infected with EBV. Little is known about the KSHV-VL or EBV-VL in the cerebrospinal fluid (CSF) in patients with KSHV-associated diseases. We hypothesized the CSF KSHV-VL, and possibly also the CSF EBV-VL, would be elevated in patients with PEL involving the CSF (CSF-PEL) and could have utility to diagnose and track disease activity.

Methods: We identified 25 HIV-infected patients with KSHV-associated diseases who underwent CSF cytology and measurement of CSF and PBMC-associated KSHV and EBV via real-time qPCR with primers for KSHV *K6* and EBV *pol* gene regions. In PBMCs, viral copies per 10^6 cell equivalents were determined using human endogenous retrovirus 3 primers for cell number quantification. In CSF, the KSHV and EBV-VL were reported as copies/mL indicating viral DNA contained within the CSF. Patients with CSF-PEL had serial analyses during treatment. We evaluated clinical correlations of the detection of CSF-KSHV, assessed sensitivity and specificity of CSF KSHV-VL at different cutpoints to predict positive cytology for PEL, and evaluated the correlation between CSF and PBMC-associated KSHV and EBV-VL using Spearman correlation.

Results: We assessed 68 paired CSF and PBMC samples obtained from 18 patients with PEL and 7 with other KSHV-associated diseases (4 KSHV-MCD, 2 KICS, 1 KS). Four of the PEL patients had confirmed CSF-PEL by cytology at ≥ 1 time point. Nine patients (2 KSHV-MCD, 7 PEL) had KSHV detected in the CSF at >1 copy/mL and every CSF sample positive by cytology for PEL had a detectable KSHV-VL. By contrast, in the patients with EBV+ PEL, the EBV-VL was positive in the CSF at >1 copy/mL in only 41% of samples with positive CSF cytology (EBV-VL range=1 copy/mL-1830 copies/mL). Cytology positive CSF-PEL samples had elevated CSF KSHV-VL (KSHV-VL range=1 copy/mL-2.5×10^6 copies/mL) compared to PEL patient samples without CSF-PEL (KSHV-VL range=1 copy/mL-2940 copies/mL). The KSHV-VL was much lower and infrequently elevated in the other KSHV-associated diseases (KSHV-VL range=1 copy/mL-440 copies/mL). In samples positive by cytology for PEL using a cut-off of ≥ 120 copies/mL, the CSF KSHV-VL had a sensitivity of 89% and specificity of 77% to detect CSF-PEL, with a positive likelihood ratio of 3.9 to predict positive cytology. Eleven PEL patients had more than 2 CSF analyses and the KSHV-VL tracked with treatment response. There was no correlation between elevated CSF and PBMC KSHV-VL levels (r=-0.11, P=0.58). In all samples, PBMC-associated KSHV and EBV were moderately correlated (r=0.47, p=0.001), and EBV in the CSF and PBMCs were weakly correlated (r=0.27, p=0.03). When evaluating only samples from patients with PEL, we saw similar results: PBMC-associated KSHV and EBV-VL were moderately correlated (r=0.51, p=0.002), and EBV-VL in the CSF and PBMCs were weakly correlated (r=0.30, p=0.04).

Conclusion: Most patients with KSHV-MCD, KICS, and KS do not have an elevated CSF KSHV-VL. In patients with PEL, an elevated KSHV-VL in the CSF is a sensitive and specific test for detecting CSF involvement, can aid in monitoring treatment, and correlates with cytology, the gold-standard to detect PEL in the CSF. The lack of correlation between the KSHV-VL in the CSF and PBMCs indicates these are measurements of disease involvement in separate anatomical compartments. The EBV-VL is not useful to detect EBV+ CSF-PEL.

4. Evaluation of the Mobilization Component of a Public Health Approach to Cervical Cancer Prevention in East Africa

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Background: Lack of screening for cervical cancer in sub-Saharan Africa is one of main reasons for the high incidence and mortality of cervical cancer in the region. Recently, we described a public health approach to cervical cancer screening featuring community-based Village Health Team (VHT) member-delivered mobilization, self-collected HPV tests, and mobile treatment. Although the approach yielded many interested women, its community penetrance and the determinants of participation are unknown.

Methods: In two communities in rural Uganda, we first trained VHT members ("VHTs") in a 1-day session to mobilize adult women over a 14-day period to attend a cervical cancer screening fair in their community. VHTs are laypersons identified and supervised by the Ministry of Health to disseminate health messages. Mobilization consisted of announcements on local radio and at churches, burial ceremonies, and market days. The mobilization message

asked community women to attend a cervical cancer screening fair, close to their residences, that would entail their listening to a health lecture before providing a cervicovaginal specimen, collected by themselves in a private setting. In order to determine penetrance of the messaging, four weeks after the fair, we started in the center of the same villages, moved centrifugally to a 5 kilometer radius, randomly selected 50% of the households we encountered, and noted Global Positioning System (GPS) coordinates on each. At each household in which adult women were present, we asked all consenting women if they had heard about the recent health fair, how they had heard, fair attendance and reasons for non-attendance where applicable.

Figure 1. Post-mobilization Interview at a Community Residence.

Results: A total of 279 households were approached, at which 259 (93%) had an adult available to address questions. At these residences, we approached 283 adult women, of whom 282 (99%) agreed to interview (Fig. 1). Most women (93%; 95% CI: 89% to 96%) reported hearing about the fairs (Fig. 2); direct communication from the VHTs was most common means of hearing the message (68%), followed by hearing from a neighbour (27%). Of those who had heard of the fair, 70% (95% CI: 63% to 76%) attended. Reasons for non-attendance included intention to attend a future fair (64%), too busy (21%), distance (6.4%), irrelevance (4.8%), fear (4.6%), and partner refusal (0.9%). Only being married (p = 0.028) was associated with attendance but age, occupation and educational level were not.

Figure 2. Kisabagwa Parish of Hoima District in Western Uganda

Conclusion: In rural Uganda, a VHT-delivered mobilization for self-collected community-based HPV testing was able to effectively penetrate participating communities and motivated a high percentage of those who heard about the fair to attend. Reasons for non-attendance (e.g., "planning to attend a future fair", being too busy) may or may not be modifiable and require deeper probing to understand root explanations. The findings lend further credence to the feasibility of this public health approach to cervical cancer screening and a starting point from which to optimize cost-effectiveness.

5. Diffuse Large B-Cell Lymphoma Tumor Microenvironment Differs Based on HIV and Antiretroviral Therapy Status

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Background: Diffuse Large B-cell Lymphoma (DLBCL) is highly associated with HIV, the commonest lymphoma subtype among HIV-infected individuals, and the commonest cause of cancer death among HIV-positive individuals in high-income countries. Despite histologically similar appearances, HIV-associated DLBCL differs biologically from DLBCL in immunocompetent populations and may also differ *within* HIV-infected populations depending on the immunologic and virologic environment in which it occurs. As lymphomagenesis is impacted by selective pressure in the local tumor microenvironment (TME), deciphering tumor-host interactions is critical to understand tumor biology in the context of HIV and to better tailor treatment in the era of cancer immunotherapy. We aimed to identify transcription-level differences related to the TME in DLBCL, based on HIV and antiretroviral therapy (ART) status.

Methods: We performed whole transcriptome sequencing (RNAseq) from 36 cases of DLBCL (22 HIV+/14 HIV-) from the ongoing Kamuzu Central Hospital Lymphoma Study in Lilongwe, Malawi. Lymphoma-related clinical and laboratory data were prospectively collected for all patients, along with HIV RNA, CD4, and ART status for the HIV-infected cohort. HIV patients were further subdivided into those who were ART-naïve (<6 months of therapy, n=11) and ART-experienced (n=10). We determined enriched gene sets using Gene Set Variation Analysis (GSVA) to compute a module score and then used linear regression to test associations of the Hallmark gene set and immune gene modules from Charoentong *et al.* Cell Reports 2017. Finally, we characterized features of the T-cell receptor (TCR) repertoire using MiXCR and calculated the clonotype diversity, assessed using Shannon entropy.

Results: Compared to HIV- DLBCL, HIV+ DLBCL cases were enriched in hypoxia-related genes and modules related to oxidative stress (q-values < 0.05 by linear regression, FDR adjustment). There were also significant differences in the immune gene signatures in DLBCL stratified by HIV status and ART duration. T-central memory cells and B cells, both activated and immature, were lowest in the HIV+ ART-naïve group (ANOVA, unadjusted p-values respectively: 0.005, 0.02, 0.003), while local Th17 expression was highest in the HIV+ ART-naïve cohort (p=0.007). We found lower MCH class II expression on HIV- DLBCL compared to HIV+ cases (Mann Whitney U test, p=0.04), and lower CD80 expression in HIV+ ART-naïve compared to HIV+ ART-experienced and HIV- DLBCL (Mann Whitney U test, p=0.03). The immune checkpoint protein CTLA4 showed a graded expression, lowest in HIV+ ART-naïve and highest in HIV- DLBCL (p=0.001). There were no differences in expression of PD1 or PD-L1 across cohorts. We identified a gradient of TCR-beta diversity based on HIV and ART status with the lowest TCR repertoire diversity in the HIV+ ART-naïve DLBCL cases (unadjusted p-value = 0.01).

Conclusion: Large-scale molecular analyses of sporadic HIV- DLBCL have revolutionized our understanding of tumor biology and identified key prognostic and predictive biomarkers. Although lymphomas in the context of HIV infection arise in a TME distinct from immunocompetent hosts, few studies have examined whether specific microenvironmental patterns are associated with HIV+ DLBCL. Our data demonstrate that a primitive inflammatory response, rather than a well-coordinated anti-tumor regulatory response, predominates the TME expression signature of HIV+ DLBCL. Moreover, we show that significant differences in the tumor niche are associated with ART status within the HIV+ group. These results highlight the heterogeneity of TME interactions in DLBCL based on HIV and ART status. Further studies to elucidate these interactions are needed, and may have important therapeutic applications, particularly with respect to cancer immunotherapy for HIV+ patients with DLBCL.

6. Risk of Smoking-Related Cancers Among Women and Men Living With and Without HIV

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Background: As people living with HIV are aging, largely due to effective ART, cancer - especially non-AIDS defining cancer - has become a more common cause of morbidity and mortality in this population. People living with HIV also have a higher prevalence of cancer risk factors, including tobacco use, compared to the United States (U.S.) general population; thus, a better understanding of the contribution of smoking to the development of cancer in people with HIV is needed. The present investigation had three aims concerning smoking-related cancers. First, to ascertain whether the effect of smoking on the incidence of these cancers differs by HIV-infection status. Second, to determine whether sex modifies the impact of risk factors for smoking-related cancers. Third, to estimate the sex-specific attributable risk of smoking on incidence of these cancers.

Methods: Data from 6,790 men in the U.S. Multicenter AIDS Cohort Study (MACS; years 1984-2018) and 3,554 women in the U.S. Women's Interagency HIV Study (WIHS; years 1994-2018) were analyzed. Incidence rates for smoking-related cancers (lung/bronchus, larynx, liver, colon, rectum, small intestine, kidneys, oral cavity, nose, middle ear, cervix, vagina, vulva, penis, anus, pancreas, esophagus, bladder, stomach, and acute myeloid leukemia,) were estimated using Poisson regression analyses. In addition, relative risks and adjusted population attributable fractions (PAFs) for these cancers were calculated.

Results: During the 121,031 person-years of study follow-up, there were 181 incident smoking-related cancers in the men and 132 in the women. Aim 1: The age-adjusted incidence rates for smoking-related cancers, per 100,000, were 214 (95% CI 184, 247) for the men and 332 (95% CI 291, 373) for the women (p<0.01) and 162 (95% CI 132, 199) for people without HIV and 327 (95% CI 295, 360) for people with HIV (p<0.01). Among those with a smoking history, rates among people living with HIV were higher than among those without HIV, when stratifying by cumulative pack-years of smoking (all p-values <0.03). Aim 2: In interaction models, the effects of smoking-related cancer risk factors did not differ significantly by sex. Aim 3: The adjusted PAFs for smoking-related cancers were higher in the men (36%, 95% CI 16, 51) than in the women (25%, 95% CI 4, 42) among all participants (p<0.01). In stratified analyses, the adjusted PAFs were estimated at 91% (95% CI 41, 99%) for cancers strongly associated with smoking (lung/bronchus and larynx), 17% (95% CI -46, 53%) for cancers moderately associated with smoking (esophagus, gum, mouth, nose, middle ear, pharyngeal, and lower urinary tract), and 10% (95% CI -20, 33%) for cancers weakly associated with smoking (acute myeloid leukemia, anal, cervix, colon/rectum, liver, pancreas, penis, salivary gland, small intestine, stomach, tongue, tonsil, and vagina/vulva). In these stratified analyses, the adjusted PAFs were higher in men than in women but not significantly different.

Conclusion: With over 121,000 person-years of follow-up, this is one of the largest cohort studies to examine the contribution of smoking on the cancer burden among people living with HIV infection relative to highly similar people without HIV. For a given smoking history, the incidence of smoking-related cancers was significantly higher among participants with HIV infection than among those without HIV – suggesting that HIV is an independent risk factor. The effect of sex on risk of these cancers is less clear due to confounding by measured and unmeasured factors. These results highlight the need for interventions to help women and men living with HIV infection to quit smoking and sustain cessation to reduce their risk of smoking-related cancers.

7. Risk of Second Primary Cancers Among HIV+/- Men With Prostate Cancer

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Background: Prostate cancer is the most prevalent malignancy among male Veterans with HIV. As most localized prostate cancers are associated with good long-term prognosis, second primary malignancies (SPM) are an important clinical issue affecting long-term outcomes. We studied the role of HIV on SPM risk using the Veterans Aging Cohort Study (VACS), a large observational cohort with cancer registry linkage and a large number of incident prostate cancer cases.

Methods: We identified 4,727 VACS subjects (1,123 HIV+) with incident prostate cancer between 1996-2017 and then used registry data to find SPMs diagnosed >180 days after prostate cancer diagnosis. We then determined the prevalence of the most common SPM types by HIV status and identified pelvic SPMs (anus, rectum, penis, testicle) as well as virally-associated SPMs. We compared the risk of SPM by HIV status using Kaplan-Meier methods and then fit Cox regression models to assess for association between HIV infection and SPM after adjusting for confounders (age, race/ethnicity, smoking status). Then among men with HIV we evaluated specific risk factors for SPM including CD4 count at cancer diagnosis.

Results: The cohort did not differ significantly by HIV status in age (mean 60 years) or race/ethnicity (64% Black). We identified 405 SPMs (9.3% of men with HIV, 8.4% uninfected) among prostate cancer patients; the most common SPM in both men with HIV and uninfected men was lung cancer. In unadjusted analyses HIV was associated with greater SPM risk (p=0.02) which persisted after adjustment for cancer risk factors (adjusted hazard ratio [HR] 1.27; 95% confidence interval [CI]: 1.01-1.59). HIV infection was not associated with a significant risk of pelvic SPMs but was associated with an increased risk of virally-associated SPMs (HR: 2.02; 95% CI: 1.16-3.50) after adjustment, including use of radiotherapy (which was more frequent in men with HIV). Last, among men with HIV, age (HR 1.05; 95% CI: 1.01-1.08) and CD4 <200 (compared to >500, HR: 2.38; 95% CI: 1.22-4.62) at prostate cancer diagnosis were independent predictors of SPM after adjustment.

Figure. Common Second Primary Malignancies by HIV Status.

Conclusion: Second malignancies are common in prostate cancer survivors. HIV infection is independently associated with SPM risk in prostate cancer survivors and may be linked to immunodeficiency at the time of initial cancer diagnosis.

8. Female Veterans Living With HIV Have an Increased Risk of Developing Cervical and Genital Cancers

Eva Clark[1,2], Liang Chen[2], Yongquan Dong[2], Suchismita Raychaudhury[2], Jennifer Kramer[2], and Elizabeth Chiao[1,2]

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Background: Women living with HIV (WLWH) are an under-studied segment of the population, especially with respect to veteran health and risk of cancer development. Although often under-diagnosed, WLWH are thought to be at higher risk for Human Papilloma Virus (HPV)-associated cancers due to their immune status. However, access to health care and cervical cancer screening often confounds the observed difference in cancer incidence. We conducted this study to determine if there have been any changes in risk or survival among WLWH who develop genital cancers during the anti-retroviral era in a single-payer health system.

Methods: Veterans living with HIV (VLWH) and age-matched controls receiving care between October 1, 1999 and December 31, 2016 were retrospectively identified using Veterans Health Administration (VHA) electronic medical records (EMR). Potentially HPV-associated cancer (cervical, genital, rectal/anal, and uterine cancer) diagnoses were identified through VHA Cancer Registry review and ICD-9/10 codes. Follow-up time was from HIV index date to cancer diagnosis, last recorded health care encounter, or study end. Demographic, lifestyle, and clinical variables were extracted from EMR for analysis. Cumulated Incidence Rates (IR) and Incidence Rate Ratios (IRR) and 95% confidence intervals (CI) for cancer risk were estimated and survival analysis were conducted using Kaplan-Meier method.

Results: We identified 1,454 female veterans with HIV and compared them to 5,816 age-matched female controls. Three and a half percent of WLWH developed cancers potentially associated with HPV infection (n = 52; including 39 cases of cervical cancer, 11 cases of genital cancer, 2 cases of squamous anal/rectal cancer, and zero cases of uterine cancer), compared to only 1.6% of HIV-negative women (n = 93; including 50 cases of cervical cancer, 24 cases of genital cancer, 7 cases of anal/rectal cancer, and 12 cases of uterine cancer). While the cervical cancer incidence rate (IR) was more than three times higher for WLWH (329.6 per 100,000 person years [py] [CI 329.2-329.952]) than for HIV negative women (IR = 92.9 per 100,000 py [CI 92.8-93.0]; incidence rate ratio [IRR] = 3.55 [CI 2.86-4.39]), the IR for genital cancer was about twice as high in WLWH (93.0 per 100,000 py [CI 92.8-93.1] compared to 44.6 per 100,000 py [CI 44.5-44.7] in HIV-negative women; IRR = 2.08 [1.45-3.00]). The IR for anal/rectal squamous cancer was also higher in WLWH (IR = 16.9 per 100,000 py [CI 16.8-17.0] compared to 13.0 per 100,000 py [CI 13.98-13.04]; IRR = 1.30 [0.58-2.90]). The IRs for uterine cancer could not be compared between the two groups as there were no cases of uterine cancer in WLWH. WLWH had higher likelihood of developing cancer than women without HIV (log rank p < 0.0001). Specifically, WLWH were more likely to develop cervical and genital cancers compared to HIV negative female veterans (log rank p values <0.0001 and 0.035, respectively).

Conclusion: Veteran WLWH are more likely to develop cervical and genital cancers than their HIV negative counterparts, in spite of equal access to health care. This is likely related to their compromised immune status, and the inability to control HPV infection. Even in single-payer health systems, WLWH continue to require special attention to ensure guideline-based high risk HPV screening for prevention of HPV-related genital cancers.

DAY ONE POSTERS

The first eight abstracts will be presented on both days. Abstracts 9-44 are on pages 55 to 90.

1. Modulation of vFLIP-Induced NF-κB Signaling in Primary Effusion Lymphoma Using NEMO Coiled Coil Mimics

2. Identification of the Kaposi's Sarcoma Progenitor as a PDGFRA(+)/Sca-1(+) Mesenchymal Stem Cell: A De Novo KSHV-Infection to Tumorigenesis Model

3. Utility of Cerebral Spinal Fluid KSHV Viral Load in Primary Effusion Lymphoma

4. Evaluation of the Mobilization Component of a Public Health Approach to Cervical Cancer Prevention in East Africa

5. Diffuse Large B-Cell Lymphoma Tumor Microenvironment Differs Based on HIV and Antiretroviral Therapy Status

6. Risk of Smoking-Related Cancers Among Women and Men Living With and Without HIV

7. Risk of Second Primary Cancers Among HIV+/- Men With Prostate Cancer

8. Female Veterans Living With HIV Have an Increased Risk of Developing Cervical and Genital Cancers

9. A Novel Radiological Method for Quantifying Pulmonary Kaposi's Sarcoma

10. IL-13 Expression Characterizes Effusions Associated With Primary Effusion Lymphoma But Not Other Disorders Caused By Kaposi's Sarcoma Herpesvirus (KSHV)

11. A Replication-Defective Gammaherpesvirus Vaccine Safe in Immunodeficient Mice Protects Against Wild-Type Virus Replication in Immune-Competent Mice

12. Association Between Lesion Morphology and KSHV DNA Content and Anti-LANA Immunoreactivity: Implications for Which Lesion to Biopsy in Patients Suspected to Have Kaposi's Sarcoma

13. BART Transcripts Expressed in EBV-Positive NK/T Lymphoma Cells Regulate Inflammatory Cytokine Expression

14. Changes in Host and Viral Gene Expression Following Mutation of Two Caspase Cleavage Sites in KSHV LANA: Implications for Pathogenesis

15. Cyclooxygenase-2 Gene Expression Regulation Triggered by KSHV-vGPCR: From Transcriptional Regulation to Control of mRNA Stability

16. Enhancer Connectomes of Primary Effusion Lymphoma Cell Lines Link Super-Enhancers to Dependency Factors

17. Epigenetic Silencing of Immune-Related Genes (IRGs) in Gammaherpesvirus-Associated Cancers

18. Epigenetic Specifications of Host Chromosome Docking Sites for Latent Epstein-Barr Virus (EBV)

19. Identification of a Novel Pathway of Post-Translational APOBEC3 Regulation by the Tumor Suppressor pVHL

20. Kaposi's Sarcoma Herpesvirus Activates the Hypoxia Response to Co-opt the Alternative HIF2α and EIF4E2-Containing Translation Initiation Complex for Replication and Oncogenesis

21. Low CD4 Count Is Associated With Delays in HIV-Associated Lymphoma Diagnosis

22. Microbial Signatures Associated With Kaposi's Sarcoma Tissues in HIV Patients in the Sub-Saharan Country of Botswana.

23. Monocyte Chemoattractant Protein-Induced Protein 1 Inhibits KSHV Infection and Targets a Specific Motif for Degradation in KSHV, EBV, and Human MicroRNAs

24. Novel Replisome-Associated Proteins at Cellular Replication Forks in EBV-Transformed B Lymphocytes

25. One-Minute Exposure to Nelfinavir Associated With Inhibition of KSHV Virion Production at 72 Hours

26. Pharmacological Activation of the Integrated Stress Response Pathway Leads to EBV Lytic Gene Expression

27. Prognostic Biomarkers for AIDS-Related non-Hodgkin Lymphoma: Measurement of Biomarkers of Microbial Translocation in the AMC-034 Study

28. Protein Inhibitor of Activated STAT1 (PIAS1) Inhibits IRF8 Activation of Epstein-Barr Virus Lytic Gene Expression

29. Regulation of Immune Surface Molecules by CDK4/6 Inhibitors in Gammaherpesvirus-Infected Tumor Cells

30. Restoration of T-Cell and NK-Cell Recognition of Primary Effusion Lymphoma by Pomalidamide

31. Salivary Shedding, Viremia, and Seroprevalence of Kaposi´s Sarcoma-Associated Herpes Virus (KSHV/HHV-8) Among a Cohort of Men Who Have Sex With Men and Transgender Women From Argentina Who Are Infected or at a High Risk of HIV/AIDS

32. Clinical Characteristics of Pulmonary Kaposi's Sarcoma and Pulmonary TB and Diagnostic Performance of Xpert MTB/RIF in AIDS-Associated Kaposi's Sarcoma Patients in Zimbabwe

33. Anti-KSHV and Anti-EBV Oral IgA Antibodies in HIV-Infected and Uninfected Cameroonians

34. Assessment of Plasma DNA Molecular Markers From Newly Diagnosed HIV(+) Lymphoma Patients in South Africa: A Pilot Study

35. Surveillance of Rhesus Macaque Oral Tissues by qPCR and Immunohistochemistry Identifying Gammaherpesvirus Infection Sites Contributing to Transmission

36. The EBV Noncoding RNA EBER1 Carries Out a Conserved In Vivo Function to Promote Hematogenous Dissemination of Infected B Cells

37. The Role of Wilms' Tumor 1 (WT1) in Kaposi's Sarcoma Herpesvirus Oncogenesis

38. Transcriptomic and Proteomic Profiling of HIV Seropositive and Seronegative Diffuse Large B-Cell Lymphoma

39. Triggering Innate Immunity Pathways During Herpesvirus Infection With 25-hydroxycholesterol

40. VDAP – Viral De Novo Assembly, Variant Discovery, and Annotation Pipeline

41. Outcome Markers for ART-Treatment of Early-Diagnosed Epidemic Kaposi's Sarcoma

42. Advancing a Holographic Approach for Point-of-Care Lymphoma Diagnostics in Botswana

43. Comparing Raman-Enhanced Spectroscopy (RESpect) Fiber-Optic Probe With Standard Raman Spectroscopy Fingerprints of Squamous Intraepithelial Lesions to Advance Point-of-Care Assessment

44. Employing the Virus Alone to Diagnose the Cancer: Quantification of Lesional KSHV DNA for the Diagnosis of Kaposi's Sarcoma in Africa

9. A Novel Radiological Method for Quantifying Pulmonary Kaposi's Sarcoma

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Background: Pulmonary Kaposi sarcoma (pKS) causes significant morbidity and mortality in patients with HIV. pKS can appear as peribronchovasclar ground-glass opacities, nodules or mass-like lesions on chest CT. Assessment of pKS for treatment response now requires measurement of evaluable disease, but the methodology is not clarified (Krown et al., _J Clin Onc_, 7, 1201, 1989) and pKS often does not lend itself to straightforward measurements. Furthermore, pulmonary and cutaneous KS may respond differently to treatment, so it is important to quantitatively assess pulmonary changes over time. To address this problem, we devised a simple quantitative scoring system using computerized tomography (CT) imaging.

Methods: This system utilizes the lung sharp algorithm viewed in lung window series of a chest CT (setting L=-500, W=2000). Six slices are defined from the upper to the lower chest - Level 1: above the sternum; Level 2: origin of the left subclavian artery; Level 3: carina; Level 4: lower margin of right pulmonary artery; Level 5 lower margin of right inferior pulmonary vein; Level 6: below the body of the sternum. At each level, a score is given to each side as follows: no disease=0, mild abnormalities=1, moderate abnormalities=2, and severe disease=3 for a total possible score of 36. To assess the methodology in practice, two radiologists scored images from KS patients independently. Inter-observer agreement was evaluated using weighted Kappa (κ) test. In a subset of patients, changes in the number of cutaneous nodular KS measurements (cKS) and pKS scores were assessed following treatment.

Results: 24 male patients (median age- 38 years) with HIV-associated pulmonary KS who were on clinical trials for KS treatment and who underwent chest CT were included in these analyses. A total of 47 chest CT scans were evaluated. Fifteen patients had a bronchoscopy confirming pKS. The median pKS score was 12 at baseline (interquartile range (IQR): 8,26) and 8 (IQR: 3, 16) following treatment. Of 17 patients with cKS and pKS data available at two different time-points, 11 patients (65%) had concordant decrease following treatment, however the correlation was not statistically significant (p=0.84). The time to score each scan was 2 minutes and the inter-observer agreement was 95.7% (κ=0.87, P<0.001).

Figure 1: Topogram of a chest CT showing the location of 6 levels for scoring of the lung and corresponding images at each level.

Conclusion: This pKS temporal scoring method is a useful tool to evaluate extent of disease, has clinical utility and excellent inter-observer agreement. A limitation of this method is the possible presence of concurrent pulmonary conditions that occur in this population, such as infection, that may mimic pKS.
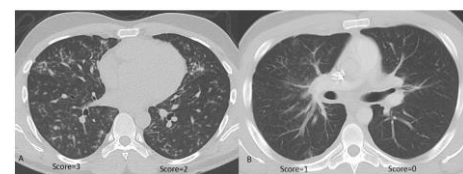
Figure 2: At level 5 there are severe abnormalities on the right (score: 3) and moderate changes on the left (score: 2). At level 4 there are mild abnormalities on the right (score: 1) and no abnormalities on the left (score: 0)

10. IL-13 Expression Characterizes Effusions Associated With Primary Effusion Lymphoma But Not Other Disorders Caused by Kaposi's Sarcoma Herpesvirus (KSHV)

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Background: KSHV causes 4 main disorders: primary effusion lymphoma (PEL), Kaposi sarcoma (KS), multicentric Castleman disease (KSHV-MCD), and the KSHV inflammatory cytokine syndrome (KICS). Effusions can occur in each of these diseases, presenting a diagnostic challenge. We analyzed serum and effusion cytokine profiles from patients with KSHV-associated conditions to identify distinct immunologic characteristics that may aid diagnosis, inform treatment, and elucidate pathogenesis.

Methods: We identified 22 HIV-infected patients with KSHV-associated diseases who presented with effusions (20 pleural effusions, 1 pericardial effusion, 1 ascites). Twenty-one patients had a diagnosis of KS. In addition, 9 were diagnosed with PEL, 8 with KICS, and 5 with KSHV-MCD. We evaluated 12 cytokines of interest in serum and effusions using a commercial multiplex assay. Peripheral blood mononuclear cell (PBMC) and effusion-associated KSHV and EBV viral DNA (KSHV-VL, EBV-VL) were quantified using PCR with primers to KSHV *K6* and EBV *pol*. Viral copies per million cell equivalents were determined using a human endogenous retrovirus 3 assay for cell number quantifications.

Results: Effusions from patients with PEL had substantially higher levels of IL-13 (med 16.9 pg/mL; interquartile range 9.7-26.9 pg/mL) compared to patients with KSHV-MCD (med <0.114 pg/mL; p=0.0037) or KICS (med <0.114 pg/mL; p=0.0003, Figure 1). Moreover, IL-13 was substantially higher in PEL effusions as compared to serum levels (med 16.9 vs. <0.12 pg/mL; p=0.007). PEL effusions also had higher IL-1ß and IL-10 levels as compared with KICS effusions (IL-1ß med 3.03 vs. 0.35pg/mL, p=0.0028; IL-10 med 51.6 vs. 2.5pg/mL; p=0.0015). KSHV-VL levels were significantly higher in PEL effusions as compared to KICS effusions (med 31.4×10^6 vs. 569 copies/10^6 cell equivalents; p=0.0005) or KSHV-MCD effusions (med 232×10^3 copies/10^6 cell equivalents; p=0.02). In both KSHV-MCD and KICS, IL-12p70, IL-4 and IL-6 levels within effusions were higher as compared with serum (p<0.05).
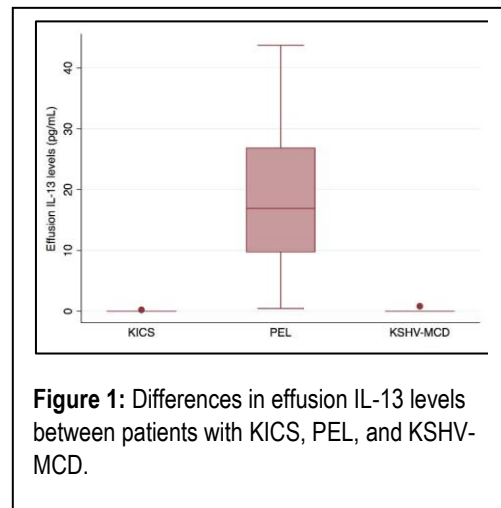
Figure 1: Differences in effusion IL-13 levels between patients with KICS, PEL, and KSHV-MCD.

Conclusion: Effusions in PEL had a distinct cytokine profile compared to the circulation or other KSHV-associated diseases, particularly with regard to markedly elevated IL-13 and KSHV-VL, which may aid in diagnosis and provide insights into PEL pathogenesis.

11. A Replication-Defective Gammaherpesvirus Vaccine Safe in Immunodeficient Mice Protects Against Wild-Type Virus Replication in Immune-Competent Mice

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Background: Epstein-Barr Virus (EBV) and Kaposi sarcoma-associated herpesvirus (KSHV) cause a spectrum of cancers. HIV+ patients are at greatest risk, even after CD4+T cell levels are restored. There is no FDA-approved vaccine for these oncogenic viruses. Replication-defective viruses infect target cells for optimal antigen presentation of virion components to the host immune system without risk of pathology in immunodeficient individuals.

Methods: We devised a strategy to produce high titer stocks of a replication-defective murine gammaherpesvirus (MVH68) in a producer cell line that expresses a codon modified viral gene. This enables the complementation of a defective virus for replication while preventing recombination with the complementing gene that leads to the unacceptable outcome of reversion to virulence. By this approach, we produced a replication-defective murine gammaherpesvirus that does not produce the essential lytic transactivator gene product RTA (RDV-RTA).

Results: A single plaque forming unit (PFU) of wild-type MHV68 killed 100% of SCID immunodeficient mice, but there was no death upon infection with 1.0×10^7 PFU of RDV-RTA. Intraperitoneal administration of RDV-RTA to immune competent C57BL6 mice yielded a virus-specific antibody and T cell response. Most importantly, in vaccinated mice there was near complete abolishment of detectable virus replication in the lungs 7 days post-infection (dpi) and virus reactivation from the spleens 16 dpi upon wild-type challenge.

Conclusion: Two doses of the novel RDV-RTA vaccine led to protection against replication of an oncogenic virus. This data demonstrates the feasibility to produce and administer replication-defective viruses to impair gammaherpesvirus infection. Future studies will investigate the immune correlates of protection and further modify replication-defective viruses to ablate latency.

