October 24–25, 2024
NIH Natcher Conference Center

19th International Conference on

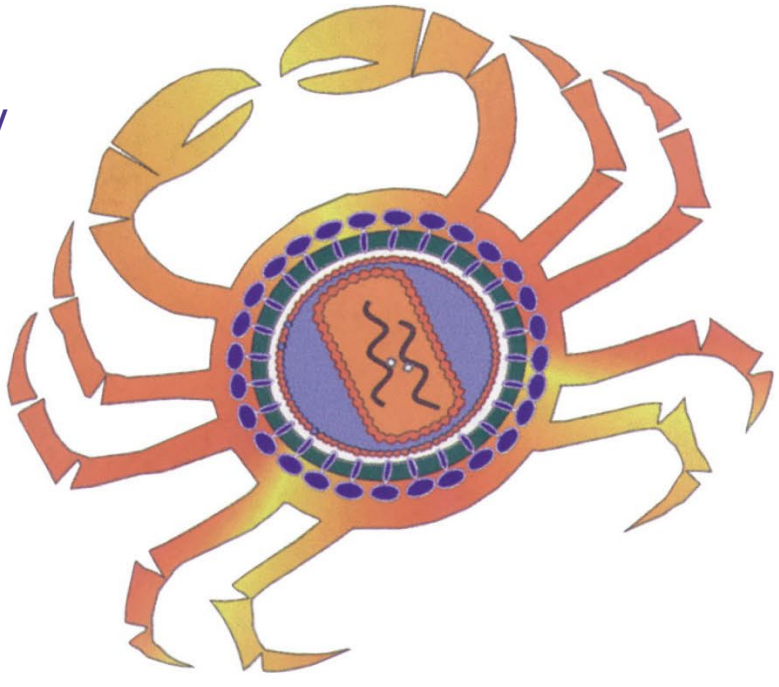
Malignancies in HIV/AIDS

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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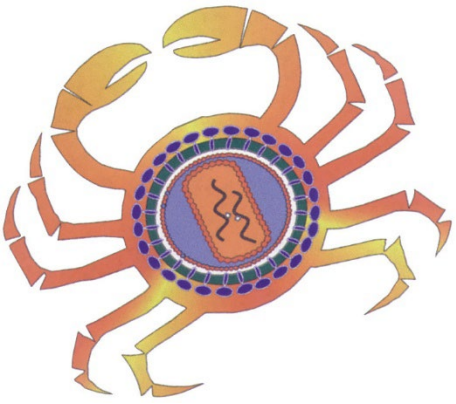

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NIH NATIONAL CANCER INSTITUTE

19th International Conference on Malignancies in HIV/AIDS

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AGENDA

All times are U.S. Eastern Daylight Time.

DAY 1: OCTOBER 24	
8:00 AM	Poster Setup (Posters will stay up for the entire day)
8:15 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
8:30–9:45 AM	**Session 1: Cancer Burden and Screening** Moderators: Eric Engels and Cameron Haas, Division of Cancer Epidemiology and Genetics, National Cancer Institute
8:30 AM	**P1: Recent Trends in Cancer Risk among People with HIV in the United States** Cameron Haas, National Cancer Institute
9:00 AM	**O1: Cancer Risk among People with HIV Who Inject Drugs in the United States, 2010-2019** Jennifer K. McGee-Avila, National Cancer Institute
9:15 AM	**O2: Incidence of Penile Carcinoma Among Men with HIV—Findings from the Potlako+ Navigation Trial, Botswana** Scott Dryden-Peterson, Botswana Harvard Health Partnership and Brigham and Women's Hospital
9:30 AM	**O3: Access to Cervical Cancer Screening Cascade in Côte d'Ivoire: A Decade Real-World Program Evaluation According to HIV Status** Antoine Jaquet, INSERM U1219 – Global Health in the Global South, Bordeaux Population Health Research, ISPED, University of Bordeaux
9:45 AM	**Break and Day 1 Poster Viewing**
10:15 AM–12:30 PM	**Session 2: Liver Cancer and Prognostic Markers and Clinical Trials** Moderators: Richard Ambinder and Samantha Vogt, Johns Hopkins School of Medicine
10:15 AM	**P2: Liver Cancer** Ghassan K. Abou-Alfa, Memorial Sloan Kettering Cancer Center

10:45 AM	**O4: Primary Effusion Lymphoma Prognostic Score (PEL-PS): A Validated International Prognostic Score in HIV-Associated Primary Effusion Lymphoma** Kathryn Lurain, HIV & AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute
11:00 AM	**O5: Lymph Node and Plasma Cell-Free DNA Sequencing among PWH Attending an FNA Clinic in Soweto, South Africa: High Accuracy of Plasma Clonal Immunoglobulin for Lymphoma** Rena R. Xian, Department of Pathology, Johns Hopkins School of Medicine and Department of Oncology, Sidney Kimmel Comprehensive Cancer Center
11:15 AM	**O6: Inclusion of People with HIV in Cancer Clinical Trials—2012 to 2024** Jesse Heitner, Harvard University Centers for AIDS Research, Massachusetts General Hospital
11:30 AM	**O7: 5-Year Update on Frontline Brentuximab Vedotin with AVD for Stage II-IV HIV-Associated Classical Hodgkin Lymphoma (AMC-085)** Paul G. Rubinstein, University of Illinois, Chicago, Section of Hematology/Oncology, Department of Medicine
11:45 AM	**O8: Abemaciclib, a CDK4/6 Inhibitor, in HIV-Associated and HIV-Negative Kaposi Sarcoma** Ramya Ramaswami, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute
12:00 PM	**O9: sEph-B4-HSA Is Effective and Tolerable in Kaposi Sarcoma: Results of the AMC-096 Phase 2 Trial** Erin G. Reid, University of California, San Diego
12:15 PM	**Lunch** On your own
12:45 PM	**Day 1 Poster Viewing**
1:45 PM–3:00 PM	**Session 3: Transplantation and Kaposi Sarcoma Tumor Environment** Moderators: Denise Whitby, Viral Oncology Section, AIDS & Cancer Virus Program, Frederick National Laboratory, and Owen Ngalamika, University of Zambia School of Medicine
1:45 PM	**P3: Transplantation from Donors with HIV to Recipients with HIV: Spotlight on Cancer** Christine Durand, Johns Hopkins School of Medicine, Sydney Kimmel Comprehensive Cancer Center
2:15 PM	**O1O: Spatial Transcriptomics of Patients with Kaposi Sarcoma Identifies Mechanisms of Immune Evasion** Joseph Ziegelbauer, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute
2:30 PM	**O11: Comprehensive Analysis of Tumor-Infiltrating Lymphocytes from Kaposi Sarcoma Tumors Reveals Public KSHV- and HIV-Specific T-Cells with Potential Therapeutic Value** Edus H. Warren, Fred Hutchinson Cancer Center, University of Washington, and Hutchinson Cancer Research Centre, Uganda

2:45 PM	**O12: Patient-Derived Xenografts of Kaposi Sarcoma Are a Novel Model to Map Herpesvirus-Driven Impacts on the Cellular Milieu of Skin Tumors** Xiaofan Li, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute
3:00 PM	**Break and Day 1 Poster Viewing**
3:30 PM–4:15 PM	**Session 4: Anal Cancer Screening** Moderators: Michael Silverberg, Division of Research Kaiser Permanente, and Margaret Borok, University of Zimbabwe Faculty of Medicine and Health Sciences
3:30 PM	**ST1: Anal Cancer Guidelines** Joel Palefsky, University of California, San Francisco, Department of Medicine
3:42 PM	**ST2: Screening for Anal Cancer among People with HIV: Benefits, Harms, and Cost-Effectiveness** Ashish Deshmukh, Cancer Prevention and Control Program, Hollings Cancer Center, Medical University of South Carolina
3:54 PM	**ST3: Implementation of Anal Cancer Screening Prevention Guidelines Requires Immediate Expansion of High-Resolution Anoscopy Infrastructure** Naomi Jay, University of California, San Francisco, Division of Medicine, Anal Neoplasia Clinic, Research and Education Center
4:06 PM	**Questions/Discussion**
4:15 PM–5:15 PM	**Session 5: Kaposi Sarcoma and Kaposi Sarcoma-Associate Herpesvirus (KSHV)** Moderators: Erle Robertson, Perelman School of Medicine, University of Pennsylvania, and Elena Cornejo Castro, Frederick National Laboratory for Cancer Research
4:15 PM	**O14: Ectopic Expression of KSHV miR-K12-9 Can Induce Transformation of Immortalized and Primary Endothelial Cells** Lauren Gay, University of Florida, Gainesville
4:30 PM	**O15: Association of Soluble Serum Biomarkers with Tumor Burden and Treatment Response in Advanced HIV-Related Kaposi Sarcoma in Resource-Limited Settings** Marta Epeldegui, University of California, Los Angeles
4:45 PM	**O16: Recent Kaposi Sarcoma Trends in Men with HIV: Associations with New to Care at Enrollment and Viral Suppression Status** Sally B. Coburn, Johns Hopkins University
5:00 PM	**End of Day One**

DAY 2: OCTOBER 25

8:00 AM	**Day 2 Poster Viewing**
8:30 AM	**Welcome** Geraldina Dominguez, AIDS Malignancy Program, Office of HIV and AIDS Malignancy, National Cancer Institute

8:45 AM	**O13: Recombinant mAbs Define Sites of Vulnerability on the KSHV gH/gL Complex** Andrew T. McGuire, Fred Hutchinson Cancer Center and Department of Global Health and Department of Pathology and Laboratory Medicine, University of Washington
9:00–10:00 AM	**Session 6: Cancer Health Disparities and New Therapeutic Approaches** Moderators: Keith Sigel, Icahn School of Medicine at Mount Sinai, and Valeria Fink, Institution Fundación Huesped, Buenos Aires
9:00 AM	**ST4: Bridging the Gap: Addressing Disparities in Cancer Treatment and Outcomes** Gita Suneja, Huntsman Cancer Institute
9:12 AM	**ST5: HIV, Health Disparities, and the Southern U.S.** Elizabeth Chiao, University of Texas MD Anderson Cancer Center
9:24 AM	**Questions/Discussion**
9:30 AM	**O17: Structural Inequities in Cancer Treatment Receipt among PWH and Cancer in the U.S. (2004–2020)** Jessica Y. Islam, H. Lee Moffitt Cancer Center and Research Institute
9:45 AM	**O18: Molecular Characterization and Survival Analysis of Cancers Arising in People Living with HIV** Mark G. Evans, Caris Life Sciences
10:00 AM	**O19: Adjuvant Immunotherapy for NSCLC in Patients Living with HIV: A Simulation Study** Keith Sigel, Icahn School of Medicine at Mount Sinai
10:15 AM	**O20: Novel Immunotherapeutic Approaches for Melanoma in People Living with HIV** Gabriele Romano, Department of Pharmacology and Physiology, Drexel University College of Medicine, and Immune Cell Regulation & Targeting Program, Sidney Kimmel Cancer Center Consortium
10:30 AM	**Break and Day 2 Poster Viewing**
11:00–12:00 PM	**Session 7: Roundtable** Moderator: Robert Yarchoan, Office of HIV and AIDS Malignancy, National Cancer Institute
11:00 AM	**KSHV/EBV Highlights and Gaps** Ethel Cesarman, Weill Cornell Medical College, Cornell University
11:06 AM	**Aging and Cancer Highlight and Gaps** Anna Coghill, H. Lee Moffitt Cancer Center and Research Institute
11:12 AM	**HPV Associated Diseases (Cervical, Anal, Vulvar, and Head and Neck) Highlights and Gaps** Mark Einstein, Albert Einstein College of Medicine
11:18 AM	**Understudied HIV-Associated Cancers in Low- and Middle-Income Countries Highlights and Gaps** Charles Wood, Louisiana State University
11:24 AM	**Perspective from the Patient/Community** Jesse Milan Jr., AIDS United

11:30 AM	**Questions from Moderator and Audience**
12:00 PM	**Lunch** On your own
12:30 PM	**Day 2 Poster Viewing** Presenters stand by their poster
1:30–3:00 PM	**Session 8: Immune Dysfunction and Junior Investigator Abstracts** Moderators: Warren Phipps, Fred Hutchinson Cancer Center, and Matthew Painschab, University of North Carolina School of Medicine
1:30 PM	**P4: Accelerated Genomic Aging in Cancer Patients with Human Immunodeficiency Virus (HIV)** Anna Coghill, H. Lee Moffitt Cancer Center and Research Institute
2:00 PM	**O21: Trends in Burkitt Lymphoma in People with HIV in South Africa (2005–2021)** Carole Motekoa, National Cancer Registry, Health Laboratory Service, Johannesburg, and University of Bern
2:10 PM	**O22: Spatial Analysis Reveals Heterogeneity in the Tumor Microenvironment of AIDS-Associated Non-Hodgkin Lymphoma (AIDS-NHL)** Laura E. Martínez, UCLA AIDS Institute and Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles
2:20 PM	**O23: Spatial and Bulk Transcriptomics Analyses Reveal Distinct Gene Expression Profiles in Archival Skin Kaposi Sarcoma Lesions Based on Disease Characteristics** Quashawn Chadwick, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute
2:30 PM	**O24: Spatial Single-Cell Transcriptomic Profiling Reveals KSHV-Driven Mechanisms in Kaposi's Sarcoma** Wen Meng, Cancer Virology Program, UPMC Hillman Cancer Center, and Department of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine
2:40 PM	**O25: Prior Cervical Cancer Screening among Cervical Cancer Patients in the Cancer Disease Hospital in Zambia** Graciela M. Nogueras Gonzalez, Department of Epidemiology, University of Texas MD Anderson Cancer Center
2:50 PM	**O26: Hepatocellular Carcinoma Survival in People with HIV and without HIV in the United States, 2001–2019** Jennifer K. McGee-Avila, National Cancer Institute
3:00 PM	**Day 2 Break and Poster Viewing**
3:30–5:15 PM	**Session 9: Implementation Science and HPV-Associated Cancers** Moderators: Joel Palefsky, University of California San Francisco School of Medicine and Chemtai Mungo, University of North Carolina School of Medicine
3:30 PM	**P5: Implementation Science to Enhance Cervical Cancer Screening** Nelly Mugo, University of Washington Department of Public Health
4:00 PM	**O27: Incidence and Risk Factors for HPV-Associated Cancers in People Living with HIV in South Africa** Tafadzwa Dhokotera, Swiss Tropical and Public Health Institute

4:15 PM	**O28: Treatment of Anal Precancer among 18-to-34-Year-Old Men Who Have Sex with Men Living with HIV: Effectiveness and Key Factors Associated with Outcomes** Rangana Bartlett, Icahn School of Medicine at Mount Sinai, Department of Medicine
4:30 PM	**O29: Induction Chemotherapy Outcomes in Patients with Locally Advanced Cervical Cancer in Botswana** Emily MacDuffie, Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania
4:45 PM	**O30: Thermal Ablation 24-Week Efficacy for the Treatment of High-grade Cervical Intraepithelial Neoplasia among Women Participating in a GeneXpert-based Human Papillomavirus Screening Trial for Cervical Cancer Prevention in Malawi** Lameck Chinula, Project-Malawi and Department of Obstetrics and Gynecology's Division of Global Women's Health, University of North Carolina, and Kamuzu University of Health Sciences
5:00 PM	**O31: A Pulsed Campaign-Based Approach for Community-Centered Cervical Cancer Prevention in East Africa: Feasibility and Reasons for Non-Participation of Residents** Miriam Laker-Oketta, Infectious Diseases Institute, Kampala, Uganda
5:15 PM	**Concluding Remarks** Geraldina Dominguez, AIDS Malignancy Program, Office of HIV and AIDS Malignancy, National Cancer Institute, and Robert Yarchoan, Office of HIV and AIDS Malignancy, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute

P1: Recent Trends in Cancer Risk among People with HIV in the United States

Author: *Cameron Haas*
National Cancer Institute

BACKGROUND
For cancers driven by viral infections, risk has declined substantially for people with HIV (PWH) as a result of improvements in access to combination antiretroviral therapy. With greater life expectancy, there is a growing number of PWH entering ages for which many cancer types increase in risk. Age group-specific estimates for PWH can inform cancer prevention and screening strategies.

METHODS
We utilize data from 14 US regions in the HIV/AIDS Cancer Match (HACM) Study from 2001 to 2019 to describe cancer incidence using age-standardized incidence rates (IRs) and trends using adjusted Poisson regression. We also assessed relative risk compared with the general population using standardized IRs (SIRs). Using data from the most recent decade (2010–2019), we estimated cancer incidence and SIRs within age groups among PWH.

RESULTS
In 2001–2004, the five cancers with the highest age-standardized IRs in PWH were lung cancer (131 per 100,000 person-years), female breast cancer (100), diffuse large B cell lymphoma (DLBCL) (85), prostate cancer (82 [males only]), and Kaposi sarcoma (KS) (74), while in 2015–2019 they were female breast cancer (102), prostate cancer (67), lung cancer (48), cervical cancer (47 [females only]), and anal cancer (45). Comparing 2015–2019 with 2010–2014, incidence of DLBCL decreased by 30%, KS by 24%, Hodgkin lymphoma (HL) by 25%, and cancers of the lung by 17% and liver by 25%. Despite declines in cancer incidence over time for some cancers, risk remained significantly elevated compared with the general population for several cancer types during 2015–2019, including for KS (SIR=214), anal cancer (17), Burkitt lymphoma (15), vulvar cancer (11), HL (6.3), DLBCL (5.6), liver cancer (1.9), and lung cancer (1.6). For nearly all these cancers, SIRs were greatest in the youngest age groups and significantly declined with increasing age. Among PWH aged 70–84 years, cancers with the greatest incidence were those of the prostate (IR=448), lung (270), female breast (202), liver (83), and colon (108).

CONCLUSIONS
Among PWH in the US, significant declines in incidence for virus-related cancers and lung cancer are evidence of continued progress in the care and treatment of PWH. These estimates provide insight into the priorities for cancer control as the population of PWH ages. As PWH enter older ages and cancer risk increases, cancer prevention and screening will play an increasingly important role to reduce cancer-related morbidity and mortality.

P2: Liver Cancer

Author: *Ghassan K. Abou-Alfa*
Memorial Sloan Kettering Cancer Center

BACKGROUND

Africa accounts for more than 70% of the Acquired Immunodeficiency Syndrome (AIDS) patients worldwide. Accolades to all the research efforts that led to the development of antiretroviral therapy. This changed the highly fatal AIDS into a chronic illness with markedly improved survival. This also led to other illnesses and comorbidities becoming a major concern. Of those is liver cancer or hepatocellular carcinoma (HCC). The risk development of HCC among patients living with Human Immunodeficiency (HIV) virus (PLWH), its biology, and how to treat all remain unanswered challenges.

