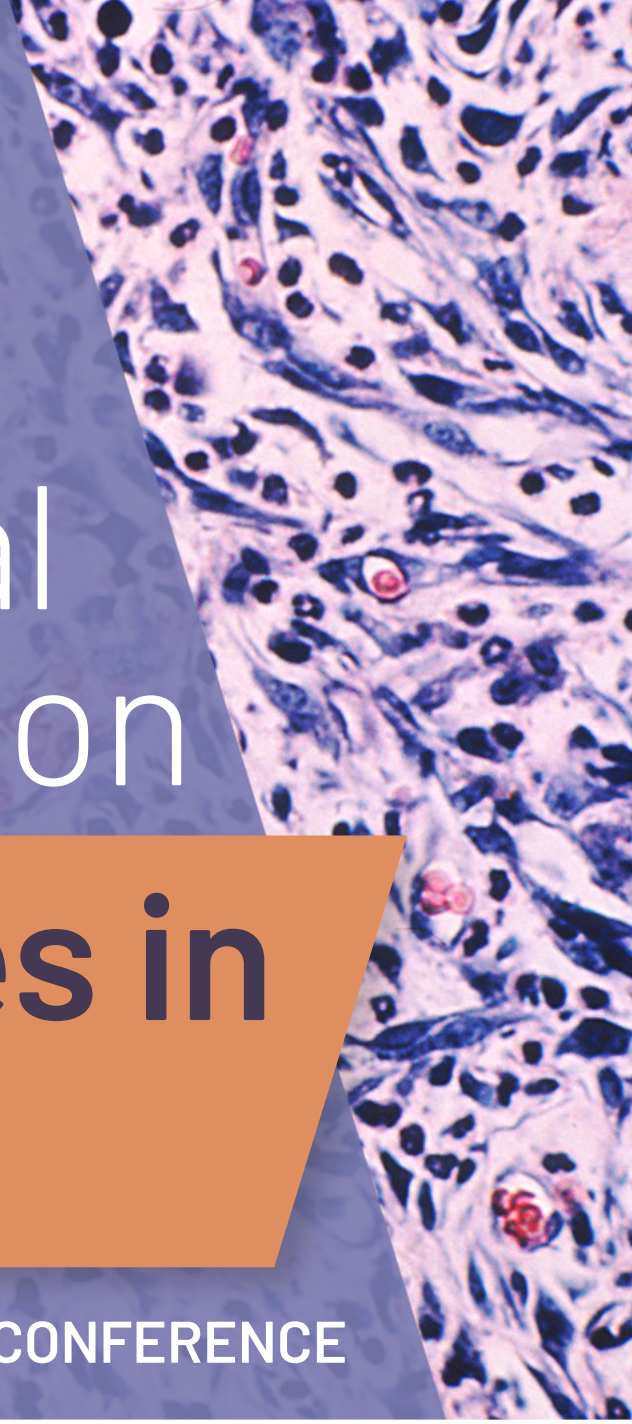
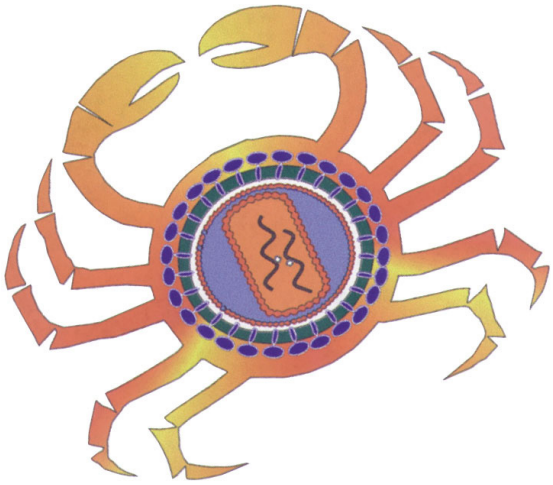


18th International Conference on

Malignancies in HIV/AIDS

OCTOBER 24-26, 2022 | VIRTUAL CONFERENCE

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



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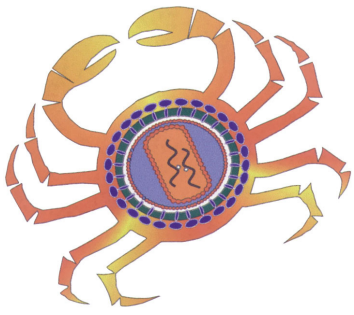

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18th International Conference on **Malignancies in HIV/AIDS**

OCTOBER 24-26, 2022 | VIRTUAL CONFERENCE

All times are U.S. Eastern Daylight Time

DAY 1: October 24

8:30 AM	**Log Into the Platform**
9:00 AM	**Opening Remarks and Welcome** Robert Yarchoan, HIV and AIDS Malignancy Branch, Center for Cancer Research, and Office of HIV and AIDS Malignancy, National Cancer Institute
9:10 AM	**Tribute to Dr. Enrique Mesri** Moderator: Ethel Cesarman, Weill Cornell Medical College **In Memoriam Presentation** Tributes: Omar Coso, Universidad de Buenos Aires, Argentina, and Ethel Cesarman, Weill Cornell Medical College
9:20 AM	**Tribute Junior Oral** Bone Marrow-Derived Human MSC as Precursors of KS Initiation and Progression Through Endothelial Differentiation and Cytokine Induction After KSHV Infection in a Pro-Angiogenic Environment Julian Naipauer, Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE), CONICET-Universidad de Buenos Aires, Buenos Aires, Argentina

9:30–11:00 AM 8:30	**Session 1: Lymphoma and EBV** Moderator: Richard Ambinder, Johns Hopkins University School of Medicine
9:30 AM	**P1: CAR T-Cell Therapy for HIV-Associated Lymphomas** Stefan Barta, University of Pennsylvania Perelman School of Medicine
10:00 AM	**O1: Multicentric Castleman Disease in Malawi: Updates From a Prospective Cohort Study and Early Results From a Phase II Safety/Efficacy Study of Rituximab Treatment** Matthew Painschab, University of North Carolina Lineberger Comprehensive Cancer Center
10:15 AM	**O2: Daratumumab Induces Cell-Mediated Cytotoxicity of Primary Effusion Lymphoma and Can Be Active Against Refractory Disease** Prabha Shrestha, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute
10:30 AM	**Questions/Discussion/Collaboration**

11:00 AM–2:00 PM	**Session 2: Anal and Cervical Cancer/HPV** Moderator: Mark Einstein, Rutgers University Medical School
11:00 AM	**P2: Anal Cancer Among Persons Living With HIV: Epidemiology, Contribution of HIV, and Modeling to Guide Cost-Effectiveness of Screening** Ashish Deshmukh, Medical University of South Carolina Hollings Cancer Center
11:30 AM	**P3: The ANCHOR Study** Joel Palefsky, University of California, San Francisco
12:00 PM	**P4: Anal Screening in People Living With HIV** Megan Clarke, Division of Cancer Epidemiology & Genetics, National Cancer Institute
12:30 PM	**O3: Risk of Progression From Anal Intraepithelial Neoplasia In Situ to Invasive Anal Cancer in PLWH Compared to HIV Uninfected People** Cameron B. Haas, Division of Cancer Epidemiology & Genetics, National Cancer Institute
12:45 PM	**O4: Anal Cancer Survival Among Persons Living With HIV in the United States** Jaimie Z. Shing, Division of Cancer Epidemiology & Genetics, National Cancer Institute
1:00 PM	**O5: Delays in Initiation of Curative Intent Chemoradiation and Patterns of Survivorship Care for Cervical Cancer Patients Living With or Without HIV in Botswana** Jessica George, Donald Bren School of Information and Computer Sciences, University of California, Irvine
1:15 PM	**O6: HIV-1 Proteins Gp120 and Tat Promote Epithelial-mesenchymal Transition and Invasiveness of Neoplastic Genital and Oral Epithelial Cells** Sharof M. Tugizov, Department of Medicine, University of California-San Francisco
1:30 PM	**Questions/Discussion/Collaboration**
2:00–3:00 PM	**Day 1 Poster Viewing**

DAY 2: October 25

8:30 AM	**Log Into the Platform**
9:00 AM	**Opening Comments** Geraldina Dominguez, Office of HIV and AIDS Malignancy, National Cancer Institute
9:15 AM–12:00 PM	**Session 3: Kaposi Sarcoma and KSHV** Moderator: Charles Wood, Louisiana State University Health Sciences Center, New Orleans
9:15 AM	**P5: Gammaherpesvirus Modulation of Host Immunity** Blossom Damania, University of North Carolina at Chapel Hill School of Medicine
9:45 AM	**P6: Development of Targeted Therapeutic Agents for KSHV-Associated Tumors and Proliferative Diseases** Robert Yarchoan, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute
10:15 AM	**O7: Antisense-to-Latency Transcript Long Noncoding RNA in Kaposi's Sarcoma-Associated Herpesvirus Perturbs Host Alternative Splicing Regulation** Yuan Hong, Department of Molecular Genetics and Microbiology, College of Medicine, University of Florida, Gainesville
10:30 AM	**O8: Bulk and Spatial Transcriptional Analysis Identifies Overlapping and Tissue-Distinct Profiles Between Kaposi Sarcoma Tumors of the Skin and Gastrointestinal Tract** Joseph M. Ziegelbauer, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute
10:45 AM	**O9: Whole Genome Sequencing of Kaposi's Sarcoma-Associated Herpesvirus from Patients of Diverse Ethnicities Reveals Variation Across the Genome, Recombination, and Infection With Multiple Variants** Vickie A. Marshall, Viral Oncology Section, AIDS and Cancer Virus Program, Frederick National Laboratory for Cancer Research
11:00 AM	**O10: Kaposi Sarcoma Patient-Derived Xenografts as a Preclinical Model for Evaluation of Novel Therapeutic Strategies** Xiaofan Li, HIV and AIDS Malignancy Branch, National Cancer Institute
11:15 AM	**O11: Immunization of Mice With Virus-Like Vesicles of Kaposi Sarcoma-Associated Herpesvirus Reveals a Role for Antibodies Targeting ORF4 in Activating Complement-Mediated Neutralization** Ting-Ting Wu, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California, Los Angeles
11:30 AM	**Questions/Discussion/Collaboration**

12:00–1:30 PM	**Session 4: Junior Investigator Research in Progress Session** Moderators: Satish Gopal, Center for Global Health, National Cancer Institute, and Warren Phipps, Fred Hutchinson Cancer Research Center
12:00 PM	**O12: K5 Undergoes Caspase Cleavage and Protects KSHV-Infected Cells From Caspase-Mediated Cell Death** Yana Astter, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute
12:10 PM	**O13: WT1 Oncogenic Isoforms Are Upregulated by KSHV vFLIP: A Potential New Immunotherapeutic Intervention for Kaposi Sarcoma** Ayana Morales, Department of Medicine, Weill Cornell Medicine
12:20 PM	**O14: Extracellular Vesicles as Biomarkers for AIDS-Associated Non-Hodgkin Lymphoma Risk** Laura E. Martínez, UCLA AIDS Institute and David Geffen School of Medicine, University of California, Los Angeles
12:30 PM	**O15: More Frequent Bone Marrow Involvement in HIV Positive vs. Negative Classical Hodgkin Lymphoma Patients in Johannesburg, South Africa: A Prospective Study** Samantha L. Vogt, Department of Medicine, Johns Hopkins School of Medicine
12:40 PM	**O16: Advanced Biological Aging in Non-AIDS-Defining Cancer Patients Living With HIV** Brittney L. Dickey, Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute
12:50 PM	**O17: Penile Human Papillomavirus (HPV) in Men Who Have Sex With Men (MSM) and Transgender Women (TGW) From Buenos Aires: Initial Experience and Sample Collection Set** Diego Salusso, Fundación Huésped, Buenos Aires, Argentina
1:00 PM	**O18: Disparities in Trends in Cancer Incidence Rates Among Persons Living With HIV During 2001–2016 in the HIV/AIDS Cancer Match Study** Qianlai Luo, National Cancer Institute
1:10 PM	**O19: Risk of Hepatocellular Carcinoma Among People Living With HIV in the United States** Jennifer K. McGee-Avila, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology & Genetics, National Cancer Institute
1:20 PM	**O20: Decreasing Incidence of Squamous Cell Carcinoma of the Conjunctiva in People Living With HIV—the South African HIV Cancer Match Study (2004–2014)** Carole Metekoua, National Health Laboratory Service, Johannesburg, South Africa
1:30 PM	**Questions/Discussion/Collaboration**
2:00–3:00 PM	**Day 2 Poster Viewing**

DAY 3: October 26

8:30 AM	**Log Into the Platform**
8:50 AM	**Opening Comments** Geraldina Dominguez, Office of HIV and AIDS Malignancy, National Cancer Institute, and Robert Yarchoan, HIV and AIDS Malignancy Branch, Center for Cancer Research, and Office of HIV and AIDS Malignancy, National Cancer Institute
9:00–11:30 AM	**Session 5: Epidemiology** Moderator: Eric Engels, Division of Cancer Epidemiology & Genetics, National Cancer Institute
9:00 AM	**P7: Kaposi Sarcoma and KSHV in the Southern United States** Sheena Knights, The University of Texas Southwestern Medical Center
9:30 AM	**P8: Years of Life Lost to Cancer Among the US HIV Population, 2006–2015** Qianlai Luo, Division of Cancer Epidemiology & Genetics, National Cancer Institute
9:45 AM	**P9: Cancer Incidence and Risk Factors for Cancer in PLHIV—The South African HIV Cancer Match Study** Mazvita Sengayi-Muchengeti, National Cancer Registry, Johannesburg, South Africa
10:15 AM	**O21: Age and Cancer Incidence in 5.2 Million People Living With HIV in South Africa** Yann Ruffieux, University of Bern, Switzerland
10:30 AM	**O22: Cancer Treatment Inequities in People Living With HIV in the United States** Jennifer K. McGee-Avila, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology & Genetics, National Cancer Institute
10:45 AM	**O23: Adjuvant Chemotherapy for NSCLC in Patients Living With HIV: A Simulation Study** Keith Sigel, Icahn School of Medicine at Mount Sinai
11:00 AM	**Questions/Discussion/Collaboration**

11:30 AM–1:30 PM	**Session 6: Clinical and Translational Studies of HIV and Cancer** Moderators: Richard Little, Clinical Investigations Branch, National Cancer Institute, and Susan Krown, Memorial Sloan Kettering Cancer Center
11:30 AM	**O24: Altered Tumor Mutational Burden and Immune Microenvironment of Non-Small Cell Lung Carcinoma Among People With HIV** Brinda Emu, Yale University School of Medicine
11:45 AM	**O25: HIV and the Incidence of Conjunctival Squamous Cell Carcinoma in South Africa: A 25-Year Analysis of the National Cancer Registry (1994–2018)** Kelsey Stuart, NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom
12:00 PM	**O26: Microbiome Changes in Oral and Anal Samples From HIV-Exposed Individuals** E. Lacunza, CINIBA, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Argentina
12:15 PM	**O27: Pomalidomide and Liposomal Doxorubicin for Kaposi Sarcoma With or Without Other KSHV-Associated Diseases** Ramya Ramaswami, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute
12:30 PM	**O28: Whole Exome Sequencing Reveals Sparse Mutational Landscape in Kaposi Sarcoma** Warren Phipps, Fred Hutchinson Cancer Research Center
12:45 PM	**O29: High-Resolution Antibody Epitope Profiling Reveals Differences Between Symptomatic and Asymptomatic KSHV Infection** Sydney J. Bennett, School of Biological Sciences, University of Nebraska-Lincoln
1:00 PM	**Questions/Discussion/Collaboration**
1:30–2:30 PM	**Day 3 Poster Viewing**
2:30 PM	**Concluding Remarks** Geraldina Dominguez and Robert Yarchoan, 18th ICMH Program Co-Chairs

Author(s): Stefan K. Barta

P1: CAR T-Cell Therapy for HIV-Associated Lymphomas

Lymphoma Program, University of Pennsylvania, Philadelphia, PA

Adoptive immunotherapy has led to significant improvement in outcomes for patients diagnosed with lymphoma. Specifically, chimeric antigen receptor modified autologous T (CART) cell therapy directed against the CD19 antigen (CART19) represents a curative option for approximately 40% of patients with relapsed or refractory large B-cell lymphoma. However, people living with HIV (PLWH) were excluded in the landmark clinical trials leading to the FDA approval of the currently available CART19 products axicabtagene ciloleucel (Yescarta®), tisagenlecleucel (Kymriah®) lisocabtagene maraleucel (Breyanzi®), and brexucabtagene autoleucel (Tecartus™). While HIV-associated lymphomas have become less common in high-income countries, the risk of non-Hodgkin lymphoma (NHL) remains significantly elevated in PLWH (Engels EA, et al. Clin Infect Dis 2017). Furthermore, NHL is the leading cause of cancer-attributable deaths in PLWH (Horner MJ, et al. Clin Infect Dis 2021). In the past, high-dose chemotherapy as well as other cellular therapies, such as autologous and allogeneic hematopoietic cell transplant, have been shown both as safe and efficacious in PLWH as in people without HIV (Alvarnas JC, et al. Blood. 2016; Ambinder RF, et al. JCO 2017). However, the entire experience with CART19 therapy in PLWH relies on case reports and anecdotal experience. It remains unclear how the effects of HIV on the host immune system or features unique to HIV-associated aggressive lymphomas affect CART manufacture, effectiveness, or toxicities associated with CART19 treatment. These and other gaps in knowledge for this vulnerable population may contribute to lives lost among PLWH.

An active research collaboration between the AIDS Malignancy Consortium (AMC) and the Center for International Blood and Marrow Transplant Research (CIBMTR) aims to characterize CART19 treatment outcomes among PLWH using data routinely collected by the CIBMTR for patients receiving cellular therapy. The primary objectives of this observational cohort study (AMC-113) are safety and efficacy of CART19 therapy in PLWH treated for lymphoid malignancies. Secondary outcomes include survival and treatment-related toxicities—specifically, Cytokine Release Syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), and infectious complications—as well as the impact of CART19 therapy on HIV disease. The analysis will be descriptive and exploratory. Preliminary findings will be presented at the meeting.

Additional ongoing work includes a prospective clinical trial to assess CART19 therapy with axicabtagene ciloleucel in relapsed or refractory HIV-associated aggressive B-cell non-Hodgkin lymphoma (AMC-112; ClinicalTrials.gov Identifier NCT05077527). This study will enroll 20 participants, including at least 6 participants with a CD4 cell count <100, and assess effectiveness and safety. The correlative studies will help to assess potential predictive biomarkers, including cytokine profiles before and after CART infusion.

It is critical to leverage research collaborations across organizations and academic institutions to increase knowledge and treatment options for underserved populations and remove unnecessary research barriers. These projects have the potential to improve access to lifesaving treatments, such as CART therapy for PLWH, and future work will expand on this paradigm. Currently, 60% of patients with aggressive lymphomas experience relapse after CART19 therapy. It will be important to characterize resistance mechanisms that may be particularly relevant to HIV-associated lymphomas as these likely differ compared to lymphomas occurring in people without HIV. For example, virally mediated lymphomas are more common in PLWH and are associated with a different tumor microenvironment and mutational profile. Furthermore, host-related differences, such as the host microbiome, have been implicated in differential response to CART therapy (Smith M, et al. Nat Med 2022), which may be particularly relevant in PLWH.

Author(s): Ashish A. Deshmukh

P2: Anal Cancer Among Persons Living With HIV: Epidemiology, Contribution of HIV, and Modeling to Guide Cost-Effectiveness of Screening

Department of Public Health Sciences, Medical University of South Carolina Hollings Cancer Center, Charleston, SC

Human papillomavirus (HPV) attributable anal cancer incidence and mortality rates continue to increase 2–6% per year in high- and middle-income countries. HIV co-infection enhances the carcinogenicity of HPV, increasing anal cancer risk (56-fold among men and 6-fold among women) among persons living with HIV (PLWHIV) compared to those without HIV. Recognizing their elevated risk, several professional organizations in high-income countries (e.g., NY State, European AIDS Clinical Society) advise anal cancer early detection programs for PLWHIV. The programs use high-resolution anoscopy (HRA) to detect anal precancerous lesions, followed by treatment to reduce anal cancer risk. However, evidence- and consensus-based guidelines for anal cancer screening are unavailable, mainly due to the lack of clarity regarding the optimal screening use. Furthermore, the scarcity of practitioners trained to perform HRA remains a critical barrier to implementing population-wide screening programs even in the highest resource settings (e.g., USA).

Recent findings from the ANCHOR study (i.e., treatment of anal precancerous lesions decreases anal cancer risk) address the critical knowledge gap necessary to understand the value and cost-effectiveness of the anal cancer screening and treatment program. Mathematical modeling offers an ideal and complementary framework to combine anal HPV and precancer/cancer epidemiology, screening performance, and treatment effectiveness (ANCHOR) data to project the population impact of the anal cancer screening program and identify a cost-effective screening approach.

The first half of this talk will provide an overview of the recent anal cancer epidemiology and burden (worldwide [by countries] and in the US [by states]) and the contribution of HIV. The second half will describe the Simulation Model of Anal Cancer (SMAC) design and initial findings demonstrating the population impact of implementing a population-wide anal cancer screening and treatment program on epidemiological measures (e.g., anal cancer risk reduction, mortality benefits), health services utilization (e.g., HRAs per cancer prevented), and implications for cost-effectiveness (e.g., incremental cost-effectiveness ratios reflecting resources needed to improve cancer prevention). Finally, recent findings from a national study describing current anal cancer screening capacity and infrastructure in the U.S. will be covered, providing implications for screening capacity development, resource mobilization, and the need to address geographical disparities to ensure equitable anal cancer prevention among persons living with HIV.

Author(s): Joel Palefsky

P3: The ANCHOR Study

University of California, San Francisco, School of Medicine

The incidence of anal cancer is substantially higher among people living with HIV (PLWH) than among the general population. Anal and cervical cancer are very similar diseases, with both associated with oncogenic human papillomavirus infection, and, similar to cervical cancer, anal cancer is preceded by high-grade squamous intraepithelial lesions (HSIL). Cervical HSIL treatment reduces progression to cervical cancer. However, screening for and treating anal HSIL is not currently standard of care in PLWH because it is not known if treatment of anal HSIL similarly reduces the incidence of anal cancer.

To determine if treatment of anal HSIL reduces the incidence of anal cancer, we performed a prospective randomized controlled trial known as the ANal Cancer/HSIL Outcomes Research (ANCHOR) study. In total, 4,459 PLWH ^{3}35 years old at 25 United States sites with biopsy-proven anal HSIL were randomized 1:1 to HSIL treatment (office-based ablation, treatment under anesthesia, topical 5-fluorouracil or imiquimod) or active monitoring (AM) without treatment. The primary outcome was time to progression to cancer. Treatment arm participants were treated until HSIL was completely resolved. Participants underwent high-resolution anoscopy (HRA) every 6 months or every 3 months if there was concern for imminent progression to cancer. Participants were biopsied any time there was concern for cancer. Those in the treatment arm were biopsied for suspected ongoing HSIL and those in the AM arm were biopsied annually.

Of 4,459 PLWH randomized, 4,446 (99.7%) were included in the time-to-progression-to-cancer analysis. The most common form of treatment was office-based target ablation of visible HSIL, primarily hyfrecation. With a median follow-up of 25.8 months, nine cases were diagnosed in the treatment arm (173/100,000 PY, 95% CI 90–332) and 21 (402/100,000 PY, 95% CI 262–616) in the AM arm. HSIL treatment resulted in a 57% reduction in anal cancer (95% CI 6%–80%, P=.029 by log-rank test). Over a 48-month period of follow-up, 0.9% of participants in the treatment arm and 1.8% of participants in the AM arm progressed from HSIL to cancer. Treatment was well tolerated, with seven study-related serious adverse events in the treatment arm and one in the AM arm.

We conclude that treatment of anal HSIL significantly reduced the risk of anal cancer. These data should inform future guidelines on screening for and treating anal HSIL as standard of care for anal cancer prevention in PLWH ^{3}35 years old. Our data may also be relevant for other groups at high risk of anal cancer. Additional implications of ANCHOR study findings include a need for better treatment modalities for anal HSIL; biomarkers for HSIL progression or regression; optimization of screening algorithms for HSIL; and scale-up of HRA training programs to increase the pool of HRA providers.

This work is funded by the National Cancer Institute (UM1CA121947).

Author(s): Megan Clarke

P4: Anal Screening in People Living with HIV

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Most anal squamous cell cancers are caused by carcinogenic human papillomavirus (HPV) infection and develop through precursor lesions that can be detected by targeted sampling and high-resolution anoscopy with directed biopsy. Recent results from the U.S. Anal Cancer HSIL Outcomes Research (ANCHOR) study demonstrate that treating anal precancers reduces the risk of anal cancer among people living with HIV (PLWH) aged 35 years and older. These results underscore the need to develop screening approaches for detecting anal precancers that can be treated to prevent invasion. To address this need, the International Anal Neoplasia Society (IANS) assembled a Task Force to develop the first set of international recommendations for anal cancer screening. Critical components of this process are to understand the prevalence of anal precancer and to evaluate diagnostic tests for anal cancer screening in different populations to make recommendations for clinical use. To inform IANS Task Force recommendations, we conducted a systematic review and meta-analysis of tests for anal cancer screening, pooling estimates of diagnostic accuracy measures and absolute risk to assess clinical performance across different populations with elevated anal cancer risk. This presentation will discuss the criteria used for evaluating diagnostic accuracy data for anal cancer screening and will summarize the results from our systematic review and meta-analysis, which provide an important foundation for the development of anal cancer screening guidelines. We will also discuss important clinical challenges that need to be considered in this process and highlight gaps in the literature that should be addressed in future studies.

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P5: Gammaherpesvirus Modulation of Host Immunity

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Gammaherpesviruses, including Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV), are DNA viruses that are globally associated with human cancers and establish lifelong latency in the human population. These viruses are also found in several different HIV-associated malignancies, including Kaposi sarcoma and several types of non-Hodgkin lymphoma. Detection of gammaherpesviral infection by host innate immune pathways is critical for suppressing replication and transmission of these viruses. Our studies have shown that the cGAS-STING innate immune DNA sensing pathway modulates reactivation and replication of KSHV and EBV.

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P6: Development of Targeted Therapeutic Agents for KSHV-Associated Tumors and Proliferative Diseases

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Persons with HIV (PWH) have an increased incidence of several Kaposi sarcoma herpesvirus (KSHV)-associated diseases, including Kaposi sarcoma (KS), primary effusion lymphoma (PEL), KSHV-multicentric Castleman disease (KSHV-MCD), and KSHV inflammatory cytokine syndrome (KICS). PWH often manifest two or more of these conditions. While there are approved agents or recommended therapies for the first three of these conditions, improved therapies are sorely needed. Recent research defining the pathogenesis of these conditions, along with the development of agents targeting relevant steps in their pathogenesis, has enabled consideration of novel targeted therapies.

Our group previously showed that the thalidomide analog pomalidomide was effective against KS (Polizzotto M, et al., J Clin Oncology, 2016; Ramaswami R, et al, Clin Cancer Res, 2022). KSHV suppresses the expression of various surface immune markers (e.g., MHC-1, ICAM-1, and B7-2), which can render cells invisible to the immune system (Davis D, et al., Oncotarget, 2017). We found that among other activities, pomalidomide increased expression of these markers in PEL cell lines, suggesting this as a possible mechanism of action. However, pomalidomide did not increase surface marker expression in KSHV-infected endothelial cells, leading us to consider other agents that might do so. CDK4/6 inhibition had been shown to have in vitro activity in PEL cell lines (Manzano M, et al., Nat Commun, 2018), and we further showed that certain drugs of this class could suppress growth of KSHV-infected endothelial cells and also enhance expression of immune surface markers on these cells (Wu Y, et al., J Translational Med, 2022). Based on these and related results, a trial of the CDK4/6 inhibitor abemacicilib in patients with KS (NCT04941274) has been initiated by our group.

KSHV-MCD is characterized by intermittent inflammatory flares largely caused by an excess of IL-6, KSHV-encoded vIL-6, and IL-10. Pathologically, KSHV-MCD is characterized by KSHV-infected plasmablasts in lymph nodes, many of which express vIL-6. However, there is evidence that induction of IL-6 and IL-10 in other cells is a key component of KSHV-MCD pathogenesis. KICS is a syndrome with similar symptoms and cytokine expression but without the pathological abnormalities of KSHV-MCD. Since vIL-6 signals through the JAK/STAT pathway, we were interested in exploring JAK/STAT inhibitors as a possible therapy. There is no established in vitro model for KSHV-MCD, and since PEL also involves autocrine or paracrine cytokine loops, we initially tested a number of these inhibitors on PEL cells. We found that the JAK2 inhibitor pacritinib was particularly effective at blocking the growth of PEL cell lines in vitro (see Abstract 67). Pacritinib also targets several other kinases, including IRAK1, FLT3, and CSF1R, and it is possible that its activity in PEL results from combined targeting of two or more kinases. Perhaps more importantly for KSHV-MCD, pacritinib effectively blocks vIL-6-induced IL-6 production by peripheral blood mononuclear cells and monocyte cell lines, suggesting that it may be worth testing against KSHV-MCD and KICS. We are currently developing a protocol to test this hypothesis.

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Author(s): Sheena Knights

P7: Kaposi Sarcoma and KSHV in the Southern United States

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We will review Kaposi sarcoma (KS) incidence trends in the United States and worldwide and review evidence of disparities among racial/ethnic groups, particularly in the southern United States. Additionally, we will review KSHV epidemiology and describe KSHV seroprevalence in a high-risk population in the southern U.S.

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P8: Years of Life Lost to Cancer Among the US HIV Population, 2006–2015

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OBJECTIVES:

We estimated years of life lost (YLLs) to all causes of death and years of life lost to cancer among persons living with human immunodeficiency virus (HIV; PLWH) in the United States (US).

DESIGN:

Linked HIV and cancer registry data from the HIV/AIDS Cancer Match Study were used to identify incident cancers and deaths among PLWH in 11 regions of the US during 2006–2015.

METHODS:

Mean YLL (MYLL) to all causes of death and MYLL to cancer during 2006–2015 were derived from the restricted mean survival estimated from Cox proportional hazards regression models. MYLLs were then upweighted to the national PLWH population to obtain all-cause total years of life lost (TYLL) and cancer-related TYLL in the US during 2006–2015.

RESULTS:

Among 466,234 PLWH in the study population, 25,772 (5.5%) developed cancer during 2006–2015. Nationally, an estimated 134,986 years of life were lost to cancer of all types during 2006–2015 among PLWH, representing 9.6% of TYLL to all causes. Non-Hodgkin lymphoma (NHL), Kaposi sarcoma (KS), anal cancer, and lung cancer were the four largest cancer contributors (45% of TYLL to cancer). The largest fraction of TYLL occurred among Black PLWH, men who have sex with men, and PLWH aged 40–59 years old.

CONCLUSION:

PLWH have higher mortality rates after developing cancer. NHL, KS, and anal and lung cancers were large contributors to the TYLL to cancer, highlighting opportunities to reduce cancer mortality through improved access to antiretroviral treatment, prevention, and screening.

Author(s): *Mazvita Muchengeti[1] on behalf of the South African HIV Cancer Match Study team (Elvira Singh[1], Victor Olago[1], Tafadzwa Dhokotera [2,3], Carole Metekoua[1], Wenlong Chen[1], Adrian Spoerri[2], Lukas Butikofer[2], Lina Bartels[2], Eliane Rohner[2], Yann Ruffieux[2], Matthias Egger[2], and Julia Bohlius[3])*

P9: Cancer Incidence and Risk Factors for Cancer in PLHIV—The South African HIV Cancer Match Study

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South Africa has the largest number of people living with HIV (PLWH) in the world and presents an opportunity to evaluate cancer risk in PLWH with sufficient power to evaluate subgroups such as children, adolescents, women, and the elderly and to explore rare cancers. The South African HIV Cancer Match (SAM) Study is a national cohort of PLWH. It was created using probabilistic record linkages of routine laboratory records of PLWH retrieved by National Health Laboratory Services (NHLS) and cancer data from the National Cancer Registry. The SAM Study aims to assess the spectrum and risk of cancer in PLWH in the context of the evolving South African HIV epidemic.

The SAM cohort currently includes 5,248,648 PLWH for the period 2004 to 2014; 69% of these are women. The median age at cohort entry was 33.0 years (IQR: 26.2–40.9). Cancers with the highest incidence rates were Kaposi sarcoma, cervix, breast, non-Hodgkin's lymphoma, and eye cancer. We summarize results from recent SAM study publications and future directions for the cohort.

The SAM Study is a unique, evolving resource for research and surveillance of malignancies in PLWH. The SAM Study will be regularly updated. We plan to enrich the SAM Study through record linkages with other laboratory data within the NHLS (e.g., tuberculosis, diabetes, and lipid profile data), mortality data, and socioeconomic data to facilitate comprehensive epidemiological research of comorbidities among PLWH.

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OTribute: Bone Marrow-Derived Human MSC as Precursors of KS Initiation and Progression Through Endothelial Differentiation and Cytokine Induction After KSHV Infection in a Pro-Angiogenic Environment

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BACKGROUND:

Cumulative evidence shows the importance of bone marrow-derived human Mesenchymal Stem Cells (hMSC) in Kaposi's sarcoma (KS) Herpesvirus (KSHV) induced tumorigenesis. However, the KS spindle-cell progenitor subpopulation identity, defining markers, and specific host conditions of KSHV-driven oncogenesis upon de novo infection are not well defined yet.

METHODS:

We carried out KSHV infection of primary hMSCs and then subjected them to MSC or KS-like pro-angiogenic culture conditions. Three days after infection or one month after the selection of infected cells, we performed whole and single-cell RNA sequencing analyses of the Differentially Expressed Genes (DEGs).

RESULTS:

We found that processes such as extracellular matrix, angiogenesis, cell differentiation, cytokine activity, and cell proliferation were significantly more overrepresented in cells infected and grown in the KS-like conditions than in MSC cell culture conditions. By single-cell RNA sequencing, we found that different cell populations express different amounts of host and viral oncogenes depending on the environmental conditions in which the cells are growing after infection, leading to a subpopulation of infected cells in a pro-angiogenic environment expressing both viral and host oncogenes.

CONCLUSIONS:

These highlight the importance of environmental conditions in KSHV reprogramming of hMSC towards endothelial differentiation and transformation and closer to KS gene expression profiles, reinforcing the notion of these cell subpopulations as plausible KS precursors.

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01: Multicentric Castleman Disease in Malawi: Updates from a Prospective Cohort Study and Early Results from a Phase II Safety/Efficacy Study of Rituximab Treatment

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BACKGROUND:

Multicentric Castleman disease (MCD) is a lymphoproliferative disorder that is highly associated with HIV and Kaposi sarcoma herpesvirus (KSHV). As opposed to many other HIV-associated cancers or opportunistic infections, KSHV-MCD tends to occur in patients who have been on antiretroviral therapy (ART) for many years with suppressed HIV viral load and preserved CD4 counts. KSHV-MCD is a rare disease, though studies from high-income countries have shown that cytotoxic chemotherapy can control the disease but with high relapse and mortality. However, treatment with rituximab can be quite effective. Reports of MCD from sub-Saharan Africa are limited, likely due to underdiagnosis. We have previously reported results from the Kamuzu Central Hospital (KCH) Lymphoma Study showing that MCD constitutes 15% of all lymphoproliferative diagnoses among HIV-infected patients in Malawi and that survival with chemotherapy is quite poor. Here we report an update on the observational cohort as well as results from the first four patients of a phase II safety/efficacy study of rituximab therapy for MCD.

METHODS:

The KCH Lymphoma Study is a prospective, observational study of pathologically confirmed lymphoproliferative disorders (2013–current). In 2021, we initiated a phase II safety/efficacy study of rituximab for MCD in Malawi. Inclusion criteria are as follows: age >18, pathologically confirmed KSHV-MCD (LANA+), new diagnosis or relapsed, HIV-infected or uninfected, in need of treatment as defined by all of 1) fever, 2) lymphadenopathy/splenomegaly, and 3) signs/symptoms attributable to MCD (malaise, weight loss, hemoglobin <10 g/dL, or platelets <100 x 103/μL). Patients are excluded if they have previously received rituximab or have extensive stage KS requiring chemotherapy. Low-risk patients are treated with four weekly doses of rituximab 375 mg/m2. High-risk patients, defined as patients with hemoglobin <8 g/dL or ECOG >2 concomitantly receive etoposide 100 mg/m2 weekly for four weeks.

RESULTS:

Since 2013, we have enrolled 32 patients with MCD. Median age is 40 years and 21 (66%) are men. All are HIV positive and only five (16%) were not on ART at the time of MCD diagnosis. Median time since HIV diagnosis and ART initiation were 6.5 years (IQR 1.8-9.8) and 6.5 years (IQR 2.9-9.1), respectively. Median CD4 count was 287 cells/ul (IQR 152-434) and HIV viral load was suppressed <400 copies/mL in all patients who were on ART prior to MCD diagnosis. Lymphadenopathy was present in all patients and 28 (88%) had B symptoms. Median hemoglobin was 7.7 g/dL (IQR 5.9-9.3). Ten (31%) patients had concomitant KS but only one (3%) had advanced KS. Two patients died before receiving any chemotherapy but the first-line chemotherapy for the others was etoposide in 19 (59%), CVP in 10 (31%), and rituximab in 1 (3%). Among those receiving etoposide or CVP, 14 (48%) achieved CR, 2 (7%) PR, 1 (3%) SD, and 12 (41%) progressive disease; of this group, 24 (83%) relapsed within 1 year. Among the entire cohort, 2-year OS is 65% and of the 16 participants still alive, only 3 have not been treated with rituximab, either in the clinical trial or under compassionate use. Since the rituximab clinical trial has started, we have enrolled four patients, including three relapsed and one new diagnosis. All patients have achieved a complete response and remain in remission after a range of 6–13 months. One patient on the high-risk arm had grade 3 neutropenia but no other grade 3/4 events have been reported.

CONCLUSIONS:

KSHV-MCD is a disease with very high morbidity and mortality in Malawi. Survival with chemotherapy is extremely poor and improved treatments are needed. Rituximab appears effective, though the clinical trial is ongoing to assess safety and efficacy in Malawi where rituximab is expensive and the supportive care and infectious environment are significantly different from high-income countries where rituximab has previously been studied.

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O2: Daratumumab Induces Cell-Mediated Cytotoxicity of Primary Effusion Lymphoma and Can Be Active Against Refractory Disease

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BACKGROUND:

Primary effusion lymphoma (PEL) is a rare, aggressive non-Hodgkin lymphoma caused by Kaposi sarcoma-associated herpesvirus (KSHV). PEL has no standard therapy, and the median overall survival remains poor, with many patients experiencing refractory disease. Therefore, there is an urgent need to develop new therapies. PEL consists of plasmablast-like post-germinal center B cells that generally express CD38, the therapeutic target of FDA-approved anti-tumor monoclonal antibody daratumumab (Dara). Dara mediates anti-tumor activity of CD38-expressing cells primarily through Fc-related functions such as complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). In this study, we aimed to assess Dara's anti-tumor activity in PEL.