12. Association Between Lesion Morphology and KSHV DNA Content and Anti-LANA Immunoreactivity: Implications for Which Lesion to Biopsy in Patients Suspected to Have Kaposi's Sarcoma

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Background: Accurate diagnosis of Kaposi sarcoma (KS) is critical for early detection as well as for ensuring that potentially toxic chemotherapy is given only when needed. Histologic diagnosis remains the gold standard, but molecular approaches targeting KSHV DNA are being developed. Despite frequent within-person heterogeneity of KS (e.g., macules, plaques, and nodules appearing in the same person), an understudied aspect of diagnosis is which lesion to biopsy. This is especially relevant in Africa, where KS is common, often fatal if diagnosed late, and can be challenging to diagnose histologically without dermatopathology training. Some research has correlated raised KS lesion morphology with anti-LANA immunoreactivity, but scant work has evaluated correlates of KSHV DNA content. Moreover, no research has included non-KS lesions or translated findings to practical implications for biopsy. We aimed to identify determinants of anti-LANA staining and KSHV DNA content in KS and non-KS lesions.

Methods: We performed 5 mm punch biopsies among consecutive patients in Uganda referred by their health care providers because of skin or mucous membrane lesions clinically suspected to be KS. Biopsies were performed at one of three different biopsy service sites in the cities of Kampala, Masaka, and Mbarara. Lesion morphology (macule/patch, plaque, nodule, or tumor) was assessed clinically, and histopathologic interpretation was derived by consensus among up to 3 U.S. pathologists. All biopsies underwent assessment of the percentage of cells staining positive for anti-LANA. DNA from KSHV ORF 26 from the biopsy tissue was quantified by real-time quantitative polymerase chain reaction.

Results: We tested 506 subjects with suspicious skin/mucosal lesions. Median age was 33 years, 38% were women, and 94% HIV-infected; 22% of lesions were macules/patches, 64% plaques, 14% nodules, and 0.6% tumors. Among lesions found to KS, nodules had more anti-LANA staining and contained more KSHV DNA than macules/patches (reference group). The mean absolute difference in % of cells positive by anti-LANA staining was +28% (p<0.001), and nodules had a mean of 5.0 times more KSHV DNA copies per 5 µl reaction (p<0.001) (Table). There was no evidence for a difference between plaques and macules/patches or for association between anti-LANA staining or KSHV DNA content with age, gender, or HIV infection. Among the non-KS lesions, there was no evidence for an association between lesion morphology and anti-LANA staining or KSHV DNA content.

	KS Lesions (N = 341)			Non-KS Lesions (N = 148)		
	Macule/ Patch	Plaque	Nodule	Macule/ Patch	Plaque	Nodule/ Tumor*
* 13 nodules & 3 tumors † 0 denotes undetectable	(n = 46)	(n = 242)	(n = 53)	(n = 62)	(n = 70)	(n = 16)
Anti-LANA staining						
% Detectable	87%	80%	92%	1.6%	2.9%	6.3%
Median % cells-positive (IQR)	20% (2% to 40%)	10% (1% to 30%)	50% (20% to 80%)	0% (0% to 0%)	0% (0% to 0%)	0% (0% to 0%)
KSHV DNA Content						
% Detectable	98%	100%	100%	15%	17%	0%
Median DNA copies, $\log_{10}$ (IQR)	4.5 (4.0 to 4.7)	4.5 (4.1 to 4.9)	5.0 (4.7 to 5.5)	0† (0 to 0)	0 (0 to 0)	0 (0 to 0)

Conclusion: Among patients with KS in East Africa, KSHV DNA content and anti-LANA staining are greater in nodules than in plaques or macules/patches; there is no evidence of a difference between plaques and macules/patches. Among non-KS lesions, there is no evidence that nodules more often contain KSHV DNA than plaques or macules, and anti-LANA-positivity is rare. The findings suggest that in patients for whom there is suspicion of KS and who have multiple lesion morphologies, nodules should preferentially be biopsied. This will be even more relevant as molecular diagnosis of KS evolves.

13. BART Transcripts Expressed in EBV-Positive NK/T Lymphoma Cells Regulate Inflammatory Cytokine Expression

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Background: EBV+ NK/T lymphoma (NKTL) is a rare disease frequently found in East Asian countries and has limited therapeutic strategies. NKTL characteristically expresses extremely high levels of BART microRNAs (miRNAs), but their functions are mostly unknown. Because EBV encoded BART miRNAs maintain persistent viral infection and inhibit apoptosis in EBV+ B lymphocytes and epithelial cells, we investigated the significance of BART miRNAs in NKTL.

Methods: EBV+NKTL cell lines, EBV+ nasopharyngeal cancer cell line (C666-1) and EBV+ gastric cancer cell line (SNU719) are naturally EBV-infected cells. AGS-EBV, MT2-EBV, Akata-EBV, and HONE1-EBV are established by *in vitro* infection of recombinant Akata EBV strain onto gastric epithelial cells, T cell, Burkitt lymphoma cell, and nasopharyngeal cancer cell, respectively. Expressions of BART miRNA and latent EBV genes were quantitated by qRT-PCR. EBV copy number per cell was calculated by qPCR. Effects of LMP1 and LMP2A on BART miRNAs expression were analyzed using inhibitors and shRNAs specific for LMP1 and LMP2A. BART transcription was inhibited by CRISPR/Cas9. Human cytokine array was performed in MT2 and MT2-EBV cells. Expression level of cytokines was measured by qRT-PCR.

Results: Among cell lines showing type II latently infection, the expression level of BART miRNAs per EBV genome was the highest in NKTL cell lines. LMP1 and LMP2A expression levels were extremely higher in NKTL cell lines compared to other cell lines. Downregulation of LMP1 and LMP2A significantly inhibited BART miRNAs expression. LMP1 and LMP2A-related signaling pathway inhibitors, which were PI3K inhibitor and NF-kB inhibitor, suppressed BART miRNAs expression in NKTL cell lines in a dose-dependent manner. Inflammatory cytokines were upregulated by inhibiting LMP1 and LMP2A signals.

Conclusion: The expressions of BART miRNAs, LMP1, and LMP2A are extremely high in NKTL cell lines compared to other cell lines. NFκB and PI3K/Akt signals induce BART miRNAs expression. LMP1 and LMP2A regulate the expression of inflammatory cytokines via BART miRNAs expression. High expression of BART miRNA found in NKTL contributes to immune evasion probably due to its specific transcriptional regulation.

14. **Changes in Host and Viral Gene Expression Following Mutation of Two Caspase Cleavage Sites in KSHV LANA: Implications for Pathogenesis**

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Background: Kaposi's sarcoma-associated herpesvirus (KSHV) expresses a small set of proteins in latency that are responsible for maintaining viral episomes, promoting growth, avoiding immune recognition, and preventing cell death among other functions. The most abundant and most studied of these proteins is the latency-associated nuclear antigen (LANA). LANA is multifunctional and carries out a large number of activities in cells to promote viral pathogenesis. Previously, we identified two caspase cleavage sites in LANA: a caspase-3 sensitive cleavage site in the N-terminus and a caspase-1 sensitive site in the C-terminus. Studies with LANA expression plasmids revealed that LANA could interfere with activation of the inflammasome in cells (a caspase-1 dependent event) and block apoptosis by interfering with caspase activity. To further elucidate the function and importance of these cleavage sites, we produced recombinant KSHV encoding mutations in the N and C-terminal caspase cleavage sites of LANA (DM) to prevent caspase cleavage of LANA. Here, we characterized the cellular and viral gene expression changes between uninfected cells and cells infected with wild type or LANA mutant viruses to further understand LANA's role in viral pathogenesis.

Methods: HEK-293T cells were infected with wild type (WT) or two different recombinant virus clones encoding DM LANA. Nuclear LANA protein was isolated from infected cells and cleavage by caspases studied using caspase-1 and 3 cleavage followed by western blot. RNA was isolated from the different cell lines and analyzed using a KSHV viral array and by RNA-seq analysis. A soluble protein array was used to evaluate differences in proteins released into the media of cells. Western blot analysis was used to evaluate the levels of proteins of interest identified in the study.

Results: Cells chronically infected with DM virus demonstrated weaker adherence to cell culture flasks than WT virus. Using a soluble receptor protein array, we were able to identify a number of differences in expression level of various adhesion molecules. Of particular interest, galectin-3 binding protein (GAL3BP) which has been shown to be elevated in KS patients, was found to be substantially elevated in the array of WT infected cells but not of DM or uninfected infected cells. RNA-Seq analysis revealed that changes in GAL3BP were occurring at the RNA level and western blot revealed elevated protein levels as well. A KSHV viral RNA array revealed about 12 different viral genes upregulated in cells infected with DM virus. Most upregulated was viral IL-6, and western blot analysis of cell lysates demonstrated that cells infected with two different clones of DM virus expressed 5-10-fold more intracellular vIL-6 than wild type. Similar increases in vIL-6 were also observed in the supernatant from DM infected cells.

Conclusion: These studies may indicate that LANA caspase cleavage sites play important roles in regulating adhesion of KSHV-infected cells, GAL3BP expression, and vIL-6 expression. These effects provide insights on the role of LANA and its caspase cleavage on KSHV biology and disease pathogenesis.

15. **Cyclooxygenase-2 Gene Expression Regulation Triggered by KSHV-vGPCR: From Transcriptional Regulation to Control of mRNA Stability**

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Background: Kaposi Sarcoma (KS) is the most frequent AIDS-related cancer and arises when endothelial cells are transformed by the KSHV virus. The constitutively active receptor vGPCR is encoded within the KSHV genome and has a key role in cell transformation and angiogenesis. For this reason, the identification of signaling events triggered by vGPCR could be of therapeutic interest. As Cyclooxygenase-2 (COX-2) is known to be an important inflammatory mediator, our goal is to characterize the link between vGPCR and COX-2 expression, through its promoter activation and mRNA stability.

Methods: We used SVEC vGPCR (endothelial cells that constitutively express vGPCR) and mECK Bac16 (murine bone marrow-derived endothelial lineage cells transfected with BAC16, a bacterial artificial chromosome harboring the full KSHV genome). Mice were injected with vGPCR expressing cells to study tumor growth and angiogenesis.

Results: We observed COX-2 mRNA and protein overexpression, compared to control cells. Co-transfecting reporter plasmid constructs with plasmids expressing a variety of MAPK kinases, we observed that vGPCR signaling has an impact both on COX-2 promoter activity and regulatory events involving mRNA 3'UTR elements. We observed that Erk1/2, activated by vGPCR, increases COX-2 promoter expression and mRNA stability. The Rac1 inhibitory drug 1A-116, provided evidence that Rac1 has an important role in COX-2 promoter activation. Treatment with the COX-2 selective inhibitory drug Celecoxib produces a significant retardation in tumor growth in a mouse model using injected cells that express vGPCR. An intradermal angiogenesis assay showed that treatment with the COX-2 inhibitory drug NS398 before inoculation of vGPCR-transformed cells abolishes the angiogenic response induced by vGPCR expression.

Conclusion: Based on all these results we conclude that vGPCR upregulates COX-2 levels in endothelial cells due to a dual effect upon its promoter region and upon elements in the 3'UTR region of mature mRNAs. Also, we can conclude that vGPCR regulates angiogenicity and tumorigenicity via COX-2 activation. These facts pinpoint COX-2 as a potential target for KS chemoprevention and therapy.

16. Enhancer Connectomes of Primary Effusion Lymphoma Cell Lines Link Super-Enhancers to Dependency Factors

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Primary effusion lymphoma (PEL) has very poor prognosis. To evaluate the contributions of transcription enhancers/promoters to PEL cell growth and survival, we used H3K27ac ChIP-seq and HiChIP to generate the PEL enhancer/promoter landscapes and connectomes in both Karposi's sarcoma associated herpesvirus (KSHV) singly infected and KHSV/Epstein-Barr virus (EBV) coinfected PEL cell lines. ChIP-seq identified > 20,000 significant H3K27ac peaks. >~ 44% of them were at enhancer region. Motif analysis of these H3K27ac peaks found significant enrichment of E2A, MEF2C, SPI1:IRF, BCL6, RBPJ, NF-kB RELA, EBF, and PRDM1 motifs. CRISPR knock out of MEF2C and IRF4 significantly reduced H3K27ac signals by ChIP-qPCR. H3K27ac HiChIP identified linkages between enhancers-enhancers, enhancers-promoters, and promoters-promoters. HiChIP also linked PEL super-enhancers (SEs) with extra-ordinary broad and high H3K27ac peaks to PEL dependency factors MYC, IRF4, MCL1, CCND2, and MDM2. CRISPRi tethering of transcription repressors to SEs significantly reduced SE target gene expression and reduced PEL cell growth. We also defined the H3K27ac ChIP-seq profiles of the KSHV and EBV genomes in PEL cells.

17. Epigenetic Silencing of Immune-Related Genes (IRGs) in Gammaherpesvirus-Associated Cancers

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Background: Epstein-Barr Virus (EBV), a human gammaherpesvirus, is one of the well-recognized human oncoviruses, and the causative agent of multiple cancers, including the Burkitt's and non-Hodgkin's lymphomas as well as cancers of epithelial orgin such as gastric and nasopharyngeal carcinoma. The overall survival rate of gastric carcinoma (GC) is only ~30% worldwide, as the fifth lowest among all types of cancers. Although the association of GC development with EBV infection remains to be confirmed, the emerging evidence supports that EBV is one of pathological factors defining a unique subset of GC, known as EBV-associated GC (EBVaGC). EBVaGC has the distinct histological and molecular characteristics, such as the significant difference in the host DNA methylation pattern comparing to EBV-negative GC. Since the immune system plays a critical role in controlling both viral infections and tumor developments, we particularly investigated whether the immune related genes (IRGs) are dys-regulated in EBVaGC due to EBV infection.

Methods: RNAseq data and 450K methylation array data of 24 EBVaGC and 25 EBV-negative GC cases obtained from NCI The Cancer Genome Atlas (TCGA) data portal (https://portal.gdc.cancer.gov). The dataset of IRGs, including nearly 4,000 genes, was custom-curated, according to the literatures and the open online sources such as InnateDB and Interferome. The expression and DNA methylation of these IRGs were evaluated. Expression of certain IRGs identified from these analyses were validated in the EBV-positive GC cell line, AGS-BX, and Burkitt's lymphoma (BL) cell line, Akata-BX, by using RT-qPCR. The antiviral potential of IRGs was further investigated. We acquired the ORFs of IRGs from the MISSION® TRC3 Human LentiORF Collection (Sigma), and stably expressed them in AGS-BX cells. We determined the impact of IRG overexpression on EBV lytic gene expression and viral genome replication by qPCR, and virion production by flow cytometry. We also transiently expressed certain ORFs of IRGs in HEK293/KSHV.r219 cells to determine their impact on the lytic replication of Kaposi's sarcoma-associated herpesvirus (KSHV), another human gammaherpesvirus.

Results: Analysis of RNAseq data unraveled that host genes are significantly down-regulated in EBVaGC, and that IRGs are enriched with statistic significance. Furthermore, analysis of methylation array data indicated that DNA hyper-methylation occurs at most loci of the down-regulated IRGs. We demonstrated that certain gene clusters are intensively methylated, including the genes cluster of Metallothionein-1 (MT1) and Homeobox A (HOXA), which correlated with their down-regulation in EBVaGC. Treatment of a DNA methyltransferase (DNMT) inhibitor, 5-azacytidine, restored the expression of MT1 and HOXA genes in AGS-BX and Akata-BX cells. Furthermore, overexpression of MT1 genes, particularly MT1G, inhibited the lytic replication of EBV but not KSHV. We also identified that HOXA10 suppresses the lytic replication of both EBV and KSHV. At last, we confirmed the antiviral potential of several other IRGs, including IRAK2 and MAL, which were subjected to EBV down-regulation in EBVaGC. The anti-gammaherpesvirus activity of above IRGs (MT1G, HOXA10, IRAK2, MAL) is never reported and warrants further investigations of their antiviral mechanisms.

Conclusion: Our results demonstrated that EBV infection induces the epigenetic silencing of IRGs through DNA hyper-methylation, which is a viral strategy effectively diminishing IRG's antiviral potential. It is likely a virus-driven vs cancer-driven event. Certain IRGs suppress lytic replication of both EBV and KSHV, indicating their broad antiviral potency. The antiviral and antitumor immunity utilize the similar immune mechanisms. Therefore, we believe that epigenetic silencing of IRGs by oncogenic viruses would generate dual benefits, increasing viral spreading within tumor environment and also promoting cellular malignant transformation. The antitumor activities of identified IRGs (MT1G, HOXA10, IRAK2, MAL) are currently under investigation.

18. **Epigenetic Specifications of Host Chromosome Docking Sites for Latent Epstein-Barr Virus (EBV)**

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Background: Epstein-Barr virus (EBV) persists as extrachromosomal episomes in most latently infected EBV-associated tumors. EBV episome maintenance requires EBNA1, a viral encoded sequence-specific DNA binding protein that tethers the viral episome to the host chromosome.

Methods: To better understand the mechanism of EBV episome maintenance and chromosome tethering, we employed circular chromosome conformation capture (4C) analysis to identify genome-wide associations between EBV episomes and host chromosomes.

Results: We found that EBV episomes in Burkitt lymphoma (BL) cells preferentially associate with large domains in the cellular genome that are enriched for repressive histone mark H3K9me3 and surrounded by AT-rich sequence. Tethering sites were also enriched for B-cell specific transcription factors EBF1 and RBP-jK, as well as sequence-specific binding sites for EBNA1. These attachment sites corresponded to transcriptionally silenced genes with enrichment in neuronal function and protein kinase A pathways. Depletion of EBNA1 from EBV latently infected BL cells led to a transcriptional de-repression of these silenced genes. EBV attachment sites in lymphoblastoid cells (LCLs) showed different correlations.

Conclusion: Since EBV gene expression is different in LCLs relative to BL, our findings suggesting that the epigenetic environment of host chromosome attachment sites confer differences in epigenetic control of viral gene expression during latency. Understanding the different mechanisms of EBV tethering may provide new opportunities for inhibition of EBV latent gene expression and genome persistence.

19. Identification of a Novel Pathway of Post-Translational APOBEC3 Regulation by the Tumor Suppressor pVHL

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Background: The apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3 (APOBEC3; A3) proteins are a family of seven cytidine deaminases that are specific for single-stranded DNA (ssDNA) templates. Initially identified due to the capacity of several members to restrict HIV-1 replication in the absence of the viral protein Vif, this family has been further demonstrated to inhibit endogenous retroelements, and endogenous and exogenous retroviruses. A3 family members localized to the cytoplasm (A3F, G, and H) induce hypermutations with an identifiable signature in the nascent, transiently single-stranded retroviral DNA genome produced by reverse transcription. Other A3 proteins, notably APOBEC3B (A3B), localize in the nucleus and induce such hypermutations in chromosomal DNA. In particular, signature A3B-induced hypermutations are found in more than 50% of human cancers and are hypothesized to provide mutational diversity from which selection can lead to increasing tumor aggressiveness, drug resistance, and/or metastasis. As such, investigations into the regulation of the APOBEC3 family in uninfected cells are particularly relevant to better understand mechanisms that could yield potential targets for therapies for both cancers and retroviral infection. However, as it stands there is little known about how A3 proteins are regulated in the absence of infection. Here, we propose a novel pathway of APOBEC3 post-translational regulation in uninfected cells that is orchestrated by the cellular tumor suppressor protein pVHL – a substrate adapter for a degradative Cullin-Ring Ubiquitin Ligase (CRL) complex – in a proteasome-dependent fashion.

Methods: Proteomic analysis of A3B-interacting proteins was conducted to identify potential cellular regulators. Human cancer cell lines with endogenous A3B expression were used to study the effect of proteasomal inhibition, as well as pVHL silencing, on endogenous A3B protein levels as determined by immunoblotting. RT-qPCR was done in parallel to test whether A3B transcription was influenced by these treatments. Additionally, co-transfection with A3 and pVHL expressing plasmids into 293T cells was used to test the effect of pVHL co-expression on the protein levels of several A3 family members and to investigate interactions between pVHL and A3 proteins through immunoprecipitation. Moreover, pVHL point mutant that does not bind Elongin C was used to elucidate if pVHL required intact CRL function to decrease A3 levels

Results: Proteomic analysis identified pVHL as a potential A3 regulator. In multiple relevant cancer cell lines, we demonstrated that proteasomal inhibition and pVHL silencing leads to increased levels of A3B protein in a post-translational manner. Additionally, we have consistently observed that ectopic co-expression of pVHL along with A3s in 293T cells induces degradation of all A3 proteins tested. Moreover, immunoprecipitation experiments in this system confirmed a protein-protein interaction between pVHL and A3s. Further experimentation has demonstrated that the pVHL-Elongin C binding that precedes the formation of a degradative CRL is required for pVHL-mediated A3 degradation.

Conclusion: These findings identify a novel cellular pathway of post-translational A3 regulation in the absence of retroviral infection. Our results strongly implicate pVHL as the key regulator of a degradative mechanism that targets the A3 family for proteasomal degradation. Importantly, we also determined that pVHL and A3 proteins are binding partners, and that pVHL-Elongin C binding is required in order to induce A3 degradation. Cumulatively, these results suggest that the pVHL-A3 dynamic may be analogous to the well-established degradative pathways of HIF1α by pVHL and of cytoplasmic A3s by HIV Vif, whereby pVHL-A3 binding and the formation of a CRL precedes polyubiquitination and subsequent proteasomal degradation of the A3 substrate. Considering the established roles that A3 proteins have in mutagenesis of retroviral genomes and of cancer cell chromosomal DNA, the discovery of a novel regulatory pathway of these proteins has profound clinical significance. Further investigations will elucidate the intricacies of this degradative dynamic between pVHL and cellular A3 proteins.

20. Kaposi's Sarcoma Herpesvirus Activates the Hypoxia Response to Co-opt the Alternative HIF2α and EIF4E2-Containing Translation Initiation Complex for Replication and Oncogenesis

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Background: Kaposi's sarcoma herpesvirus (KSHV) is a γ-herpesvirus associated with Kaposi's sarcoma and lymphoproliferative disorders associated with AIDS. KSHV targets the oxygen sensing machinery by regulating the expression of the hypoxia inducible factors (HIFs) reprogramming the gene expression profile of the infected cell to hypoxia-like. This raises a fundamental question as to whether or not KSHV targeting of the hypoxia response could be part of a viral survival and replication strategy to control the translation machinery. Thus, we sought to investigate if the ability of KSHV to target the HIFs enables the formation of the alternative eIF4E2 containing hypoxic translation complex, eIF4F^H, for enhanced initiation of viral protein synthesis in normoxia.

Methods: To investigate the role of the alternative eIF4F^H translation machinery during KSHV lytic cycle, we performed siRNA targeted silencing of the components of eIF4F^H in the KSHV reactivation cell line iSLK.KSHV219. To test whether this hypoxic translation machinery is involved in protein synthesis and is actively participating in KSHV mRNAs translation in normoxia, we performed puromycin incorporation assays and did polysome profiling in non-targeting and eIF4E2 silenced reactivated cells. To show that viral mRNAs are actually translated via the eIF4F^H complex in normoxia we performed eIF4E2 and HIF2α targeted RNA immunoprecipitation. Furthermore, to validate our results in a pathophysiological system, we performed eIF4E2 transient silencing in productively infected Human Mesenchymal Stem Cells (hMSCs). These cells are a relevant target of viral oncogenesis because long-term cultured KSHV infected hMSCs manisfest a transformation phenotype _in vitro_.

Results: Using iSLK.KSHV219 cell lines, we found that KSHV reactivation regulates the expression of the activator of eIF4F^H (HIF2α) in normoxia. Both HIF2α and eIF4E2 siRNA targeted silencing resulted in a reduction in viral protein expression decreasing production of infectious viral particles from reactivated iSLK.KSHV219 cells cultured in normoxia. Also, eIF4E2 silencing reduced _de novo_ protein synthesis in reactivated cells. HIF2α and eIF4E2 targeted RNA immunoprecipitation showed KSHV mRNAs bound to eIF4F^H in normoxia. Polysome profiling revealed that eIF4E2 silencing reduces accumulation of viral mRNA in translational active polysomes fractions in normoxia. Moreover, eIF4E2 silencing in _de novo_ productively infected hMSCs decreased lytic protein expression, production of infectious viral particles and dramatically reduced the remainder of protein synthesis left upon KSHV induced translation shut-off. In addition, it inhibited the activation of the Kaposi's Sarcoma oncogenic driver PDGFRA through down-regulation of its ligands PDGFA and B and reduced VEGF production from infected cells.

Conclusion: Together, these findings show that KSHV induced hypoxia-like environment in the cell promotes the formation of the alternative eIF4F^H translation complex, activated by HIF2α, augmenting engagement of viral mRNAs to host ribosomes which is necessary for optimal viral replication, pathogenesis and to bypass host translation shut-off.

21.   Low CD4 Count Is Associated With Delays in HIV-Associated Lymphoma Diagnosis

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Background: HIV is associated with the development of aggressive B-cell non-Hodgkin lymphomas (NHL) and Hodgkin lymphomas (HL). Insofar as these lymphomas are highly treatable and have been associated with long-term survival over 50%, timely diagnosis is important. We set out to determine the time from initial presentation with the signs and symptoms of lymphoma until a pathological diagnosis was confirmed.

Methods: A retrospective medical record review of HIV-infected patients receiving care at the HIV clinic at Johns Hopkins Hospital and developed an aggressive, B-cell lymphoma between 2000 to 2015 was undertaken. The review included demographic data, CD4 count and viral load at the time of lymphoma diagnosis, antiretroviral use, clinical history prior to lymphoma diagnosis including clinic visits, emergency room visits, hospital admissions and constitutional symptoms such as fevers, weight loss, night sweats, and/or lymphadenopathy. Invasive procedures undertaken to pursue a definitive diagnosis such as fine needle aspiration, core or excisional biopsy, endoscopy and/or surgical specimens were noted. Frequencies and continuous measures were compared between NHL and HL by Fishers exact and Kruskal-Wallis tests respectively.

Results: Among 27 patients diagnosed with aggressive, B-cell, HIV-associated lymphomas, 19 (70.4%) were diagnosed with NHL and 8 (29.6%) were diagnosed with HL. Sixteen (59%) of the 27 patients were male, mean age and CD4 count were 46.8 years and 160 cells/uL respectively. Nineteen patients (70.4%) were on antiretrovirals at the time of lymphoma diagnosis and 11 patients (40.7%) had an undetectable viral load. Average interval from presentation until a confirmed lymphoma diagnosis was 11.1 weeks and was not different between NHL and HL. Fifty-nine percent (16/27) of patients had at least 1 non-diagnostic invasive procedure performed prior to pathological confirmation of their lymphoma.

Among patients with a CD4 $\leq$150 cells/uL (n = 15), average diagnostic interval from first presentation to pathological confirmation of lymphoma was higher than in the CD4 >150 cells/uL group (14 weeks vs. 7.5 weeks; p=0.026). Though low numbers, a peripheral lymph node biopsy from palpable lymphadenopathy yielded lymphoma diagnosis in most patients with CD4 >150 cells/uL relative to CD4 $\leq$150 cells/uL (66.7% vs. 13.3%) where extranodal sites were more common as the site of lymphoma diagnosis. Fewer patients with a CD4 count $\leq$150 cells/uL had an undetectable viral load (20% vs 66.7%; p =0.022). There was no difference in age, gender, or antiretroviral exposure between the two CD4 groups.

Conclusion: PLWH with signs and symptoms of lymphoma experienced substantial delays from presentation to diagnosis. Delays were particularly pronounced in patients with a CD4 count $\leq$150 cells/uL perhaps due to the large differential diagnosis for constitutional symptoms in severely immunocompromised individuals. Most patients required more than 1 invasive procedure prior to confirmation of a lymphoma diagnosis. There may be an opportunity to improve diagnostic yield by incorporating new molecular approaches. These diagnostic approaches might be particularly useful for patients with advanced HIV disease whose intervals between symptoms and diagnosis are the longest.

22. Microbial Signatures Associated With Kaposi's Sarcoma Tissues in HIV Patients in the Sub-Saharan Country of Botswana.

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Kaposi's sarcoma (KS) continues to be one of the most prevalent AIDS defining opportunistic cancers in Sub-Sahara Africa. It is well established that KS is caused by infection with the oncogenic virus referred to as Kaposi's sarcoma associated herpesvirus (KSHV/HHV-8). The disease is manifested predominantly in the extremities in endemic KS seen in elderly individuals; however, in HIV-positive immunocompromised individuals the tumors also invade the major organs and oral cavity with increased mortality. Our studies were based on the hypothesis that in KS tissue the microbiome contributes to pathogenesis and that a dysbiotic microbiome leads to increased pathogenesis. Twenty-three individuals with diagnosis of KS who were HIV positive were enrolled at an oncology clinic in Botswana and tumor samples were obtained for analysis. Using a pan-microarray technology combined with bioinformatics analyses we characterized the signatures of viral, bacteria, fungal and parasitic agents associated with the KS samples. The virome showed that Herpesviridae, which includes HHV-8 was the most prominent as expected, but that Adenoviridae, Papillomaviridae and some Retroviridae signatures were also highly represented in KS tissues of HIV positive patients. Hierarchical clustering showed that there were 2 prominent groups that show extensive signal for KSHV and other oncogenic viruses and that two samples had almost undetectable signals. This was similar for Adenoviridae and Papillomaviridae and is unexplained at this time. The genomic composition of the viral agents showed that most were dsDNA followed by ssRNA-RT and ssRNA viral agents. The microbiome showed the dominant families as Enterobacteriaceae, Mycobacteriaceae, Streptococcaceae, Alcaligenacaceae as well as some members of the Neisseriaceae and Chlamydiaceae families. The dominant groups of fungi include Malassezia, Rhodotorula and Fusarium and the most prominent group of parasites belonged to the Entamoeba Genus with signatures of histolytica, dispar, invadens and nutalli being the most abundant species identified. Acanthamoeba and Blastocystis were also prevalent in these tissues. The strong signatures of Papillomaviridae suggests that there may be cooperative events that can occur with other oncogenic viral agents contributing to the pathogenesis of KS or could also be due to the high prevalence of HPV in HIV patients. Additionally, the presence of Blastocystis organisms also demonstrated association with immunocompromised individuals as is known for this Genus and could be unique to KS in the HIV population in Sub-Sahara Africa. The significance of these results will require more studies with comparisons with tissues from HIV negative control patients and provide information as to the organisms that are unique to this cohort of patients. Nevertheless, this nascent area of study is exciting, and these results provide some initial insights into the tumor- associated microbial signatures of KS in HIV-positive patients.

23. Monocyte Chemoattractant Protein-Induced Protein 1 Inhibits KSHV Infection and Targets a Specific Motif for Degradation in KSHV, EBV, and Human MicroRNAs

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Background: Kaposi's sarcoma-associated herpesvirus (KSHV) expresses 12 pre-miRNAs during latency that are converted into 25 mature miRNAs. Host factors that are targeted by KSHV miRNAs play key roles in viral life cycle and cellular activities such as tumorigenesis, immune response, and apoptosis. Although KSHV miRNA sequences are highly conserved in cell lines and clinical samples, their expression levels vary. The recent discovery that monocyte chemoattractant protein-induced protein 1 (MCPIP1) is induced by multiple inflammatory cytokines and can cleave some human miRNA precursor molecules (pre-miRNAs) raised the possibility that host factor, MCPIP1 could act as a negative regulator of viral miRNA biogenesis. If MCPIP1 could inhibit biogenesis of viral miRNAs, then we further hypothesized that KSHV may possess mechanisms to inhibit MCPIP1-mediated host defense mechanisms. In addition, MCPIP1 can degrade IL-6 and IL-6 causes many symptoms associated with KSHV diseases.

Methods: We analyzed gene expression changes induced 48 hours after KSHV infection in primary endothelial cells. Cleavage efficiency and binding affinity between pre-miRNAs and MCPIP1 were measured to characterize MCPIP1 specificity. 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. Antiviral activities of MCPIP1 against KSHV were investigated by quantifying genome copies and viral gene expression.

Results: We observed that increased MCPIP1 expression alters KSHV miRNA biogenesis by directly degrading most viral miRNAs and changing expression of the miRNA biogenesis factor, Dicer. Interestingly, we found that MCPIP1 degraded specific human, KSHV, and EBV pre-miRNAs with the different efficiencies. Our gel shift assays revealed that MCPIP1 binding does not differ between pre-miRNAs that are degraded or resistant to MCPIP1. We found that mutations in key locations of pre-miRNAs inhibited MCPIP1-mediated degradation of both KSHV and human pre-miRNAs. Increased MCPIP1 expression caused a decrease in KSHV latent gene expression and a decrease in viral genome copies per cell. A KSHV pre-miRNA, miR-K6, which is resistant to MCPIP1 mediated degradation, generates a mature miRNA that decreased MCPIP1 expression by directly targeting the MCPIP1 3' UTR. A miRNA cluster deleted mutant KSHV containing miR-K10 and miR-K12 also suppressed MCPIP1 expression. These results suggest that there may be additional mechanisms by which miR-K10, miR-K12 or other viral products inhibit MCPIP1 expression.

Conclusion: Taken together, these results demonstrated that MCPIP1 inhibited KSHV infection and suppressed viral miRNA biogenesis by directly degrading KSHV pre-miRNAs and altering expression of miRNA biogenesis factors. However, KSHV can circumvent the antiviral consequences of MCPIP1 functions through repression of MCPIP1 expression. Increasing MCPIP1 expression might be a potentially therapeutic strategy to inhibit spreading of infection and decrease expression of inflammatory cytokines.