METHODS

A thorough read of the field of incidence of HIV among PLWH is key. This has been developed by many investigators. We present herein our already published effort to add to the relentless effort to better understand the biology of the disease. The third link of this trifecta challenge of providing therapy is discussed as well.

RESULTS

HCC is very common at the epicenter of HIV in sub-Saharan Africa (SSA). In view of shared means of transmission co-infection with HIV and Hepatitis B (HBV) is common. Based on very few population-based surveillance programs and mostly observational cohort studies, the mean proportion of HIV patients with HIV-HBV co-infection in SSA is 7.8%. It varies though from nil to close to 30% in different regions of SSA. This may be partly attributed to the HIV co-infection with HBV enhancing the hepatocarcinogenic potential. An impaired immune T-cell response against HBV in HIV plus HBV co-infected patients leads to higher levels of HBV replication and increased rates of reactivation. HIV infection itself also increases reactive oxygen, thus promoting immune-mediated liver injury. A concern about HIV medications hepatotoxicity leading to increased risk of HCC deserves further study. These pre-clinical concerns no doubt would have an impact onto the therapeutic indications for HCC in PLWH. A persistent limited access to HCC therapy in Africa is present with only an average 5% of healthcare workers have access to the novel checkpoint inhibitors to treat advanced HCC. The situation for PLWH is more dire. In the absence of or limited experience, there remains a lack of comfort to apply any therapy for PLWH diagnosed with HCC. The long-breath endless repeated experience of the NCI AIDS Malignancy Consortium (AMC) to initiate a study evaluating the biology and potential therapy for PLWH diagnosed with HCC will be discussed in detail.

CONCLUSIONS

HCC in PLWH remains a poorly understood disease with certain pre-clinical suggestions implying a potentially more complex matter than in HBV related HCC. The continued limited access and discomfort using any therapy for HCC at the epicenter of the HIV infections in Africa further encumber that challenge. A novel approach to provide a potential accessible therapy with multiple correlatives on board of such clinical trial is the way the AMC continues to endeavor.

P3: Transplantation from Donors with HIV to Recipients with HIV: Spotlight on Cancer

Author: *Christine Durand*

Johns Hopkins School of Medicine, Johns Hopkins Sydney Kimmel Comprehensive Cancer Center

Solid organ transplantation from donors with HIV to recipients with HIV (HIV D+/R+) is an emerging practice, implemented in the United States under the HIV Organ Policy Equity (HOPE) Act in 2015. A potential risk of this practice is an increased incidence of post-transplant cancers, due to overlapping risk factors such as immunosuppression from HIV, immunosuppressive medications to prevent rejection, and an increased prevalence of oncogenic viruses in donors with HIV. This presentation will present outcomes from the first HIV D+/R+ kidney and liver transplantation trials in the United States with a focus on post-transplant malignancies.

P4: Accelerated Genomic Aging in Cancer Patients with Human Immunodeficiency Virus (HIV)

Author: *Anna Coghill*
H. Lee Moffitt Cancer Center and Research Institute

The improved survival of the HIV population with effective antiretroviral therapy has translated into a higher prevalence of cancers linked to aging. This changing epidemiology, and the poor survival rates for people living with HIV (PWH) diagnosed with certain cancers, both contribute to the increased prominence of cancer as a cause of death in the US HIV population. We expect that this pattern of increasing, age-related cancer mortality will impact all regions globally as the average lifespan continues to lengthen.

This talk is based on the premise that accelerated aging in PWH may be a driver of poor cancer prognosis and will review results from a study that evaluated this hypothesis using DNA-based aging metrics, including accelerated epigenetic aging and a higher prevalence of clonal hematopoietic (CH) mutations. This study of 136 cancer patients, including a subset of patients enrolled into the HIV Genomic Aging Project in Oncology (R01 CA268973), provided evidence that PWH and cancer harbor a higher prevalence of CH mutations and accelerated, mortality-related epigenetic aging when compared to PWoH diagnosed with the same types of cancer. Key findings included (1) epigenetic age acceleration (GrimAge clock) in PWH compared to PWoH that remained statistically significant after adjustment for immune cell composition (e.g., CD4 T-cell %), and was associated with increased mortality (HR=1.11; 95%CI: 1.04-1.18), as well as (2) a four-fold increase in CH mutation prevalence in PWH compared to PWoH (OR=4.1, 95%CI: 1.3-13.9) and uniquely poor 5-year survival for PWH with CH (38%) versus without CH (59%).

Ongoing work to document rates of genomic aging, including CH mutation prevalence before and after cancer therapy, in HIV-related Kaposi sarcoma patients will be discussed, as will ideas for future aging research in the setting of HIV and cancer, including immune and inflammatory marker stability during and after cancer therapy, and exploration of potentially targetable senescence-associated markers in the tumor microenvironment.

P5: Reaching the Cervical Cancer Elimination Goal: Getting Interventions that Work to the People Who Need Them

Author: *Nelly Mugo*

Kenya Medical Research Institute and Department of Global Health, University of Washington

Cervical cancer is one of the few malignancies that has a known causative agent (high-risk HPV infection), tools for diagnosis and treatment of precancer lesions, cure for early-stage cancer, and a highly effective prophylactic vaccine that works with a single dose.

Even with this know-how, cervical cancer remains the fourth most common cause of cancer death globally and the most common cause of cancer death among women in many low- and middle-income countries.

The evidence on efficacy of the single-dose HPV vaccine brings new hope to cervical cancer elimination, and global efforts towards adoption and population vaccine delivery continue. Efforts to advance knowledge on screening interventions and strategies to expand population coverage and uptake of treatment for screen-positive women continue.

Population coverage, leaving no one behind, is required for the world to reach the 2018 World Health Organization Cervical Cancer Elimination goal. Is this feasible?

O1: Cancer Risk among People with HIV Who Inject Drugs in the United States, 2010–2019

Authors: *Jennifer K. McGee-Avila[1], Cameron B. Haas[1], Eric A. Engels[1], Carol-Ann E. Swain[2], Tabassum Z. Insaf[2], Colby Cohen[3], Jennifer H Hayes[4], Tyler Adamson4, Meredith S. Shiels[1], Qianlai Luo[1]*

[1]National Cancer Institute, Rockville, MD; [2]New York State Department of Health, Albany, NY; [3]Florida Department of Health, Tallahassee, FL; [4]Maryland Department of Health, Baltimore, MD

BACKGROUND

People with HIV who inject drugs (PWHWID) experience unique cancer risks due to delayed HIV diagnosis and treatment, other cancer risk factors, and the accumulation of structural disadvantage (e.g., housing instability, current or former history of incarceration), and barriers to general HIV and cancer care delivery. We aimed to identify cancers that occur at elevated rates and to evaluate racial/ethnic disparities among this historically marginalized (social and economic) group.

METHODS

We used data from the HIV/AIDS Cancer Match (HACM) Study, a population-based linkage of 13 HIV and cancer registries in the United States for the years of 2010-2019 to calculate rates of 10 cancer types among Black, Hispanic, and White PWHWID. Other racial/ethnic groups could not be included due to the limited number of PWHWID with cancer in our study. We estimated rate ratios using Poisson regression stratified by sex and compared PWID to all other HIV risk groups adjusted for age, sex, race/ethnicity and region by cancer type. We also compared risk by race/ethnicity within PWID, estimated age-standardized rates (ASR) and rate ratios using Poisson regression, with Black PWHWID as the reference.

RESULTS

There were 3,252 incident cancers from 2010 to 2019 among 151,669 PWHWID. Among PWHWID, the largest racial/ethnic group was Black PWHWID (41.6%), followed by Hispanic (35.7%), and White (17.3%). Among male PWHWID compared to other risk groups, cancer rates were significantly elevated for liver (RR 3.4 95%CI 3.1,3.7) and lung cancer (RR 1.5 95%CI 1.4, 1.6). Female PWHWID had elevated rates of cancers of the liver (RR 4.1 95%CI 3.2,5.1), lung (RR 1.7 95%CI 1.6,1.9), and anus (RR 1.6 95%CI 1.3,1.9) compared to other risk groups. Among Black PWHWID, the highest incidence rates were for lung, liver, and prostate cancers, and among both Hispanic and White PWHWID, non-Hodgkin lymphoma, lung, and liver cancers had the highest rates. Cancer rates varied substantially among PWHWID across racial/ethnic groups. Compared to Black PWHWID, White PWHWID had a 23% increase in lung cancer incidence, and Hispanic PWHWID had a 34% decrease in lung cancer incidence. Compared to Black PWHWID, prostate cancer rates were 61% lower in White PWID and 47% lower in Hispanic PWID. Rates of anal cancer were elevated among Hispanic PWHWID, a 67% increase compared to Black PWHWID.

CONCLUSIONS

PWHWID are at a particularly high risk of certain cancer types, especially cancers of the lung and liver, likely reflecting the high prevalence of smoking and hepatitis C in PWID compared to other HIV risk groups. Significant differences in incidence rates between racial/ethnic groups exist and more work is warranted to better understand targeted interventions (e.g., prevention efforts in HPV, reduction in HCV, and removing barriers to care) to reduce the disparities by cancer type among PWHWID.

Table 1. **Age-standardized cancer Incidence (per 100,000 person-years) and rate ratios among people with HIV who inject drugs, 2010–2019**

	Age Standardized Incidence Rate (s.e.)			Incidence Ratio (95% confidence interval)		
Cancer	Black	White	Hispanic	Black (ref.)	White	Hispanic
Lung	164.5 (8.1)	195.0 (15.2)	93.8 (7.2)	1.00	**1.23 (1.02-1.47)**	**0.66 (0.55-0.80)**
Liver	107.6 (6.5)	83.0 (10.2)	104.4 (7.4)	1.00	0.76 (0.58-1.00)	1.08 (0.88-1.31)
NHL	89.0 (6.3)	83.3 (9.7)	86.6 (6.7)	1.00	0.90 (0.69-1.17)	1.02 (0.81-1.28)
Prostate	114.5 (6.9)	43.3 (7.8)	61.0 (6.1)	1.00	**0.39 (0.27-0.56)**	**0.53 (0.41-0.69)**
Breast	42.3 (4.3)	41.2 (6.6)	25.9 (3.6)	1.00	0.96 (0.66-1.39)	**0.67 (0.47-0.95)**
Anus	26.9 (3.4)	39.2 (6.9)	44.1 (4.9)	1.00	1.38 (0.91-2.11)	**1.67 (1.16-2.39)**
Colon	28.3 (3.4)	18.4 (4.7)	15.6 (3.0)	1.00	0.63 (0.37-1.08)	**0.51 (0.31-0.84)**
HL	21.5 (3.2)	11.3 (3.7)	24.1 (3.5)	1.00	**0.49 (0.25-0.96)**	1.17 (0.75-1.83)
KS	24.8 (3.6)	19.3 (4.8)	13.5 (2.6)	1.00	0.75 (0.43-1.29)	**0.44 (0.26-0.77)**
Cervix	21.6 (3.4)	15.7 (4.2)	17.7 (3.1)	1.00	0.79 (0.43-1.45)	1.00 (0.60-1.69)

Note. s.e.: standard error; NHL: Non-Hodgkin lymphoma; KS: Kaposi Sarcoma; HL: Hodgkin lymphoma.

Funding: NCI, CDC, NPCR

O2: Incidence of Penile Carcinoma among Men with HIV—Findings from the Potlako+ Navigation Trial, Botswana

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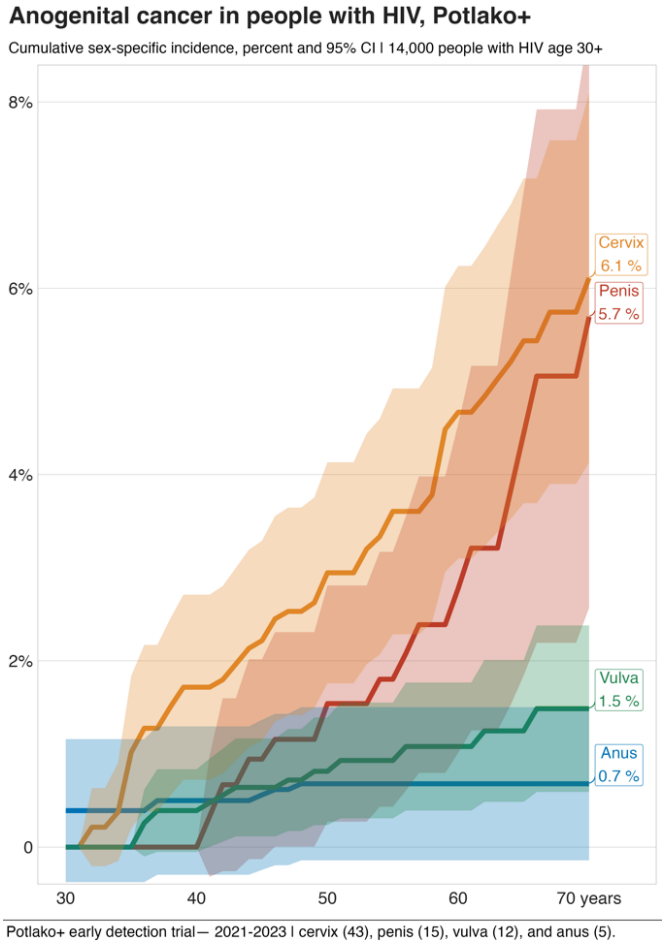
BACKGROUND

Incidence of penile squamous cell carcinoma among men with HIV (MWH) in southern Africa is poorly understood due to considerable barriers to diagnosis related to stigma, poor acceptance of surgical treatment, and unfamiliarity among healthcare providers. In the context of an ongoing community-randomized trial (Potlako+) supporting cancer diagnosis and treatment in rural communities in Botswana, we sought to estimate the cumulative incidence of penile cancer among men with HIV and compare with other HPV-associated malignancies.

METHODS

To estimate the cumulative incidence of penile, cervical, anal, and vulvar carcinoma, we utilized the harmonized data collection of Potlako+/Thabatse and Ya Tsie trials from 20 communities in southern and northeastern Botswana. The Potlako+ trial provides clinician/patient education and enrolls patients with suspected cancer at their primary health facilities. Patients are followed to initiation of cancer care or determination of a benign diagnosis. The Ya Tsie HIV prevention trial (2013 to 2018) obtained a population representative sample of the communities through interviews and HIV testing at randomly selected households. Incident cancers diagnosed (1 January 2021 to 31 December 2023) among community residents aged 30 to 70 were included. Additionally, patients at the four principal cancer treatment centers in Botswana are consented to capture additional cancers of Potlako+ residents that were diagnosed outside of the community clinic. We assumed an annual population growth of 1% and HIV incidence of 1%. Age-specific confidence limits were estimated using the Poisson approximation.



RESULTS

During the period of observation, there were an estimated 3494 men and 8578 women with HIV aged 30 to 70 residing in the study communities. Median age was 53 for men and 51 for women. Fewer than 1% of men had been circumcised as an infant. Penile cancer was the most frequently diagnosed cancer among MWH. A total of 15 incident penile cancers were diagnosed during 11,210 person-years of follow-up of men (incidence 134 per 100,000). All men were receiving ART and majority had nodal involvement. The cumulative incidence of penile cancer among MWH by age 70 was 5.7% (95% CI 2.6 to 8.8%) with greatest risk after age 50. Observed incidence of penile cancer was similar to cervical cancer among women (6.1%, 95% CI 4.1 to 8.1%) and greater than vulvar cancer (1.5%, 95%

CI 0.6 to 1.5%) or anal cancer among both men and women (0.7%, 95% 0 to 1.5%).

CONCLUSIONS

Penile squamous cell cancer is common among men with HIV in this rural African context. Further investigation is needed to better understand population at risk and assess approaches of precancerous lesion screening and treatment to reduce the penile cancer burden.

O3: Access to Cervical Cancer Screening Cascade in Côte d'Ivoire: A Decade Real-World Program Evaluation According to HIV Status

Authors: *Simon Boni[1,2,3], David Goore[3], Franck Gnahatin[1], Mesmin Adie[1], Denise Kpebo[4], Apollinaire Horo[5], Innocent Adoubi[1,6], Antoine Jaquet[3]; on behalf of the IeDEA West Africa Collaboration*

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BACKGROUND

The global cervical cancer (CC) elimination strategy recommends to achieve a 70% coverage for CC screening and 90% of precancerous lesions treated in eligible women. While integration of CC screening services in HIV care has been implemented in many high burden settings such as sub-Saharan Africa, access to CC screening and care among women living with HIV (WLHIV) remains poorly documented at a population level. We evaluated progress towards these WHO CC elimination targets according to HIV status in Côte d'Ivoire during the 2010-2021 period.

METHODS

A CC screening registry was initiated in Côte d'Ivoire since 2010, collecting standardized individual-level data from all health facilities offering visual inspection with acetic acid (VIA). Initially restricted to the economic capital (Abidjan), the registry progressively expanded to the three most populated administrative regions accounting for almost half of nationwide eligible women. The CC screening coverage was estimated based on the 2021 population census and Spectrum 2023 (HIV national database) in women aged 25-49 years from the general population and in WLHIV. CC screening and care cascade indicators (VIA-positivity, same-day cryotherapy/thermal ablation) were compared according to HIV status, using Chi-square test. Access to cryotherapy/thermal ablation and associated factors were analyzed through a logistic regression model.

RESULTS

A total of 66,268 women aged 34 years (Interquartile range: [28 ; 41]) in median were screened for CC, 11,251 (17.0%) being WLHIV. The estimated CC screening coverage was 4.4% (95%CI [2.6-5.2]) in all women, and 14.8% (95%CI [14.6-15.1]) in WLHIV. Overall, VIA positivity rate was 6.4% (95% CI: 6.2 – 6.5), higher in WLHIV (9.1% [95% CI: 8.6 – 9.7]) compared to their HIV-uninfected counterparts (5.8% [95% CI : 5.6 – 7.0]), p<0.001. Among the 4,210 VIA-positive women, 3,500 (83.1%) were eligible for same-day cryotherapy/thermal ablation (83.9% in WLHIV). Access to same-day cryotherapy/thermal ablation was 59.1% (57.1% in women without HIV and 65.2% in WLHIV, p<0.001), declined over time from 71.7% before 2015 to 51.9% in 2021. In WLHIV, It decreased from 72.8% to 44.2% (p<0.001), but was higher in those screened in HIV specialized clinics (81.6%) versus HIV-integrated facilities (53.2%), p<0.001). Globally, access to same-day treatment was higher in WLHIV (aOR= 1.55 [CI: (1.32-1.84]) and women screened in secondary level (aOR=1.82 [CI: 1.49-2.23]) or tertiary level facilities (aOR=1.79 [CI: 1.54-2.09]) compared to primary level facilities.