METHODS:

Cells from the effusions of eight PEL patients, as well as five PEL-derived cell lines, were assessed for their surface CD38 expression by flow cytometry. Dara's anti-tumor effects on PEL were then determined by measuring complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) of PEL cell lines. Finally, to determine if Dara might show clinical benefit, two patients with refractory PEL with leptomeningeal involvement were treated with Dara either as a monotherapy or in combination with the immunomodulatory drug, pomalidomide, and responses were assessed under a clinical trial for patients with KSHV-associated diseases (NCT00006518).

RESULTS AND CONCLUSIONS:

PEL cells from all eight PEL patients expressed high levels of CD38. The five PEL cell lines were also positive for CD38 expression. Dara bound to CD38 on PEL cell surfaces with a saturating concentration of <1 µg/mL. Despite high surface CD38 levels, Dara did not induce human complement-mediated CDC of PEL cell lines. Upon further analysis, PEL cell lines were found to express high levels of complement-inhibitory proteins (CIPs) CD46, CD55, and CD59 on their surfaces. Inhibiting both CD55 and CD59 using neutralizing antibodies led to partial but significant increases in Dara-induced CDC activity, suggesting that high levels of CIPs are at least partially responsible for the resistance of PEL cell lines to Dara-induced CDC. Ability of Dara to induce ADCC of PEL cell lines was also examined, first by using Jurkat-ADCC reporter cells and then by using PBMCs from healthy donors as effector cells. In both assays, Dara led to a significant and dose-dependent increase in ADCC of PEL cell lines, particularly in those lines with high CD38 levels. Also, two FDA-approved drugs, all trans-retinoic acid (ATRA) and pomalidomide, significantly increased surface CD38 levels in low-CD38-expressing PEL cell lines, resulting in increased Dara-induced ADCC. Finally, in the two patients treated with Dara, one showed a complete response to Dara and pomalidomide and then a decrease in the number of PEL cells in his central nervous system with Dara alone. The other had improvement in performance status and resolution of malignant ascites with Dara alone. Taken together, these data support the use of Dara in PEL either alone or in combination with ATRA or pomalidomide.

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03: Risk of Progression From Anal Intraepithelial Neoplasia In Situ to Invasive Anal Cancer in PLWH Compared to HIV Uninfected People

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BACKGROUND:

Rates of anal cancer are elevated in immunosuppressed populations, particularly among people living with HIV (PLWH), where rates are nearly 20-fold higher compared to the general population. Anal intraepithelial neoplasia grade III (AIN3) is a precursor to invasive anal cancer (IAC). While the majority of AIN3 do not progress to IAC and some regress completely, an estimated 1-5% will progress to cancer within 5 years of detection. Recent results from the Anal Cancer/HSIL Outcomes Research (ANCHOR) study trial have shown that the treatment and removal of precancerous lesions significantly reduced risk of progression to IAC in PLWH. We aimed to identify populations with quicker progressing lesions and inform the frequency for interval follow-up for higher risk populations.

METHODS:

We utilized data from 13 participating regions in the HIV/AIDS Cancer Match (HACM) Study, a population-based linkage between cancer and HIV registries in the United States. We identified individuals with a cancer registry diagnosis of AIN3 and/or IAC and determined their HIV status. We described patient and tumor characteristics for AIN3 and IAC according to HIV status. We estimated average annual percentage change (AAPC) of AIN3 and IAC over time using Poisson regression among men and women living with HIV, and men and women without a diagnosis of HIV, separately. We estimated 5-year cumulative incidence of IAC following AIN3 diagnosis stratified by sex and HIV status and hazard ratios using adjusted Cox Proportional Hazards models.

RESULTS:

We observed 6,365 and 23,256 cases of AIN3 and IAC, respectively, over ~1 billion person-years of observation during 1996–2018 in people without HIV. Among PLWH, we observed 2,554 and 2,098 cases of AIN3 and IAC, respectively, during 4.5 million person-years. Men with HIV had the highest rates of AIN3 (Table 1), among whom men who have sex with men (MSM) accounted for approximately 80% of diagnoses. Overall, the rates of AIN3 increased 10% per year during the study time period, with evidence of a greater increase among females with HIV and a slower increase among females without HIV compared to men with HIV (pinteraction<0.001). The 5-year cumulative incidence of IAC following AIN3 diagnosis ranged from 1.1% in females with HIV to 5.2% in males without HIV. There was no evidence of statistical difference in risk of an IAC diagnosis following AIN3 by HIV status or sex after accounting for registry and year of diagnosis.

CONCLUSIONS:

Rates of AIN3 diagnoses have increased over the last two decades, including among MSM with HIV, who are at the greatest risk of IAC. There was no evidence for differences in cumulative incidence of IAC following AIN3 between men and women with and without HIV.evidence of statistical difference in risk of an IAC diagnosis following AIN3 by HIV status or sex after accounting for registry and year of diagnosis.

Table 1. Summary of results for risk and trends of anal intraepithelial neoplasia grade 3 (AIN3) and progression to invasive anal cancer (IAC) according to HIV status and sex during 1996–2018.

Population	Number of AIN3	Incidence rate (per 100,000 person-years)	AAPC* OF AIN3 (95% CI)	5-year cumulative incidence of IAC following AIN3	Hazard ratio** of IAC following AIN3 (95% CI)
Men with HIV	2,211	68.4	12% (11-14%)	2.3% (1.5-3.1%)	Reference
Females with HIV	343	27.7	23% (18-27%)	1.1% (0.1-2.1%)	1.0 (0.9-1.1)
Men without HIV	3,776	0.74	11% (10-12%)	5.2% (3.6-6.8%)	1.0 (0.9-1.0)
Females without HIV	2,589	0.48	8% (7-9%)	3.2% (2.3-4.2%)	1.0 (0.9-1.1)

AAPC = average annual percentage change
*** Poisson regression models were adjusted for year of AIN3 diagnosis, age, race and ethnicity, and registry**
****Cox proportional hazards model was adjusted for age, registry, and year of AIN3 diagnosis**

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04: Anal Cancer Survival Among Persons Living With HIV in the United States

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BACKGROUND:

Anal cancer risk is elevated among persons living with HIV (PLWH). Increases in anal cancer incidence in the United States (US) have been observed. We estimated overall survival (OS) and anal cancer-specific survival (CSS) among anal cancer patients living with HIV and identified characteristics associated with survival.

METHODS:

We used HIV/AIDS Cancer Match Study data on anal cancer patients diagnosed during 2001–2018 in the US at ages 20-79 years, categorized as living with or without HIV. Adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) were calculated using Cox models. Five-year OS and CSS were calculated by HIV status.

RESULTS:

Among 21423 total anal cancer patients, 2320 were living with HIV, of whom 1009 (43.5%) died. Anal cancer patients living with HIV were more likely to die compared to those without HIV (aHR=1.57 [95% CI=1.45–1.70]), adjusting for year of cancer diagnosis, sex, age at anal cancer diagnosis, race/ethnicity, histology, cancer stage, and registry region. When stratified by sex, female anal cancer patients living with HIV had significantly poorer OS compared to those without HIV (**Figure A**, p<0.0001). Among anal cancer patients living with HIV, notable characteristics associated with poorer OS were: Black vs. White race/ethnicity (aHR=1.22, 95% CI=1.04–1.43), adenocarcinoma vs. squamous cell carcinoma (SCC) (aHR=2.30, 95% CI=1.43–3.72), distant vs. localized cancer stage (aHR=3.56, 95% CI=2.81–4.50), no surgery (aHR=1.38, 95% CI=1.17–1.63), and AIDS (aHR=1.42, 95% CI=1.1451.76). Of the 7549 total deaths in the population, 2513 (33.3%) were due to anal cancer. HIV status was not significantly associated with anal cancer-specific mortality. When stratified by sex, male anal cancer patients living with HIV had significantly better anal CSS compared to those without HIV (**Figure B**, p<0.0001). Among anal cancer patients living with HIV, notable characteristics associated with poorer CSS were: adenocarcinoma versus SCC (aHR=3.57, 95% CI=1.26–10.08), distant vs. localized cancer stage (aHR=7.17, 95% CI=4.22–12.19), and no treatment (aHR=1.85, 95% CI=1.11–3.08). Five-year OS was significantly lower among anal cancer patients living with HIV (53.7% [95% CI=51.3%–56.0%]) vs. those without HIV (64.6% [95% CI=63.8%–65.4%]). Five-year CSS was not significantly different between anal cancer patients living with HIV (80.5% [95% CI=77.6%–83.0%]) and those without HIV (77.1% [95% CI=76.2%–78.0%]).

CONCLUSIONS:

HIV status and several characteristics among persons living with HIV were significantly associated with poorer survival in anal cancer patients. Our findings emphasize the importance of anal cancer screening and treatment in PLWH and other high-risk groups in the US.

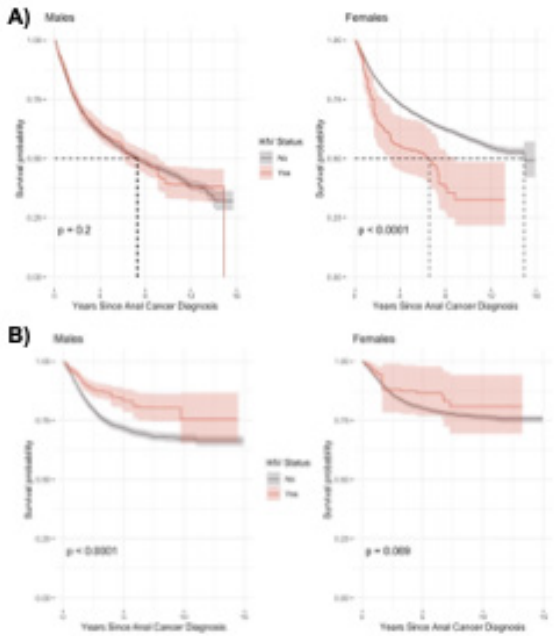

Figure: *Weighteda Kaplan-Meier survival curves for A) OS and B) anal CSS among persons diagnosed with anal cancer; aKaplan-Meier curves were weighted by year of anal cancer diagnosis, age at anal cancer diagnosis, race/ethnicity, histology, anal cancer stage, and registry region.*

Author(s): Jessica George[1], Shawna Tuli[1], Palak Patel[2], Barati Monare[3], Lisa Bazzett-Matabele[4,5], Peter Vuylsteke[6,7], Katharine A. Rendle[8], and Surbhi Grover[3,9]

05: Delays in Initiation of Curative Intent Chemoradiation and Patterns of Survivorship Care for Cervical Cancer Patients Living With or Without HIV in Botswana

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BACKGROUND:

The goal of this study was: (a) to assess delays from date of pathology review to initiation of curative intent chemoradiation (CRT) treatment for HIV- and HIV+ women with locally advanced CC in Botswana (2013-2019), (b) to investigate patterns of survivorship care for HIV- and HIV+ patients with advanced stage cervical cancer (CC) who were treated with CRT in Botswana, and (c) to prospectively evaluate factors associated with retention in survivorship care among the CRT-treated population between 2015-2022.

METHODS:

We prospectively enrolled women with or without HIV in Botswana with locally advanced CC (stages IB2-IVB) into an observational cohort study (2013-2022) and used logistic regression to evaluate association between delays in CC treatment initiation (time from date of pathology review to initiation of curative intent CRT ≥ 90 days for patients enrolled between 2013 -2019). We also used logistic regression to analyze patterns of survivorship care following RT and assess factors associated with retention in survivorship care for patients enrolled between 2015-2022, in accordance with the national CC guidelines recommending survivorship care every 6 months for the first 2 years and annually for the subsequent 3 years following the end of treatment (EOT).

RESULTS:

Of the 1,405 CC patients, 964 (68.6%) were treated with RT and 111 (7.9%) were treated with curative intent CRT. Median age among the cohorts were similar (48 years RT vs. 46 years CRT). Two-thirds of women were HIV+ and, at the end of treatment, most patients had CC stage II (36.3% RT vs. 53.2% CRT) and III (31% RT vs. 28.8% CRT) disease among the cohorts. Slightly less than half (43.2%) of the patients treated with curative intent CRT experienced delays in CC treatment initiation ≥90 days. On multivariable analysis adjusting for age, distance from the treatment clinic, HIV status, stage, and year of diagnosis, these patients were less likely to experience delays in CC treatment initiation ≥90 days for: stages III-IV disease (OR 0.62, p=0.038) vs. stages I-II disease. Of the 852 RT patients eligible for the first 2 years of survivorship care, 627 (73.6%) attended at least 1 follow-up via office visit or phone call, and 201 (23.6%) followed up every 6 months for the first 2 years. For the subsequent 3 years of survivorship care, of the 722 RT patients eligible for follow-up care, 362 (50.1%) attended at least 1 follow-up via office visit or phone call, and 101 (14%) followed up every year for the subsequent 3 years. On multivariable analysis adjusting for age, HIV status, disease stage, and treatment type, patients were less likely to follow up every 6 months for the first 2 years at disease stages III-IV (OR 0.5, p=0.008) vs. I-II and with definitive treatment type (OR 0.6, p=0.04) and palliative treatment type (OR 0.2, p=0.01) vs. curative treatment type.

CONCLUSIONS:

We have found that delays in treatment initiation are common especially for stage I and II CC patients living further away from the centralized treatment clinic, and that most CC patients with advanced disease do not adhere to the recommended survivorship care plan. Together, our complementary studies support the need for targeted strategies to reduce delays in treatment initiation, and to implement interventions aimed at improving patient adherence to the national survivorship care plan in Botswana.

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O6: HIV-1 Proteins Gp120 and Tat Promote Epithelial-Mesenchymal Transition and Invasiveness of Neoplastic Genital and Oral Epithelial Cells

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BACKGROUND:

The incidence of human papillomavirus (HPV)-associated anogenital and oropharyngeal cancer in human immunodeficiency virus (HIV)-positive individuals is substantially higher than in HIV-uninfected individuals. However, the molecular mechanisms underlying HIV-1-associated promotion of HPV malignancy are not fully understood. Here, we showed that HPV-16-immortalized genital and oral epithelial cells and HPV-negative oral cancer cells that undergo prolonged contact with cell-free HIV-1 virions or with viral proteins gp120 and tat respond by becoming more invasive.

METHODS:

BHPV-16-infected cervical CaSki and SiHa cells, oral SCC-47, and HPV-18-infected HeLa cell lines, and HPV-negative cervical C-33 A, oral HSC-3, and pharyngeal Detroit-562 cancer cells were treated with cell-free HIV-1 virions and viral proteins gp120 and tat, each at 10 ng/ml for 5 to 7 days. Cells were evaluated quantitatively for epithelial mesenchymal transition (EMT) with H&E staining. Cells that displayed a typical cobblestone shape were counted as epithelial cells, while cells with elongated spindle-like morphology and protrusions were counted as mesenchymal cells (i.e., EMT cells). Live EMT cells were also examined by phase-contrast inverted digital microscopy (Leica). In vitro invasion assays were performed using the collagen cell invasion assay.

RESULTS:

The interaction of cell-free virions and gp120 and tat proteins with epithelial cells substantially reduced the expression of E-cadherin and activated the expression of vimentin and N-cadherin. EMT induced by the HIV-1 gp120 and tat proteins was accompanied by activation of the Snail transcription factor. EMT induced by gp120 and that led to detachment of poorly adherent cells from the culture substratum; these cells remained capable of reattachment, upon which they co-expressed both E-cadherin and vimentin, indicative of an intermediate stage of EMT. The reattached cells also expressed stem cell markers CD133 and CD44, which may play a critical role in cancer cell invasion and metastasis. Inhibition of transforming growth factor (TGF)- ß1 and MAPK signaling and vimentin expression, and restoration of E-cadherin expression reduced HIV-induced EMT and the invasive activity of HPV-16 immortalized anal and cervical epithelial cells.

CONCLUSIONS:

These results suggest that the interaction of HIV-1 with neoplastic epithelial cells may lead to their de-differentiation into cancer stem cells that are resistant to apoptosis and anti-cancer drugs. Thus, this pathway may play a critical role in the development of invasive cancer.

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07: Antisense-to-Latency Transcript Long Noncoding RNA in Kaposi's Sarcoma-Associated Herpesvirus Perturbs Host Alternative Splicing Regulation

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BACKGROUND:

Kaposi's sarcoma-associated herpesvirus (KSHV) is the etiologic agent for primary effusion lymphoma, Multicentric Castleman's disease, and Kaposi's sarcoma, an AIDS-associated malignancy. Recent transcriptome studies have uncovered multiple non-coding RNAs in KSHV, most of which are expressed during the lytic stage. The antisense-to-latency transcript (ALT) is a lytic transcript of approximately 10,000-nucleotides that predominantly resides in the nucleus. It is transcribed from the antisense to the KSHV latency-associated region including LANA, vFlip, vCyclin, and most of the microRNA genes. Due to its high abundance upon lytic reactivation, extreme long length, and particular location across the latency region, studying the function of ALT and its interactome can provide important insights into how viral lncRNAs play a role in the viral-host interaction.

METHODS:

To study potential functions of ALT, we performed RNA antisense purification (RAP) from lytically induced BC3 cells with 4-thiouridine labeling and UV cross-linking, followed by isobaric-labeling mass spectroscopy. Target validation was performed using RNAscope and IFA co-localization. Additionally, we knocked down and overexpressed ALT in BCBL1 cells to examine changes in alternative splicing (AS) by RNAseq using splicing analysis tools, including rMATS and IRFinder.

RESULTS:

We identified 51 host proteins and three KSHV proteins, ORF11, ORF59, and ORF51, as direct ALT binding partners in RAP. Interestingly, 41 of the identified host proteins are involved in splicing regulation, including PTBP1, PTBP2, HNRPLL, HNRNPDL, HNRNPA2B1, U2AF2, and SRSF1, suggesting that ALT may perturb splicing via a sponging mechanism. ALT lncRNA expression dramatically increases during immediate early lytic replication, when it forms uniformly spread punctate dots in the nucleus when visualized by RNAscope. By the late lytic stage, it condenses into larger punctates. These results suggest the continuous transcription of ALT may create splicing factor-containing nuclear condensates, which concentrate the splicing components in areas in the nucleus. RNAseq-based splicing analysis revealed AS events in ALT knockdown and overexpression conditions and identified that these AS events are associated with nonsense-mediated mRNA decay (NMD) by inappropriate exon skipping and nonconserved cryptic exon inclusion. U2AF2 and SRSF1 are core-splicing factors required for many splicing events. Interestingly, PTBP1/2 are strong suppressors of cryptic exon inclusion, suggesting that sponging of these factors by ALT during lytic reactivation increases these splicing events, leading to NMD.

CONCLUSIONS:

Our findings indicate that the KSHV lncRNA ALT perturbs host mRNA splicing by association with many splicing factors, leading to AS events during lytic replication. Since most KSHV genes, especially the lytic transcripts, are not spliced, ALT-dependent sponging during lytic reactivation may function as a novel viral host shut-off mechanism.

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08: Bulk and Spatial Transcriptional Analysis Identifies Overlapping and Tissue-Distinct Profiles Between Kaposi Sarcoma Tumors of the Skin and Gastrointestinal Tract

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BACKGROUND:

Kaposi sarcoma (KS), caused by Kaposi sarcoma herpesvirus (KSHV), is a multicentric tumor characterized by abnormal vasculature and proliferation of KSHV-infected spindle cells. KS commonly involves the skin but in severe cases KS can also involve the gastrointestinal tract (GI). Here, we sought to compare the cellular and KSHV gene expression signatures of skin and GI KS lesions.

METHODS:

Skin and GI KS were compared to normal matched samples using bulk RNA sequencing. Twenty-two paired samples of KS and normal tissue were obtained (skin [10 pairs] and GI [12 pairs]) from 19 patients with KS, of whom 17 had concurrent HIV infection. Seven paired samples were from patients who had received prior KS therapy. Three patients provided both skin and GI samples at the same time point. KS skin lesions from three participants were analyzed using a spatial transcriptomics platform.

RESULTS:

These analyses identified 370 differentially expressed genes (DEGs) unique to cutaneous KS and 58 DEGs unique to GI KS, compared to normal skin or GI tissues. Twenty-six DEGs overlapped between skin and GI KS, including FLT4, which encodes for a VEGF-C and VEGF-D receptor, and STC1, a secreted glycoprotein. KSHV infection of primary lymphatic endothelial cells (LECs) resulted in increased RNA expression of STC1 and increased secretion of STC1 protein. KSHV infection also boosted angiogenic properties of these cells and repression of STC1 inhibited angiogenesis in KSHV-infected cells. The analyses of KSHV expression from KS lesions identified certain transcriptionally active areas of the viral genome, specifically ORF75, that were consistently expressed. Some of these expression patterns were similar and some patterns differed between KS lesions and laboratory infections of LECs with KSHV. This investigation also identified gene expression patterns in KS lesions that could distinguish participants with only having KS versus those with KS and other KSHV-associated diseases. Spatial transcriptomic analysis found high expression of STC1, FLT4, angiogenic markers, and inflammatory genes restricted to specific regions of multiple KS skin sections.

CONCLUSIONS:

This study demonstrates that complex patterns of gene expression are found in KS tissue that differ from the canonical latent/lytic programs seen in KSHV cell lines. These differences in viral gene and clinically relevant host gene expression in skin and GI KS may offer insights into the pathogenesis of these forms of KS.

This work was supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health.

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09: Whole Genome Sequencing of Kaposi's Sarcoma-Associated Herpesvirus From Patients of Diverse Ethnicities Reveals Variation Across the Genome, Recombination, and Infection With Multiple Variants

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BACKGROUND:

KSHV causes Kaposi's sarcoma (KS); primary effusion lymphoma (PEL), a variant of multicentric Castleman's disease (MCD); and KSHV inflammatory cytokine syndrome (KICS). Historically, KSHV genome analysis was limited to variable genes, primarily K1 and K15, constituting <3% of the viral genome. KSHV subtypes defined by K1 have unique geographical distributions, but the association with disease risk is unclear. Subtypes A and C are common in Europe and North America, while B and A5 are predominant in Africa. Subtypes D, E, and F were first identified in isolated indigenous populations in the Pacific, South America, and in the San people of Botswana, respectively. Recent advances in next-generation sequencing have resulted in the publication of approximately 148 whole KSHV genomes, mostly from Africa.

METHODS:

We have developed a target enrichment protocol for near full-length KSHV genomes, the details for which have been recently published (PMID: 35608873). We sequenced KSHV genomes from 78 patients with KSHV-associated malignancies enrolled in clinical trial 01-C-0038 (NCT00006518) at the National Cancer Institute (NCI) HIV and AIDS Malignancy Branch (HAMB), Bethesda, MD, USA. For 23 individuals, more than one tissue was sequenced. All participants gave informed consent.

RESULTS:

We have obtained 101 near full-length sequences of KSHV subtypes A, B, C, and F, and the first reported E. Polymorphisms, determined using KSHV reference genome NC_009333.1, were identified in coding and non-coding regions of viral sequences obtained from various patients, which may have phenotypic correlations and require further investigation. Comparisons of genomes, obtained from different compartments, such as effusions, oral fluids, and PBMC, within the same patients yielded no consequential sequence differences. Multiple KSHV genomes of divergent subtypes were identified in 17 samples from 12 individuals. We also observed high levels of recombination.

CONCLUSIONS:

This study represents the largest and most diverse analysis of KSHV sequences to date among patients with KSHV-associated diseases and provides important new information on global KSHV genomics.

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010: Kaposi Sarcoma Patient-Derived Xenografts as a Preclinical Model for Evaluation of Novel Therapeutic Strategies

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BACKGROUND:

Kaposi sarcoma (KS) is a malignancy defined by hyperangiogenesis, inflammatory infiltrates, and endothelial cells infected with KSHV. KS is an AIDS-defining malignancy and a major cause of morbidity and mortality in people living with HIV globally. KS may be successfully treated with antiretroviral therapy, chemotherapy, and/or the immunomodulatory therapy pomalidomide, but tumor response is varied and relapse is frequent. The exploration of novel therapies is hampered by the lack of a preclinical animal model.

METHODS:

Fifteen KS biopsies (12 cutaneous KS and 3 gastrointestinal KS) were embedded in matrigel and implanted subcutaneously into 32 immunodeficient NOD SCID gamma mice (NSG mice) as intact or minced specimens, and with or without VEGF supplementation. At the experimental endpoints, the patient-derived xenograft (PDX) explants were sectioned, subjected to immunohistochemistry, and analyzed with HALO software.

RESULTS:

1. KS-PDX were maintained in recipient mice for long periods that ranged from 103 to 272 days, until the experimental endpoint. PDX tumor implant sizes have not increased over the first or second passage.
2. The cellularity increased in KS-PDX explants compared to input biopsies based on staining of the human-specific NUMA-1 marker.
3. KS histological features, including hyper-angiogenesis and slit-like structures, were recapitulated in KS-PDX examined.
4. LANA+ cells in all cutaneous KS-PDX explant samples examined were consistently and sometimes dramatically elevated compared to levels in the input biopsy. VEGF supplementation of the matrigel used for embedding was beneficial to LANA+ endothelial cell expansion.
5. The Ki-67 proliferation marker and sporadic expression of viral IL-6 overlapped with LANA+ areas, and, more importantly, immunofluorescence revealed that most Ki-67-positive cells were LANA positive.

CONCLUSIONS:

KS-PDXs are maintained in NSG and retain pathological attributes of KS in patient biopsies. The successful maintenance of KSHV-infected endothelial cells with proliferative potential suggests that patient-derived cutaneous KS xenografts may serve as a preclinical model to test novel and patient-personalized therapies.

This work was supported by the Intramural Research Program of the National Cancer Institute.

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O11: Immunization of Mice With Virus-Like Vesicles of Kaposi Sarcoma-Associated Herpesvirus Reveals a Role for Antibodies Targeting ORF4 in Activating Complement-Mediated Neutralization

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BACKGROUND:

The development of a prophylactic vaccine for Kaposi sarcoma-associated Herpesvirus (KSHV) would prevent consequences from infection such as Kaposi sarcoma and primary effusion lymphoma. Non-infectious enveloped virus-like vesicles (VLVs) that lack capsids and viral genomes hold a vaccine potential by presenting a repertoire of viral structural proteins to the immune system without the safety risk of an infectious virus. Here, we study the immunogenicity of KSHV VLVs produced from a viral mutant that is defective in capsid formation and DNA packaging.

METHODS:

A KSHV mutant that produces only VLVs was generated by deleting 60 amino acids from the major capsid protein. VLVs were isolated by ultracentrifugation and characterized with cryo-electron microscopy and mass spectrometry. Mice were immunized with VLVs to assay immunogenicity. T cell responses were measured with ELISpot and AIM assays. Antibody responses were assayed with ELISA, immunofluorescence, multiplexed bead-based assay, and neutralization assay.

RESULTS:

Mice immunized with adjuvanted VLVs generate KSHV-specific antibodies and T cells. VLV immune sera neutralize KSHV infection, and this neutralization is enhanced by the complement system. Complement-enhanced neutralization by VLV immune sera is dependent on antibodies targeting the short consensus repeat (SCR) region of viral open reading frame 4 (ORF4). However, complement-mediated enhancement was not detected in the sera of KSHV-infected humans which contained few neutralizing antibodies.

CONCLUSIONS:

Our study supports the utility of KSHV VLVs as a multi-antigen vaccine platform to stimulate a diverse immune response and underscores a potential benefit of complement-mediated antibody function in a KSHV vaccine.

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012: K5 Undergoes Caspase Cleavage and Protects KSHV-infected Cells From Caspase-Mediated Cell Death

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BACKGROUND:

Kaposi sarcoma-associated herpesvirus (KSHV) has evolved mechanisms to block apoptosis, in part, by interfering with caspase activation. We previously reported that KSHV latency-associated nuclear antigen acts as a pseudo-substrate for caspases-1 and -3, thereby interfering with their inflammasome and apoptotic activity during latency. To better understand the potential role of other KSHV proteins in affecting caspase activity, we screened the KSHV proteome for potential caspase cleavage sites. While many KSHV proteins had high-scoring potential caspase cleavage sites, we decided to focus on the early lytic proteins K3 and K5, as they may play a beneficial role for the virus during lytic activation. We hypothesized that K3 and/or K5, in addition to downregulating expression of immune surface markers, may have an additional role in altering caspase-mediated events.

METHODS:

The KSHV proteome was screened for potential caspase cleavage sites using SitePrediction, a free online program. To determine if K3 and K5 are affected by caspases in cells, primary effusion lymphoma (PEL) cells were treated with the pan-caspase inhibitor, ZVAD, prior to lytic induction and then proteins were analyzed by Western blot. To determine if K5 is cleaved by caspases, K5-FLAG protein was purified from K5-FLAG-expressing BJAB cells, exposed to various caspases, and then examined by Western blot using anti-FLAG antibody. The molecular weight of a K5-FLAG peptide produced from cleavage was determined using mass spectrometry. BJAB K5-FLAG cells were treated with α-fas, an apoptotic stimulus, to study the activation of caspases and cleavage of K5-FLAG in vitro. Additionally, wild type and K5 knockout BAC16-infected iSLKK cells were also treated with α-fas to study the extent of cell death. Finally, we explored the activity of the full-length and truncated GFP-K5 against immune surface marker expression using FACS analysis.

RESULTS AND CONCLUSIONS:

Of 87 KSHV proteins screened, 66 had high-scoring potential caspase cleavage sites, including the early lytic proteins K3 and K5. Treatment of PEL cells with the pan-caspase inhibitor, ZVAD, followed by lytic induction with butyrate led to higher levels of intact K3 and K5, suggesting these proteins may be cleaved by caspases during lytic activation. Supporting this finding, caspases-3 and -8 readily cleaved K5-FLAG, resulting in a 6 kDa FLAG-containing peptide by Western blot. Mass spectrometry analysis confirmed cleavage of K5-FLAG at one of the predicted cleavage sites from Site Prediction. Treatment of BJAB-K5 FLAG cells with α-fas lead to a decrease in full-length K5-FLAG and generation of the 6 kDa fragment and significantly inhibited α-fas-induced caspase-mediated cell death. To determine if K5 plays a protective role in virus-infected cells, wild type and K5 knockout BAC16-infected iSLKK cells were treated with α-fas. K5 knockout cells had higher levels of cell death compared to wild type, supporting that K5 protects virus-infected cells from caspase-mediated cell death. To see whether the cleavage of K5 affects its ability to downregulate immune surface markers, FACS analysis revealed that both full-length and truncated K5 led to significant MHC-I downregulation, although the truncated form was slightly less effective. Overall, these data suggest that K5 not only downregulates surface marker expression to avoid immune recognition, but it may have an additional role in mitigating caspase-mediated cell death during KSHV lytic replication and promoting viral persistence in cells.

This work was supported in part by the Intramural Research Program of the National Cancer Institute.

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013: WT1 Oncogenic Isoforms Are Upregulated by KSHV vFLIP: A Potential New Immunotherapeutic Intervention for Kaposi Sarcoma

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BACKGROUND:

Wilms' tumor 1 (WT1) is overexpressed and associated with poor prognosis in several hematologic and solid malignancies and has shown promise as an immunotherapeutic target. WT1 has over 36 different isoforms for which the most abundant are a result of alternative splicing at two independent sites resulting in the expression of four major oncogenic proteins that contribute to promotion of angiogenesis and tumorigenicity. WT1 expression can recruit myeloid derived suppressor cells (MDSC) in the tumor microenvironment. We evaluated WT1 expression in a large cohort of >300 individuals with HIV-associated KS and determined that KSHV infection accounts for this upregulation through the viral oncoprotein vFLIP. There are a number of WT1 directed therapies, including peptide vaccines, dendritic cell vaccines showing promise in clinical trials, as well as TCR engineered T cells, cytotoxic T lymphocytes, and recombinant antibodies in preclinical studies.

METHODS:

We used immunohistochemistry to evaluate 303 biopsies of advanced HIV-associated KS from clinical trial AMC066/A5263 with single and antibody combinations and performed image analysis. The effects of KSHV on WT1 and whether KSHV latent viral vFLIP influences WT1 expression was examined in vitro using endothelial cell culture models with analysis of WT1 isoforms using qRT-PCR. WT1 siRNA was used to examine effects of WT1 on KSHV gene expression. We tested a T cell receptor mimic antibody, ESK-1, specific for WT1 peptide/HLA-A02 expression, for its ability to bind KSHV-infected or vFLIP-expressing endothelial cells.

RESULTS:

Moderate to strong WT1 expression was demonstrated in 65% of the 303 KS biopsies and in 92% of nodular lesions. WT1 expression significantly correlated with increased histopathologic stage, expression of the viral latent oncoprotein (LANA; r=0.687, p=0.0001), and was inversely correlated with the quantity of CD8+ T cells (r=-0.2536 p=0.0001). We have found the presence of MDSC within KS tumors where there is increased WT1 expression, and we characterized the expression of immunoregulatory molecules. Our results indicate that KSHV infection, and specifically vFLIP, influences WT1 expression by upregulating major oncogenic isoforms of WT1 (A, B, C, D) and increased binding of ESK-1, a T cell receptor-like human monoclonal antibody that recognizes WT1 peptides presented on MHC HLA-A0201. WT1 also plays a role in controlling latent viral gene expression.

CONCLUSIONS:

Major oncogenic isoforms of WT1 are overexpressed upon KSHV infection and are upregulated by vFLIP. WT1 inhibition appears to impact latent viral gene expression negatively. Immunotherapeutic targeting of WT1 is possible given the interventions available, and understanding of the possible immunosuppressive cellular components in the KS tumor microenvironment, including MDSC, will guide appropriate combinations of anti-WT1 interventions and immune checkpoint inhibitors.

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014: Extracellular Vesicles as Biomarkers for AIDS-Associated Non-Hodgkin Lymphoma Risk

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BACKGROUND:

Chronic HIV infection increases the risk of B cell non-Hodgkin lymphoma (NHL). Although combination anti-retroviral therapy (cART) has improved the overall survival of persons living with HIV, NHL remains a significant cause of morbidity and mortality among HIV-infected individuals in the post-cART era. Extracellular vesicles (EVs) are nanometer-sized membrane-enclosed particles secreted into the extracellular milieu by all cell types that can carry nucleic acids, proteins, lipids, and metabolites, and can express immunoregulatory molecules on their surface. Tumor cell-derived EVs can remodel the tissue microenvironment and have been implicated in the pathophysiology of hematologic malignancies. Emerging evidence shows that tumor cells secrete EVs that carry bioactive programmed death-ligand 1 (PD-L1) on their surface to inhibit anti-tumor responses, further playing a role in lymphomagenesis and promoting the growth of cancer. We recently showed that plasma-derived EVs bearing PD-L1, CD40, CD40L, or TNF-RII were significantly reduced after cancer treatment among AIDS-NHL participants in the AIDS Malignancy Consortium (AMC) 034 clinical trial. Additionally, EVs bearing PD-L1 significantly correlated with plasma levels of IL-10 at baseline (before cancer treatment), and CD40-, CD40L-, and TNF-RII-bearing EVs showed significant positive correlations with plasma levels of IL-10, CXCL13, sCD25, sTNF-RII, and IL-18 at baseline (molecules previously shown to be elevated preceding an AIDS-NHL risk). In this study, we investigated the relationship between AIDS-NHL and serum-derived EVs bearing PD-L1 and other B7 molecules, and molecules important for B cell activation.

METHODS:

EVs were measured in archived serum from AIDS-NHL cases (n=51) and HIV+ controls (n=53) who were participants in the Multicenter AIDS Cohort Study (MACS). Samples were selected prior to AIDS-NHL diagnosis for cases (mean 1.25 years; range of 2–36 months) with a matched time point for controls. EVs were isolated using a total-exosome isolation reagent for serum (Invitrogen) and were analyzed by Luminex multiplex immunometric assay for PD-L1, CD40, CD40L, TNF-RII, IL-6Rα, B7-H3, ICAM-1, and Fas Ligand (R&D Systems). Logistic regression models were used to associate levels of biomarkers (natural log-transformed) expressed on EVs with AIDS-NHL status, adjusting for age and CD4+ T cell count. In all comparisons made, two-tailed p values of less than 0.05 were considered statistically significant.

RESULTS:

Increased concentrations of several EV-associated biomarkers were significantly associated with AIDS-NHL, including PD-L1 (OR=1.55, 95% CI: 1.10–2.20), TNF-RII (OR=2.93, 95% CI: 1.55–5.53), and IL-6Rα (OR=2.99, 95% CI: 1.19–7.52).

CONCLUSIONS:

Our findings suggest that EVs bearing PD-L1, TNF-RII, or IL-6Rα can serve as biomarkers of NHL risk. The presence of these molecules on EVs provide insight into the type of co-stimulatory or co-inhibitory molecules secreted by tumor-derived EVs. We plan to investigate the role of B7 molecules CD80 and CD86 on EVs and their co-stimulatory (CD28) and co-inhibitory (CTLA-4) partners. Further characterizing the proteome and RNA content of EVs will also provide information on tumor-specific materials delivered to recipient cells, which can be important for sustaining tumor growth, metastasis, or remodeling the tumor microenvironment.

Author(s): Samantha L. Vogt[1,2,3], Nomathemba Tshabalala[3], Neil A. Martinson[1,3], Wendy Stevens[4], Philippa Ashmore[5], Atul Lakha[6], Vinitha Philip[6], Richard F. Ambinder[2,5,7], Rena R. Xian[2,5,7]*, Moosa Patel[4]*
*These authors contributed equally.

015: More Frequent Bone Marrow Involvement in HIV Positive vs. Negative Classical Hodgkin Lymphoma Patients in Johannesburg, South Africa: A Prospective Study

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BACKGROUND:

Classical Hodgkin lymphoma outcomes in people living with HIV (PLWH) in South Africa are worse than those in HIV-negative patients. Delayed diagnosis resulting in advanced stage disease and poor organ status have been proposed as main contributors to inferior outcomes. We set out to evaluate the presenting characteristics of newly diagnosed classical Hodgkin lymphoma patients receiving care in Johannesburg, South Africa to better understand the disparate treatment outcomes.

METHODS:

With appropriate approvals from the Human Research Ethics Committee of the University of the Witwatersrand and the Johns Hopkins Institutional Review Boards, we conducted a prospective, observational study of newly diagnosed patients with classical Hodgkin lymphoma at Chris Hani Baragwanath Academic and Netcare Olivedale Hospitals in Johannesburg, South Africa between March 2021 to August 2022. To be eligible for this study, all participants were required to be ≥18 years. Participants provided a brief clinical history including presence or absence of B-symptoms and consent for medical record and pathologic review. Medical record chart review included HIV status, CD4 count and viral load at the time of lymphoma diagnosis, basic laboratory data including full blood count and complete metabolic profile, review of diagnostic pathology, and staging workup.