24. Novel Replisome-Associated Proteins at Cellular Replication Forks in EBV-Transformed B Lymphocytes

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Background: The most common lymphomas in HIV-infected individuals include Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL), both derived from B lymphocytes. Up to 50% of BL and nearly all immunoblastic DLBCL are Epstein-Barr virus (EBV)-positive. The pathogenesis of such HIV-associated lymphomas is multifactorial including impaired immune surveillance and EBV infection. In transformed B cells, EBV successfully overcomes barriers to DNA replication (i.e. replication stress) resulting in sustained cell proliferation. To understand how EBV overcomes replication stress, we investigated the composition of proteins associated with the replication machinery at cellular DNA replication forks.

Methods: We examined replication forks using isolation of Proteins on Nascent DNA (iPOND)-mass spectrometry in EBV-transformed B lymphocytes. We validated replisome-associated novel candidates by iPOND-western blotting and examined expression of 3 candidates in EBV-transformed and BL cell lines, in EBV-infected B blasts in the blood of immunocompromised transplant recipients, and in primary B cells newly-infected with EBV. We also impaired the expression of the 3 candidates and investigated the effects on cell survival, cell cycle, and cell proliferation.

Results: We identified several cellular proteins at forks in EBV-transformed B lymphocytes; these proteins had previously not been described in replisomes of cancer or non-cancer cells. Of eight candidate replisome-associated proteins that we validated at replication forks in EBV-transformed and BL cell lines, three zinc finger proteins (ZFPs) were upregulated early in B cells newly-infected with EBV in culture as well as expressed at high levels in EBV-infected B blasts in the blood of immunocompromised transplant recipients. Expressed highly in S- and G2-phase cells, knockdown of each ZFP resulted in stalling of proliferating cells in the S-phase, cleavage of caspase 3, and cell death.

Conclusion: We report the identification of 3 cancer-associated proteins bound to the replication machinery in EBV-transformed and Burkitt lymphoma cells. They are upregulated in newly-infected B cells, expressed highly in proliferating cells, and contribute to cell survival and cell cycle progression. These proteins represent novel targets for intervention of EBV-positive HIV-AIDS lymphomas while simultaneously offering a window into how the replication machinery may be similarly altered in other cancers.

25. One-Minute Exposure to Nelfinavir Associated With Inhibition of KSHV Virion Production at 72 Hours

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Background: Present evidence suggests that the mode of transmission of KSHV is salivary. Whereas condoms may prevent HIV transmission, there is no comparable widely accepted intervention to prevent KSHV transmission—although it has been suggested that discouraging the use of saliva as a sexual lubricant may be helpful. An alternative and perhaps complementary approach would be an intervention to inhibit or diminish KSHV salivary shedding. Previous investigators have demonstrated that viral shedding can be substantially inhibited with valganciclovir[1]. However, systemic valganciclovir may lead to pancytopenia. Gantt et al. reported that nelfinavir, an anti-retroviral protease inhibitor, inhibited KSHV shedding by cells in tissue culture with an EC_{50} of 7.4 µM (3.5 times more potent than ganciclovir)[2]. Systemic nelfinavir often leads to diarrhea. Since the site of viral shedding, the oral mucosa, is readily accessible, we hypothesize that a local antiviral formulation might inhibit shedding with minimal systemic exposure. Local antiviral drug delivery might involve a mouthwash or "swish and spit" therapy, that would reduce KSHV shedding in the saliva, and salivary transmission to uninfected partners/family members.

Methods: We created a KSHV positive iSLK cell line. Virus harvested from a Vero cell line harboring the KSHV recombinant virus rKSHV.219[3] was used to infect the RTA inducible iSLK cell line[4]. rKSHV.219 expresses GFP constitutively and upon lytic induction expresses RFP driven by the PAN promoter. The established iSLK cell line (5r219) can be induced for lytic induction using 1 µg/ml of doxycycline (Fig. 1). After 1 hr induction, the cells were treated with 1 mM nelfinavir mesylate for 1 min or 5 min. The drug was removed, and the cells were incubated in medium

Figure 1. KSHV 5r219 cells express GFP and RFP upon lytic induction.

Figure 2. KSHV inhibition with short duration NFV exposure.

containing only doxycycline. The cell culture supernatants were harvested at 72 h and viral genomes quantified using qPCR assays. Intracellular nelfinavir concentrations were also measured using liquid chromatography with tandem mass spectrometry over the range of 8.4-4190 ng/mL. Concentrations were normalized to a reported value of ng/million cells. Cell viability was determined using the CellTiter-Glo assay.

Results: We investigated the anti-viral effects of brief exposures such as might be achieved with a mouth rinse. Exposure to nelfinavir concentrations of 1 mM for 5 min or 1 min led to a 90% reduction in virion DNA in culture supernatant at 72 hours (Fig. 2). There was no significant cytotoxicity. Intracellular nelfinavir was detected in both exposure times with concentrations after 1 min exposure being > 3 µg/million cells for up to 48 hours post-treatment.

Conclusion: Brief exposure to nelfinavir led to sustained intracellular drug concentrations and inhibition of KSHV virion release without toxicity. Further investigation of a mouthwash-like product designed for integration into daily personal hygiene practices for seropositive individuals is warranted.
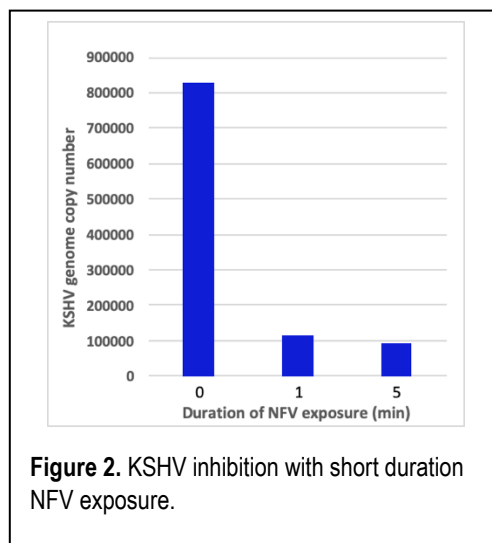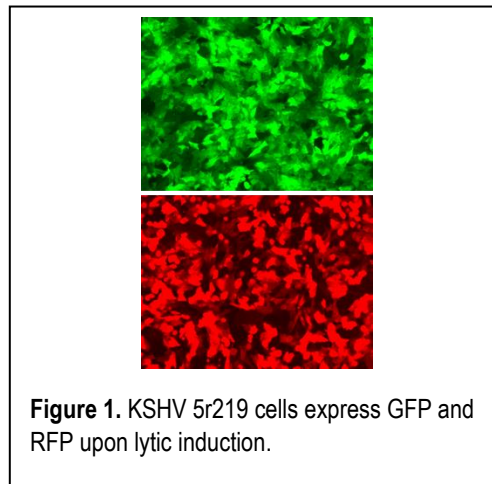
26. Pharmacological Activation of the Integrated Stress Response Pathway Leads to EBV Lytic Gene Expression

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Background: There are four stress kinases that respond to distinct stress stimuli and phosphorylate the alpha subunit of eukaryotic translation initiation factor 2 (eIF2α) (1). This convergent pathway is referred to as the integrated stress response (ISR) and the kinases that phosphorylate eIF2α are PKR-like ER kinase (PERK), double-stranded RNA-dependent protein kinase (PKR), heme-regulated eIF2α kinase (HRI), and general control non-derepressible 2 kinase (GCN2). Previously we have reported that the unfolded protein response pathway activates the PERK branch of the ISR and EBV lytic gene expression (2-3). We investigated whether activation of each of the other stress kinases would also activate EBV lytic infection.

Methods: The Akata Burkitt lymphoma cell line and an engineered derivative cell line (BX1-Akata) carrying a recombinant EBV that constitutively expresses a green fluorescent protein (GFP) were used. CCT020312 was used to activate PERK, arsenite was used to activate HRI, poly (I:C) was nucleofected into cells to activate PKR, and halofuginone was used to activate GCN2 (1, 4). qRT-PCR was performed for quantification of lytic gene transcripts and fluorescence microscopy was used to determine the number of lytic cells expressing GFP.
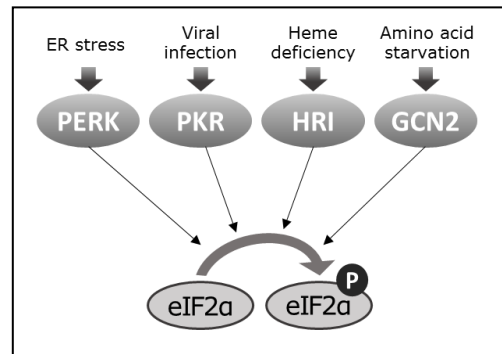
Results: Pharmacological activation of each of stress response kinases in Akata cells induced EBV lytic gene expression as assessed by increased EBV Zta, Bmrf1 and gp350 RNA levels in a time-dependent manner and GFP expression in BX1-Akata cells.

Conclusion: We have shown that all four branches of the ISR lead to activation of EBV lytic gene expression. Each of these ISR branches may offer interesting opportunities for pharmacologic interventions that stimulate EBV lytic viral gene expression and ultimately contribute to a targeted therapeutic strategy for treating patients with EBV-associated malignancies.

References:

1. Pakos-Zebrucka K et al. (2016) The integrated stress response. *EMBO Rep*
2. Shirley C et al. (2011) Bortezomib induction of C/EBPβ mediates Epstein-Barr virus lytic activation in Burkitt lymphoma. *Blood*
3. Lee J et al. (2019) Pharmacologic Activation of Lytic Epstein-Barr Virus Gene Expression Without Virion Production. *Journal of Virology*
4. De Gassart A et al. (2016) An inhibitor of HIV-1 protease modulates constitutive eIF2alpha dephosphorylation to trigger a specific integrated stress response. *Proc Natl Acad Sci U S A*

27. Prognostic Biomarkers for AIDS-Related Non-Hodgkin Lymphoma: Measurement of Biomarkers of Microbial Translocation in the AMC-034 Study

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Background: AIDS-related non-Hodgkin lymphoma (ARL) is the most common cancer in HIV infected individuals in the United States and other countries in which HIV-positive persons have access to effective combination anti-retroviral therapy (cART). While, the incidence of AIDS, and ARL, has decreased with cART, ARL is still a significant clinical problem, accounting for 23-30% of AIDS-related deaths in developed countries. Currently, LDH and/or IPI scores are the only biomarkers used routinely to assess NHL prognosis; therefore, the development of additional, better prognostic biomarkers is of great clinical importance, as common techniques for assessing NHL prognosis (i.e., positron emission tomography [PET]) are costly, and have significant limitations when used in HIV-infected patients. Therefore, identifying a group of molecules that efficiently provide prognostic information for ARLs is of great relevance and may provide useful tools for clinicians. In prior work, we showed that pre-treatment, post-diagnosis plasma levels of some cytokines, including IL-6, IL-10 and CXCL13, have the potential to serve as indicators of response to treatment and survival in ARL. In this study, we examined novel prognostic biomarkers for response to treatment and/or survival in persons with ARL, including biomarkers of microbial translocation and inflammation.

Methods: We quantified plasma levels of biomarkers of microbial translocation and inflammation (sCD14, LBP, FABP2, EndoCab, IL-18, MCP1, sCD163, IP-10/CXCL10, TARC/CCL17, TNFα, BAFF/BLyS, sTNFR2, sCD44 and sIL2Rα) by multiplexed immunometric assays (Luminex) in plasma samples obtained from ARL patients enrolled in an AMC trial comparing infusional combination chemotherapy (EPOCH: etoposide, vincristine doxorubicin, cyclophosphamide and prednisone) with concurrent or sequential rituximab (AMC protocol #034). Plasma was collected prior to the initiation of therapy (n=59), as well as after treatment initiation (n=29).

Results: Several of the microbial translation biomarkers and B-cell stimulatory cytokines/chemokines that we measured were seen to decrease significantly after treatment with EPOCH and Rituximab, including: sCD14, sCD25, sTNFR2, IP10 (CXCL10) and TNF-alpha. Moreover, pre-treatment plasma levels of Endocab IgM levels trended higher, and IL-18 levels lower, in those who showed a complete response to therapy, when compared to partial/non-responders. Elevated Endocab IgM is associated with decreased microbial translocation, and lower IL-18 levels with a relatively lower level of systemic inflammation. Moreover, we observed that pre-treatment plasma levels of sCD14, sCD25, sTNFRII and EndoCab IgM were associated with overall survival, and that pre-treatment levels of sCD25, sTNFRII, IL-18 and EndoCab IgM were also associated with progression-free survival.

Conclusion: This suggests that ARL patients who responded to therapy in the AMC-034 study had lower pre-treatment levels inflammation and microbial translocation than those who did not respond optimally. Additionally, baseline assessment of several biomarkers provided prognostic information on overall or progression-free survival in this study.

28. **Protein Inhibitor of Activated STAT1 (PIAS1) Inhibits IRF8 Activation of Epstein-Barr Virus Lytic Gene Expression**

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Background: Epstein-Barr virus (EBV), a major human oncogenic pathogen, establishes life-long persistent infections. In latently infected B lymphocytes, the virus persists as an episome in the nucleus. Periodic reactivation of latent virus is controlled by both viral and cellular factors, while the dynamic regulation of viral latency and reactivation by host factors remains incompletely understood.

Method: Chromatin-immunoprecipitation assay and luciferase reporter assay were used to identify the promoter binding and activation. The protein-protein interaction was detected using immunoprecipitation assay. RT-qPCR was used to detect lytic gene expression in EBV-positive epithelial cells transfected with IRF8/PU.1.

Results: We show that IRF8 directly binds to EBV genome and regulates EBV lytic gene expression in synergy with PU.1 and EBV transactivator RTA. Furthermore, our study reveals that PIAS1 antagonizes IRF8/PU.1-mediated lytic gene activation through binding to and inhibiting IRF8.

Conclusion: Our results establish IRF8 as a transcriptional activator for an EBV lytic gene and define PIAS1 as an inhibitor of IRF8 to maintain viral latency.

29. Regulation of Immune Surface Molecules by CDK4/6 Inhibitors in Gammaherpesvirus-Infected Tumor Cells

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Background: Cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors have recently been approved for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. Kaposi sarcoma-associated herpesvirus (KSHV), the cause of several tumors including primary effusion lymphoma (PEL), potently downregulates immune surface molecules, such as major histocompatibility complex class I (MHC-I), ICAM-I, and B7-2; this enables the virus to evade T cell and natural killer (NK) cell immunity. It also facilitates oncogenesis by KSHV and presents a challenge for its therapy. Our group recently reported that pomalidomide and related drugs could prevent KSHV-induced downregulation of these markers (Davis DA, *Oncotarget*, 2017). A recent study reported that cyclin D2 (function by forming complex with CDK4/6 to regulate G1/S transition) was required for survival of primary effusion lymphoma (PEL) cells (Manzano M et al., *Nat. Communcations*, 2018). CDK4/6 inhibitors have recently been reported to reverse MHC-I downregulation in a mouse model of breast cancer (Goel S et al., *Nature*, 2017). Here, we explored the ability of three FDA approved CDK4/6 inhibitors, abemaciclib, palbociclib, and ribociclib, to upregulate expression of MHC-I, PD-L1, ICAM-1, and B7-2 on the surface of lymphomas caused by KSHV and Epstein-Barr virus (EBV).

Methods: PEL and Burkitt lymphoma cell lines (JSC-1 , BCBL-1, Akata and Raji) were treated with inhibitors for 3 days and the number of viable cells and surface protein expression assessed. The CellTiter-Glo® Luminescent Cell Viability Assay was utilized to determine the viability of the cells in response of CDK4/6 inhibitor treatment. For induction of lytic infection, butyrate was added. Flow cytometry was used to measure the expression of surface molecules in response to CDK4/6 inhibitors treatment.

Results: CDK4/6 inhibitors inhibited cell growth in PEL cell lines including JSC-1 (KSHV+/EBV+) and BCBL-1 (KSHV+) cell lines. A similar inhibitory effect was observed for two EBV-positive Burkitt's lymphoma cell lines: Akata and Raji. Pretreatment with CDK4/6 inhibitors variously increased MHC-I surface expression during latent infection in all the test cell lines. It also prevented the downregulation of MHC-I surface expression during lytic replication in KSHV-infected cells to varying degrees. Also, the CDK4/6 inhibitors increased surface expression of PD-L1, ICAM-1 and B7-2 to different degrees in all cell lines tested.

Conclusion: Besides the direct inhibitory effect on the tumor cell growth, CDK4/6 inhibitors enhanced expression of MHC-I and the co-stimulatory molecules, ICAM-1 and B7-2 in KSHV and EBV-induced lymphoma lines. This activity can potentially thwart virus-induced immune evasion and enhance NK and cytotoxic T cell killing of the tumors. These effects, plus the direct toxicity, provide a rationale for the use of these drugs in these tumors. However, the enhancement of PD-L1 expression may reduce T cell immunity, suggesting that the drugs may be best used in combination with anti-PD-1 or anti-PD-L1 antibodies.

30.   Restoration of T-Cell and NK-Cell Recognition of Primary Effusion Lymphoma by Pomalidamide

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Background: Primary effusion lymphoma (PEL) is an aggressive non-Hodgkin's lymphoma caused by Kaposi's sarcoma-associated herpesvirus (KSHV) that develops primarily in patients with AIDS. KSHV uses various immune evasion strategies to avoid the recognition of infected cells by the host immune system. One is by downregulating various immune markers on the surface of infected cells. We previously found that pomalidamide (Pom), an FDA-approved immunomodulatory drug, can increase the surface expression of MHCI, ICAM-1, and B7-2, immune markers involved in the activation of both T-cells and natural killer (NK) cells, on the surface of PEL cell lines. Most of Pom's cellular activities, such as cytokine regulation and direct cytotoxicity of tumors, are attributed to the degradation and/or downregulation of cellular transcription factors IKZF1, IKZF3, CK1α, IRF4, and cMyc when Pom binds to its cellular target cereblon, a cellular E3 ubiquitin ligase. Here, we sought to understand the mechanism by which Pom increases the immune markers as well as determine whether these increases lead to enhanced recognition of PEL cells by the T-cells and NK-cells.

Methods: To study the functional consequence of Pom-induced increases in ICAM-1 and B7-2, we performed a T-cell activation assay using a Jurkat T-cell line engineered to express luciferase under the IL-2 promoter (IL2-Jurkat) as effector cells and performed NK-mediated cytotoxicity assay using YTS NK cell line as the effector cells. To study the mechanism of Pom-induced increase in surface markers, we generated Pom-resistant (PomR) cells *in vitro* by culturing a PEL cell line, BCBL-1, in increasing concentrations of Pom. We also used a small molecule BET inhibitor JQ-1 to independently inhibit the level of IKZF1, IRF4, and cMyc to study the role of these factors in the increase of immune surface markers.

Results: We compared the levels of ICAM-1 and B7-2 in PEL lines, EBV-infected Burkitt's lymphoma cell lines, and a virus-negative lymphoma cell line and found that the surface levels of these markers are drastically reduced in PEL lines compared to other lymphoma lines. Consistent with this observation, we also found that the PEL lines show the lowest level of T-cell activation. Upon treatment with Pom, the PEL cell lines showed an increase in their ability to activate both the T-cells and NK-cells. These increases could be prevented by blocking ICAM-1 and/or B7-2 on the PEL cell surface suggesting that both ICAM-1 and B7-2 are important for T-cell immunity against PELs. The PomR cells expressed 85% lower level of cereblon and only show a minor decrease in IRF4 and cMyc upon Pom-treatment relative to wild type (WT) PELs. Pom no longer upregulated ICAM-1 and B7-2 on the surface of PomR cells nor did it increase T-cell and NK-cell activation. Further, inhibiting Pom-cereblon downstream targets IKZF1, IRF4, and cMyc using JQ-1 also did not change the surface expression of ICAM-1 or B7-2.

Conclusion: Our data indicate that Pom is able to restore both T-cell and NK-cell recognition of PEL cells by raising the levels of ICAM-1 and B7-2 and thus, provide a rationale for the clinical use of Pom and related immunomodulatory drugs in treating PELs and potentially other KSHV-associated tumors. The increases in these markers are dependent on Pom's interaction with cereblon but seem to be independent of Pom-cereblon downstream targets IKZF-1, IRF4, and cMyc. We are currently exploring whether these increases are mediated by changes in cytokines known to be regulated by Pom or MARCH proteins that are involved in degradation of these surface markers.

31. **Salivary Shedding, Viremia, and Seroprevalence of Kaposi´s Sarcoma-Associated Herpes Virus (KSHV/ HHV-8) Among a Cohort of Men Who Have Sex With Men and Transgender Women From Argentina Who Are Infected or at a High Risk of HIV/AIDS**

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Background: Kaposi´s sarcoma remains as one of the most frequent viral cancers among HIV-infected individuals in Latin America including Argentina. However data on Kaposi's sarcoma associated herpesvirus (KSHV/ HHV-8) is scarce in this setting. Men who have sex with men (MSM) and transgender women (TGW) are the populations mostly affected by HIV/ AIDS in Argentina. As part of a project studying virally induced AIDS-malignancies, we aim to study KSHV infection and associated factors within a cohort of people with or at high risk of HIV/AIDS in Argentina. Baseline data is presented.

Methods: MSM and TGW were recruited at Fundación Huésped between April 2018 and May 2019. All patients signed informed consent prior to study procedures. Samples derived from blood and saliva were collected and stored at -70°C, medical information was recorded. DNA from whole blood and saliva samples were extracted using QIAamp DNA Mini Kit (QIAGEN) and PCR reactions were performed. KSHV serology was done by indirect immunofluorescence assay.

Results: Patients recruited: 56 MSM (49 HIV+) and 10 TGW (6 HIV+). Median age was 36 years for MSM and 28 for TGW. Countries of birth for the participants were Argentina (n=54), Peru (n=4), Venezuela and Colombia (n=3; each) and Paraguay (n=2). All TGW and 7 MSM were current or past sexual workers. No patient ever received blood transfusions, two MSM used intravenous drugs in the past, 35 participants used non-intravenous drugs, 16 used stimulants and 37 ever used tobacco. Among HIV+ participants, median CD4 cell count was 714 cells/ul (interquartile range: 458- 966). One patient had previous Kaposi´s sarcoma and no patient had active clinical disease. Serological analysis showed that 76% of the population was infected with KSHV (90% of the TGW and 69% of the MSM). KSHV was detected in 34% of the saliva samples (6/10 TGW and 16/55 MSM; 18/22 HIV+) and in 21% of whole blood samples (4/10 TGW and 8/56 MSM; 10/55 HIV+). In seven patients KSHV was detected in both blood and saliva. Use of non-intravenous drugs and alcohol consumption were associated with positive serology (p=0.020 and 0.018, respectively).

Conclusion: Prevalence of KSHV infection was high among the studied population. Seroprevalence was 76%. Viral mucosal shedding was higher than viremia. TGW have a very high frequency of KSHV-infection (90%), and a tendency to higher salivary shedding and viremia than MSM. This study is expected to inform public health policies and to help building KS prevention strategies.

32. Clinical Characteristics of Pulmonary Kaposi's Sarcoma and Pulmonary TB and Diagnostic Performance of Xpert MTB/RIF in AIDS-Associated Kaposi's Sarcoma Patients in Zimbabwe

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Background: Pulmonary Kaposi's sarcoma (pKS) is a common presentation of visceral KS. Diagnosis of pKS in African settings is difficult because of overlapping clinical and radiographic findings with common lung infections such as bacterial pneumonia and pulmonary tuberculosis (pTB). Since chemotherapy for AIDS-KS could increase susceptibility to infection, early identification and treatment of pTB could improve KS treatment outcomes in African settings where there is a high burden of both pTB and AIDS-KS. However, the performance of modern molecular methods for pTB diagnosis has not been investigated in AIDS-KS where the presence of pKS could affect pTB diagnosis. We investigated the prevalence and clinical characteristics of pKS, pTB and non-TB pneumonia (NTBP) along with the diagnostic performance of Xpert MTB/RIF for TB screening among AIDS-KS patients in Zimbabwe.

Methods: Prospective cohort study of adult patients presenting for initial evaluation of KS in Harare, Zimbabwe. Participants were evaluated by clinical symptoms, chest radiography, spirometry, sputum collection and bronchoscopy with bronchoalveolar lavage (BAL). Cutaneous KS was confirmed by histological findings of KS on skin biopsy; pKS was defined as visualization of endobronchial lesions consistent with KS. pTB was defined as either a positive MGIT culture of sputum or BAL, or a positive BAL Xpert MTB/RIF. NTBP was defined as an infiltrate on chest radiography (CXR), detection of a pathogenic bacteria or fungus, and one clinical symptom of infection. Categorical variables were compared between cases and controls by Fisher's exact test with α=0.05. Point estimates were expressed with 95% confidence intervals (CI). **Results:** AIDS-KS was confirmed by skin biopsy in 172/202 (85%) participants. Among confirmed AIDS-KS cases the prevalence of pKS was 64% (CI 57-72%). The prevalence of pTB and NTBP was 10% (CI 5-14%) and 13% (CI 8-18%), respectively. The presence of any cough, fever, night sweats or weight loss was not different between pTB and non-TB cases (47% vs 52%; p=0.8). Abnormal chest radiography was common in patients with pKS, however there was no single abnormal radiographic finding that was predictive of pKS. Six-month mortality was not different between pKS and non-pKS cases (17% vs 13%, p=0.45), or between pTB and non-TB cases (18% vs 17%, p=1.0).

Performance of sputum Xpert MTB/RIF (Table 1): Sensitivity 24% (CI 7-50%); Specificity 100% (CI 98-100%); Positive Predictive Value 100% (CI 40-100%); Negative Predictive Value 92% (CI 87-96%).

Table 1. Diagnostic performance of clinical pTB screening with Xpert MTB/RIF		Pulmonary TB		
		Yes	No	
Sputum Xpert MTB/RIF	Positive	4	0	4
	Negative	13	155	168
		17	155	172

Conclusion: There was a high prevalence of pKS among Zimbabwean AIDS-KS patients. Clinical symptoms alone did not distinguish between pKS, pTB and NTBP. Abnormal chest radiography is common in patients with pKS, however many features overlap with pulmonary infections. There should be a high suspicion for pKS in AIDS-KS patients with any respiratory symptom or abnormal chest radiographic findings. Better screening tools are needed to identify pKS and distinguish pKS from pTB and NTBP.

33. Anti-KSHV and Anti-EBV Oral IgA Antibodies in HIV-Infected and Uninfected Cameroonians

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Background: In sub-Saharan Africa, EBV and KSHV infections are highly prevalent; both are important viral causes of cancer. Systemic humoral responses to KSHV have been extensively studied, however, antibody responses at mucosal surfaces in the oral cavity have been investigated for EBV, but not KSHV. Because both viruses are transmitted by oral fluids, it is imperative to understand oral immunity, and correlates of viral control in the oral cavity.

Methods: We developed a multiplex assay measuring IgA against 63 KSHV-encoded proteins, as well as EBV-encoded EBNA-1, EA(D) and VCA. Samples from individuals without KS enrolled in a KS case-control study in Cameroon were tested to investigate the relationships between anti-KSHV and anti-EBV IgA in oral fluids, serum anti-KSHV IgG, and KSHV/EBV DNA viral load (VL) in blood and oral fluids, as well as HIV infection and socio-demographic factors.

Results: We examined 833 control individuals. Median age was 39 years; 57% were men, 64% were HIV infected. KSHV was detected in 8% of blood and 23% of saliva samples; EBV, in 83% and 87% of the samples, respectively. Proportion of IgA responders above background varied by antigen from ~3% to 46% (mean: 11%), e.g. for KSHV: K8.1 60%, ORF73 25%; for EBV: EBNA-1 5%, EA(D) 4%, VCA 19%.

Overall, anti-KSHV IgA levels in oral fluids were higher in females and lower in HIV infected persons, while anti-EBV IgA were higher in HIV infected participants and decreased very slightly with age. Anti-KSHV oral IgA levels were lower, irrespectively of HIV infection, in individuals who shed KSHV or had higher oral KSHV VL; conversely, IgA were higher in those with detectable KSHV in blood. Anti-EBV IgA levels were also higher in those with detectable EBV in blood, only if HIV uninfected.

Conclusion: In Cameroonian adults with and without HIV, anti-KSHV and anti-EBV oral IgA were detectable; the proportion varied widely by antigen. Lower anti-KSHV IgA were associated with oral KSHV detection and viral load. The relationships between oral IgA levels, oral and blood VL, and HIV infection were different for KSHV and EBV. This suggests that differences in mucosal as well as systemic immune control of the two viruses might contribute to differing epidemiologic and pathogenetic mechanisms operating in this region.

34. Assessment of Plasma DNA Molecular Markers From Newly Diagnosed HIV(+) Lymphoma Patients in South Africa: A Pilot Study

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Background: Diagnostic delays for Hodgkin (HL) and non-Hodgkin lymphoma (NHL) in people living with HIV (PLWH) is common. This is partly related to potential confounding diagnoses, such as co-infections, that might explain similar signs/symptoms. This is especially true in South Africa (SA) where the most common cause of death in PLWH is TB[1]. Many patients with symptoms that might reflect either TB or lymphoma are empirically treated for TB, and only after treatment failure are they referred for excisional biopsy to exclude lymphoma. We are interested in developing a non-invasive blood test ("liquid biopsy") that might facilitate lymphoma diagnoses in PLWH. Our previous work showed that patients with EBV (+) HL virtually always have detectable plasma EBV DNA[2]. Similarly, PLWH with B-cell lymphoma typically have detectable (tumor-derived) clonal immunoglobulin (cIg) in plasma cell-free DNA (cfDNA)[3]. Since virtually all HL and approximately 50% of NHL in PLWH are EBV-associated[4], we hypothesize that EBV DNA and/or cIg may be useful plasma biomarkers in PLWH. To assess the feasibility of studying such molecular markers in plasma DNA in PLWH, we analyzed plasma from PLWH with newly diagnosed lymphoma from SA.

Methods: After approval from domestic and SA IRBs, and participant informed consent, we collected plasma using specialized collection tubes and processed the specimens locally using cfDNA-optimized protocols. Processed plasma was shipped to Baltimore for molecular analyses took place. cfDNA was extracted, and cfDNA integrity was evaluated by high-sensitivity electrophoresis. EBV copy number was determined by qPCR targeting viral internal repeats[2]. cIg was evaluated by next-generation sequencing (NGS) of the *IGH* gene. Somatic mutations were also assessed by NGS to confirm presence of tumor DNA.

Results: Plasma was collected and cfDNA was isolated from 9 SA patients with B-cell lymphoma (4 HL; 5 NHL). cfDNA integrity and recovery was significantly higher in the 9 SA specimens when compared to a set of archived frozen plasma (N=10) not optimized for cfDNA. This was true by cfDNA fragment size (median 131 vs. 161 bp, p<0.0001), fraction cfDNA of all recovered DNA (median 85.6% vs. 56.7%, p=0.003) and cell-free genomic equivalents (GE) (median 10608 GE/mL vs. 1020 GE/mL, p=0.008). EBV DNA was detected in all 6 patients with EBV(+) lymphoma (median 4126 copies/mL), but was below threshold for all 3 with EBV(-) lymphoma (median 0.4 copies/mL). Overall, 5 of 9 plasma specimens showed cIg rearrangements, while 4 did not demonstrate dominant clones. Lastly, somatic mutation NGS showed high sequence yield and quality control metrics comparable to genomic DNA isolated from fresh tissue.

Conclusion: In this small series, we demonstrate that cfDNA recovery from optimally collected and processed specimens results in high quality and quantity cfDNA sufficient for a number of molecular and NGS analyses. Our preliminary data show complete plasma EBV concordance with tumor EBV status, and cIg detection in plasma in >50% of the patients. Somatic mutation panel analysis shows high quality control metrics similar to fresh genomic DNA. While our studies are ongoing, these data show promise of evaluating plasma DNA molecular markers for the diagnosis of lymphoma in PLWH.

35. Surveillance of Rhesus Macaque Oral Tissues by qPCR and Immunohistochemistry Identifying Gammaherpesvirus Infection Sites Contributing to Transmission

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Background: Gammaherpesviruses are a clinically significant cause of cancer and are primarily transmitted via saliva. However, the specific sites of viral replication in oral tissues resulting in salivary shedding are poorly understood. Rhesus macaques (RM) are naturally infected with three gammaherpesviruses: retroperitoneal fibromatosis herpesvirus (RFHV), an ortholog of KSHV, rhesus lymphocryptovirus (RLCV), closely related to EBV, and rhesus rhadinovirus (RRV). Rhesus macaques have been used as models of gammaherpesvirus-associated malignancies in the context of SHIV/SIV infection and offer an opportunity to study oral biology of gammaherpesviruses in greater detail.

Methods: Oral fluid and oral tissues from 30 RM experimentally infected with SIV or not were collected during necropsy. These included buccal and gingival tissue, parotid, submandibular and sublingual salivary glands, submandibular lymph nodes, adenoid, palatine and inguinal tonsil, soft palate and tongue. DNA was extracted and tested by qPCR for RRV, RLCV, and RFHV viral load. *In situ* hybridization targeting viral DNA was performed, for all 3 viruses, in all tissue types and highly positive tissues were used to phenotype the cells harboring viral DNA.