CONCLUSIONS

In 2021, CC screening program performances remained particularly low regarding the 2030 CC elimination goals. Strengthening health education and wider integration strategies are needed to improve access to CC screening in Côte d'Ivoire. The low access to cryotherapy/thermal ablation is unacceptably low, particularly in WLHIV, raising the need to improve/expand integration of cryotherapy/thermal ablation in integrated HIV services and primary healthcare facilities. Overcoming delivery gaps and implement monitoring/tracing strategies for positively screened women is a priority as HPV-based primary screening in being scaled-up in the country.

O4: Primary Effusion Lymphoma Prognostic Score (PEL-PS): A Validated International Prognostic Score in HIV-Associated Primary Effusion Lymphoma

Authors: *Kathryn Lurain[1], Ramya Ramaswami[1], Eric Oksenhendler[2], David Boutboul[2], Alessia Dalla Pria[3], Laura Ulrich[3], Krithika Shanmugasundaram[1], Thomas S. Uldrick[1], Mark Bower[3], Robert Yarchoan[1], Laurence Gerard[2], and Seth M. Steinberg[4]*

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BACKGROUND

Primary effusion lymphoma (PEL) is a rare, B-cell non-Hodgkin lymphoma (NHL) caused by Kaposi sarcoma herpesvirus (KSHV). It is most common in people with HIV and presents as malignant body cavity effusions with inflammatory signs and symptoms. 80% of tumors are also EBV positive. Little is known about prognostic factors in PEL, and the International Prognostic Index (IPI) has not been validated in PEL. In a large international cohort, we sought to develop and validate a prognostic model in HIV-associated PEL.

METHODS

We collected demographic and clinical data from patients with HIV$^+$ PEL who received first-line anthracycline-containing chemotherapy. The training set used to develop the predictive model was identified from patients treated at the National Cancer Institute (NCI) in the United States and Chelsea and Westminster Hospital (CWH) in the United Kingdom from 2000 to 2022. We performed univariate Kaplan-Meier analyses to determine prognostic factors of overall survival (OS). Factors with unadjusted p-values <0.10 were candidates for inclusion in the Cox proportional hazards model. We applied backward and stepwise selection to determine independent factors for inclusion in the final Cox model. The factors identified in the Cox model were able to form two groups of patients who were predicted to have good or poor survival. The factors included in the Cox model were then applied to a validation set identified from patients with HIV$^+$ PEL treated with first-line anthracycline-containing chemotherapy at the Hôpital Saint-Louis in France over the same period. T-cell counts and peripheral blood KSHV viral loads were not measured uniformly across institutions and could not be evaluated in the Cox model.

RESULTS

For the training cohort, we identified 59 patients with PEL treated with first-line anthracycline-containing chemotherapy at NCI and CWH. The median OS was 10.6 years and not statistically different between institutions (P=0.27). In univariate analysis, 3 factors were statistically negative prognostic factors: ECOG 3-4, hemoglobin <8 g/dL, and IPI 4-5. Two factors were statistically positive prognostic factors: extracavitary only disease, albumin ≥2.55 g/dL, platelets ≥135 K/L, and EBV$^+$ tumors. In the multivariable Cox model, only 2 factors, ECOG ≥3 (P=0.007; hazard ratio [HR]=4.0 [95% CI: 1.5-11.1]) and hemoglobin <8 g/dL (P=0.006; HR=3.8 [95% CI: 1.5-9.7]) were jointly associated with lower survival probability. After forming groups based on the permutations of hemoglobin and ECOG, a scoring system was devised using patients with no negative prognostic factors (score 0: hemoglobin ≥8 g/dL and ECOG ≤2) versus patients with 1-2 negative prognostic factors (score 1: hemoglobin <8 g/dL and/or ECOG ≥3) resulting in a median OS of 10.6 years (IQR: 10.6-not estimable) versus 0.8 years (IQR: 0.3-2.8 years), p<0.0001, respectively.

The validation cohort was similar to the training cohort in terms of patient and disease characteristics. When we applied the multivariable model to the 58 patients in the validation cohort, this is how ECOG and hemoglobin jointly predicted OS in this cohort: (ECOG ≥3: P=0.0003; HR=7.7 [95% CI: 2.5-23.1] and hemoglobin <8 g/dL: P=0.21; HR=1.7 [95% CI: 0.8-3.7]). Median OS in patients with score 0 was 16.9 years (IQR:8.7-16.9) versus 0.6 years (IQR: 0.3-1.0) in those with score 1-2 (p<0.001), validating the potential usefulness of the PEL-PS score.

CONCLUSIONS

Using the largest international cohort of patients with HIV-associated PEL ever evaluated, we developed and validated the PEL-PS, which is easily implementable in any clinical setting using ECOG and hemoglobin. Low hemoglobin may be a surrogate marker for KSHV-associated inflammation and elevated IL-6 levels, and this association should be evaluated further.

O5: Lymph Node and Plasma Cell-Free DNA Sequencing among PWH Attending an FNA Clinic in Soweto, South Africa: High Accuracy of Plasma Clonal Immunoglobulin for Lymphoma

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BACKGROUND

HIV is associated with the development of aggressive B-cell lymphomas. As curative intent remains the mainstay of therapy, timely diagnosis is of utmost importance. In low-resource settings, fine needle aspiration (FNA) represents an early step in the clinical triage of potential lymphoma in patients with lymphadenopathy. This study explores the diagnostic utility of clonal immunoglobulin (clg) next generation sequencing (NGS) in lymph node (LN) and plasma samples from people living with HIV (PWH) attending an FNA clinic in South Africa.

METHODS

A prospective, observational cohort of patients undergoing FNA at Chris Hani Baragwanath Academic Hospital in Soweto, South Africa, was undertaken. Study participants were enrolled at time of FNA from September 2021 to December 2022 and underwent serial follow-up visits over 8 months or until development of lymphoma or death. Whole blood was collected in cell-stabilizing tubes and an additional FNA pass of the LN was collected in ThinPrep vials from each participant. Plasma cell-free DNA (cfDNA) and LN FNA genomic DNA (LN) were isolated. Both samples underwent NGS of the immunoglobulin heavy chain gene as previously described. NGS data were analyzed for evidence of clg rearrangements in either cfDNA or gDNA independently and blinded to the FNA cytology diagnosis.

RESULTS

One hundred and forty-six PWH undergoing FNA were enrolled, including 70 males (48%). The median age was 40 years (IQR 33-49) and median CD4 count was 210 (IQR 102-408; n=139). Cytological findings suggestive of lymphoma were seen in 19 participants (13%). An additional two participants, who had reactive cytologic findings, were subsequently diagnosed with lymphoma during the follow-up period. The initial analysis of all lymphoma participants (n=21) and matched non-lymphoma participants (n=34) is summarized. Fifty-two participants had paired cfDNA and LN NGS, while three participants only had either LN (n=2) or cfDNA (n=1) results. NGS of the LN showed a range of clonal results in participants without lymphoma, which was not observed in plasma. Among 12 non-lymphoma participants who had a clonal result in the LN, the FNA cytology diagnoses were tuberculosis (TB, n=9), reactive (n=2) and blood/non-diagnostic (n=1). A single participant with TB had a detectable clg in cfDNA. The LN analysis yielded a sensitivity of 43% (9/21), a specificity of 64% (21/33) and an accuracy of 55% for lymphoma. The cfDNA analysis yielded a sensitivity of 55% (11/20), a specificity of 97% (32/33) and an accuracy of 81% for lymphoma. The two patients who were subsequently diagnosed with lymphoma had clg sequences detectable in cfDNA at the time of the FNA.

CONCLUSIONS

To our knowledge, this is the first study to compare the diagnostic utility of detecting clg sequences in plasma and LN FNA in PWH presenting with lymphadenopathy. While sensitivity for lymphoma is similar in plasma and LN, specificity is far greater in plasma. The high false positive rate in LN FNA in participants without lymphoma has not been previously reported in PWH, especially not in the context of a high rate of TB coinfection and is a potential pitfall of implementing clonality testing of LN FNA for the diagnosis of lymphoma.

O6: Inclusion of People with HIV in Cancer Clinical Trials—2012 to 2024

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BACKGROUND

Cancer has become the leading cause of death for people with HIV (PWH). As stated in each NCCN cancer treatment guideline, the "best management for any patient with cancer is in a clinical trial." However, people with HIV have frequently been excluded from cancer clinical trials by restrictive entry criteria and bias encountered in healthcare settings. To improve access, in 2017, the HIV Working Group of the American Society of Clinical Oncology (ASCO) recommended the inclusion of most PWH without interacting medications and preserved CD4 cell count. Similar guidance from the FDA in 2020 is utilized by IRBs at many cancer centers in the US. We examined trends of inclusion of PWH in cancer clinical trials in the context of these recommendations and advocacy by PWH.

METHODS

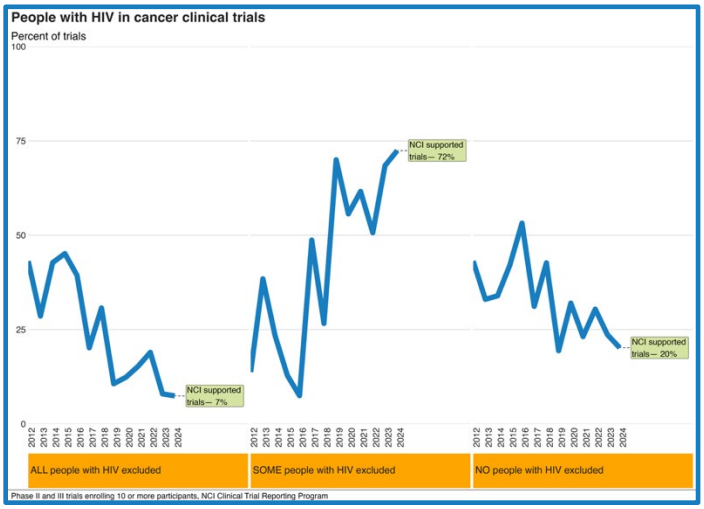
We utilized the database of the Clinical Trials Reporting Program (CTRP) of the National Cancer Institute (NCI), which includes all cancer clinical trials funded directly or indirectly by the NCI (including all trials conducted at the 72 Designated Cancer Centers). All phase II or III trials enrolling at least 10 participants from 2012 to 2024 were included. We first identified trials that included HIV-relevant factors (e.g. HIV diagnosis, CD4 cell count, antiretroviral therapy) in trial entry criteria. Subsequently, trials were classified by an iterative text string detection algorithm as excluding all PWH or excluding some PWH dependent on HIV-relevant factors. Trials excluding all PWH on any antiretroviral treatment were considered excluding all PWH. We undertook a manual review of 5% of trials.

RESULTS

A total of 9,321 trials were identified. All PWH were excluded in 4,217 (46%); some PWH included in 1,250 (14%); all PWH included in 3,617 (40%) trials. From 2012 to 2024, the proportion of trials excluding all PWH declined from 43% to 7% and the proportion of including some PWH increased from 13% to 72%. The proportion of trials including all PWH decreased from 43% to 20% during the period. Cancer centers with the largest number of active trials appeared less inclusive of PWH.

CONCLUSIONS

People with HIV continue to face substantive challenges to cancer clinical trial participation in the United States, likely impairing clinical and scientific outcomes. Consideration should be given to the revision of guidance to reduce barriers to participation by PWH and align with criteria for other chronic conditions.



O7: 5-Year Update on Frontline Brentuximab Vedotin with AVD for Stage II–IV HIV-Associated Classical Hodgkin Lymphoma (AMC-085)

Authors: *Paul G. Rubinstein[1], Deukwoo Kwon[2,3], Amy Chadburn[4], Lee Ratner[5], David H. Henry[6], Ethel Cesarman[4], Juan Carlos Ramos[7], Elad Sharon[8], Erin G. Reid[9], Richard F. Ambinder[3], Ronald Mitsuyasu[10], Nicolas Mounier[11], Caroline Besson[12], and Ariela Noy[13] for the AIDS Malignancy Consortium and the Lymphoma Study Association, Michelle A. Rudek[3]*

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BACKGROUND

In the phase 3 ECHELON-1 (E1) study (NCT01712490), treatment with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (BV-AVD) significantly improved modified progression-free survival (PFS) in patients with newly-diagnosed Stage III/IV cHL compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Recently, a 6-year overall survival was also demonstrated. Persons living with HIV (PLWH) were excluded from all BV clinical trials. AMC-085 (NCT01771107) was a phase 1/2 open label study of BV-AVD for previously untreated stage II-IV HIV-associated Hodgkin lymphoma. At 2 years, AMC 085 reported a progression free survival (PFS) of 87% and an overall survival (OS) of 92% for advanced stage disease, with comparable safety to the BV-AVD in the non-HIV population. Here we report pre-planned 5 year follow-up.

METHODS

Between March 2013, and March 2019 41 patients with previously untreated Stage II-IV HIV-associated-cHL were enrolled on AMC 085 and planned to receive six cycles of BV-AVD on days 1 and 15 of a 28-day cycle. An interim PET scan after cycle 2 (PET2) and end of treatment (EoT) PET were required. Strong CYP3A4 inhibitors were excluded, and growth factor support was mandated. Peripheral neuropathy (PN) in patients with ongoing symptoms at the EoT was monitored during the extended follow-up. Kaplan-Meier method was used to estimate PFS and OS. Descriptive statistics was used for adverse event data.

RESULTS

Of the 41 patients enrolled, 34 had advanced stage and 7 stage 2B HIV-cHL. Current median follow up is 67 months. The 5 year PFS and OS was 78% (95% CI:60-88%) and 89% (95% CI: 74-95%) respectively for the entire cohort. For advanced stage disease the 5 year PFS and OS were 77% (95% CI:57-88) and 87% (95% CI:69-95%), respectively. For comparison, the 5 year PFS for the E1 study for BV-AVD was 82% and 75% for the ABVD arm. Historical data of HIV-cHL with ABVD for advanced stage disease demonstrated a 5 year OS of 71-81% (Xicoy, Haematolgica, 2007, Montono, JCO, 2012). Four patients died, though 1 died in complete remission due to trauma. The remaining deaths were due to febrile neutropenia, disease progression, and a patient who only received one cycle of chemotherapy, and elected treatment discontinuation died of infection 1 month after withdrawal. 36/39 were PET 2 negative and all had an EoT negative PET without any correlation to relapse. Six patients of 41 (15%) had grade (G) 3 peripheral neuropathy at EoT, with no G4 neurologic toxicities. At 5 years, 83% had resolved neuropathy to baseline with a median time of resolution of 15.3 months (range: 1 to 26 months), with only 1 patient having persistent G3 peripheral neuropathy, similar to the E1 study where 19% of the BV-AVD arm had continued neuropathy.

CONCLUSIONS

With a median follow-up of 67 months, PLWH and stage II-IV HL treated with BV-AVD enjoyed a PFS and OS of 78% and 89% respectively, with all events occurring within 3 years of enrollment. Neuropathy resolved to baseline in 83% of patients similar to the non-HIV BV-AVD studies. Compared to historical controls, PFS and OS appear similar to the non-HIV population and superior to trials of advanced stage HIV-cHL treated with ABVD.

O8: Abemaciclib, A CDK4/6 Inhibitor, in HIV-Associated and HIV-Negative Kaposi Sarcoma

Authors: *Jose Mercado Matos[1], Kathryn Lurain[1], Anaida Widell[1], Irene Ekwede[1], Ijeoma Agwu[1], Margaret Namubiru[1], Ralph Mangusan[1], Thomas Odeny[1], Crystal Lu[1], Seth Steinberg[2], Denise Whitby[3], Robert Yarchoan[1], Ramya Ramaswami[1]*

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BACKGROUND

Kaposi sarcoma (KS), caused by Kaposi sarcoma herpesvirus (KSHV), is a multicentric angioproliferative tumor seen in people with and without HIV. Abemaciclib is an oral cyclin-dependent kinase (CDK) inhibitor that targets CDK4 (cyclin D1) and CDK6 (cyclin D3) cell cycle pathways, thus inducing cell cycle arrest. Abemaciclib is licensed by the Food and Drug Administration for use in a subset of patients with early and metastatic breast cancer. *In vitro* studies of KSHV-infected cell lines have shown that CDK4/6 inhibitors, such as abemaciclib, enhance T-cell activation and increase host immune cell surface expression, thereby hindering virus-associated immune evasion. Here, we investigated the safety and activity of abemaciclib in participants with KS.

METHODS

In this open label, non-randomized, two-stage Phase I/II study of participants with KS, there were two primary objectives. In Phase I, we evaluated the safety and tolerability of abemaciclib in participants with KS using a 3+3 dose de-escalation design to identify a maximum tolerated dose (MTD). The first group of participants were treated at dose level 1 (DL) of 200mg twice daily for days 1-28 of a 28-day cycle. Dose de-escalation of abemaciclib was permitted for individual participants who experienced toxicities. In Phase II, we assessed the overall response rate of abemaciclib of all participants and stratified by prior systemic KS therapy (Arm 1 target: 15 participants with previously treated KS and Arm 2 target: 10 participants with untreated KS). Adherence to antiretroviral therapy (ART) among people with HIV (PWH) for at least 8 weeks was required prior to enrollment. Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE v.5.0). KS response was evaluated using the modified AIDS Clinical Trials Group criteria.

RESULTS

Twenty-five cisgender men (18 PWH) with a median age of 47 years were enrolled in this ongoing study. Twenty participants had severe (stage T1) KS. In the Phase I portion, 6 participants were enrolled at 200mg twice daily without dose-limiting toxicities and was the MTD for Phase II. In the Phase II portion, 12 participants (10 PWH) were enrolled to Arm 1, and 7 participants (4 PWH) were enrolled to Arm 2. The baseline median HIV viral load among PWH was <20 copies/ml. Two participants in Arm 1 did not proceed after one cycle due to grade 2 anxiety unrelated to study therapy and these participants were replaced. The most common grade 1 and 2 adverse events related to abemaciclib were anemia and diarrhea. In 12 participants, recurrent grade 3 and grade 4 neutropenia led to dose reductions of abemaciclib.

Among the 23 evaluable participants receiving ≥ 2 cycles, 18 participants had a partial response (78% [95% confidence interval: 56-93%]), 4 participants had stable disease and 1 pt had progressive disease. All 7 participants in Arm 2 with previously untreated KS had a partial response. The baseline median CD4 T-cell count among all participants was 416 cells/μL (interquartile range: 237-608 cells/μl), and this did not change after 2 cycles (P=0.32) or at the end-of-treatment (P=0.9).

CONCLUSIONS

Abemaciclib is a novel oral therapeutic option for KS in participants with and without HIV. Adverse events were within the expected toxicity profile of abemaciclib and were managed with individual dose reductions and other supportive measures. There was no significant impact on the CD4 T-cell count among all participants. Activity was notable for participants who had not received prior systemic therapy for KS.