RESULTS:

Among 30 patients enrolled with classical Hodgkin lymphoma, 18 patients (60%) were HIV-positive. Fifty-three percent were female, mean age was 41 years, and 97% of patients were diagnosed with advanced stage disease and B-symptoms. Majority of patients (56.7%) had bone marrow involvement, including 11/18 (61%) PLWH. Among PLWH, mean CD4 count was 221 and 50% of patients had an undetectable viral load at time of diagnosis. There was no statistical difference in age, sex, stage, performance status, or International Prognostic Index by HIV status. For 8 PLWH, the bone marrow biopsy established the diagnosis. PLWH were noted to have lower mean hemoglobin (8.0 vs 10.9; p=0.02) and albumin levels (2.8 vs 3.7; p=0.003). Patients with bone marrow involvement at time of diagnosis were more likely to be HIV-positive (85% vs 15%; p=0.02), have a lower CD4 count (132 vs 361; p=0.004), mean white blood cell count (3 vs 10; p=0.002), hemoglobin (7.5 vs 10.4; p=0.01), platelet count (84 vs 449; p=<0.001), absolute lymphocyte count (514 vs 1639; p=<0.001), and albumin (2.7 vs 3.6; p=0.004).

CONCLUSIONS:

Advanced stage disease and bone marrow involvement are common at time of diagnosis for patients with classical Hodgkin lymphoma in Johannesburg, South Africa. Bone marrow biopsy, performed during the workup and evaluation of cytopenias, provided the initial diagnosis of Hodgkin lymphoma in over 40% of PLWH. Bone marrow involvement was significantly associated with a lower CD4 count among PLWH and a lower absolute lymphocyte count in all patients, regardless of HIV status. Traditional laboratory markers of poor prognosis, including anemia, lymphopenia, and hypoalbuminemia, were more common among patients with bone marrow involvement and suggest high-risk disease.

Author(s): Brittney L. Dickey[1], Ryan Putney[1], Anders Berglund[2], Anna E. Coghill[1]

016: Advanced Biological Aging in Non-AIDS-Defining Cancer Patients Living With HIV

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BACKGROUND:

With widespread use of antiretroviral therapy (ART), people with HIV (PHIV) are living longer and are now at risk for age-related co-morbidities, including non-AIDS-defining cancers (NADCs). Given this epidemiological trend, it is important to understand how prolonged HIV infection and immune dysfunction may relate to molecular features of aging that can impact cancer risk and outcomes. Methyl groups naturally accumulate on human DNA over time, and methylation patterns can therefore be translated into metrics of biological aging. We compared epigenetic measures of aging, accounting for differences in immune cell composition, between PHIV receiving treatment for an NADC and matched HIV-uninfected NADC patients at Moffitt Cancer Center in Tampa, Florida (Moffitt).

METHODS:

PHIV with a verified solid tumor NADC diagnosis between 2004 and 2021 were identified using the Moffitt health research information system. To be included, patients needed to have an archived specimen amenable for DNA extraction (whole blood, buffy coat, or PBMC) collected within one year of their cancer diagnosis. HIV-uninfected controls were identified in a similar manner and matched to cases by tumor site, reported age within 5 years, tumor sequence (primary vs non-primary), and treatment status. DNA was extracted using the QIAGEN Autopure LS automated DNA extractor and then assayed using the Illumina MethylationEPIC BeadChip, which provides the methylation status of 850,000 sites across the human genome. Methylation array data were translated into a biological age using the epiTOC2 clock, which provides an estimate of the total number of stem cell divisions (TNSC), as well as GrimAge, which has been associated with mortality. Methylation data were also used to determine immune cell composition (CD4 T cells, CD8 T cells, B cells, neutrophils, Natural Killer cells, and monocytes) following the methods of Teschendorff. Biological age, immune cell proportions, and age acceleration were compared across HIV status using the Wilcoxan rank sum test. Finally, age acceleration was determined for both clocks as the difference (residuals from a linear model) in the observed age for PHIV and a NADC diagnosis compared to the predicted age based on the HIV-uninfected patients. Age acceleration is reported from linear models both unadjusted and adjusted for immune cell composition.

RESULTS:

DNA methylation patterns were assessed in 65 NADC patients with HIV and 64 HIV-uninfected NADC patients. Biological age assessed using both the epiTOC2 and GrimAge epigenetic clocks was significantly elevated in PHIV ($p=1.2e-09$ and $p=.0.017$, respectively). When methylation data were used to determine immune cell composition, the proportion of CD4 memory ($p=0.013$) and naïve cells ($p=0.003$) and neutrophils ($p=0.006$) was significantly lower in PHIV, while the proportion of B memory ($p=0.0014$) and CD8 memory ($p<0.0001$) cells was significantly higher in PHIV. Biological age was significantly accelerated in PHIV compared to HIV-uninfected patients using both epiTOC2 and GrimAge clocks, with the difference in the GrimAge clock remaining statistically significant after adjustment for immune cell composition ($p<0.001$).

CONCLUSIONS:

The results of this study show that accumulated DNA methylation across the genome can be used to determine biological age differences in NADC patients with and without HIV. Using these metrics, we observed a higher biological age in PHIV with a NADC diagnosis compared to their HIV-uninfected counterparts.

Author(s): Diego Salusso[1], Ana Gun[1], Martin Abba[2], and Valeria Fink[1]

O17: Penile Human Papillomavirus (HPV) in Men Who Have Sex With Men (MSM) and Transgender Women (TGW) From Buenos Aires: Initial Experience and Sample Collection Setup

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BACKGROUND:

HPV is one of the most common sexually transmitted infections, causing a variety of lesions ranging from warts to malignancies. Even though penile cancer is a rare entity, penile infections might represent a reservoir for transmission to other anatomical locations, with greater potential to develop malignancy. There are no data regarding the prevalence of penile HPV infection in our setting and in the population of MSM and TWG. This project was developed under the AIDS Malignancy Consortium (AMC) scholar program and has the support of HPV experts of the AMC network. The project aims to better understand the penile HPV infection epidemiology and its relation to infection in other anatomical sites, particularly in anal and oral locations.

METHODS:

This is a cross-sectional study to evaluate the prevalence of penile HPV in MSM and TGW from Buenos Aires in an ongoing cohort where anal and oral HPV infection is studied. The protocol and the informed consent form have been developed and approved by the Ethics Committee. A data collection form has been designed to gather epidemiological and clinical information. Regarding penile sampling, since there are no standardized techniques, it was necessary to set up an adequate sampling methodology.

RESULTS:

The intention of this abstract is to share the setup of the sampling technique. The initial proposal was to perform a urethral swab. After receiving advice from AMC experts and performing an exhaustive bibliographic search, we decided to change the technique and take samples from the penile surfaces, including glans, shaft, foreskin, and balanopreputial sulcus. Initially, we attempted to brush with the Digene® collection device with no success in obtaining DNA. The second attempt was done through a two-step method: an initial rubbing with a 600-grit emery paper followed by swabbing of the entire surface. The 600-grit emery paper was initially cut into 4x4 cm pieces and then sterilized. The paper was rubbed gently on the skin of the glans, foreskin, balanopreputial sulcus, and shaft. Then, we swabbed the exfoliated areas with a Dacron swab previously imbibed with sterile saline solution and kept it in 1 mL of specimen transport medium (Digene®). This technique was not successful either. As we suspected that a considerable amount of exfoliated cells remained in the sandpaper, the next samples were sent with both the swab and the sandpaper in the same specimen transport medium. This last technique allowed us to obtain DNA for HPV testing. The procedure was well tolerated by all studied participants. Having solved this issue has allowed continuing the recruitment.

CONCLUSIONS:

We encountered several difficulties obtaining good-quality samples. There is little information available and no standardized collection method has been published. There are no studies published in our region to address this issue. Through collaborative work with AMC and the local laboratory team, we were able to explore different possibilities until one of them has proven useful. The next step is to continue using this technique with the following participants.

Author(s): Qianlai Luo[1], Marie-Josèphe Horner[1], Cameron Haas[1], Ruth Pfeiffer[1], Eric A. Engels[1], David Riedel[2], Xiao-Cheng Wu[3], Wendy Patterson[4], Lou Gonsalves[5], Suzanne Speers[5], and Meredith Shiels[1]

O18: Disparities in Trends in Cancer Incidence Rates Among Persons Living With HIV During 2001–2016 in the HIV/AIDS Cancer Match Study

[1]National Cancer Institute, Bethesda, MD; [2]University of Maryland, Baltimore, MD; [3]Louisiana State University Health Sciences Center, New Orleans, New Orleans, LA; [4]New York State Department of Health, Albany, NY; [5]State of Connecticut Department of Public Health, Hartford, CT

BACKGROUND:

The improved efficacy, earlier use, and wider availability of antiretroviral therapy (ART) since the mid 1990s has resulted in a decrease in overall cancer risk among persons living with HIV (PLWH) in the United States. It remains unclear whether rates were changing differently across racial or ethnic group (non-Hispanic White, non-Hispanic Black, Hispanic) and transmission risk groups (men who have sex with men (MSM), persons who inject drugs (PWID), heterosexual/other).

METHODS:

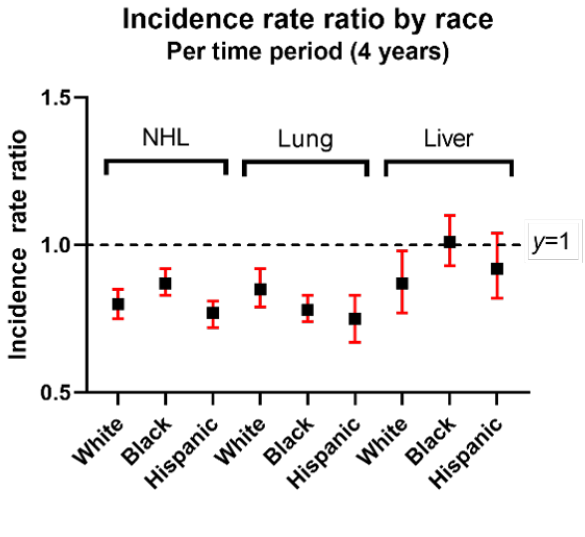
We used data on PLWH aged ≥20 years old from the HIV/AIDS Cancer Match Study during 2001–2016 from 13 regions and investigated the most common cancers: non-Hodgkin lymphoma (NHL), Kaposi Sarcoma (KS), cervix, lung, anus, liver, Hodgkin lymphoma, prostate, breast, and colon. We then used Poisson regression to assess time trends (time periods: 2001–2004, 2005–2008, 2009–2012, 2013–2016) of each individual cancer site by race/ethnicity and by risk group, adjusting for age, registry, and risk group (or race/ethnicity). Significant differences in cancer trends were assessed with interaction terms between race/ethnicity and time periods, and between risk group and time periods.

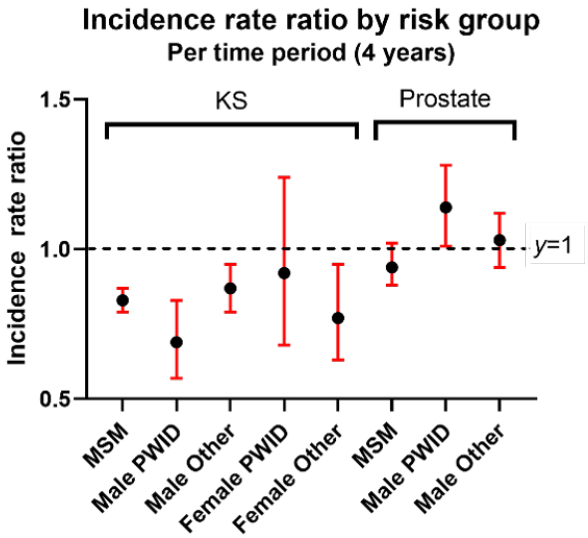
RESULTS:

There were 28,582 cancers in our follow-up period. There were significant differences in incidence rates over time across racial/ethnic groups for NHL, lung, and liver cancers. Between 2001–2004 and 2013–2016, NHL rates declined about 50% in White and Hispanic individuals with HIV and 33% in Black individuals with HIV (p-interaction=0.006); lung cancer rates declined 43% in White PLWH and over 50% in Black and Hispanic PLWH (p-interaction=0.041); liver cancer rates only declined among White PLWH (39%; p-interaction=0.006), with stable rates among Black and Hispanic PLWH. By risk group, there were significant differences in trend for KS and prostate cancer. Between 2001–2004 and 2013–2016, among PLWH, KS declined 36% in MSM, over 60% in male PWID, and 27% in men with heterosexual or other modes of transmission (p-interaction=0.048); prostate cancer rates increased 41% in male PWID (p-interaction=0.033) but didn't change in other risk groups.

CONCLUSIONS:

NHL, lung, and liver cancer rate trends were different across racial/ethnic groups. KS and prostate cancer rate trends were different across risk groups. The causes for disparities in these cancer trends need further investigation.





Author(s): Jennifer K. McGee-Avila[1], Ilona Argirion[1], Thomas R. O'Brien[1], Eric Engels[1], Marie-Josèphe Horner[2], Qianlai Luo[1], and Meredith Shiels[1]

O19: Risk of Hepatocellular Carcinoma Among People Living With HIV in the United States

[1]Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology & Genetics, National Cancer Institute, Rockville, MD; [2]Trans-Divisional Research Program, Division of Cancer Epidemiology & Genetics, National Cancer Institute, Rockville, MD

BACKGROUND:

Hepatocellular carcinoma (HCC) is the primary histological subtype of liver cancer, comprising up to 75% of such cases in the U.S. People living with HIV (PLWH) have a higher risk of HCC than the general population. A higher proportion of PLWH are coinfected with hepatitis B (HBV) or hepatitis C virus (HCV) due to shared transmission modalities such as injection drug use. Highly active antiretroviral therapy has improved survival from HIV infection, creating increased opportunities to develop liver cancer due to prolonged hepatic inflammation caused by chronic infection with HBV or HCV.

METHODS:

We used data from the HIV/AIDS Cancer Match (HACM), a population-based HIV and cancer registry linkage in the U.S. We compared HCC risk in PLWH to the general population using standardized incidence ratios (SIRs), standardized by race/ethnicity, age group, calendar period, and registry. SIRs were estimated by race/ethnicity, age group, HIV transmission risk group, and calendar period. Multivariable Poisson regression was used to estimate incidence rate ratios (RRs) among PLWH by race/ethnicity, age group, HIV transmission risk group, and calendar period. In addition, data from Symphony Health, a Texas-based health aggregator of medical claims, was used to determine the prevalence of HBV and/or HCV infection among people with HCC. Adjusted odds ratios identified predictors of HBV and HCV infection in PLWH with HCC.

RESULTS:

There were 1,530 incident HCC cases from 2001–2016 in PLWH during over 4 million person-years of follow-up. Compared to the general population, the overall SIR was 2.92 (95% CI 2.75-3.09). The risk of HCC was strongly elevated across all racial/ethnic and age groups. Rates were highest among NH-White PLWH (SIR 3.86; 95% CI 3.48-4.27) PLWH aged 40-49 (SIR 4.81; 95% CI 4.31-5.35) or aged 20-39 (SIR 4.15; 95% CI 2.82-5.89). Among PLWH, HCC risk was similar across racial/ethnic groups but increased with age. Compared to men who had sex with men (MSM), men who injected drugs had almost 4 times the risk of HCC (RR 3.93; 95% CI 3.38-4.55) while female PWID had a 60% increased risk (RR 1.61; 95% CI 1.28-2.01), and men with other or unknown HIV transmission had a 50% increased risk (RR 1.48; 95% CI 1.27-1.73). Between 2001–2004 and 2013–2016, rates of HCC declined 16% (RR 0.84; 95% CI 0.69-1.03). In the subset of cases with Symphony Health data, there were a total of 146 HCC cases, 38 persons coinfected with HBV, 84 persons with HCV, and 16 persons co-infected with both HBV and HCV. Compared to MSM, persons who inject drugs (PWID) had 85% decreased odds of HBV infection (aOR 0.15; 95% CI 0.05-0.50) and 8 times the odds of HCV infection (aOR 8.03; 95% CI 2.61-24.7).

CONCLUSIONS:

Utilizing recently updated population-based linked-surveillance data, we found risk of HCC has declined over time among PLWH, though rates remain significantly elevated compared to the general population, with particularly high risk among people who inject drugs. Prevention and treatment of HBV and HCV are needed to reduce HCC risk in this population.

Author(s): Carole Metekoua[1], Eliane Rohner[2], Yann Ruffieux[2], Victor Olago[1], Tafadzwa G. Dhokotera[2], Matthias Egger[2], Julia Bohlius[3],and Mazvita Muchengeti[1]

O20: Decreasing Incidence of Squamous Cell Carcinoma of the Conjunctiva in People Living With HIV—the South African HIV Cancer Match Study (2004–2014)

[1]National Health Laboratory Service, Johannesburg, South Africa; [2]University of Bern, Bern, Switzerland; [3] University of Basel, Basel, Switzerland

BACKGROUND:

The HIV epidemic has changed the patterns of squamous cell carcinoma of the conjunctiva (SCCC) in Sub-Saharan Africa. The main risk factors of SCCC are immunodeficiency and high exposure to ultraviolet (UV) light. Little is known about the epidemiology of SCCC among people living with HIV (PLWH) in South Africa, which has the highest number of PLWH in the world. We assessed the incidence of SCCC among PLWH in South Africa and examined associated risk factors.

METHODS:

We used data from the South African HIV Cancer Match (SAM) study, a nationwide cohort of PLWH in South Africa.* This cohort was created through a probabilistic record linkage of routine HIV-related laboratory records from the National Health Laboratory Service and cancer records from the National Cancer Registry from 2004 to 2014. We calculated crude incidence rates, analyzed trends using joinpoint models, and obtained yearly incidence rates and hazard ratios (HR) from Royston-Parmar flexible parametric survival models.

RESULTS:

Among 5,247,968 PLWH who contributed 15,479,126 person-years, 1,059 incident SCCCs were diagnosed. The crude overall SCCC incidence rate was 6.8/100,000 person-years (95% confidence interval [CI] 6.4-7.3). The SCCC incidence rate decreased between 2004 and 2014 (Figure 1) with an annual percentage decrease of 10.9% (95% CI 8.3-13.3; p value for trend <0.001). PLWH in areas closer to the equator had a higher risk of developing SCCC (Figure 2). Lower CD4 cell count and middle age at first HIV-related laboratory test were additional risk factors for SCCC (Table 1). In contrast, sex and settlement type were not associated with the risk of developing SCCC.

CONCLUSIONS:

We found that the SCCC incidence rate among PLWH in South Africa decreased over calendar time. This decline may be explained by an increase in the antiretroviral therapy coverage from 1% in 2004 to 48% in 2014. The risk of developing SCCC was associated with lower CD4 counts and residence closer to the equator, indicative of higher UV exposure. Further studies are needed to better understand etiology and outcomes of SCCC among PLWH in South Africa.

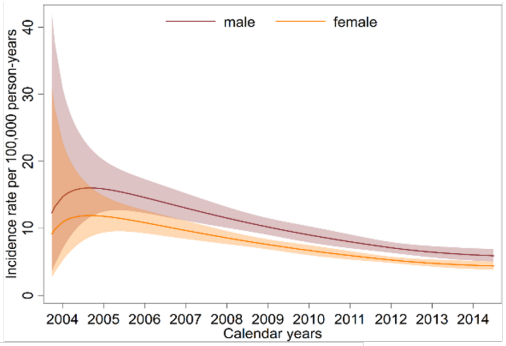


Figure 1: Yearly SCCC incidence rates

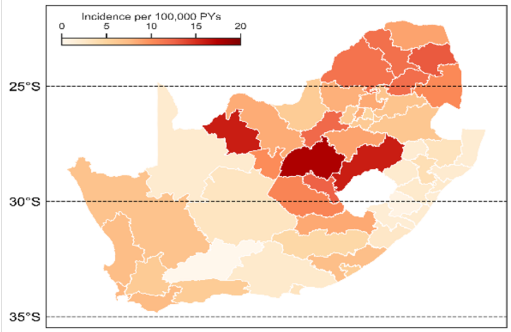


Figure 2: Incidence rates by district

Table 1: Crude incidence rates of squamous cells carcinoma of the conjunctiva per 100,000 person-years and hazard ratios (HR)

	No. of PLWH	SCCC cases	Incidence rate (95% CI)	Unadjusted HR (95% CI)*	Adjusted HR (95% CI)*
Sex					
male	1,635,639	369	8.36 (7.55-9.25)	1	1
female	3,606,652	690	6.24 (5.79-6.72)	0.76 (0.67-0.86)	0.95 (0.83-1.08)
Age at first HIV-related laboratory record [years]					
≤29	2,047,447	209	3.34 (2.92-3.83)	1	1
30-39	1,771,963	514	9.61 (8.81-10.5)	2.87 (2.45-3.37)	2.42 (2.05-2.84)
40-49	955,059	256	9.46 (8.37-10.7)	2.81 (2.34-3.38)	2.31 (1.92-2.79)
50-59	373,361	63	6.56 (5.13-8.40)	2.93 (1.46-2.56)	1.63 (1.23-2.17)
≥ 60	99,798	17	7.89 (4.9-12.69)	2.28 (1.39-3.73)	1.97 (1.20-3.24)
Calendar period at first HIV-related laboratory record					
2004-2009	2,117,601	702	8.15 (7.57-8.77)	1	1
2010-2014	3,130,367	357	5.20 (4.69-5.77)	0.56 (0.49-0.65)	0.61 (0.53-0.70)
First CD4 cell count recorded [cells/µl]					
0-200	1,571,571	546	12.5 (11.5-13.6)	1	1
201-350	1,233,075	202	5.45 (4.75-6.25)	0.44 (0.38-0.52)	0.49 (0.42-0.58)
351-500	854,42	84	3.29 (2.66-4.08)	0.27 (0.21-0.34)	0.31 (0.25-0.40)
≥ 501	958,22	54	1.92 (1.47-2.51)	0.16 (0.12-0.21)	0.20 (0.15-0.26)
missing	630,682	173	8.52 (7.34-9.89)	0.69 (0.58-0.82)	0.73 (0.61-0.86)
Settlement type					
Rural	2,781,683	566	7.01 (6.46-7.62)	1	1
Urban	2,463,792	493	6.66 (6.09-7.27)	0.95 (0.94-1.07)	0.95 (0.83-1.08)
District location (latitude)					
<25°S	382,764	126	11.5 (9.65-13.7)	1	1
25°S-29°S	3,657,475	736	7.04 (6.55-7.57)	0.61 (0.51-0.74)	0.67 (0.55-0.82)
30°S-34°S	1,205,237	197	5.01 (4.36-5.76)	0.44 (0.35-0.55)	0.51 (0.40-0.64)

*We assumed proportional hazards

Author(s): Yann Ruffieux[1], Mazvita Muchengeti[2], Victor Olago[2], Tafadzwa G. Dhokotera[3], Julia Bohlius[3], Matthias Egger[1], Eliane Rohner[1]

O21: Age and Cancer Incidence in 5.2 Million People Living With HIV in South Africa

[1]University of Bern, Bern, Switzerland; [2]National Health Laboratory Services, Johannesburg, South Africa; [3]University of Basel, Basel, Switzerland

BACKGROUND:

Cancer incidence generally increases with older age, but few studies have specifically assessed this association in people living with HIV (PLWH) in sub-Saharan Africa. We examined incidence rates of various cancer types as a function of age in PLWH in South Africa.

METHODS:

We used data from the South African HIV Cancer Match (SAM) study, a nationwide cohort of PLWH in South Africa.* This cohort was created through a probabilistic record linkage of routine HIV-related laboratory records from the National Health Laboratory Services and cancer records from the National Cancer Registry from 2004 to 2014. We modeled incidence rates per 100,000 person-years (py) as a function of age and sex for the most common cancer types using flexible parametric survival models.

RESULTS:

We included 5,222,827 PLWH with 15,376,297 person-years of follow-up. A total of 19,749 PLWH developed an infection-related cancer and 8,764 developed an infection-unrelated cancer. The most common cancers were cervical cancer (n=7,418), Kaposi sarcoma (n=6,380), breast cancer (n=2,748), and non-Hodgkin lymphoma (n=2,590). In PLWH younger than 55 years, the incidence rate of infection-related cancers was higher than that of infection-unrelated cancers (Figure A). However, above that age, infection-unrelated cancers became the dominant incident cancer type. The risk of Kaposi sarcoma peaked at the age of 31 in women and 34 in men (Figure B). In both men and women, the rates of non-Hodgkin lymphoma increased until the age of 45 and stabilized thereafter (Figure C). Cervical cancer risk in women increased steadily from the of age 20 onwards (Figure D).

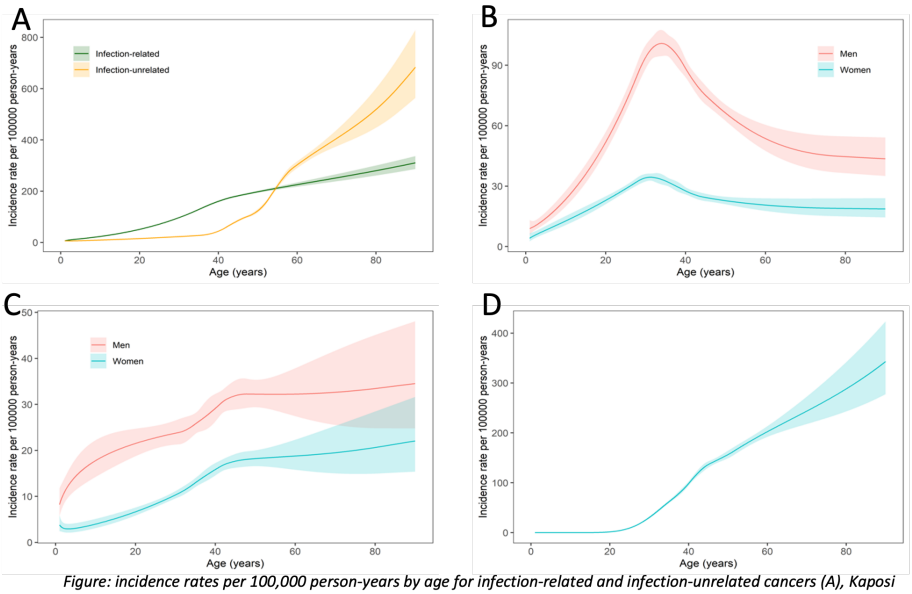


Figure: incidence rates per 100,000 person-years by age for infection-related and infection-unrelated cancers (A), Kaposi

***Muchengeti M. et. al. Cohort profile:** the South African HIV Cancer Math (SAM) Study, a national population-based cohort. BMJ Open. 2022.*

CONCLUSIONS:

The risk of developing most cancer types increased with age, with the rate of infection-unrelated cancers overtaking that of infection-related cancers after age 55. However, the rates of Kaposi sarcoma peaked in middle-aged PLWH, and those of non-Hodgkin lymphoma stabilized after age 45. This may be due to complex interactions between age and duration of HIV-induced immunodeficiency and carcinogen exposure. As PLWH in South Africa become older, prevention and early detection of infection-unrelated cancers will become increasingly important. Meanwhile, prevention strategies for infection-related cancers remain essential to reduce the cancer burden in young PLWH.

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O22: Cancer Treatment Inequities in People Living With HIV in the United States

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BACKGROUND:

People living with HIV (PLWH) are at increased risk of both AIDS-defining (i.e., Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer) and non-AIDS-defining cancers. Prior work with data from 1996–2010 reported that PLWH with cancer in the US were less likely to receive cancer treatment. However, an updated analysis is warranted to see if the disparity in receipt of cancer treatment persists for PLWH.

METHODS:

We used data from the HIV/AIDS Cancer Match (HACM) Study, a population-based HIV and cancer registry linkage in 13 U.S. states, to examine diffuse large B-cell lymphoma (DLBCL), Hodgkin-lymphoma (HL), and cancers of the cervix, lung, anal, prostate, colon, and breast. For each cancer type, we estimated adjusted prevalence odds ratios (aOR) and 95% confidence intervals using logistic regression to assess the relationship between HIV status and cancer treatment adjusted for race, age at cancer diagnosis, sex, cancer stage, year of cancer diagnosis, and region. In addition, we used logistic regression to identify predictors of cancer treatment receipt in PLWH by cancer site, including race, age at cancer diagnosis, sex, HIV mode of transmission, cancer stage, calendar year period of cancer diagnosis, and region.

RESULTS:

We evaluated 11,657 PLWH with cancer and 2,687,946 patients with cancer without HIV. A total of 9,030 PLWH with cancer received any cancer treatment (77.5%) compared to 2,218,200 individuals with cancer without HIV (82.5%) who received any cancer treatment. HIV was associated with lower odds of receiving cancer treatment compared to people with cancer and no HIV for cervical cancer (aOR=0.46, 95% CI: 0.35-0.60), DLBCL (0.55, 0.50-0.62), HL (0.64, 0.53-0.76), lung cancer (0.57, 0.52-0.62), prostate cancer (0.74, 0.66-0.83), and colon cancer (0.60, 0.50-0.74). Non-Hispanic (NH)-Black PLWH with lung cancer were less likely to receive cancer treatment compared to NH-White PLWH. People who inject drugs (PWID), PWID/men who have sex with men (MSM), and heterosexual PLWH were less likely to be treated for DLBCL, lung cancer, and prostate cancer compared to MSM. In contrast, PWID were more likely to receive cancer treatment for anal cancer than MSM. For PLWH with DLBCL, those diagnosed in 2011–2014 were 46% more likely to receive treatment (aOR=1.46, 1.00-2.12) compared to those diagnosed in 1996–2000.

CONCLUSION:

Inequities in receipt of cancer treatment persist for PLWH in the US. We saw, for some cancers, PLWH had lower odds of receiving cancer treatment, even after controlling for important factors. Beginning in 2018, the National Comprehensive Cancer Network (NCCN) published cancer treatment guidelines explicit for PLWH. Despite improvements in HIV-related treatment, inequitable receipt of cancer treatment will continue to prolong and exacerbate disparities among people with cancer with and without HIV.

Author(s): Emi Hayashi[1], Lesley Park[2], Michael J. Silverberg[3], Xuesong Han[4], Kimberly Stone[1], Juan Wisnivesky[1], Chung Yin Kong[1], and Keith Sigel[1]

O23: Adjuvant Chemotherapy for NSCLC in Patients Living With HIV: A Simulation Study

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BACKGROUND:

Lung cancer is the leading cause of cancer morbidity and death in people with HIV (PWH). PWH may differ from people without HIV in tumor behavior, comorbidity burden, life expectancy, and quality of life. Thus, tailoring lung cancer management to PWH is a major priority. Despite this, there have been no randomized controlled trials (RCTs) of lung cancer treatment specific to PWH. We therefore developed and used a simulation model to begin to provide personalized estimates on the benefits and harms of adjuvant chemotherapy for PWH after lung cancer resection.

METHODS:

Using data from several large HIV cohorts (Veterans Aging Cohort Study, Kaiser Permanente Northern California, Mount Sinai) combined with SEER-Medicare data and published clinical trials, we parameterized a simulation model (Comorbidity Lung Treatment Model-HIV, "COLT-MH") of lung cancer natural history, treatment, and outcomes. COLT-HM was then validated using HIV-specific data from the National Cancer Database. After model validation, we simulated multiple RCTs comparing quality-adjusted life expectancy (QALE) with or without adjuvant platinum-based chemotherapy following lobectomy. We first compared QALE gains in subgroups of PWH without major comorbidities according to age, sex, smoking status (current or former smoker) and HIV clinical characteristics (CD4 count and HIV viral load). Then we repeated these analyses in patients with coronary artery disease (CAD) or chronic obstructive pulmonary disease (COPD).

RESULTS:

For PWH with stage IIA NSCLC, adjuvant chemotherapy was associated with net QALE gains for all patients younger than 61 years, regardless of HIV disease control. Patients with CD4 counts >500 cells/mm3 and undetectable HIV RNA were all projected to benefit from chemotherapy (i.e., have net QALE gains) regardless of age, sex, or smoking status. In the setting of worse HIV disease control, older patients were less likely to benefit from adjuvant chemotherapy, and with very poor HIV control (CD4<200 cells/mm3, VL>1000 copies/mL), most patients over age 60 did not benefit. In contrast, all patient groups with stage IIB or IIIA, HIV RNA <1,000 copies/mL, and CD4>350 were projected to have favorable QALE gains with adjuvant chemotherapy. Having comorbidities (CAD, COPD) reduced the benefits of chemotherapy for patients with stage II-IIIA NSCLC, however, and reduced the proportion of patient groups that were projected to benefit from chemotherapy.

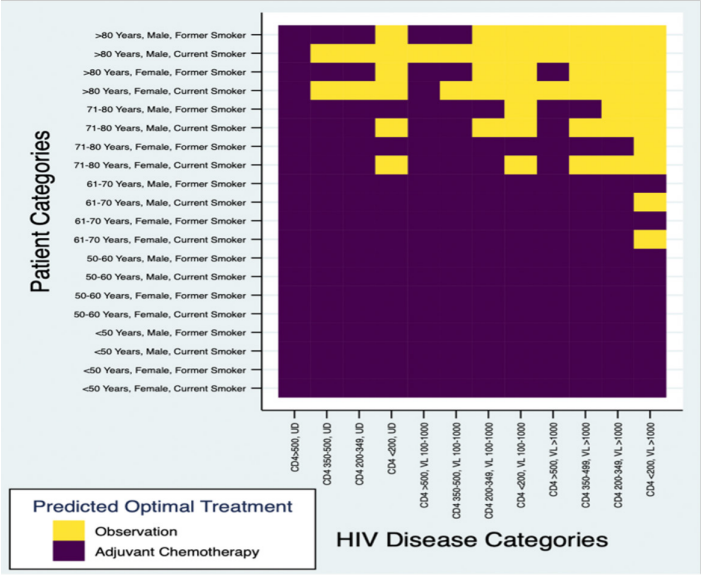

Figure. Estimated treatment strategy associated with greatest QALE gains according to patient age, sex, smoking status, and HIV disease

CONCLUSIONS:

Our simulated RCTs of adjuvant chemotherapy provided estimated benefits of adjuvant chemotherapy for NSCLC in PWH. We found that PWH with suboptimal HIV disease control had fewer QALE gains with chemotherapy for stage IIA NSCLC but that a wider group benefited from chemotherapy with stage IIB and IIIA disease. By consolidating data from available trials, observational studies, and HIV cohorts, COLT-MH can provide personalized projections of optimal treatment regimens for PWH with NSCLC and eventually project the efficacy of novel lung cancer therapies (i.e., immunotherapy) as clinical trial data become available.

Author(s): Syim Salahuddin[1], Ramsey Yusuf[1], Shruti Desai[1], Kishu Ranjan[1], Jianlei Gu[2], Daiwei Tang[2], Yong Kong[2], Hongyu Zhao[2], Yuval Kluger[1], Kurt Schalper[1], and Brinda Emu[1]

O24: Altered Tumor Mutational Burden and Immune Microenvironment of Non-Small Cell Lung Carcinoma Among People With HIV

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BACKGROUND:

Non-small cell lung carcinoma (NSCLC) is a leading cause of cancer death among people living with HIV (PLWH), with increased incidence compared to uninfected NSCLC patients. We explored whether HIV-associated immunological changes lead to an immunoregulatory tumor microenvironment (TME) that limits tumor-specific responses among PLWH.

METHODS:

A tissue microarray was constructed with tumors from 18 HIV+ and 19 HIV- NSCLC patients (matched for histological subtype, stage, year of diagnosis, age, sex, and smoking status), and incubated with metal-conjugated antibodies for evaluation by imaging mass cytometry (IMC). IMC marker scores were extracted by automated cell segmentation, and single-cell data were analyzed by PhenoGraph. In addition, whole exome sequencing was performed on tumor tissue.

RESULTS:

HIV+ and HIV- tumors demonstrated differential distribution of tumor-infiltrating CD8+ T-cell clusters defined by marker expression patterns. Two clusters were significantly elevated in HIV+ tumors (20.3% and 19.9% vs. 9.2% and 4.7% in HIV- tumors, $p<0.0001$ for both). The first cluster exhibited an activated effector memory phenotype (CD45RO+CD25+). The second cluster resembled a previously described effector burned-out "Ebo" CD8+ T cell subset with co-expression of immune checkpoint and proliferation markers (PD-1+LAG-3+Ki67+). Within tumor-infiltrating CD4+ T cells, a cluster characterized by checkpoint protein expression (PD-1+ and LAG-3) was also highly represented in HIV+ cases (35.2% vs. 9.8% in HIV- cases, $p<0.0001$). Finally, HIV+ tumor-associated macrophages (TAM) had higher expression of immunoregulatory molecules (PD-L1, PD-L2, B7-H3, B7-H4, IDO1, and VISTA), confirmed by the expansion of three clusters comprising 58.8% of TAMs vs. 17.8% in HIV- tumors ($p<0.0001$). Discrimination of cells between HIV+ and HIV- TME was further confirmed by spectral graph theory. Furthermore, tumor mutational burden and neoantigen calling was higher among HIV+ tumors, suggesting more antigenic tumors among PLWH.

CONCLUSIONS:

Our study suggests that the TME of HIV+ patients is characterized by a unique immune landscape, distinct from that of HIV-patients, with evidence of expansion of immune cells with enhanced immunoregulatory phenotypes and associated with impaired anti-tumor responses. These differences may be due to long-standing viral replication and destruction of lymphoid architecture. Further studies are necessary to elucidate the impact of these findings on prognosis and response to treatment, particularly checkpoint inhibitor-based approaches.

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O25: HIV and the Incidence of Conjunctival Squamous Cell Carcinoma in South Africa: A 25-Year Analysis of the National Cancer Registry (1994–2018)

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BACKGROUND:

Human immunodeficiency virus (HIV) is an important risk factor for conjunctival squamous cell carcinoma (CSCC). Although national CSCC incidence rates are cross-sectionally associated with HIV prevalence on a population level, it is unclear how an evolving HIV epidemic and widespread antiretroviral therapy (ART) provision have impacted temporal trends. South Africa is home to the world's largest HIV seropositive population and is one of only a few African nations with a representative national cancer registry system, making it the ideal setting for such a study. Using a combination of data sources, we aimed to describe the incidence and epidemiological profile of CSCC in South Africa over a 25-year period (1994–2018), and relate these to the national HIV epidemic.

METHODS:

Incident cases of histologically diagnosed CSCC (based on the International Classification of Diseases for Oncology Version 3) were identified from the South African National Cancer Registry (NCR), a nationwide pathology-based cancer surveillance agency. Crude and direct age-standardized incidence rates (ASIRs) per 100,000 persons (Segi World Standard Population) were calculated using national population statistics (Statistics South Africa mid-year population estimates) and compared by age, sex, and population group. Demographic and incidence trends were described and analyzed using joinpoint regression software. Incidence rates were compared to modelled national HIV- and ART-related statistics (The Thembisa Project) for the same time period.