Results: Rhesus gammaherpesviruses were detected in the oral fluid and oral tissues of all 30 animals examined; many were positive for more than one virus. By qPCR, the highest levels of RFHV were identified in gingiva, tongue, and submandibular lymph nodes while the highest levels of RLCV and RRV were detected in adenoid and palatine tonsil. Using ISH, most infection events for all three viruses were visualized in lymphoid tissues including lymph node and palatine tonsil. Multiplexing ISH with antibody-based phenotyping revealed a broad range of infected cell types including B- and T-lymphocytes, fibroblasts, epithelial cells, and NK-cells. Certain infected cell types, especially for RFHV, remain unidentified and phenotyping experiments are ongoing.

Conclusion: This is the first study examining RRV, RLCV, and RFHV viral load in rhesus oral tissues and oral fluid and may provide insights into human gammaherpesvirus biology within the oral compartment.

36. The EBV Noncoding RNA EBER1 Carries Out a Conserved In Vivo Function to Promote Hematogenous Dissemination of Infected B Cells

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Background: The ability of gammaherpesviruses to establish lifelong latency in circulating B cells is critical to chronic infection and tumorigenesis. However, the precise determinants that mediate *in vivo* latency remain unclear. Like EBV and KSHV, murine gammaherpesvirus 68 (MHV68, MuHV-4, ɣHV68) establishes lifelong latency in B cells and is associated with the development of B cell lymphoma, providing a robust *in vivo* infection model to define specific determinants of infection and disease. Using this system we have previously demonstrated a critical *in vivo* role for the viral noncoding RNA *TMER4* in MHV68 dissemination and establishment of peripheral latency. Although the EBV-encoded RNAs 1 and 2 (*EBER1* and *EBER2*) are among the first noncoding RNAs ever identified, their biological roles during *in vivo* infection remain unknown. Here we defined the *TMER4* species that is required for function and examined whether EBV *EBER1* provides functional conservation of *TMER4* activity.

Methods: A refined series of MHV68 recombinant viruses were generated. Viruses were tested in wild-type mice *in vivo*, and parameters of dissemination and latency were examined using multiparametric flow cytometric analyses and limiting dilution nested PCR.

Results: Egress of infected B cells from the lung draining lymph node was blocked in the absence of *TMER4*, preventing hematogenous dissemination of virus-infected cells. A series of refined *TMER4* structural and processing mutant viruses revealed that the essential function of *TMER4* is carried out by a 155 nt intermediate RNA species rather than full-length *TMER4*. Further, replacement of *TMER4* with the Epstein-Barr virus noncoding RNA *EBER1* but not the related adenovirus VA RNA I (*VAI*) fully restored the attenuation of *TMER4*-deficient viruses.

Conclusion: Together, these findings demonstrate that MHV68 *TMER4* and EBV *EBER1* carry out a conserved function *in vivo* to promote hematogenous dissemination of infected B cells. This work provides new insight into the impact of viral noncoding RNAs *in vivo*, and identifies a potential new target for intervention to prevent gammaherpesvirus infection and disease.

37.   The Role of Wilms' Tumor 1 (WT1) in Kaposi's Sarcoma Herpesvirus Oncogenesis

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Background: Kaposi Sarcoma (KS), caused by KSHV, is the most common malignancy globally in people living with HIV (PLWH). It occurs predominantly in sub-Saharan Africa where it is associated with high mortality after diagnosis. Wilms' Tumor 1 (WT1) is a promising cancer antigen for which therapeutic vaccines have demonstrated benefit in patients with leukemias and solid tumors, and it has served as a prognostic marker in patients with myelodysplastic syndromes and leukemias. Different isoforms of WT1 exist and are thought to have diverging functions as either tumor suppressors or oncogenes in leukemias and in solid tumors.

Methods: We examined WT1 expression by immunohistochemistry (IHC) in biopsies of KS tumors from 3 different cohorts. We utilized HALO analysis software to quantitate WT1 expression in our expanded cohorts. The first cohort consisted of 11 KS cases (both HIV associated and non-HIV associated) from WCM, the second cohort consisted of 23 KS cases of predominantly HIV associated KS from Kampala, Uganda, and the third cohort consisted of 157 cases of advanced HIV associated KS from a large AIDS clinical trial AMC066/A5263. We investigated WT1 expression *in-vitro* in a KSHV infection model of endothelial cells. We also examined target gene expression in these models with and without WT1 in the setting of WT1 lentiviral shRNA.

Results: WT1 overexpression was noted in 9/11 cases from WCM. A second cohort analysis of 23 cases from Kampala, Uganda of predominantly HIV associated KS, demonstrated WT1 overexpression, 2+--3+ in 100% of all plaques and nodules in 21 of 23 cases. In our largest cohort from ACTG AMC066/A5263, we found WT1 overexpression in the majority of cases, 2+--3+ (1+--3+ scale) in 56.7% or 89 of the 157 cases examined. 65.5% of KS tumors with histopathologic stages of plaques and nodules had 2+--3+WT1 staining. Moreover, we found a positive correlation between LANA and WT1 with a correlation coefficient of r=0.589, examined in our largest cohort from AMC066. *In-vitro*, WT1 was upregulated in endothelial and 293T cells upon *de novo* KSHV infection. In successful knockdown of WT1 using lentiviral WT1 shRNA *in vitro* in the setting of KSHV infection, in endothelial and 293T cell lines, we noted that pAKT and BCL-2 expression was downregulated.

Conclusion: We have found the majority of KS cases have WT1 overexpression, particularly in our expanded cohorts of HIV/AIDS associated KS, correlated with increased histopathologic stage and LANA staining. KSHV infection increases WT1 expression *in-vitro* in endothelial cell culture models, consistent with a major 'tumorigenic' isoform, cugWT1. Knockdown of WT1 in KSHV infection leads to downregulation of p-AKT and BCL-2 consistent with a feedback loop mechanism, suggesting a role for the PI3K/AKT pathway in regulating WT1 function and downstream BCL-2 target gene expression to promote tumorigenesis. In KS cases that overexpress this protein, WT1 may be a promising target as a biomarker and immunotherapy.

38. Transcriptomic and Proteomic Profiling of HIV Seropositive and Seronegative Diffuse Large B-Cell Lymphoma

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Background: Among people living with HIV, 25 to 40% will develop a malignancy, and approximately 10% will develop non-Hodgkin's lymphoma (NHL). While antiretroviral therapy (ART) reduced the incidence of NHL in HIV seropositive patients, there is still a 9-fold increased risk of NHL, particularly diffuse large B-cell lymphoma (DLBCL), compared to the general population. This elevated prevalence suggests additional factors beyond a compromised immune system contribute to the development of DLBCL in the HIV setting. Evidence in the literature points to the strong possibility that ART affects other molecular pathways and may contribute to the development of DLBCL. We analyzed RNA and protein expression in HIV seropositive and seronegative DLBCL formalin-fixed paraffin-embedded tissues (FFPET). By comparing gene and protein expression between *de novo* DLBCL tissues from post-ART HIV seropositive and HIV seronegative patients, we will generate genomic and proteomic profiles of HIV-associated DLBCL to inform the potential mechanisms involved in the development of DLBCL in patients with an underlying HIV infection.

Methods: RNA was extracted from DLBCL FFPET samples with a minimum 80% tumor content that were pair-matched for sex, DLBCL subtype, and EBV status. RNA-sequencing (n = 3 per group) and Tandem mass tag mass spectrometry (TMT-MS) proteomics (n = 5 per group) studies were performed. After paired-end sequencing (150 cycles) on the Illumina HiSeq 3000, samples were demultiplexed and mapped to the human genome (GRCh37.75) prior to differential gene expression analysis with edgeR and gene set enrichment analysis. The JunctionSeq R package was used to determine alternative isoform usage between the two groups MS raw files processed with MaxQuant and differential analysis was performed with limma after data preprocessing. The use of human tissues and clinical data for this study was approved from the University of Arkansas for Medical Sciences Institutional Review Board in accordance with the Declaration of Helsinki.

Results: Within the differentially-expressed genes (65 up-regulated; 93 down-regulated; 158 total; $\log_2$ fold change > 2, FDR *P*-adj. < 0.1) in HIV seropositive DLBCL tumors compared to HIV seronegative DLBCL tumors, 45 were classified as HIV-interacting molecules according the HIV-1 human interaction database (ncbi.nlm.nih.gov) including VEGFA, CXCL12, TERT, and FOXP3. Alternative isoform usage was identified in 22 transcripts of the HIV seropositive associated tissues. Differential protein expression between the two groups identified 72 molecules ($\log_2$ fold change > 2, unadjusted *P* < 0.05, coverage = 7008 proteins).

Conclusion: In this pilot study, we compared gene and protein expression between DLBCL tissues from post-ART HIV seropositive and de novo HIV seronegative patients to yield a catalogue of molecules differentially expressed in HIV-related DLBCL. Investigation of these molecules suggests that the mechanism of DLBCL development may differ in patients with an underlying HIV infection. Follow-up studies are ongoing to validate these genomic and proteomic profiles. Elucidation of the pathways involved in the development of DLBCL in HIV seropositive patients could lead to novel targeted therapies for this at-risk population.

39. Triggering Innate Immunity Pathways During Herpesvirus Infection With 25-hydroxycholesterol

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Background: Kaposi's Sarcoma Herpesvirus (KSHV/HHV-8) expresses several viral products during latency and lytic replication cycle that block innate immune responses. It is therefore of interest to study antiviral approaches that can tip the balance for the host and help the host mount an effective immune response. Recently, we have described how 25-hydroxycholesterol (25HC), a derivative of cholesterol, can block KSHV *de novo* infection of primary endothelial cells (HUVEC) at a post-entry step and decreases viral gene expression of LANA and RTA. While we found that cholesterol-25-hydroxylase (CH25H), the enzyme that converts cholesterol to 25HC (and is interferon-inducible in macrophages), is not interferon-inducible in HUVEC, it is not known whether CH25H is interferon-inducible in human primary B cells. It was also unknown how 25HC inhibits KSHV infection and if it inhibits additional gammaherpesviruses.

Methods: To determine whether CH25H is interferon-inducible in B cells, we treated PBMCs with interferon-alpha, -beta, and -gamma and measured for CH25H mRNA expression by quantitative RT-PCR (qRT-PCR). And to test the antiviral effect of 25HC against Epstein-Barr Virus (EBV), we performed *de novo* infection of primary B cells and measured apoptosis using flow cytometry. We also measured viral transcripts using qRT-PCR. To characterize the pathways triggered by 25HC, we performed RNA sequencing of primary endothelial cells that have been treated with 25HC and *de novo* infected with KSHV. Validation was performed by qRT-PCR. Functional studies are currently underway using combinatorial siRNA knockdown of candidate target genes.

Results: CH25H mRNA levels increased in PBMCs in response to Type I interferons. We also found that 25HC increased apoptosis in EBV-infected cells and decreased the number of cells among the lymphoblastoid cell lines (LCLs). 25HC downregulated an RNA Pol III-transcribed EBV transcript, but not an RNA Pol II EBV transcript. We have found that type I interferon responsive genes, including several inflammatory cytokines and chemokines, were increased with 25HC treatment. Several pattern-recognition receptors, both cytoplasmic and membrane-bound, were also increased by 25HC treatment. On the other hand, KSHV viral gene expression was globally depressed in samples that were treated with 25HC.

Conclusion: CH25H is inducible in human PBMCs by Type I interferons. Exogenous 25HC rendered infected primary B cells unable to complete its EBV-induced transformation into LCLs. RNA-Seq data hints at activation of Type I interferon-related immune pathways by 25HC. Our studies aim to elucidate how we can augment these intrinsic antiviral responses in the host and, hopefully, pave the way for developing new therapeutic strategies for multiple viral infections.

40.   VDAP – Viral De Novo Assembly, Variant Discovery, and Annotation Pipeline

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Background: Double-stranded DNA viruses infect a wide range of hosts and, in humans specifically, are associated with numerous malignancies and significant mortality. Advances in next-generation sequence technologies make it possible to acquire high-coverage sequence data for individual viral species or populations. Numerous computational tools and analysis pipelines have been developed, yet as most of these tools are for command line use only and the analysis of these viruses is typically done on an ad-hoc basis, it is difficult for individual laboratories to reproduce the data and know what types of comparative analyses are feasible to perform across different studies. However, the availability of high-quality sequences and consistently called variants is essential to understand the effect viral genome diversity has on transmission, disease progression and viral evolution. In an effort to minimize the variability in the analysis of viral whole-genome data, we developed a pipeline with the aim of providing researchers with a roadmap to consistently produce consensus sequences and variant lists for downstream analyses.

Methods: Using previously published computational tools, we constructed a multi-step assembly pipeline for viral genomes named VDAP. The pipeline provides users with tools for quality control, genome assembly and SNP calling of paired-end short read data.

Results: We evaluated the effectiveness as well as the limitations of VDAP on three different datasets from Kaposi's sarcoma-associated herpesvirus (KSHV). VDAP delivers a suitable pipeline for generating *de novo* assemblies and identifying variants from viral short-read data.

Conclusion: In order for viral genomic data to be universally interpretable and comparable, certain steps in the viral genome assembly have to be performed consistently across studies. VDAP provides a publicly available and reproducible *de novo* assembly pipeline for viral genomes that allows to run a complete viral genome assembly and variant discovery pipeline in a single step, but also offers enough room for those familiar with the command line to fine tune or add individual steps.

41. Outcome Markers for ART-Treatment of Early-Diagnosed Epidemic Kaposi's Sarcoma

Owen Ngalamika[1], For Yue Tso[2,3], Salum Lidenge[2,3,4,6], Sody Munsaka[7], John T. West[3,8], and Charles Wood[2,3,8]

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Background: Early-diagnosed HIV-associated Kaposi's Sarcoma (EpKS) treated exclusively with anti-retroviral therapy (ART) can result in either KS remission (REM) or progression (PROG). Immunological biomarkers and/or immune responses against Kaposi's sarcoma-associated herpes virus (KSHV) associated with either outcomes are unknown.

Methods: Using flow cytometric techniques, we investigated the immunological markers associated with REM or PROG in a cohort of Zambian early-diagnosed HIV+ KS patients who were only on ART. We had a total of 22 participants, 12 were EpKS cases and 10 were non-KS HIV+ controls. Among the EpKS cases, 6 were male and 6 were female, while the 5 controls were male and 5 were female. The median age of the study participants was 41 (IQR 34-47). We compared the baseline and longitudinal changes in cellular immunophenotypes between patients who experienced good or poor responses to ART. In addition, we longitudinally detected and quantified cytokines and chemokines in plasma using cytometric bead arrays. Finally, we quantified KSHV neutralizing antibodies.

Results: The HIV-1 viral load was not significantly different at baseline and at time of remission or progression between REM and PROG individuals. At baseline, PD1$^+$ CD4 effector memory (T_{EM}) cells proportion of naïve CD8 T cells were significantly higher in REM compared to PROG individuals (0.22 vs 0.08; p=0.034) at baseline. At the time of remission or progression, PD1-positive CD8 T effector cells were significantly higher in REM than PROG individuals (0.25 vs 0.09; p=0.021). In addition, PD1$^+$ CD8 T_{EM} cells were significantly higher in REM than PROG individuals (0.57 vs 0.28; p=0.016) at the time of remission or progression. Consistent with this finding, the proportion of PD1$^+$ CD8 T_{EM} cells was significantly higher at baseline than at the time KS worsened in PROG individuals (0.41 vs 0.28; p=0.028). No significant deviation from baseline was detected in the same immunophenotype in REM individuals (0.64 vs 0.57; p=0.146). At follow-up, REM individuals also had a significantly higher proportion of PD1$^+$ CD4 T_{EM} cells than PROG individuals (0.40 vs 0.23; p=0.014). Furthermore,

We also observed that the plasma levels of the T cell chemoattractant chemokine IP-10 (CxCL-10) reduced in both groups and the controls upon treatment. However, there were no obvious differences in other cytokines among the groups. KSHV nAb were detected in all the study participants; however, no statistically significant difference in neutralization was evident between REM and PROG subjects nor was a temporal deviation from baseline nAb levels detected.

Conclusion: In contrast to expectations, high PD-1 expression, a potential checkpoint regulator of both CD8 and CD4 T cell subsets, was associated with remission in response to ART-only for early-diagnosed HIV+ KS patients. Hence, further studies will be needed to determine whether PD1 expression is useful in determining early-diagnosed EpKS patients that require ART alone or ART plus cancer chemotherapy at the time of diagnosis. Longitudinal reduction in the T cell chemoattractant IP-10 associated with disease progression for KS patients on ART was also observed. However, this may be related to the effect of ART on HIV disease.

42. Advancing a Holographic Approach for Point-of-Care Lymphoma Diagnostics in Botswana

Cesar M. Castro[1,2], Hyungsoon Im[1], Angela Marquard[1], Aliyah Sohani[3], Hakho Lee[1], Scott Dryden-Peterson[4,5], Bruce Chabner[2], and Ralph Weissleder[1,6]

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Background: HIV infection and aggressive lymphomas remain highly interconnected in sub-Saharan Africa. Longstanding pathology bottlenecks challenge timely and accurate lymphoma diagnoses. Under the auspices of the US National Cancer Institute, we developed a portable cancer diagnostic platform leveraging both holography for surface marker detection and cloud computing. While local proof-of-concept testing on clinical biopsies demonstrated outstanding diagnostic performance, we were motivated to further optimize our approach for facile, point-of-care performance for field testing in Botswana by lay healthcare personnel.

Methods: Given the small size of lymphocytes and need for intracellular detection (i.e. Ki-67), we developed a novel assay exploiting glass cell-capture technology along with a freeze-dried (lyophilized) antibody cocktail for long term storage and absent need for refrigeration. Moreover, to circumvent the need for continuous and reliable cellular data transmission for cloud computing-based diagnostic readouts, we sought to harness machine learning tactics to custom develop algorithms for on-device analytics. The optimized approach was tested on clinical specimens attained from patients with suspicious adenopathy concerning for Non-Hodgkin's Lymphoma. Recently, we launched the *Chedza* ("light") Study in Botswana to ascertain the diagnostic performance of our approach using fine needle aspirates procured from accessible superficial adenopathy.

Results: Our optimized platform comprised a portable, battery-powered device weighing 1.4 kilogram and costing ~ US $180 compared to >$1,000 with our previous smartphone-based iteration. A disposable microfluidic cartridge we developed equipped with functionalized antibody chemistry selectively captured B lymphocytes from fine-needle-aspirates. The holographic images generated were successfully used to train a computational neural network algorithm to effectively distinguish B cells from artifacts, debris, and noise. The algorithm successfully quantitated and measured lymphoma cells using clinically used markers. Small molecule chromogens conferred the ability to measure intracellular markers such as Ki-67 for proliferation. We showed that glass slides can be activated, lyophilized and used for immunocapture and subsequent analysis within a disposable kit format. In all, machine-learning driven readouts were generated in 5 minutes compared to 12 second readouts achieved using cloud computing and wireless data; yet readouts occurred entirely on device. In the US study, our diagnostic performance noted 91% sensitivity / 100% specificity and an 86% accuracy for distinguishing aggressive (actionable) from indolent lymphomas. Data from *Chedza* is currently being collected and any notable updates would be presented.

Conclusion: Our optimized diagnostic platform confers various advantages over conventional approaches for low resource countries. From the assay standpoint, more efficient use of expensive specialty reagents and expansion of shelf-life could be attained. Advantages of holography over immunocytology lie in its read-outs (holograms), much larger fields of view, higher throughout, and specialist-independence (trained algorithms obviate full reliance on skilled pathologists). Importantly, whether 12 seconds or 5 minutes, the timeliness of our readouts overcomes the almost invariable multi-month pathology delays in Sub-Saharan Africa. Prompt evaluation with judicious and accurate use of chemotherapy stockpiles could make inroads in this highly lethal HIV-associated malignancy.

43. Comparing Raman-Enhanced Spectroscopy (RESpect) Fiber-Optic Probe With Standard Raman Spectroscopy Fingerprints of Squamous Intraepithelial Lesions to Advance Point-of-Care Assessment

Melissa Agsalda-Garcia[1], Tiffany Shieh[1], Ryan Souza[1], Nicholas Loi[1], So Yung Choi[2], Eunjung Lim[2], Anupam Misra[3], Tayro Acosta-Maeda[3], Jeffrey Killeen[4], Cris Milne[5], and Bruce Shiramizu[1,5]

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Background: Screening and diagnosing anal squamous intraepithelial lesions (ASIL) potentially requires multiple visits with initial anal cytology screening and follow up biopsies with high resolution anoscopy (HRA). Amongst HIV-positive Native Hawaiian and other Pacific Islander men who have sex with men and transgender women, ASIL screening and diagnoses are challenging due to stigma and access to care. Use of standard laboratory Raman spectroscopy (RS) previously showed a range of fingerprints from ASIL tissues. With the long term goal to improve point of care assessment for ASIL screening and diagnosis, a side-by-side comparison of RS fingerprints was performed using a standard laboratory RS instrument and a portable fiber-optic Raman-enhanced spectroscopy (RESpect) probe.

Methods: Following IRB guidelines, participants undergoing medically-indicated HRA and anal biopsies for pathology diagnosis work-up. A duplicate anal biopsy specimen from one of the sites was flash frozen in liquid nitrogen. Sections of the frozen biopsies were placed on aluminum slides and RESpect probe signatures were obtained. The same sections were then transported to the RS lab where RS microscopic signatures were captured with 40 point scans using a Raman microscope at a 50x magnification with an exposure setting of 15 seconds per accumulation. Spectral data was processed in MATLAB and baselined and normalized using GRAMS and Spectragryph software.

Results: A total of 19 participants were included in this study: 6 with negative anal biopsy, 7 with low-grade intraepithelial lesions (LSIL), and 6 with high-grade intraepithelial lesions (HSIL). The spectra data for all the patients within each biopsy grade were averaged into one spectra for both the RS and RESpect probe. There were several areas that differed between the two instruments mainly in the 700-1000 cm^{-1} area where the peaks were more defined for RS in comparison to the RESpect probe which could be due to it being a microscope system. However, both instruments revealed an area around 1100-1160 cm^{-1} where the averaged negative biopsy spectra had a lower intensity in comparison to the averaged ASIL spectra (LSIL and HSIL).

Conclusion: Although differences between the systems resulted in some peaks differences when using RS and the RESpect probe, there were still some areas that were consistent between the two systems that can be used to potentially distinguish ASIL from negative anal biopsies. Results from this study identify the 1100-1160 cm^{-1} spectral area as a potential area that may separate the ASIL from the negative anal biopsies and set a foundation for future studies with a larger sample size while also taking HIV status into consideration. Supported in part by R21CA216830 and U54MD007584.
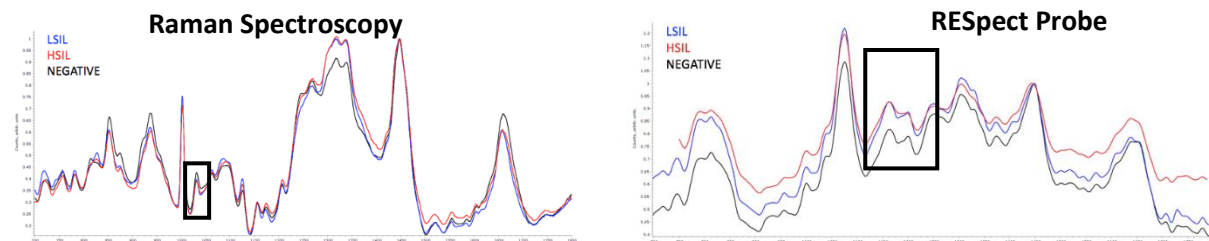
44. Employing the Virus Alone to Diagnose the Cancer: Quantification of Lesional KSHV DNA for the Diagnosis of Kaposi's Sarcoma in Africa

Jeffrey Martin[1], Aggrey Semeere[2], Ryan Snodgrass[3], Andrea Gardner[4], Esther Freeman[5], Racheal Ayanga[2], Megan Wenger[1], Duncan McCloskey[3], Robert Lukande[2], Miriam Laker-Oketta[2], Toby Maurer[1], David Erickson[3], and Ethel Cesarman[4]

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Background: Inaccessibility, delays in result generation and communication, and deficiencies in accuracy currently limit histopathologic diagnosis of Kaposi sarcoma (KS) in sub-Saharan Africa. As an alternative to pathology, we hypothesized that quantification of lesional DNA from the etiologic agent, KSHV, could distinguish KS from non-KS mimickers and be developed into a low-cost point-of-care diagnostic test. We earlier presented proof-of-concept findings from a small number of participants from a single site. We now report expanded testing on additional participants from several field sites.

Methods: We performed 5 mm punch biopsies among consecutive patients in Uganda referred by their health care providers because of skin or mucous membrane lesions suspected clinically to be KS. The biopsies were performed at one of three different biopsy service units in the cities of Kampala, Masaka, and Mbarara. Histopathologic evaluation of the biopsies was done in Uganda and by up to three pathologists in the U.S. (including anti-LANA staining). In laboratories in the U.S., DNA from KSHV ORF 26 from the biopsy tissue was quantified by real-time quantitative polymerase chain reaction (qPCR), performed standardly, and by loop-mediated isothermal amplification (LAMP), performed in a novel portable device named Tiny Isothermal Nucleic Acid Quantification System (TINY), which can run on several energy sources (including solar). Using US consensus histopathology as the gold standard and receiver operating characteristics (ROC) curves, we estimated the sensitivity and specificity and area under the curve (AUC) of qPCR and LAMP via TINY for the diagnosis of KS.

Results: We tested 506 participants with suspicious skin or mucosal lesions, suspected by their healthcare providers to be KS, who were referred for a biopsy. Median age was 33 years, 38% were women, and 94% were HIV-infected; 22% of lesions were macules, 64% plaques, and 14% papules/nodules. Gold standard pathology revealed that 341 biopsies were KS, 150 not KS and 15 indeterminate. Compared to this gold standard, sensitivity of African pathology for KS was 94% and specificity 71%. When evaluated qualitatively (presence or absence), PCR for KSHV DNA had 99% sensitivity for KS but only 81% specificity. Quantification of KSHV DNA by qPCR found an AUC of 0.98 for the diagnosis of KS; at one optimal cut-point (2485 KSHV DNA copies per 5 µl reaction), sensitivity for KS was 97% and specificity was 93% (Figure). In LAMP via TINY, AUC was 0.96, with one optimal cut-point yielding 93% sensitivity and 94% specificity (Figure).
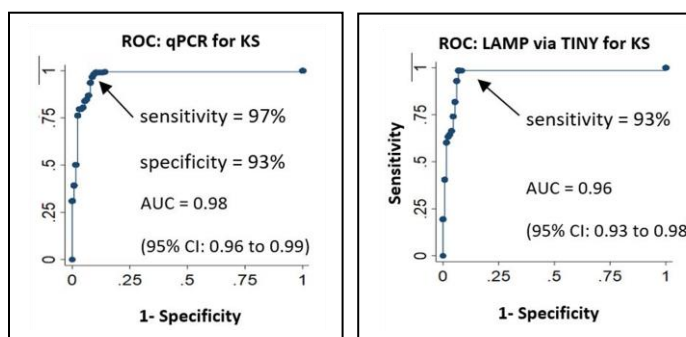
Conclusion: In East Africa, local African pathology lacked specificity for KS and qualitative detection of KSHV DNA by PCR in skin lesions was also non-specific for the diagnosis of KS. The latter is almost certainly because of ambient endemic KSHV infection. In contrast, quantification of KSHV DNA from skin lesions, using either qPCR or a new portable device employing LAMP, has both high sensitivity and specificity and accurately distinguished a high fraction of cases of KS from non-KS. The findings set the stage for additional field testing in Africa and validation of a point-of-care nucleic acid amplification-based diagnostic test for KS.

DAY TWO POSTERS

The first eight abstracts will be presented on both days. Abstracts 45-86 are on pages 94 to 135.

1. Modulation of vFLIP-Induced NF- κB Signaling in Primary Effusion Lymphoma Using NEMO Coiled Coil Mimics

2. Identification of the Kaposi's Sarcoma Progenitor as a PDGFRA(+)/Sca-1(+) Mesenchymal Stem Cell: A De Novo KSHV Infection to Tumorigenesis Model

3. Utility of Cerebral Spinal Fluid KSHV Viral Load in Primary Effusion Lymphoma

4. Evaluation of the Mobilization Component of a Public Health Approach to Cervical Cancer Prevention in East Africa

5. Diffuse Large B-Cell Lymphoma Tumor Microenvironment Differs Based on HIV and Antiretroviral Therapy Status

6. Risk of Smoking-Related Cancers Among Women and Men Living With and Without HIV

7. Risk of Second Primary Cancers Among HIV+/- Men With Prostate Cancer

8. Female Veterans Living with HIV Have an Increased Risk of Developing Cervical and Genital Cancers

45. Assessing Clinical Trial Self-Perceived Competence Among International Sites Participating in the AIDS Malignancy Consortium

46. Assessing Testosterone Replacement Therapy With Unsatisfactory Anal Cytology and Histological High-Grade Anal Lesions in Older Men Who Have Sex With Men

47. Challenges of Recruiting HIV+ Participants to a Cancer Prevention Trial

48. Beyond T Staging: Severity of Disease at Time of Diagnosis in a Community-Based Sample of Patients With Newly Diagnosed Kaposi's Sarcoma in East Africa

49. Biologic, Clinical, and Sociodemographic Predictors of Standard-of-Care Therapy for Non-Hodgkin Lymphoma Patients With an HIV Diagnosis

50. PLWHA: Perceptions of and Practices for Cancer Screening and Preventive Behaviors

51. Burkitt Lymphoma in the Antiretroviral Therapy Era: Stable Incidence and Poor Survival

52. Cancer Risk Following Lymphoid Malignancies Among HIV-Infected People

53. Cause of Death After Cancer Diagnosis in the Johns Hopkins HIV Clinical Cohort

54. Changes in HIV-Related Cervical Cancer Over a Decade (2009-2019) in Côte d'Ivoire

55. Clinical Profile and Outcome of HIV-Infected Patients With Head and Neck Cancers

56. Cumulative Incidence of Breast Cancer Among Women With HIV in North America From 2000 to 2015

57. Determinants of Survival Among a Community-Based Sample of Adults With HIV-Related Kaposi's Sarcoma Identified by Rapid Case Ascertainment

58. Early Progression and Immune Reconstitution Inflammatory Syndrome During Treatment of Mild-to-Moderate Kaposi's Sarcoma in Low-Resource Settings: Incidence, Long-Term Outcomes, and Effects of Early Chemotherapy

59. Clinical Factors Associated With Cervical Cancer Screening History in Women With Cervical Cancer in Botswana

60. Treatment Toxicities and Response of Cervical Cancer in Women With and Without HIV in Botswana: (Ipabalele Study-1 U54 CA190158-01)

61. Factors Associated With Increased Toxicity in HIV-Infected Women Undergoing Chemoradiation in Botswana (Ipabalele Study-1 U54 CA190158-01)

62. Impact of HIV Infection on the Natural History of HPV-Associated Cervical Cancer (Ipabalele Study-1 U54 CA190158-01): Comparison of Three Cohorts

63. Human Papillomavirus Characterization of Anogenital Malignancies in Patients in Botswana

64. Oncogenic and Sexually Transmitted Infections Associated with Precancerous CIN and Invasive Cervical Tumors in Patients in Botswana (Ipabalele Study-1 U54 CA190158-01)

65. Identification and Characterization of Pretreatment Tumor Infiltrating Lymphocytes in Tumor Biopsies of Locally Advanced Cervical SCC Patients in Botswana

66. Identifying Delays in Cervical Cancer Treatment for HIV-Positive Patients at a Tertiary Care Center in Botswana

67. Understanding the Role of Traditional Healers in Cervical Cancer Treatment in Botswana

68. Impact of Treatment and HIV Status on Quality of Life Before, During, and After Cervical Cancer Treatment in Women in Botswana (Ipabalele Study-1 U54 CA190158-01)

69. Building Research Capacity Through Program Development and Research Implementation in Resource-Limited Settings: The Ipabalele Study: Determining the Effect of HIV on the Natural History of Cervical Cancer In Botswana

70. Long-Term Outcomes of 58 Patients With HIV and KSHV-Associated Multicentric Castleman Disease

71. Mentoring and Career Development Core: Successful Course and Mentoring Program in Botswana

72. HPV-Associated Cervical Lesions in Women With Controlled HIV Infection in Uganda

73. ''I swore to myself that men should never see my private parts unless I am giving birth": Women's Experiences With Self-Sampling During Community-Based Cervical Cancer Screening in Rural Uganda

74. Impact of Kaposi's Sarcoma on Quality of Life Among HIV-Infected Adults Initiating Antiretroviral Therapy in East Africa

75. Incidence and Predictors of Kaposi's Sarcoma Immune Reconstitution Syndrome Among Kaposi's Sarcoma Patients Initiating Antiretroviral Therapy and Chemotherapy in Uganda

76. Investigation of Kaposi's Sarcoma in the Era of Antiretroviral Therapy in East Africa: Feasibility of Rapid Case Ascertainment

77. What Happens After the Biopsy? Pace and Determinants of the Communication of Pathology Results to Patients With Suspected Kaposi's Sarcoma in Uganda

78. Why Are They Diagnosed So Late? Understanding the Circumstances Preceding Diagnosis Among Patients With Kaposi's Sarcoma Identified by Rapid Case Ascertainment in East Africa

79. "People Don't Heal From Cancer": Barriers and Facilitators to Chemotherapy Initiation and Adherence for Patients With Kaposi's Sarcoma in Western Kenya

80. Kaposi's Sarcoma Rates Among People With HIV Living in the United States Between 2008 and 2015: State-Specific Trends

81. Metformin as a Potential Chemoprotective for Development of Invasive Anal Carcinoma in HIV-Infected Patients: A Nested Case-Control Study

82. Preliminary Results of Intra-Lesional Nivolumab for Treatment of Limited Cutaneous Kaposi's Sarcoma in HIV-Positive and HIV-Negative Men

83. Patterns in Long-Term Opioid Prescription Use Among Patients With Cancer Who Are HIV-Infected and HIV-Uninfected

84. Statin Exposure Is Associated With Decreased Risk of Cancer

85. Statin Use and Human Papillomavirus-Related Anal Dysplasia in HIV-Positive Men Who Have Sex With Men

86. Willingness to Participate in HPV Vaccination Programs Among HIV-Positive Women in Lagos, Nigeria

45. Assessing Clinical Trial Self-Perceived Competence Among International Sites Participating in the AIDS Malignancy Consortium

Jeannette Lee[1], Maria Botello-Harbaum[2], Rebecca Medina[2], Shelly Lensing[1], and Meredith Zozus[1]

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Background: The AIDS Malignancy Consortium (AMC) is devoted to conducting clinical trials of therapeutic and prevention strategies for cancer in HIV-infected persons. The AMC has expanded its activities to Sub Saharan Africa and Latin America and recently identified a need to prepare Clinical Investigators (CIs) and Study Coordinators (SCs) who can initiate, manage, and coordinate AMC's protocols. The AMC conducted a survey of AMC clinical investigators and study coordinators in these geographic regions to assess their self-perceived competency in several domains of clinical trial activities. These results will be used to guide the development and implementation of professional development modules to enhance proficiency in clinical trial domains.