O9: sEph-B4-HSA Is Effective and Tolerable in Kaposi Sarcoma: Results of the AMC-096 Phase 2 Trial

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BACKGROUND

Kaposi sarcoma (KS), an endothelial cell tumor dependent on VEGF-Notch-Ephrin signaling caused by human herpesvirus-8 (HHV8), often recurs requiring serial therapies in affected persons. sEphB4-Human Serum Albumin (sEphB4-HSA) is a novel recombinant single fusion protein consisting of HSA at the c-terminus, engineered to increase circulatory half-life. sEphB4, blocks EphB4-induced phosphorylation of EphrinB2, expressed in KS tumor cells, inhibiting migration of endothelial cells and disrupting angiogenesis, leading to cell growth inhibition and death. The primary objective of this phase 2 study was to evaluate the clinical response & tolerability of sEphB4-HSA in KS.

METHODS

Key inclusion criteria included biopsy proven KS, age ≥18 years, adequate hematologic, renal, and hepatic function, and those with human immunodeficiency virus (HIV) were required to be on a stable antiretroviral therapy (ART) regimen ≥12 weeks. Key exclusions were symptomatic visceral KS, active cardiac disease, >1+proteinuria. For those with HIV, no minimum CD4 count or maximum HIV viral load (VL) was specified. sEphB4-HSA was administered intravenously days 1 & 15 of 28-day cycles at a starting dose of 15 mg/kg for the first 3 participants; data demonstrating drug accumulation led to a revised starting dose of 10mg/kg for subsequent participants. Up to 12 cycles were allowed.

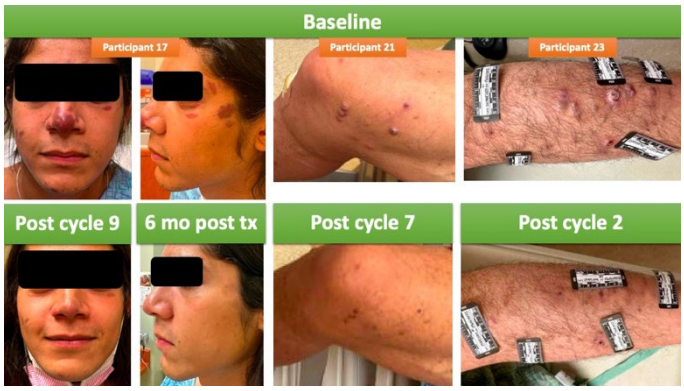
RESULTS

Twenty-one of 23 participants enrolled from five AMC sites received at least one dose of protocol therapy. All participants were male, with 4% identifying as Asian, 17% Black, and 65% White; 44% identified as Hispanic vs. 48% non-Hispanic. Mean age was 46 years. One participant had non-HIV KS. In participants with HIV, median baseline CD4 cell count was 478/mm^3 and HIV viral load was 286 copies/ml. Among the 20 participants evaluable for response, partial response (PR) occurred in 14 (70%), see figure for examples. The median time to response was 4 months (range 1-10). Two serious adverse events occurred (skin infections), both considered unrelated to sEphB4-HSA. Common adverse events at least possibly related to sEphB4-HSA (# of participants experiencing, # highest grade [gr]) included hypertension (21, 14 gr 3), proteinuria (8, 4 gr 2), headache (7, 2 gr 2), and fatigue (7, 1 gr 2).

CONCLUSION

The pre-specified null-hypothesis was rejected based on obtaining joint probabilities of clinical response ≥60% and unacceptable toxicity ≤10%. Single agent sEphB4-HSA is a novel targeted therapeutic tolerable and active in KS, with responses occurring as early as cycle 1. Assessment of secondary and exploratory objectives, including quality of life, pharmacokinetics and pharmacodynamics, and T cell activation studies, is ongoing and will be updated at the meeting.

Support: NIH: 2 UM1 CA121947-14; VasGene Therapeutics



O10: Spatial Transcriptomics of Patients with Kaposi Sarcoma Identifies Mechanisms of Immune Evasion

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BACKGROUND

To identify the cell types that are infected with KSHV and the immune interactions in Kaposi sarcoma (KS) lesions, we performed spatial transcriptomics with seven KS skin tumors.

METHODS

We used a single-cell RNA-sequencing reference dataset from five healthy skin donors with a method to conduct spatially informed cell-type deconvolution for spatial transcriptomics. This allowed us to predict the relative amounts of each cell type within the 55 µm spots in the patient sample sections. We included custom probes for five KSHV genes (ORF72, K12, PAN, ORF75, K8.1) that allowed us to measure human and KSHV expression patterns at the same time.

RESULTS

These methods allowed us to define spots with and without KSHV transcripts in the same tissue section. We determined a human gene panel of 75 genes that accurately determines whether a spot is KSHV-infected. We also identified the latent and lytic KSHV gene expression profiles in these KS skin samples. We then compared the spatial gene expression data of KS skin samples with six normal skin samples and found higher expression of marker genes corresponding to macrophages/dendritic cells, lymphatic endothelial cells, and vascular endothelial cells in the KS skin lesions when compared to normal skin samples. Within one important KS tumor section with an equal number of KSHV-infected and uninfected spots, we compared uninfected and infected spots and found increased markers for lymphatic and vascular endothelial cells, but decreased markers of fibroblasts and macrophages in the KSHV-infected spots. When comparing human gene expression between KSHV-infected spots and uninfected spots, one of the top differentially expressed genes in the KSHV-infected spots was *STC1*, which we previously found to be elevated in our bulk RNA-sequencing analyses of KS tissue with matched normal tissue (PMID: 37740179). Additionally, we showed that levels of secreted STC1 protein increased after KSHV-infection of primary lymphatic endothelial cells. Others have previously reported that STC1 protein is secreted and can inhibit the chemotactic response of macrophages to monocyte chemotactic protein and other stimuli. Our spatial transcriptomic results from thousands of spots across multiple KS tumors indicated a correlation between high levels of *STC1* and decreased expression of macrophage markers, suggesting that STC1 might prevent macrophages from infiltrating to KSHV-infected endothelial cells. We also discovered expression of other immune inhibitory factors at interesting locations in KS tumors.

CONCLUSIONS

The inverse correlation of high expression levels of *STC1* and macrophage markers in the skin KS tumors, combined with previous reports of STC1 protein inhibiting macrophage chemotaxis present a model where KSHV infection of endothelial cells increases STC1 protein secretion from these infected cells. Secreted STC1 protein then prevents macrophage chemotaxis to areas of KSHV infection in this model. Together these data offer mechanisms by which KSHV infection may remodel skin tissue and inhibit immune responses against KSHV infection.

O11: Comprehensive Analysis of Tumor-Infiltrating Lymphocytes from Kaposi Sarcoma Tumors Reveals Public KSHV- and HIV-Specific T-Cells with Potential Therapeutic Value

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BACKGROUND

KS most commonly develops in the setting of T-cell deficiency or dysfunction. In sub-Saharan Africa, primary infection with KSHV occurs in childhood, but most cases of KS in people living with HIV (PLWH) and people without HIV infection develop many years, often decades, later. This suggests that loss or impairment of a T-cell component of pre-existing KSHV-specific immunity underlies KS development. Strategies that preserve or restore the T-cell component of KSHV-specific immunity in PLWH and others at risk hold promise for the prevention or treatment of KSHV-associated disease.

METHODS

We hypothesized that KS tumors contain significant populations of KSHV-specific T-cells and performed comprehensive T-cell repertoire profiling of >500 biospecimens from >200 adults with KS, including 299 KS tumors from 106 PLWH and 38 adults without HIV infection. We also performed scRNAseq with capture of T-cell receptor (TCR) alpha and beta chain sequences on 20 PBMC samples from 9 of the 144 individuals. Computational analysis of the TCR sequence data was performed to identify TCR alpha-beta pairs that were likely to be specific for peptide antigens encoded by KSHV or HIV and to predict their MHC restriction. Jurkat-based reporter T-cells carrying a *NR4A1*-mNeonGreen transgene that is expressed after TCR ligation were transduced with recombinant lentiviruses encoding TCRs with predicted specificity for KSHV-encoded peptides and predicted MHC restriction. TCR-transduced Jurkat reporter cells were co-cultured with COS-7 cells that had been transiently co-transfected with (i) a plasmid encoding the predicted class I MHC restricting element for that TCR, and (ii) a library of 93 plasmids collectively encoding all curated open reading frames (ORFs) in the KSHV genome. KSHV ORFs with MHC-dependent T-cell stimulatory activity were iteratively subcloned to identify the minimal interval with stimulatory activity. Synthetic peptides encoded by the sequence in the minimal stimulatory region were tested for MHC-dependent recognition by TCR-transduced Jurkat T-cells as well as primary $CD8^+$ T-cells.

RESULTS

Computational analysis of 2.85 million TCR beta chain sequences and 61,763 paired TCR alpha-beta sequences revealed 14,698 TCR alpha-beta pairs that are predicted to be specific for either KSHV or HIV, found in KS tumors from multiple patients (i.e., “public”), and strongly associated with a specific MHC class I or II allele. Lentiviruses encoding an initial subset of 20 predicted KSHV- or HIV-specific “public” alpha-beta TCRs were constructed. Jurkat reporter cells transduced with two similar public TCRs (shared by 14 individuals with KS) predicted to be KSHV-specific and restricted by HLA-B*45:01 were reactive with COS-7 cells co-transfected with a plasmid encoding HLA-B*45:01 and a plasmid encoding KSHV *ORF6*. Plasmids encoding a nested set of *ORF6*-derived minigenes were used to map the minimal interval in *ORF6* that contained the stimulatory activity to a short region encoding a nonameric peptide with predicted high-affinity binding to HLA-B*45:01. The synthetic nonameric peptide was recognized by TCR-transduced Jurkat T-cells and primary $CD8^+$ T-cells when pulsed at nanomolar concentration onto HLA-B*45:01$^+$, but not HLA-B*45:01$^-$, target cells. Six public TCRs showed high-affinity recognition of HIV-encoded peptides, including $Gag/Pol_{982\text{-}990}$ (1 TCR), HIV $Vpr_{34\text{-}42}$ (2 TCRs), and $Nef_{71\text{-}79}$ (3 TCRs), all presented by HLA-B*42:01.

CONCLUSIONS

Comprehensive analysis of T-cells infiltrating KS tumors from PLWH and people without HIV infection from Uganda reveals a population of public T-cells carrying TCRs with high-affinity specificity for KSHV- and HIV-encoded peptides. Evaluation of additional predicted KSHV- and HIV-specific TCRs is in progress. Functional analysis of KSHV- and HIV-specific T-cells infiltrating KS tumors and circulating in peripheral blood may provide insights into the pathogenesis, natural history, and treatment response of KS and other KSHV-associated diseases and could provide a blueprint for specific immune interventions that would be effective for the prevention or treatment of KS and KSHV-associated diseases.

O12: Patient-Derived Xenografts of Kaposi Sarcoma Are a Novel Model to Map Herpesvirus-Driven Impacts on the Cellular Milieu of Skin Tumors

Authors: *Xiaofan Li[1], Zoë Weaver Ohler[2], Amanda Day[2], Laura Bassel[2], Anna Grosskopf[1], Bahman Afsari[1], Takanobu Tagawa[1,3], Ralph Mangusan[1], Kathryn Lurain[1], Robert Yarchoan[1], Joseph Ziegelbauer[1], Ramya Ramaswami[1], Laurie T. Krug[1]*

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BACKGROUND

Kaposi sarcoma (KS) is defined by hyperangiogenesis, inflammatory infiltrates, and Kaposi sarcoma herpesvirus (KSHV) infected spindle cells. The exploration of novel therapies is hampered by the lack of a patient-derived preclinical animal model. Here, we characterize patient-derived KS xenografts (PDXs) in immunodeficient NOD/SCID/gamma (NSG) mice.

METHODS

Tested variables included VEGF supplementation of matrigel and tumor dissociation prior to implantation, in addition to human IL-6 expression. Thirteen cutaneous KS biopsies from patients with HIV were subcutaneously implanted into NSG or NOG mice transgenic for human IL-6. Key pathological features of KS were monitored by immunohistochemistry and immunofluorescence for KSHV LANA and markers of endothelial cells and proliferation. Spatial transcriptomic analysis was performed on two pairs of KS biopsies and their respective PDX to examine five viral transcripts (*v-cyclin*, *kaposin*, *ORF75*, *K8.1*, and *PAN*) and host gene expression, and analyze cellular composition and predict gene signatures. Last, cell cultures derived from two PDX explants were profiled for cell type by immunoblot, virus infection by qRT-PCR and ELISA for chemokine production.

RESULTS

Neoplastic CD34+ spindle cells with positive immunohistochemistry staining for KSHV LANA revealed that infected endothelial cells were maintained for long periods in recipient NSG mice. Regardless of the tested variables and clinical history of patient volunteers, there was a mean 4.1-fold increase in LANA+, human endothelial cells density in twelve of thirteen KS-PDX compared to respective input biopsies. The Ki-67 proliferation marker overlapped with LANA+ cells, consistent with virus-driven cell expansion. Spatial transcriptome analysis revealed increased expression of viral transcripts from latent and lytic gene classes in the KS-PDX. In addition, signatures genes of KS tumors and infected primary endothelial cells exhibited a heightened expression profile in the KSHV+ regions of the KS-PDX. Cells with characteristics of tumor associated fibroblasts were derived from KS-PDX and propagated *in vitro* for 15 passages. These KSX fibroblast-like cells were permissive for *de novo* KSHV infection, and KSX-476 produced CXCL12 upon infection, suggesting this cell type may produce a known ligand of CXCR4 upregulated on KSHV+ endothelial cells in the tumor microenvironment.

CONCLUSIONS

Taken together, the reproducible expansion of KSHV-infected endothelial cells across PDX from multiple donors, in addition to the recapitulation of a KS tumor gene signature, supports the application of patient-derived cutaneous KS xenografts as a pre-clinical model to test novel therapies.

O13: Recombinant mAbs Define Sites of Vulnerability on the KSHV gH/gL Complex

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BACKGROUND

Kaposi sarcoma-associated herpesvirus (KSHV) is an oncogenic virus that causes Kaposi sarcoma, one of the most common malignancies in people living with HIV worldwide. KSHV also causes primary effusion lymphoma and multicentric Castleman disease. Infection is common in sub-Saharan Africa and often occurs early in childhood, while in the Western Hemisphere, infection is rare in the general population but more frequent in men who have sex with men. A vaccine that prevents KSHV infection and/or associated morbidity and mortality represents a critical unmet need. Although, the types of immune responses a vaccine would need to elicit have not been well defined, it is likely that neutralizing antibodies will be an important component of an effective vaccine response. The gH/gL glycoprotein complex is an important target of KSHV- neutralizing antibodies; however, the epitope specificities targeted by these antibodies remain undefined.

METHODS

We produced recombinant gH/gL and used it as a probe to isolate gH/gL-specific memory B cells from KSHV+ PBMC samples using single cell sorting. Antibody transcripts were recovered using RT-PCR and then cloned into expression vectors to produce recombinant monoclonal antibodies (mAbs). The mAb affinities for gH/gL were measured by biolayer interferometry (BLI). The epitopes of the mAbs were determined by a combination of competitive binding analyses using BLI and negative stain electron microscopy. The ability of the mAbs to neutralize KSHV infection of Vero and EBV+ lymphoblastoid cell lines (LCLs) was measured in vitro using recombinant KSHV reporter viruses.

RESULTS

From one gH/gL seropositive donor, we isolated a panel of 10 monoclonal antibodies (mAbs) that bind recombinant gH/gL with nanomolar affinities. Epitope binning analyses revealed that the mAbs bind to 5 distinct epitope regions on gH/gL. At least one highly potent neutralizing mAb mapped to the EphA2 binding site as determined by inhibition of the receptor-ligand interaction and negative stain electron microscopy of the mAb/gH/gL complex. The other neutralizing mAbs target novel sites of vulnerability outside of the EphA2 binding site. We are currently defining the molecular details of these epitopes using electron microscopy.

CONCLUSIONS

These mAbs help to define the relevant epitope targets for KSHV vaccine design, have utility in understanding the role of antibodies in preventing KSHV infection, and provide valuable tools to understand the molecular details of the KSHV entry process.

O14: Ectopic Expression of KSHV miR-K12-9 Can Induce Transformation of Immortalized and Primary Endothelial Cells

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BACKGROUND

The KSHV microRNAs (miRNAs) contribute to viral infection in numerous and varied ways. While there is some targeting and functional overlap, the individual miRNAs can also play distinct, nonredundant roles. Through experiments carried out in endothelial cells, we observed that miR-K12-9 in particular displays unique properties that set it apart from the other viral miRNAs. First, Telomerase-Immortalized Vein Endothelial (TIVE) cells were infected with a panel of KSHV mutants, each lacking one of the 12 miRNA genes. While all of the infected cell lines had some phenotypical differences from WT-infected cells, those infected with the miR-K12-9 knockout mutant (ΔmiR-K12-9) had a distinct morphology and growth habit. They grew much larger than ordinary cells while the rate of proliferation slowed significantly. RNA-seq on the ΔmiRK12-9-infected cells showed numerous differentially expressed genes compared to WT.

METHODS

To further study this miRNA, we generated Telomerase-Immortalized Microvascular Endothelial (TIME) cells expressing either the miR-K12-9 hairpin or a scramble control miRNA from a lentivirus. Cell proliferation assays and colony formation assays were used to characterize cells. NOD/SCID mice were injected subcutaneously, and tumor growth was monitored.

RESULTS

After approximately one month in culture, while the scramble-transduced control cells remained normal, two of the three miR-K12-9 lentivirus-transduced cell lines began to change in appearance. In cell proliferation assays, these two cell lines showed significantly higher proliferation than the controls. They formed colonies in soft agar while the control cells did not. When NOD/SCID mice were injected with the transduced cell lines, only those receiving the miR-K12-9-expressing cells developed tumors. In order to determine whether or not these results were reproducible, we repeated the TIME cell transductions and one out of three newly-transduced cell lines expressing miR-K12-9 again showed hallmark phenotypes of transformation. Importantly, this phenomenon could be reproduced in primary endothelial cells, HUVECs, as well.

CONCLUSION

To our knowledge, this is the first report where expression of a single viral miRNA has led to cellular transformation of endothelial cells, the progenitor cell type of Kaposi's sarcoma.

O15: Association of Soluble Serum Biomarkers with Tumor Burden and Treatment Response in Advanced HIV-Related Kaposi Sarcoma in Resource-Limited Settings

Authors: *Marta Epeldegui[1], Carlee Moser[2], Younjung Choi[2], Margaret Borok[3], Thomas B. Campbell[4], Patrick MacPhail[5], Otoniel Martinez-Maza[1], Susan E. Krown[6] for the AMC-066/A5263 protocol team*

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BACKGROUND

Molecules associated with systemic inflammation, immune activation, and angiogenesis have been implicated in the pathogenesis of Kaposi sarcoma (KS). In a previous study (JAIDS, 2023, 94:165-73) we showed that baseline serum levels of several soluble biomarkers, especially C-reactive protein (CRP) and interleukin (IL)-10, were associated with treatment response in previously untreated, limited-stage KS, particularly among those receiving ART without concomitant chemotherapy. In this study, we investigated whether pre-treatment serum levels of the same panel of soluble biomarkers were associated with tumor burden and treatment response of advanced-stage AIDS-KS.