RESULTS:

Over the 25-year study period, 9,016 CSCC cases were reported to the NCR (female: 56%, Black African: 86.8%, mean age: 41.5 years). The overall ASIR was 0.78, with sex-specific rates of 0.82 and 0.75 for females and males, respectively (rate ratio: 1.10, 95% confidence interval: 1.06–1.14). Two distinct epidemiological patterns of disease were identified: 1) older White males, and 2) younger Black African females, with consistently higher rates observed in the latter. Between 1994 and 2009, there was an almost sixfold increase in the ASIR of CSCC (from 0.22 to 1.28, annual percentage change [APC]: 15.4%), accompanied by a dramatic shift from the first to the second epidemiological profile. Despite rising national HIV seroprevalence, the CSCC ASIR has demonstrated a sustained decline between 2009 and 2018 (from 1.28 to 0.56, APC: 7.8%), with a corresponding reversal in the demographic trends. Annual CSCC frequency was highly correlated (r=0.96) with the estimated number of HIV-positive individuals not on ART.

CONCLUSIONS:

The findings from this study highlight the evolving trends and disease burden of CSCC in South Africa. The changing epidemiological profile of the disease is a likely reflection of at-risk populations disproportionately affected by the HIV epidemic in the country. Widespread ART provision is correlated with declining CSCC rates over the last decade, highlighting the effectiveness of ART as a cancer control measure on a population level. These findings are in keeping with reported trends for other HIV-related cancers and have important implications for future incidence studies and public health policy.

DATA SOURCES

South African National Cancer Registry
Statistics South Africa
The Thembisa Project

Author(s): Ezequiel Lacunza[1], Valeria Fink[2], Maria E. Salas[1], Romina Canzoneri[1], Julian Naipauer[3], Omar Coso[3], Omar Sued[2], Pedro Cahn[2], Sion Williams[4], Enrique A. Mesri[4], and Martín C. Abba[1] on behalf of University of Miami CFAR Sylvester Comprehensive Cancer Center-Argentina Consortium for Research and Training in Virally Induced AIDS Malignancies

O26: Microbiome Changes in Oral and Anal Samples From HIV-Exposed Individuals

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BACKGROUND:

Accumulating evidence indicates that the microbiome plays a significant role in HIV immunopathogenesis as well as in HIV-associated complications. In Argentina, men having sex with men (MSM) and transgender women (TGW) are at the highest risk for infection with HIV and AIDS-related viruses. The aim of this study was to provide the first characterization of the oral and anal microbiome from HIV-negative and HIV-positive MSM and TGW cohorts.

METHODS:

One hundred thirty oral and anal DNA-derived samples were obtained from 78 participants and subject to whole metagenomics sequencing for further microbiome analysis.

RESULTS:

A significantly lower alpha diversity and higher beta diversity were found in the anal samples compared with oral samples. Significant differences in the microbiome composition were found among subjects associated with HIV infection, gender, sex behavior, CD4+ T cell counts, antiretroviral therapy (ART), and the presence of HPV-associated precancerous anal lesions. For viruses, results confirm the occurrence of oncogenic viromes in this high HIV-risk population. The HIV-associated oral microbiome was characterized by the enrichment of several bacteria related to periodontal disease pathogenesis. Conversely, predominantly anal bacteria showed a significant decrease in HIV-infected subjects (Coprococcus comes, Finegoldia magna, Blautia obeum, Catenibacterium mitsuokai). TGW showed enrichment in species related to sexual transmission, which is in concordance with the fact that the majority of recruited TGW are or have been sexual workers. Prevotella bivia and Fusobacterium gonidiaformans were positively associated with the presence of anal precancerous lesions among HIV-infected subjects. Enrichment of Holdemanella biformis and C. comes were associated with detectable viral load and ART untreated patients. Metabolic pathways were distinctively affected according to whether the predominant factors were associated with sexual behavior or HIV pathogenesis. Gene family analysis identified bacterial gene signatures, which may have potential as prognostic and predictive biomarkers of HIV/AIDS-associated malignancies.

CONCLUSIONS:

We have identified distinctive microbial features at two easily accessible sites that are related to HIV immunopathogenesis, which could also be implemented as potential biomarkers to predict the risk of precancerous anal lesions or as therapeutic targets.

Funding: NIH U54 CA221208

Author(s): Ramya Ramaswami[1], Kathryn Lurain[1], Anaida Widell[1], Irene Ekwede[1], Ralph Mangusan[1], Jomy George[1], Seth Steinberg[2], Denise Whitby[3], Thomas S. Uldrick[1], an d Robert Yarchoan[1]

O27: Pomalidomide and Liposomal Doxorubicin for Kaposi Sarcoma With or Without Other KSHV-Associated Diseases

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BACKGROUND:

Kaposi sarcoma herpesvirus (KSHV) is the causative agent of Kaposi sarcoma (KS), a multicentric angioproliferative tumor, and other diseases, including a form of multicentric Castleman disease (MCD) and KSHV inflammatory cytokine syndrome (KICS). KS can be difficult to treat when it occurs with MCD or KICS, resulting in high mortality rates. Liposomal doxorubicin (dox), a chemotherapy, and pomalidomide (pom), an immunomodulatory drug, are FDA-approved therapies for KS. The safety and activity of the combination (pom/dox) in KS alone or with other KSHV-associated diseases are unknown.

METHODS:

The primary objective of this Phase I/II study was to evaluate safety, tolerability, and antitumor activity of pom/dox in two groups of participants with KS requiring systemic therapy: Group I (G1)—severe KS alone (T1 disease, widespread skin disease, and/or recurrent following other systemic therapy); and Group II (G2)—KS with concurrent KSHV-MCD or KICS. Patients received dox at 20 mg/m2 intravenously on day 1 of a 28-day cycle combined with pom once daily on days 1 to 21 at escalating dose levels (DL) (I - 2mg, II - 3mg, or III- 4mg) in a 3+3 design until plateau of response or other pre-specified criteria. Participants received 81mg of aspirin daily as thromboprophylaxis. Dose limiting toxicities (DLTs) were evaluated in the first 2 cycles (or 8 weeks) of treatment. In the Phase II section of the study, additional participants were treated at the maximum tolerated dose (MTD) for both groups that was established in the Phase I portion. The primary objective for safety was assessed using the Common Terminology Criteria for Adverse Events (CTCAE v.4.0). In all participants, the activity of pom/dox with respect to KS responses was evaluated using modified AIDS Clinical Trial Group (ACTG) criteria at the start of every cycle. For participants in G2, KICS and MCD responses were evaluated using a Clinical Benefit Response (CBR) criteria using symptoms and laboratory parameters associated with these diseases.

RESULTS:

Fifty-one participants (37 participants in G1 and 14 participants in G2) were enrolled in this ongoing study. Severe (T1) KS was noted in 89% of G1 participants and among all participants in G2. Forty-nine participants (96%) were HIV-infected and 38 (75%) had prior chemotherapy for KS (30/37 G1 and 7/14 G2). All participants with HIV were on antiretroviral therapy with a baseline median CD4 count of 369 cells/μL (interquartile range (IQR): 329–444) and median HIV VL of 20 copies/ml (IQR: <20–75). There were no DLTs at DLIII for G1, and additional participants were treated at the MTD of 4mg of pom. In G2, grade 3 rash and pharyngeal edema were DLTs observed at 3mg of pom (DLII). Therefore, the MTD in G2 was 2mg of pom. The most common CTCAE grade 3/4 toxicity was neutropenia. The KS responses were evaluated among participants receiving >2 cycles at any dose level; 24 of 34 participants in G1 had a response (22 partial and 2 complete; 71% [95% confidence interval (CI) 53–85%]), and 5 of 11 participants in G2 had a response (4 partial and 1 complete; 45% [95% CI 17-77%]). Among participants with KS in G2 with KICS (8 participants) or MCD (6 participants), 9 of 14 had response (64% [95% CI 35-87%]) per the CBR criteria.

CONCLUSIONS:

This is the first study that combines two approved therapies for the treatment of KS. Pom/dox was well-tolerated and active in heavily pretreated participants with KS alone. Among participants with KS with concurrent active KSHV-associated diseases, activity for KS, KICS, and MCD was noted, but pom/dox was less well-tolerated in this group.

This study was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute (NCI) and a Cooperative Research and Development Agreement between Bristol-Myers Squibb/ Celgene and the Center for Cancer Research, NCI.

Author(s): Warren Phipps[1,2,3], Bhavneet Bhinder[4], Andrea Towlerton[1,3], Peter Mooka[3], James Kafeero[3], Scott Adams[1,3], Olivier Elemento[4], and Ethel Cesarman[4]

028: Whole Exome Sequencing Reveals Sparse Mutational Landscape in Kaposi Sarcoma

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BACKGROUND:

Despite the large number of studies that have focused on understanding Kaposi sarcoma-associated herpesvirus (KSHV) and the viral mechanisms contributing to KS pathogenesis, the cellular genome of KS remains largely unexplored. We sought to evaluate whether cellular genetic alterations in biologically relevant genes could be identified in KS tumors and to determine if any intratumoral mutations were associated with KS clinical presentation or clinical outcomes.

METHODS:

We performed whole exome sequencing on KS tumors and matched normal control skin from adults with KS receiving treatment at the Uganda Cancer Institute in Kampala, Uganda. Samples were mapped and analyzed using computational pipelines for DNA alterations. Immunophenotyping was performed on a subset of formalin-fixed, paraffin-embedded KS tissues to estimate tumor content. Logistic regression analysis was used to evaluate associations between molecular pathway alterations and clinical variables.

RESULTS:

Seventy-eight KS tumor biopsies from 59 participants with KS were sequenced; 46 (78%) participants had HIV infection, and the majority (53; 90%) were poor-risk T1 tumor stage by ACTG staging criteria. Average sequencing coverage of KS tumors was 130X (range, 56X–251X). IHC with LANA confirmed 30%–80% tumor cells in 5/6 cases with tissue blocks available, indicating sufficient tumor cell content for mutation identification. We found a very low mutational burden in all but one specimen, with a mean of 17 mutations per tumor sample. This average mutational count is lower than all 33 tumor types included in the Cancer Genome Atlas (TCGA). Few recurrent mutations were seen, and the most commonly affected pathway was RTK/RAS (16% of cases). Mutational signatures included defective DNA mismatch repair and smoking in a subset of cases. Correlation with clinical parameters indicated that overall mutational counts were higher in HIV-seronegative than HIV-seropositive participants. Percent of genome altered based on gene copy numbers was also higher in HIV-seronegative than HIV-seropositive participants and was higher in nodular compared to macular lesions, in T1 vs T0 stage, and in patients with edema.

CONCLUSIONS:

Our study demonstrates that KS tumors carry a very low burden of cellular genetic alterations and that there are no common recurrent clonal mutations in cellular cancer-related genes in the majority of KS cases. Lesions that take longer to develop (such as in HIV-seronegative individuals or in more advanced stage disease) may accumulate more alterations, but these remain low compared to other cancers. The sparse mutational landscape observed in most KS tumors suggests KSHV and viral oncogenic mechanisms are more important than clonal transformation in driving KS tumorigenesis.

Author(s): Sydney J. Bennett[1,2], Dicle Yalcin[2], Sara R. Privatt[1,2], Owen Ngalamika[3], Salum J. Lidenge[4,5], John T. West[2], and Charles Wood[1,2]

O29: High-Resolution Antibody Epitope Profiling Reveals Differences Between Symptomatic and Asymptomatic KSHV Infection

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BACKGROUND:

Kaposi sarcoma-associated herpesvirus (KSHV) is the aetiologic agent of sub-Saharan African endemic Kaposi sarcoma (EnKS) and HIV-associated epidemic KS (EpKS). The humoral immune response against KSHV has been studied using infected-cell immunofluorescence assays and immunoassays against recombinant proteins. The latency-associated nuclear antigen (LANA) has been established as the most antigenic KSHV protein, and seroreactivity to LANA, along with K8.1, are common determinants of KSHV infection. While protein-level antigenicity of a near-complete KSHV proteome has been reported, the epitopes within those proteins have not yet been defined. We have recently demonstrated the utility of phage display in facilitating high-resolution epitope mapping of the highly antigenic LANA protein. The objective of the current study was to utilize a phage library expressing a tiled KSHV peptidome to identify all potential epitopes in the remainder of the KSHV proteome.

METHODS:

A phage library expressing systematically derived linear 56-amino acid peptides with 28-amino acid overlap that tile across the KSHV proteome (VirScan) was coupled to patient sera phage immunoprecipitation and sequencing (PhIP-Seq). Epitope data were derived from high-throughput sequencing of patient barcoded immunoprecipitated phage DNA. Recognition of each KSHV protein was determined by quantifying the number of reactive peptides derived from each protein (breadth) and the frequency with which those reactive peptides were targeted (magnitude). The approach supported intra- and inter-individual/group repertoire comparisons across the entire KSHV proteome.

RESULTS:

Breadth and magnitude of 1,988 KSHV peptides were quantified across 62 sub-Saharan African KS patients and 22 KSHV-infected asymptomatic individuals. A comparison of the antibody repertoires from those two groups revealed that KS patients had significantly increased magnitudes compared to KSHV-infected asymptomatic individuals (Mann-Whitney, $p<0.01$). Further, we found that the breadth of the anti-KSHV response correlated with the magnitude (Spearman $r=0.8$). In agreement with previous findings, we identified LANA, K8.1, ORF65, and ORF38 as the most antigenic KSHV proteins. High-resolution epitope profiling of these proteins revealed focal points of antigenicity. The most consistently targeted regions within the aforementioned proteins were K8.129-56 and ORF65140-168 in both KS patients and asymptomatic individuals. Interestingly, K15, also known as LAMP, was targeted by 88% of EnKS patients with a focal point of recognition at K15393-448. In contrast, EpKS patients and asymptomatic individuals had low, broad reactivity to K15. Finally, recognition of the KSHV glycoproteins (gB, gH, gL, gM, gN) was low and inconsistent across individuals and groups.

CONCLUSIONS:

Application of tiled phage display immunoprecipitation supported the generation of the highest resolution map of antigenicity across the entire KSHV proteome to date. Comparative analyses of the antibody repertoire demonstrated an increased magnitude of anti-KSHV responses in KS versus asymptomatic controls. The antibody repertoires defined here will inform predictive and prognostic models as well as diagnostic and therapeutic development.

Poster List

DAY ONE POSTERS

1. Association Between HIV Viremia and Breast Cancer Risk Among Women With HIV in North America (1996–2016)
2. Better Prognosis in ART-Naïve HIV-Associated DLBCL: An Update From the Kamuzu Central Hospital Lymphoma Study
3. HIV-Associated Differences in the Tumor Immune Microenvironment of Non-AIDS-Defining Cancers
4. Opportunities for Malignancy and HIV Research in the MACS WIHS Combined Cohort Study (MWCCS)
5. Knowledge of Kaposi Sarcoma Among Oncology and HIV Providers in Kenya
6. Risk of Burkitt Lymphoma Development in Children With Acute Malaria Predicted by Lytic Epstein-Barr Virus Reactivation
7. People Living With HIV (PLWH) Survivorship Care Plan to Promote Cancer Screening
8. Design of a Phase III Efficacy and Immunogenicity Trial of 9-Valent Human Papillomavirus (HPV) Vaccine in the Prevention of Oral Persistent Infection in Men Living With HIV
9. Psychosocial Barriers to Oncology Clinical Trial Participation: A Review of Patients Referred to the HIV-AIDS Malignancy Branch at the National Cancer Institute
10. Lung Cancer Screening Adherence Among People Living With HIV Treated at an Integrated Health System in Florida
11. Overexpression of P53, YAP1, and Epstein-Barr Virus Nuclear Antigen, but not CDKN2A/p16INK4a, Frequently Detected in Ocular Surface Squamous Neoplasia
12. Association of Anemia on Non-AIDS-Defining Malignancy in People With HIV Following ART Initiation
13. Impact of Multi-Agent Systemic Therapy on All-Cause and Disease-Specific Survival for People Living With HIV Who Are Diagnosed With Non-Hodgkin Lymphoma: Population-Based Analyses From the State of Georgia
14. IFN-γ Responses to Human Gamma-Herpesviruses in Individuals From Uganda
15. Elucidating Potential Anti-Viral Mechanisms of Baricitinib Against HIV-1
16. Increased Tumor T-Cell Receptor Repertoire Clonality Associates With HIV/ART Status and Improved Outcome in a Cohort of Diffuse Large B-Cell Lymphoma Patients
17. Establishment of National Cancer Management Guidelines for Botswana
18. The Impact of Multiple Recruitment Strategies on the Enrollment Rates for CAMPO Clinical Trials Aimed at Preventing HPV-Related Cancers for Persons Living With HIV in Puerto Rico

DAY TWO POSTERS

19. A Contemporary Update on Disease Stage at Diagnosis and Survival Among Adults With HIV-Associated Kaposi Sarcoma in East Africa
20. AIDS-Related Kaposi's Sarcoma Tissue Resource for Immune Profiling
21. Salivary Shedding, Viremia, and Seroprevalence of Kaposi´s Sarcoma-Associated Herpes Virus Among a Cohort of Men Who Have Sex With Men and Transgender Women in Argentina
22. Prevalence and Determinants of Kaposi's Sarcoma-Associated Herpesvirus (KSHV) Antibody Positivity Among Adults Living With HIV in East Africa
23. Association of Serum Biomarkers With Clinical Response of Limited-Stage AIDS/KS in Resource-Limited Settings: Results From the ACTG A5264/AMC-067 Clinical Trial
24. ORF48 Is Required for Optimal Lytic Replication of Kaposi's Sarcoma-Associated Herpesviruses
25. Prospective Cohort Suggests Two Types of Kaposi Sarcoma Lesions: Proliferative and Inflammatory
26. The Emerging Fifth Epidemiologic Subtype of Kaposi Sarcoma in HIV-negative Men Who Have Sex With Men: A Review of Cases From a Tertiary Care Center in NYC From 2001 to 2021
27. Incidence, Predictors, and Biomarkers of Kaposi Sarcoma Immune Reconstitution Syndrome Kaposi Sarcoma Patients Initiating Antiretroviral Therapy and Chemotherapy in Uganda
28. The Persistence of HIV Proviral Diversity, Transcription, and Nef Protein in Kaposi's Sarcoma Tumors During Antiretroviral Therapy
29. Upregulation of Cell Surface Glycoproteins in Correlation With KSHV Latency in the Kaposi Sarcoma Tumor Microenvironment
30. Teledermatology to Promote the Diagnosis of Kaposi Sarcoma in East Africa

31. Effects of Maternal HIV Infection on Transplacental Transfer and Loss of Maternally Acquired Antibodies to Kaposi's Sarcoma-Associated Herpesvirus (KSHV) and on Risk of Primary KSHV Infection in Kenya
32. Optimized and Simultaneous DNA, RNA, and miRNA Isolation From Kaposi's Sarcoma Biopsies Frozen in RNAlater
33. Before or After: When Does KS Occur in Relation to ART Initiation in East Africa?
34. Aquaporin 3: Gatekeeper of the Oxidative Stress in Kaposi's Sarcoma-Associated Virus (KSHV)-Associated Primary Effusion Lymphoma (PEL)
35. Participant-Identified Interventions for Diagnosis and Treatment of People Living With HIV-Associated Kaposi's Sarcoma in Western Kenya: A Qualitative Analysis
36. Serial Profiling of Tumor-Infiltrating T-Cells in Kaposi Sarcoma
37. Pacritinib Suppresses Kaposi Sarcoma-Associated Virus (KSHV) Viral Genes and Induces Apoptosis in Primary Effusion Lymphoma Cells
38. Phage Display Epitope Profiling of KSHV LANA Revealed Differential Recognition of a Dominant C-Terminal Epitope Between KS Patients and Controls
39. Role of Histone Lysine Demethylases (KDMs) in Promoting KSHV Persistent Infection

DAY THREE POSTERS

40. Socioeconomic Inequalities in the Coverage of Cervical Cancer Screening Among Women Living With HIV in Five Low- and Middle-Income Countries
41. Characterizing Stigma-Based Clusters of People with HIV-Associated Kaposi's Sarcoma in East Africa
42. Early Engagement with Patient Navigation for HIV-Associated Kaposi's Sarcoma in East Africa
43. Barriers and Facilitators of High-Resolution Anoscopy Among People Living With HIV (PLWH): A Cross-Sectional Study in Puerto Rico
44. Delays In Cervical Cancer Treatment Initiation for Patients Living With or Without HIV In Botswana 2013–2019
45. Patterns of Survivorship Care of Cervical Cancer Patients With or Without HIV Infection In Botswana 2015–2022
46. Peripheral Immune Profiles of Cervical Cancer Patients With and Without HIV Infection Undergoing Chemoradiation in Botswana
47. High-Risk Human Papillomavirus (HPV) Distribution According to HIV Status Among Women With Invasive Cervical Cancer in Abidjan, Côte d'Ivoire, 2018–2020
48. We Built It: Why Didn't Some of Them Come? Reasons for Non-Engagement With Community-Based Cervical Cancer Prevention Interventions
49. Affordable Smartphone Confocal Microscopy for Cervical Pre-Cancer Screening: Initial Field Experience
50. Significance of HIV Status in Cervical Cancer Patients Receiving Curative Chemoradiation Therapy, Definitive Radiation Alone, or Palliative Radiation in Botswana
51. A Public Health Approach to Cervical Cancer Prevention in East Africa Through Community-Based HPV Vaccination, Self-Administered Screening, and Mobile Treatment
52. Engagement in Home-Based vs Clinic-Based Anal Precancer Screening Among Men Having Sex With Men: Interim Baseline Data From the Prevent Anal Cancer Self-Swab Study
54. Healthcare Costs and Financial Barriers to Diagnosis and Treatment of People Living with HIV-Associated Kaposi's Sarcoma in Western Kenya: A Qualitative Analysis
55. The Experience of Social Support in People with HIV-Associated Kaposi's Sarcoma in Western Kenya: A Mixed Methods Approach

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1: Association Between HIV Viremia and Breast Cancer Risk Among Women With HIV in North America (1996–2016)

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BACKGROUND:

A few studies have suggested lower risk of breast cancer comparing women with versus without HIV. Given the latency of breast cancer development, the cumulative impact of replicating HIV or uncontrolled HIV infection may influence breast cancer carcinogenesis. Yet, the role of HIV viremia has not been assessed. We examined the association between HIV viremia and breast cancer incidence among women with HIV using varying measures of HIV RNA exposure.

METHODS:

We included women (≥18 years of age) living with HIV enrolled in the NA-ACCORD with no history of any cancer, ART initiation date observed, >2 viral load measurements following ART initiation, and ≥6 months of follow-up from 1996–2016. Women were followed from ART initiation to the earliest of incident breast cancer diagnosis, death, first occurrence of loss to follow-up, 12/31/2016, or cohort-specific end date for capturing cancer diagnoses. We assessed the association between HIV viremia and breast cancer incidence using Cox models to estimate hazard ratios. HIV viral load was assessed as: 1) viral load at ART initiation; 2) time-updated viral load; 3) time-updated unsuppressed viral load (>200 copies/mL); and 4) cumulative viral load (cVL). cVL (copy-years) was calculated from ART initiation to the end of follow-up.

RESULTS:

There were 29 breast cancers diagnosed among 5,839 women with HIV who contributed 36,829 person-years. Median follow-up was 5 years (IQR 2, 9), median baseline age was 40 years (IQR 33, 48), and median baseline calendar year was 2007 (IQR: 2002, 2011). Women were predominantly Black (61%) and 45% had an AIDS diagnosis prior to ART. Viral load at ART initiation was not associated with breast cancer incidence. Time-updated viremia was associated with increased breast cancer risk. cVL was inversely associated with breast cancer, but estimates were not statistically significant.

Table 1. Crude (HR) and adjusted (aHR) hazard ratios and 95% confidence intervals (CI) for the association of HIV viremia and breast cancer risk

HIV viral load parameter	HR	95% CI	aHR*	95% CI
Viral load at ART (per $\log_{10}$ ↑)	1.02	0.77, 1.35	1.00	0.75, 1.33
Time-updated viral load (per $\log_{10}$ ↑)	**1.10**	**1.02, 1.18**	**1.14**	**1.06, 1.23**
Time-updated unsuppressed viral load	**1.37**	**1.15, 1.63**	**1.46**	**1.22, 1.74**
Cumulative viral load (per $\log_{10}$ copy-year ↑)	0.73	0.52, 1.02	0.76	0.54, 1.08

**Adjusted for: age at ART initiation (per 1-year increase), AIDS diagnosis prior to ART, calendar year, race/ethnicity, BMI, and smoking history.*

CONCLUSIONS:

The association between HIV viremia and breast cancer qualitatively differed depending on how viral load was measured. Further research is needed to explore these conflicting findings. Given the equivocality of these results, and that time-updated HIV viremia was suggestive of increased breast cancer risk, age-appropriate screening among women with HIV remains an important aspect of clinical care.

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2: Better Prognosis In ART-Naïve HIV-Associated DLBCL: An Update From the Kamuzu Central Hospital Lymphoma Study

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BACKGROUND:

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype among both HIV-positive (HIV+) and HIV-negative (HIV-) individuals. Furthermore, treatment with anti-retroviral therapy (ART) likely impacts immune pressures on developing tumors in HIV-infected individuals. We previously showed no association of outcome with DLBCL cell-of-origin (COO) when stratified by HIV status but demonstrated molecular differences in the tumor microenvironment; we also previously showed that a model consisting of Eastern Cooperative Oncology Group score (ECOG) >1 and lactate dehydrogenase (LDH) > twice upper limit of normal (ULN) performed as well as IPI in our population. We hypothesized stratifying by ART duration prior to DLBCL diagnosis in a larger set of patients would reveal differences in outcome, DLBCL morphology, and COO, and allow us to further evaluate prognostic biomarkers.

METHODS:

The Kamuzu Central Hospital (KCH) Lymphoma Study has prospectively enrolled patients with newly diagnosed lymphomas in Malawi since 2013 who receive standardized treatment and follow-up. Diagnostic, pre-treatment tissue biopsies were evaluated at KCH, aided by conventional immunohistochemistry (IHC), after which formalin-fixed paraffin-embedded (FFPE) tissue blocks were submitted to UNC for further IHC and analysis. Epstein-Barr virus (EBV) status was determined by EBER-ISH and EBV-positive cases were excluded. One hundred two FFPE tissue blocks were available for study, including 26 HIV+/ART-naïve, 37 HIV+/ART-experienced, and 39 HIV- cases after EBV exclusion (n=10). All patients were treated with conventional CHOP chemotherapy, and 25 (24%) also received rituximab. HIV+/ART-experienced cases are defined as patients who had been prescribed antiretroviral medication for six months or more at the time of diagnosis. COO was determined using the Hans algorithm. Morphology was determined by a pathologist via H&E staining as either centroblastic or immunoblastic. Univariate Cox regression models of overall survival (OS) and progression-free survival (PFS) were performed, as well as multivariate analysis using a baseline Cox regression model of ECOG >1 and LDH > twice ULN. All statistical analyses were performed in R Studio, version 2022.02.0.

RESULTS:

There was no relationship between morphology (p=0.444) or COO (p=0.173) and ART status by Pearson's chi-squared, and no differences in OS or PFS by morphology (p=>0.9). COO was only significant in the PFS multivariate analysis, in which non-GC cases had worse survival (HR=2.0, p=0.023). Co-expression of MYC and BCL2 was not associated with ART status (p=0.64) but was associated with a worse outcome in both OS and PFS (HR=3.61, p=0.01; HR=3.58, p=0.01), while expression of MYC alone was prognostic in only PFS (HR=3.5, p=0.007). Compared to HIV+/ART-naïve, both HIV+/ART-experienced and HIV- cases had decreased OS (HR=2.3, p=0.05 and HR=3.29, p=0.004, respectively) and decreased PFS (HR=2.87, p=0.012 and HR=3.3, p=0.003, respectively).

CONCLUSIONS:

These data confirm that among HIV-associated DLBCL, ART-naïve patients have an improved prognosis compared to ART-experienced, and this is likely related to differences in tumor biology that are not seen via traditional biomarkers (morphology, COO), while double-expression of MYC and BCL2 remains prognostic but does not associate with ART status. Ongoing studies in this population will attempt to understand the tumor immune microenvironment of HIV-associated DLBCL in order to search for therapeutic targets.

Author(s): Anna E. Coghill[1], Nathan Van Bibber[1], Brooke Fridley[1], Jordan Fenion[2], Yoko Derose[2], Jon Mahlow[2], and Gita Suneja[2]

3: HIV-Associated Differences in the Tumor Immune Microenvironment of Non-AIDS-Defining Cancers

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BACKGROUND:

Effective antiretroviral therapy has translated into increased life expectancy for people living with HIV (PWH), resulting in a growing number of patients surviving to older ages when chronic diseases such as non-AIDS-defining cancer (NADC) are more common. Our prior work has demonstrated that patients with HIV have higher cancer-specific mortality compared to patients without HIV, and these outcome disparities persist after accounting for patient demographics, tumor stage, and cancer treatment initiation. A novel approach to identify factors that may drive poor cancer outcomes in PWH is needed; one compelling hypothesis is that immune dysfunction resulting from HIV influences the molecular profile of cancers that develop in PWH.

METHODS:

Tissue microarrays (TMAs) from PWH diagnosed with either prostate or anal cancer were obtained from the NCI-sponsored AIDS Cancer Specimen Resource. Comparison TMAs were created from HIV-uninfected prostate and anal cancer patients selected from the biorepositories at Moffitt Cancer Center and Huntsman Cancer Institute. In addition, one pan-cancer TMA was created at Moffitt to include tumors from PWH diagnosed with a range of NADCs and matched tumors from HIV-uninfected patients diagnosed with the same cancer type. Slides from these TMAs were stained using the Akoya Biosciences' OPALTM 7-Color Automation IHC kit on the BOND RX autostainer (Leica Biosystems). The OPAL 7-color kit uses tyramide signal amplification conjugated to individual fluorophores to detect targets (i.e., one fluorophore per marker). After staining, slides were imaged using the Vectra®3 Automated Quantitative Pathology Imaging System, and multi-layer TIFF images were exported to the HALO Image Analysis Platform to translate images into quantitative marker abundance data. We compared marker positivity by HIV status, adjusted for tumor site and patient age and race, using odds ratios (ORs) generated from beta-binomial regression models and the interactive Tumor Immune MicroEnvironment application (**http://itime.moffitt.org/**.)

RESULTS:

Multiplex immunofluorescence staining of tissues from 45 PWH (prostate cancer=22; anal cancer=14; other=9) and 238 HIV-uninfected patients (prostate cancer=216; anal cancer=5; other=17) demonstrated marked, HIV-related differences in the tumor immune microenvironment. We stained for 15 different markers to characterize the tumor immune infiltrate, and the abundance of six of these immune markers was statistically significantly ($P<0.05$) higher in tumors from PWH compared to tumors from patients without HIV, even after adjustment for age, race, and tumor site. This included differences in infiltration of T-cells (CD8+ [OR=1.50] and delta-gamma [OR=1.81]), B-cells (CD20+ OR=1.67), and macrophages (CD163+ OR=1.98), as well as differences in expression of clinically targetable immune checkpoint molecules (PD-L1 [OR=3.83] and TIM3 [OR=1.76]). The T-regulatory cell phenotype (CD3+CD8+FOXP3+) was also statistically significantly more abundant in tumors from PWH (OR=2.19). Dendritic cell (CD11c+) expression was observed less frequently in tumors from PWH (OR=0.63).

CONCLUSIONS:

Our data indicate that NADCs developing in the setting of HIV are immunologically distinct, supporting the need to assess whether such differences are associated with treatment outcomes or provide novel therapeutic opportunities for PWH and cancer.

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4: Opportunities for Malignancy and HIV Research in the MACS WIHS Combined Cohort Study (MWCCS)

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BACKGROUND:

The MACS WIHS Combined Cohort Study (MWCCS) is a longitudinal study of adults living with HIV and without HIV at 13 sites across the U.S. MWCCS is a merger of two longstanding cohorts: MACS was a study of men who have sex with men started in 1984 and WIHS was a study of women who had risk factors for HIV started in 1994.

METHODS:

The MWCCS integrates these two longstanding, longitudinal studies and will continue follow-up of the current participants in addition to recruiting new participants with characteristics that reflect the current U.S. population living with HIV or at risk for HIV. MWCCS has detailed information on many risk factors for cancer, including behavioral, medical, genetic, and virologic factors. There is a repository of biospecimens available for testing as well. MWCCS conducts medical record confirmation of self-reported cancers as well as cancer registry matching for all participants.

RESULTS:

This abstract is to present the MWCCS to investigators who may not be familiar with the opportunities for research in HIV and cancer within MWCCS. There are 874 AIDS-defining cancers confirmed in MACS and WIHS between 1984–2020 among PLWH. In addition, between 1984–2020, there are many non-AIDS-defining cancers, including: anal (n=56), colorectal (n=59), lung and bronchus (n=117), breast (n=79), prostate (n=113), liver (n=38), and head and neck cancers (n=40), as well as smaller numbers of participants with other cancers. We welcome early-stage investigators and others interested in using our data and specimens to submit proposals for research within MWCCS.

CONCLUSION:

Details about our study are at **https://statepi.jhsph.edu/mwccs/work-with-us**, or reach out to MWCCS malignancy working group chairs Dr. Amber D'Souza and Dr. Shehnaz Hussain for more information.

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5: Knowledge of Kaposi Sarcoma Among Oncology and HIV Providers in Kenya

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BACKGROUND:

In sub-Saharan Africa (SSA), the burden of HIV-associated malignancies such as Kaposi sarcoma (KS) remains high, despite widespread access to antiretroviral therapy. KS diagnoses are often made in late stages of disease, when interventions are less effective with poor prognoses. Delayed diagnoses and poor outcomes in cancer have been linked to low provider knowledge, though little is known about provider knowledge regarding KS in SSA. We aimed to assess clinical knowledge of KS among providers who treat KS in Kenya.

METHODS:

We approached all healthcare providers working in either oncology referral clinics or selected HIV primary care clinics in the AMPATH network in Kenya from August 2019-January 2020. KS knowledge was assessed using a self-administered structured questionnaire adapted from prior experience in East Africa, which included 38 questions regarding KS classification, morphology, symptomatology, diagnosis, and management.

RESULTS:

Overall, oncology providers performed significantly better than HIV providers on the knowledge survey, scoring an average of 5.4 percentage points higher (95% CI 0.3 to 10.4, p<0.05) in an adjusted multivariate regression model adjusting for age, education, and level of provider (Table 1). The most significant factor associated with overall performance and subsection performance was provider type, with medical and clinical officers performing the best among all cadres. Performance on the survey was lowest in the subsection regarding KS treatment and management.

CONCLUSIONS:

Assessing gaps in KS-specific knowledge among diverse cadres of health professionals may be especially important in resource-limited areas where burden is high and lower-level cadres are often providing front-line HIV and cancer care.

Table 1. Adjusted multivariate regression evaluating factors associated with total and subsection performance on 38-item Knowledge of Kaposi Sarcoma Questionnaire

	Multivariate Regression Model Using Continuous Outcome Variable – Percentage % Correct on Total Survey and Subsections					
Characteristic	Mean % difference in total knowledge scores[a] (95% CI)	Mean % difference in classification knowledge sub-scores[b] (95% CI)	Mean % difference in morphology knowledge sub-scores[c] (95% CI)	Mean % difference in diagnosis knowledge sub-scores[d] (95% CI)	Mean % difference in symptom knowledge sub-scores[e] (95% CI)	Mean % difference in treatment knowledge sub-scores[f] (95% CI)
Patient care responsibility						
HIV primary care	Ref	Ref	Ref	Ref	Ref	Ref
Oncology	**+5.4*** (0.3 to 10.4)	+5.1 (-2.1 to -12.3)	+2.2 (-7.6 to 12.1)	**+12.18**** (4.7 to 19.7)	+4.2 (-6.0 to 14.5)	+4.8 (-1.1 to 10.8)
Age, per 10-year increment education	-1.2 (03.9 to 1.5)	-0.9 (-4.8 to 2.9)	-0.7 (-6.0 to 4.6)	-0.11 (-4.2 to 3.0)	-1.6 (-7.1 to 3.9)	-1.8 (-5.0 to 1.3)
Non-university	Ref	Ref	Ref	Ref	Ref	Ref
University	+1.6 (-2.6 to 5.8)	+2.2 (-3.8 to 8.2)	+1.6 (-6.6 to 9.8)	+4.30 (-1.9 to 10.5)	-1.4 (-9.9 to 7.1)	+1.4 (-3.5 to 6.3)
Provider type						
MO/CO	Ref	Ref	Ref	Ref	Ref	Ref
Nurse	**-12.8**** (-18.7 to -6.9)	**-9.9*** (-18.3 to -1.5)	**-13.2*** (-24.6 to -1.8)	**-20.6**** (-29.3 to -11.9)	**-14.9*** (-25.9 to -2.1)	**-12.5**** (-19.4 to -5.7)
Pharmacist	**-23.6****(-31.4 to -15.8)	**-24.5**** (-35.6 to -13.3)	**-15.7*** (-30.9 to -0.49)	**-22.8**** (-34.3 to -11.2)	**-35.3**** (-51.1 to -19.5)	**-20.9**** (-30.0 to -11.8)
Other Direct Provider	**-27.7****(-32.9 to -22.6)	**-27.7**** (-35.1 to -20.3)	**-23.2**** (-33.2 to -13.1)	**-31.9**** (-39.6 to -24.8)	**-30.2**** (-40.6 to -19.7)	**-26.9**** (-32.9 to -20.9)

***p<0.05 |**p<0.01**

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6: Risk of Burkitt Lymphoma Development in Children With Acute Malaria Predicted by Lytic Epstein-Barr Virus Reactivation

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BACKGROUND:

Burkitt lymphoma (BL) remains one of the most common pediatric cancers in sub-Saharan Africa. The two critical co-factors in the etiology of BL are EBV infection and repeated *Plasmodium falciparum* (Pf) malaria infections. Elevated levels of antibodies to EBV lytic antigens in BL patients suggest that lytic reactivation of EBV precedes tumorigenesis. Malaria-induced reactivation of EBV has been reported in earlier studies based on presence of EBV DNA in plasma of children with acute malaria and subsequent clearance following treatment* but other studies argued with improved malaria control, effects of malaria on EBV viral load in whole blood was no longer evident**. In evaluating past studies, it was clear that no single study evaluated EBV in both mucosal (e.g., saliva) and systemic (cell-associated in PBMC and cell-free in plasma) compartments. Additionally, we wanted to determine if the viral DNA detected by qPCR is representative of cell-associated infection or attributable to virions.