Methods: An electronic surveys for investigators and study coordinators were adapted from the Joint Task Force for Clinical Trials Competency. Respondents were asked to rate their level of competence to their current role using a five-point 0 to 4 scale where higher levels reflected greater perceived competency. We determined the percentage of respondents who reported competence or mastery for each competency and averaged the percentages by domain. A total of 35 investigators and 17 study coordinators completed the survey.

Results:

Clinical Investigator Domains	% competent
Scientific Concepts and Research Design	63.4
Ethical and Participant Safety Considerations	86.6
Medication Development and Regulation	59.3
Clinical Trials Operations and Good Clinical Practices	71.8
Study and Site Management	59.3
Data Management and Informatics	49.8
Leadership and Professionalism	62.0
Communication and Teamwork	60.3
Engaging with Communities	44.2
Study Coordinator Domains	
Scientific Concepts and Research Design	77.7
IRB, National Regulatory authority, sponsor approval, informed consent	59.1
Adverse Event Reporting	53.7
Privacy and Patient Confidentiality	81.3
Preparedness and Regulation	52.1
Study Activities at Site	56.8
Screening, Enrollment and Management of Study Participants	77.9
Data Management and Informatics	69.5

Conclusion: The results of the surveys identified areas for the AMC to focus on in preparing investigators and study coordinators to implement AMC clinical trials. The AMC is currently working with its international sites to develop materials for investigators and coordinators.

46. **Assessing Testosterone Replacement Therapy With Unsatisfactory Anal Cytology and Histological High-Grade Anal Lesions in Older Men Who Have Sex With Men**

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Background: Older HIV-infected men who have sex with men (MSM) have a high prevalence of hypogonadism, and higher prevalence of testosterone replacement therapy (TRT). MSM are at high-risk for detection of a cancer and precancer, histological high-grade squamous intraepithelial lesion (hHSIL). HPV16/18 is a major cause of anal hHSIL and higher serum testosterone levels increase the prevalence of HPV16/18 infections in MSM. Exogenous testosterone treatment is significantly associated with unsatisfactory cervical cytology in transmasculine men. Associations between self-reported TRT and unsatisfactory anal cytology and hHSIL in cis-MSM is unclear.

Methods: Of 296 HIV-infected/-uninfected MSM screened for anal hHSIL using nylon-flocked (NF) and Dacron swabs, High-Resolution Anoscopy with biopsy, each was surveyed about TRT use. Anal swabs were evaluated as unsatisfactory or satisfactory for cytology; biopsies were assessed for hHSIL using international standards and summarized using *Lower Anogenital Squamous Terminology Standardization* nomenclature. Sociodemographic and behavioral data were collected. Two multivariable logistic regression models compared odds of unsatisfactory cytology and hHSIL relative to current TRT use, controlling for the effects of age, race, HIV-infection, and number of receptive anal intercourse (RAI) partners, and for cytology, swab-collection order.

Results: Nearly 43% of participants showed hHSIL. Men are best described as 55 ($\pm$11) years old, mostly White non-Hispanic (75%), and HIV-infected (56%). Nearly 30% reported current TRT use, most often gel (18%) or injectable (12%) forms. Nonetheless, 46% reported any history of TRT with 32% gel use and 27% injectable use. Multivariable analyses showed no association between current TRT and unsatisfactory cytology (adjOR: 0.8 (95% CI: 0.4, 1.5). Among these men, NF-swab for cytology showed higher odds of unsatisfactory cytology over Dacron-swab: adjOR: 2.9 (1.7, 4.6). Similarly, adjusted analyses showed odds of hHSIL was not associated with self-reported TRT use (adjOR: 1.1 (0.6, 2.1)). Men reporting $\geq$2 RAI partners within 2 years of examination showed 89% higher odds of hHSIL than men reporting none (adjOR: 1.9 (1.0, 3.5)). HIV and CD4-count characteristics were not associated with (adjusted) odds of either unsatisfactory cytology or hHSIL.

Conclusion: While testosterone-replacement therapy was common among these older MSM, its use was not associated with unsatisfactory specimens for anal cytology, or with hHSIL. These findings are consistent with other analyses explored by this research group. Further study of the biological role sex hormones, including testosterone, play in screening test performance, anal high-risk HPV infections and (anal) hHSIL is important to improving the health of older HIV-infected adults.

47. Challenges of Recruiting HIV+ Participants to a Cancer Prevention Trial

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Background: As deaths from AIDS decrease, people with HIV are at increasing risk of anal cancer. The incidence of anal cancer is 15 to 90 times higher in HIV-infected populations than in the general population, which has rates of 1.5 and 1.9 per 100,000 for men and women. Men who have sex with men (MSM) are particularly susceptible with rates of 131 cases per 100,000 for men who have sex with men (MSM), followed by heterosexual men and women, who have rates of 46 and 30 per 100,000. The ANCHOR study (NCT02135419) was designed to test the hypothesis that treatment of anal high-grade squamous intraepithelial lesions (HSIL) will lead to a reduction of 75% of incident anal cancer. To achieve the goal of randomizing 5058 HIV+ men and women, 35 years of age and older with HSIL into the study, approximately 15000 participants are targeted for screening.

Methods: The study employs multiple methods to reach potential participants to be screened for the study. This report summarizes the distribution of sources of information on the study as reported by persons screened for the trial, and the demographic characteristics of the screenees.

Results: Since March 2015, over 8,000 participants have been screened from 23 clinics in 14 cities. A national campaign was implemented in conjunction with support for local recruitment strategies and monetary incentives for participants. The average age of the participants was 52 years of age and 20% were women. The study attracted a diverse HIV population: 27% were non-Hispanic whites, 44% were non-Hispanic African-Americans, 23% were Hispanic, and 6% were of other ethnic/racial groups.
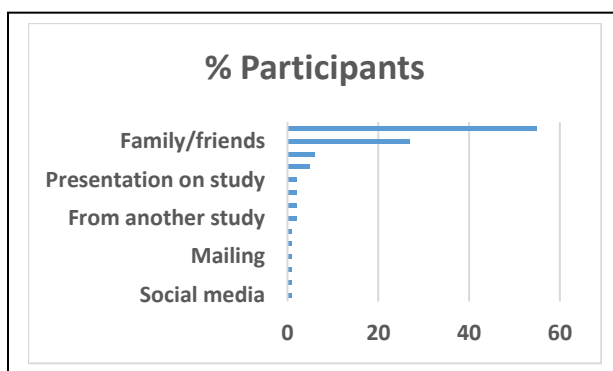
To date, the top four sources of information about the study reported by screenees were physician or other health care provider (55%), friends and/or family (27%), ANCHOR brochure or palm card (6%) and community center (5%).

There was variation between race/ethnic groups and insurance status with respect to how participants heard about the study. Those who heard about the study from a physician or other health provider. Participants who heard about the study from a doctor or health provider were more likely to be non-Hispanic white and have private insurance. Those who were learned about the study from family or friends were more likely to be from a minority population and covered with public insurance.

Conclusion: The ANCHOR study has been successful in reaching a diverse population. To date, there are minority and insurance differences with respect to referral sources.

48. Beyond T Staging: Severity of Disease at Time of Diagnosis in a Community-Based Sample of Patients With Newly Diagnosed Kaposi's Sarcoma in East Africa

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Background: There is no universally accepted system for staging Kaposi's sarcoma (KS). ACTG T staging was developed in a resource-rich setting prior to potent antiretroviral therapy. The World Health Organization (WHO) recently offered another system based on functional disability. In Africa, knowledge of extent of disease at time of diagnosis is important to understand delays in diagnosis, elucidate KS prognosis, and guide treatment. Most available data from this region has used ACTG staging but with limited description of what merited T1 classification. Additionally, what is available may be distant from time of diagnosis, and often from tertiary care populations not representative of KS in the community.

Methods: Using a rapid case ascertainment approach, we identified consecutive patients ≥18 years of age newly diagnosed with KS from 2016-2019 in outpatient and inpatient facilities in AMPATH (Kenya), Masaka Regional Referral Hospital and Mbarara Regional Referral Hospital (Uganda). Rapid case ascertainment prospectively identifies suspected diagnoses by electronic medical record and pathology laboratory search as well as clinician notification. As quickly as possible after diagnosis, we evaluated the extent of KS and its complications by patient interview and physical examination. We documented individual symptoms and signs as well as ACTG T stage and WHO KS Treatment Guidelines stage.

Results: We enrolled 264 patients within 60 days of newly diagnosed KS, 61% from Kenya and 39% from Uganda. Median age was 35 years (interquartile range 30 to 42), 69% were men, and median CD4 count was 239 cells/mm^3 (IQR 87-408). The majority of patients (82%) had ACTG T1 disease at time of enrollment. Of these patients with ACTG T1 disease, a minority had more than one T1 qualifying symptom (28%). Of all patients enrolled, 64% had WHO KS Treatment "severe" stage disease. This difference in T1 staging and WHO severe stage was primarily driven by the difference in edema classification (Table 1): of all enrolled patients, 70% had KS related edema (qualifying them as T1), but only 46% of patients had painful or disabling tumor-associated (qualifying them as WHO severe stage).

Finding	All Participants (N = 264)	ACTG* T0 (N = 48)	ACTG* T1 (N = 216)	WHO** Mild/Moderate (N = 95)	WHO** Severe (N = 169)
≥ 50 skin lesions	37%	36%	37%	30%	41%
Median # anatomic regions with KS	6 (IQR 4-10)	6 (IQR 4-10)	6 (IQR 3-10)	5 (IQR 4-9)	6 (IQR 3-10)
Disabling oral cavity lesions**	12%	15%	12%	0%	20%
Edema					
Any edema on physical exam	78%	31%	88%	76%	79%
Edema on exam related to KS*	70%	0%	85%	61%	75%
Painful or disabling KS edema**	46%	0%	55%	0%	72%

*Krown ACTG Criteria, Journal of Clinical Oncology, 1989 ** WHO Guidelines on the Treatment of Skin HIV Associated Conditions, 2014

Conclusion: This study represents a very detailed, prompt description of KS patients as close as possible to KS diagnosis in HIV primary care settings in East Africa. In this community-based sample, most patients had ACTG T1 disease and/or WHO "severe" stage KS. However, there are notable differences between these staging systems when applied to KS in this sub-Saharan African population, which has not been previously reported. Ultimately, by linking more detailed description of KS severity at time of diagnosis in sub-Saharan Africa beyond traditional ACTG staging with mortality data, we will be able to build better prognostic models of disease, and help further delineate sub-populations that would benefit from early intervention with chemotherapy in addition to ART in this setting.

49.   Biologic, Clinical, and Sociodemographic Predictors of Standard-of-Care Therapy for Non-Hodgkin Lymphoma Patients With an HIV Diagnosis

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Background: People living with HIV/AIDS (PLWHA) diagnosed with Non-Hodgkin lymphoma (NHL) have been shown to demonstrate poorer all-cause survival outcomes compared to HIV- patients with NHL. Various factors have been reported to influence these outcomes, including co-morbidities, receipt of some therapy, HIV-related stigma, and demographic data. However, investigations of biomarkers of HIV status and disease control, e.g. CD4 counts and viral load, along with other clinical parameters, have been limited. In addition, the role of not simply providing "some" treatment but whether the cancer treatment delivered met criteria for accepted guideline-concordant care remains to be elucidated.

Methods: Using methods similar to those described by the NCI HIV/AIDS Match Study, the Georgia Department of Public Health linked data from the Georgia Cancer Registry (GCR) and the Georgia HIV/AIDS Surveillance Registry to identify all adults aged $\geq$ 18 years diagnosed with NHL between 2004-2012 who also had a diagnosis of HIV and/or AIDS documented prior to or during any portion of this time period. Included in the linkages were individual laboratory data (CD4 counts, dichotomized as CD4< or $\geq$200 cells/mm^3), and viral load (dichotomized as < or $\geq$400 copies/mL). GCR data supplied sociodemographic, clinical, and facility-related variables. Additionally, the cancer-HIV data linkages were linked to the Georgia Hospital Discharge Database (GHDD) for all cases with $\geq$1 hospitalizations prior to or following the NHL diagnosis (through 2012), and used ICD-9 diagnosis codes from hospitalization to construct a modified Charlson-Deyo comorbidity index score as well as augment insurance data for each patient. Logistic regression was applied to examine factors that predicted receipt of standard-of-care (SOC) therapy, defined as multi-agent chemotherapy +/- radiation therapy. Monoclonal antibody therapy was not coded as separate from systemic chemotherapy in the registry during the time period examined so its use could not be defined. Analyses were conducted with SAS 9.4.

Results: Using the constructed Georgia population-based dataset, out of a total of 2901 cancer cases and 2486 HIV/AIDS cases diagnosed between 2004 and 2012, 328 adults $\geq$18 years were identified with HIV+ NHL. Of these cases, 61.6% received SoC NHL therapy, 30.2% did not receive SoC, and 8.2% were considered indeterminate related to SoC treatment. Among the NHL patients, about 2/3 were diagnosed with diffuse large B-cell lymphoma (DLBCL), with nearly 70% diagnosed at either stage III/IV, >80% were male, >69% were black, and median age at cancer diagnosis was 43 years. About 17% were uninsured. The majority of patients had a CD4 count<200 cells/mm^3 (66%) and over 80% had a viral load of $\geq$400 copies/mL in the last tests recorded prior to their NHL diagnoses. The strongest single predictor of SoC NHL therapy was CD4 count. HIV+ individuals with more intact immune function (CD4$\geq$200) were more likely to receive SoC (OR=6.81, p<0.001).

Conclusion: The National Comprehensive Cancer Network (NCCN) and other groups have established guidelines to assist oncologists with decision-making related to HIV+ malignancies, including NHL. Such guidelines advise co-management between an oncologist and HIV specialist, close attention to potential drug-drug interactions, continuation of HIV therapy during cancer treatment, and use of standard-of-care therapy recommended for all cancers regardless of HIV status. The ~38% of Georgia patients with HIV+ malignancies who did not receive SoC represent a need for increased education among oncologists regarding the importance of treating all cancers per guidelines, without HIV viral load as a reason to impede care.

50. PLWHA: Perceptions of and Practices for Cancer Screening and Preventive Behaviors

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Background: As HIV treatment has become more successful, people living with HIV/AIDS (PLWHA) are living longer, with life expectancies meeting those for their HIV- peers. However, longer life has put them at risk for other diseases, e.g., cancer. In addition, PLWHA often has other cancer-causing co-infections, greater exposure to carcinogens, e.g., tobacco, and heightened effects of aging and HIV on the immune system. These factors combine to lead to an increased incidence of Non-AIDS-Defining Cancers (NADC), such as non-small cell lung cancer, anal cancer, Hodgkin lymphoma, colorectal, and other malignancies. Outcomes for HIV+ malignancies have been shown repeatedly to be poor, but the underlying reasons are not well elucidated. PLWHA have been reported to participate in non-communicable disease screening, including for cancer, at significantly lower rates vs. HIV- populations. Providers, who are often infectious disease specialists, may focus on managing HIV/concomitant infections and overlook need for screening. Barriers to participate in screening, already problematic in rural and underserved urban settings, may be exacerbated for PLWHA. Significant gaps in understanding of PLWHA views towards and uptake of cancer prevention and screening interventions limit the ability to design and test efficacious interventions.

Methods: The primary aim of the study was to assess the knowledge, attitudes and practices among PLWHA and healthcare providers in rural and urban underserved settings regarding perceived risk of cancer; uptake of cancer screening and preventive behavior; barriers/facilitators to cancer screening participation; and preferences for strategies to promote screening. IRB approval was obtained from multiple regulatory oversight groups. PLWHA were recruited from a rural Ryan White clinic (N=60) and large urban HIV clinic (N=118). A quantitative survey derived from the "Study of Health Behaviors and Disease Prevention" tool was administered (N=178). Focus groups, held separately for men and women, were conducted at both study sites to collect qualitative data.

Results: Participants were predominantly African-American (90.4%); female (57.1%); of lower socio-economic status (87%); and had $\leq$12 years education (65.7%); 28.6% had no type of health insurance., Only 37% reported participating in regular cancer screening, although 68.5% reported seeing a dentist routinely. Among women $\geq$50 years old who met eligibility for breast cancer screening, 100% of women in the rural setting were screened while 55% of those in the urban setting received breast screening (p=0.009). For women $\geq$21 years who met eligibility for cervical screening, 11% of eligible rural women were not screened, while 45% of eligible HIV+ women in the urban setting were not screened (p=0.003). No significant differences were found based on setting for colorectal screening. For beliefs about HIV and cancer risk, urban patients were more likely than rural patients to strongly disagree with the statement that HIV+ individuals are at higher risk for cancer (p<0.001). Findings from the qualitative data revealed costs to the patient, physician recommendation, and HIV diagnosis were the top reasons participants identified as reasons to pursue cancer screening or not.

Conclusion: PLWHA experience serious disparities in uptake of cancer screening and prevention. Systematic reminders implemented in the rural site resulted in significant differences in guideline concordant (for HIV+ and HIV-) screening and care vs the urban setting. If patients' HIV clinic provider recommended screening or prevention for cancer, there was a higher likelihood that the patient would comply with such activities and behaviors. Both PLWHA and their providers demonstrated gaps in knowledge of increased risk for cancer among PLWHA and need to pursue screening. Evidenced-based strategies specific to PLWHA are needed to increase awareness and enhance uptake of cancer screening among this at-risk population.

51. Burkitt Lymphoma in the Antiretroviral Therapy Era: Stable Incidence and Poor Survival

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Background: Despite advances in diagnosis and treatment of both HIV and Burkitt lymphoma (BL), persons living with HIV (PLWH) remain at high risk for BL. We conducted this study to determine if there have been any changes in risk or survival among PLWH and BL during the anti-retroviral era.

Methods: Veterans living with HIV (VLWH) and age-matched controls receiving care between October 1, 1999 and December 31, 2016 were retrospectively identified using Veterans Health Administration (VHA) electronic medical records (EMR). BL diagnosis was identified through VHA Cancer Registry review and ICD-9/10 codes. Follow-up time was from HIV index date to BL diagnosis, death, last recorded health care encounter, or study end. Demographic, lifestyle, and clinical variables were extracted from EMR for analysis. Hazard ratios (HR) and 95% confidence intervals (CI) for BL risk and survival were estimated in univariate ($p<0.25$) and multivariate ($p<0.10$) time-varying Cox proportional models.

Results: We identified 45,215 VLWH, of whom there were 120 prevalent BL cases; 84 of those developed BL during our follow-up period (incidence rate [IR] = 21.2 per 100,000 person years, 95% CI: 17.1-26.3). The IR was variable over the study period. Median CD4 count at BL diagnosis was 238 cells/mL, (SD: 324.74) and increased over time. Median survival was shorter in VLWH with BL compared to HIV-negative veterans with BL ($p<0.05$). After adjustment, the risk of BL diagnosis in VLWH was 38% less in black men compared with white men (HR: 0.620 [0.393-0.979], $p<0.0401$). VLWH with an undetectable viral load for at least 40% of the follow up period were 74% less likely to develop BL (HR: 0.261, 95% CI 0.143-0.478, $p<0.0001$) and 86% less likely to die after diagnosis (HR: 0.141, 95% CI 0.058-0.348, $p<0.0001$). Regarding ART regimens, most VLWH (54%) were not on ART when diagnosed with BL. Of those who were taking ART at time of BL diagnosis the majority were on regimens with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) backbone (n=21, 42.9%) or a protease inhibitor (PI) backbone (n=19, 38.8%). Six (12.3%) were taking regimens that included an integrase inhibitor. Mean survival did not differ significantly when groups were compared based on ART backbone. Regarding chemotherapy regimens, those treated with EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone, with or without rituximab) had the longest mean survival at 8.95 years (SE 1.52, n = 18, 15.0%), compared to those treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone; mean survival = 6.66 years [SE 0.98, n=37, 30.8%]), Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine; mean survival = 1.96 years [SE 0.33, n=19, 15.8%]), and those who did not receive chemotherapy (mean survival = 0.14 years [SE 0.06, n=10, 8.3%]).

Conclusion: BL incidence among VLWH did not improve between 2000 and 2016. Survival after BL diagnosis in male VLWH remains dismal as compared to their HIV-negative counterparts, although veterans with prolonged periods of undetectable viral load showed better survival.

52.   Cancer Risk Following Lymphoid Malignancies Among HIV-Infected People

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Background: HIV-infected people have increased risk of AIDS-defining and non-AIDS-defining cancers. Because HIV-infected people are living longer due to combined antiretroviral therapy (cART), they may be diagnosed with multiple cancers over their lifetime. Lymphoid malignancies are some of the common cancers among HIV-infected people. Lymphoma survivors have increased risk of certain second primary cancers in the general population, but second cancer risk among HIV-infected people is poorly understood. Herein, we comprehensively characterized the cancer risk and patterns of second primary cancers following lymphoid malignancies among HIV-infected people.

Methods: We used data from the HIV/AIDS Cancer Match Study which links 10 HIV and cancer registries in the US (1996-2015). We ascertained incident first lymphoid and non-lymphoid malignancies from the linked cancer registries. Lymphoid malignancies included non-Hodgkin lymphomas (AIDS-defining and non-AIDS-defining), Hodgkin lymphomas, and plasma cell neoplasms. Risk of first non-lymphoid malignancy following a lymphoid cancer diagnosis was assessed using Cox regression models with age as the time scale, lymphoid malignancy diagnosis as time-dependent variable, and adjusted for sex/risk group, race/ethnicity, and calendar year (Model 1). We additionally adjusted for prior AIDS diagnosis, and time since HIV diagnosis as time-dependent variables (Model 2).

Results: Among 531,460 HIV-infected people included in our study, 6,513 first lymphoid and 18,944 first non-lymphoid malignancies were diagnosed. In Model 1, risk of non-lymphoid cancer following a lymphoid malignancy diagnosis was increased overall (adjusted hazard ratio [aHR]=2.7; 95%CI=2.3-3.2), and specifically for cancers of the oral cavity (aHR=2.6; 95%CI=1.2-5.5), colon (2.4; 1.1-5.0), rectum (3.6; 1.9-6.7), anus (3.6; 2.5-5.1), liver (2.0; 1.2-3.5), lung (1.6; 1.1-2.4), vagina/vulva (6.1; 2.3-16.3), and central nervous system (CNS) (5.0; 1.6-15.6), Kaposi sarcoma (4.6; 3.4-6.2), other non-lymphocytic leukemias (9.7; 6.1-15.4), and miscellaneous cancers (3.4; 2.1-5.3). In Model 2, aHRs were attenuated overall (aHR=1.7; 95%CI=1.5-2.0) and for each cancer and were no longer significant for cancers of the oral cavity, colon, liver, lung, and CNS. Overall non-lymphoid cancer risk was increased following AIDS-defining (aHR=1.7; 95%CI=1.5-2.0) or non-AIDS-defining lymphoid malignancy (2.0; 95%CI=1.6-2.5), or following any non-Hodgkin lymphoma (1·8; 1·6–2·1), Hodgkin lymphoma (1·9; 1·4–2·5), or plasma cell neoplasm (2·1; 1·2–3·5). Cancer risk overall was increased at both ≤6 or >6 months after lymphoid malignancy. Adjustment for prior AIDS diagnosis and time since HIV diagnosis resulted in greater attenuation in the aHRs for cancers occurring ≤6 months after lymphoid malignancy diagnosis (Model 1, aHR=7·3; Model 2, aHR=2·7) compared to >6 months after lymphoid malignancy diagnosis (Model 1, aHR=1·8; Model 2, aHR=1·5). Risk was increased for cancers of the oral cavity, rectal squamous cell carcinoma, anus, and liver, and non–lymphocytic leukemia >6 months after lymphoid malignancy diagnosis and was not attenuated in Model 2.

Conclusion: HIV-infected people with lymphoid malignancies have increased risk of subsequent non-lymphoid cancers. Immunosuppression may play a common role in the etiology of some, but not all cancers. Physicians involved in medical care of HIV–infected people should be aware of the possibility of second primary cancer diagnosis following a diagnosis of a lymphoid malignancy. Because most cancers occurring after lymphoid malignancies are associated with immunosuppression, restoration of immune function with cART should continue to remain a priority in the clinical management of HIV infection as it may lower the risk of subsequent cancers.

53.   Cause of Death After Cancer Diagnosis in the Johns Hopkins HIV Clinical Cohort

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Background: People living with HIV (PLWH) who are diagnosed with cancer have higher mortality compared to those without HIV diagnosed with cancer. This increased mortality may be due to cancer, HIV, or other causes. We examine cause of death (COD) among PLWH with cancer enrolled in HIV clinical care. We examined CD4 cell count at and after cancer diagnosis to explore the role of immune impairment.

Methods: We examined causes of death after cancer diagnosis among 218 PLWH enrolled in the Johns Hopkins HIV Clinical Cohort who were diagnosed with an incident, first cancer between 1997-2014 with follow-up through March 2016. Using a competing events framework, we compared risk of death due to cancer, HIV, other infection (e.g. sepsis), chronic disease (including cardiovascular, liver, and kidney disease), and other death (e.g. overdose, suicide). We examined the association between baseline CD4 category, a 25% decline in CD4 (using the lowest CD4 value in the first year following cancer diagnosis), and risk of all-cause and cancer-specific mortality using Cox proportional hazards models. Models were adjusted for baseline viral suppression, ART, demographic covariates, initial cancer treatment (chemotherapy, radiation, surgery, other treatment), and cancer severity. The 25% CD4 decline models also included an interaction with baseline CD4.

Figure 1: Cause-Specific Mortality after Cancer Diagnosis in JHHCC.

Cancer severity was determined by SEER 5-year mortality estimates based on cancer type and stage. COD was ascertained via medical record review and linkage to the Social Security Death Index.

Results: The study population was 68% male and 77% non-Hispanic Black. The most common cancer types were non-Hodgkin's lymphoma [N=38], lung cancer [N=28], and Kaposi's sarcoma [N=26]. The stacked cumulative incidence of the causes of death for all PLWH with cancer are shown in Figure 1. At 5 years following cancer diagnosis, the cumulative incidence of mortality was 46.7% (95% CI=39%, 53%). 5-year mortality due to cancer was 28.8%; HIV was 5.2%; other infection was 3.3%; chronic disease was 6.0%; and other mortality was 3.4%. Among all AIDS defining cancers, 5 year cancer-specific mortality was 22%, as compared to 32% among all non-AIDS defining cancers. 34% had baseline CD4<200 and 57% experienced at least a 25% CD4 cell decline in the year following diagnosis. For those receiving chemotherapy and/or radiation, 75% had a decline versus 29% of those receiving other treatment (p-value <0.001). Baseline CD4<200 did not significantly increase risk of all-cause mortality (HR=1.34; 95% CI= 0.87-2.06) nor cancer specific mortality (HR=1.33; 95% CI=0.75-2.35). Similarly, there was no significant association between a 25% decline in CD4 and either all-cause mortality (HR=1.22; 95% CI= 0.47-3.20) or cancer specific mortality (HR=0.91; 95% CI= 0.26-3.19). Cancer severity and cancer treatment were the most significant predictors of mortality risk in all models. In a sensitivity analysis among those with 5-year SEER mortality risk <50%, baseline CD4<200 was significantly associated with both all-cause mortality (HR=2.12; 95% CI=1.12-4.01) and cancer-specific mortality (HR=2.65; 95% CI=1.10-6.37), and a 25% CD4 decline was also associated with all-cause mortality (HR=3.71; 95% CI=1.16-11.9).

Conclusion: Cancer-specific mortality is the cause of death for the vast majority of PLWH diagnosed with a cancer and cancer severity is the overwhelming predictor of death in the population. Among those with less severe cancer type/stage, low baseline CD4 contributes to increased mortality risk.

54. Changes in HIV-Related Cervical Cancer Over a Decade (2009-2019) in Côte d'Ivoire

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Background: Major improvements have occurred in HIV care with a lager access to antiretroviral treatment (ART) and cervical cancer (CC) prevention over the past decade in sub-Saharan Africa. However, there is limited information on changes in the burden of HIV-related CC at a population level. Our objective was to describe and compare the characteristics of HIV-related CC over a decade in Côte d'Ivoire.

Methods: A repeated cross-sectional study was conducted in the three referral hospitals of Abidjan where the great majority of CC were diagnosed in the country during the 2009-2010 and 2018-2019 periods. During these periods, all women diagnosed with CC were systematically tested for HIV based on the national algorithm. A common questionnaire was administered to collect demographic information, CC risk factors (tobacco use and hormonal contraceptive use), HIV characteristics (ART exposure, last known CD4 count) and cancer stage (FIGO) at CC diagnosis.

Results: During the 2009-2010 and 2018-2019 periods, 148 and 144 women with invasive CC were diagnosed, with median [IQR] age at CC diagnosis of 49 [40-57] years and 53 [43-61] years ($p < 10^{-2}$), respectively. The estimated HIV prevalence was 24.8% and 19.4% (p=0.27), respectively. Compared to women diagnosed with CC in 2009-2010, those diagnosed in 2018-2019 presented with higher tobacco use (16.1% versus 2.7%, $p < 10^{-4}$) and hormonal contraceptive use (11.8% versus 0.7%, $p < 10^{-4}$). An advanced FIGO stage (III, IV) was documented in 73.9% and 75.9% (p=0.72) of women during these two periods. Comparison of HIV-related CC between the two periods are summarized in the following table:

	2009-2010 (n=37)	2018-2019 (n=28)	p-value
Age, median (IQR)	44 (36.5 – 48.5)	47 (41.0 – 54.0)	0.09
Current/former tobacco use, n (%)	0 (0.0)	4 (14.3)	0.04
HIV status prior to CC diagnosis*, n (%) Unknown Known, no ART use Known on ART	21 (56.8) 14 (37.8) 2 (5.4)	6 (21.5) 2 (7.1) 20 (71.4)	$<10^{-4}$
CD4 cell count, median (IQR)*	331 [256 – 460]	532 [292 – 883]	0.15
CC staging (FIGO)**, n (%) I, II III, IV	6 (19.3) 25 (80.7)	7 (38.9) 11 (61.1)	0.13

*Missing values (n=47), **Missing values (n=16)

Conclusion: Despite major improvements in access to care and ART in HIV-infected women in Côte d'Ivoire, the proportion of women diagnosed with CC and infected with HIV remains high. Meanwhile, other risk factors for CC including tobacco and hormonal contraceptive use increased over time, stressing the need to strengthen the preventive program based on CC screening in this high-risk population. The increase in the proportion of HIV-infected women diagnosed with CC and presenting with FIGO stage I/II deserves further investigation as it could potentially reflect an improved access to CC screening and/or earlier access to CC care through HIV services.

55. Clinical Profile and Outcome of HIV-Infected Patients With Head and Neck Cancers

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Background and Aims: Overall 57.5% of global head and neck cancers (HNC) excluding esophageal cancers occur in Asia, especially in India. Tobacco and alcohol act synergistically and are the two most important etiological factors responsible for about 75% of squamous HNC. Human papillomavirus (HPV) infection has been identified as a causal factor in a subset of head and neck squamous cell cancers, primarily oropharyngeal cancers. Research suggests that HIV-infected individuals are at higher risk for oral HPV infection and HPV-associated HNC (western data). Within the HIV cohort at Tata Memorial Hospital (TMH). HNC incidence was second to NHL, though an increase in proportion incidence vis-à-vis the HIV-negative population was not noted at TMH . Based on incidence rates at TMH and known viral association, HNC represents an important second cancer to study in the context of HIV infected patients in India. We studied the clinical profile, prevalence of HPV infection, p16 status and overall survival of HIV infected patients with head and neck cancer.

Methods: This is a prospective study, consecutive patients diagnosed with HIV infected patients with head and neck cancer in the period February 2014-march 2016 who were treatment naïve were included in the study after valid informed consent. In addition to histopathology study, IHC (P16, P53) and HPV DNA PCR of tumor tissue was done. Demographic features, HIV related details (CD4 count at diagnosis, ART regimen), histological diagnosis, stage, treatment details, response, toxicity and status at last follow up were recorded. The primary objective was overall survival (OS). Statistical analysis was done using PASW software package (version 18). Descriptive statistics were summarized with median and range, survival outcomes were analyzed with Kaplan Meier method.