METHODS

Participants were PLWH with advanced, previously untreated KS enrolled in AMC066/A5263 (NCT01435018; Lancet, 2020, 395: 1195-1207), a prospective, randomized, open-label clinical trial of three regimens of chemotherapy with ART conducted in sub-Saharan Africa and South America. Participants included in this analysis were assigned to either paclitaxel (PTX) + ART (the active control) or bleomycin + vincristine (BV) + ART, whose KS clinical response classified them as non-progressors (Complete or Partial response, CR/PR, within 12 weeks lasting ≥24 weeks or stable for ≥24 weeks) or progressors (progression without prior response or CR or PR lasting <24 weeks) , and had stored serum at weeks 0, 3 and 12. Serum biomarkers of inflammation (CRP, IL-6, IL-8, IL-10, G-CSF, sTNFr-2), immune activation (sCD25/sIL-2rα, CXCL10/IP10, CCL2/MCP1), angiogenesis (VEGF, MMP-2 and HGF) and anti-angiogenesis (MMP-9, endoglin), were measured by Luminex to determine whether pre- or post-treatment levels were associated with KS response and to assess the relationship between baseline biomarker levels and tumor burden, assessed by cutaneous lesion counts (≤50 vs >50), and the presence or absence of oral KS, visceral KS or KS-associated edema. Wilcoxon rank-sum tests were used to compare the levels of biomarkers between groups; analyses were not adjusted for multiple comparisons.

RESULTS

131 participants met the analysis inclusion criteria, 70 received PTX and 61 received BV, 82 non-progressors and 49 progressors. In univariate analysis, higher baseline KS tumor burden, i.e., >50 skin lesions, oral KS presence, and/or visceral KS presence (but not edema), was associated with higher pre-treatment levels of several inflammatory and immune activation biomarkers, and lower pre-treatment anti-angiogenic marker (Table 1). Although associations of baseline biomarker levels with subsequent KS response were not observed, at weeks 3 and 12, progressors showed higher levels of several markers of inflammation and immune activation, including IL6, IL10, TNFR2 and IP10, than non-progressors.

CONCLUSIONS

Pre-treatment levels of soluble serum biomarkers were associated with greater KS tumor burden but were not associated with the response of advanced AIDS/KS to treatment with chemotherapy + ART. Differential levels of several serum biomarkers were noted on treatment in progressors and non-progressors, suggesting that an increase in KS tumor burden was associated with higher levels of inflammation and immune activation.

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Table 1. Biomarker levels associated with KS tumor burden, median values in pg/ml or log10 pg/mL (CRP).

	CRP	IL-6	IL-10	sTNFRII	sCD25	MCP-1	IP-10	MMP-9
≤50 lesions	6.92	3.59						
>50 lesions	7.11	5.25						
p-value	**0.049**	**0.006**						
Oral KS absent		3.86	5.24	3.68	3.04	152.2	97.5	4.33
Oral KS present		5.22	10.84	3.88	3.17	164.3	118.8	4.18
p-value		**0.046**	**<0.001**	**<0.001**	**0.004**	**0.034**	**0.04**	**0.017**
Visceral KS absent		4.18		3.76	3.07			4.31
Visceral KS present		6.04		3.92	3.18			4.09
p-value		**0.041**		**0.034**	**0.009**			**0.010**

O16: Recent Kaposi Sarcoma Trends in Men with HIV: Associations with New to Care at Enrollment and Viral Suppression Status

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BACKGROUND

Incidence of Kaposi Sarcoma (KS) sharply declined with effective HIV treatment. Recent studies indicate potential stagnation in this decline among subgroups of people with HIV (PWH). KS declines may be slowing due to HIV diagnostic delays, PWH presenting late to/dropping out of care, or inability to maintain viral suppression. We sought to investigate these potential contributors to persistent KS incidence by evaluating recent trends in KS by new to HIV care status assessed at enrollment and viral suppression status among men with HIV (MWH) in North America.

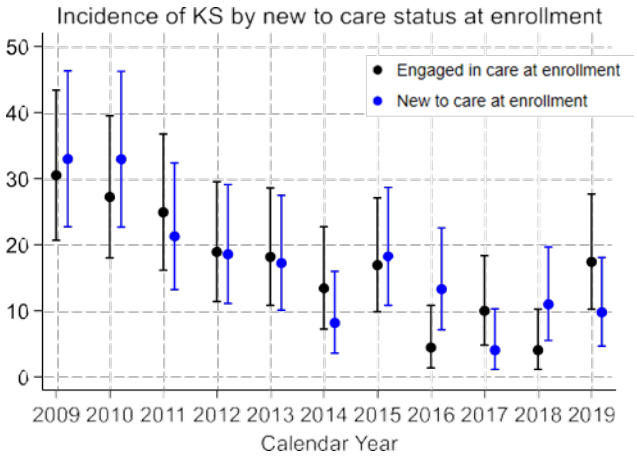
METHODS

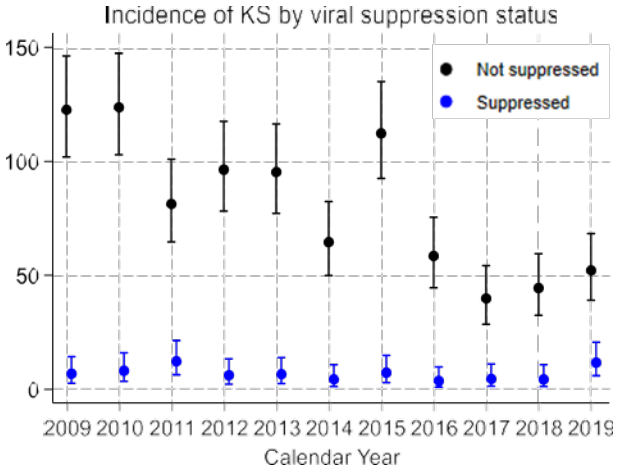
We estimated annual KS incidence rates among adult men enrolling in 2009 or later in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) in cohorts contributing validated cancer diagnoses. MWH were followed from NA-ACCORD enrollment date until the first of a KS diagnosis, loss-to-follow-up (2 years without a viral load), death or 12/31/2019. Incidence rates were stratified by whether MWH were new to care at enrollment and by viral suppression status (<200 vs. ≥ 200 copies/mL) at KS diagnosis/censoring. New to care was defined as having no evidence of a: suppressed viral load, CD4 count, antiretroviral treatment, or AIDS-defining illness prior to enrollment.

We calculated incidence rate ratios (aIRR) with 95% confidence intervals to estimate the association between being new to care or virally un-suppressed and KS incidence. Estimates were mutually adjusted for new to care and viral suppression status, race/ethnicity, age, and CD4 count at enrollment.

RESULTS

Among 40,090 (167,378 person-years [PY]) MWH, there were 235 KS diagnoses (IR: 14.0 per 10,000 PY). Annual KS rates declined from 31.8 to 7.1 cases per 10,000 PY from 2009 to 2018 but increased to 14.1 cases per 10,000 PY in 2019. Incidence rates were similar comparing those new to care versus those already engaged in care at enrollment across calendar years (aIRR 0.9 95% CI 0.7, 1.2, figure). Rates were consistently higher among virally unsuppressed versus suppressed men (aIRR 5.0 95% CI 3.7, 6.6). KS rates in virally unsuppressed MWH declined from 122.7 cases to 52.1 cases per 10,000 PY from 2009-2018. KS rates were stable in virally suppressed MWH (4.3- 8.0 per 10,000 PY) but increased in 2019 to 11.6 cases per 10,000 PY.





CONCLUSIONS

KS incidence rates did not differ by new to care status assessed at enrollment and were consistently higher in virally unsuppressed MWH, though this difference decreased over time. This may indicate that KS persists in men due to poor HIV control; however more research is required to confirm this hypothesis. Our new to care definition may also capture MWH re-engaging care and should be interpreted accordingly. Increases in KS rates merit continued KS monitoring among PWH already engaged in care, and clarifying KS incidence among those new to or re-entering HIV care.

O17: Structural Inequities in Cancer Treatment Receipt among PWH and Cancer in the United States (2004–2020)

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BACKGROUND

People with HIV (PWH) are less likely to receive cancer treatment compared to those without HIV. While some clinical and sociodemographic factors have been explored, the impacts of area-level social determinants of health (SDoH) and markers of access to care as drivers of disparate cancer treatment for PWH are unknown. Our objective was to characterize the role of area-level SDoH and healthcare access factors in cancer treatment receipt among PWH and cancer in the U.S.

METHODS

We used the National Cancer Database (2004–2020) to identify PWH (18–89 years) using ICD-9 and ICD-10 codes. We included the 15 most common cancers among PWH. Our main outcome was the receipt of any treatment, including systemic therapy, surgery, radiotherapy, and hormone therapy. Our main SDoH exposures included (1) area-level education or percent of adults without a high school degree and (2) area-level income or median income quartiles within the patient's ZIP codes. Race and ethnicity were categorized as non-Hispanic (NH) Black, NH-White, Hispanic/Latinx, NH-Asian, and other. We evaluated healthcare access factors including insurance status, distance to care, and type of cancer treatment facility (e.g., academic/research hospital vs. community clinic). We examined each exposure in separate models using hierarchical multivariable logistic regression to estimate adjusted odds ratios (aOR) with 95% confidence intervals (95% CI), clustering at the facility level to account for unmeasured differences across reporting facility and adjusting for age, sex, year of diagnosis, stage at diagnosis, and cancer type.

RESULTS

We included 31,928 PWH with cancer, among whom 25% did not receive curative treatment. Overall, 40% of PWH were aged ≥60 years, 38% were NH-Black, 70% were male, and 43% of patients resided in the South. Forty-two percent were diagnosed with stage I/II cancer and the most common cancers included lung (22%), DLBCL (13%), anal (13%), and colorectal (12%) cancers. Among patients who received any treatment, 44% received surgery, 44% received chemotherapy, 12% received hormone therapy, and 11% received radiation. After adjustment for age, sex, year of cancer diagnosis, cancer stage at diagnosis, and cancer type, we found that compared to NH-White PWH, NH-Black PWH (aOR: 0.74; 95% CI: 0.69-0.80) and Hispanic/Latinx PWH (aOR: 0.86; 95% CI: 0.76-0.97) were less likely to receive cancer treatment. When evaluating healthcare access factors, factors associated with lower odds of receiving cancer treatment included: living with Medicaid (aOR: 0.84; 95% CI: 0.78-0.92) or without insurance (aOR: 0.70; 95% CI: 0.60-0.81) vs. Medicare insurance; receiving care at a community cancer program (aOR: 0.58; 95% CI: 0.49-0.68) and a comprehensive community cancer program (aOR: 0.79; 95% CI: 0.70-0.90) vs. an academic/research hospital; and living closer to their oncologist [<2 miles away (aOR: 0.69; 95% CI: 0.57-0.83) or between 2 and 9 miles (aOR: 0.89; 95% CI: 0.69-0.95) vs. living over 45 miles away]. Next, compared to those in the highest quartile educational attainment (Q4), PWH in the lower quartiles were less likely to receive cancer treatment (Q1 vs. Q4 aOR:0.71; 95% CI: 0.64-0.78). Residing in the lower quartiles of household income was also negatively associated with cancer treatment receipt compared to those in the highest income quartiles (Q1 vs. Q4: aOR: 0.69; 95% CI: 0.62-0.79). Associations of area-level SDoH were consistent among NH-White and NH-Black PWH, however, we did not observe associations among Hispanic/Latinx PWH and NH-Asian PWH, specifically.

CONCLUSION

Area-level markers of social disadvantage are associated with lack of cancer treatment receipt among PWH, suggesting structural factors may impact this long-standing treatment inequity.

O18: Molecular Characterization and Survival Analysis of Cancers Arising in People Living with HIV

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BACKGROUND

The use of anti-retroviral therapies has afforded longer lifespans to people living with HIV (PLWH). Consequently, PLWH have more frequently developed non-AIDS-defining cancers (non-ADCs). Studies indicate that PLWH have increased mortality from non-ADCs compared to individuals without HIV. Moreover, cancers developing in the setting of HIV tend to present at more advanced stages and demonstrate greater genomic instability. Unfortunately, few studies have reported how HIV may contribute to the unique molecular characteristics of non-ADCs. Utilizing a large real-world patient cohort, we sought to explore tumor molecular features and survival in PLWH and cancer.

METHODS

The study cohort was identified from the Caris CODEai data platform. De-identified patients whose insurance claims data listed an ICD-10 code indicating past HIV infection were classified as HIV+, while those without this code were considered HIV-. Their tumor samples underwent DNA sequencing (592-gene panel by NextSeq technology or whole exome sequencing by NovaSeq technology) and whole transcriptome sequencing (NovaSeq) at Caris Life Sciences (Phoenix, AZ). Chi-square, Fisher's exact, and Mann-Whitney U tests were used to determine statistical significance. Real-world overall survival (OS) was calculated using insurance claims of patients from time of sample collection to last contact. Hazard ratios (HRs) were calculated using the Cox proportional hazards model (log-rank test).

RESULTS

A total of 1,722 PLWH were identified in the Caris database. The cohort had a median age of 60 years (range = 3–90), and 61% were male. The greatest number of these individuals had non-small cell lung cancer (n=366), colorectal cancer (n=181), or anal carcinoma (n=103). Pan-cancer survival analysis revealed that HIV+ status was associated with poorer survival in three cancer types: anal carcinoma (HR = 1.4, 95% CI: 1.1-1.8, p = 0.0106), neuroendocrine neoplasms (HR = 1.6, 95% CI: 1.1-2.4, p = 0.0188), and uterine serous carcinoma (HR = 2.19, 95% CI: 1.1-4.4, p = 0.0269). The prevalence of HIV infection was 9% in anal carcinoma, 0.7% in neuroendocrine neoplasms, and 0.3% in uterine serous carcinoma.

In anal carcinoma, the most frequent pathogenic alterations in HIV+ cases occurred in *PIK3CA* (36.5%) and *KMT2D* (14.0%); in neuroendocrine neoplasms, changes in *TP53* (38.5%) and *PIK3CA* (3.8%) were most common; in uterine serous carcinoma, *TP53* (100.0%) and *FBXW7* (20.0%) were most often mutated. However, the prevalence of these alterations did not significantly differ between HIV+ and HIV- cases. Among PLWH, high tumor mutational burden (TMB ≥10 mutations/megabase) and PD-L1 expression by immunohistochemistry were consistently observed within the three tumor types, although the occurrence rates were not significantly different from those documented in HIV- cases. Transcriptomic analysis showed that immune-related genes, including *CTLA4* ($p < 0.001$), *TIM3* ($p < 0.001$), *FOXP3* ($p < 0.001$), *TOX* ($p < 0.001$), *CD39* ($p < 0.01$), *PD-L2* ($p < 0.01$), *CD80* ($p < 0.01$), *CD86* ($p < 0.05$) and *IDO1* ($p < 0.05$), had lower RNA expression in HIV+ anal carcinoma compared to HIV- tumors. A similar trend was appreciated for *CD80* ($p < 0.05$), *CD274* ($p < 0.01$), and *HNF1A* ($p < 0.001$) in uterine serous carcinoma, although none of the immune-modulating genes demonstrated significantly suppressed expression in HIV+ neuroendocrine neoplasms.

CONCLUSIONS

This large patient cohort analysis revealed significantly inferior OS for PLWH who develop certain non-ADCs, particularly anal, neuroendocrine, and uterine serous cancers, compared to people without HIV. Overall, similar pathogenic genetic alterations, TMB status, and PD-L1 expression were observed when comparing tumor types by HIV status. However, tumoral RNA expression of specific immune-modulating genes was decreased in the presence of HIV infection within some cancers, which may provide a molecular rationale for the unique characteristics of non-ADCs arising in PLWH.

O19: Adjuvant Immunotherapy for NSCLC in Patients Living with HIV: A Simulation Study

Authors: *Andrew Draheim[1], Lesley Park[2], Michael J. Silverberg[3], Chung Yin Kong[1], Keith Sigel[1]*

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BACKGROUND

Non-small cell lung cancer (NSCLC) is a leading cause of cancer morbidity and death in people with HIV (PWH). Relative to people without HIV (PWoH), PWH experience a 1.2 to 1.8-fold worse survival rate with lung cancer, a severe disadvantage. In addition, many PWH with NSCLC have major comorbidities (most commonly chronic obstructive lung disease (COPD)), further complicating NSCLC outcomes. Therefore, identifying management strategies that may improve treatment outcomes in PWH with NSCLC is necessary. Despite this, no randomized controlled trials (RCTs) of lung cancer treatment specific to PWH have been conducted. Two recent immune checkpoint inhibitor (ICI) immunotherapy trials have demonstrated benefits in PWoH when combined with adjuvant chemotherapy for stage IB-IIIA NSCLC. While the study of immunotherapy in PWH is limited, retrospective analyses suggest that the toxicity profile is similar to the general population. In this study, we aimed to determine the indications for ICI combined with adjuvant chemotherapy in PWH with NSCLC by adapting a simulation model and running in-silico comparative trials of platinum-based adjuvant chemotherapy and immunotherapy versus adjuvant chemotherapy alone post-resection.

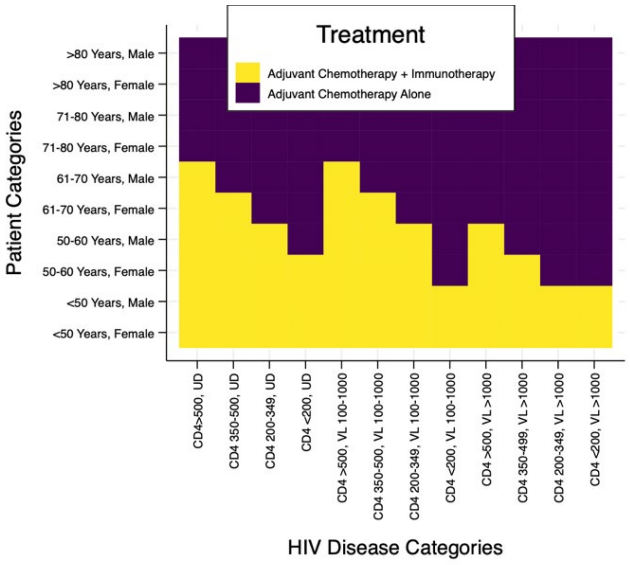
METHODS

We updated our previously developed and validated simulation (Comorbidity Lung Treatment Model-HIV, "COLT-MH") of lung cancer natural history, treatment and outcomes that was parameterized using HIV cohort data (Veterans Aging Cohort Study, Kaiser Permanente Northern California, Mount Sinai) combined with SEER-Medicare data and published clinical trials. ICI impacts were modeled by calibrating the model to survival and toxicity outcomes published in the PEARLS/KEYNOTE-091 RCT. We simulated multiple RCTs comparing quality-adjusted life expectancy (QALE) after treatment with platinum-based adjuvant chemotherapy, with or without ICI, following lobectomy (see Figure). We first compared QALE gains in subgroups of PWH without major comorbidities according to age, sex, and HIV clinical characteristics (CD4 count and HIV viral load) stratified by NSCLC stage. Then we repeated these analyses in patients with chronic obstructive pulmonary disease (COPD).