METHODS:

To address these questions, we enrolled children ages 2–10 years from a malaria-endemic high-risk region of Western Kenya with acute uncomplicated malaria (blood smear [BS] positive for Pf) and, as comparison, age- and sex-matched control children without evidence of fever or malaria (RDT-, BS-). We collected saliva and blood samples (separated into plasma and PBMC), extracted DNA, and measured EBV viral load by qPCR. Furthermore, bisulfite sequencing was used to identify EBV genome methylation patterns to assess whether we were detecting cell-associated DNA (methylated) vs virion-derived DNA (unmethylated).

RESULTS:

When first test EBV load in the saliva, we found that there was no difference in the frequency of EBV shedders (59% acute and 49% healthy controls), mean viral load in those individuals shedding or age effect on viral load. In contrast, when we evaluated EBV load in PBMC, the highest EBV load was found in children <5 years with acute malaria compared to all other groups. EBV DNA was also frequently detected in the plasma of both groups (35% acute, 30% healthy controls).

CONCLUSIONS:

Our results suggest that malaria does not affect control of EBV in the mucosal compartment. Rather, the effect of acute malaria on the viral load set-point in PBMC was age dependent and occurs primarily in younger children where immunological control of malaria has not yet developed. The paradox in these results is that the incidence of BL is highest in children between the ages of 6 and 8 years, suggesting that repeated malaria infections set the stage for BL, but an acute malaria infection is likely not the final precipitating event.

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7: People Living With HIV (PLWH) Survivorship Care Plan to Promote Cancer Screening

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BACKGROUND:

The advances in effective anti-retroviral therapy (ART) have changed HIV into a chronic disease. As death from HIV/AIDS has decreased for people living with HIV (PLWH), mortality from other chronic diseases of aging, particularly the burden of non-AIDS-defining cancers (NADC), has significantly increased. PLWH are diagnosed with cancer more often, at a younger age, at more advanced stage (despite frequent encounters with the healthcare system), and with higher mortality compared to HIV- individuals. Overall, cancer risk is nearly 70% higher among PLWH than in the general HIV- population. PLWH are at significantly increased risk for multiple cancers compared to patients who are HIV-. Reasons for increased risks include high rates of smoking, immunosuppression, interaction between HIV and other infectious agents (e.g., HPV), chronic infection, and, likely, tumor biology. Multiple studies have demonstrated worse outcomes among PLWH for a variety of cancers, although the exact etiology, particularly patient behavior, underlying these repeated findings remains to be elucidated. One possible reason for poor outcomes may be lack of screening. PLWH 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 the need for cancer screening. Barriers to participate in cancer screening, already problematic in rural and underserved urban settings, may be exacerbated for PLWH. Significant gaps in understanding perceptions and views of PLWH towards and uptake of cancer prevention and screening interventions limit the ability to design and test efficacious interventions. Previous studies from our group showed few PLWH were in receipt of recommended cancer screening despite being at increased risk due to age and HIV status as well as other factors, e.g., smoking.

METHODS:

In collaboration with community partners, an intervention to promote guideline-concordant cancer screening and prevention among PLWH was identified. The proposed intervention is the use of a *PLWH Survivorship Care Plan (HSCP)*, modeled after the Cancer Survivorship Care Plan that has been used by cancer programs for two decades. No such tool currently exists or has been studied in the HIV+ population to help clinicians ensure recommended cancer surveillance, preventive care, and early detection are provided. Using a mixed-methods approach, we designed and implemented a feasibility and acceptability pilot study of an HSCP to examine the attitudes towards, comprehension of, and acceptability by PLWH and their providers from seven rural and underserved urban settings in Georgia.

RESULTS:

Herein, we report on the quantitative data related to the PLWH. The study was initiated in July 2021 and accrual was closed in August 2022. Subjects were eligible if they had a diagnosis of HIV, had no previous diagnosis of cancer, could read and speak English, and provided informed consent. Demographic data: 106 PLWH were enrolled: 68% were born male, identified as male; 67% were Black; median age, 38; 42% had ≤12 years education; 51% reported a household income of <$20K/year; 37% had a previous diagnosis of AIDS (CD4 count <200); and 6.6% reported a previous abnormal cervical or anal Pap test. For disease screening, 74% of respondents indicated they thought screening or finding disease early was very important, but only 13% of females had ever been screened for cervical cancer; 48% indicated no provider had ever previously recommended screening for non-communicable diseases, including cancer. Forty-eight percent reported they strongly/moderately agreed that having HIV/AIDS represented an increased risk for cancer, but nearly the same proportion (43%) were neutral/unsure. When asked specifically about the *HIV Survivorship Care Plan*, 46% responded the care plan would be very helpful, and 57% thought reminders about screening procedures due would also be very helpful. Over 58% of respondents indicated that using the HSCP to receive a schedule of preventive and healthy behaviors to follow would be very helpful.

CONCLUSIONS:

This pilot study of an *HIV Survivorship Care Plan* enrolled a diverse sample of PLWH across the state of Georgia. Quantitative data demonstrated this population is not consistently recommended for, or participates in, prevention/screening activities, but respondents expressed high value for early detection of disease, including cancer. The HSCP was viewed by the sample as potentially useful to promote better screening uptake. This tool also represents an opportunity to educate PLWH about their risk of non-communicable diseases, particularly cancers.

Author(s): Anna R. Giuliano[1], Timothy J. Wilkin[2], Luisa L. Villa[3], Michael J. Schell[1], and Eduardo Lazcano-Ponce[4]

8: Design of a Phase III Efficacy and Immunogenicity Trial of 9-valent Human Papillomavirus (HPV) Vaccine in the Prevention of Oral Persistent Infection in Men Living With HIV

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BACKGROUND:

The incidence of oropharyngeal cancer (OPC) caused by human papillomavirus (HPV) is significantly increasing among men in several middle- and high-resource countries, including the US, countries in the EU, and those in Latin America, such as Brazil and Mexico. As with other cancers caused by HPV, HPV-related OPC incidence is significantly elevated among people living with HIV (PLWH). Unlike cervical and anal cancers, there is no reliable method to screen for pre-cancerous lesions to prevent OPC or to detect OPC early. As seven high-risk HPV types (16/18/31/33/45/52/58) covered by the 9-valent HPV (9vHPV) vaccine cause >90% of OPC, vaccination may offer a viable method to prevent HPV-related OPC. Effectiveness studies conducted in the US and UK have observed significant declines in vaccine type oral HPV infections in both men and women following introduction of 4vHPV vaccination, suggesting that vaccination against HPV may prevent the infections that cause OPC and, hence, OPC. Definitive efficacy trials are needed to assess the benefits of vaccination to reduce OPC incidence, especially among those at highest risk of disease, men living with HIV. An ongoing clinical trial (NCT04199689) was designed to evaluate 9vHPV vaccine efficacy against HPV oral persistent infection, a surrogate endpoint for HPV-related head and neck cancers among men without HIV. Parallel to this trial, we designed a second trial to evaluate 9vHPV vaccine efficacy against HPV oral persistent infection among men living with HIV (NCT04255849).

METHODS:

In this double-blind, placebo-controlled, international (Puerto Rico, Mexico, Brazil) trial, men living with HIV aged 20–50 years (N = 500) are randomized 1:1 to receive 9vHPV vaccine or placebo on day 1, month 2, and month 6. The primary objective is to demonstrate whether 9vHPV vaccination reduces incidence of HPV6/11/16/18/31/33/45/52/58-related 6-month oral persistent infection. Oral rinse and gargle samples are collected on day 1, month 7, month 12, and every 6 months thereafter for HPV detection by PCR. Primary analyses will be performed in per-protocol populations. Efficacy in this case-driven study will be analyzed upon accrual of ≥31 primary efficacy endpoint cases. Serum is collected at day 1 and months 7, 12, 24, 36, and 42; anti-HPV antibody titers will be measured by competitive Luminex immunoassay. Data will be summarized as geometric mean titers and seropositivity rates. Serious adverse events (AEs) are collected through 6 months after the last vaccination; deaths and vaccine-related serious AEs will be collected throughout the study.

RESULTS:

Trial enrollment launched 02/23/21. To date (August 2022), 306 men are on study with an expected accrual completion date of February 2023. Among men on study with baseline oral specimens analyzed to date (*N* = 176), the enrollment visit oral 9vHPV combined prevalence is 11 (6.2%) overall with an oral HPV 16 prevalence of 2 (1.1%). There are no significant differences at enrollment of the combined 9vHPV prevalence or the oral HPV 16 prevalence.

CONCLUSIONS:

This trial is expected to generate important data regarding the potential for 9vHPV vaccine to prevent HPV-related head and neck disease among men living with HIV.

Author(s): Megan E. Hansen, Tishiya Carey, Nicole Hester, Carla Calhoun, Kirsta Waldon, Ralph Mangusan, Anaida Widell, Irene Ekwede, Kathryn Lurain, Robert Yarchoan, and Ramya Ramaswami

9: Psychosocial Barriers to Oncology Clinical Trial Participation: A Review of Patients Referred to the HIV-AIDS Malignancy Branch at the National Cancer Institute

HIV & AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD

BACKGROUND:

There are extensive psychosocial barriers to enrollment in cancer clinical trials. These barriers are compounded in populations with health disparities, such as individuals with HIV infection and cancer.

METHODS:

We performed a retrospective review for patients referred to protocols within the National Cancer Institute HIV-AIDS Malignancy Branch (HAMB) in the NIH Clinical Center in Bethesda, MD between 2012–2021. Participants screening for protocols from any part of the United States are required to pay for their first visit, but, if eligible, all transportation requirements are covered within the protocol. We reviewed HIV- and KSHV-associated disease characteristics, psychosocial barriers prior to referral, and psychosocial acuity at the time of presentation using a validated scale of psychosocial acuity from the University of Michigan Department of Social Work (Klett S, et al. 2014). The scale was used to score patients across seven domains for psychosocial needs. For each domain, acuity was scored on a scale from 1-4, with "1" representing patients who have their needs met in an adequate fashion and "4" representing patients in crisis who require significant advocacy to meet their basic needs. Finally, we reviewed referrals to services made within the NIH system to address these barriers and whether patients enrolled in a clinical trial within the HAMB program.

RESULTS:

Sixty-eight patients (64 cisgender male, 4 cisgender female) were included in this review. Forty-one percent of patients were Black, 88% had HIV, and 97% had KS. The most common psychosocial barriers prior to presentation were insurance (41%), finances (42%), mental health (42%), and substance use (28%). At presentation, median psychosocial acuity for transportation and lodging, insurance and finances, and mental health and substance use was 2 (range 1-4), meaning that intervention is required. Ninety-four percent of patients were seen by social work, 54% by occupational therapy, 57% by physical therapy, 68% by nutrition, and 25% by psychiatry. All patients returned for a second clinic visit, and 97% enrolled in an experimental clinical trial protocol.

CONCLUSIONS:

This single-center study highlights the wide-ranging social needs of clinical trial participants with HIV-associated malignancies. With engagement of a multidisciplinary team, the majority of patients were ultimately able to be involved in a clinical trial for cancer treatment despite these issues.

Author(s): Jessica Y. Islam[1], Shuang Yang[2], Matthew Schabath[1], Jiang Bian[2], and Yi Guo[2]

10: Lung Cancer Screening Adherence Among People Living With HIV Treated at an Integrated Health System in Florida

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BACKGROUND:

In the United States (US), lung cancer is the leading cause of cancer-related mortality among people living with HIV (PLWH). PLWH are more likely to be diagnosed at an advanced stage of lung cancer and have worse survival compared to their HIV-negative counterparts. Annual screening for lung cancer using low-dose computed tomography (LDCT) is recommended to reduce lung cancer mortality by identifying surgically curable early-stage disease. However, to our knowledge, currently no data exist demonstrating trends in LDCT usage among PLWH in the US. Our objective was to characterize LDCT adherence among HIV-positive adults and compare adherence to those without HIV treated at one integrated health system in Florida, a state with a high HIV burden in the US.

METHODS:

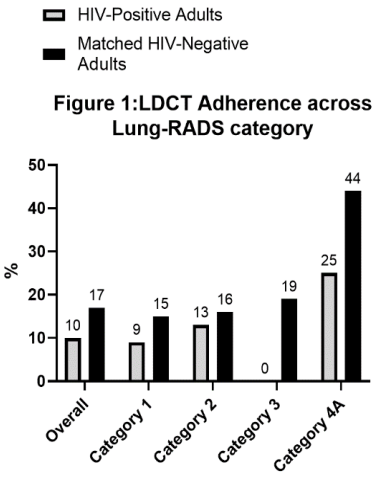

Figure 1:LDCT Adherence across Lung-RADS category

Our study population was drawn from the University of Florida (UF) Health Integrated Data Repository (IDR), which includes patients seen at any UF affiliated health facility (>1 billion observations). Using the UF IDR, we identified individuals who underwent at least one LDCT procedure between January 1, 2012, and October 31, 2021, using relevant Current Procedural Terminology (CPT) codes (S8032, G0297, 71271). Lung cancer screening adherence was defined as a second LDCT within recommended observation window (Table 1). The categories of the LDCT results and appropriate observation windows were defined based on the Lung Imaging Reporting and Data System (Lung-RADS®). We excluded those with LDCT results above category 4A given care recommendations are not standardized. We matched each HIV-positive adult with 4 randomly selected HIV-negative patients based on (+/- 1 year) age, Lung-RADS category, and calendar year. We used weighted Fischer's exact test to compare adherence across HIV status.

RESULTS:

Overall, we included 73 HIV-positive patients and 292 matched HIV-negative adults with a history of at least one LDCT. PLWH were more likely to be male (66% vs. 52%, p<0.04), non-Hispanic Black (53% vs. 23%, p<0.001), live in urban areas (86% vs. 60%, p<0.001), and live in an area of high poverty (45% vs. 31%, p<0.001). PLWH were more likely to be diagnosed with lung cancer after first LDCT (8% vs. 0%, p<0.001). Overall, 48% and 41% of adults were diagnosed with 1 or 2 Lung-RADS categories, respectively. Figure 1 summarizes adherence to LDCT based on the recommended observation windows (Table 1). Although not statistically significant, we observed that 17% of HIV-negative and 10% of HIV-positive adults were adherent to annual LDCT screenings (p=0.197). Importantly, only 25% of PLWH diagnosed with category 4A were adherent compared to 44% of HIV-negative (p=0.494).

Table 1: Definition of Lung-RADS category and recommended observation window for management

Category	Follow-up procedure	Observation window
1	Continue annual screening with LDCT	9 to 15 months
2		
3	6-month LDCT	3 to 9 months
4A	3-month LDCT or PET/CT	2-4 months

CONCLUSIONS:

Our results suggest that PLWH may have poorer adherence to lung cancer screening compared to their HIV-negative counterparts.

Author(s): Peter Julius[1], Stepfanie N. Siyumbwa[1], Phyllis Moonga[2], Fred Maate[1], Trevor Kaile[1], Jazmine Snow[3], Kristen Peterson[3], Patience Gihozo[3], Sam Streeter[3], Salan Kaur[3], Annika Evans[3], Kandali Samwel [4], Guobin Kang[5], John T. West[5], Charles Wood[5], and Peter C. Angeletti[3]

11: Overexpression of P53, YAP1, and Epstein-Barr Virus Nuclear Antigen, but not CDKN2A/p16INK4a, Frequently Detected in Ocular Surface Squamous Neoplasia

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BACKGROUND:

The etiopathogenesis of ocular surface squamous neoplasia (OSSN) is currently unknown. We aimed to determine the prevalence of oncogenic viruses, including human papillomavirus (HPV), Epstein-Barr virus (EBV), Merkel cell virus (MCV), Kaposi sarcoma virus (KSHV), and adenovirus infection in OSSN samples, as well as the abnormal expression of p53 and Yess-associated protein (YAP1), a novel therapeutic target. We evaluated the relationship between viral, p53, and yap1 status with clinicopathologic variables.

METHODS:

We prospectively enrolled 243 OSSN patients (preinvasive, 29.6% and invasive, 70.4%) from Zambia using a cross-sectional design and obtained formalin-fixed paraffin-embedded and fresh frozen tissue samples between November 2017 and March 2020. Immunohistochemistry (IHC) targeting CDKN2A/p16INK4a (p16) (HPV), Epstein-Barr Virus Nuclear Antigen-1 (EBNA1) (EBV), and MCPyV large T-antigen (MCV), as well as polymerase chain reaction (PCR), were used to determine the prevalence of oncogenic viruses in OSSN. Abnormal expression of p53 and YAP1 was evaluated using IHC.

RESULTS:

Most patients were female (61%) and HIV positive (72%), with a median age of 38 (IQR: 31.0–45.0) years; 99.6% of the cancers were unilateral. IHC on 243 FFPE blocks revealed positive expression in 89.0%, 4.9%, and 0% for EBNA1, p16, and MCPyV large T-antigen, respectively. EBNA1 IHC was expressed in all OSSN preinvasive stages (CIN1, 100%; CIN2, 85.7%; CIN3, 95.8%; and CIS, 83.8%) and invasive cancers (89.2%). p16 was not expressed (0%) in preinvasive OSSN. IHC demonstrated abnormal expression of p53 (81.3% vs 0%) and YAP1 (99.6% vs 4.3%, p 0.001) proteins in OSSN tumors vs adjacent normal tissue, respectively. On 178 frozen samples, PCR detected EBV, HR-HPV, and MCV in 80.3%, 9.0%, and 13.5% of tumors, respectively. KSHV and adenovirus were negative by PCR. EBV was PCR detected in all preinvasive (CIN1, 100%; CIN2, 100%; CIN3, 77.8%; and CIS, 82.6%) and invasive (79.5%) grades of OSSN. High HIV viral loads were associated with the presence of EBV (p=0.022). PCR found HR-HPV in 0% of CIN1, 0% of CIN2, 0% of CIN3, 13% of CIS, and 7% of invasive OSSN. Poorly differentiated carcinomas were significantly associated with HR-HPV infection by PCR (p=0.036) and p16 (p=0.001) expression by IHC.

CONCLUSIONS:

EBV (EBNA1) protein and genome expression in all grades of preinvasive and invasive OSSN is consistent with a possible causative role for EBV in OSSN. In this study, the role of HR-HPV in OSSN was not established. The expression of YAP1 and p53 in OSSN, but not in the adjacent normal epithelium, makes them a potential novel diagnostic and therapeutic target.

Author(s): Raynell Lang[1,2], Sally B. Coburn[1], M. John Gill[2], Michael A. Horberg[3], Michael J. Silverberg[4], Angel Mayor[5], Ronald J. Bosch[6], Charles S. Rabkin[7], and Keri Althoff[1]

12: Association of Anemia on Non-AIDS-Defining Malignancy in People With HIV Following ART Initiation

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BACKGROUND:

People with HIV (PWH) have both increased rates of anemia and non-AIDS-defining malignancy (NADC) compared with the general population. The cause of anemia is complex and multifactorial among PWH; however, the association between anemia and incident NADC (known in the general population) may be overlooked. We aimed to estimate the association of anemia and its severity with incident NADC among PWH in North America who had initiated antiretroviral therapy (ART).

METHODS:

We included PWH (≥18 years) enrolled in the NA-ACCORD with adjudicated malignancy data, with no prior cancer diagnosis, and on ART between 01/01/2007–12/31/2016. Participants were followed to the earliest of NADC diagnosis, death, loss to follow-up (18 months without viral load or CD4), cohort-specific cancer validation end date, or 12/31/2016. Annual median hemoglobin measurements were categorized into mild (11.0–12.9g/dL men, 11.0–11.9g/dL women) and moderate/severe (<10.9g/dL regardless of sex) anemia. Discrete time-to-event models using a complementary log-log link estimated crude and adjusted hazards ratios (aHR) and 95% confidence intervals ([,]) for NADC by time-updated anemia (yes vs. no) and anemia severity. Adjusted models include race/ethnicity, HIV acquisition risk, cohort, and time-updated variables of year, age, smoking, BMI category, AIDS diagnoses, Hepatitis C and B infection, median annual CD4 count (≤200cells/mm^3) and median annual HIV RNA (>200 copies/mL). Inverse probability of anemia and censoring weights were used to address the time-dependent confounding of variables on the anemia and NADC association.

Table 1: Hazards ratios for NADC among PWH with and without anemia and by anemia severity category measured from median hemoglobin annually.

Total (N=301,421)	N (%)	HR (95% CI)	aHR (95% CI)
No Anemia	244,658 (81)	Ref	Ref
Mild Anemia	40,134 (13)	3.41(3.08,3.77)	3.01(2.71,3.33)
Moderate/Severe	16,629 (6)	10.46(9.40,11.64)	8.21(7.30,9.23)
Males (N=265,305)			
No Anemia	219,593 (83)	Ref	Ref
Mild Anemia	33,980 (13)	3.69(3.33,4.10)	3.11(2.79,3.46)
Moderate/Severe	11,732 (4)	12.22(10.93,13.65)	8.65(7.65,9.79)
Females (N=36,116)			
No Anemia	25,065 (69)	Ref	Ref
Mild Anemia	6,154 (17)	1.41(0.90,2.19)	1.84(1.18,2.87)
Moderate/Severe	4,897 (14)	3.10(2.07,4.64)	3.93(2.58,5.97)

Adjusted models include race/ethnicity, HIV acquisition risk, cohort, year, age, smoking, BMI category, AIDS diagnoses, Hepatitis C (HCV) and B infection (HBV), Median Low (≤200cells/mm^3) CD4 count, Median unsuppressed HIV RNA (>200 copies/mL).

RESULTS:

Among 67,228 PWH contributing 301,421 annual median hemoglobin observations, 244,658 (81%) were not anemic, 40,134 (13%) had mild, and 16,629 (6%) had moderate/severe anemia. The median follow-up time was 3.0 (IQR:1.6–5.3) years. There were 2,744 diagnoses of incident NADC over the study period. On average, median hemoglobin decreased within the 3 years prior to NADC diagnosis, decreasing by a median of 0.7g/dL within the year prior to diagnosis. The proportion of PWH with anemia was greatest among those diagnosed with hematologic and gastrointestinal malignancies. In adjusted analyses, the risk of NADC was higher among PWH with anemia (aHR 4.27 [3.91, 4.67]) (vs. no anemia) and greater among males (aHR 4.43 [4.03, 4.85]) than females (aHR 2.47 [1.75, 3.50]). The risk of NADC diagnosis increased with worsening anemia severity among both males (3.1-fold mild, 8.7-fold moderate/severe anemia) and females (1.8-fold mild, 3.9-fold moderate/severe anemia), compared with those with no anemia.

CONCLUSIONS:

Among PWH initiated on ART, anemia is associated with a higher risk of incident NADC diagnosis, which increased with anemia severity, especially among males. Identification of anemia should warrant investigations into the underlying etiology, including screening for NADC, particularly among males and those with moderate/severe anemia.

Author(s): Joseph Lipscomb[1], Jeffrey M. Switchenko[1], Christopher R. Flowers[2], Theresa W. Gillespie[1], Pascale M. Wortley [1], A. Rana Bayakly[1], Lyn Almon[1], and Kevin C. Ward[1]

13: Impact of Multi-Agent Systemic Therapy on All-Cause and Disease-Specific Survival for People Living With HIV Who Are Diagnosed With Non-Hodgkin Lymphoma: Population-Based Analyses From the State of Georgia

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BACKGROUND:

For people living with HIV (PLWH) who subsequently are diagnosed with non-Hodgkin lymphoma (NHL), this study investigates the impact of standard-of-care (SoC) cancer treatment on all-cause, NHL-specific, and also HIV-specific survival outcomes in a population-based sample from the state of Georgia. Recent analyses from Georgia, focusing on a population-based sample of PLWH diagnosed with NHL within 2004–2012, identified several factors associated with receipt of SoC cancer treatment. SoC was defined as multi-agent systemic therapy (MAST) consisting of combinations of chemotherapy and monoclonal antibody agents. Predictors of MAST included being diagnosed with advanced-stage (Ann Arbor stage III or IV) disease, having private health insurance, the mode of HIV transmission, and having a CD4 count ≥200 cells/mm^3. This new study investigates an outcome not previously explored, i.e., whether receipt of SoC cancer treatment would lead to better survival, and was designed to address a gap in the literature related to patient-level analyses on impact of cancer therapy on survival for PLWH. The survival analysis herein uses MAST as representative of SoC for NHL among PLWH; a broad set of covariates, including CD4 counts and viral load level measured near time of NHL diagnosis; and a statistical modeling strategy acknowledging competing mortality risks.

METHODS:

Building on matching techniques employed by the NCI's HIV/AIDS Cancer Match Study, the Georgia Department of Public Health linked data from the Georgia Cancer Registry (GCR) and the Georgia HIV/AIDS Surveillance Registry (GHASR) to identify all adults (age ≥18) diagnosed with any cancer within 2004–2012 who had a diagnosis of HIV and/or AIDS on record prior to or during any portion of this period. Linkages were performed using established techniques. CD4 counts (cells/m^3) and viral load readings (copies/mL) for PLWH were obtained from GHASR, serving as markers for the patient's HIV status. Linked cancer-HIV files were also linked to the Georgia Hospital Discharge Database to generate a modified Charlson-Deyo comorbidity index score and other variables. Diagnosis of NHL was defined by ICD-0-3 histology codes. Excluded were cases where patients were diagnosed with a second primary cancer in 2004–2012 or if missing a diagnosis of either NHL or HIV. For all patients in this analysis, the HIV/AIDS diagnosis preceded the NHL diagnosis. GCR provided cause of death information for patients known to not have survived through 2017 based on ICD-10 codes; deaths were categorized as "NHL-specific," "HIV-specific," and "All Other." NHL-specific deaths included those with HIV disease "resulting in malignant neoplasms" (B21).

RESULTS:

The Georgia registry-based sample consisted of 328 HIV+ adults (age≥18) diagnosed with NHL within 2004–2012; of these, 184 met all inclusion criteria. In multivariable survival analyses using both traditional Cox models and also Fine-Gray models, which formally recognize that NHL and HIV are competing mortality risks, we found that SoC cancer treatment was significantly associated with better all-cause and NHL-specific survival, but not better HIV-specific survival. These analyses controlled for both the patient's CD4 count (< vs ≥200 around the time of NHL treatment) and NHL stage (Ann Arbor III/IV vs II/I). In these models, CD4<200 and stage III/IV were both associated with worse all-cause and worse HIV-specific survival, while the influence on NHL survival was in that same direction but not significant.

CONCLUSION:

The interrelationships involving HIV status, cancer stage at diagnosis, and therapy received for both cancer and HIV/AIDS create scenarios requiring complex analyses. Future work should embrace a multi-level perspective by expanding the geographic base and the cancers examined, deepening the level of clinical detail brought to bear, and incorporating the perspectives and recommendations of patients and providers.

Author(s): Angela Nalwoga[1,2], Romin Roshan[3], Conner Jackson[1], Kyle Moore[3], Vickie Marshall[3], Wendell Miley[3], Nazzarena Labo[3], Marjorie Nakibuule[2], Stephen Cose[2,4], Robert Newton[5], Denise Whitby[3], and Rosemary Rochford[1]

14: IFN-g Responses to Human Gamma-Herpesviruses in Individuals From Uganda

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BACKGROUND:

T-cell immunity is paramount in preventing the development of human gamma-herpesviruses (Kaposi sarcoma herpesvirus-KSHV and Epstein-Barr virus-EBV) associated tumours. It has been hypothesised that viral reactivation of both KSHV and EBV is prevented by T-cell immunity but with little evidence. However, most of what we know is based on studies of T-cell immunity in well-resourced countries.

METHODS:

To understand how T-cell responses to EBV and KSHV compare in an adult population in rural Uganda, we recruited HIV- adults aged 3 to 89 years from the General Population Cohort. We measured IFN-γ responses in peripheral blood mononuclear cells (PBMC) to a cocktail of lytic and latent EBV peptides as well as overlapping peptides across the entire KSHV proteome using the *ex-vivo* ELISPOT assay, and we measured viral load in PBMC using real-time PCR as well as immunophenotypes using flow cytometry.

RESULTS:

KSHV-specific T-cell responses were of low intensity and heterogeneous with no evidence of immune dominance. In contrast, IFN-γ responses to EBV peptides were frequent and intense. When we examined KSHV load, we observed that individuals with KSHV DNA in PBMC had a higher IFN-γ response to the latent ORF-73 (latent associated nuclear antigen) and a lower IFN-γ response to a late lytic glycoprotein K8.1 compared to individuals without KSHV DNA in PBMC.

CONCLUSIONS:

In summary, KSHV T-cell responses are low in intensity and heterogeneous compared to EBV in immune-competent individuals.

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Author(s): Monica D. Reece[1], Lindsey Ramirez[2], Baek Kim[2]*, and Christina Gavegnano[1,3,4,5,6]*

15: Elucidating Potential Anti-Viral Mechanisms of Baricitinib Against HIV-1

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**Denotes senior authors/PIs.*

BACKGROUND:

Existing antiretroviral therapy (ART) cannot target the HIV-1 reservoir in people living with HIV (PWH), a major barrier to cure. HIV-infected myeloid/CD4 T cells drive elevated inflammation even with suppressed peripheral viremia. Chronic inflammation facilitates reservoir maintenance (long-lived lifespan by upregulation of bcl-2 and cell-survival markers) and reservoir reactivation (IL-15 reactivation of virus in T cell/myeloid sanctuaries). Upregulated bcl-2 is also associated with survival of cancerous cells. Bcl-2 production is controlled by pSTAT5 downstream of the Jak STAT pathway, which is inhibited by baricitinib as used in this study. Persistent inflammation in PWH also drives non-AIDS comorbidities, including HIV-associated neurocognitive dysfunction (HAND), cardiovascular disease, and impaired immune reconstitution. We target an unmet clinical need for safe, specific, potent inhibitors of persistent inflammation in PWH driving viral persistence and comorbidities. Our group recently demonstrated ruxolitinib (Jak 1/2 inhibitor) is safe, is well tolerated, and reduces key markers of immune activation associated with HIV persistence, disease progression, and comorbidities in PWH (A5336, n=60). Baricitinib is a Jak 1/2 selective inhibitor and is FDA approved for moderate to severe RA (2018), is the first and only immunomodulator approved for COVID-19, and was recently approved for alopecia areata (2022). Baricitinib blocks IFN-α/β, IL-1α/β, TNF-α, CRP, D-dimer, IL-6, IL-7, and IL-15, with qd dosing and renal clearance, and our team has garnered a recently funded Phase2a human study to evaluate baricitinib-mediated reduction of the CNS HIV-1 reservoir. Here, we investigate direct-acting antiviral mechanisms of baricitinib.

METHODS:

Physiologic concentrations of baricitinib were used to evaluate its impact on 1) late reverse transcription viral products (RT-qPCR), 2) the viral replication cycle in HIV-GFP vector-transduced primary human T cells and macrophages (Φ), and 3) effects on pSTAT5-mediated IL-15-driven signaling.

RESULTS:

Baricitinib does not confer any block on late RT gene products in primary T cells or Φ; however, a reduction in viral replication is observed in the HIV-GFP vector system in T cells (Dunnett's multiple comparisons test, α=0.05; T cells ****μM, IC_{50} = 0.0209 μM; Φ not significant at concentrations tested). We also demonstrated that baricitinib blocks IL-15-mediated pSTAT5 production in a primary T cell model ($p<0.0001$), underscoring that direct-acting antiviral properties and potential to block viral reactivation are mechanistically linked to pSTAT blockade by baricitinib.

CONCLUSIONS:

Baricitinib blocks pSTAT5-induced IL-15 activation in primary T cells, highlighting a mechanistic link between this block and potential to reseed infection with IL-15-reactivated virus across latent stores as well as potential implications for clearing and preventing cancerous cell survival. Baricitinib significantly reduces HIV-1 replication in CD4 T cells at physiologic concentrations not linked to any effect on late HIV-1 RT gene products. Previous data demonstrate potent anti-HIV effects in Φ, which may be a cell-specific modulation of pro-HIV events by baricitinib independent of direct interference with the viral replication cycle measured here. These data demonstrate that baricitinib confers direct-acting antiviral effects, and in addition to existing data, further bolster the mechanistic link across blockade of inflammation, Jak-STAT signaling, and inhibition of viral replication. These data provide a foundation for additional human studies in PWH with a baricitinib-containing regimen, towards reduction of inflammation and ongoing viral replication across sanctuary sites systemically.

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16: Increased Tumor T-Cell Receptor Repertoire Clonality Associates With HIV/ART Status and Improved Outcome in a Cohort of Diffuse Large B-Cell Lymphoma Patients

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BACKGROUND:

Highly associated with HIV, diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma worldwide and likely differs biologically based on HIV status and antiretroviral therapy (ART) exposure. Recent studies suggest increased tumor T-cell receptor (TCR) repertoire clonality associates with improved response to immune checkpoint inhibitors (ICI). HIV decreases CD4+ and naïve T-cell counts and leads to a clonal TCR repertoire due to T cells targeting HIV-specific epitopes. We therefore hypothesized HIV+ DLBCL would have more clonal TCR repertoires compared to HIV-.

METHODS:

The Kamuzu Central Hospital Lymphoma Study has prospectively enrolled patients with newly diagnosed lymphomas in Malawi since 2013. All patients receive standardized treatment and follow-up. We extracted DNA from 68 pre-treatment formalin-fixed paraffin-embedded (FFPE) DLBCLs from this cohort (QIAmp DNA FFPE Advanced) and performed TCR sequencing (immunoSEQ, Adaptive Biotechnologies). ART-experienced was defined as greater than 6 months of ART prior to DLBCL diagnosis. Thirty-six FFPE tumors (n=12 HIV-, n=8 HIV+/ART-naïve, n=16 HIV+/ART-experienced) had >100 productive templates and passed quality control, meeting inclusion criteria for analysis. Of these, two tumors were EBV+ by EBER-ISH (n=1 HIV+/ART-experienced, n=1 HIV-). We used random downsampling to 100 productive templates due to template count variation. To test associations with clinical/demographic variables, we used ANOVA with Bonferroni correction, Pearson's correlation, or Wilcoxon signed-rank test. For survival analysis, we generated binary variables from median cutoff, then calculated hazard ratios (HR) by Cox regression and produced Kaplan-Meier curves.

RESULTS:

TCR repertories from HIV+/ART-naïve tumors were more clonal than those from HIV- (productive Simpson clonality: 1.4-fold change, adj. p=0.023; max productive frequency: 3.3-fold change, adj. p=0.027) and HIV+/ART-experienced patients (productive Simpson clonality: 1.4-fold change, adj. p=0.052; max productive frequency: 2.6-fold change, adj. p=0.05). There were no differences between HIV- and HIV+/ART-experienced tumor clonality or in total productive template count by HIV/ART status. When analyzing HIV+ and HIV- tumors together, high clonality correlated with improved event-free (productive Simpson clonality: HR 0.26, p=0.011) and overall survival (productive Simpson clonality: HR 0.32, p=0.031). This trend was maintained when analyzing HIV+ and HIV- tumors separately. Age was not associated with tumor TCR clonality or outcome. Non-germinal center tumors trended toward worse event-free survival (HR 2.15, p=0.12), but not overall survival.

CONCLUSIONS:

The TCR repertoire in HIV+/ART-naïve DLBCL was more clonal than HIV- and HIV+/ART-experienced cases. Longer duration of ART exposure prior to DLBCL diagnosis appeared to restore overall TCR repertoire diversity in the developing tumor. Increased tumor TCR clonality was associated with improved outcome in our cohort, irrespective of HIV/ART-status. Based on these results, HIV+/ART-naive DLBCL patients may represent a subset of lymphoma patients who would benefit from ICI.

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17. Establishment of National Cancer Management Guidelines for Botswana

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BACKGROUND:

Cancer is the second leading cause of death worldwide with an increasing incidence globally, more so in low-middle-income countries (LMICs). The use of standardized evidence-based guidelines has significantly improved care for cancer patients. Botswana, like other LMICs, has an increasing burden of cancer with high cancer-related morbidity and mortality. The increased HIV burden in Botswana has contributed significantly to cancer epidemiology, including the disproportionate standards of care. The national cancer guidelines were developed to provide standardized care for four of the most pressing malignancies: cervical, breast, colon, and head and neck cancers.

METHODS:

The Ministry of Health and Wellness (MOHW) and local oncology experts identified prevalent malignancies in need of standardized care in Botswana. An initial draft was compiled based on the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and European Urology Association (EUA) Guidelines. Panel consultations with local generalists and oncologists across Botswana were conducted to ensure applicability across private and public sectors. A final review involved international medical, surgical, and radiation oncology experts and was assessed by the MOHW. The last review meeting was then conducted for relevant updates.

RESULTS:

The MOHW published the 100-page "National Guidelines for the Management for Cervical, Breast, Colon, Head & Neck Cancer" in 2020. All-inclusive recommendations were compiled for the four malignancies and designed for use at all health care centers within Botswana. The guidelines were grouped under "minimal" or "ideal" recommendations, where "minimal" includes baseline standard of care and "ideal" refers to interventions only available in the private sector. Current gaps in cancer management and implementation goals were also included.

CONCLUSIONS:

The National Cancer Guidelines in Botswana provide a platform for standardized care and a route to curb the increasing incidence in Botswana. This will ultimately change the course of cancer management for cervical, breast, colon, and head and neck cancers. Future directions include finalizing all other cancer guidelines and planning for their dissemination and implementation.

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18: The Impact of Multiple Recruitment Strategies on the Enrollment Rates for CAMPO Clinical Trials Aimed at Preventing HPV-Related Cancers for Persons Living With HIV in Puerto Rico

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BACKGROUND:

The California-Mexico-Puerto Rico (CAMPO) Consortium (part of the National Cancer Institute-funded US-Latin American-Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network [ULACNet]) conducts clinical trials (CTs) to prevent HPV-related cancers among people living with HIV (PLWH) in Mexico and Puerto Rico (PR). In PR, different recruitment strategies are being implemented to enroll 1,400 PLWH for ULACNet-101, the first of three CTs under the CAMPO Consortium. We aimed to evaluate the effectiveness of different recruitment strategies implemented for the enrollment of PLWH in ULACNet-101 in PR.

METHODS:

We analyzed data from the pre-screening database containing demographic and clinical characteristics, and the mode of study recruitment of interested participants in ULACNet-101 in PR. Passive strategies involve (1) advertisements through printed flyers and banners at HIV-specialized clinics; (2) TV, radio, and newspaper advertising; (3) social media promotion through Facebook, Instagram, Twitter, and YouTube; and (4) word of mouth by friends, family, and previous participants. Active strategies include (1) onsite clinic promotion and pre-eligibility by research assistants in HIV clinics, (2) outreach phone calls to participants of previous studies, and (3) provider referrals. A study team member pre-screens potential participants for eligibility over the telephone, surveys participants for the type of referral (passive vs. active), and then schedules an onsite appointment at the University of Puerto Rico Comprehensive Cancer Center Hospital. Descriptive statistics were used.