Results: 13 patients with head and neck cancers were accrued. There were 10 males and 3 females. The median age was 49 years. 9 patients were known HIV positive on HAART. In them the median period from HIV positivity to cancer was 56 months (range 37-211months) and median HIV viral load 20 copies/ml . Over all the median CD4 counts is 592 cells/cumm (range 99-800) .9(69.2%) were tobacco users. The sites were buccal mucosa in 6 patients, tongue in 2 patients, pyriform fossa in 2 patients, and one each of hard palate, lower lip and lower alveolus. Most patients had advanced stage of cancer (92%). The histopathology was squamous cell carcinoma in all cases. EBER, P16 staining and P53 staining on tumor tissue was done in 11 cases, all were negative for EBER, 3(23%) were positive for P16 and all were positive for P53. HPV by PCR in tumor tissue was checked in 7 patients, 5(71%) were positive. 11 patients underwent surgery, of these all received concurrent radiotherapy and 1 patient also received chemotherapy. One patient received radiotherapy and chemotherapy. One patient received oral metronomic therapy. Three patients expired. The mean overall survival was 35.7 months (95% CI- 22.4-48.7). The 4-year survival was 60%.

Conclusion: Significant number of HIV infected patients with head and neck cancers were in routine clinical care for HIV. Most patients have good immunologic and virologic control of HIV, but advanced stage of head and neck cancer. A high proportion of HPV positivity in tumor tissue is noted. Most patients could complete planned treatment and overall survival is good.

56. Cumulative Incidence of Breast Cancer Among Women With HIV in North America From 2000 to 2015

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Background: A substantial proportion of women with HIV are aging and reaching age groups at higher risk of several cancers, including breast cancer. The burden of breast cancer is poorly characterized in women with HIV in part due to the need for a large sample size from which sufficient breast cancer cases could arise. The objective of this study was to describe the cumulative incidence of breast cancer with respect to calendar time, race, and CD4 count at ART initiation among women in a large North American cohort study.

Methods: Women ≥30 years old, who were prescribed ART, observed in the North American AIDS Cohort Collaboration on Research and Design from 1 Jan 2000 to 31 Dec 2015, had no history of cancer at entry into this study and had at least six months of follow-up were included. Study entry was 1 Jan 2000, age 30, ART initiation date, study enrollment date, or cohort-specific cancer observation window start, whichever came last. Study exit was the date of an invasive breast cancer diagnosis, date of death, loss to follow-up, administrative censoring at 31 Dec 2015, or the end of the cohort-specific cancer observation window, whichever came first. Diagnoses were validated using standardized abstraction which included linkages with cancer registries and/or manual record review for cancer site and pathology. We utilized unadjusted Kaplan-Meier methods to estimate breast cancer cumulative incidence by race (Black vs. White), and CD4 count at ART initiation (<350 cells/µL vs. ≥350 cells/µL) and log-rank tests to determine statistical differences in the hazard of breast cancer by these factors. Estimates were stratified by calendar time (<2008 vs. ≥2008).

Results: We included 11,341 women in this analysis, contributing 57 incident breast cancer diagnoses with 78,777 years of follow-up, corresponding to an overall cumulative incidence of 5.1%. Median follow-up was 6 (IQR: 3 to 11) years, with median age at study entry of 40 (IQR: 35 to 48). Among cases, median age at diagnosis was 53 (IQR: 46 to 58) and the median CD4 count at ART was 298 (IQR: 146 to 424) cells/µL. Sixty-one percent of cases were Black. Incidence did not differ by race (p=0.62), CD4 count (p=0.56), or calendar period (p=0.13). Within calendar period there were no significant differences by race or CD4 count (**Figure 1**). Findings should be interpreted cautiously at ages ≥65, given limited follow-up time (2,205 person-years).

Figure 1: Cumulative Incidence of Breast Cancer from 2000-2015 in the NA-ACCORD.

Conclusion: We observed lower than anticipated cumulative incidence of breast cancer, underscoring recent studies indicating a potentially lower risk of breast cancer in women with versus without HIV. We also found no differences in breast cancer incidence by race, calendar time or CD4 count at ART initiation. Further investigation is required to characterize breast cancer in women with HIV, especially as this population continues to age and more follow-up time is observed. Future analyses will include regression methods to estimate adjusted risk ratios for breast cancer and account for the competing risk of death given the potential differential impact of mortality by race among women with HIV in North America.

57. Determinants of Survival Among a Community-Based Sample of Adults With HIV-Related Kaposi's Sarcoma Identified by Rapid Case Ascertainment

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Background: Our current understanding of the factors that determine survival following diagnosis of HIV-related Kaposi sarcoma (KS) in sub-Saharan Africa has been shaped either by data from the pre-anti-retroviral therapy era, extrapolation of findings from resource-rich settings, or patients from tertiary care settings and clinical trial populations. Moreover, survival data obtained during routine HIV care is potentially fraught with measurement error, missing data, and considerable loss to follow-up. These limitations have hampered our knowledge of accurate, contemporary, representative estimates of survival and the factors that determine prognosis. To address this, we designed a cohort study of a community-based sample of adults with newly diagnosed HIV-related KS.

Methods: HIV-infected adults with a new diagnosis of KS were identified from 3 primary care networks in Kenya and Uganda using rapid case ascertainment (RCA). KS diagnosis was confirmed by histopathology, unless the only available lesions were deemed unsafe for biopsy. After interview and physical examination at the time of RCA, participants were then longitudinally followed with evaluation every 16 weeks. To achieve complete ascertainment of vital status, we tracked patients in the community if they failed to return to their health care facilities. A death adjudication process, including interviews of relatives and record review, was done to understand contribution of KS to death.

Results: Among the 367 participants identified with newly diagnosed KS, 31% were women, the median (IQR) age was 35 (30-42) years, hemoglobin 11 (9-13) g/dl, CD4 count 245 (97-422) cells/mm^3, and 41% had undetectable plasma HIV RNA. A total of 141 participants died; cumulative incidence of death (95% CI) at 6 months, 12 months and 18 months was 33% (28%-38%), 38% (33%-44%) and 43% (37%-49%), respectively. Of those who died, 76% had ever received chemotherapy, and we were certain that KS contributed to death in 34% but unsure in 62%. Hemoglobin level, CD4 count, plasma HIV RNA viral load, number of KS lesions and number of sites with KS lesions were associated with death in adjusted analyses (Table). Age, sex, ACTG T1 stage and presence of edema were not associated with death.

Conclusion: In a representative community-based sample, a high incidence of mortality denotes the seriousness of the prognosis of KS in HIV-infected adults in the ART era. Lower hemoglobin, lower CD4 count, higher plasma HIV viral load and greater extent of KS are associated with poor survival. Unacceptably poor survival of HIV-infected adults with KS calls for better management of this malignancy, through a multi-faceted approach that includes early detection, improved access to diagnosis, and access to better chemotherapy.

Table. Determinants of Death in Patients with KS

Characteristic	*HR (95% CI)	P
Number of KS lesions		
1-49	Ref.	
≥50	1.6 (1.0-2.6)	0.048
Number of sites with KS lesions, quartiles		
	Ref.	
	1.2 (0.57-2.6)	0.62
	2.2 (1.1-4.7)	0.033
	3.7 (1.8-7.5)	<0.01
Haemoglobin, quartiles, g/dl		
2.6-8.7	Ref.	
8.8-10.6	0.69 (0.41-1.2)	0.16
10.7-12.5	0.29 (0.15-0.57)	<0.01
12.6-17.7	0.22 (0.10-0.49)	<0.01
CD4+ T cell, count/mm³		
≤50	Ref.	
51-200	0.53 (0.29-0.96)	0.037
201-500	0.35 (0.18-0.69)	<0.01
>500	0.25 (0.10-0.62)	<0.01
HIV RNA, plasma log$_{10}$ copies/ml		
≤ 40	Ref.	
41-1,000	0.87 (0.46-1.6)	0.65
1,001-10,000	0.93 (0.38-2.3)	0.87
>10,000	2.2 (1.2-4.1)	0.01

*Hazard ratio adjusted for directed acyclic graph-informed confounding: sex, age, CD4 count and plasma HIV RNA

58. **Early Progression and Immune Reconstitution Inflammatory Syndrome During Treatment of Mild-to-Moderate Kaposi's Sarcoma in Low-Resource Settings: Incidence, Long-Term Outcomes, and Effects of Early Chemotherapy**

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Background: Initiation of antiretroviral therapy (ART) for AIDS-associated Kaposi sarcoma (KS) may be associated with early KS progression (KS-PD), sometimes with immune reconstitution inflammatory syndrome (KS-IRIS). Little is known about the relationship of these early events to long-term outcomes.

Methods: Early KS-PD and KS-IRIS outcomes were assessed in the A5264/AMC067 clinical trial in which 190 participants with limited-stage AIDS-KS were randomized to initiate ART with either immediate oral etoposide (ET) or as-needed ET after PD on ART alone. Early KS-PD was defined as KS-PD within 12 wks of ART initiation. When early KS-PD was concerning for KS-IRIS, additional evaluations were performed. Suspected KS-IRIS was defined as early KS-PD accompanied by a CD4+ count increase $\geq 50/mm^3$ or plasma HIV-1 RNA decrease $\geq 0.5 \log_{10}$ copies/mL from baseline. The trial clinical outcome was categorized as Failure, Stable and Response at 48 and 96 wks driven by KS status compared to baseline.

Results: Fifty of 190 participants had early KS-PD (27%; 95% CI, 21–34%); of these, 28 had suspected KS-IRIS (15%; 95% CI, 10–21%). Incidence rates of both early KS-PD (16% versus 39%; P< 0.001) and suspected KS-IRIS (7% versus 21%; P = 0.003) were lower with immediate ET compared to ART alone. Early KS-PD and KS-IRIS were both associated with a higher rate of Failure and a lower cumulative incidence of KS tumor response by wk 96:

Clinical Outcome		Early KS Progressive Disease			Suspected KS-IRIS		
		Yes (N=45)	No (N=118)	P	Yes (N=25)	No (N=138)	P
48 weeks	Failure (%)	37 (82)	53 (45)	< 0.001*	22 (88)	68 (49)	< 0.001*
	Stable (%)	1 (2)	21 (18)		0 (0)	22 (16)	
	Response (%)	7 (16)	44 (37)		3 (12)	48 (35)	
		Yes (N=38)	No (N=81)		Yes (N=20)	No (N=99)	
96 weeks	Failure (%)	27 (71)	39 (48)	0.040*	15 (75)	51 (52)	0.088*
	Stable (%)	0 (0)	4 (5)		0 (0)	4 (4)	
	Response (%)	11 (29)	38 (47)		5 (25)	44 (44)	
		Yes (N=50)	No (N=140)		Yes (N=28)	No (N=162)	
Cumulative incidence of KS response, % (95% CI)		22 (11, 35)	64 (52, 74)	< 0.001**	18 (5, 37)	59 (48, 68)	0.007**

*Wilcoxon exact test stratified by study arm; ** Gray's test stratified by study arm

Conclusion: Early KS-PD, including suspected KS-IRIS, was common after starting ART for AIDS-KS and was associated with worse longer-term clinical outcomes. Starting ART concurrently with oral ET chemotherapy reduced the incidence of both early KS-PD and suspected KS-IRIS compared to ART alone. Early identification of individuals at high-risk for these events could be used as a strategy to improve AIDS-KS treatment in low-resource settings.

59. **Clinical Factors Associated With Cervical Cancer Screening History in Women With Cervical Cancer in Botswana**

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Objective: Cervical cancer is the leading cause of cancer death in women in Botswana. This issue is compounded by a high burden of co-infection with HPV and HIV. Women encounter significant barriers to cervical cancer screening including access to health care facilities and education about the need for screening. In this analysis, we aim to describe differences in presentation between women with locally advanced cervical cancer who did and did not receive screening and also consider differences in women with HIV.

Methods: We prospectively enrolled patients with histologically confirmed cervical cancer between April 2014-July 2019 at Princess Marina Hospital in Botswana. Demographics and clinical characteristics of patients were recorded and months from screening to path diagnosis was calculated.

Results: Of 816 women, 495 (60.7%) had previously been screened at least once at the time of diagnosis. Number of screenings are as follows: 430 patients had one screen, 41 had two screens, 9 had three screens, and 15 had an unknown number of screens. Of 801 with known HIV status, 566 (70.7%) were HIV positive.

Women who received screening were significantly younger at treatment initiation than those who were not screened (mean±SE age: 48±0.5 vs. 54±0.8 years, respectively, p<0.001). They also presented at an earlier stage (p<0.001). Women with HIV were more likely to have previous screening than those without HIV (66% vs. 51%, respectively, p<0.001). Performance status and distance traveled for care did not differ between groups.

In women who did receive screening, the mean ± SD time from last screening before cancer diagnosis and pathology diagnosis of cancer was 24 ± 42 months, with a median of 12 months. There was no significant difference in time to cancer diagnosis between women with early and late stage disease. However, women with HIV had longer duration between screen and cancer diagnosis compared to women without HIV (mean±SE delay: 27±2 vs. 16±3 months, respectively, p=0.02).

In the subset of women with HIV, there was no significant difference in screening history when stratified by nadir CD4 count or nadir viral load. However, CD4 count at diagnosis was significantly higher in women who had been screened compared to those who had not (mean±SE CD4 cell count: 504±17 vs. 433±20, respectively, p=0.009).

Conclusion: Women who have previously received cervical cancer screening in Botswana were younger, diagnosed with earlier stage disease, and living with HIV infection. The average time between last screening before cancer diagnosis and pathological diagnosis of cancer was 24 months and women with HIV were more likely to experience delay in cancer diagnosis after screening compared to women without HIV. Women with HIV who had received screening were shown to have higher CD4 counts at diagnosis than those who were not screened. These results suggest that efforts to screen for cervical cancer are identifying women at risk and referring them for cancer treatment at an earlier stage of disease. However, delays in cancer diagnosis are still significant and although women with HIV who received screening have higher CD4 counts, they are experiencing more significant delays in cancer diagnosis after screening than their counterparts without HIV infection.

60. Treatment Toxicities and Response of Cervical Cancer in Women With and Without HIV in Botswana: Ipabalele Study-1 U54 CA190158-01

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Objective: Cervical cancer is the leading cause of cancer death in women in sub-saharan Africa. This issue is compounded by a high burden of co-infection with HPV and HIV. It remains unclear whether toxicities experienced while on treatment and overall treatment response differ between women with and without HIV.

Methods: Patients with histologically confirmed cervical cancer were prospectively enrolled between Jan 2015-June 2019 to Ipabalele study at the only radiation oncology facility in Botswana. Clinical and treatment characteristics, on-treatment toxicities, and treatment response of patients were recorded. Toxicity was evaluated on treatment using CTCAE 4.0 grading. Treatment response was characterized using SCCAg level <2.2 ng/ml at the end of treatment and 3 months post treatment.

Results: A total of 256 patients were enrolled. Women with HIV comprised 74.6% (n=188) of the cohort. Median CD4 at baseline was 464.0 (IQR: 283.0-644.0) and the post treatment CD4 was 96.0 (64.0-128.0) while the median 3 months post treatment CD4 Count was 177 (IQR: 145-242). The median VL was not detectable at the end of treatment and 3 months post treatment.

Women with HIV were significantly younger than those without (mean±SE: age 44.5±0.6 vs. 55.5±1.4, respectively, p<0.001). They were also significantly more likely to be single rather than married, widowed, or divorced (72.7% vs. 55.6%, p=0.009). Stage at presentation was not significantly different based on HIV status. There was no difference in treatment received in the HIV infected vs. uninfected women. Both groups received a median total dose of 46Gy with a brachytherapy dose of 28 Gy.

Creatinine at baseline was not significantly different (mean±SE: Cr 70.1±7.0 vs. 62.6±2.3 in HIV± and HIV-, respectively, p=0.54). Similarly, hemoglobin level was not significantly different in HIV infected vs. uninfected women (mean±SE: Hb 11.9±0.6 vs. 13.3±1.4, p=0.35). However albumin level was lower for HIV infected vs. uninfected (mean±SE: Albumin 39.5±0.5 vs. 41.8±0.4, p=0.001). On-treatment grade 3/4 hematologic (hemoglobin, white blood count (WBC), neutrophil) and renal toxicity did not differ by age, stage or HIV status. However, higher hematologic toxicity including hemoglobin and WBC levels was associated with receipt of more cycles of chemotherapy (p=0.011). Creatinine levels reflecting renal toxicity of grade 3/4 was associated with a lower total radiation dose (mean±SE: 28.62 ±8.024 Gy vs. 46.392±0.328 Gy, p=0.001). Multivariable analysis (MVA) adjusting for HIV, stage, age and treatment showed that lower hemoglobin during treatment was associated with higher stage disease (OR=1.9, p=0.05) and older age (OR=1.0, p=0.03), and likewise WBC toxicity was associated with older age (OR=0.9, p=0.01).

Overall, 59% (n=144) of patients completed treatment. There was no difference in treatment completion based on age, stage or HIV status. Overall, 66.5% (n=107 of 161) of patients demonstrated treatment response at the end of treatment; MVA showed higher age and higher number of chemo cycles to be positively associated with treatment response (OR=0.9, p=0.01 and OR=0.6, p=0.01, respectively). At three months 67.7% (n=44 of 65) had treatment response. On UVA, treatment response was also associated with higher median brachytherapy dose (p=0.049).

Conclusion: Women treated for cervical cancer in Botswana had high rate of HIV infection. Although these women are generally younger, they do not present with more advanced disease. Overall 59% of patients completed their full prescription of treatment and over 65% demonstrated response at end of treatment and at 3 months post-treatment. HIV status was not associated with treatment completion or response. These results suggest that women in Botswana with well-managed HIV experience similar toxicities and outcomes to uninfected women.

61.   Factors Associated With Increased Toxicity in HIV-Infected Women Undergoing Chemoradiation in Botswana (Ipabalele Study-1 U54 CA190158-01)

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Background: Sub-Saharan African bares one of the highest global burdens for cervical cancer. Persistent HPV infection and infection with HIV lead to increased risk for acquiring cervical cancer. In Botswana, cervical cancer is the leading cause of cancer death in women and the prevalence of HIV is 34% in adult women. Standard treatment for locally advanced cervical cancer is chemoradiation (CRT), yet limited research has focused on the impact of HIV status on treatment toxicities in women with cervical cancer. In this study, we demonstrate the factors that increase toxicities during CRT for HIV-infected women with cervical cancer.

Methods: Patients with histologically confirmed cervical cancer were prospectively enrolled between Jan 2015-June 2019 to Ipabalele study at the only radiation oncology facility in Botswana. A cohort of 180 HIV-infected women were included in analysis. Patient records were reviewed for treatment toxicities using CTCAE 4.0 criteria.

Results: 180 HIV-infected women with diagnosed cervical cancer were followed for a periodof 3 months post-treatment. Mean age of cohort was 44 years old (range 22-71 years old). 97% of patients were on anti-retrovirals (ART) at the time of diagnosis for a mean of 7 years (range 0-19). Most patients were on tenofovir (61%), NNRTI (42%) or zidovudine (AZT, 30%) based regimen. Baseline mean$\pm$SD CD4 count was 484$\pm$247 cells/µL and mean$\pm$SD end of treatment CD4 was 110$\pm$100 cells/µL with an average change of -381 cells/µL. Mean$\pm$SD 3 month post-treatment CD4 count was 198$\pm$87 cells/µL. The majority of participants had stable, undetectable viral load between baseline, EOT (end of treatment), and 3 month follow-up (83%, 86%, and 86%, respectively). The mean total RT dose given during treatment was 47.44 Gy (external beam radiation and boost), 24.5Gy brachytherapy, and 4 chemotherapy cycles. 119/177 (67%) suffered a grade 3-4 toxicity, nearly all of which were hematologic in nature. Baseline lab values, CD4 counts and viral loads before and after treatment, stage of cancer, and extent of treatment received were all evaluated for association with worsening toxicity during treatment. Among those on ART, patients on zidovudine based regimens have a significantly higher rate of Grade 3-4 toxicity leukocyte toxicity (57% vs. 17%, p<0.001) and neutrophil toxicity compared to those who are not on AZT based regimens (28% vs. 7%, p <0.001), while patients on tenofovir regimens had lower rates of grade 3-4 neutrophil toxicities (8% vs 23%, p=0.001), and leukocyte toxicity (19% vs 45%, p=0.001). Changes in CD4 at the end of treatment were not associated with toxicity.

Conclusion: ART treatments impacted the extent of toxicity seen in patients, with those on AZT regimens experiencing higher rates of hematologic toxicities and those on tenofovir regimens demonstrating lower rates. Viral load remained undetectable and constant through treatment for the vast majority of women.

62. Impact of HIV Infection on the Natural History of HPV-Associated Cervical Cancer (Ipabalele Study-1 U54 CA190158-01): Comparison of Three Cohorts

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Background: Persistent HPV-infection and infection with HIV are known to increase the risk of cervical cancer. Sub-Saharan Africa carries a large burden cervical cancer and HIV. In Botswana, cervical cancer is the most prevalent cause of cancer death in women and while widespread implementation of a public ART program has significantly reduced mortality due to AIDS-related infections, cervical cancer incidence continues to rise at a rate of 3%/year. The aim of this study is to determine the effect of HIV infection on the natural history of HPV-associated cervical cancer.

Methods: In order to map the natural history of HPV in a high-prevalence HIV region, three cohorts were followed in Botswana. Cohort 1 was designed to investigate early infection and included females, HPV- and HIV-uninfected recruited in early years of university. Cohort 2 was designed to investigate precancerous HPV-infected women diagnosed with cervical intraepithelial neoplasia (CIN), both HIV-uninfected or HIV-infected. Cohort 3 were women with locally advanced cervical cancer, HIV-infected or HIV-uninfected receiving curative chemoradiation. In order to demonstrate demographic and clinical characteristics, univariate analysis and prevalence statistics were calculated as follows.

Results: A total of 1726 females were enrolled. 1123 females in Cohort 1, 349 females in Cohort 2, and 254 females in Cohort 3. The median age was youngest in Cohort 1 (19, range 18-33), then cohort 2 (40, range 19-70), and eldest in cohort 3 (47, range 22-74). Only 3% of cohort 3 (7/246) were ever smokers while 11% (129/994) in cohort 1 were ever smokers. HIV prevalence in Cohort 2 and Cohort 3 was 77%, 267/348 and 75%, 187/250, respectively. Among those who were HIV-infected in cohorts 2 and 3, 98 and 99% were on ART treatment, respectively. The highest prevalence of current sexual activity was in cohort 2 (n=305, 88%), then cohort 1 (n=737, 66%), and lowest in cohort 3 (n=123, 50%). Cohort 1 most commonly had 1 sexual partner (n=402, 55%), while cohort 2 most commonly had >5 (n=137, 45%), and cohort 3 most commonly had 3 lifetime sexual partners (n=70, 31%). Respondents in cohort 2 were more likely to have been ever diagnosed with an STI (n=150, 43%) than cohort 1 (n=63, 6%) or cohort 3 (n=0, 0%). Only 8 individuals (1%) in cohort 1 had been screened for cervical cancer, while 99% (n=342) in cohort 2 were screened, and 63% (n=154) in cohort 3. The most common CIN pathologies for Cohort 2 included CIN III (n=185, 60%) and CIN II (n=34, 11%). HIV-infected individuals in Cohort 2 were more likely to have a diagnosis of CIN II (63.8%, 148/232) vs. CIN I (11.2%, 26/232) or CIN III (10.5%, 9/232). Similar patterns were seen for HIV-uninfected individuals (CIN II 48.6%, CIN I 10.5%, and CIN III 2.6%). Among the cervical cancers diagnosed in cohort 3, stage IIB was most common (n=95, 40%), followed by IIIB (n=62, 26%). Among HIV-infected women in cohort 3, the majority had stage IIB cancer (77/182, 42.3%) followed by stage IIIB (50/182, 27.4%), while among HIV-uninfected women 33.8% (20/59) had stage IIB and 23.9% (14/59) had stage IIIB.

Conclusion: Three prospective cohorts of patients were enrolled in Botswana to determine the role of HIV infection over the natural history of cervical cancer. Potentially important differences in the baseline characteristics of participants of each are noted and may represent factors associated with different stages of the progression towards cancer. Future analyses will determine the behavioral, clinical, immunological and microbiological factors effecting the history of cervical cancer in HIV-infected women.

63. Human Papillomavirus Characterization of Anogenital Malignancies in Patients in Botswana

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Background: Human papillomavirus (HPV) is one of the most common sexually transmitted infections worldwide and is known to play a significant role in the tumorigenesis of many different cancers. Anogenital malignancies have become a significant public health issue especially in countries with high prevalence of human immunodeficiency virus (HIV). In sub-Saharan Botswana, HIV remains one of the most prevalent sexually transmitted infections (STIs) within its two million inhabitants. Research has established that disease progression and severity from HPV-associated anogenital malignancies is exacerbated in cases with HIV co-infections. This study investigates the association and influence of HPV subtypes in various anogenital malignancies and hypothesizes that a specific or set of common HPV signatures are predominant etiological contributors to the pathology of all anogenital types in patients with or without HIV infection.

Methods: Six anogenital types were represented in this study, including: anal, vulvar, penile, vaginal, anorectal, as well as head and neck. A total of 97 specimens originating from patients presenting for radiation. Biopsy samples were obtained for microbiome screening analysis using pan-pathogen PathoChip microarrays.

Results: Microbiome signature analysis detected Papillomaviridae with the most significant and strongest hybridization signal intensity of human viral family signatures within all anogenital types. A rich HPV infection profile was found for each anogenital cohort, specifically 13 common HPV signatures were identified. However, no unique signatures characterized any single cohort, thus each HPV subtype was represented in at least two anogenital regions. High-risk HPV-16 was a consistent signature represented and 55.8% prevalent throughout all anogenital specimens. Of the remaining 12 other HPV signatures representing in all anogenital types, HPV subtypes 54 and 61 had the strongest HSI and were most prevalent, at 72.6% and 73.9%, respectively. High-risk HPV-18 was a signature detected in all anogenital specimens excluding anal and vulvar regions, thus 41.8% prevalent among all types. Whereas HPV-41 was 35.1% prevalent among all anogenital types, a signature only detected in the head and neck and vaginal specimens.

Conclusion: Oncogenic subtype HPV-16 was identified consistently within all anogenital specimens screened, potentially contributing to similar pathology and rate of malignant progression throughout all types of anogenital regions. In order to expand this study, clinical outcome data can be correlated to significantly high expression of certain HPV types, helping to pinpoint particular HPV signature(s) that correlate specifically to progressed disease severity. Ultimately, gaining insights on HPV association with different anogenital malignancies and their influence in disease development can provide opportunities for more efficient treatment and preventative strategies, to hopefully alleviate the public health burden in less developed countries.

64. Oncogenic and Sexually Transmitted Infections Associated With Precancerous CIN and Invasive Cervical Tumors in Patients in Botswana (Ipabalele Study-1 U54 CA190158-01)

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Background: While the rate of global cervical cancer incidence has significantly shifted in the last decade given screenings implemented in many public health systems worldwide, cervical cancer remains one of the most prominent forms to affect women in low-to-middle income countries. In the sub-Saharan African country Botswana, HIV prevalence is extremely high and is known to exacerbate the rate of cervical intraepithelial neoplasia (CIN) progression to invasive tumors. It has also been well established that high-risk HPV subtypes, such as 16 and 18, play major contributory roles in cervical tumorigenesis. However, due to economic, political and social restrictions, preventative screening technologies are limited. In this study, PathoChip microarray technology was utilized as a pan-pathogen screening technique to identify HPV and other oncogenic and sexually transmitted infections (STIs) in precancerous CIN stages and invasive cervical cancer specimens originating from patients in the Botswana enrolled in the Ipabalele Study. Additionally, longitudinal analysis of patients first diagnosed with cervical cancer and their microbiome infection profile throughout follow-up visits up to 12 months post-diagnosis was observed.

Methods: Biopsy samples were obtained, totaling 23 non-cancer and CIN I, 77 CIN II/III and cervical squamous cell carcinoma (SCC), and 181 invasive cervical cancer specimens to comprise the pre-cancerous and invasive tumor analysis. Patient samples for post-diagnosis longitudinal analysis were organized into three separate cohorts: 159 baseline specimens, 126 specimens in post 3-6 months, and 44 specimens in post 9-12 months from diagnosis.

Results: Microbiome signature species analysis identified 1996 viral, 71 bacterial, 32 fungal and 4 parasitic signatures among CIN II/III and SCC specimens when compared to non-cancer/CIN I. Papillomaviridae was identified as a prominent viral family signature, ranking 23 out of 88 signature viral families. 40 HPV signatures characterize CIN II/II and SCC, HPV-103 subtype was the most prevalent at 81.8% and had the strongest hybridization signal intensity (HSI). High-risk HPV 18 and 16 were also prevalent signatures in CIN II/III and SCC, 20% and 16.7% respectively. MAT analysis plotting hotspot regions within a genome highlighted HPV-16 viral genes E6 and E7 at significant levels in CIN II/III and SCC samples. 23 STI and 9 oncogenic signatures were detected among CIN II/III and SCC specimens with *candida albicans* found in 53%, and oncogenic human-T lymphotropic virus 1 found in 28%. Signature breakdown analysis of CIN II and CIN III stages found a significant increase in HPV, STI and oncogenic virome profiles in CIN III cases, where 38 unique signatures emerged. The most predominant unique STI and oncogenic signatures in CIN III identified *chlamydophila pneumoniae* and oncogenic human-T lymphotropic virus 4. The invasive cervical cancer samples detected a similarly rich HPV infection profile to CIN II/III and SCC specimens, totaling 39 HPV signatures significantly identified. High-risk HPV 16 and 18 subtypes were found at 16.1% and 3% among all invasive tumor specimens. Whereas, low-risk HPV-6b was found at 29.3% among all clinical samples. Specifically, viral genes E6, E1 and L1 had high signal intensities. Longitudinal analysis of cervical cancer samples collected post-diagnosis identified 25 HPV signatures to persist from baseline through to 9-12 months post-diagnosis, including high-risk types 16 and 18. Interestingly, 4 low-risk HPV signatures were cleared by 9-12 months, where only low-risk HPV-9 emerged as a new signature in 3-6 months post diagnosis. Furthermore, an increasing trend of HPVs, STIs and oncogenic infection profiles continuing from baseline to 3-6 months was observed, but no unique HPV infections were introduced in 9-12 months post diagnosis, and trends in STI and oncogenic viral infections decreased.

Conclusion: A rich microenvironment of HPVs, STIs and oncogenic viruses was maintained throughout precancerous stages of intraepithelial neoplasia and intensified in invasive cervical cancer cases. Particularly high-risk HPV-16 and HPV-18 types were consistent signatures throughout cervical tumorigenesis and persisted into a year post-diagnosis. To further expand on the current analysis requires correlation of HIV infections with HPV and STI persistence/clearance throughout the progression of cervical malignant lesions into invasive tumors. This will provide significant understanding of the dynamics of the dysbiotic microenvironment and potentially provide insights into pathology and rate of disease severity. This study will aid explanation of clinical outcomes and pave the way for new efficient therapeutic strategies to reduce the heightened burden of cervical cancer incidence and related deaths in Botswana, as well as in other developing countries.

65. Identification and Characterization of Pretreatment Tumor Infiltrating Lymphocytes in Tumor Biopsies of Locally Advanced Cervical SCC Patients in Botswana

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Background: Despite the implementation of screening programs and vaccines against high-risk human papillomavirus (HR-HPV), cervical cancer (CaCx) remains the leading cancer among women in Botswana. Persistent infection with HR-HPV especially in women with HIV infection is a known etiological factor in the development of cervical intraepithelial neoplasia and CaCx. However, the interaction between tumor cells and the microenvironment plays a fundamental role in disease progression. Since tumor infiltrating lymphocytes (TILs), mainly CD4 and CD8 T cells are a major component of the tumor microenvironment, this study aimed to characterize pretreatment intratumoral and peritumoral lymphocyte markers in patients with locally advanced cervical cancer.

Methods: Immunohistochemistry (IHC) was performed to evaluate quantity and distribution of CD4+ and CD8+T infiltrating lymphocytes as well as expression of CD14, PD-1, PD-L1 and FOXP3 on formalin-fixed paraffin embedded tissue sections of 69 cervical cancer patients. Positively stained TILs were counted in ten high power fields at 40X magnification and the counts were averaged. The frequency of positive stained TILs was recorded as: 1+ = low TILs (<25%), 2+ = moderate (25%-50%), and 3+ = high lymphocytic infiltrate (>50%).

Results: A total of 68 cervical carcinoma patients were enrolled. Of those, 48 (70.6 %) were HIV infected and 20 (29.4%) were HIV uninfected. The median age was 50 years (IQR= 42-58) and the baseline median CD4 count among the HIV infected patients was 525 (IQR: 344-592). Overall, infiltration of CD4+ lymphocytes was greater (44/68; 64.7 %) compared to CD8+ lymphocytes (26/68; 38.2 %). There was no difference in TIL staining by HIV status for all markers examined. The patients with HPV 16 and/or 18 displayed high (>50%) CD14+ lymphocytic infiltration (56.5%) compared to patients with other HR HPV genotypes (34.8%). Patients from lower FIGO stages (I to II) appeared to have higher percentages of CD4+ TILs compared to those with higher stages III to IV (71.7% stage I-II vs 50.0% stage III-IV). Stratification according to age revealed that compared to younger patients (age ≤50 years), older patients (age >50 years) had a lower expression of PD1+ and PD-L1+ TILs.