RESULTS

For PWH with stage IB-II NSCLC, patients younger than 71 years old, no comorbidities, CD4 counts >500 cells/mm^3, and relatively controlled HIV RNA were all projected to benefit from immunotherapy and chemotherapy (i.e., have net QALE gains). Older patients (>60 years old) and patients with worse HIV disease characteristics were less likely to benefit from immunotherapy and adjuvant chemotherapy. Those with very poor HIV control (CD4<200 cells/mm^3, VL>1000 copies/mL) over age 60 did not benefit. Simulated trials in stage IB-II in patients with COPD yielded even fewer groups likely to substantially benefit from immunotherapy. For stage IIIA patients there was no projected QALE benefit associated with immunotherapy plus adjuvant chemotherapy over adjuvant chemotherapy alone.

Figure. Projected optimal treatment strategy by age, sex, HIV characteristics.



CONCLUSIONS

Our simulated RCTs estimated benefits of adjuvant chemotherapy with immunotherapy for NSCLC in PWH. We found that PWH with suboptimal HIV disease control and COPD had fewer QALE gains when adding immunotherapy for stage IB-II NSCLC, but those without COPD and adequate viral control benefited. By consolidating data from RCTs, observational studies, and HIV cohorts, COLT-MH can provide personalized projections of optimal treatment regimens for PWH with NSCLC for personalized treatment guidance as well as informing future PWH-specific treatment trials.

O20: Novel Immunotherapeutic Approaches for Melanoma in People Living with HIV

Authors: *Lindsay N Barger[1,2], Olivia S El Naggar[1], Binh Ha[1], Gabriele Romano[1,3]*

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BACKGROUND

Antiretroviral therapy (ART) has significantly improved the lives of people living with HIV (PLWH) and strongly reduced the incidence of AIDS-defining cancers, among other benefits. However, non-AIDS- defining cancers (NADCs) have increased in recent years, and cutaneous melanoma poses a significant risk. PLWH and cutaneous melanoma experience 4X higher mortality rates than melanoma patients without HIV, despite ART. The causes of the HIV-associated mortality increase are not clear, but it is known that melanoma patients bearing immunologically “cold” tumors with an exhausted/suppressive immune infiltrate consistently show the worst responses to anti-cancer therapy.

METHODS

We performed the first spatial transcriptomic study on melanomas from PLWH (and matched uninfected controls, n=11) using the Nanostring GeoMX platform. To study the observed immune dysregulation functionally, we have developed an in vitro human co-culture system (melanoma cells, T-cells, myeloid cells) and a novel “all mouse” melanoma and HIV co-morbidity model (Yumm1.7 syngeneic model, co-infected with EcoHIV chimeric virus).

RESULTS

Our data show that melanomas from PLWH have an exhausted tumor microenvironment compared with the uninfected controls with melanoma (e.g., elevated LAG-3, PD-1 expression). In addition, patient sample analyses revealed enhanced myeloid suppressive signaling (e.g., IDO1) and augmented fibrotic markers in PLWH, consistent with increased presence and activity of myeloid-derived suppressor cells (MDSCs). We are currently characterizing the immune suppressive features of PLWH-derived MDSCs using our co-culture system. Importantly, our novel mouse model reflects the major immunological changes observed in patient samples, including immune checkpoint upregulation, increased MDSC abundance, and fibrosis. In addition, infected mice developed melanoma more rapidly and succumbed to the pathology earlier than uninfected mice.

CONCLUSIONS

Overall, our preliminary data suggest that HIV-induced chronic inflammation drives melanoma- specific mortality in PLWH by favoring a "cold" TME and that strategies to inhibit MDSCs immune-suppressive phenotype and/or abundance are a candidate adjuvant approach to tailored immune checkpoint therapy to treat melanoma in PLWH.

O21: Trends in Burkitt Lymphoma in People with HIV in South Africa (2005–2021)

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[1]National Cancer Registry, Health Laboratory Service, Johannesburg, South Africa; [2]University of Bern, Bern, Switzerland; [3]University of Stellenbosch, Stellenbosch, South Africa; [4]Department of Microbiology and Immunology, National Health Laboratory Service, Tygerberg, South Africa; [5]Swiss Tropical and Public Health Institute, Allschwil, Switzerland; [6]University of Basel, Basel, Switzerland

BACKGROUND

Burkitt lymphoma (BL) is an aggressive form of non-Hodgkin lymphoma (NHL) associated with HIV. While its epidemiology is well studied among people with HIV (PWH) in high-income countries, data from Africa are limited. This study examines the trends and risk factors associated with BL among PWH in South Africa from 2005 to 2021.

METHODS

We used data from the South African HIV Cancer Match (SAM) study, a cohort of PWH 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. We included individuals with multiple HIV records on two or more days without any restriction on age. We calculated crude incidence rates, analyzed temporal trends using Joinpoint models and obtained age-specific incidence rates and hazard ratios (HR) from Royston-Parmar flexible parametric survival models.

RESULTS

We included 9,891,226 PWH (66% female) contributing 57,078,079 person years and 798 incident BL diagnoses. The median baseline CD4 count was 312 cells/µl (interquartile range [IQR] 167-493) among all included PWH and 244 cells/µl (IQR 122-409) among those with an incident BL diagnosis. The BL incidence rate decreased annually from 2005 to 2021 (Figure 1) by an average of 16% (95% Confidence Interval [CI] 13% to 22%) among female individuals and 14% (CI 10% to 18%) annually among male individuals. Age-specific incidence rates showed a bimodal pattern (Figure 2), peaking among children and less prominently among middle-aged adults. The risk of BL among PWH was higher in male than female individuals and declined with higher baseline CD4 counts (Table 1).

CONCLUSIONS

This study is one of the largest on BL among PWH. It shows that lower CD4 counts were linked to higher BL rates and a sustained decline in HIV-associated BL incidence in South Africa as ART coverage increased.

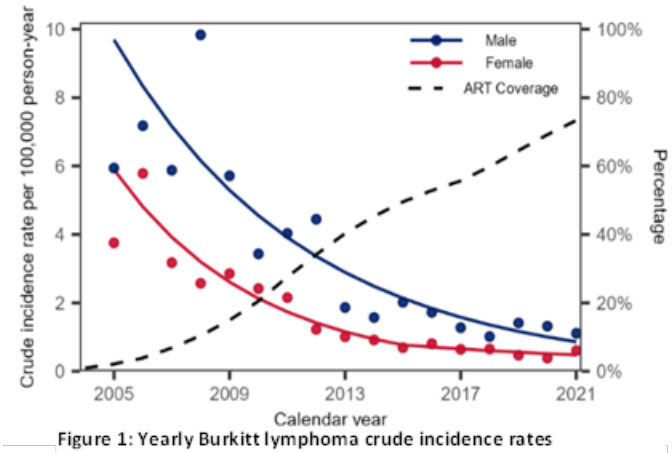

Figure 1: Yearly Burkitt lymphoma crude incidence rates

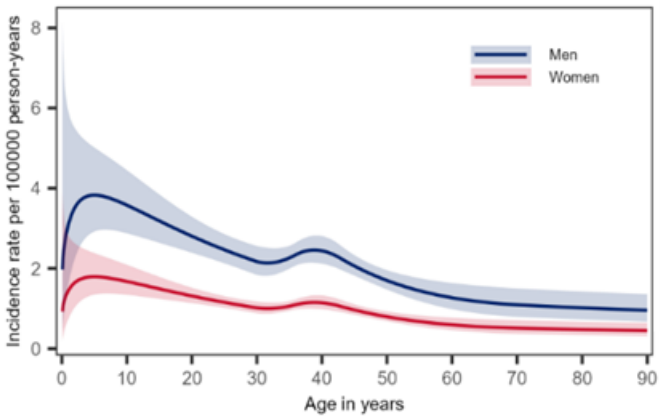

Figure 2: Age-specific Burkitt lymphoma incidence rates

Table 1: Crude incidence rates of Burkitt lymphoma per 100,000 person-years and adjusted Hazard ratio

	No. of PWH	No. of BL cases	Incidence rate (95% CI)	Adjusted Hazard Ratios (95% CI) *
Sex				
Female	6,574,129	414	1.0 (0.9 – 1.1)	1
Male	3,317,097	384	2.2 (2.0– 2.4)	1.8(1.6 – 2.0)
Age at first lab record [years]				
0-14	535,001	84	2.8 (2.2 - 3.4)	1
15-29	3,428,491	207	1.0 (0.9 - 1.1)	0.4(0.4 - 0.5)
30-44	4,191,502	385	1.6 (1.4 - 1.7)	0.5(0.5 - 0.6)
44-59	1,479,779	111	1.5 (1.2 - 1.8)	0.5(0.4 - 0.6)
≥60	256,453	11	1.1 (0.6 - 2.0)	0.4(0.2 - 0.6)
First CD4 cell count recorded [cells/µl]				
<200	2,519,199	289	2.0 (1.8 - 2.2)	1
200-349	1,608,827	108	1.1 (0.9 - 1.3)	0.8(0.7 - 0.9)
350-499	2,102,248	176	1.3 (1.1 - 1.6)	0.7(0.5 - 0.8)
≥500	2,004,073	117	1.0 (0.8 - 1.2)	0.6(0.5 - 0.7)
Missing	1,656,879	108	1.4 (1.1 - 1.7)	0.6(0.5 - 0.7)
Calendar period of the first lab record				
2004-2009	2,141,265	336	1.8 (1.6 – 2.0)	1
2010-2015	4,815,891	341	1.1 (1.0 - 1.2)	0.5(0.4 - 0.5)
2016-2021	2,934,070	121	1.5 (1.3 - 1.8)	0.4(0.3 - 0.5)

*We assumed proportional hazards and the model was adjusted for all variables in the table

PWH: People with HIV; CI: Confidence Interval; BL: Burkitt lymphoma

O22: Spatial Analysis Reveals Heterogeneity in the Tumor Microenvironment of AIDS-Associated Non-Hodgkin Lymphoma (AIDS-NHL)

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BACKGROUND

Lymphomas remain a leading cause of cancer morbidity and mortality for people living with HIV (PLWH) and even in those optimally treated with combination anti-retroviral therapy (cART). PLWH have an 11-to-17-fold higher risk of developing non-Hodgkin lymphoma (NHL) compared to people not living with HIV (PNLWH). NHL is a rapidly growing cancer that develops more aggressively in PLWH, depending on the tumor subtype. The most common subtypes of AIDS-associated NHL (AIDS-NHL) are Diffuse large B-cell lymphoma (DLBCL) and Burkitt's lymphoma (BL). The tumor microenvironment (TME) is a complex ecosystem composed of tumor cells, stromal cells, immune cells, and the extracellular matrix. The TME is crucial for tumor progression as it provides nutrients and a space for the tumor to grow, and promotes cancer cell survival, local invasion, and metastasis. Little is known about the complex interplay between tumor cells, stromal cells, and immune cells and their reciprocal relationship in the TME of AIDS-NHL patients. Thus, this study sought to describe the spatial and immune landscape of AIDS-NHL using imaging mass cytometry (IMC).

METHODS

We used IMC to characterize the tumor microenvironment of AIDS-NHL using a cohort of 32 DLBCLs from the USC Residual Tissue Repository. We created a data analysis pipeline and first converted raw IMC images into single-cell data. Imaged ROIs underwent cell segmentation to compute an average marker expression score for each individual cell. Phenograph and k-means clustering on the intensity of lineage markers (CD45, CD3, CD4, CD8, CD20, CD68, CD138, CD14, CD163, CD11b, CD11c, CD31, and αSMA) was used to classify major cell subsets in lymphoma tissue: $CD4^+$ T-cells, $CD8^+$ T-cells, $CD20^+$ B-cells, $CD138^+$ plasma B-cells, $CD14^+$ myeloid cells, $CD163^+$ myeloid cells, $CD11b^+$ myeloid cells, $CD11c^+$ myeloid cells, and $CD31^+$ endothelial cells.

RESULTS

We identified four TMEs with heterogenous phenotypes. TMEs 1 and 2 were enriched in $CD138^+$ plasma B-cells, with orthogonal enrichment in $CD163^+$ M2-macrophages and $CD8^+$ T cells or $CD20^+$ B-cells and $CD4^+$ T-cells, respectively. TME 3 was highly enriched in $CD14^+$ myeloid cells and $CD20^+$ B-cells. TME 4 was depleted in B-cells but had a relatively similar abundance of all other cell lineages. $CD11b^+$ myeloid cells were depleted in TMEs 1 and 3. Results from multi-group differential expression testing (Kruskal-Wallis) between TMEs showed significant differences in activation and exhaustion marker expression levels in $CD4^+$ and $CD8^+$ T-cells (CD25, CTLA-4, ICOS, PD-1, PD-L1, PD-L2, CXCR5, CD40, CD40L, IL-6 and CD80). In addition, we observed altered patterns of HLA-DR, CD40, and CXCR5 expression in myeloid subsets, especially between TMEs 1, 2, and 4. Follicular $CD8^+$ T-cells were present in all TMEs.

CONCLUSIONS

Spatial profiling of lymphoma tissue suggests that the tumor and immune microenvironment in AIDS-NHL is heterogeneous. The $CD138^+$ B-cell and $CD20^+$ B-cells observed in TME 1, 2, 3, and 4 are potentially malignant cells. We observe that differences in TME composition are associated with differential activation and exhaustion profiles, implicating spatial interactions as a factor. This work provides a basis for further spatial profiling which may serve to inform clinical design of personalized therapeutic approaches for AIDS-NHL.

O23: Spatial and Bulk Transcriptomics Analyses Reveal Distinct Gene Expression Profiles in Archival Skin Kaposi Sarcoma Lesions Based on Disease Characteristics

Authors: *Quashawn Chadwick[1], Ned Cauley[2], Nina Bubenko[3], Xiaolin Wu[3], Bahman Asfari[1], Laura Bassel[4], Maria Hernandez[5], Kathryn Lurain[1], Robert Yarchoan[1], Joseph Ziegelbauer[1], Noemi Kedei[5], Laurie Krug[1], Xiaofan Li[1], Ramya Ramaswami[1]*

[1]HIV and AIDS Malignancy Branch, Center for Cancer Research, NCI; [2]CCR Collaborative Bioinformatics Resource, Center for Cancer Research, NCI; [3]CCR Genomics Technology Laboratory, Frederick National Laboratory; [4]Center for Advanced Preclinical Research, Frederick National Laboratory; [5]Spatial Imaging Technology Resource, Center for Cancer Research, NCI

BACKGROUND

Kaposi sarcoma (KS), caused by Kaposi sarcoma herpesvirus (KSHV) is an angioproliferative tumor that typically manifests as vascular and hyperpigmented cutaneous lesions. Other diseases caused by KSHV include multicentric Castleman disease (MCD), primary effusion lymphoma (PEL) and KSHV-associated inflammatory cytokine syndrome (KICS). Patients may present with KS alone or these KSHV-associated diseases (KAD) can occur concurrently. Novel sequencing technologies that evaluate archival KS tissues may further our understanding of cellular and viral characteristics of HIV-associated KS.

METHODS

Participant and HIV characteristics were obtained at the time of biopsy. Gene expression profiling of 42 confirmed KS skin samples was performed using a custom nCounter PanCancer ImmunoOncology panel with the addition of KSHV probes according to the manufacturer's instructions. Quality control (QC) checks were applied in R Studio according to the Nanostring's nCounter analysis guidelines and normalization was performed with RUVseq followed by DESeq2 for differential expression analysis. Spatial RNA profiling was performed using the GeoMx digital spatial profiling (DSP) platform on 4 fresh frozen paraffin-embedded (FFPE) tissue sections randomly selected from participants with concurrent KS and KAD. LANA, CD45 and CD31 expression in these samples identified KS ($LANA^+$, $CD31^+$) and other areas of interest (AOIs) including vessels ($LANA^-$, $CD31^+$) and immune cells ($CD45^+$) on the tissue sections. QC checks, quartile-3 normalization, and differential expression analysis were applied in R studio according to Nanostring's recommendations using the GeoMxTools R package. Gene Set Enrichment (GSEA) analysis was performed using the R package ClusterProfiler. Genes for each differential expression comparison output were ranked according to the Signal2Noise scores, which were calculated using the formula defined in the GSEA manual.

RESULTS

Archival skin KS samples were obtained from 42 cisgender men with HIV with a median age of 40 years (interquartile range (IQR): 32-52 years). Fifty-six percent of the participants were Black. The median duration of HIV infection was 8.1 years (IQR: 0.8-15), and participants had a median HIV viral load of 61 copies/mL (IQR: 20-484.5). The median $CD4^+$ T-cell count was 126 cells/μL (IQR: 59.5-288.5). Forty-seven percent had KS alone and 53% had other KAD, including KICS in 30%, MCD in 16%, PEL in 9%, and both MCD and PEL in 4%. Compared to participants with KS alone, samples from participants KS and concurrent KAD (KICS or MCD and/or PEL) had differential expression of 26 genes including increased expression of the cellular genes STC1 (log2FC=2.02, p-adjusted (padj)=0.001), a secreted glycoprotein, and MKI67 (log2FC=1.11, padj=0.02), a common proliferation marker. Pathway analyses identified lower expression of genes associated with cytokine activity in lesions from participants with KS with concurrent KAD as compared to those with KS alone. Spatial RNA profiling from 4 KS samples of participants with KS and concurrent KAD identified increased expression of PDGFRB (log2FC=1.42, padj=0.0001) and NOTCH3 (log2FC=2, padj=0.001), both involved in vascular development, in LANA+ areas as compared to other AOIs.

CONCLUSION

These sequencing data of archival skin HIV-associated KS samples highlighted differentially expressed genes that were driven by disease characteristics, such as the presence of concurrent KAD.

O24: Spatial Single-Cell Transcriptomic Profiling Reveals KSHV-Driven Mechanisms in Kaposi's Sarcoma

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BACKGROUND

Kaposi's sarcoma (KS), a prevalent malignancy in AIDS patients, is driven by Kaposi's sarcoma-associated herpesvirus (KSHV). Characterized by high angiogenesis and inflammation, the detailed mechanisms underlying the KS tumor microenvironment remain inadequately understood.