RESULTS:

Until August 26, 2022, 338 (65.7% male and 34.3% female; mean age 53.6 ± 12.3 years) potential participants have been pre-screened, and 285 (84.3%; 72.3% male and 27.7% female) were determined to be eligible for enrollment. One hundred twenty-seven (45.5%) of 279 eligible participants that agreed to participate in ULACNet-101 have been enrolled. Preliminary analysis suggests substantially more potential participants pre-screened were referred due to active strategies (73.7%) versus passive strategies (26.3%), with onsite clinic promotion of the study leading to referrals (42.0%), followed by outreach calls (16.3%) and provider referral (15.3%). A significant difference was observed in eligibility status by recruitment strategy. Among those eligible participants, 24.4% were referred by a passive strategy versus 75.6% were referred by an active strategy ($p = 0.04$).

CONCLUSIONS:

In the initial experience enrolling participants in ULACNet-101 at the PR site, we observe onsite recruitment in HIV clinics as an effective active research strategy for PLWH. Additional innovative efforts, including the evaluation of a newly implemented 14-week advertising campaign and patient navigation strategies, are under planning.

This project was supported by the National Cancer Institute (Grant #U54CA242646 for CAMPO and Grant #R25CA240120 for CAPAC), National Institute of General Medical Sciences (Award #U54GM133807), and National Institute on Minority Health and Health Disparities (Grant #2U54MD007587).

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19: A Contemporary Update on Disease Stage at Diagnosis and Survival Among Adults With HIV-Associated Kaposi Sarcoma in East Africa

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BACKGROUND:

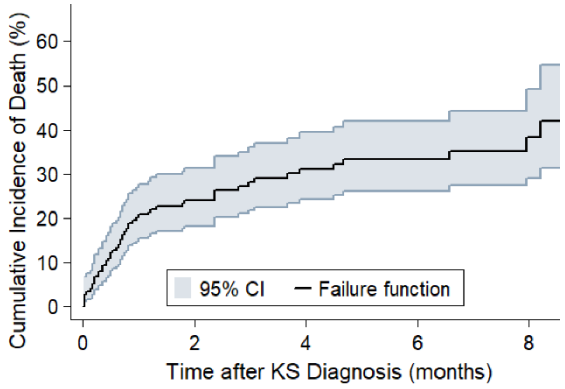
Stage at the time of diagnosis and survival after diagnosis are critical parameters regarding the control of any cancer in any geographical setting. Stage integrates patient willingness and ability to seek care as well as the health care system's ability to diagnose cancer if it presents. Survival captures both biologic aggressiveness of the cancer and the health care system's ability to intervene. Unlike in resource-rich settings where publicly funded cancer surveillance routinely monitors these parameters, these data are virtually non-existent in resource-limited regions. This is particularly true for Kaposi sarcoma (KS) in East Africa, for which recent changes in chemotherapy guidelines as well as the COVID-19 pandemic (and all of its manifestations) dictate an update regarding stage and survival.

METHODS:

Beginning in October 2021, we evaluated HIV-infected adults (age ≥18 years) with a new diagnosis of KS from 4 different primary care facilities (and their associated inpatient units) in Kenya (Academic Model Providing Access to Healthcare [AMPATH]) and Uganda (Infectious Diseases Institute in Kampala; Masaka Regional Referral Hospital; and Mbarara Regional Referral Hospital) using rapid case ascertainment. KS diagnosis was confirmed by pathology, except when lesions were in locations deemed unsafe to biopsy. At the time of biopsy, participants were examined to document the extent of KS lesions. Participants were then longitudinally followed with evaluation every 12 weeks to monitor vital status and use of the health care system.

RESULTS:

Among 180 HIV-infected adults identified with a diagnosis of new-onset KS, 31% were women, and the median (IQR) age was 35 (29-42) years. The median (IQR) number of anatomic sites with KS lesions were 7 (4-11); 26% of participants had oral KS lesions that interfered with either eating or speaking, 74% had KS-associated edema, and 86% had ACTG stage T1 (advanced KS). At the time of KS diagnosis, 95% of the participants were taking ART, the median (IQR) CD4+ T-cell count was 197 (46-354) cells/mm^3, and 46%, 20%, 11%, and 23% had plasma HIV RNA of <40, 40-1000, 1001-10,000, and >10,000 copies/ml, respectively. Over a median follow-up of 2.6 months (IQR: 0.75 to 5.5), a total of 56 participants died, and 3 were lost to follow-up. The cumulative incidence of death (95% CI), using Kaplan-Meier estimation, at 2 months, 4 months, 6 months, and 8 months was 24% (18%-31%), 31% (24%-39%), 33% (26%-42%), and 38% (29-49%), respectively (Figure).



CONCLUSIONS:

In a very recently assembled community-based sample of adults with HIV-associated KS in East Africa, the majority have advanced disease at the time of KS diagnosis, and survival is poor. These findings are virtually unchanged from parameters obtained in the 5 years prior, indicating there has been no improvement in these aspects of the control of KS in the region. Similar data from other regions are needed to yield an even more complete understanding of contemporary KS epidemiology in sub-Saharan Africa. Along with primary prevention of KS (i.e., reducing its incidence), novel approaches are needed for earlier detection, more efficient linkage to oncologic care, and more potent therapeutics.

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20: AIDS-Related Kaposi's Sarcoma Tissue Resource for Immune Profiling

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BACKGROUND:

Kaposi's sarcoma (KS) often improves after the introduction of highly active antiretroviral therapy (HAART); however, many individuals will have recurrent KS that requires chemotherapy. In studies with CD4 and CD8 matched cohorts, there are disparate outcomes, indicating that the immune profile within the tumor may yield better evidence for prognosis. The AIDS and Cancer Specimen Resource (ACSR) is the largest source of malignancy specimens from persons living with HIV (PLWH) available to researchers and stores a collection of Kaposi's sarcoma tissue samples representing a year-long study of HAART efficacy in newly diagnosed patients [Anti-Retrovirals for Kaposi's Sarcoma (ARKS) study]. Although virally responsive to HAART, about one-third of KS patients developed progressive KS defined as either death or requiring systemic chemotherapy during the study timeframe. The ARKS collection is a valuable resource to better understand the immune profile of KS lesions, which can lead to improved treatments and outcomes. The goal of this ACSR project was to perform multiplex immunofluorescence (mIF) on these KS tissues to test whether immunological makeup at diagnosis would be associated with clinical outcome.

METHODS:

The ACSR created a tissue microscopic array (TMA) that included 145 unique tumor biopsies collected from among the 224 KS participants and linked to clinical outcome. All KS tissues were sectioned, and H&E stains were generated. The stained tissues were pathologically reviewed to determine tumor content and identify the optimal region for core extraction. One tumor core was extracted from each of the 145 KS FFPE donor blocks and used to create a total of four unique TMAs. The cores were distributed such that subtypes (patch, nodular, plaque), disease progression (progressors, non-progressors), and survival status (alive/dead) were evenly distributed across the four TMAs. We used mIF to stain the four arrays for LNA1, CD3, CD4, CD8, CD20, and CD68. We used Opal 7 Solid Tumor Immunology Kit (Akoya Biosciences) to stain TMAs. Imaging was performed on the Vectra 3 scanner (Akoya Biosciences). Here, we present the data for the first panel of six markers: LNA1, CD3, CD4, CD8, CD20, and CD68.

RESULTS:

We have developed a customized tumor immune marker profile for a large sampling of KS tumors. We performed cell segmentation and cell count analysis (Visiopharm) and correlated the results with patient outcomes. KS-infected tumor cells are identified by LNA1 staining. Tumor-associated T-cells are tagged and profiled by CD3, CD4, and CD8 expression. B-cells, while not frequently found in these tumors, can be seen. CD68-positive macrophages are also present. A second panel, consisting of LNA1, CD3, PDPN, CD163, PD-L1, and HHV-8 K8.1, is currently in development.

CONCLUSIONS:

This KS TMA/mIF resource is the first high-density data set of the immune landscape in KS tumors. This resource and related clinical data represent a high-value resource to the research community studying cancer pathogenesis in PLWH to find novel approaches to KS treatments. In adherence with the ACSR's mission to provide resources to support HIV/AIDS research, the TMAs, related ARKS specimens, and associated images and data in the ACSR inventory will be made available to eligible researchers for additional testing or data mining.

Author(s): Valeria Fink[1], Celeste Pérez[2], Ezequiel Lacunza[3], Ana Gun[1], Carolina Pérez[1], Macarena Sandoval[1], Victoria Iannantuono[1], Mónica Tous[2], Martín Abba[3], Omar Coso[4], Pedro Cahn[1], and Enrique Mesri[5] on behalf of University of Miami CFAR Sylvester Comprehensive Cancer Center-Argentina Consortium for Research and Training in Virally Induced AIDS Malignancies

21: Salivary Shedding, Viremia, and Seroprevalence of Kaposi´s Sarcoma-Associated Herpes Virus Among a Cohort of Men Who Have Sex With Men and Transgender Women in Argentina

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BACKGROUND:

Kaposi´s sarcoma is still one of the most frequent AIDS-defining cancers among people with HIV in Latin America. Data on Kaposi's sarcoma-associated herpesvirus (KSHV) remain scarce. Men who have sex with men (MSM) and transgender women (TGW) are the populations most affected by HIV 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 in Argentina. Updated baseline data are presented.

METHODS:

MSM and TGW were recruited at Fundación Huésped between April 2018 and August 2021. All patients signed informed consent prior to study procedures. Medical information was obtained and samples derived from blood and saliva were collected and stored at -70°C. DNA from whole blood and saliva samples was extracted using QIAamp DNA Mini Kit (QIAGEN); IFA for lytic antibodies on TPA-induced BCBL-1 cells and PCR reactions were performed. KSHV serology was done by indirect immunofluorescence assay.

RESULTS:

Patients recruited: 144 MSM (111 with HIV) and 81 TGW (39 with HIV). The median age was 33.9 years (interquartile range [IQR] 29.1–41-5). Participants were born in Argentina (n=179), Venezuela (n=14), Peru (n=11), Paraguay (n=9), Colombia (n=7), Ecuador (n=3), and Brazil and Bolivia (n=1 each). Almost all TGW (91%) and 13% MSM were current or past sexual workers. Deep kissing was reported by 96% of participants. Two percent of subjects used intravenous drugs in the past, 61% used non-intravenous drugs, 21% used stimulants, and 55% ever used tobacco. Among TGW, 38% were receiving gender-affirming hormones. Among participants with HIV (PWH), median CD4 cell count was 622 cells/ul (IQR: 408–807 cells/ul). Six patients had previous or concomitant Kaposi´s sarcoma, and four had active clinical disease. Serological analysis showed that 65% of the population was infected with KSHV (68% of the TGW and 36% of the MSM; 72% PWH). KSHV was detected in 29% of the saliva samples (33% TGW and 26% MSM; 77% PWH) and in 15% of whole blood samples (13% TGW and 15% MSM; 81% PWH). Eighteen patients had KSHV detected in both blood and saliva, all with positive serology. KSHV in saliva and whole blood, as well as positive KSHV serology, were associated with HIV infection (p= 0.043, 0.046 and 0.014, respectively).

CONCLUSIONS:

In this expanded cohort, the prevalence of KSHV infection remains high among the studied population. Seroprevalence was 65%; in particular, among TGW (68%). Salivary shedding was higher than viremia. People with HIV were more likely to have KSHV infection detected by any of the used techniques. This study is expected to provide information that might aid in the design of public health policies and KS prevention strategies.

This work is funded by National Institutes of Health 2P30AI073961/U54 CA221208.

Partial results were presented at IAS 2019 and ICMH 2019.

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22: Prevalence and Determinants of Kaposi's Sarcoma-Associated Herpesvirus (KSHV) Antibody Positivity Among Adults Living With HIV in East Africa

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BACKGROUND:

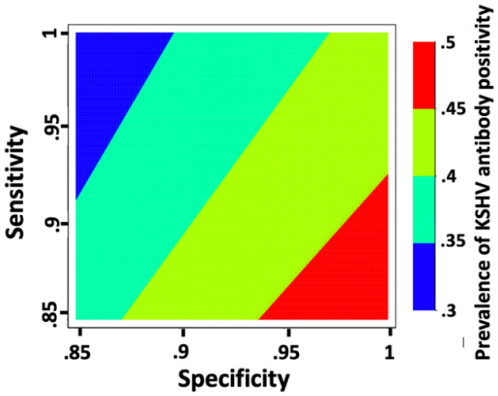
Persons living with HIV who are also KSHV infected are a group with amongst the highest risk for KS. As such, understanding and monitoring KSHV prevalence amongst HIV-infected individuals is an important objective for the control of KS. To date, data on KSHV prevalence amongst HIV-infected persons in East Africa—one of the world's hotbeds for KS—are both sparse and variable.

METHODS:

In a cross-sectional design, we studied a consecutive sample of HIV-infected adults (≥ 18 years old), without KS, identified just prior to starting antiretroviral therapy (ART) at an ambulatory HIV clinic in Mbarara, Uganda. The clinic serves a wide catchment of both urban and rural-based patients, and the study sample is known as the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort. Results from two enzyme immunoassays (with synthetic K8.1 and ORF 65 antigens as targets) and one indirect immunofluorescence assay (using an induced BCBL cell line) to detect antibodies to KSHV (all performed at CDC) were combined to classify KSHV antibody positivity. Given uncertainty in true assay sensitivity and specificity, we made, after estimating raw KSHV prevalence, corrections with a) a Bayesian method that accounts for a prior literature-based distribution of KSHV prevalence and assay sensitivity and specificity; and b) a frequentist approach, the Rogan-Gladen estimator, which corrects for a range of presumed assay sensitivity and specificity. Determinants for KSHV infection were depicted with marginal prevalence ratios (PR) and differences (PD) estimated after directed acyclic graph-informed control of confounding.

RESULTS:

We evaluated 725 HIV-infected participants between 2005 to 2013, in whom median age was 35 years (interquartile range (IQR): 29-40), 69% were women, and median CD4 count was 167 cells/µl (IQR: 95-260). Raw prevalence of KSHV antibody positivity was 42% (95% CI: 38% to 45%). The estimate using Bayesian analysis was nearly unchanged at 42% (95% CI: 38% to 47%), and the range of corrected estimates varied from 31% (95% CI: 24% to 38%) to 49% (95% CI: 43% to 55%) using Rogan-Gladen (Figure 1). Male sex (PR=1.6; 95% CI: 1.3-1.9; PD=+0.20; 95% CI: +0.11 to +0.30), older age at sexual debut (PR=1.1 comparing age at 75th to 25th percentile; 95% CI: 0.99-1.3), and higher physical health score (a quality-of-life metric from the Medical Outcomes Study; PR=1.3 comparing scores at 75th to 25th percentile; 95% CI: 1.03-1.5) were independently associated with higher KSHV prevalence. More education (PR=0.63 comparing ≥4 years of secondary school to no school; 95% CI: 0.44-0.90) was protective against KSHV prevalence. We found no strong evidence for a role for age, alcohol use, or other measurements of sexual behavior, SES, or well-being.



CONCLUSION:

Among HIV-infected adults in Western Uganda, KSHV prevalence is ~40%, with no substantive change after various correction approaches. This estimate differs from several others in the region (as high as 80%), highlighting the need for assay comparison studies using identical specimens. To the extent HIV does not influence KSHV acquisition, the findings may also represent KSHV prevalence in the general population. The impact of male sex on KSHV acquisition confirms prior regional work. Its mechanism is not understood, but its presence, in part, explains the higher incidence of KS among men.

Author(s): Marta Epedlegui[1], Di Chang[2], Jeannette Lee[2], Margaret Borok[3], Aggrey Bukuru[4], Naftali Busakhala[5], Catherine Godfrey[6], Mina C. Hosseinipour[7], Minhee Kang[8], Cecilia Kanyama[7], Deborah Langat[9], Rosie Mngqibisa[10], Noluthando Mwelase[11], Mulinda Nyirenda[12], Wadzanai Samaneka[3], Brenda Hoagland[13], Thomas Campbell [14], Otoniel Martinez-Maza[1], and Susan E. Krown[15]

23: Association of Serum Biomarkers With Clinical Response of Limited-Stage AIDS/KS in Resource-Limited Settings: Results From the ACTG A5264/AMC-067 Clinical Trial

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BACKGROUND:

Molecules associated with systemic inflammation, immune activation, and angiogenesis have been implicated in the pathogenesis of Kaposi sarcoma (KS), but associations between levels of these molecules with the outcomes of KS treatment are not well defined. We investigated whether pre-treatment serum levels of these biomarkers were associated with response of limited-stage AIDS/KS to treatment with antiretroviral therapy (ART) with "immediate" or delayed ("as needed") oral etoposide (ET) chemotherapy.

METHODS:

Sera from 184 participants in a completed, open-label, randomized trial (Clin Infect Dis 2018;67:251-60) were obtained before and during treatment. Levels of soluble markers of inflammation (CRP, IL-6, IL-8, IL-10, G-CSF, sTNFR2), immune system activation (sCD25/IL-2Ra, CXCL10/IP10, CCL2/MCP1), and angiogenesis (VEGF, MMP-2, MMP-9, endoglin, HGF) were measured by Luminex multiplex assays.

RESULTS:

Baseline CRP ($p=0.08$) and IL-10 ($p=0.012$) levels were significantly higher in participants whose KS progressed than in those with durable partial responses or stable disease for both arms combined. Baseline CRP remained highly associated with response ($p=0.01$) in the "as needed" arm but not the "immediate" arm. CRP was the only baseline factor associated with KS response ($p<0.01$) in the final multivariate model that included both clinical and routine laboratory features and serum biomarkers. Participants in the "immediate" ET arm showed significantly greater decreases from baseline to week 4 in CRP ($p=0.044$), IL-6 ($p<0.001$), IL-10 ($p<0.001$), sCD25/IL-2Rα ($p<0.001$), G-CSF ($p=0.034$), and sTNFR2 ($p<0.001$) compared to those in the "as needed" ET arm. These observations are consistent with amplification by ET of ART-induced modulation of inflammation and immune activation and accord with the observations that immediate ET treatment was associated with a significantly longer time to KS progression, a reduced incidence of KS-IRIS, and a higher KS response rate than ART alone.

CONCLUSIONS:

Baseline biomarkers of inflammation, particularly CRP, are informative as predictors of clinical outcomes in limited-stage AIDS/KS patients initiating ART and may prove useful in identifying patients who would benefit from treatment with immediate etoposide in addition to ART.

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Author(s): Beatriz H.E.S. Veronese[1], Noah Benscher[1], Amy Nguyen[1], Khushil Patel[1], Salma Drew[1], Zhe Ma[1,2]

24: ORF48 is required for optimal lytic replication of Kaposi's Sarcoma-Associated Herpesviruses

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BACKGROUND:

Kaposi's sarcoma-associated herpesvirus (KSHV) is a DNA virus that is linked to several human malignancies. Evasion of the host's innate immune response is essential for KSHV viral infection, replication, latency, transmission, and lifelong persistence, which leads to cancer development. Studies indicate that KSHV encodes a vast network of proteins that aid in the suppression of innate immunity-related pathways. One of the essential pathways, the cGMP-AMP synthase (cGAS) and stimulator of interferon genes (STING) pathway is able to inhibit the reactivation of KSHV from latency. Previously, we have identified multiple cGAS/STING inhibitors encoded by KSHV, which highlights the critical anti-KSHV role of this pathway and also suggests the importance of these inhibitors on optimal KSHV lytic replications. In this study, we aim to further characterize one of these inhibitors, KSHV ORF48. Our hypothesis is that ORF48 targets the cGAS/STING pathway to negatively regulate innate immunity, which will facilitate KSHV replication.

METHODS:

To investigate the role of ORF48 in the KSHV life cycle and pathogenesis, we first constructed a set of recombinant viruses that included either wild-type (WT) or two deleted ORF48 (KSHV.BAC16dORF48#1 or KSHV.BAC16dORF48#4). Furthermore, we established iSLK cell lines that carry each of these viruses, as iSLK.BAC16 systems are very commonly used to study KSHV lytic replication. We used doxycycline to reactivate these KSHV variants into the lytic cycle in iSLK cells and harvested the cells at 0h, 24h, 48h, and 72h to study the lytic replication status. These cells were further subjected to RNA extraction and RT-PCR to detect lytic gene transcriptions. We also evaluated KSHV lytic protein levels using western blot. KSHV intracellular and extracellular genomes were also measured using qRT-PCR. Also, supernatants of each condition were collected to infect naïve cells to monitor infectious virions in each group.

RESULTS:

We found that compared with the WT group, iSLK cells carrying the two recombinant viruses KSHVdORF48#1 and #4 displayed significantly reduced lytic KSHV gene transcription, lytic KSHV protein expression, KSHV genome copies, and infectious KSHV virions, which indicates the critical role of ORF48 on optimal KSHV lytic replication.

CONCLUSIONS:

Overall, our results suggest that the removal of ORF48 significantly abolishes KSHV lytic life cycle. We are further dissecting the mechanism of ORF48 on innate immunity and KSHV lytic replication.

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25: Prospective Cohort Suggests Two Types of Kaposi Sarcoma Lesions: Proliferative and Inflammatory

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**Contributed equally to the manuscript.*

INTRODUCTION:

Kaposi Sarcoma is one of the most prevalent cancers in sub-Saran Africa, today, affecting both HIV-positive and -negative males, females, and children in the region. Yet, prospective data from the region are limited. We report on LCCC1424, a prospective study that was conducted on a KS cohort of newly diagnosed patients who were initiating chemotherapy under local standard of care (Bleomycin/Vincristine). Between February 2017 to June 2019, patients were recruited in Lilongwe, Malawi. The primary objective of the study was to estimate complete response rate and to estimate overall and progression-free survival at 48 weeks. Further objectives were to identify factors associated with survival and response. Exploratory research to identify biomarkers or subsets of KS through RNA of lesion biopsies and DNA sequencing of Kaposi Sarcoma-associated herpesvirus was undertaken.

METHODS:

The Kaplan-Meier method was used to estimate OS and PFS, with a two-sided 95% CI calculated using the log-log transformation model. The Cox proportional-hazards regression model was used to estimate the hazard ratios for multiple clinical variables. The multivariate logistic regression model was used to explore the association between the CR and clinical variables. Bioinformatic analysis was performed on CLC Genomics Workbench, and RNA sequencing analysis was performed DESeq2. The ML phylogenetic tree was built using BEAST v1.10.4.

RESULTS:

One hundred twenty-two patients were enrolled; 98 (80.3%) were male with a median age of 36 (32–43 age range); 18 (15%) were classified good risk tumour (T_0) and 67 (55%) had a poor illness severity (S_1). Forty-three patients (35%) had a Karnofsky performance score ≤70, where 8 (6.8%) patients had visceral presentation of KS and 41 (35%) had oral involvement. Sixty-four (51%) patients knew of their HIV status prior to KS diagnosis, with 61 (50%) on ART. Sixty-seven patients (58%) had an HIV viral load less than 1000 copies/ml; 35 patients (35%) achieved a complete response and 28 patients (28%) achieved partial response at 48 weeks. RNA sequencing of patient biopsies was performed on 95 biopsies, resulting in two patient clusters defined by the differential expression of proliferative and inflammatory genes. KS lesions could be divided into tightly latent, extended latent, and lytic based on KSHV gene expression. Sixteen high-coverage KSHV genomes were isolated from plasma or FFPE biopsies, and an evolutionary relationship to other African KSHV isolates suggests that two subtypes of KSHV are present.

CONCLUSIONS:

As with many studies within the region, loss to follow-up was substantial beyond 2 years. At year 1, overall survival approached 61%, whereas complete responses were achieved in only 35%. HIV viral load or ART use did not emerge as independent predictors of response or survival.

Author(s): Ayana Morales[1], Gabrielle Benson[1,2], Stephanie Glavan[2], Rosemary Giuliano[2], and Mark Andrew Dickson[1,2]

26: The Emerging Fifth Epidemiologic Subtype of Kaposi Sarcoma in HIV-negative Men Who Have Sex With Men: A Review of Cases From a Tertiary Care Center in NYC From 2001 to 2021

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BACKGROUND:

Kaposi sarcoma (KS) is a vascular tumor caused by human herpesvirus 8, also known as Kaposi sarcoma herpesvirus. There are 4 widely accepted distinct epidemiologic subtypes of KS: classic, endemic, iatrogenic, and epidemic (HIV-associated) forms. An emerging 5th subtype is increasingly recognized: non-epidemic KS in men who have sex with men (MSM) who are HIV-negative and have no other known causes for immunodeficiency. Our objectives were to characterize a cohort of non-epidemic KS seen at the Sarcoma Medical Oncology or Dermatology Clinics at Memorial Sloan Kettering Cancer Center in New York City from 2000 to 2021 to identify risk factors, presentation, treatment course, and prognosis of these patients.

METHODS:

Following IRB approval, a retrospective observational study was performed. Eligible patients were identified through the Electronic Health Records (EHR). The patients were characterized based on age at presentation, sex, gender identity, comorbidities, coinfections, and treatments and outcomes amongst other factors. Study data were collected and managed using REDCap software.

RESULTS:

Seventy-two patients were identified, giving a prevalence of 10.8% of this 5th subtype in our population. The median age at time of diagnosis was 58 (range: 32-83). At initial diagnosis, 46% (33/72) of patients underwent observation, 50% (36/72) received localized treatment (i.e., excision, cryotherapy. or topical therapy), and 4% (3/72) received systemic treatment with chemotherapy. The median duration of follow-up was 22 months. In follow-up, 43% (31/72) of patients had progression of disease requiring recurrent treatment: 24% (17/72) received localized treatment while 18% (13/72) received chemotherapy. Patients who received chemotherapy, predominantly pegylated liposomal doxorubicin, received treatment for a median duration of 13 months (range: 2-72 months). By the end of the follow-up period, 7 patients had died, of which 2 deaths were attributed to KS; 10% (7/72) of patients were diagnosed with a lymphoproliferative disorder.

CONCLUSIONS:

This study is the largest yet, to our knowledge, to characterize the non-epidemic KS subtype in HIV-negative MSM, an underrecognized category who present at a younger age compared to classic KS. It is important to recognize this KS subtype to identify these individuals, who despite not having HIV are at increased risk for KS. Accurate recognition of this subtype may also allay patient concerns regarding overall prognosis, given that the majority of these patients present with indolent disease and have favorable outcomes compared to the epidemic variant of KS. Additional research is needed to understand the potential increased risk of lymphoproliferative disorders.

Author(s): Innocent Mutyaba[1,2], Ponsiano Ocama[2], Moses Kamya[2], Jackson Orem[1,2], Corey Casper[3,4,5], and Warren Phipps[4,5]

27: Incidence, Predictors, and Biomarkers of Kaposi Sarcoma Immune Reconstitution Syndrome Kaposi Sarcoma Patients Initiating Antiretroviral Therapy and Chemotherapy in Uganda

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BACKGROUND:

Diagnosis of Kaposi sarcoma immune reconstitution inflammatory syndrome (KS-IRIS) is challenging. Optimal management of KS-IRIS remains unknown. We sought to describe the cumulative incidence and predictors of KS-IRIS in 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 monthly on initiation of KS treatment. Suspected KS-IRIS diagnosis was based on worsening of KS and decrease of HIV VL >1 log within 12 weeks of starting ART. Competing risks survival regression methods were used to determine incidence and predictors of KS-IRIS.

RESULTS:

Among the 84 participants studied, median age was 31.5 years (18–75); 76.2% were male. ACTG staging of KS was T1 for 84.5%, I1 for 54.8%, and S1 for 71.4% of participants. HHV-8 viremia was detected in over 95% and oral shedding in 61.9% of the participants at baseline. Median plasma concentration was 7.2 (5.5–8.3) for C-reactive protein (CRP) and 1.2 (0.3–1.5) for IFN-γ. At 90 days from ART initiation, 30 patients developed KS-IRIS, 2 patents died, and 52 were censored. The medium time to KS-IRIS was 48 days (13–87). KS-IRIS cumulative incidence was 35.7% (25.7%–45.9%). In the multivariate model, KS-IRIS was significantly associated with baseline abnormal chest X-ray findings (HR=3.04 [1.04–8.90], p=0.04), WBC (HR=0.75 [0.57–0.99] per 1000 cells/dl increase, p=0.05), CD4 count (HR=0.86 (0.76–0.99) per 50 cells/dl increase, p=0.03), CRP (HR=15.68 (1.04–236.67) per log increase, p=0.05), and IFN-γ (HR=0.15 [0.04–0.50] per log increase, p=0.002) but not with platelet count (p=0.54).

CONCLUSIONS:

KS-IRIS remains common even in the context of concurrent ART and cancer chemotherapy. The risk of KS-IRIS increased with pulmonary KS and high CRP, and decreased with increasing WBC, CD4 count, and IFN-γ. These factors warrant further study for their potential as biomarkers of KS-IRIS development to facilitate prevention, early diagnosis, and appropriate management of KS-IRIS.

Author(s): David J. Nolan[1], Rebecca Rose[1], Rongzhen Zhang[2], Alan Leong[2], Gary B. Fogel[3], Larissa Lopes Silva Scholte[4], Jeffrey M. Bethony[4], Paige Bracci[5], Susanna L. Lamers[1], and Michael S. McGrath[2]

28: The Persistence of HIV Proviral Diversity, Transcription, and Nef Protein in Kaposi's Sarcoma Tumors During Antiretroviral Therapy

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BACKGROUND:

Epidemic Kaposi's sarcoma (KS), caused by co-infection with Human Herpes Virus 8 (HHV-8) and the Human Immunodeficiency Virus (HIV), is a major cause of mortality in sub-Saharan Africa where seroprevalence of both viruses is highest worldwide. Antiretroviral therapy (ART) significantly reduces the risk of developing KS, and for those with KS, tumors frequently resolve with ART alone. However, for unknown reasons, a significant number of KS cases do not resolve and can progress to death despite improved $CD4^+$ T-cell counts and undetectable plasma HIV viral loads.

METHODS:

To explore how HIV responds to ART in the KS tumor microenvironment, we sequenced HIV *env-nef* found in DNA and RNA isolated from plasma, peripheral blood mononuclear cells, and fresh frozen tumor biopsies, before and after ART, in four Ugandan study participants who had unresponsive or progressive KS after 180-250 days of ART. We also performed parallel immunohistochemistry experiments to detect viral proteins on matched formalin-fixed tumor biopsies.

RESULTS:

Our sequencing results showed that HIV proviral diversity and RNA expression in KS tumors are maintained after ART despite undetectable plasma viral loads. The presence of spliced transcripts in the sequence data from KS tumors after ART was consistent with a persistent and transcriptionally active viral reservoir. Immunohistochemistry staining confirmed the continued presence of HIV Nef protein in the tissue-resident macrophages of the KS tumors.

CONCLUSIONS:

Overall, our results demonstrated that HIV located in KS tumors continues to be transcriptionally and translationally active, even after ART has reduced plasma HIV viral load to undetectable levels and restored immune function, which could influence tumor maintenance and progression. Continued studies using a larger cohort and additional methods that define the HIV transcriptionally and translationally active reservoir in the KS tumor niche could lead to novel therapies for KS.

Author(s): Sara R. Privatt[1,2], Owen Ngalamika, Charles Wood[1,3], John T. West[3]

29: Upregulation of Cell Surface Glycoproteins in Correlation With KSHV Latency in the Kaposi Sarcoma Tumor Microenvironment

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BACKGROUND:

HIV-associated epidemic Kaposi sarcoma (EpKS) remains one of the most prevalent cancers in sub-Saharan Africa despite widespread uptake of anti-retroviral therapy and HIV-1 suppression in treated individuals. Previously, our lab reported differential gene expression profiling of EpKS tumors versus normal skin revealing increased expression of T-cell chemoattractants despite little T-cell infiltration into the KS microenvironment. The transcriptomic data also revealed dysregulation of glucose and lipid metabolism in the KS tumors. Utilizing this data set, we sought to identify potential cell surface biomarkers that might serve as therapeutic targets against KSHV infection and KS tumorigenesis.

METHODS:

We have enumerated a list of cell surface proteins whose genes were upregulated more than sixfold in the EpKS tumor microenvironment and were correlated with viral latency (high latency associated nuclear antigen [LANA]). Among this list are two members of the VEGF angiogenesis pathway, KDR (VEGF receptor 2) and FLT4 (VEGF receptor 3), as well as the metalloprotease (ADAM12), the netrin-1 axon receptor (UNC5A), the primary sperm receptor in the *zona pellucida* (ZP2), and T-cell activation marker OX40. To characterize the endothelial lineages present in the KS tumors, we stained for the prospero homeobox-1 (Prox-1) and the phosphoglycoprotein CD34 as markers for lymphatic endothelial and vascular endothelial cells, respectively. Each protein was comparatively evaluated for co-localization with KSHV LANA using multicolor immunofluorescence in KS tissues, KSHV-infected L1T2 cells, uninfected TIVE cells, and murine L1T2 tumor xenografts.

RESULTS:

Five surface glycoproteins (KDR, FLT4, UNC5A, ADAM12, and CD34) were associated with LANA positive cells, and were also found in seemingly uninfected cells in the KS microenvironment. KS tumors (N=2; 30 fields) evinced both Prox-1 and CD34 expression with 61% of cells double-positive, 28% CD34 only, and 2% Prox-1 only. *In vitro* L1T2 cultures showed evidence of only FLT4 and KDR indicative of active VEGF signaling, whereas mouse L1T2 xenograft tumors largely recapitulated human KS cell surface expression profiles, excepting CD34 and Prox-1.

CONCLUSIONS:

Staining of KS tumors suggests that the majority of cells co-express markers of both vascular endothelial and lymphatic endothelial lineages, suggesting KS-associated dedifferentiation to a more mesenchymal/progenitor phenotype. Cell surface marker evaluation suggests that protein expression patterns in KSHV cell culture differ from those in the tumor microenvironment, and while L1T2 tumors are more similar to KS in the expression of tumor-associated glycoproteins, they do not fully recapitulate the human tumor microenvironment.

Author(s): Megana Rao[1], Aggrey Semeere[2,3], Sigrid Collier[4], Philip Odhiambo[5], Celestine Lagat[5], Elyne Rotich[5], Samson Kiprono[5], Jeffrey Martin[3], David Felker[1], and Toby Maurer[6]

30: Teledermatology to Promote the Diagnosis of Kaposi Sarcoma in East Africa

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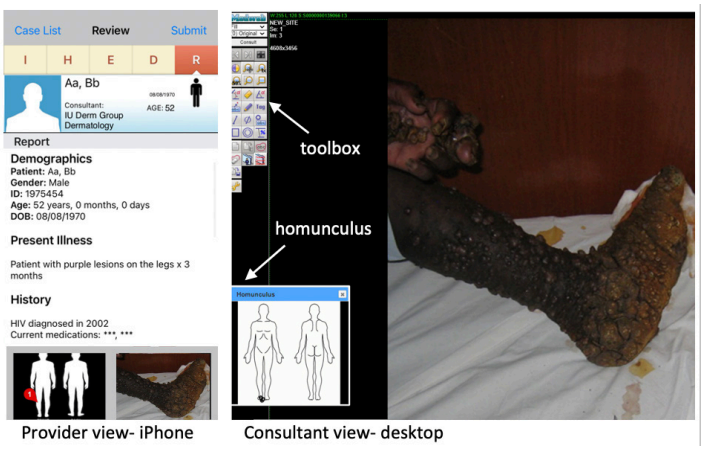
BACKGROUND:

In East Africa, patients diagnosed with Kaposi Sarcoma (KS) are most commonly diagnosed at advanced stages of the disease, which is a major contributor to poor survival rates in KS patients in this region of the globe. The reasons for late-stage diagnosis are multifaceted, including that patients need to be seen by several providers at different clinics prior to receiving a KS diagnosis. This may reflect a deficiency in recognizing KS at a primary care level. We hypothesize that integrating a dermatologic consultation system to primary care providers (PCPs) will increase and expedite KS diagnoses and therefore facilitate earlier recognition of this condition. The dermatologic consultation system entails use of an asynchronous store-and-forward teledermatology (TD) system through which PCPs send web-based consults which are then received by dermatologists who respond to the communication. While TD has been used for decades in resource-rich settings, the feasibility of implementing TD in HIV primary care settings in LMIC's has not been assessed. It is our aim to document and examine the implementation of this system, with particular attention to facilitating early KS diagnosis.

METHODS:

HIV primary care clinics were selected based on sites from which PCP's sent KS cases to our established biopsy service. Typically, 4–6 medical/clinical officers examine 80–120 patients daily. PCPs in HIV primary care clinics see patients and will utilize an application (app), MedWeb, to send a consult to the dermatology team. The app captures a history and high-resolution images with an optional dictation system. The dermatologist will view and respond to the consult via the same app. Consultants include local dermatologists (in Kampala, Mbarara, and Eldoret). One of four types of consult responses is generated, 1) condition is banal—no treatment is needed; 2) a diagnosis, workup, and plan are suggested to PCP; 3) patient will need a biopsy to rule out KS; 4) patient will need to be scheduled in dermatology clinic. The system and platform are secure and encrypted, and data and images are stored on a server hosted by AMPATH in Kenya.



Provider view- iPhone Consultant view- desktop

RESULTS:

Ten sites in Kenya and Uganda have been identified as the primary HIV care clinics where TD has been implemented. During setup of provider interfaces, data about clinic sites and workflow will be collected. These data include clinic information, provider training level (medical officer, clinical officer), number of providers, number of clinic rooms, and volume and types of clinic visits. The TD app will generate back-end reports about average time to complete a consult and reply to a consult. The initial data to be evaluated include staff usage rates (engagement of providers) and the distribution of consult results.

CONCLUSIONS:

In East Africa, where patient presentation with advanced-stage KS continues to be one of the most deadly (and potentially preventable) problems regarding HIV-related malignancies, we have taken initial steps in the creation of a TD system. This includes establishing the interest of PCPs and clinic sites and installing the technical infrastructure. Our immediate next steps are to assess provider usage/engagement of the system and the distribution of dermatologic consult outcomes.

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31: Effects of Maternal HIV Infection on Transplacental Transfer and Loss of Maternally Acquired Antibodies to Kaposi's Sarcoma-Associated Herpesvirus (KSHV) and on Risk of Primary KSHV Infection in Kenya

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BACKGROUND:

HIV infection in pregnant women has been shown to reduce transplacental antibody transfer directed to several antigens, reducing a child's initial defense against infection and leading to poorer childhood health outcomes. Whether HIV infection during pregnancy affects anti-KSHV antibody transplacental transfer and loss of maternally acquired antibodies in infants is unknown. We aimed to identify whether HIV infection during pregnancy leads to [1] reduced anti-KSHV antibody transplacental transfer, and in children born to women living with HIV; [2] faster declines in maternally acquired anti-KSHV antibodies; and [3] earlier age of child KSHV seroconversion.