Conclusion: Our study shows higher CD4+ TIL infiltration in cervical cancer patients compared to CD8+ TIL infiltration. We also observed a higher percentage of TILs in cervical cancer tissue from patients infected with HPV 16 and/or 18. These findings support the need for additional studies to investigate the link between frequency and/or tumor tissue distribution of TILs with treatment response, as a basis for evaluating whether TILs can serve as prognostic biomarkers for cervical cancer staging and stratification this population.

66. Identifying Delays in Cervical Cancer Treatment for HIV-Positive Patients at a Tertiary Care Center in Botswana

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Background: Cervical cancer disproportionately affects and kills more women in low and middle income countries (1). With one of the highest HIV infection rates, Botswana has to navigate the challenges of HIV/AIDS treatment and cervical cancer care. Previous studies have outlined barriers to care in Botswana including a limited primary care system, insufficient health promotion and information(1). Our aim was to examine delays in cervical cancer care in patients with and without HIV. Similar analyses have defined delays as >1 months between detecting symptoms to visiting 1st doctor, >3 months between consultation and diagnosis, and >3 months between diagnosis and starting treatment (2).

Methods: Patients with biopsy-proven cervical cancer were enrolled from January 2015 through to June 2019 at Princess Marina Hospital in Botswana. Exclusion criteria were patients with unknown HIV diagnosis at the time of enrollment or prior to cancer diagnosis. Demographic information collected included age, FIGO stage, performance status, cancer treatment, and HIV status/treatment. The primary outcome was defined as differences in time from first cancer associated symptoms to diagnosis, time from diagnosis to visit, from seeing first doctor to presenting at a tertiary care facility, from biopsy to date of visit, from diagnosis to starting radiation therapy, and from oncology clinic to starting radiation therapy between patients with and without HIV. Categorical variables were analyzed using chi squared test and continuous variables were analyzed with 2-sided t-test.

Results: Of 848 patients enrolled in the study, 586 patients were HIV positive at the time of cancer diagnosis and 579 (68%) had HIV diagnosis prior to cancer diagnosis. There were no significant differences in chemoradiation treatment between patients with and without HIV. HIV positive patients were significantly more likely to wait after experiencing first symptoms to visit the doctor than HIV negative patients (mean$\pm$SD: 5$\pm$0.9 mos. vs. 2$\pm$0.5 mos., p = 0.04), however all patients experienced delays in presentation to care defined as greater than 1 month. Although there were no significant differences in time from from diagnosis to starting cancer treatment (4 mos vs. 3 mos, p=0.41), all patients met the definition of a delay in care (> 3 months). There were no significant differences between time from visiting the first doctor to presenting at a tertiary care facility (13 vs 11 mos, p= 0.59), time from the date of biopsy to follow up visit (5 mos vs 4 mos, p= 0.59), time from the date of diagnosis to follow up visit (3 mos, p = 0.85), and time from oncology clinic to radiation treatment (3 mos vs 2 mos, p=0.73).

Conclusion: All patients regardless of HIV status had delays in care by standard definitions. HIV status was likely to delay initial presentation after experiencing symptoms, however once care was accessed, no significant differences in delay were noted. It is possible that symptoms of HIV may confound cervical cancer symptoms, delaying access to care. As HIV positive patients are at increased risk of cervical dysplasia and cancer, future efforts should be focused on patient education of symptoms and screening practices.1) Matenge, Tjedza, et al. Barriers to accessing cervical cancer screening among HIV positive women in Kgatleng district, Botswana: A qualitative study. *PLoS One.* 2018, Oct 24; 13(10).2) Bhatia, Rohini et al. Patient Factors Associated With Delays in Obtaining Cancer Care in Botswana. *Journal of Global Oncology.* 2018, Aug; 4:1-13.

67. **Understanding the Role of Traditional Healers in Cervical Cancer Treatment in Botswana**

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Background: Cervical cancer disproportionately affects women in low and middle income countries and is the leading cause of cancer deaths in Botswana (1). Previous studies have described challenges in treatment in Botswana, including distance from treatment centers, poor healthcare systems, easier access to traditional healers, financial opportunity costs, limited cancer awareness, and cancer stigma (1). Our objective was to understand the impact of traditional healers in cervical cancer treatment in Botswana.

Methods: Patients with cervical cancer confirmed by pathology were enrolled from January 2015 through June 2019. Demographic information collected included age at the time of diagnosis, FIGO stage, performance status, cancer treatment and HIV status/treatment. A semi-structured interview was performed with patients regarding the use of a traditional healer. Patients were followed through initial treatment. The primary outcome was to see if there was a delay in care for patients seeking out traditional healers vs. those who did not. Data was collected for time from patient's first symptoms to visiting first doctor, from seeing first doctor to visiting a tertiary care facility, from pathology diagnosis to date of visit, from the date of biopsy to date of visit, months from pathology diagnosis to starting radiation therapy, and from visiting Princess Marina Hospital to receiving radiation treatment. Categorical variables were analyzed using chi squared test and continuous variables were analyzed with 2-sided t-test.

Results: Of the 848 patients enrolled, 89 (10%) were seeing a natural healer at the time of cancer diagnosis. 585 (69%) were HIV positive. Patients seeing traditional healer had higher stage of disease (56% with Stage III/IV disease vs 45%, $p < 0.001$). Of the HIV positive patients in the cohort, viral load, and CD4 count were similar while rates of antiretroviral treatment were significantly lower in patients seeing a natural healer (96% vs. 89%, $p=0.01$). There were no differences in time to care from date of diagnosis or biopsy to date of first clinic visit, and from starting cancer treatment to transferring for radiation treatment in patients who utilized traditional healers vs. those who did not. Only 10 of the 89 patients using traditional healers were taking traditional medicine and only 20 of them were seeking cancer-related care. Patients reported using traditional healers for spiritual care and to understand their illness.

Conclusion: Patients seeking out traditional healers present with a higher stage of disease, which may present a delay in care not measured by variables in our study. Often patients are not only seeking out medical care but also spiritual care, potentially providing ancillary support at the time of diagnosis. In South Africa, natural healers have been used as a tool to help educate and destigmatize cervical cancer screening and treatment (2). Future areas of study could include incorporation of traditional healers in cervical cancer screening and treatment.

References:

1. Grover, Surbhi et al. Cervical Cancer in Botswana: current state and future steps for screening and treatment programs. *Journal of Global Oncology.* 2015. Vol 5. Article 239.
2. Nelson, Jennifer, et al. Healers in a non-traditional role: a focus group study of Sangoma's knowledge of and attitudes to cervical cancer prevention and screening in Johannesburg, South Africa. *Sexual and Reproductive Healthcare.* 2010. 195-196.

68. **Impact of Treatment and HIV Status on Quality of Life Before, During, and After Cervical Cancer Treatment in Women in Botswana (Study-1 U54 CA190158-01)**

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Background: A significant portion of Botswana's women undergo chemoradiation (CRT) for cervical cancer, the most common cancer in women in Botswana, at any given time, but little is understood about CRT's impact on patients' quality of life, especially in light of high rates of HIV co-infection.

Methods: Patients with histologically confirmed cervical cancer were prospectively enrolled between Jan 2015-June 2019 to Ipabalele study at the only radiation oncology facility in Botswana. The European Organization for Research and Treatment of Cancer Core Quality of Life (QLQ-C30) and cervical cancer-specific (QLQ-Cx24) questionnaires were used. Questionnaires were completed prior to treatment, at the conclusion of treatment, and 3 months post-treatment.

Results: 256 participants were enrolled into this protocol. 248 had QLQ-C30 Qol data available at baseline, end of treatment and three months follow up; 228 had completed QLQ-Cx24 Qol data at these time points. Both the HIV-infected and HIV-uninfected groups saw an increase over time in their global health status, with demonstrated mean±SD for the global health status score for HIV-infected and HIV-uninfected, respectively, as follows: at the start of treatment 65.3±24.6 vs 64.7±24.4, at the end of treatment 68.7±25.0 vs 71.4±24.6, and at 3-month post treatment 78.1±16.2 vs 76.3±11.7. Compared to treatment initiation, there was about 1.3 (SD=0.9) and 1.5 (SD=1.5) fold increase in the global health score at the end of treatment for the HIV-infected and HIV-uninfected respectively; similarly there was a respective increase of 1.6 (SD=1.6) and 1.5 (SD=1.0) fold at 3 months post treatment for the same groups.

With regard to differences found between the HIV-infected vs. uninfected groups, we found no differences in self-reported global health status, functional scale, and symptom scale as captured within the QLQ-C30 except for the following statistically significant findings: HIV-uninfected participants were more likely than HIV-infected participants to report appetite loss at the conclusion of treatment (change in mean score ± SE: 33.33(34.43) in HIV-infected vs 23.22(29.03) in HIV-uninfected, p=0.04) and feeling satisfied with their emotional functioning at 3 months post-treatment (93.12(15.74) vs 86.51(27.53), p=0.05); HIV-infected patients were more likely to report increased satisfaction with their cognitive functioning at 3 months post-treatment relative to those without HIV infection (84.92(22.50) vs 77.54(22.56), p=0.05). Additionally, we found that amongst the participants who completed the QLQ-CX24 questionnaire, HIV-uninfected patients were more likely to report peripheral neuropathy (19.89(27.30) vs 12.25(20.12), p=0.05) and menopausal symptoms (20.43(30.99) vs 11.23(22.19), p=0.03) than HIV-infected participants at 3 months post-treatment. No other differences between the groups in the QLQ-CX24 function scale or symptom scale were found.

Conclusion: Going through the experience of chemoradiation to treat cervical cancer affects a patient's quality of life in many ways. HIV status does impact some facets of quality of life, though the mechanism through which HIV status is impacting these dimensions is not well understood. More research is needed to further elaborate the role of HIV status in affecting cervical cancer patients' quality of life before, during, and after chemoradiation.

69. **Building Research Capacity Through Program Development and Research Implementation in Resource-Limited Settings: The Ipabalele Study: Determining the Effect of HIV on the Natural History of Cervical Cancer in Botswana**

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Introduction: The global burden of cancer continues to increase in low- and middle-income countries, particularly in sub-Saharan Africa (SSA). Botswana is a middle-income country in SSA with the second highest prevalence of HIV globally. In the context of improved survival of HIV-infected women in Botswana, an increase in HPV-associated cervical cancer has been documented over the last decade. This poses a serious public health dilemma with devastating consequences for women in this population. There is an urgent need to obtain information to understand more clearly the epidemiology, pathogenesis, risk factors, and optimal preventive and therapeutic strategies for targeting HPV-associated cervical cancer in the setting of HIV infection. We initiated the Ipabalele ("take care of yourself" in Setswana, the national language of Botswana) program to both address this need for new knowledge and to initiate long-term research program capacity building in the region. This study was funded by the Sub-Saharan African Collaborative HIV and Cancer Consortia-U54.

We will describe the components of the Ipabalele program, which includes three main projects addressing basic, translational and behavioral research questions, as well as a number of essential cores to support the activities of the three projects. Implementation of this program occurred through the involvement of local stakeholders in Gaborone, Botswana and the Perelman School of Medicine at the University of Pennsylvania in collaboration with the National Cancer Institute, National Institutes of Health.

Methods and Procedures: Our multidisciplinary approach aims to provide a comprehensive understanding of the problem by simultaneously implementing three complementary research studies aimed at identifying its molecular, behavioral and clinical determinants in the setting of southern Africa. Three participant cohorts were designed to represent the early, intermediate and late stages of the natural history of cervical cancer, respectively.

The functional structure of the program is coordinated through the development of a number of essential programmatic cores. These cores allow for full integration of each of the studies within the designed cohorts while providing support for the implementation of pilot studies led by local junior investigators. Each project of the Ipabalele program includes a built-in capacity building component, promoting the establishment of long-lasting functional and physical infrastructure for future research activities.

70. Long-Term Outcomes of 58 Patients With HIV and KSHV-Associated Multicentric Castleman Disease

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Background: Multicentric Castleman disease (MCD) is a rare HIV-associated systemic lymphoproliferative disease caused by Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpes virus 8 (HHV-8). Patients with HIV and KSHV-MCD may also have Kaposi sarcoma (KS) and are at increased risk of developing non-Hodgkin lymphoma, especially primary effusion lymphoma (PEL). The historical overall survival was 2.5 years, but this has improved following the development of improved therapies for KSHV-MCD. Here, we present the long-term outcomes of the largest prospective study of KSHV-MCD and HIV+ patients in North America.

Methods: We evaluated long-term outcomes and concurrent diagnoses (KS and PEL) that influenced overall survival for patients with HIV and KSHV-MCD in a natural history study with 5 optional treatment regimens for KSHV-MCD flares. This included high-dose zidovudine and ganciclovir, sirolimus, rituximab (R) with liposomal doxorubicin (R-LD) followed by interferon-α or high-dose zidovudine with valganciclovir (AZT/VGC), or rituximab plus infusional chemotherapy (R-EPOCH).

Results: There were 58 participants (54 male, 4 female) with a median (range) age of 44 years (26-68). All were diagnosed with HIV+ and had a median HIV VL <50 copies/mL (range: 50 – 64100) and median CD4 count 180 cells/μL (range: 3-1319) at KSHV-MCD diagnosis. All patients were on combined antiretroviral therapy at study entry, 38 patients had received prior therapy for KSHV-MCD (18 patients with R-based therapy), and 39 patients had a concurrent diagnosis of KS. Twenty-five patients (43%) were diagnosed with KSHV-MCD at our institution; 18 of these patients were initially referred for management of KS. Nine patients (15%) developed PEL after entry and 1 patient had been diagnosed with PEL prior to KSHV-MCD. Patients diagnosed with PEL were treated with R-EPOCH. The median duration of follow-up was 4.1 years. Of the treatment options available in this study, the majority [52 patients (89%)] received R-LD, often followed by high-dose AZT/VGC. The 5-year overall survival was 80% (95% confidence interval (CI), 66% to 88%). Eleven patients died: 4 from PEL, 4 from KSHV-MCD and associated complications, 2 from KS and sepsis, and 1 from pancreatic cancer. A concurrent diagnosis of KS was not a significant prognostic factor (hazard ratio (HR) 2.4; 95% CI, 0.5-11.1, P=0.3). However, a diagnosis of PEL among those with KSHV-MCD was associated with worse survival (HR 3.4; 95% CI, 0.99-11.6, P=0.05, figure 1)

Conclusion: KSHV-MCD is an under-diagnosed but highly treatable condition if recognized. Physicians need to identify and promptly treat concurrent diagnoses of PEL and KS that may contribute to morbidity and mortality.
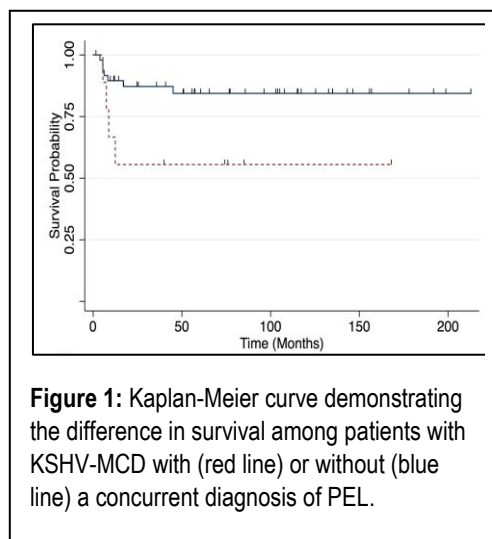
Figure 1: Kaplan-Meier curve demonstrating the difference in survival among patients with KSHV-MCD with (red line) or without (blue line) a concurrent diagnosis of PEL.

71. **Mentoring and Career Development Core: Successful Course and Mentoring Program in Botswana**

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Background: U54 CA190158 is an NIH-funded consortium grant to the University of Botswana (UB) and University of Pennsylvania (PENN) focused on studies related to cervical cancer in HIV infected women in Botswana. The Mentoring and Career Development Core is aimed at building research capacity for faculty at UB. The primary objectives of the Core are to provide educational workshops in biomedical research methods and develop a pilot grant mentoring program for junior faculty.

Methods: The Core directors (ON and HMF) and additional faculty developed an educational program which includes a 2-day workshop entitled "Course on Grant Writing and Research Training" and a mentored pilot grant program for research proposals related to cancer in HIV infected individuals in Botswana. The course has been held annually on the UB campus since 2015, with instructors from both UB and PENN. The typical curriculum involves a half-day of lectures on topics such as: epidemiology of cancer in HIV subjects in Botswana, treatments available for HIV cancer patients in Botswana, preparation of a research protocol, how a biostatistician can assist with protocol development, ethical conduct and IRB submission guidelines, developing a theoretical framework, and how to write a pilot grant application. At the conclusion of the lectures, participants interested in submitting a pilot grant application as a principle investigator (PI) are asked to present their research ideas to the other participants. The remaining time on day 1 and the morning of day 2 are spent with participants gathered in small groups. Senior research faculty from UB and PENN circulate among the groups assisting the PIs in developing their Specific Aims. The last few hours of day 2 are spent with each PI presenting their Specific Aims and hypotheses to the entire class, with time set aside for discussion. The course directors then assign scientific mentors to each PI based on the topic of their research proposal. The intent is for the mentor to assist the PI to develop their pilot grant application, including how to craft the Abstract, Specific Aims and Research Strategy (i.e., Significance, Innovation and Approach). A mentoring plan completes the application. Several scientists from UB and PENN review each application. Written feedback is provided, along with a score using a NIH 1-9 scoring system. Pilot grants are funded for a period of one year.

Results: Over the last 4 years, the number of course attendees ranged from 60-90 and a number of faculty from both UB and Penn participated. To date, 16 pilot grant applications have been received, 8 pilot grants have been funded and 2 pilot projects have been completed. Six projects are ongoing and are expected to result in publications. Because of U54-supported pilot grant funding and mentorship, the 2 grantees who completed their projects have presented their research at international meetings, published research papers (3 published, 2 additional papers in review) and were promoted at UB.

Conclusion: The Mentoring and Career Development Core has successfully provided educational workshops in research methods and developed a pilot grant mentoring program for junior faculty. Skills in both clinical research methods and grant writing acquired from these courses, have impacted the careers of junior faculty in Botswana. Trainees are better equipped to successfully conduct and publish research studies, establish a broader network of scientific collaborators, and obtain grant funding.

72. HPV-Associated Cervical Lesions in Women With Controlled HIV Infection in Uganda

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Background: HIV and high-risk human papilloma virus (HR-HPV) are important risk factors for cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (ICC). We evaluated the prevalence of visual inspection with acetic acid (VIA) abnormalities and HR HPV subtypes in HIV+ women on antiretroviral therapy (ART), as well as risk factors for CIN2/3 and ICC in a cervical dysplasia cohort study in Uganda.

Methods: We recruited HIV-infected women with cervical dysplasia from HIV care facilities in Kampala, Jinja and the Uganda Cancer Institute in Kampala, Uganda. Screening was performed by trained mid-wives and nurses. Consenting women with a VIA lesion >1cm^2 or with suspected cancer were assessed for study eligibility. We enrolled HIV-infected women who were virally suppressed in the past (HIV viral load <1000c/mL) and on ART for at least three months. Sociodemographic data was obtained by interview. Endocervical cells for HPV genotyping and cervical biopsy for histology of VIA+ cervical lesions were collected at colposcopy. Biopsy specimens were categorized as CIN 1, 2, 3 or invasive cancer using hematoxylin and eosin stain. HR-HPV was detected using Linear Array HPV Genotyping (Roche). HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were categorized as high-risk. HPV types 16, 18, 31, 35, 45, and 52 were further categorized as vaccine-preventable. Descriptive statistics were used to determine prevalence of VIA abnormalities and prevalence of one or multiple HR-HPV genotypes. We used logistic regression models to identify demographic characteristics, time on ART, and immune status (CD4 count and CD4/CD8 ratio) and HR-HPV infection related factors associated cervical dysplasia and ICC (none, CIN 1, CIN 2/3, ICC).

Results: From June 2017 – July 2019, we screened 6710 HIV+ women for cervical dysplasia using VIA. 399 (5.9%) were VIA+ and 144 met full eligibility criteria. A total of 123 HIV+ women have complete data at time of analysis. The median age was 34 years. Median time on ART was 68 months (IQR, 36-109). Most women (99, (80%)) had HIV-VL ≤20 copies/mL, 15 (12%) had HIV-VL 20-200 copies/mL, and 9 (7%) had HIV-VL >200 copies/mL. Median CD4 count was 656 cells/μL (IQR 432-873). Only 5 (4%) women had CD4 count below <200; 9 (7%) between 200 - 350; and 109 (89%) had >350 cells/μL. The 123 women included 32 (26%) who were HPV-negative, 15 (12%) with low-risk HPV only and 76 (62%) with HR-HPV; with 26 (21%) having ≥2 HR-HPV strain detected. Among women with HR-HPV, 36 (47%) carried ≥1 HR-HPV type not covered by a vaccine. Seven women (6%) were diagnosed with ICC at enrollment; 40 (33%) with CIN 2/3, 36 (29%) with CIN 1, and 40 (33%) had no dysplasia. HR-HPV was detected in 90% of women with CIN 2/3, 58% of women with CIN 1, and 30% of women without dysplasia. Exclusively vaccine-preventable HR-HPV types were detected in all 7 women with invasive carcinoma. Infection with one or more HR-HPV strains was associated with lower CD4 count (odds ratio (OR), 95% confidence interval (CI): 1.28 (1.12, 1.46) per 100 cells/μL lower) and lower CD4/CD8 ratio (OR (CI), 5.03 (2.27, 11.15) comparing <1 to ≥1). No other baseline factors, including plasma HIV RNA, were associated with HR-HPV infection. Demographic factors and time on ART were not associated with dysplasia. Low CD4 count and CD4/CD8 ratio were associated with CIN 2/3 (OR (CI), 1.35 (1.12, 1.61) per 100 cells/μL lower and 5.76 (2.05, 16.2) comparing <1 to ≥1, respectively). HR-HPV was associated with CIN 2/3 (OR (CI), 15.8 (4.5, 56)) or CIN1 (OR (CI), 3.68 (1.37, 9.89)). Results suggested that odds of CIN 2/3 were higher with infection by multiple HR-HPV types (OR (CI), 6.67 (0.75, 60), P=0.09, comparing >1 HR-HPV to 1 HR-HPV).

Conclusion: In women attending HIV clinics on long standing ART in Central Uganda, VIA prevalence is 5.9%, which is lower than previously published estimates. Immune dysfunction, as measured by CD4 count or CD4/CD8 ratio remains the strongest risk factor for shedding HR HPV and for CIN2/3 or ICC. Preservation of immune function through early initiation of ART may lead to better control of HR HPV and decrease risk of cervical cancer. Nonetheless, cervical cancer screening remains an important form of secondary cervical cancer prevention. Infection with HR HPV genotypes not covered by the HPV vaccines available in Uganda is highly prevalent. There is need to investigate the role of these HPV genotypes in the development of cervical cancer among HIV-infected women in this setting.

73. *'I swore to myself that men should never see my private parts unless I am giving birth":* Women's Experiences With Self-Sampling During Community-Based Cervical Cancer Screening in Rural Uganda

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Background: Cervical cancer screening strategies incorporating self-collected cervicovaginal specimens are of increasing interest, and studies have found that offering self-testing in health facilities is acceptable and even preferable to women. However, the population and screening experience within health facilities may be distinct from community-based screening, where women are less familiar with cervical cancer screening and physical quarters for testing are less structured. To date, little is known about how women in the community-based screening may feel and react to being asked to provide a self-collected sample for cervical cancer screening at a community venue. As part of a larger study that evaluated a public health approach to cervical cancer screening through community-based self-administered HPV testing and mobile treatment provision in western Uganda, we explored factors contributing to screening decision-making, women's experiences with human papillomavirus (HPV) self-sampling in the community, and suggestions to improve uptake of cervical cancer screening.

Methods: The study was conducted in three rural Ugandan districts (Hoima, Kiboga and Kyankwanzi). We trained Village Health Team (VHT) members, a cadre similar to community health workers, to mobilize adult women to attend an HPV screening fair in their community. After the training, the VHTs mobilized women in the target communities to attend the health fair within their community. Venues were mainly playgrounds and community centres (Figure). On the day of the fair, the study team and VHTs provided educational talks and instructions for self-collection of a vaginal sample for HPV after which the women provided a sample. Immediately after the health campaign, we selected 18 women from among those who had participated in the HPV self-testing and conducted in-depth interviews. All interviews were audio recorded and transcribed. Data were analyzed using content thematic approach.
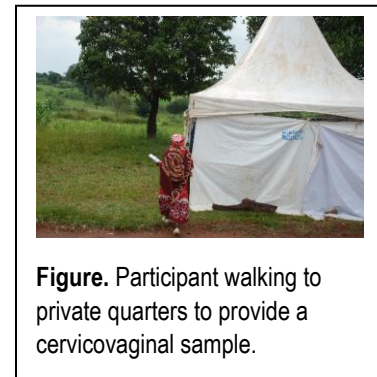
Figure. Participant walking to private quarters to provide a cervicovaginal sample.

Results: The major motivators for women's attendance of the health fair and provision of self-sample collection for cervical cancer screening included information given during the educational talks, preference for self-sampling which assured women of privacy as well as being less uncomfortable or invasive than a pelvic exam, perception of cancer risk, encouragement from peers, screening being free and proximity to screening sites. "*What helped me is that our VHT came and told me that health workers (HWs) are coming to test us for cervical cancer but they (HWs) will not spread your legs to test you but rather it will be yourselves to test on your own...and it so happened that the testing is for free, and I said that I can't miss this opportunity, let me go and I had to come.*" Most women reported positive experiences with sampling in a community setting and believed that majority of the other women are likely to accept the self- sample collection..."*I and my colleagues with whom we screened were very happy and others remained yearning for it when we told them about it. We want doctors to come back another time… so that they (other women) can also come and be screened.*" Women found the rooms and the tools used for sample collection appropriate….*" Even the rooms were very good. There was not any person who could peep through and the tools they gave us… were soft and could not hurt us inside.*" Suggestions to improve uptake of cervical cancer screening included more health education using VHTs and women who have undergone self-sample collection as well as organizing additional regularly scheduled community screening events.

Conclusion: In this qualitative study of women in rural Uganda, HPV self-sampling in the community was highly acceptable and addressed the concerns of women, particularly those of privacy and the fear of embarrassment during a pelvic examination. Thus, the community-based approach has potential to increase uptake of cervical cancer screening in Uganda and other low-income countries.

74. Impact of Kaposi's Sarcoma on Quality of Life Among HIV-Infected Adults Initiating Antiretroviral Therapy in East Africa

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Background: In sub-Saharan Africa, widely increased access to combination antiretroviral therapy (ART) has improved survival after diagnosis of Kaposi sarcoma (KS) compared to the pre-ART era, but mortality among patients with KS is still considerably greater than HIV-infected persons without KS. Furthermore, among those patients with KS who are treated initially with ART and who do survive, little is known about how well they fare, function, and feel — their quality of life — compared to those without KS.

Methods: Among HIV-infected adults initiating first-time ART, we compared those presenting with KS to those without KS using participants from the Antiretrovirals in Kaposi Sarcoma (ARKS) trial and the Uganda AIDS Rural Treatment Outcomes (UARTO) Cohort, respectively. Quality of life (QOL) was measured using a culturally adapted version of the Medical Outcomes Survey-HIV instrument prior to ART initiation (baseline) and at weeks 16, 32, and 48 following initiation. The MOS-HIV contains 35 items, summarizing QOL in 11 domains with scores ranging from 0-100, with a higher score indicating better QOL; further transformation and standardization of QOL domains produces summary mental and physical health scores centered at a score of 50 with standard deviation of 10. To ascertain the independent effect of KS versus Non-KS on QOL among those who survived, we created a mixed effects model adjusted for directed acyclic graph-informed confounding. We adjusted for age, gender, body mass index, education, literacy, income, Filmer-Pritchett asset index, history of cryptococcosis or tuberculosis, CD4+ T cell count and plasma HIV RNA.

Results: We examined 224 participants with KS and 730 without KS, among whom 64% were women. Prior to ART initiation, median values were 34 years old (interquartile range (IQR): 28 to 39), 159 CD4+ T cells/mm^3 (IQR: 78 to 265), and 5.1 log$_{10}$ plasma HIV RNA copies/ml (IQR: 4.6 to 5.5). After excluding planned study visits after death, 99% of expected visits were completed among those with KS (781/788) and 87% among those without KS (2,876/3,299). After adjusting for confounding, those with KS had worse scores in most QOL domains at baseline compared to those without KS, most notably in Role Functioning and Pain (Table). After 48 weeks of ART among those who survived, those with KS continued to lag behind those without KS in PF, RF, SF, and PHS but showed no evidence of significant difference compared to those without KS in GHP, Pain, Energy, HD, and CF and exceeded those without KS in MF, QOL, HT, and MHS (Table).

Table. Comparison of QOL between HIV-infected patients with KS and without KS

QOL Concept	Prior to ART KS vs. Non-KS (95% CI)	48 Weeks After ART KS vs. Non-KS (95% CI)
Global Health Perception (GHP)	-4.0* (-8.1 to 0.1)	6.9 (-1.4 to 15.2)
Physical Functioning (PF)	-3.7 (-6.5 to -0.8)	-7.9 (-14.7 to -1.2)
Role Functioning (RF)	-16.3 (-21.2 to -11.4)	-8.1 (-8.3 to -7.9)
Pain	-11.9 (-15.5 to -8.3)	3.4 (-3.8 to 10.7)
Social Functioning (SF)	-9.5 (-12.9 to -6.1)	-4.4 (-11.7 to -3.0)
Mental Functioning (MF)	-4.8 (-7.5 to -2.1)	5.6 (0.3 to 10.9)
Energy	-4.2 (-7.5 to -0.9)	2.9 (-3.8 to 9.6)
Health Distress (HD)	-9.2 (-11.8 to -6.7)	2.1 (-3.9 to 8.1)
Cognitive Functioning (CF)	-0.5 (-2.4 to 1.5)	0.0 (-3.8 to 3.8)
Quality of Life (QOL)	-10.4 (-13.6 to 7.2)	25.1 (20.3 to 30.0)
Health Transition (HT)	-10.0 (-13.8 to -6.2)	22.8 (14.4 to 31.1)
Physical Health Summary (PHS)	-4.3 (-4.8 to -3.8)	-0.6 (-0.7 to -0.5)
Mental Health Summary (MHS)	-3.4 (-4.7 to -2.1)	7.3 (5.1 to 9.1)

* adjusted mean difference in QOL scores of those with KS minus those without KS

Conclusion: Amongst HIV-infected adults at the time of ART initiation in East Africa, those with KS had worse QOL compared to those without KS. In the first year of ART, among individuals who survived, those with KS became comparable to or exceeded those without KS in 9 of 13 QOL domains. The findings indicate that some patients with KS can be treated with ART alone but further emphasize the need to predict those who will do well with ART versus those who need other therapeutic interventions.

75. Incidence and Predictors of Kaposi's Sarcoma Immune Reconstitution Syndrome Among Kaposi's Sarcoma Patients Initiating Antiretroviral Therapy and Chemotherapy in Uganda

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Background: Treatment of epidemic Kaposi sarcoma (KS) with antiretroviral therapy (ART) can be complicated by a severe clinical worsening due to KS immune reconstitution inflammatory syndrome (KS-IRIS). Diagnosis of KS-IRIS is challenging, and the optimal management of KS-IRIS remains unknown. We therefore sought to describe the cumulative incidence and predictors of KS-IRIS among HIV-seropositive KS patients initiating concurrent cancer chemotherapy and ART in Kampala, Uganda.

Methods: We enrolled adult HIV-infected patients with biopsy-proven KS and followed them every 3 weeks following initiation of therapy to assess KS response. Oral swabs and plasma samples were collected at every clinic visit, and Human herpesvirus-8 (HHV-8) DNA was quantified in these samples by polymerase chain reaction (PCR). Suspected KS-IRIS diagnosis was based on worsening of KS (an increase in number/size of lesions) with a concurrent decrease of HIV VL >1.0 $\log_{10}$ copies/mL within 12 weeks of starting ART. Kaplan-Meir and Cox regression methods were used to determine incidence and predictors of KS-IRIS.

Results: We enrolled 73 participants with median age 31 years (range 18-75); 76% were male. Participants generally had late-stage KS; ACTG staging of KS was T1 for 86%, I1 for 54%, and S1 for 76% of participants. At baseline, median HIV VL was 5.3 log copies/mL (range 2.35 – 6.67), and CD4 T-cell count was 191 cells/dL (range 3-1437). HHV-8 DNA was detected in oral swabs from 21 (28%) and in plasma from 67 (93%) of the participants at baseline. Among samples positive for HHV-8 DNA, the median amount detected from oral swabs was 4.3$\log_{10}$ copies/mL (range 2.37 – 5.91) and from plasma was 4.0 $\log_{10}$ copies /mL (range 2.34 – 5.73)

The cumulative incidence of suspected KS-IRIS was 46.7% (36%-59%). The medium time to KS-IRIS development from ART initiation was 52 days (interquartile range: 34-69). In univariate analysis, KS-IRIS was associated with baseline abnormal chest x-ray (HR=2.58 [1.04-6.4], p=0.04), and pre-treatment CD4 count <150cells/mL (HR=2.07 [1.05-4.07], p=0.04); there was a trend towards significance for detection of oral KSHV shedding (HR=2.9 [0.83 - 10.15], p=0.09), and platelet count <200 (HR=2.19 [0.94-5.09], p=0.07). In multivariate analysis, KS-IRIS was associated with a platelet count <200 (HR=11.57 [2.39-55.96], p=0.02), abnormal chest x-ray (HR=7.13 [1.66-3.99], p=0.01), and detection of oral KSHV shedding (HR=5.56[1.17 – 26.23], p=0.03). Analyses of the impact of suspected KS-IRIS on treatment outcomes and survival are ongoing.