METHODS

We utilized Spatial Single-Cell *In-Situ* Transcriptomic Analysis (SSTA) to investigate 49 Formalin-Fixed Paraffin-Embedded (FFPE) KS tumor samples from 43 patients. These samples included various stages: patch (12 samples), late patch/early plaque (3 samples), plaque (11 samples), and nodular (23 samples). The cohort comprised 26 AIDS-associated KS (epKS), 8 classic KS (cKS), 1 iatrogenic KS (iKS), and 8 with unknown HIV status. We used a 310-gene panel, covering both cellular and KSHV transcripts, to characterize the molecular profiles of tumor cells and their microenvironment.

RESULTS

SSTA generated a dataset with 957,903,593 transcripts across 6,996,998 cells, averaging 82 transcripts per cell. These were classified into 10 major cell types: endothelial cells, fibroblasts, keratinocytes, pericytes, erythrocytes, monocytes, macrophages, dendritic cells, B cells, and T cells. Tumor cells, identified by KSHV transcripts and markers of endothelial, mesenchymal, or precursor cell types, constituted 27% of the cell population. The proportion of KS tumor cells was 6% in patch, 17% in plaque, and 33% in nodular stages. Remarkably, 5% of non-tumor cells were also KSHV-infected, with 25% of these expressing lytic genes such as ORF50, 57, 65, 59, and K9. Notably, 52% of tumor cells expressed ORF-K2 (vIL-6), with the highest expression observed in nodular KS. Additionally, KS tumors exhibited extravasated erythrocytes and extensive immune cell infiltration, including macrophages and T cells, within areas of proliferative spindled endothelial cells.

CONCLUSIONS

SSTA effectively detects cellular and viral transcripts in KS samples, providing insights into the molecular and cellular dynamics of KS across different stages in a spatial manner. Variations in KSHV gene expression and cell compositions enhance our understanding of the specific mechanisms driving KS pathology.

O25: Prior Cervical Cancer Screening among Cervical Cancer Patients in the Cancer Disease Hospital in Zambia

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BACKGROUND

Women living with human immunodeficiency virus (WLHIV) have a 6 times higher risk of developing invasive cervical cancer compared to their HIV-negative counterparts.[1] In 2018, Zambia had a 14.2% HIV prevalence among women aged 15 to 49, with an estimated 26,000 new HIV diagnoses in women each year.[2] The relationship between advanced cancer stage at presentation and cervical cancer screening in low- and middle-income countries is not well understood, especially among WLHIV. This study aimed to investigate the relationship between prior cervical cancer and patient characteristics amongst newly diagnosed cervical cancer patients seeking treatment at the Cancer Disease Hospital (CDH) in Zambia and among these patients.

METHODS

The study includes newly diagnosed untreated patients aged ≥18 years who presented with histologically confirmed cervical cancer to Cancer Disease Hospital (CDH) in Zambia for treatment and responded to a health-related social needs survey adapted from the Centers for Medicare Services. Descriptive statistics were used to summarize the data, and chi-squared and Wilcoxon-rank sum tests were used to explore group differences.

RESULTS

177 cervical cancer patients were prospectively enrolled on this IRB approved study between June 2022 and August 2024, with 55% (N=97) WLHIV. The median age of these patients was 50 (IQR: 43-57). 49% of them had advanced-stage cancer (stage III/IV); only 28% of the 177 patients had undergone prior cervical cancer screening. WLHIV with prior cervical cancer screening had 1.5 higher odds for advanced-stage cancer (p=0.4). On multivariate analysis (n=177), patients with knowledge about the risks and symptoms of cervical cancer and secondary or tertiary education attainment had higher odds of having a prior cervical cancer screening while adjusting by HIV status (OR = 6.6, 95%CI: 2.9-15.3, p<0.001, OR = 2.9, 95%CI: 1.2-6.7, p=0.02, and OR = 1.1, 95%CI: 0.5-2.5, p=0.8, respectively). Among WLHIV, 33% had undergone prior cervical cancer screening. The multivariate analyses showed WLHIV patients with knowledge about their risks and symptoms (OR = 4.9, 95%CI: 1.7-14.1, p=0.004), secondary or tertiary education (OR = 3.5, 95%CI: 1.2-10.4, p=0.03), and years on ART (OR = 1.1, 95%CI: 1.0-1.2, p=0.08) had higher odds of having a prior cervical cancer screening.

CONCLUSIONS

The study results showed that knowledge of cervical cancer risks and symptoms and level of education attainment were associated with reporting a prior cervical cancer screening. Further investigation is warranted to understand how health-related social needs could impact access to and acceptance of screening among WLHIV in Zambia.

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O26: Hepatocellular Carcinoma Survival in People with HIV and without HIV in the United States, 2001–2019

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BACKGROUND
The risk of hepatocellular carcinoma (HCC) is elevated among people with HIV (PWH), compared to the general population. Understanding survival disparities among people with HCC by HIV status and whether survival has improved over time among PWH remains poorly understood.

METHODS
We used 2001-2019 data from the HIV/AIDS Cancer Match (HACM) Study, a population-based linkage of 13 HIV and cancer registries in the U.S. We estimated the association between HIV and liver cancer-specific and all-cause mortality among people with HCC using multivariable-adjusted Cox proportional hazard models, adjusting for year of cancer diagnosis, sex, age at cancer diagnosis, race and ethnicity, stage at diagnosis, region, and treatment. Among PWH with HCC, we identified predictors of HCC-specific and all-cause mortality and estimated adjusted hazard ratios (aHRs) for year of cancer diagnosis, sex, age at cancer diagnosis, race and ethnicity, stage at diagnosis, treatment, HIV acquisition group, and AIDS status.

RESULTS
There were a total of 67,785 people with hepatocellular carcinoma, 1,533 with HIV, and 66,252 without HIV. Among PWH, there were a total of 1,220 deaths, and the proportion due to HCC was 61.4% (749 deaths). Compared to people without HIV, a higher proportion of PWH were men (86.4% v. 78.0%), younger at time of cancer diagnosis (median age of 56.6 v. 62.1 years) and Black (44.4% v. 19.7%) or Hispanic (28.2% v. 19.8%) individuals. Among PWH, people who inject drugs (PWID) were the largest HIV acquisition group (57.6%). Two- (30.8% vs 41.4%) and 5-year overall survival (15.8% v. 25.5%) was poorer for PWH compared to people without HIV, respectively. In adjusted analyses, HIV was associated with 35% higher all-cause mortality (aHR 1.35 95%CI: 1.27, 1.43), and the association did not differ by sex. In adjusted analyses, HCC-specific mortality was also elevated in PWH. Compared to people without HIV, PWH had an 8% increase in HCC-specific mortality (aHR 1.08 95% CI:1.00, 1.16). HIV was associated with HCC-specific mortality among men (aHR 1.09 95%CI: 1.01, 1.17), but not among women (aHR 1.01 95%CI: 0.81, 1.24). Factors that were associated with greater all-cause and HCC-specific mortality were similar and included male sex, older age at HCC diagnosis, later cancer stage at time of diagnosis, and non-receipt of surgery, chemotherapy, or radiation. Among PWH with HCC, we observed greater mortality for those whose HIV acquisition risk group was reported as men who have sex with men. All-cause mortality fell during the study period (compared to 2001-2003, 2016-2019 aHR 0.74 95%CI: 0.55, 1.01) and the decline was statistically significant (p-trend=0.0001). Similarly, for HCC-specific mortality declined across calendar periods from 2001-2003 to 2016-2019 (p-trend=0.05).

CONCLUSIONS
HIV is associated with elevated all-cause mortality among PWH with HCC compared to those without HIV. HCC-specific mortality was elevated amongst men with HIV. As more PWH are living longer, more work will be needed to prioritize opportunities for HCC prevention, diagnosis, and treatment in a population at increased risk.

Funding: NCI, CDC, NPCR

O27: Incidence and Risk Factors for HPV-Associated Cancers in People Living with HIV in South Africa

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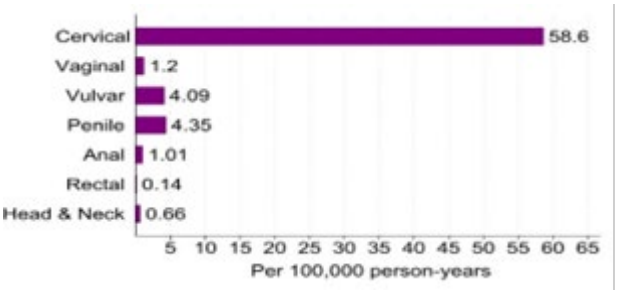
BACKGROUND
People living with HIV (PLWHIV) are at increased risk of developing HPV-associated squamous cell carcinoma (SCC). We analyzed incidence rates and risk factors for HPV-associated SCC in PLWHIV in South Africa.

METHODS
We used data from the South African HIV Cancer Match Study (doi:10.1136/bmjopen-2021-053460) and included PLWHIV aged ≥15 years with ≥2 HIV-related laboratory records at distinct time points within the study period, 2004-2014. We selected HPV-associated SCC using ICD-O-3 classification. We calculated the incidence rate for each HPV-associated SCC per 100,000 person-years. We used Cox regression models to determine the association of baseline risk factors and HPV-associated SCC with 95% confidence intervals (CI), stratified by province: CD4 cell counts, age, calendar period, ethnicity, settlement type, and sex, where applicable. We defined baseline as the first HIV-related laboratory record.

RESULTS
We included 4,574,526 PLWHIV with 13.9 million person-years follow-up time and observed 6,890 HPV-associated SCC cases. The incidence rate was highest for cervical cancer (58.6/100,000 pys; 95% CI: 57.2-60.2; see Figure). Lower CD4 cell counts were associated with a higher risk of HPV-associated SCC, except for head and neck (see Table). The risk for HPV-associated SCC increased with age, except for penile, anal, and rectal cancers. While the risk for cervical cancer decreased over calendar periods, the risk increased for vaginal and vulvar, as well as anal and rectal SCCs. There was no evidence for an association of ethnicity or settlement type with HPV-associated SCC in PLWIH in South Africa.

Figure: Incidence Rates of HPV-associated SCC



CONCLUSIONS
In South Africa, HIV control remains crucial for cancer prevention, especially among the ageing HIV population. The lack of an association between immunodeficiency and head and neck SCC requires further investigation. The high risk of cervical cancer and increasing trends in other HPV-associated anogenital SCCs highlight the need to intensify HPV control efforts in South Africa.

Table: Risk factors for developing HPV-related SCC in women and men living with HIV in South Africa

Variable	Cervical HR (95% CI) n=5,929	Vaginal & Vulvar HR [95%CI] n=536	Penile HR [95%CI] n=164	Anal & Rectal HR [95%CI] n=160	Head and Neck HR [95%CI] n=91
Baseline CD4 [cells/μL]					
<=200	1	1	1	1	1
201-350	0.84 [0.79-0.89]	0.70 [0.57-0.87]	0.78 [0.54-1.11]	0.47 [0.32-0.71]	1.16 [0.70-1.93]
351-500	0.81 [0.75-0.88]	0.60 [0.46-0.77]	0.55 [0.33-0.93]	0.49 [0.30-0.79]	1.25 [0.70-2.24]
>=501	0.80 [0.74-0.86]	0.60 [0.47-0.77]	0.47 [0.25-0.89]	0.37 [0.21-0.64]	0.94 [0.49-1.81]
Baseline age [years]					
15-29	0.28 [0.25-0.30]	0.53 [0.43-0.67]	0.36 [0.18-0.71]	0.56 [0.36-0.86]	0.27 [0.07-0.98]
30-39	1	1	1	1	1
40-49	2.02 [1.90-2.15]	1.23 [0.98-1.54]	1.48 [1.05-2.08]	1.22 [0.82-1.81]	6.17 [3.09-12.3]
50-59	2.97 [2.75-3.21]	1.99 [1.49-2.66]	1.36 [0.81-2.26]	1.40 [0.80-2.46]	21.2 [10.7-42.2]
60+	4.18 [3.65-4.77]	2.33 [1.32-4.09]	1.05 [0.33-3.37]	1.89 [0.68-5.23]	39.9 [17.4-91.5]
Calendar period of first laboratory record					
2004-2006	1	1	1	1	1
2007-2010	0.82 [0.76-0.88]	1.06 [0.84-1.34]	0.84 [0.55-1.27]	1.29 [0.82-2.00]	1.13 [0.63-2.00]
2011-2014	0.83 [0.76-0.90]	1.39 [1.04-1.85]	0.83 [0.49-1.39]	1.83 [1.08-3.10]	1.05 [0.52-2.09]

HR Hazard Ratio, CI confidence interval, SCC squamous cell carcinoma; multivariate analyses adjusted for baseline CD4, baseline age, calendar period, ethnicity, settlement type, and sex where applicable.

O28: Treatment of Anal Precancer among 18-to-34-Year-Old Men Who Have Sex with Men Living with HIV: Effectiveness and Key Factors Associated with Outcomes

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BACKGROUND

People living with HIV (PLH), particularly men who have sex with men (MSM), are at highest anal cancer risk. Treating anal precancer, i.e., high-grade squamous intraepithelial lesions (aHSIL), in PLH significantly reduces anal cancer risk. Guidelines suggest anal cancer screening for MSM living with HIV (MSMLH) starting at age 35 due to the known low epidemiologic anal cancer risk in MSMLH younger than 35 (<35). Recent data published by our group found no anal cancer cases among 1,255 MSMLH <35 despite high aHSIL prevalence (47%). To date, aHSIL treatment outcomes in this population are unknown.

Table 1: Cohort characteristics and outcomes

Characteristic	
Age, median, range	30 (22-34)
Age, n (%)	
<25	6 (7)
25-29	32 (36)
30-34	51 (57)
Race/ethnicity	
Black	16 (17)
White	21 (24)
Hispanic	31 (35)
Other	21 (24)
HPV	
HPV16 alone	2 (2)
HPV16 + other	27 (33)
Others	54 (65)
Vaccinated, n (%)	29 (33)
Number of HSIL, median, range	2 (1-6)
Treatment, n (%)	
Electrocautery Ablation	74 (83)
Fulguration	11 (12)
Excision	2 (2)
Topical	2 (2)
24 Month Outcome	
Overall Recurrence	47 (53)
- Persistence	27 (30)
- Metachronous	33 (37)

METHODS

Between 2014 and 2020, 89 MSMLH <35 years of age with aHSIL were analyzed among participants in our anal cancer screening program. We routinely collected information on demographics, sexual practices and HIV disease characteristics. All participants were treated with either electrocautery ablation, excision, or topical therapy. Twenty-four-month surveillance data were then assessed for recurrent disease, stratified by either index lesion persistence (i.e., a recurrent lesion in the treated octant) or new incident (metachronous) aHSIL. Recurrence rates were thus calculated with 95% confidence intervals according to the binomial distribution. We then conducted univariable analyses of predictors of lesional persistence/recurrence.

RESULTS

Median cohort age was 30 (range 22-34) and more than half were Black or Hispanic. Only one-third received at least one dose of the HPV vaccine. Anal HPV16 infection was common (35%) and the median number of aHSIL was 2 (range 1-6). The majority of participants (83%) were treated with electrocautery ablation. Within 24 months, more than one-half of aHSIL recurred; 30% (95% confidence interval (CI] 21%-41%) had persistent index aHSIL and 37% (95% CI: 27%-48%) developed new, metachronous lesions. No incident anal cancers were found. In univariable analyses of potential predictors of aHSIL persistence/recurrence, only the number of baseline lesions was a significant predictor (p=0.04).

CONCLUSIONS

Recurrent disease is common after treating MSM living with HIV younger than 35 years for aHSIL. Considering the risk of screening fatigue, combined with the limited resources for aHSIL treatment and low anal cancer risk, our findings provide additional support for deferring anal cancer screening among MSMLH to age 35 and above, when it might have a more significant impact.

O29: Induction Chemotherapy Outcomes in Patients with Locally Advanced Cervical Cancer in Botswana

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BACKGROUND

The standard treatment of locally advanced cervical cancer globally is chemoradiation (CRT); however, preliminary reports of international studies suggest a survival benefit with induction chemotherapy (IC). In Botswana, a sub-Saharan African low- and middle-income country (LMIC), the COVID-19 pandemic disrupted standard treatment pathways, and in response patients were prescribed IC in an effort to bridge to radiotherapy (RT) or CRT. The feasibility and outcomes of patients treated with IC+RT/CRT in a LMIC have not been described previously.

METHODS

This prospective observational study compared outcomes of locally advanced cervical cancer patients who received IC+RT/CRT (n=67) between 2019 and 2022 to historical controls who received CRT (n=169) or RT alone (n=111) between 2014 and 2019. IC+RT/CRT consisted of four cycles of paclitaxel and carboplatin followed by external beam RT and brachytherapy with or without weekly concurrent cisplatin. Overall survival (OS) was estimated using the Kaplan-Meier method. Multivariable Cox regression (aHR) adjusted for age, disease stage, HIV status, and treatment group were used to identify factors associated with OS.

RESULTS

The median age across cohorts was 49 years (IQR 42-61 years) and 68.7% (n=347) were living with HIV infection. FIGO stage III represented 45.7% of the cohort. Among those who were prescribed IC, 70.3% received ≥3 cycles and 7.7% received 1-3 cycles. After receipt of IC, 65.9% received RT alone and 6.6% received CRT with ≥1 cycle of concurrent chemotherapy. Among all patients, median follow-up was 22.1 months (95% CI 19.6-24.7 months) and 2-year OS was 55.6% (95% CI 50.9-60.8%). The 2-year OS of the IC+RT/CRT cohort (84.4% [95% CI: 75.4-94.4%]) did not significantly differ from the historical CRT cohort (80.0% [95% CI 74.086.4%]; p=0.46) but was higher than the historical RT only group (31.2% [95% CI: 23.0-42.4%]; p<0.001). On MVA, improved OS was associated with receiving ≥3 cycles of IC. Secondary analysis among those prescribed IC+RT/CRT (n=91) demonstrated no difference in 2-year OS (69.2% [95% CI: 59.8-80.2%]; p=0.065) compared to CRT historical controls. However, receipt of prescribed IC+RT/CRT was associated with improved survival.

CONCLUSION

Survival of patients who received IC+RT/CRT was similar to historical controls who received standard CRT and was associated with ≥3 cycles of IC. This remained true for those prescribed IC+RT/CRT, demonstrating real-world feasibility of prescribing IC treatment in a low-resource setting. This treatment pathway with IC may provide an alternative option for providers in LMICs who experience delays in access to CRT.

O30: Thermal Ablation 24-Week Efficacy for the Treatment of High-Grade Cervical Intraepithelial Neoplasia among Women Participating in a GeneXpert-based Human Papillomavirus Screening Trial for Cervical Cancer Prevention in Malawi

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BACKGROUND
We evaluated the 24-week efficacy of thermal ablation (TA) for treatment of high-grade cervical intraepithelial neoplasia (CIN2+) among women with high-risk human papillomavirus (HPV) in Malawi.