METHODS:

From 2011 to 2015, we enrolled and prospectively followed 369 pregnant Kenyan women through delivery, and, if delivered at Chulaimbo Hospital, children were followed through age two years. Enrolled women were HIV tested according to Kenyan Ministry of Health national guidelines. All children were HIV-negative and identified as HIV-exposed uninfected (HEU) or HIV-unexposed uninfected (HUU). Cord and maternal venous blood at delivery and child venous blood at ages 6, 12, 18, and 24 months were tested for antibodies to 20 KSHV proteins by multiplex immunoassay (K8.1, ORF73, K3, K5, K10.5, K11, ORF6, ORF11, ORF25, ORF33, ORF37, ORF38, ORF50, ORF52, ORF55, ORF59, ORF61, ORF65, ORF72). T-tests were used to compare log-transformed levels of a) maternal antibody at delivery, b) cord blood antibody, and c) 6-month child antibody by maternal HIV status. We modeled a) anti-KSHV antibody transplacental transfer (defined as the log ratio of cord-to-maternal antibody levels) and b) loss of maternal antibodies (defined as the log ratio of 6-month-to-cord-blood antibody levels) in HEU vs HUU by linear regression. KSHV seropositivity by 24 months, defined as detection of antibody to any KSHV protein and excluding 6-month samples due to residual maternal antibodies, was compared in HEU vs HUU using chi-square test. False discovery rate was used for multiple comparison adjustments.

RESULTS:

Of the 369 women enrolled, 95% of HIV-positive and 97% of HIV-negative were KSHV seropositive. Of those, 227 delivered at the study hospital. There were 169 mother-child pairs with KSHV-seropositive mothers and paired serology data for cord and maternal venous blood at delivery. Maternal antibody levels at delivery did not differ by HIV status (except ORF50, which was significantly higher in HIV-negative mothers, $p<0.01$). Transplacental transfer of antibodies against 12 KSHV proteins (ORF73, K10.5, ORF11, ORF25, ORF33, ORF37, ORF52, ORF55, ORF59, ORF6, ORF61, ORF72) was significantly reduced in HIV-positive mother-child pairs. For 138 children, paired cord blood and 6-month serology data were available. Cord blood antibody levels for K5, ORF50, ORF61, and ORF72 were significantly lower in HEU neonates, but no difference was seen in antibody levels at age 6 months ($p=0.99$ for all 20 proteins). Change in antibody levels from delivery to 6 months did not differ in HEU vs HUU, except the decline for ORF50 was slower in HEU children ($p<0.01$). Of the 171 children with serology between ages 12 and 24 months, KSHV seropositivity by two years of age was 66% in HEU and 79% in HUU ($p=0.03$).

CONCLUSIONS:

Adult KSHV seropositivity and child KSHV seroconversion in this Kenyan mother-child cohort are some of the highest reported. Women living with HIV had reduced transplacental transfer of anti-KSHV antibodies, and HEU neonates began with lower levels of anti-KSHV antibodies, exposing them to greater risk of KSHV infection. However, these differences dissipated quickly, with HEU and HUU infants having similar anti-KSHV antibody levels at 6 months of age. These results show the impact of maternal HIV infection on early childhood KSHV susceptibility. However, by two years of age, HUU were more likely to be KSHV seropositive. This may be due to a number of factors, including improved healthcare access for HIV-positive mothers and their children, and requires investigation.

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32: Optimized and Simultaneous DNA, RNA, and miRNA Isolation From Kaposi's Sarcoma Biopsies Frozen in RNAlater

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BACKGROUND:

Punch biopsies for Kaposi sarcoma (KS) present unique challenges for the extraction of nucleic acids (DNA, RNA, miRNA) due to the tissue composition of the biopsy, which may include epidermis, dermis, and hypodermis. In addition, if the punch biopsies have been stabilized in RNAlater for a long duration (e.g., 10 to 20 years), they can further develop a recalcitrant texture that impedes the thorough homogenization required for nucleic acids extraction using conventional methods. Herein, we developed a protocol that enables the simultaneous isolation of DNA, RNA, and miRNA from KS punch biopsies collected from people living with HIV (PLWH) and enrolled in the Antiretrovirals for Kaposi's Sarcoma (ARKS) study.

METHODS:

Samples were obtained through the AIDS and Cancer Specimen Resource (ACSR) and were stored at -80oC in RNAlater for 12 to 16 years. A series of mechanical and chemical tissue disruption steps were taken sequentially. First, if a KS biopsy weighed ≥10mg, it was divided in half and transferred to 1.5 mL tubes. Multiple tissue grinding steps were then performed using liquid nitrogen and followed by stainless-steel beads in a mechanical beater. The commercially available AllPrep DNA/RNA/miRNA Universal Kit was used for simultaneous nucleic acid extraction. Lysis was performed using a denaturing salt buffer with β-mercaptoethanol at a final concentration of 1%. Nucleic acid isolation was performed using a modified protocol of the QIAGEN AllPrep DNA/RNA/miRNA Universal Kit. Once extraction was completed, DNA and RNA quantification and purity analyses were performed using fluorescence and photometry. DNA and RNA integrity were assessed through electrophoresis (TapeStation and Bioanalyzer).

RESULTS:

A total of 137 samples were successfully processed. Nucleic acid yield is directly related to size, tissue composition, and weight of the biopsy (5.7 to 56.2 mg; average: 26.7 mg). Further optimization, in addition to tissue disruption, required combining the reagents from different kits and adding additional washing steps so that DNA and RNA yields improved considerably and consistently. The DNA average yield was 51260 ng, while the RNA average yield was 25714 ng. The DNA integrity number (DIN) averaged 6.03, while the RNA integrity number (RIN) averaged 8.4. Statistical analyses show that once the sample is properly stored in RNAlater, storage time has no significant effect on RNA or DNA yields and integrity.

CONCLUSIONS:

Techniques that allow for the simultaneous isolation of DNA, RNA, and miRNA from the same biological sample are especially relevant in the context of precious and unique tumor samples stored in biorepositories. In this context, the presence of more than one sample from the same patient or a large section that would allow for separate DNA and RNA isolation is rare. The protocol developed here provides optimized nucleic acid yields in a simultaneous isolation approach, increasing the number of molecular studies that can be performed on a single sample to accelerate the development of improved therapeutic treatments and preventive strategies against Kaposi's sarcoma. The workflow described here can be applied to other difficult-to-lyse tissues to maximize the yield and potential downstream applications.

Author(s): Aggrey Semeere[1], Helen Byakwaga[1], Miriam Laker[1], Esther Freeman[2], Naftali Busakhala[3,4], Megan Wenger[5], Charles Kasozi[6], Matthew Semakadde[6], Winnie Muyindike[7], Philippa Kadama-Makanga[1], Elyne Rotich[4], Edwin Sang[4], Samson Kiprono[4], and Jeffrey Martin[5]

33: Before or After: When Does KS Occur in Relation to ART Initiation in East Africa?

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BACKGROUND:

Even with nominal widespread availability of antiretroviral therapy (ART) in sub-Saharan Africa, Kaposi's sarcoma (KS) remains an important source of morbidity and mortality among HIV-infected patients. Reducing KS incidence will require understanding why patients continue to develop KS despite access to ART, beginning with understanding the contribution of two distinct scenarios—the fraction of KS that occurs *before* patients initiate ART versus the fraction that occurs *after* ART start.

METHODS:

We studied, via a rapid case ascertainment mechanism, consecutive HIV-infected adults (≥18 years) with newly diagnosed KS attending inpatient and outpatient facilities at one of three primary care networks in East Africa: AMPATH in western Kenya, Masaka Regional Referral Hospital in Uganda, and Mbarara Regional Referral Hospital in Uganda. All KS was biopsy confirmed except for allowance of lesions in locations deemed unsafe to biopsy. Participants were asked about the date they first recognized lesions that subsequently were found to be KS and, if relevant, date of first ART use; those with missing data were excluded. Date of the biopsy that documented KS was found in local biopsy services or pathology records.

RESULTS:

Between July 2016 and November 2021, we enrolled 431 patients diagnosed with new HIV-related KS and 388 fulfilled eligibility criteria (23 excluded for lack of lesion dating and 20 for lack of ART date). Participants were a median 35 years old (interquartile range (IQR): 30-41), and 71% were men. All KS was biopsy confirmed. Participants had a median of 6 body sites affected by KS (IQR:4-10), and 93% had T1 stage (advanced) KS. Median time between participant's first recognition of lesions and diagnosis was 6.5 months (IQR:3-12). Based on dates of participants' first recognition and ART use as well as biopsy date, 34% developed KS before ART start, and 40% developed KS at least 90 days after ART start. A further 8.0% first noted lesions and had their biopsy within 90 days of ART start, suggesting unmasking immune reconstitution inflammatory syndrome (IRIS) and true biologic occurrence of KS before ART. The remainder, 18%, had uncertain ascertainment because the participant's first lesion recognition was before ART and a median 228 days (IQR: 154-639) prior to the biopsy, which occurred after ART start. These long durations call into question the reliability of participant dating.

CONCLUSION:

In a community-based sample of HIV-infected patients recently diagnosed with KS in East Africa, research-level measurement allows for ascertainment of timing of KS onset in relation to ART initiation in most participants. However, because ascertainment is vitally dependent upon participants' initial recognition of lesions and subsequent recall, the process is inherently limited, and an important fraction cannot be classified. Nonetheless, there were sizeable fractions of participants who developed KS *before* starting ART and *after* starting ART, indicating that interventions on two fronts are needed to reduce KS incidence. Among those who developed KS after ART start, more work is needed regarding whether KS occurred despite ART-mediated suppression of HIV replication.

Timing of KS in relation to ART initiation	Masaka Uganda (n=106)	Mbarara Uganda (n=78)	AMPATH Kenya (n=204)	Overall (N=388) (95% CI)
% Developed KS before ART	26%	40%	36%	34% (30 to 39%)
% Developed KS after ART	49%	33%	38%	40% (35 to 45%)
% Uncertain: possible IRIS	16%	2.7%	4.9%	8.0% (5.2 to 10%)
% Uncertain: unreliable dates	9.0%	24%	21%	18% (15 to 22%)

Author(s): Olivia Poworzek, Melanie Klemond, Morgan Mroz, Khalil Qadri, and Neelam Sharma-Walia

34: Aquaporin 3: Gatekeeper of the Oxidative Stress in Kaposi's Sarcoma-Associated Virus (KSHV)-Associated Primary Effusion Lymphoma (PEL)

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BACKGROUND:

Primary effusion lymphoma (PEL) is a rare and aggressive tumor of hematopoietic and lymphoid tissues. Kaposi's sarcoma-associated herpesvirus (KSHV) infection is a risk factor for PEL development and is found predominantly in late-stage AIDS patients. PEL has a poor prognosis, and there is a critical need for antiviral drugs targeting KSHV with fewer adverse effects. Aquaporins (AQPs), integral membrane proteins, also known as water channel proteins, facilitate the uptake of hydrogen peroxide (H_2O_2)-reactive oxygen species (ROS) into cells, thus mediating the downstream intracellular signaling involved in cancer cells. In addition, ROS-mediated oxidative stress has been established to regulate KSHV lytic cycle reactivation in latently infected PEL cells. Here, we evaluated if AQPs, specifically AQP3, play a role in ROS transmission and control oxidative stress and KSHV-infected PEL cell survival.

METHODS:

We used quantitative real-time polymerase chain reaction (qRT-PCR), Western blot analysis, immunoprecipitation, siRNA transfection, oxidative stress gene array, and ROS/peroxidase measurement assays in this study.

RESULTS:

Here, we screened for all AQPs within KSHV+ and KSHV- cells; results demonstrated an increased gene expression of AQP3 in KSHV-infected cells. Western blot findings revealed an increased protein level of AQP3. Silencing or inhibiting AQP3 resulted in a significant decrease in ROS and latency gene expression in KSHV-infected PEL cells. Interestingly, we observed increased expression of antioxidant enzymes in the AQP3-silenced KSHV-infected PEL cells.

CONCLUSIONS:

Our study establishes a critical role for AQP3-mediated ROS and oxidative stress in regulating the KSHV lifecycle and PEL cell death. Further understanding the role of AQP3 as a gatekeeper to ROS in KS and PEL in vivo models will elucidate its therapeutic potential.

Author(s): Rhea Singh[1,2*], Linda Chemtai[3*], Aggrey Semeere[4], Sigrid Collier[5], Helen Byakwaga[4], Devon McMahon[1], Miriam Laker-Oketta[4], Celestine Lagat[3], Alexis Strahan[1], Merridy Grant[6], Lisa Butler[7], Ingrid Bassett[1], Samson Kiprono[8,4], Toby Maurer[9], Jeffrey Martin[10], Naftali Busakhala[11,4], and Esther Freeman[1]
*Both authors contributed equally to this work.

35: Participant-Identified Interventions for Diagnosis and Treatment of People Living With HIV-Associated Kaposi's Sarcoma in Western Kenya: A Qualitative Analysis

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BACKGROUND:

Kaposi sarcoma (KS) is one of the most common HIV-associated malignancies in sub-Saharan Africa. Most patients with HIV-related KS continue to be diagnosed at advanced stages of disease, and chemotherapy initiation and adherence remain sub-optimal. To improve KS outcomes in this setting, it is essential to create context-specific interventions targeting early diagnosis, chemotherapy initiation, and adherence.

METHODS:

Semi-structured interviews were conducted from a purposive sample of adults newly diagnosed with HIV-associated KS in Western Kenya. The Behavior Change Wheel (BCW), a commonly adapted tool for understanding necessary interventions from the patient's perspective, was used to develop the overarching a priori themes, while allowing for inductive themes to emerge per the framework analysis method.

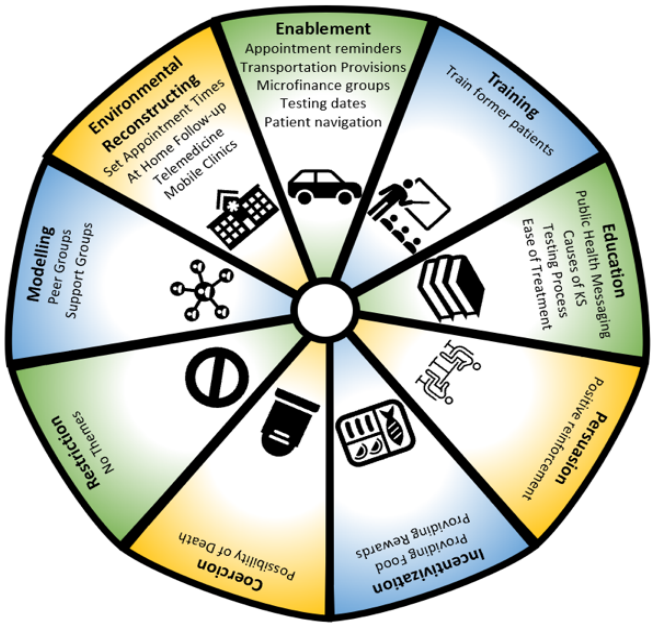
RESULTS:

Common themes were mapped using the BCW nine intervention function categories: education, persuasion, incentivization, coercion, training, restrictions, enablement, modelling, and environmental reconstruction. Common proposed interventions included increased information on steps to HIV/KS diagnosis and more readily available HIV testing (education). Across most interviews, participants noted appointment reminders, transportation provisions, and microfinance groups would be helpful initiatives (enablement). Peer support and support groups were well received as interventions to encourage patients by modelling positive behaviors (modelling). Lastly, many patients requested at-home or telemedicine appointments for non-chemotherapy visits due to transportation and travel cost for appointments (environmental reconstruction).

CONCLUSIONS:

Participant-identified interventions to improve KS diagnosis and treatment in people living with HIV, when analyzed in the context of the BCW, provide valuable insights with respect to development of appropriate and acceptable interventions. Future interventions could include increased use of peer navigators, appointment reminder systems, transportation supplements, and consideration of telemedicine or off-site appointments.

Figure 1: *Prominent Intervention Themes Mapped onto the Nine BCW Intervention Functions*



Author(s): Andrea M.H. Towlerton[1,2], Shashidhar Ravishankar[1], David G. Coffey[1,3], Peter Mooka[2], James Kafeero[2], Vésteinn Thorsson[4], Warren T. Phipps[1,2,3], and Edus H. Warren[1,3]

36: Serial Profiling of Tumor-Infiltrating T-Cells in Kaposi Sarcoma

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BACKGROUND:

Kaposi sarcoma (KS) tumors contain abundant T- and B-lymphocytes, but the influence of tumor-infiltrating lymphocytes on the natural history of KS is undefined. We performed serial T-cell receptor (TCR) repertoire analysis and single-cell transcriptional profiling of T-cells in tumors and blood from HIV$^+$ and HIV$^-$ adults with KS to explore their significance in epidemic and endemic KS.

METHODS:

Serial blood samples, tumor biopsies, and a biopsy of normal skin were obtained at multiple time points over one year from 82 HIV$^+$ and 26 HIV$^-$ adults with KS presenting to the Uganda Cancer Institute for treatment. TCR repertoire analysis of 576 tumor, normal skin, and blood samples, and single-cell RNA sequencing of T-cells from 48 tumor and blood samples, was performed.

RESULTS:

T-cells infiltrating KS tumors are highly oligoclonal, suggesting selective migration into or proliferation within the tumor microenvironment, and twice as clonal in epidemic than in endemic KS. TCR repertoire analysis strongly suggests the existence of a public KS-specific T-cell response in KS tumors that persists over both space and time. Dominant T-cell clones in KS tumors are often expanded in the peripheral blood. In both epidemic and endemic KS, expanded clones detected in tumor and blood display transcriptional profiles of cytotoxic CD4$^+$ T-cells and terminal effector memory CD8$^+$ T-cells. The transcriptional profile of many expanded T-cell clones drifts in a consistent manner over the 1-year course of treatment and observation. CD8$^+$ T-cells with specificity for HIV-encoded peptides are frequently detected in epidemic but not endemic KS tumors.

CONCLUSIONS:

TCR repertoire analysis and single-cell transcriptional profiling of T-cells infiltrating epidemic and endemic KS tumors support the existence of a potentially KS-reactive immune response that could potentially be manipulated for therapeutic benefit.

Author(s): Yiquan Wu, Victoria Wang, and Robert Yarchoan

37: Pacritinib Suppresses Kaposi Sarcoma-Associated Virus (KSHV) Viral Genes and Induces Apoptosis in Primary Effusion Lymphoma Cells

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BACKGROUND:

The IL-6/JAK/STAT3 pathway is hyperactive in primary effusion lymphoma (PEL) and KSHV-associated multicentric Castleman's disease (MCD). It has been shown that inhibition of STAT3-induced apoptosis in PEL cells (Aoki Y. et al., Blood, 2003 101:1535). STAT3 is downstream of JAK signaling, and we hypothesized that JAK inhibitors may have activity in PEL. With this background, we tested the effects of five JAK inhibitors (ruxolitinib, AZD1480, baricitinib, peficitinib, and pacritinib), on different PEL cells lines.

METHODS:

Inhibitors were purchased from various commercial sources; pacritinib was also provided by CTI BioPharma. PEL cell lines (JSC-1 and BCBL-1) were treated with inhibitors. The viability of the treated cells was assessed using the CellTiter-Glo® Luminescent Cell Viability Assay and flow cytometry. To assess the global change of cellular mRNA expression in response to pacritinib treatment, mRNA sequencing was applied. Potential key targets were knocked down using shRNA. Real-time PCR was utilized to further confirm the mRNA expression data from sequencing. The Human Phospho-Kinase Antibody Array was used to measure the changes of cellular kinase activation in response to pacritinib treatment.

RESULTS:

Among the tested JAK inhibitors, pacritinib, a novel JAK2 inhibitor that also targets multiple kinases including FLT3 and IRAK1, exhibited the strongest inhibitory effect. As shown by flow cytometry and trypan blue counting, 1 μM pacritinib efficiently inhibited cell growth and induced apoptosis of PEL cell lines. Several cellular kinases, including STAT3, were inhibited, as revealed by the kinase profile array. Studies using inhibitors of other kinases targeted by pacritinib suggested that FLT3, which is involved in B cell development, may be a key target for pacritinib's growth inhibition of PEL. Decreased expression of KSHV viral genes, including RTA and LANA, by pacritinib were also observed by both RNA-Seq and qPCR. Expression of several host genes, including several cyclins, and interleukin 6 (IL6) were also downregulated. Finally, pacritinib suppressed KSHV viral-IL6(vIL6)-induced IL6 production by peripheral blood mononuclear cells.

CONCLUSIONS:

Pacritinib inhibited cell growth and induced cell apoptosis; this effect appeared to be at least in part through its inhibition of the FLT3 pathway. The downregulation of KSHV viral genes and human genes, including IL6, may be attributed in part to the blocking of the JAK2/STAT3 pathway by pacritinib; the downregulation of vIL6-induced IL6 production may result from inhibition of JAK2 plus IRAK1.These results suggest that pacritinib is worth testing for the treatment of PEL and/or KSHV-MCD.

This research was supported by the Intramural Research Program of the National Cancer Institute (NCI); some pacritinib was provided by CTI BioPharma under a Cooperative Research and Development Agreement with NCI.

Author(s): Sydney J. Bennett[1,2], Dicle Yalcin[2], Sara R. Privatt[1,2], Owen Ngalamika[3], Salum J. Lidenge[4,5], John T. West[2], and Charles Wood[1,2]

38: Phage Display Epitope Profiling of KSHV LANA Revealed Differential Recognition of a Dominant C-Terminal Epitope Between KS Patients and Controls

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BACKGROUND:

The incidence of Kaposi sarcoma (KS) parallels the prevalence of Kaposi sarcoma-associated herpesvirus (KSHV) infection, particularly in sub-Saharan Africa, Peru, and the Mediterranean. KSHV infection typically occurs during childhood and enters latency typified by the expression of latency-associated nuclear antigen (LANA). The humoral antibody response in infected individuals has been characterized, demonstrating LANA to be the most antigenic protein. Despite its antigenicity, specific LANA epitopes have not been systematically profiled.

METHODS:

In the current work, a bacteriophage T7 library displaying 56-amino acid KSHV LANA peptides with 28-amino acid overlap (VirScan) was utilized to define epitopes in LANA targeted by sera derived from a cohort of 62 sub-Saharan African KS patients and 22 KSHV-infected asymptomatic controls (Asy). Intra- and inter-patient breadth and magnitude of the anti-LANA responses were measured at the peptide and amino acid levels. Based on these data, a detailed epitope map of LANA was derived, with a high-resolution focus on the N- and C-termini.

RESULTS:

Overall, the central repeat region showed high antigenicity, but the responses to this region could not be confidently mapped due to intrinsic sequence variability. The conserved N-terminus was targeted with low breadth and magnitude. Nevertheless, in a minority of individuals, antibodies specific to the nuclear localization sequence and a portion of the proline-rich regions of the N-terminus were evident. In contrast, the first half of the highly conserved C-terminal domain was consistently targeted with high magnitude in both KS and Asy groups. A 24-amino acid epitope derived from the first half of the C-terminus was found to be highly antigenic in both groups, where HIV status did not impinge on the extent of recognition. Although this epitope was not included in crystal structures of the LANA partial C-terminus, it was predicted to adopt a random-coil structure.

CONCLUSIONS:

Coupled with functional and predicted secondary structure domain annotations, VirScan revealed fine-resolution epitope mapping of the N- and C-terminal domains of LANA that is consistent with previous seroepidemiological studies. Further investigation is warranted to determine whether the identified epitope has therapeutic, diagnostic, or viral decoy potential. VirScan is now being applied to the entire KSHV proteome, the findings of which are anticipated to inform KSHV vaccine design, prognostic modeling, and therapeutic development.

Author(s): Dawei Zhou[1], Tai-Wei Li[1], Guillaume Fiches[1], Zhenyu Wu[1], Youngmin Park[1], Yinchong Wang[1], Jun Qi[2], Netty Santoso[1], and Jian Zhu[1]

39: Role of Histone Lysine Demethylases (KDMs) in Promoting KSHV Persistent Infection

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BACKGROUND:

Histone methylation is one of the critical epigenetic events regulating KSHV infection, which is under active investigation. Several KDMs have been recently identified contributing to epigenetic regulation of KSHV infection through interaction with viral factors. However, most of these reported KDMs demethylate the histone inactive marks (H3K27, H3K9) and possess gene transactivation activities. KDM5 paralogs (A-D) belong to the Jumonji domain-containing histone demethylases. KDM5 demethylases are capable of removing tri- and di-methylations of lysine 4 of histone H3 (H3K4me3, me2) that usually peak at the promoter regions of actively transcribed genes, and they generally play a role in gene suppression. KDM5A/B play a role in controlling cell proliferation and differentiation. There is clear evidence that KDM5A/B are oncogenes overexpressed, amplified, or mutated in multiple types of human cancers. KDM5-specific inhibitors have been actively developed, and some already showed promising therapeutic potential for treating certain types of cancers. Our recent study of KSHV epigenetic regulation identified that KDM5 histone demethylases are subjected to KSHV regulation and in return control its infection.

METHODS:

We determined the impact of KSHV lytic reactivation on KDM5A/B expression by measuring their mRNA (RT-qPCR) and protein (immunofluorescence assay [IFA]) levels. We also employed an RNAi approach to determine the impact of KDM5A/B knockdown on KSHV lytic reactivation rate by quantifying KSHV lytic gene transcription (RT-qPCR) and protein (immunoblotting). To gain molecular insight on how KDM5A/B regulates KSHV viral gene expression, we determined the protein-protein interaction of KDM5A/B with KSHV LANA by protein co-immunoprecipitation (co-IP). The dynamic association of KDM5A/B with KSHV lytic and latent promoters was measured by chromatin immunoprecipitation (ChIP) coupled RT-qPCR. JQKD82 is a highly potent, KDM5-selective inhibitor that has demonstrated antitumor activity in a mouse model of multiple myeloma developed by the group of Dr. Jun Qi, a medicinal chemist who has collaborated with our group for a long time. We preliminarily tested JQKD82's effect on reversing KSHV latency and triggering the death of KSHV-infected tumor cells by measuring cell proliferation and viability.

RESULTS:

The main findings from our current studies include: (i) KSHV lytic reactivation led to the elevation of KDM5A/B protein level; (ii) KDM5A/B depletion induced KSHV lytic reactivation; (iii) KDM5A/B protein interacted with KSHV LANA and dynamically associated with KSHV lytic and latent promoters; (iv) JQKD82 showed the promising effect to induce KSHV lytic reactivation in KSHV-positive PEL cells and also promote their cell death.

CONCLUSION:

KDMA/B are newly identified host epigenetic regulators that control KSHV infection through regulation of H3K4 methylation. Meanwhile, KSHV also induces KDM5A/B protein expression to promote its persistent infection and tumorigenesis. KDM5A/B can serve as promising host gene targets for treating KSHV-associated tumors as their specific KDM inhibitors (KDMis) have the potential to induce a viral oncolytic effect promoting the "killing" of KSHV-infected tumor cells.

Author(s): Derrick Bary Abila[1,2], Elizabeth Nakiyingi Kiyingi[1], Provia Ainembabazi[2,3], Racheal Nalunkuma[1], Ruth Ketty Kisuza[1], Chemutai Beliza[1], Eddy Kyagulanyi[1], Boaz Mwesigwa[4], Sulaiman B. Wasukira[3,5], Henry Wabinga[1], and Nixon Niyonzima[6]

40: Socioeconomic Inequalities in the Coverage of Cervical Cancer Screening Among Women Living With HIV in Five Low- and Middle-Income Countries

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BACKGROUND:

Women living with HIV (WLWHIV) are at a high risk of developing cervical cancer, and the World Health Organization (WHO) recommends that they are screened from the age of 25 years. We aimed to describe the socioeconomic inequalities in the coverage of cervical cancer screening among WLWHIV in LMICs.

METHODS:

We conducted a weighted secondary data analysis of the Demographic and Health Surveys (DHS) completed in Cameroon, Ivory Coast, Lesotho, Namibia, and Zimbabwe. These were the only countries that tested women for HIV and had questions on cervical cancer screening in DHS between 2010 and 2019. Our analysis included WLWHIV aged 25 to 49 years. Absolute and relative socioeconomic inequalities were calculated using the Slope Index of Inequality and Concentration Index, respectively, by wealth quintile.

RESULTS:

A total of 2,950 WLWHIV were included in this study. The proportion of women who had ever been screened for cervical cancer was highest in Namibia (35.7%) and lowest in Ivory Coast (1.8%.) The pooled estimate of the coverage of cervical cancer screening was 16.5% [95% confidence interval (CI): 6.1–27.0]. In all the countries, higher proportions of WLWHIV in the richest wealth quintile were screened compared to those in the poorest wealth quintile. In all the countries, higher proportions of WLWHIV in the urban areas were screened compared to those in the rural areas.

CONCLUSIONS:

There exist pro-rich and pro-urban inequalities in the utilization of cervical cancer screening. Cervical cancer screening programs in LMICs need to innovate solutions aimed at reducing the inequalities to accessing cervical cancer screening by WLWHIV.

Author(s): Sigrid Collier[1,2], Aggrey Semeere[3], Helen Byakwaga[3], Miriam Laker-Oketta[3], Linda Chemtai[4], Celestine Lagat[4], Chinmay Yalameli[1], Toby Maurer[5], Ingrid Bassett[6], Samson Kiprono[4], Jeffrey Martin[7], Naftali Busakhala[4]*, Esther Freeman[6]*
*Both authors contributed equally to this work.

41: Characterizing Stigma-Based Clusters of People with HIV-Associated Kaposi's Sarcoma in East Africa

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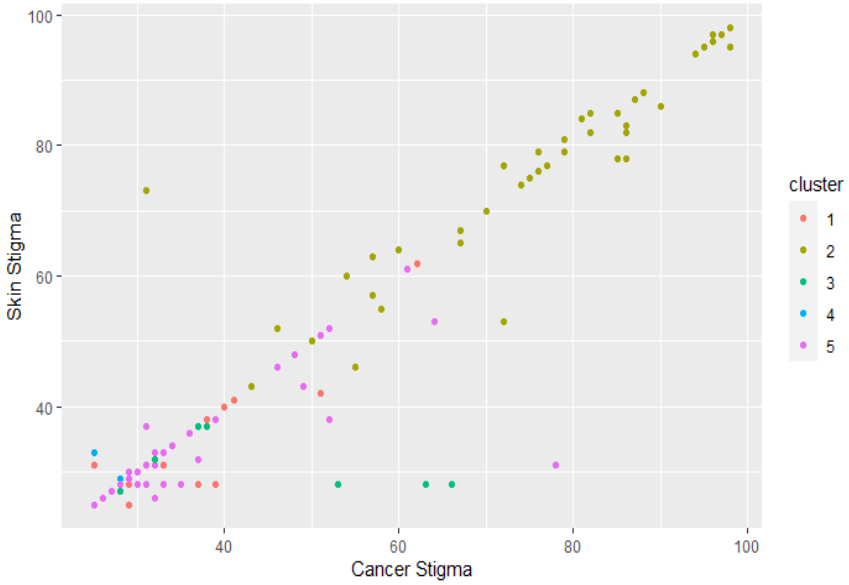
BACKGROUND:

Patients with HIV-associated Kaposi's sarcoma (KS) may simultaneously experience stigma from three origins—HIV infection, cancer, and visible skin lesions. It is not known to what extent these three forms of stigma vary between KS patients and whether KS patients sort into distinct sub-groups ("clusters") based on their stigma perceptions.

Figure 1: Association of Cancer Stigma and Skin Stigma by Cluster



METHODS:

Participants in a longitudinal cohort study using a community-based rapid case ascertainment approach to identify newly diagnosed adults (>18 years of age) with HIV-associated KS were asked to complete three questionnaires adapted from the Berger HIV Stigma Scale to assess cancer, HIV, and skin disease stigma. Cluster analysis is a technique for sorting individuals into groups based on a set of characteristics such that individuals within a group are more similar to each other than individuals in other groups. We analyzed for stigma-based clustering using a Partitioning Around Medoids algorithm to perform an unsupervised machine learning based on age, sex, CD4+ T-cell count, ACTG stage at the time of KS diagnosis, death at the end of the study period (224 weeks), time from diagnosis to the stigma measure, cancer, HIV, and skin disease stigma scores.

RESULTS:

We included a total of 307 measurements of stigma from 92 participants in this analysis. The participants' median age was 37 years (IQR 33, 41), median CD4+ T-cell count was 320 (IQR 200, 481), and 91.2% (52/92) had ACTG stage T1 disease at the time of diagnosis. We identified k=5 clusters (Figure 1). Cluster 1 on average had higher stigma scores for cancer (median: 79, IQR: 70, 86), HIV (median: 76, IQR: 59, 86), and skin disease (median: 79, IQR 80, 85). Cluster 1 also tended to have stigma scores measured closer to the time of diagnosis (mean: 57.5 weeks, SD: 36.3). Cluster 2 included only female participants, while cluster 3 included male participants. Cluster 4 included only ACTG Stage T0 and cluster 5 included only ACTG Stage T1. Clusters 2, 3, 4, and 5 had lower stigma scores (Figure 1).

CONCLUSIONS:

Among patients with HIV-associated KS in East Africa, we identified five distinct clusters based on stigmatization and other key factors. This suggests that there may be distinct phenotypes within HIV-associated Kaposi's sarcoma and their complex experience with stigma. Clusters with high levels of stigmatization may represent especially vulnerable subsets of KS patients who would benefit from future targeted interventions. Future research should focus on understanding whether healthcare engagement, delays in diagnosis and receiving chemotherapy, and mortality vary between stigma-based clusters.

Author(s): Sigrid Collier[1]*, Aggrey Semeere[2]*, Helen Byakwaga[2], Miriam Laker-Oketta[2], Linda Chemtai[3], Celestine Lagat[3], Toby Maurer[4], Ingrid Bassett[5], Jeffrey Martin[6], Samson Kiprono[3], and Esther Freeman[5]
*Both authors contributed equally to this work.

42: Early Engagement with Patient Navigation for HIV-Associated Kaposi's Sarcoma in East Africa

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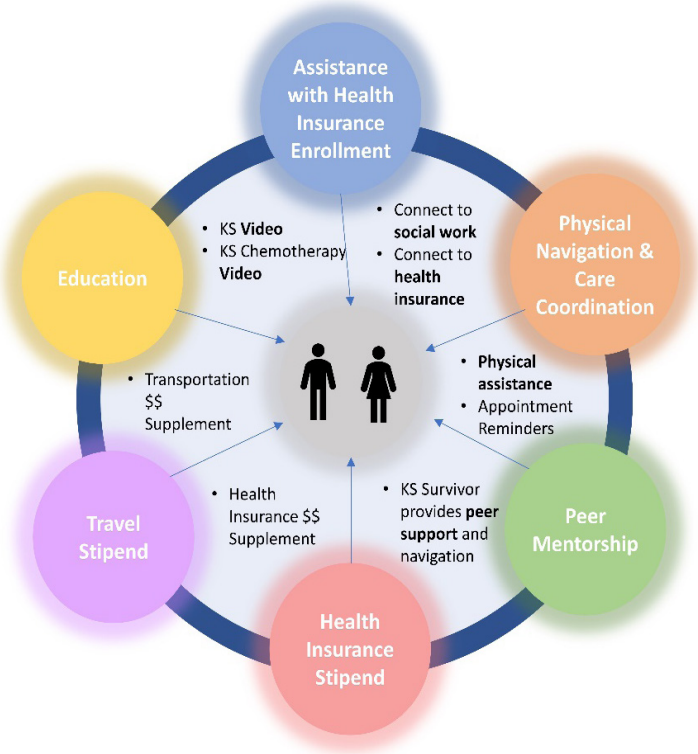
Kaposi's Sarcoma (KS) is commonly diagnosed at advanced stages of disease, when chemotherapy is warranted in addition to ART. However, only 50% of KS patients who qualify for chemotherapy receive it and adherence is sub-optimal. To improve KS outcomes, we urgently need context-sensitive, tailored interventions targeting treatment initiation and adherence. Patient navigation is a strategy to promote timely access to diagnosis and treatment of cancer and other chronic diseases. Patient navigators help address barriers to care, educate people on their health condition, and regularly contact people about their treatment status. In other contexts, navigation has improved various outcomes across the HIV and cancer continuums.

Figure 1: Multicomponent Navigation Strategy for KS Treatment Adherence



METHODS:

We used the Intervention Mapping framework to identify theory- and evidence-based interventions targeting key barriers and facilitators to chemotherapy identified during in-depth interviews with KS patients. The final six primary components of the multicomponent strategy are outlined in Figure 1. In collaboration with dermatology and oncology physicians, clinical officers, and nurses, the Kaposi's Sarcoma Center of Excellence (KCE) at The Academic Model Providing Access to Healthcare (AMPATH) had fully implemented this multicomponent navigation strategy by July 2021. Patients with KS who meet criteria for chemotherapy (based on any of the following: local guidelines, ACTG T1 disease, or WHO criteria for moderate to severe KS) are invited to participate in the program. A multi-level evaluation focused on implementation and effectiveness began in October of 2021 and is ongoing.

RESULTS:

A total of 67 patients with newly diagnosed KS who had indications for chemotherapy were approached to enroll in the navigation program, and 63 (94%) agreed to participate. A total of 403 encounters with a patient navigator and 282 encounters with a peer navigator have been documented Navigators assisted participants with locating clinics, health insurance enrollment, and reminders about clinic visits. Peer mentors shared their experiences with chemotherapy, and educational videos about KS and KS treatment.

CONCLUSIONS:

In a prototypic medical center in East Africa, the majority of eligible patients with advanced-stage KS have engaged with a context-specific, multi-component navigation strategy developed for patients with KS. Early success with high levels of engagement gives hope for future effectiveness of this navigation strategy.

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43: Barriers and Facilitators of High-Resolution Anoscopy Among People Living With HIV (PLWH): A Cross-Sectional Study in Puerto Rico

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BACKGROUND:

Currently, there are no official anal cancer screening guidelines; however, experts recommend anal pap as the primary screening tool in settings where high-resolution anoscopy (HRA) is available. While HRA with biopsy is the gold-standard procedure for the diagnosis of high-grade squamous intraepithelial lesions (HSIL) and anal cancer, information on its uptake is limited. This study aims to assess barriers and facilitators for HRA uptake in a sample of Hispanic People Living with HIV/AIDS (PLWH) in Puerto Rico.

METHODS:

A cross-sectional study was conducted in Puerto Rico among PLWH from 2020–2021. Through a telephone interview, participants (n=212) answered questions regarding sociodemographics, knowledge and attitudes about anal cancer, and history of anal cancer screening. Participants were excluded if they had missing information on HRA awareness and HRA uptake, for a final sample size of 202 PLWH. Chi-square test, Fisher exact test, and logistic regression models were used to assess factors associated to HRA uptake.