Conclusion: Suspected KS-IRIS is common in adults with late-stage KS, even when ART and cancer chemotherapy are given concurrently. Factors associated with the development of KS-IRIS included suspected pulmonary KS, a lower platelet count, and uncontrolled KSHV replication, which could reflect higher pathogen burdent or dysregulated immune and inflammatory responses. These factors warrant further study to better understand the pathogenesis of KS-IRIS and to evaluate their potential to serve as biomarkers of risk of KS-IRIS development

76. Investigation of Kaposi's Sarcoma in the Era of Antiretroviral Therapy in East Africa: Feasibility of Rapid Case Ascertainment

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Background: Rapid case ascertainment (RCA) refers to expeditious and detailed examination of patients with medical conditions shortly after diagnosis. It is most commonly used in resource-rich settings to facilitate research for rapidly progressive cancers where delays in ascertainment prohibit relevant measurement. HIV-related Kaposi's sarcoma (KS) remains amongst the commonest and most fatal cancers in Africa. We sought to apply RCA to study KS in the era of widespread availability of antiretroviral therapy (ART) in East Africa.

Methods: We searched for newly diagnosed KS among HIV-infected adults (≥18 years) attending inpatient and outpatient facilities at one of three primary care networks in East Africa: AMPATH in western Kenya, the Masaka Regional Referral Hospital, and Mbarara Regional Referral Hospital in Uganda. Searching entailed periodic querying of the HIV ambulatory clinic electronic medical record (EMR); regular manual review of records at the histopathology laboratory (HL) and relevant clinic venues (medical wards, dermatology, and oncology clinic); and receipt of sporadic notification by field clinicians. Upon identification of potential cases, a study team verified eligibility for RCA and attempted to perform an RCA evaluation with detailed clinical and laboratory evaluation. We estimated feasibility as the pace of RCA performance after health system diagnosis of KS, accommodating death as a competing event using the Aalen-Johansen estimator.

Results: Between July 2016 and April 2019, we identified 548 patients with suspected new HIV-related KS. Of these, 75% were from AMPATH, 17% were from Masaka and 9% from Mbarara. Patients had a median age of 36 years (Interquartile range: 31-43), and 66% were men. Clinician notification yielded 84% of cases, EMR 7%, HL 8% and clinical venues 1%. Of the 548 patients, 376 were eligible for RCA and the rest were ineligible (59% did not have KS; 31% had previously diagnosed KS; 6% could not be consented (due to language barrier, under age or incarceration); and 4% were HIV-uninfected or had received substantial cancer care elsewhere). RCA was performed on 286 patients. RCA was performed within 7 days after health system diagnosis of KS for 33% of eligible patients; within 14 days for 48%; within 1 month for 62%; within 3

Figure: Cumulative incidence of performing RCA with death as a competing event.

months for 70%; and within 6 months for 73% (Figure). Reasons why RCA was not performed included intervening death (66%), inability to locate the patient (25%), and refusal to participate (7%).

Conclusion: We found that RCA — an important tool for research in resource-rich settings — is also feasible for the investigation of KS in Africa. There are, however, particular challenges in Africa, such as transportation and rapid demise after diagnosis, which limit RCA and require innovative solutions. Feasibility of RCA for KS suggests that RCA is also potentially feasible to study other cancers in Africa.

77. What Happens After the Biopsy? Pace and Determinants of the Communication of Pathology Results to Patients With Suspected Kaposi's Sarcoma in Uganda

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Background: The universal gold standard for most cancer diagnoses is histopathology. Beyond providing diagnostic certainty to the patient, pathologic confirmation also enables prognostication and informs the appropriate use of potentially toxic therapies including chemotherapy. In sub-Saharan Africa, Kaposi sarcoma (KS) is one of the most common cancers and has many clinical mimickers; proper management therefore relies heavily on pathologic diagnosis. While much has been chronicled about the lack of pathology services in Africa, when pathology is available, little beyond anecdote is known in the region about how quickly pathology results are communicated to patients— the critical first step in the appropriate clinical management of whatever pathologic condition is found.

Methods: In Uganda, we evaluated consecutive patients referred for skin or mucosal membrane biopsy because of clinical suspicion for KS. Punch biopsies were performed at one of three clinical sites in Kampala, Masaka, and Mbarara. Upon performing the biopsy, we obtained contact information for the patient and, if provided, his/her designate. After obtaining pathology results, we attempted to contact the patient if they had not already returned on their own. If unsuccessful, we attempted to communicate results to the patient's designate. Using the Aalen-Johansen estimator, we calculated cumulative incidence of results communication from date of biopsy to date of communication with either i) the patient; ii) his/her designate; or iii) a date of death prior to results communication. We used proportional hazards regression to assess determinants of communication with the patient.

Results: From January 2017 to January 2019, we biopsied 958 patients whose median age was 34 years (interquartile range (IQR): 29-40); 63% were men and 94% were HIV-infected. Patients reported a median round-trip travel cost to biopsy facility of $3.83 USD (IQR: $2.19-$10.14), and a median one-way travel time of 2 hours (IQR: 1-4). Overall, 77% had a histopathology result of KS. At 1 month following biopsy, 55% of patients had been directly reached to communicate results; 12% had their designate reached (but without assurance that the designate had communicated with patient); and 6% had died prior to communication of results (Table and Figure). Spending less than $2.19 USD on travel to the biopsy facility was independently associated with faster communication of results to the patient (hazard ratio = 1.4, 95% CI: 1.1 to 1.7).

Table: Cumulative incidence of direct communication of pathology results to patients

Time after biopsy	% (95% CI) of patients reached
2 weeks	23% (21 to 26)
1 month	55% (52 to 58)
3 months	64% (61 to 67)
6 months	66% (63 to 69)
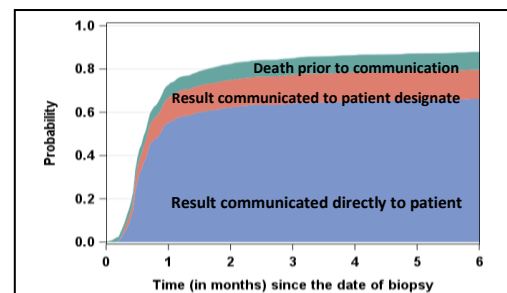
Figure: Cumulative incidence of various communication outcomes after performing a biopsy.

Conclusion: Among patients receiving a skin biopsy in Uganda for suspected KS, only about one-quarter had their results directly communicated to them within two weeks following biopsy and only about one-half were reached within one month. This communication of a critical medical test result is much slower than in resource-rich settings. New strategies to hasten communication of biopsy results are needed. The findings also highlight the need for reliable point-of-care diagnostic tests for KS and other cancers that could preclude these delays.

78. **Why Are They Diagnosed So Late? Understanding the Circumstances Preceding Diagnosis Among Patients With Kaposi's Sarcoma Identified by Rapid Case Ascertainment in East Africa**

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Objective: Despite the possibility of remission when diagnosed and treated early, most HIV-related Kaposi sarcoma (KS) in sub-Saharan Africa is diagnosed too late for available treatment to be effective. A recent study in Zimbabwe found that training primary care physicians in the early detection of KS detection had no effect on decreasing the prevalence of late stage diagnosis of KS. One explanation of this finding is that primary care providers rarely encounter early stage KS, i.e., patients present to providers too late for early detection in the clinic to be effective. We sought to explore the events from patients' first recognition of skin lesions until time of KS diagnosis.

Methods: Via a rapid case ascertainment approach, we interviewed consecutive HIV-infected adults newly diagnosed with KS from 2016 to 2019 at three community-based health care networks in Kenya and Uganda. Cases were identified from outpatient, inpatient, and laboratory searches. Guided by Andersen's model of total patient delay, we documented when patients first noticed suspicious skin lesions and all subsequent medical care events until KS diagnosis including number of persons consulted, time durations between consultations, opinions received, and interventions pursued.

Results: We identified 270 participants with newly diagnosed KS in whom median age was 35 years, 30% were women, and 42% had only primary education. Most (84%) had advanced KS (ACTG stage T1). Participants were the first to notice lesions 97% of the time and the lower extremities were the first site where lesions were noticed (71% of cases). Participants reported that they first sought help a median of 1 month after noticing suspicious lesions (interquartile range (IQR): 4 to 9 weeks; absolute range: 1 day to 3 years). Biomedical providers were the first persons consulted by 98% of participants. Overall, a median of 3 biomedical providers (IQR: 1 to 3; absolute range 1 to more than 5) were consulted over a median of 3 different visits (IQR: 2 to 5; absolute range 1 to 16) prior to receiving a KS diagnosis. While 42% of the first people consulted suspected KS or a form of cancer (Table), only 23% of participants received a KS diagnosis from the first provider consulted. Attribution to witchcraft and use of Traditional Health Providers (THP) were present but not common: 8.0% of providers consulted had attributed lesions to witchcraft or recommended traditional medicine, and 6.3% of participants admitted consulting a THP or using traditional medicine. Self-medication was common; 20% of participants reported using unspecified creams, oral, or injectable medicines. The median time from first lesion identification to KS diagnosis was 13 weeks (IQR: 4 to 34 weeks; absolute range 1 day to 84 months).

Table. Opinion of First Person Consulted

Opinion	Percentage (N = 270)
Definitely KS	0%
Suspected KS	40%
No opinion	21%
Other	12%
Sign of HIV	10%
Skin infection	7.8%
Medication side effect	3.6%
Witchcraft	3.6%
A form of cancer	2.0%

Conclusion: In a representative community-based sample of HIV-infected adults newly diagnosed with KS, we observed delays in the diagnosis of KS that can be attributable to both patients and health care providers. Given the severe extent of disease that most participants had at time of diagnosis, their reported average duration from time of first lesion identification to KS diagnosis was shorter than expected. This suggests either underreporting of the time duration or that participants did not recognize lesions on themselves until lesions had become extensive. Interventions to promote early KS diagnosis should target both the public and the health care system.

79. "People Don't Heal From Cancer": Barriers and Facilitators to Chemotherapy Initiation and Adherence for Patients With Kaposi's Sarcoma in Western Kenya

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Background: Kaposi's sarcoma (KS) is one of the most common HIV-associated malignancies in sub-Saharan Africa (SSA). Survival after KS diagnosis is poor in SSA, with an estimated three-year mortality of 45% (Semeere, 2015). Our previous research in Kenya has shown that only half of patients with indications for chemotherapy receive it, but the reasons for this gap remain unknown (Freeman, 2017). The aim of this study was to conduct semi-structured interviews with KS patients in order to better understand barriers and facilitators of chemotherapy initiation, delay, and adherence.

Methods: All patients >18 years with newly diagnosed KS between 2016-2019 within the AMPATH (Academic Model Providing Access to Healthcare) clinic network in Western Kenya were enrolled in the parent study. From this cohort, 20 patients were purposively selected to participate in semi-structured interviews based on whether they had completed (n=10) or not completed (n=10) chemotherapy for advanced stage KS. We based the interview guide on the situated Information, Motivation, Behavioral Skills (sIMB) framework, in which the core patient centered IMB constructs are situated into the socioecological context of receiving care (Rivet Amico, 2011). We then analyzed the data using framework analysis, which included development of a coding framework *a priori*, coding of transcripts, and charting codes onto a series of thematic matrices (Ritchie and Spencer, 1994). The thematic matrices comprised barriers and facilitators to chemotherapy initiation and adherence, based on patient factors per the IMB model and situated contextual factors.

Results: Patient factors that were barriers to chemotherapy initiation and adherence included misconceptions about cancer and chemotherapy, challenges enrolling in national health insurance, and difficulty arranging transport to oncology clinic. Community stigma towards KS patients surrounding HIV, skin disease, and cancer diagnosis demotivated many of the patients from seeking care. Patients were often told they were bewitched or had a contagious condition, leading to social isolation. Community misconceptions that cancer is not curable, cancer treatment requires surgery or even amputation, and that chemotherapy hastens an inevitable death further demotivated patients from starting treatment. Situated contextual barriers patients faced were HIV related co-morbid illnesses, chemotherapy side effects, lack of money for medical services or transport, limited oncology centers, and difficulty obtaining HIV and oncology treatment at the same facility. Patient factors that facilitated chemotherapy initiation and adherence included health literacy, motivation to treat disfiguring lesions, symptom improvement on chemotherapy, prioritization of self-care, resilience while experiencing side effects or stigma, and the ability to navigate the health system. Situated contextual facilitators for patients were patient-centered providers, obtaining national health insurance, and subsidized chemotherapy.

Conclusion: Interviews with KS patients in Kenya suggest the need to promote public health campaigns with reliable cancer and chemotherapy information, improve education about the chemotherapy process and side effects, increase oncology service ability, support enrollment in national health insurance, and increase incorporation of chronic disease care into existing HIV treatment networks. Furthermore, specific findings about layered HIV and cancer stigma highlight unique challenges with chemotherapy initiation and adherence for patients with HIV associated malignancies.

80.   Kaposi's Sarcoma Rates Among People With HIV Living in the United States Between 2008 and 2015: State-Specific Trends

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Background: Rates of Kaposi Sarcoma (KS) declined dramatically starting in the mid-1990s among people with HIV (PWH) in the United States due to the use of effective antiretroviral therapy (ART). In contrast, recent studies have suggested that rates might be increasing in certain racial/ethnic and age groups, and in certain regions of the country. However, these studies did not assess trends among PWH. We conducted a comprehensive assessment of recent secular trends in KS incidence among PWH in the US by age, sex, race/ethnicity and state.

Methods: We obtained the number of incident KS cases from 38 cancer registries, and the number of PWH from CDC HIV surveillance data by state, calendar year, age, sex, and racial/ethnic group from 2008-2015, limited to ages 20-59 (age range where 95% of persons with KS are HIV-infected). We estimated age-standardized KS rates and annual percent changes (APCs) in rates by age, sex, race/ethnicity, and state.

Results: During 2008-2015, the age-adjusted KS rate among PWH was 116/100,000. Rates were higher among males (145/100,000) than females (22/100,000), and highest in younger age groups (25-29: 184/100,000; 30-34: 191/100,000). KS rates were highest among whites (139/100,000), and lowest among blacks (102/100,000). The three states with highest KS rates were Washington (186/100,000), Georgia (183/100,000), and California (170/100,000). KS rates among PWH nationwide decreased significantly (APC=-3.7%/year, p<0.001) from 137/100,000 to 101/100,000 between 2008 and 2015. The decline was more rapid and significant among men (APC=-4.0%/year, p<0.001), but not among women (APC=-1.5%/year, p=0.61). KS rates declined across all age groups, except among 30-34-year-olds where rates were stable (APC=0.35%, p=0.66). The most rapid decline occurred among 50-54-year-olds (APC=-6.5%, p=0.04). KS rates declined rapidly among whites (APC=-7.0%; p<0.001) and blacks (APC=-2.8%; p=0.009), while no significant trends were observed among Hispanics (APC=-1.3%; p=0.58) and other race/ethnicities (APC=1.9%; p=0.75). Declines in KS rates were observed in Arizona (-10.3%/year), Kentucky (-9.3%/year), Pennsylvania (-9.1%/year), California (-4.6%/year), and New York (-4.1%/year). Of the remaining 22 states with estimable, but non-significant trends, rates declined in 16 states and increased in 5 states. When grouped by region, KS rates declined 3.4% per year in the Northeast (p=0.02), 5.7%/year in the Midwest (p=0.08), 3.1%/year in the South (p=0.09) and 4.7%/year in the West (p=0.003).

Conclusion: KS incidence rates among PWH have decreased nationally between 2008 and 2015. Though we did not find evidence of significant increases in KS rates in any age, sex, or racial/ethnic group or in any geographic region or state, demographic and geographic disparities persisted. These disparities in HIV-associated KS may reflect the differences in access to ART treatment for PWH in different states and across demographic groups.

81. Metformin as a Potential Chemoprotective for Development of Invasive Anal Carcinoma in HIV-Infected Patients: A Nested Case-Control Study

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Background: Invasive anal carcinoma (IAC) is the fourth most common cancer among HIV-infected persons in the United States. A variety of ablative or topical immunomodulatory approaches have been studied to treat anal high-grade squamous intraepithelial lesions (HSIL), the immediate IAC precursor. However, no specific modality of treatment for anal HSIL has been unequivocally proven to favorably alter the natural history of anal intraepithelial neoplasia. Metformin may be an attractive cancer chemopreventive agent that suppresses the transformative and hyperproliferative processes that initiate anal carcinogenesis via its molecular targeting of specific signaling pathways (including PI3K/mTOR) involved in HPV oncogenesis. Our study aim was to evaluate whether metformin use reduced the incidence of invasive anal carcinoma (IAC) in HIV-infected patients.

Methods: A nested case-control study of adult (≥18 years) HIV-infected patients was conducted using data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) We used incidence density sampling, employing 5:1 control:case matching on gender, race, HIV risk factor, age, and calendar year at IAC diagnosis. Eligible subjects were required to have ≥ 6 months follow-up, ≥ 1 HIV viral load measurement; those with prevalent IAC were excluded. Time-at-risk began with the maximum of baseline cohort enrollment date, cohort malignancy ascertainment start date, or age 18 date and ended with the minimum of cohort close date, malignancy ascertainment stop date, last laboratory date plus 12 months, death date, or IAC diagnosis date. Unadjusted and adjusted IAC incidence odds ratios (OR) were estimated using conditional logistic regression. Covariates adjusted for included: HCV (+ antibody or detectable RNA) and HBV (+HBsAg, HBeAg, or detectable DNA) status, smoking history, absolute CD4, HIV plasma viral load (pVL), and antiretroviral therapy (ART) status.

Results: Between 1997 and 2015, 106,643 met eligibility criteria to be included in the case-control analysis. During 761,773 person-years (pyrs) at-risk, 549 incident IAC cases were documented (72 per 100,000 pyrs). Using incidence density sampling, 2745 matched controls were selected. Control characteristics [% or median (IQR)]at the time point of matching were: 6% metformin exposed (≥ 30 days), calendar year 2008 (2004, 2011), age 50 (44,56), 4% female, 43% non-white, 37% MSM, 24% HCV +, 8% HBV +, 29% ever smoked, 26% not on ART, 60% with CD4 ≥350 cells, and 59% with undetectable HIV pVL (<200 copies). The unadjusted and adjusted incidence IAC ORs (95% CI) for metformin were: 0.94 (0.63-1.39) and 0.88 (0.59-1.32), respectively.

Conclusion: No significant preventive effect for metformin was found in this analysis. However, given the number of cases available, the low prevalence of metformin exposure, and wide effect estimate confidence intervals, a clinically meaningful preventive effect could have been missed. If, as believed from animal models, metformin may act late in oncogenesis, an unknown proportion in the control group may not have been at risk for IAC (because they were not infected with oncogenic HPV) or susceptible to a putative metformin effect (given oncogenic HPV) because they had not progressed to late stages of oncogenesis (≥ HSIL histology). A longitudinal cohort analysis is underway to minimize concerns regarding potential selection bias introduced by the matching design.

82. Preliminary Results of Intra-Lesional Nivolumab for Treatment of Limited Cutaneous Kaposi's Sarcoma in HIV-Positive and HIV-Negative Men

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Background: Kaposi sarcoma (KS) is a low-grade vascular tumor associated with infection with human herpesvirus 8 (HHV-8). It often appears in HIV-positive individuals. HIV-negative men who have sex with men (MSM) also have a higher risk of developing KS than men in the general population. They often develop KS at an earlier age, and they have a clinical course that is more typical of classical KS than epidemic KS. Intra-lesional chemotherapy (vinblastine) can induce regression of injected tumors but it is often painful.

Methods: This is a phase 1 trial to evaluate the safety and tolerability of intra-lesional injections of nivolumab to treat cutaneous KS. We aimed to include 6 HIV-positive and 6 HIV-negative individuals who have fewer than 25 KS lesions and no evidence of visceral disease. They must not have had KS treatment within the last 28 days, or active autoimmune disease that required systemic immunosuppression. A single KS lesion was selected for injection for each participant and the other lesions (if any) served as control. We injected 1 mL (10mg) of nivolumab into the selected KS lesion, every 2 weeks for 4 doses. Skin biopsy of the injected KS lesion was performed at screening and then repeated at week 26. Photographic documentation of up to 5 marker lesions were obtained. AIDS Clinical Trials Group (ACTG) KS criteria was used for response assessment.

Results: Between May 2018 and July 2019, eight male participants received four doses of intra-lesional nivolumab every 2 weeks. Three participants were HIV-positive, five were HIV-negative and seven were MSM. Median age was 61 years. Median CD4 was 706 cells/uL. All HIV-negative participants had laboratory documentation of HIV serostatus within 12 months. All HIV-positive participants had undetectable HIV viral loads on antiretroviral therapy. None had active hepatitis B or C infection. All participants had at least one prior treatment for KS. No grade 3 or higher treatment-related adverse events were reported during the follow-up period. There was no injection site pain, redness or swelling reported. There were also no autoimmune adverse events during the study period. To date, six participants have completed all study procedures. All participants had qualitative reduction of KS lesions and HHV-8 staining in their skin biopsies at week 26 compared to baseline. Two participants had complete resolution of the injected lesion. One participant with complete response of the injected lesion also had fading of other lesions; this was not observed in the other participants with multiple lesions. Three participants had relative increase in the infiltrating CD8^{+} T cells in the biopsied KS lesion compared to baseline. The percentage of circulating CD4+ and CD8+ T cells expressing PD-1 decreased from 3.2% and 4.1%, respectively prior to treatment, to nearly zero after 2 intra-lesional nivolumab injections. The frequency of PD-1 expressing lymphocytes increased back to baseline level at 20 weeks after the last injection.

Conclusion: Intra-lesional nivolumab was safe and well-tolerated in HIV-positive and HIV-negative men with limited cutaneous KS. This modality of administration appears to be able to recruit CD8^{+} T cells to the skin and resulted in reduction in the density of HHV-8^{+} KS cells. Our result demonstrated that intra-lesional injection of nivolumab could cause transient and reversible decreases in the percentage of T cells expressing PD-1 in the peripheral blood. It appears that intralesional nivolumab can have a profound effect on T cell PD-1 occupancy but not have any systemic effects.

83. Patterns in Long-Term Opioid Prescription Use Among Patients With Cancer Who Are HIV-Infected and HIV-Uninfected

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Background: After years of focusing on increasing pain management, the United States (US) has recently faced a national epidemic of opioid-associated drug overdoses. Chronic pain, which affects a substantial number of adults in the US, has been historically treated with long-term, high-dose opioids. While both cancer and HIV are associated with chronic pain, treatment with opioids has not been studied in this comorbid population. This study aims to examine the potential disparity of opioid prescription patterns in a matched cohort of HIV-infected and HIV-uninfected patients with cancer.

Methods: A total of 320 patients who are HIV-infected and were diagnosed with cancer between 2005-2018 at Boston Medical Center (BMC), a safety net hospital in Boston, were matched on a maximum 4:1 ratio with patients with cancer who are HIV-uninfected (n=945), resulting in a total cohort of 1265 study participants. Matching factors included sex, primary cancer site, cancer diagnosis age ±5 years, and cancer diagnosis date within the same calendar year. Potential demographic differences between the patients with cancer who were HIV-infected and HIV-uninfected were assessed with a two-group, independent t-test and a chi-square test of independence. The primary outcome of interest was opioid prescriptions in the year of cancer diagnoses. Standardized proportional incidence ratios (PIRs) using the age and sex distribution of the HIV-uninfected cancer patients in 2005 as the standard were used to compare changes in opioid prescribing frequency across study years. Multivariable logistic regression was used to assess the association between HIV infection status and receiving any opioid prescription in the year of cancer diagnosis, controlling for sex, race, ethnicity, language spoken, insurance type, relationship status (partner or no partner), and age at cancer diagnosis ($\leq$50 years old, 51-60 years old, or >60 years old). Additional multivariate analyses were performed on the HIV-infected and HIV-uninfected cohorts separately, using the listed covariates to assess potential differences between the two cohorts.

Results: The most common primary cancer sites among patients infected with HIV were prostate cancer, followed by lung, liver, cervical, and lymphoma cancers. Patients infected with HIV were more likely to be older (p=0.0004), diagnosed with cancer at a younger age (p=0.0002), Hispanic (p=0.03), single (p<0.0001), have died of cancer-related causes (p=0.03) or have a primary cancer site other than the prostate (p=0.03). Patients infected with HIV were less likely to be white (p<0.0001), have commercial insurance (p=0.004), or be deceased from any cause (p=0.0006). Statistically significant age-sex standardized opioid prescription prevalence increases were only seen among the HIV-uninfected cohort in 2014 (PIR: 2.6, 95% CI: 1.2, 2.0) and the HIV-uninfected cohort in 2017 (PIR: 1.7, 95% CI: 1.0, 1.5). Among patients with cancer at BMC from 2005-2018, the odds of having an opioid prescription in the same year as cancer diagnosis was 1.3 times higher (95% CI: 1.0, 1.8) for those infected with HIV compared to those not infected in multivariate analysis. Compared to those who were diagnosed with cancer at $\leq$50 years old, those diagnosed between the ages of 51-60 had 1.8 times the odds (95% CI: 1.3, 2.5) and those diagnosed at >60 years old had 1.4 times the odds (95% CI: 1.0, 1.9) of receiving an opioid prescription. Additionally, those receiving free care were 50% less likely to receive an opioid prescription compared to those with commercial insurance (95% CI: 0.2, 0.9), while those on Medicaid were 40% more likely to receive an opioid prescription compared to those with commercial insurance (95% CI: 1.0, 2.0).

Conclusion: These results suggest that patients with cancer who are HIV-infected may be more likely to receive an opioid prescription compared to patients with cancer who are HIV-uninfected at BMC between 2005 and 2018. Additional studies are warranted to further understand how differences in opioid prescribing impacts both the potential for opioid-associated drug overdose and long-term opioid-associated effects.

84. Statin Exposure Is Associated With Decreased Risk of Cancer

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Background: Beyond inhibition of cholesterol biosynthesis, statins appear to have pleiotropic effects, including modulation of cell growth, apoptosis, and inflammation. Statins may reduce cancer risk, particularly among people living with HIV who experience chronic inflammation and immune activation. We used the Veterans Aging Cohort Study (VACS), a large observational cohort with cancer registry linkage and detailed pharmacy data, to address these questions.

Methods: We followed patients between 2002-2017, starting from first statin prescription or a random clinic visit date in the same year for those unexposed to statins (non-users). We fit a propensity score model for statin use including demographic, clinical, and laboratory variables to match statin users to non-users. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CI) associated with statin use for all cancers, microbial cancers (associated with bacterial or oncovirus coinfection), non-microbial cancers, and specific common cancers.

Results: The propensity score-matched sample (N=47,940) included 7,335 HIV+ and 16,635 uninfected statin initiators. Incident cancers were diagnosed in 1,160 HIV+ and 2,116 uninfected patients. Death was reported in 1,667 (7.0%) statin users, and 2,215 (9.2%) non-users. Statin use was associated with a 24% decreased risk of microbial cancers (HR 0.76; 95% CI 0.69 – 0.85). Statin use was not associated with non-microbial cancers (p= 0.966). Statin use was associated with lower risk of death (HR 0.67; 95% CI 0.63 – 0.72). Results were similar in analyses stratified by HIV, except for non-Hodgkin lymphoma, where there was a significant interaction with HIV (p=0.012).

Figure 1: Propensity score-matched hazard ratios for cancer groups† and specific cancer types.

Conclusion: Statin exposure was associated with lower risk of microbial, but not non-microbial, cancer incidence. It was also associated with decreased mortality. These findings were largely consistent between HIV+ and uninfected patients.

*There were only 6 anal squamous cell carcinoma and 0 Kaposi sarcoma cases. Results for HIV+ patients only are presented.

†Microbial cancers include: human papillomavirus (HPV)-related oral cavity and pharynx squamous cell carcinoma (SCC), anal SCC, hepatocellular carcinoma (HCC); stomach, lung, cervical, vulva, vagina, and penis cancers; Hodgkin lymphoma, non-Hodgkin lymphoma, and Kaposi sarcoma

85.   Statin Use and Human Papillomavirus-Related Anal Dysplasia in HIV-Positive Men Who Have Sex With Men

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Background: Despite a significant decline in the incidence of HIV-associated malignancies, the incidence of anal cancer among men who have sex with men (MSM) living with HIV continues to rise. In HIV-positive MSM, anal cancer is over 80 times as high compared to HIV-negative individuals. It has been hypothesized that in high-grade anal intraepithelial squamous neoplasia samples of HIV-positive MSM, higher numbers of regulatory T cells (Tregs) found in the epithelial layer of tissue may further permit progression to invasive cancer. Recent studies have shown that HMG-CoA reductase inhibitors ("statins") appear to significantly increase both the circulating and tumor infiltrating Tregs in some malignancies, and a range of mechanisms have been proposed for the immunomodulatory properties of this medication class. In this study, we evaluate whether statin use correlated with a higher risk of histologic anal squamous intraepithelial lesions among HIV-positive MSM.

Methods: A retrospective chart review was performed on 70 patients who underwent high-resolution anoscopy (HRA) evaluation in the Anal Dysplasia Clinic at Tufts Medical Center between 2009 and 2017. Data was acquired for age, race, HIV status, smoking status, CD4+ count, hyperlipidemia and/or hypercholesterolemia diagnosis, statin prescription, high-risk human papillomavirus (HR-HPV) status in anal canal by molecular probe, and anal tissue pathology reports obtained by HRA. Patients were designated as statin users as long as they had been prescribed a statin for at least six months before baseline. Descriptive statistics were performed for characteristics of statin and non-statin users at baseline with p-values obtained from Wilcoxon rank-sum test, Chi-squared test, and independent sample t-test. Multivariate Logistic regression (MLR) analyses yielding adjusted odds ratios (AORs) utilized statin use, presence of tissue LSIL (low-grade squamous intraepithelial lesion), presence of tissue HSIL (high-grade squamous intraepithelial lesion), and presence of any HPV-related histologic abnormality as primary outcomes; age, race, current smoking status, CD4+ count, and statin use as predictors.

Results: For all patients (n=70), the median age at baseline was 50 years (interquartile Range 47-56) with 79% being white, 6% black, and 11% Hispanic. Forty-eight patients were identified as non-statin users (69%) and 22 patients were identified as statin users (31%). Men who were statin users were significantly older than non-statin users (53 vs. 49 years, respectively; p=0.009), and had a lower prevalence of anal HR-HPV subtypes at baseline (8 vs. 29 patients, respectively; p=0.041). White race was the only predictor associated with the outcome of LSIL in the MLR with white HIV-positive MSM patients having 80% reduced odds of being diagnosed with LSIL compared to non-white HIV-positive MSM (OR, 0.20 [95% CI, 0.06-0.75], p=0.017). There was no statistically significant relationship between statin use and HRA findings of tissue HSIL or LSIL.

Conclusion: HIV-positive MSM who self-identified as white were less likely to be diagnosed with tissue LSIL compared to non-white patients, which may reflect a variety of social and biological determinants of health. Statin use did not correlate with the presence of any grade of tissue dysplasia or tissue evidence of HPV infection as ascertained by HRA. HIV+ MSM statin users did have a lower prevalence of anal HR-HPV subtypes at baseline. Further studies are needed to examine the relationship between statins, HPV-related disease, regulatory T cells and tumorigenesis.

86. Willingness to Participate in HPV Vaccination Programs Among HIV-Positive Women in Lagos, Nigeria

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Background: The uptake of HPV vaccination currently remains low in Nigeria. HIV+ve women have a higher prevalence of oncogenic Human Papilloma Virus infection which increases the risk of developing invasive cervical cancer in comparison with the general population. HPV vaccination has been shown to effectively prevent the development of cervical cancer due to HPV Types 16 and 18. This study was conducted to assess the willingness of HIV +ve women currently attending a clinic in Lagos, Nigeria to participate in HPV vaccination programs.

Methods: Self administered questionnaires were administered to 203 women with ages ranging fron 21 to 43 years. Data was analyzed with SPSS version 18 data editor. Univariate Odds Ratios (OR) and 95% Confidence Intervals (CI) were used to determine the correlates of Willingness to Participate (WTP).

Results: A total of 87 women (38.5%) reported that they would be willing to receive HPV vaccination. Greater willingness was associated with sexual onset less than 14 years (OR = 1.33, 95% CI: 1.25–1.53), fewer doses of vaccine (OR = 1.35, 95% CI: 1.15–1.62), lower cost of vaccine (OR = 1.46, 95% CI: 1.23–1.65) and availability of incentives (OR = 1.36, 95% CI: 1.22–1.52). Decreased WTP was associated with concerns about physical harm (OR = 0.45, 95% CI: 0.12–0.74), stigma (OR = 0.81, 95% CI: 0.42–0.88) and (OR = 0.78, 95% CI: 0.43–0.94).

Conclusion: The low level of WTP among the respondents indicates that much work needs to be done in health education if HPV vaccination uptake among this group would be increased. More studies have to be conducted among this group before considering incorporating HPV vaccination regimes in the treatment protocol.

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