RESULTS:

The majority of individuals in the study were 50 years of age or older (67.3%) with a median age of 54 (IQR, 46-58). Individuals self-identified as either men (66.8%), women (32.2%), or transgender (1.0%). Almost half of participants (43.8%) identified as men who have sex with men (MSM). The majority of participants reported having an annual income of less than $15,000 (66.7%). HRA awareness and uptake were 30.7% and 19.3%, respectively. Among those who had not undergone HRA, lack of knowledge about HRA (63.8%), lack of physician recommendation (62.6%), and lack of awareness of HRA (60.5%) were the most common barriers. The most common facilitators among those who had undergone the procedure were doctor recommendation (84.6%), to stay healthy (76.9%), and to prevent anal cancer (53.9%). Adjusted multivariate logistic regression models showed that MSM were more likely to have heard of HRA (OR=2.53, 95% CI: 2.53 1.02–6.27) when compared to the other sexual risk groups. Adjusted multivariate regression models also showed that participants who expressed being worried about developing anal cancer (OR=5.06, 95% CI: 1.10–22.06) and those who knew where to go for concerns about their anal health (OR=7.18, 95% CI: 2.09–24.64) were more likely to have undergone HRA than those who did not.

CONCLUSIONS:

Concerns about anal health and knowledge of where to go with concerns about their anal health were positive predictors of HRA uptake. Health care providers for PLWH have the opportunity to increase knowledge and awareness about HRA, thus decreasing existing barriers. Official anal cancer screening guidelines are needed for provider recommendation for HRA. As the ANCHOR study has recently shown that treating HSIL prevents anal cancer, understanding of barriers and facilitators to screening and diagnosis of HSIL has become of great importance.

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44: Delays in Cervical Cancer Treatment Initiation for Patients Living With or Without HIV in Botswana 2013–2019

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BACKGROUND:

Our objective is to present delays in treatment initiation of curative intent chemoradiation (CRT) for patients with advanced and locally advanced stage cervical cancer (CC) and living with or without human immunodeficiency virus (HIV).

METHODS:

Between 2013–2019, women in Botswana with locally advanced CC (stages IB2-IVB), living with or without HIV, were prospectively enrolled in an observational cohort study. Delay was primarily defined as 90 or greater days between the date of pathology review and the date of initiation of CRT. Associations between delays in CC treatment initiation and 24-month survival from treatment initiation were evaluated via logistic regression modeling.

RESULTS:

Among the 111 curative patients with locally advanced CC disease, 71 (64%) were women living with HIV (WLWH) with a median CD4 count at cancer diagnosis of 364.6 cells/μL (IQR, 166.5-602 cells/μL) and 43 (60.6%) with viral load <400 cells/μL. Median age of the entire cohort was 46 years. At the end of treatment, most patients had CC stage II (53.2%) and III (28.8%) disease. Slightly less than half (43.2%) of patients experienced delays in CC treatment initiation ≥90 days. On univariable analysis, patients were less likely to experience delays in CC treatment initiation ≥90 days for: stages III-IV disease (OR 0.60, p=0.001) vs. stages I-II disease, and year of diagnosis 2018–2019 (OR 0.69, p=0.036) vs. before 2016. Patients were more likely to experience delays in CC treatment initiation ≥90 days for: 100-500 km (OR 1.44, p=0.017) and 500 km (OR 2.04, p=0.008) vs. <100 km from the treatment clinic. Only stage remained significant in multivariable analysis when adjusting for age, distance from the treatment clinic, HIV status, stage, and year of diagnosis. For survival, univariable analysis indicated that patients were significantly less likely to survive 24 months if they experienced delays in treatment initiation ≥90 days (OR 0.43, p=0.032) and were more likely to survive 24 months with total radiation dose EQD2 ≥75 Gy (OR 2.61, p=0.042) vs. <75 Gy. On multivariable analysis adjusting for age, HIV status, stage, EQD2, chemotherapy cycles received, and delay, patients were significantly less likely to survive 24 months if they experienced delays in treatment initiation ≥90 days (OR 0.31, p=0.031).

CONCLUSIONS:

Our results indicate that delays in care for patients with CC in Botswana are common, particularly for those living farther away from the centralized treatment clinic, and are less common for those with advanced stages of CC disease. Furthermore, our paper is the first to show an association between delays and decreased survival at 24 months. Future interventions should aim to reduce delays in treatment initiation by focusing on patients who live farther away from the treatment clinic and initiating timely treatment for stage I and II CC disease.

Author(s): Jessica George[1], Shawna Tuli[1], Barati Monare[2], Lisa Bazzett-Matabele[3,4], Peter Vuylsteke[5,6], Katharine A. Rendle[7], and Surbhi Grover[2,8]

45: Patterns of Survivorship Care of Cervical Cancer Patients With or Without HIV Infection In Botswana 2015–2022

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BACKGROUND:

Our objective is to present patterns of survivorship care of cervical cancer (CC) patients treated with radiation therapy (RT) in Botswana with or without human immunodeficiency virus (HIV), and to prospectively evaluate factors associated with retention in survivorship care in this population.

METHODS:

Between 2015–2022, women in Botswana with CC (stages IA-IVB), with or without HIV, were prospectively enrolled in an observational cohort study and treated with RT. The Botswana national cervical cancer guidelines recommend survivorship care every 6 months for the first 2 years and annually for the subsequent 3 years following the end of treatment (EOT). Factors associated with retention in survivorship care were analyzed using logistic regression.

RESULTS:

Of the 1,405 CC patients, 964 (68.6%) were treated with RT. Of those, 852/964 (88.4%) completed treatment before 1/1/22 and should have at least 1 follow-up visit by the time of analysis for the first 2 years. The median age was 48 years (IQR 41.6-59.6) and 566 (66.4%) were women living with HIV (WLWH). Among WLWH, the median CD4 count at the time of cancer diagnosis was 443 cells/μL (IQR 280-653), 6.2% had a detectable viral load, and 95.1% were on antiretroviral treatment. In regard to treatment in the cohort, 39.7% (n=338) received RT alone and 55.3% (n=471) received chemoradiation. Stage distribution at the EOT was: I 9.9% (n=84), II 36.3% (n=309), III 31% (n=264), and IV 17.7% (n=151). For the first 2 years of survivorship care, 627/852 (73.6%) attended at least 1 follow-up via office visit or phone call, and 201/852 (23.6%) followed up every 6 months for the first 2 years. For the subsequent 3 years of survivorship care, 722/964 (74.9%) completed treatment before 1/1/20 and should have at least 1 follow-up visit by the time of analysis. Of those, 362/722 (50.1%) attended at least 1 follow-up via office visit or phone call, and 101/722 (14%) followed up every year for the subsequent 3 years. On multivariable analysis adjusting for age, HIV status, disease stage, and treatment type, patients were less likely to follow up every 6 months for the first 2 years at disease stages III-IV (OR 0.5, p=0.008) vs. I-II and with definitive treatment type (OR 0.6, p=0.04) and palliative treatment type (OR 0.2, p=0.01) vs. curative treatment type.

CONCLUSIONS:

Our results indicate that the majority of patients with CC in Botswana are not adhering to the recommended survivorship care plan, especially those with advanced stage disease. Future interventions should aim to improve patient adherence for all CC patients.

Author(s): Surbhi Grover[1,2], Luis Cocka[3], Emily MacDuffie[1], Xiang Lin[4], Memory Bvochora-Nsingo[5], Sebathu Chiyapo[6], Dawn Balang[6], Nicola Zetola[1,7], Doreen Ramogolo-Masiere[8,9], Zhi Wei[3], Hao Shen[2], and Erle Robertson[10]
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46: Peripheral Immune Profiles of Cervical Cancer Patients With and Without HIV Infection Undergoing Chemoradiation in Botswana

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BACKGROUND:

Cervical cancer (CC) poses a significant disease burden in low- and middle-income countries (LMICs), particularly in countries with high HIV prevalence, despite uptake of antiretroviral therapy (ART). The immune profiles of patients undergoing CC treatment and the difference due to HIV status in the ART era have not been extensively investigated.

METHODS:

CC patients with and without HIV infection undergoing chemoradiation (CRT) with curative intent were enrolled in Botswana. Blood samples were collected at three time points: treatment initiation (initial), end of treatment (EOT), and three months after treatment completion (M3). Peripheral mononuclear cell (PBMC) samples and cytokines from these time points were analyzed with multi-parameter flow cytometry.

RESULTS:

Peripheral blood from 131 women (HIV+ N=89, HIV- N=42) was analyzed. Women living with HIV (WLWH) presented with a median baseline CD4 count of 454 cells/μL. Two-year overall survival (OS) was 78% (95% confidence interval [CI] 70%-84%) for the cohort, 78% (95% CI 69%-85%) for women with HIV, and 77% (95% CI 63%-86%) for those without HIV (p=0.865). Flow cytometry performed on PBMCs revealed that WLWH had significantly lower peripheral CD4 frequency at the initial visit than women without HIV (52.5% vs. 72.0%, p<0.001). No significant changes in CD4 frequency (52.5% to 50.9%) or CD8 frequency (39.9% to 41.4%) were observed in WLWH. A significant decrease in CD4 frequency (72% to 60.55%, p<0.001) and an increase in CD8 frequency (20.9% to 31.5%, p<0.001) was seen in women without HIV by M3. Women underwent similar T cell activation over the course of CRT marked by loss of CCR7, increased CD57, and increased IFN***γ*** expression regardless of HIV status. On multivariate analyses, improved survival was associated with a higher frequency of cytokine (IL-2 and IFN***γ***)-expressing CD4 T cells in WLWH. Poorer survival was associated with reduced expression of IL-2 by CD4 T cells and the presence of proinflammatory CD8 T cells starting at EOT and magnified at M3.

CONCLUSIONS:

In CC patients undergoing CRT, WLWH demonstrated relative stability of CD4 and CD8 T cell frequency throughout treatment; however, women without HIV had a significant loss of peripheral CD4 frequency and CD4/CD8 T cell ratios throughout the course of treatment. CD8 and CD4 T cell subsets, overall, had similar changes in activated phenotypes (loss of CCR7-, increase in CD57, and decrease in naïve repertoires) regardless of HIV status. Improved OS was associated with increased IL-2-expressing T cells. Overall, immune profiles of WLWH were less variable than those in women without HIV on CRT, although both groups demonstrated global T cell activation while on treatment regardless of HIV status. These findings may suggest that HIV infection, even if well managed on antiretrovirals, may still differentially impact immune response to CRT.

Author(s): Simon Boni[1,2], Vanessa Tenet[3], Apollinaire Horo[4], Aristophane Tanon[5], Judith Didi-Kouko-CouLibaly[6], Boris Tchounga[7], Innocent Adoubi[2,8], Clifford Gary[3], Antoine Jaquet[9], on behalf of The IeDEA West Africa Collaboration

47: High-Risk Human Papillomavirus (HPV) Distribution According to HIV Status Among Women With Invasive Cervical Cancer in Abidjan, Côte d'Ivoire, 2018–2020

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BACKGROUND:

High-risk human papillomavirus (HR-HPV) is the causative agent of Invasive Cervical Cancer (ICC). While developing countries are implementing screening and immunization programs mainly targeting HR-HPV 16/18, we aimed at investigating whether co-infection with HIV plays a role in HR-HPV genotype distribution in Côte d'Ivoire.

METHODS:

From July 2018 to June 2020, cervical biopsy samples were prospectively and consecutively collected from women with suspected ICC attending the five major cancer facilities of Abidjan, Côte d'Ivoire. Paraffin-embedded cervical specimens from confirmed histopathological diagnosis of ICC from national histopathology labs were collected and sent to the International Agency for Research on Cancer (IARC) for additional histopathological reading and HR-HPV genotyping. These samples underwent HPV DNA testing using the Luminex genotyping kit HPV and a clinically validated GP5+/6+ Polymerase Chain Reaction (PCR) for the detection of the 14 targeted HR-HPV genotypes. HIV status was documented using the national algorithm. Distribution of HR-HPV was compared according to HIV status. Comparisons were made using Chi-square test or exact test when appropriate. A p-value ≤0.05 was considered for statistical significance.

RESULTS:

A total of 170 confirmed ICC cases with a median age of 52 (Interquartile Range: 43-60) years were identified, including 43 (25.3%) HIV-positive and 127 (74.7%) HIV-negative women. Among the 43 HIV-infected women, 37 (86%) were on antiretroviral treatment (ART) prior their ICC diagnosis with a median CD4 count of 526.5 [373-833] cells/mm^3 at ICC diagnosis. The overall HR-HPV prevalence was 90.6% [Confidence Interval (CI): 85.2- 94.5], including 89.8% and 93.0% HIV-uninfected and HIV-infected women, respectively (p=0.8). Among the 154 women with a positive HR-HPV test, the most prevalent HR-HPV types were HPV 16 (n=87; 56.5%), HPV 18 (n=30; 19.5%), HPV 45 (n=13; 8.4%), and HPV 35 (n=7; 4.6%). HPV 16/18 was retrieved in 117 (76.0% [CI: 68.4-82.5]) women (79% in HIV-uninfected and 67.5% in HIV-infected women, p=0.15), while HPV 16/18/45 was found in 130 (84.4% [CI: 77.7 - 89.7%]) women, including 100 (87.7%) and 30 (75.0%) HIV-uninfected and HIV-infected women, respectively (p=0.05). No association between HPV 16 (p=0.8), HPV 18 (p=0.2), HPV 45 (p=0.6), HPV16/18 (p=0.14), and HIV status was reported.

CONCLUSIONS:

The reported distribution of HR-HPV genotypes in Côte d'Ivoire confirm the major implication of 16/18 genotypes in ICC and should support the scale-up of an HPV16/18 vaccination program regardless of HIV status in a time of universal access to ART. The higher proportion of 16/18/45 HR-HPV taken together in HIV-infected women deserves further attention as partial genotyping relying on these three genotypes remains a triage option to treat positively screened women through HPV-based ICC screening programs.

Author(s): Miriam Laker-Oketta[1], Miriam Nakalembe[1], Philippa Kadama-Makanga[1], Sandra Oketch[2], Melissa Assenzio[3], Yan Yuan[3], Andrew Kambugu[1], Amber Smith[4], Emily Herfel[4], Jeffrey Martin[3] and Megan Huchko[4]

48: We Built It: Why Didn't Some of Them Come? Reasons for Non-Engagement With Community-Based Cervical Cancer Prevention Interventions

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BACKGROUND:

Sub-Saharan Africa, especially East Africa, bears the brunt of the global cervical cancer burden, a fact mainly explained by vast underutilization of prevention interventions (HPV vaccination and screening for pre-cancer). In particular, health care facilities-based delivery of these interventions, which has worked well in resource-rich settings, has failed to achieve population coverage. To address this, we recently in Kenya and Uganda developed a campaign-based approach in which we deliver HPV screening and HPV vaccination directly in residents' communities, very close to where they live. While many residents attended the health fairs and took advantage of the services provided so close to home, some did not; it is these non-attendees that threaten WHO 90-70-90 goals. We sought to determine why, despite the convenience of the fairs and services, some residents declined to engage in them.

METHODS:

In collaboration with local leaders within selected prototypic rural areas in western Kenya and western Uganda, we chose locations centrally located within the communities (within walking distance for many residents) to hold a series of health fairs related to cervical cancer prevention. These fairs, which were promoted to residents by community health workers, offered education followed by free-of-charge self-collection of cervicovaginal specimens for HPV screening for eligible women (ages 30 to 64 yrs) and HPV vaccination for eligible girls (10 to 14 yrs). After the fairs were completed, we conducted a door-to-door probability sample of the community to ascertain the fraction of service-eligible residents who were aware that the fairs occurred; the fraction of those who attended amongst those who were aware; and, through open-ended questions, the reasons for fair non-attendance.

RESULTS:

After 10 fairs were completed in Kenya and Uganda, we interviewed, via a door-to-door probability sample, 578 screening-eligible women (n=416 in Kenya and n=162 in Uganda) and 147 (Kenya, 101; Uganda, 46) parent/guardians of vaccine-eligible girls. Overall, 78% of screening-eligible women (Kenya, 85%; Uganda, 64%) had been aware of the fairs, and of those who were aware, 54% (Kenya, 51%; Uganda, 63%) did not attend. The most commonly cited reason for non-attendance was competing domestic, job-related, or social responsibilities (Table). This was followed by personal health conditions that prohibited attendance, fear of the physical aspects of the screening, and claims of prior screening. Among parent/ guardians of vaccine-eligible girls, 82% (Kenya, 91%; Uganda, 63%) were aware of the fairs and, of those, 37% did not take/send their eligible girls to the fair (Kenya, 33%; Uganda, 52%). The most cited reasons were girls being in school (43%), competing responsibilities or illness of parents (18%), a belief that their daughters were too young (9%), and "no reason" (9%). Only 2% of parent/guardians stated that they did not believe in vaccines.

Reasons for Fair Non-Attendance among Screening-Eligible Women	Kenya (n=181)	Uganda (n=66)	Overall (n=247)
Competing social/job/ domestic responsibilities	51%	29%	45%
Illness or post-partum	10%	22%	13%
Fear of the process	12%	9.2%	11%
Felt not needed—screened in the past	10%	11%	10%
Aware of fair too late or forgot	5.0%	5.0%	5.0%
Did not see benefit	1.2%	9.2%	3.0%
Other*	11%	15%	13%

*Most common "Other" reasons: discouraged from attending; venue too far; and had insufficient information about the fair.

CONCLUSIONS:

Among residents of rural Uganda and Kenya who declined to engage in cervical cancer prevention-related health fairs held in central locations in their communities, we found several reasons for non-attendance. Competing responsibilities were the most prominent reason, many of which may be modifiable. Misperceptions about the safety, efficacy, or intent of the services—which may be less modifiable—were uncommon. These findings now form a rationale for modification of the messaging around and implementation of community-based campaigns like ours to maximize participation.

Author(s): Philippa Kadama Makanga[1], Aggrey Semeere[1], Miriam Nakalembe[1], Miriam Laker-Oketta[1], Robert Lukande[2], Megan Huchko[3], Esther Freeman[4], Nachiket Kulkarni[5], Jeffrey Martin[6], Kang Dongkyun[5]

49: Affordable Smartphone Confocal Microscopy for Cervical Pre-Cancer Screening: Initial Field Experience

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BACKGROUND:

Sub-Saharan Africa (SSA) has the highest rates of cervical cancer incidence and death compared to the rest of the world. More efficient methods to detect and enable treatment of precancerous lesions in a single visit, like confocal microscopy, are important to improve detection and treatment of cervical pre-cancer. We piloted a prototype in vivo low-cost smartphone confocal micro-endoscope among women presenting to a cervical cancer screening clinic in Kampala, Uganda. We describe the initial experience of piloting a smartphone confocal micro-endoscope (SCME) device fitted with colposcopy (Figure 1) for cervical cancer screening in an urban clinic by lower cadre staff.

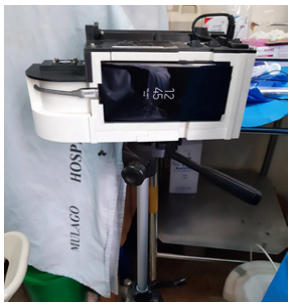

Fig 1. SCME device mounted and ready for use in the clinic

METHODS:

We screened women aged 18 to 60 years who presented for cervical cancer screening at the Kawempe National Referral Hospital Kampala and evaluated the experience of their providers (nurses). Nurses received a 2-day training by the study doctors on how to use the SCME device during routine Visual Inspection with Acetic acid (VIA) based cervical cancer screening. The training included video demonstrations and a session with dummies. The SCME device was used to take cervical images before and after VIA (Figure 2). Endoscopic images were obtained using the SCME device at 12 and 6 o'clock if VIA was negative and on precancerous lesions if VIA was positive. Women were interviewed using a questionnaire to assess their experience after screening with the SCME device. A self-administered questionnaire was used to assess the experience of the nurses who had used the SCME device for 6 months.

Fig 2. A Nurse using the device to take images

RESULTS:

Between November 2021 and July 2022, 178 women with a median age of 36 years and median parity of 4 were screened. Of these, 78 (44%) had previous screening experience and 97 (54%) were HIV positive. Of the women screened, 44 (25%) were VIA positive, 78% were comfortable screening with the SCME device, and 81% were willing to use it again during screening (Table 1). Confocal images from 60% of the women showed distinguishable cellular features. However, images from 40% of the remaining women were challenging to analyze due to motion artifacts and/or weak signals. Four of the nurses were interviewed. Their median age was 47 years and median duration of service was 23 years. Three of the nurses have diplomas in nursing and one has a degree in nursing. The mean score of the nurses' experience with the device was highest (85%) in relation to its usefulness to their work and 71% regarding their satisfaction and willingness to use the device. The SCME device scored an average of 63% in terms of ease of use and 57% with regard to the ease of learning how to use it.

Table 1: Participant Experience Screening With the SCME Device

Experiences	Agree	Neutral	Disagree
The procedure was comfortable (n=78) (%)	53(68.0)	17(21.8)	8(10.3)
The procedure caused me some pain (n=82) (%)	21(25.6)	27(32.9)	34(41.5)
I was satisfied with the care received (n=76) (%)	61(80.3)	12(15.8)	3(4.0)
Intimidated by the presence of the device (n=82) (%)	25(30.5)	18(22.0)	39(47.6)
Willing to be screened again with the device (n=81) (%)	67(82.7)	11(13.6)	3(3.7)

CONCLUSION:

Women were comfortable and willing to screen again with the SCME device. The nurses were satisfied with the SCME device and are willing to use it. However, more work is needed to make it easier to learn how to use and operate the SCME device.

Author(s): Kinza Meghani[1], Priya Puri[2], Lisa Bazzett-Matabele[3], Peter Vuylsteke[3], Barati Monare[4], Doreen Ramogola-Masire[4], Rebecca Ketlametsw[4], Tlotlo B. Ralefala[4], Memory Bvochora[4], Sebathu Chiyapo[4], and Surbhi Grover[2,4]

50: Significance of HIV Status in Cervical Cancer Patients Receiving Curative Chemoradiation Therapy, Definitive Radiation Alone, or Palliative Radiation in Botswana

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BACKGROUND:

Cervical cancer associated with human papillomavirus (HPV) is a leading cause of death worldwide, with the highest disease burden in sub-Saharan Africa (SSA). Women living with human immunodeficiency virus (HIV; WLWH) are at a substantially higher risk for developing cervical cancer, thereby classifying cervical cancer as an AIDS-defining illness. In Botswana, a middle-income country in SSA, cervical cancer has the highest cancer incidence and mortality for women due to a high HIV prevalence and limited early screening. This study investigates the significance of HIV on the overall survival of cervical cancer by various treatment categories (curative chemoradiation, definitive radiation alone, or palliative radiation alone) among patients with locally advanced cervical cancer.

METHODS:

This study included patients diagnosed with cervical cancer stages IB-IV between April 2013 and November 2020, prospectively enrolled in the Botswana Prospective Cancer Cohort (BPCC) at Gaborone Private Hospital and a gynecological multidisciplinary team (MDT) clinic at Princess Marina Hospital. Baseline demographic and laboratory covariates were summarized by descriptive statistics. Overall survival (OS) was estimated by the Kaplan-Meier method. For various treatment groups, comparisons of 2-year OS by HIV status were performed by the log-rank test, univariate Cox regression analyses, and multivariable Cox analyses adjusting for cancer stage, RT dose, number of chemotherapy cycles, and baseline hemoglobin levels.

RESULTS:

A total of 1,131 patients were diagnosed with stage IB-IV cervical cancer in the BPCC. Among these women, 69.8% were WLWH (n=789). For the 465 patients who received curative chemoradiation treatment, HIV status was not significantly associated with OS in unadjusted (p=0.987) and adjusted analysis (p=0.578). For the patients who completed RT-only treatment, HIV status was significantly associated with OS in unadjusted analysis (HR=1.77, p=0.002), but not in adjusted analysis (p=0.227). Similarly, HIV status was significantly associated with OS for the 198 patients receiving definitive (high dose) RT alone in unadjusted analysis (HR=1.95; p=0.014), but not in adjusted analysis (p=0.073). For the 154 patients receiving palliative (low dose) RT, HIV status was not associated with OS in unadjusted (p=0.835) or adjusted analysis (p=0.359).

CONCLUSIONS:

In Botswana, a resource-limited country, no differences were detected in 2-year overall survival for cervical cancer patients living with HIV receiving antiretroviral therapy (ART) compared to patients living without who initiated treatment, demonstrating that patients can receive chemoradiation, radiation alone, or palliative radiation with no evidence that HIV leads to worse outcomes.

Author(s): Miriam Nakalembe[1], Miriam Laker-Oketta[1], Philippa Makanga[1], Sandra Oketch[2], Melissa Assenzio[3], Andrew Kambugu[1]; Amber Smith[4], Emily Herfel[4], Megan Huchko[4], and Jeffrey Martin[3]

51: A Public Health Approach to Cervical Cancer Prevention in East Africa Through Community-Based HPV Vaccination, Self-Administered Screening, and Mobile Treatment

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BACKGROUND:

In resource-limited settings, HPV-based screening and vaccinations are effective but underutilized for cervical cancer control in both HIV-infected and -uninfected populations. In particular, health care facilities-based delivery of these interventions, which has worked well in resource-rich settings, often fails to achieve population coverage. We recently, in Uganda, developed a community-based campaign approach featuring self-collected HPV-based cervical cancer screening at community-based health fairs, followed by treatment by a mobile team. To further expand this "public health approach" to cervical cancer prevention, we assessed the feasibility of adding HPV vaccination to the campaigns, and we evaluated the acceptability of the program to residents in another setting—Kenya.

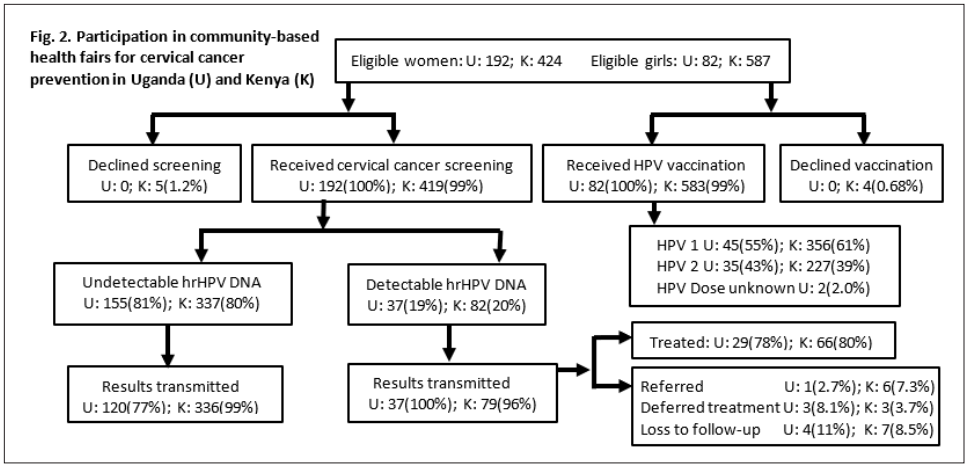
METHODS:

Working in collaboration with local Ministries of Health, we evaluated campaigns in rural districts in each of western Uganda and western Kenya. In these districts, Community Health Workers mobilized residents to attend health fairs within their communities that provided (i) HPV screening using self-collected cervicovaginal specimens for women ages 30 to 64 years old; and (ii) HPV vaccination for girls 10 to 14 years. Women who tested positive for HPV were re-contacted for ablative therapy (or, if needed, LEEP) provided by a mobile treatment team. After fair completion, we conducted a probability survey of households to learn the percent of service-eligible residents who were aware of the fair and the percent who elected to attend the fairs.

Fig. 1. Local residents receiving instructions regarding cervical cancer screening at a community health fair in Uganda.

RESULTS:

Fig. 2. Participation in community-based health fairs for cervical cancer prevention in Uganda (U) and Kenya (K)



We evaluated 10 fairs performed from Dec. 2021 to June 2022 (Fig. 1), at which 616 screening-eligible women and 669 vaccine-eligible girls attended; 99.2% of the women received screening, and 99.4% of girls got vaccinated (Fig. 2). Among screened women, HIV prevalence was 21% and HPV prevalence was 20%. Of the HPV-infected women, 80% received ablative therapy or LEEP in the community and 11% had treatment referred or deferred. Among girls who came to the fair, 74% came with their school group or parent/guardians, and 26% came on their own. Post-fair surveys found that 62% of service-eligible residents in Uganda and 85% in Kenya were aware of the fairs, and, of those aware, 42% in Uganda and 55% in Kenya attended the fairs.

CONCLUSION:

In both Uganda and Kenya, community-based campaigns featuring HPV vaccination, self-collected HPV testing, and a mobile treatment team were feasible and readily accepted by residents. The program requires optimization regarding initial participation and cost-efficiency, but it represents a promising public health approach towards achieving global health equity in the realm of cervical cancer.

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52: Engagement in Home-Based vs Clinic-Based Anal Precancer Screening Among Men Having Sex With Men: Interim Baseline Data From the Prevent Anal Cancer Self-Swab Study

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BACKGROUND:

As part of an organized program, men having sex with men (MSM) may soon be asked to engage in screening for anal cancer, a highly stigmatized condition. Screening engagement among individuals randomized to a home-based self-sampling arm was compared with those randomized to standard clinic-based sampling.

METHODS:

MSM and transgender individuals were recruited from the community and then randomized to receive a self-sampling kit at home or to make an appointment at a clinic for clinic-based swabbing. Screening engagement was defined as the proportion of participants completing screening in each study arm. Specimen adequacy was assessed for HPV genotyping. Intention-to-treat analyses were stratified by race and HIV status. Factors associated with any screening were assessed by multivariable logistic regression. Individuals randomized January 9, 2020, through June 1, 2022, were included.

RESULTS:

A total of 207 individuals were randomized. Characteristics did not differ by study arm, including age (median, 46 years), HIV status (28% people with HIV), and race (65% white non-Hispanic, 20% Black non-Hispanic, 13% Hispanic). The majority (89%) of home-based persons returned the swab while 74% of clinic-based individuals completed swabbing ($p = 0.004$). Among people with HIV, 88% of home-based individuals screened compared to 52% in the clinic arm ($p = 0.002$). Among Black participants, 100% (24/24) in the home-based arm screened compared to 61% (11/18) in the clinic-based arm ($p < 0.001$). After stratifying by time of enrollment (pre-COVID-19 vs COVID-19), overall results did not change, with a higher proportion of persons in the home-based arm engaging in screening compared to those in the clinic-based arm. Specimen adequacy for HPV genotyping was similar in the home-based (96%) and clinic-based (92%) arms.

After adjustment by time of enrollment and age, individuals in the home-based arm had higher engagement in screening compared to those in the clinic-based arm (adjusted OR (aOR) 4.00, 95% CI 1.63-9.82). Compared to individuals with ≤12 years of school, those with more years of school had higher odds of engaging in any screening. For example, persons with 13-15 years of school had 3.7 times higher odds to screen (aOR 3.66, 95% CI 1.13-11.81) than those with relatively fewer years of school. While non-significant, HIV-negative individuals had 2.4 times higher odds of screening than people with HIV (aOR 2.4, 95% CI 0.92-6.32).

CONCLUSIONS:

People at highest risk for anal cancer may be more likely to screen if they are able to self-collect swabs at home rather than attend a clinic. Home-based screening may be particularly attractive to people with HIV and Black individuals. Swabs collected in both home-based self-sampling and standard clinic-based sampling have comparable and high adequacy for HPV genotyping.

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54: Healthcare Costs and Financial Barriers to Diagnosis and Treatment of People Living with HIV-Associated Kaposi's Sarcoma in Western Kenya: A Qualitative Analysis

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BACKGROUND:

Financial barriers and high healthcare costs impede early diagnosis and treatment for various cancers. In low-resource settings, financial barriers may be amplified for people living with HIV-associated malignancies, such as Kaposi's Sarcoma (KS). KS remains prevalent with high mortality in sub-Saharan Africa; understanding the role of financial barriers in this context is an important step toward ensuring timely diagnosis and treatment.

METHODS:

Eighty-eight semi-structured interviews were conducted using a purposive sample of adults newly diagnosed with HIV-associated KS in western Kenya. Interviews were coded using framework analysis based on the grounded model of help-seeking behavior.

RESULTS:

In the 88 semi-structured interviews, lack of financial support and high healthcare costs were described as prominent barriers for diagnosis and treatment of KS (Table 1). We grouped these into eight major categories, with the most prominent themes being lack of financial support, high healthcare costs, getting fired, no insurance knowledge, and having to support one's family. Lack of financial support from an individual's friends and family was a commonly cited barrier to attending appointments and obtaining medications. Some individuals had no knowledge of insurance policies such as the National Hospital Insurance Fund (NHIF) of Kenya or were not eligible, thus requiring out of pocket payment for healthcare expenses. The high healthcare costs for chemotherapy were expressed as a major deterrent in many interviews. Some participants reported paying 40,000 shillings (approx. 350 USD) for one "chemotherapy injection." For those who had to support families during KS treatment, many noted being unable to afford treatment.

CONCLUSIONS:

Assessing financial barriers for people living with HIV-associated KS is a crucial step in creating the interventions necessary to promote early diagnosis and efficient treatment in this population. Future studies should aim to understand whether health insurance coverage can overcome the financial barriers to diagnosis and treatment of KS.

Table 1: Characteristics of barriers for diagnosis and treatment of KS

Patient Age, Gender, Strata	Themes	Quotes
Male, 36, Treatment Non-Starter	Lack of Financial Support 	*"When I went home, I had a profoma [card where one uses to get collection from a fund raiser], I tried collecting cash with it, but everyone told me they did not have money…I am the eldest and the breadwinner so there was no one really to help me."*
Male, 40, Treatment Non-Completer	High Healthcare Costs 	*"The treatment of this cancer is very expensive, and I would not have afforded because of the high cost. Like an injection is 40,000 and I got 7 injections, how much would I have needed for 7 injections? That is almost 200,000, where would I get that kind of money?"*
Male, 30, Treatment Non-Completer	No National Health Insurance Fund (NHIF) knowledge 	*"I had not registered… I didn't see its importance."*
Male, 34, Late-Stage Diagnosis	Fired from Job 	*"Where I had been working my boss fired me because of those wounds- so these wounds were bleeding so much, so there is a time these wounds bled so much."*
Male, 34, Late-Stage Diagnosis	Have to Support Family 	*"I don't have [money]…I am very weak right now; I am unable to provide for the family. (Silence)."*

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55: The Experience of Social Support in People with HIV-Associated Kaposi's Sarcoma in Western Kenya: A Mixed Methods Approach

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BACKGROUND:

For people with HIV-associated malignancies in low-resource settings, the process involved in diagnosis and treatment is complex and time-consuming. In this context, social support may be an important contributor to the timely diagnosis and treatment of HIV-associated Kaposi's Sarcoma (KS). The aim of this study is to explore the experience of social support in people with HIV-associated KS.

METHODS:

We nested a convergent mixed-methods study in a longitudinal cohort of people with HIV-associated KS in western Kenya from February 2019–December 2020. We measured social support using the 12-item Multidimensional Scale of Perceived Social Support (MSPSS). We also conducted semi-structured interviews, using purposive sampling stratified by timing of diagnosis and chemotherapy status. Interviews were analyzed using framework analysis with a priori themes informed by MSPSS and social support constructs (informative, instrumental, and emotional support).

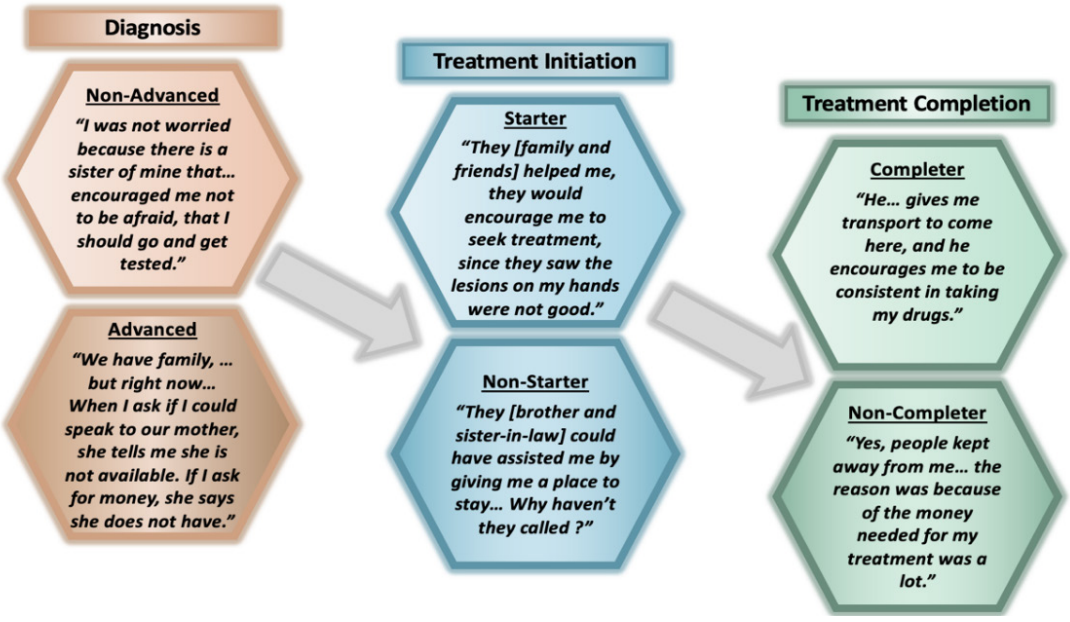
RESULTS:

A total of 118 adults (61.1% male) with median age of 36.5 (IQR: 31.0, 42.0) completed the MSPSS questionnaires during at least one study visit. The median overall social support score across all time points was 84.0 (66.0, 84.0). In the semi-structured interviews, key themes among participants with advanced diagnosis or who did not start/complete treatment included lack of instrumental and emotional support. Participants who completed chemotherapy described larger support networks, access to instrumental support, and a friend or family member who was a healthcare worker.

CONCLUSIONS:

Social networks are important sources of instrumental and emotional support in people with HIV-associated KS, and lack of social support may contribute to delays in diagnosis and treatment of KS.

Figure 1: Qualitative Representation of Social Support in HIV-Associated Kaposi's Sarcoma: Experiences of Social Support Contributing to KS Diagnosis and Treatment



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In Remembrance

Enrique A. Mesri, Ph.D.
(1960-2022)

The Office of HIV and AIDS Malignancy at NCI and the Program Committee for the 18th International Conference on Malignancies in HIV/AIDS (ICMH) mourn the loss of Enrique A. Mesri, Ph.D., professor at the University of Miami. Dr. Mesri was the University of Miami Principal Investigator and Director of the CFAR/Sylvester-Argentina Consortium for Research and Training in AIDS Malignancies. His contributions to the understanding of the mechanisms of oncogenesis by the Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) were significant, exemplified by his extensive publication and citation record. Dr. Mesri leaves a tremendous legacy in viral oncology through his work in HIV/AIDS and cancer. He was a mentor par excellence, Dr. Mesri was passionate about training the next generation of scientists, in this country and internationally.