METHODS
In a single-arm prospective study, we offered screen-eligible participants HPV cervicovaginal self-sampling, VIA and colposcopy if HPV+, and TA if HPV+/TA-eligible by colposcopy. At colposcopy, we performed cervical biopsy for any abnormal lesions (or Pap smear if colposcopy was normal) and endocervical curettage (ECC). Participants who underwent TA for CIN2+ but had no CIN2+ on ECC had a week 24 post-treatment follow-up where a provider-collected cervical sample for HPV testing, colposcopy-directed cervical biopsy or Pap smear, and ECC were obtained. Participants with CIN2+ on ECC were referred for excisional treatment. Our study outcomes were cure rate for CIN2+ and HPV clearance at 24-week post-TA treatment.

RESULTS
We enrolled 1,250 participants between June 2020 and February 2022. Overall, 476 (38.1%) were HPV+, of whom 469 (98.5%) had colposcopy performed. At enrolment, 55 participants had CIN2+, of whom 27 had CIN2+ on ECC, 2 were pregnant, and 7 were lost to follow-up. Among 19 participants with 24-week data, the efficacy of TA for CIN2+ was 95% (95% CI: 66%, 99%), whereas among 18 participants with HPV data at week 24 post-TA, HPV clearance was 61% (95% CI: 36%, 83%). We observed no significant difference in the efficacy of TA for CIN2+ between women living with HIV (WLWH) (92%) and those without HIV (100%) (p= 0.49). However, HPV clearance was higher in the women without HIV (100%) than WLWH (46%) (p=0.03).

CONCLUSIONS
Our study showed that the efficacy of TA for CIN2+ was similar to that reported in the most recent metanalysis of TA efficacy, 94 % (95% CI: 91%, 96%). However, HPV clearance was only 61%. The study was limited by the small sample size.

O31: A Pulsed Campaign-Based Approach for Community-Centered Cervical Cancer Prevention in East Africa: Feasibility and Reasons for Non-Participation of Residents

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BACKGROUND

Facility-based cervical cancer prevention in resource-limited settings has limited population reach, including often failing to reach women who are unaware of underlying HIV infection. We evaluated an alternative—a community-based approach that integrates HPV vaccination and cervical cancer screening for all eligible residents. We also directly assessed why in this approach, despite centrally located cervical cancer prevention services, some residents chose not to participate.

METHODS

In rural Kenya and Uganda, Community Health Workers (CHW) mobilized residents to attend Health Fairs in central locations in their communities, at which women aged 30 to 64 were offered self-collected HPV screening, and girls aged 10 to 14 received HPV vaccination. Door-to-door probability sampling was subsequently conducted to assess attendance at the Fairs. In-depth interviews explored reasons for non-attendance. Data were analysed using a convergent mixed methods approach.

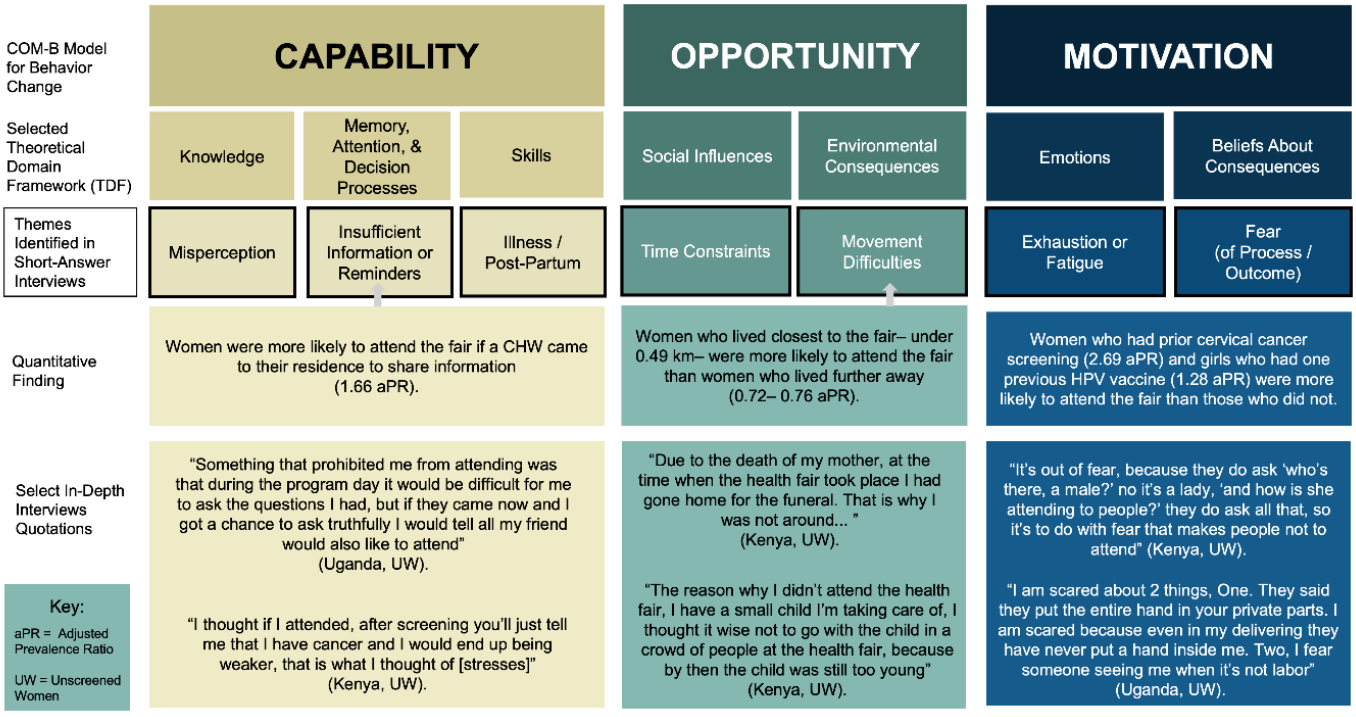
RESULTS

During ten Health Fairs with 610 screening-eligible women and 765 vaccine-eligible girls, 99.7% of women screened and 95% of girls were vaccinated. HPV prevalence was 20%, and 78% of HPV-positive women returned for treatment. Among the 78% of women and 82% of caregivers of adolescents who reported awareness of the Fairs during the post-Fair survey, 46% and 63%, respectively, attended the Fairs. Attendance was highest among women who received in-person invitations. The most frequent reason for non-attendance was time constraints followed by privacy concerns and fear of pain from the procedures (Fig.). Misperceptions about vaccines were uncommon.

CONCLUSIONS

In East Africa, a pulsed community-based approach shows potential to substantially increase use of cervical cancer prevention services. To ultimately reach the WHO vaccination and screening targets for cervical cancer elimination, understanding reasons for non-participation in prevention services will likely require directly asking community residents who do not participate. In our preliminary assessment, we found that time constraints, rather than misinformation, was the most frequent reason for non-participation, a finding which merits deeper investigation to guide future adaptations in Health Fair structure.

Reasons for Health Fair Non-Attendance Among Age-Eligible Non-Attenders



ST1: Anal Cancer Guidelines

Author: *Joel Palefsky*
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Department of Medicine

The ANCHOR study showed that treating anal high-grade squamous intraepithelial lesions (HSIL) could reduce the risk of progression to anal cancer by 57% in people with HIV (PWH). Most participants were treated with hyfrecation, a form of target ablation of lesions performed under high resolution anoscopy. Hyfrecation was safe and well tolerated in the study population, which closely resembled that of the overall U.S. HIV population. Based on these results, the Centers for Disease Control and Prevention published the first federal guidelines recommending screening for anal HSIL in PWH beginning at age 35 years or 45 years depending on their sex at birth, gender, and risk factors for HIV acquisition. CDC guidelines also recommended hyfrecation as first-line therapy for anal HSIL. The International Anal Neoplasia Society published similar guidelines for PWH and extended their recommendations to other groups not living with HIV at high risk of anal cancer. Other professional societies around the world have likewise published recommendations, and these vary with respect to age of initiation of screening, choice of screening test, use of high resolution anoscopy, and treatment recommendations. This presentation will summarize the current guidelines and highlight key areas where further information is needed to optimize screening and treatment guidelines in the future.

ST2: Screening for Anal Cancer among People with HIV: Benefits, Harms, and Cost-Effectiveness

Author: *Ashish A. Deshmukh, PhD, MPH*

Cancer Prevention and Control Program, Hollings Cancer Center, Medical University of South Carolina, Charleston, SC

People with HIV (PWH) have disproportionately elevated (~30-fold compared with people without HIV) anal cancer risk, making them a high-priority group for targeted anal cancer screening. Following the success of the Anal Cancer-HSIL Outcomes Research (ANCHOR) trial, the US Department of Health and Human Services (HHS), International Anal Neoplasia Society (IANS), and French Society of Coloproctology have released consensus guidelines recommending anal cancer screening use beginning at age 35 years for men who have sex with men (MSM) with HIV and 45 years for other risk groups (women with HIV, heterosexual men with HIV). A major area of uncertainty for evidence generation has been the absence of data on the long-term clinical outcomes and cost-effectiveness of screening. Particularly, the optimal age to initiate screening and optimal interval remain unknown. Furthermore, the benefits versus harms of available screening options (primary screening with anal cytology, primary HPV testing, or cytology and HPV co-testing and triage strategies) also remain unknown. Mainly, given the differences in clinical performance associated with these screening options, their long-term risk/benefit profile and cancer prevention and mortality benefits could greatly vary. This presentation will cover new data addressing these critical foundational clinical and policy-relevant questions. In particular, guided by data from the ANCHOR trial, The North American AIDS Cohort Collaboration on Research and Design study, The US HIV Surveillance System, and several meta-analyses, we developed a microsimulation model (R01CA232888) representative of anal cancer natural history in association with HIV natural history and treatment outcomes. The model compared all strategies recommended by HHS and IANS and determined the optimal screening approach. The outcomes of interest were the trade-off of harms (i.e., high-resolution anoscopies [HRAs] and biopsies) versus benefits (cancer cases averted, life years gained) and cost-effectiveness of anal cancer screening (incremental cost-effectiveness in terms of dollars per quality-adjusted life year). This presentation will discuss efficient strategies that optimize HRA utilization and concurrently maximize anal cancer prevention and mortality benefits. We will also discuss inefficient strategies that provide marginal to no benefits but substantially increase HRA use and are not cost-effective. By addressing these critical knowledge gaps, the findings from this research offer foundational data to further update anal cancer screening guidelines.

ST3: Implementation of Anal Cancer Screening Prevention Guidelines Requires Immediate Expansion of High-Resolution Anoscopy Infrastructure

Author: *Naomi Jay*

University of California, San Francisco, Division of Medicine, Anal Neoplasia Clinic, Research and Education Center

Anal cancer is a rare malignancy affecting less than 2 per 100,000 persons in the general population but is greatly elevated in certain populations including persons with HIV, women with a history of vulvar precancers or cancer, solid organ transplant recipients and men who have sex with men (MSM). In particular MSM with HIV have the highest rates of anal cancer exceeding 70/100,000 at age 45+[1]. Guidelines for screening to prevent anal cancer in persons with HIV were released by the CDC in July 2024[2]. Guidelines for screening in all populations considered at-risk had been previously published by the International Anal Neoplasia Society (IANS) and other medical associations.[3]

The objective of preventive screening is to identify anal high-grade squamous intraepithelial lesion (HSIL), the cancer precursor. Persons with positive screening results are then referred for high-resolution ansocopy (HRA) exams to identify suspected lesions and confirm the diagnosis with biopsies using the magnification and lighting of visualization devices such as a colposcope. Biopsy-proven HSIL can then be treated under HRA visualization to prevent progression to cancer. The ANCHOR study showed that treatment of anal HSIL in persons with HIV is effective in preventing progression to cancer compared to those with untreated HSIL[4]

The importance of HRA procedures for anal cancer screening prevention protocols cannot be underestimated. However, there is limited access to clinics offering HRA and in many cities and countries it is unavailable. To implement anal cancer prevention screening that meets the needs of the proposed populations in the guidelines, the availability of HRA will need to be dramatically increased.

HRA requires advanced specialty training. It can be provided by MDs or advanced practice clinicians including NPs or PAs. HRA has been incorporated into many specialty practices such as infectious diseases, colorectal surgery, gastro-enterology, gynecology, sexual health, or dermatology. Training includes didactic courses and ideally hands-on mentoring with an experienced HRA provider. Although HRA has many similarities to cervical colposcopy, it is known to be more difficult to learn with a long learning curve to competency; and there are far fewer experienced mentors to provide the hands-on training that is common for learning cervical colposcopy.

Therefore, successful implementation of the recommended screening guidelines must include strategies to expand the HRA infrastructure including development and funding of clinics, training opportunities, and shortening the learning curve to competency. Strategies should also include improvement in the sensitivity and specificity of screening tools to minimize unnecessary referrals to HRA as well as innovations in high-resolution equipment. Finally, improvement in reimbursement or coverage for the procedures is needed to incentivize clinicians to incorporate screening into their practices.

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[3]Stier et al. (2024) International Anal Neoplasia Society's consensus guidelines for anal cancer screening. Int J Cancer 154(10):1694-1702

[4]Palefsky et al. (2022) Treatment of anal HSIL to prevent progression to anal cancer. NEJM 386:2273-2282.

ST4: Bridging the Gap: Addressing Disparities in Cancer Treatment and Outcomes

Author: *Gita Suneja*
Huntsman Cancer Institute

This talk will address the critical disparities in cancer treatment and outcomes among people living with HIV (PLWH), drawing from the modern literature utilizing multi-institutional studies and national databases. The presentation will examine recent data on disparities in access to cancer care, quality of cancer care, increased treatment toxicities, and compromised health-related quality of life during cancer therapy for PLWH. It will delineate key drivers of these disparities, encompassing factors such as stigma, healthcare provider limitations, and systemic barriers like inadequate healthcare accessibility. The lecture will advocate for a holistic cancer equity framework, emphasizing the importance of addressing both immediate social needs and broader social determinants of health. Finally, it will propose a crucial discussion question: how to effectively implement and disseminate evidence-based, community-engaged strategies to enhance access to cancer therapy and improve the overall treatment experience for PLWH, with the aim of reducing these significant health disparities and improving cancer outcomes.

ST5: HIV, Health Disparities and the Southern U.S.

Author: *Elizabeth Chiao*
University of Texas MD Anderson Cancer Center, Department of Epidemiology, Houston, TX

Although innovative HIV prevention and treatment approaches (as well as increased resources) have led to substantial overall improvements in HIV outcomes, specific subpopulations remain at high risk for poor outcomes. For example, national U.S. epidemiologic data have consistently shown that the U.S. South is disproportionately affected by HIV, with over 60 percent of individuals diagnosed with HIV in 2018 residing in the Southern U.S. The South also has some of the highest poverty levels and most negative health indicators in the country; 9 of the 10 states with the worst overall health ratings are in the Southern states. Other subpopulations include young minority men and individuals who live in poorer communities throughout the U.S. Furthermore, epidemiologic data disaggregated by race, age, and geography demonstrate that these specific subpopulations within the southern U.S. continue to have increased poor HIV and HIV-related cancer outcomes. Cancer disparities may partially be driven by differences in changing epidemiologic dynamics of oncoviruses such as KSHV. In addition, social factors that impact access and engagement in healthcare, including historic and systemic race-based inequality, lower health literacy, and stigma are also likely drivers of disparities. More work is needed to identify and address these growing geographic and demographic disparities.

DAY ONE POSTERS

1. Implementation of Teledermatology to Identify and Expedite Care for Kaposi Sarcoma in East Africa
2. Differential Epstein-Barr Virus (EBV) Reactivation by P. Gingivalis Serotypes
3. Kaposi Sarcoma in Relation to HIV Diagnosis: Which Comes First in East Africa in the “Treat All” Era?
4. Systematic Evaluation of the Clinical and Radiographic Manifestations of Pulmonary Kaposi Sarcoma in the Era of the Antiretroviral Rollout in Zimbabwe
5. HIV-Related Kaposi Sarcoma in the “Treat All” Era in East Africa: Update on Stage at Time of Diagnosis and Survival
6. A Rapid Skin Biopsy DNA Extraction for Diagnosing Kaposi’s Sarcoma in Sub-Saharan Africa
7. Artificial Intelligence-Based Diagnosis of Kaposi Sarcoma Using Digital Surface Photography in Dark-Skinned Patients in Uganda
8. Development of an Intersectional Stigma Instrument for Individuals Living with HIV and Cancer: Evaluation of Item Acceptability and Comprehension through Cognitive Debriefing
9. Clinical, Social, and Healthcare System Determinants of Survival among Patients with HIV Diagnosed with Kaposi Sarcoma in the United States (2004–2020)
10. Characterization of Kaposi Sarcoma-Associated Herpesvirus in an Anaplastic Variant of Gastrointestinal KS
11. Reclassification and Comprehensive Characterization of Lymphoproliferative Disorders in a Mexican HIV-Infected Cohort (1983–2019)
12. RBM25 Is a New Restriction Factor against KSHV
13. Travel Time from Cancer Center Is Associated with Disparities in Non-Hodgkin Lymphoma Diagnosis among People Living with HIV in Malawi
14. Heterogeneity of Oncogenic and Survival Signaling Pathways in Primary Effusion Lymphoma: Implications for Precision Targeting and Combination Therapy
15. Lack of Evidence for Kaposi’s Sarcoma Associated Herpesvirus Association with Osteosarcoma in Sub-Saharan Africa
16. Human Cerebral Brain Organoids Infected with HIV-1: A New Model for EBV Positive Central Nervous System Lymphomas in HIV-1 Infection
17. Identifying Cellular Regulators of Latency and Lytic Replication Using the Ubiquitome
18. WT1 Upregulation by Lytic Induction of Kaposi Sarcoma Herpesvirus
19. Suspected Causes of Death among Adults with HIV-Associated Kaposi Sarcoma in East Africa in the “Treat All” Era
20. Frequent Expression of *KSHV ORF75*, a Lytic Gene, in Kaposi Sarcoma Lesions: Role of Sp1 Transcription Factors
21. The Impact of B Vitamin Complex Supplementation with Antiretroviral Therapy on Aged HIV-Infected Patients with Malignancies at Hill Top Hospital, Lusaka, Zambia
22. Using the KSHV Ubiquitome as a Tool to Identify Inhibitors of Latency and Lytic Replication
23. Human Herpes Virus-8 Shedding Heterogeneity Is Due to Varying Rates of Reactivation from Latency and Immune Containment
24. Preclinical Development of Immunotherapy Combining Anti-CD47 Antibody with KSHV Lytic Inducing Agents for Primary Effusion Lymphoma
25. Characteristics, Survival, Social Factors, and Trends in HIV-Associated Lymphomas: A 23-Year Analysis Since the Implementation of c ART, a County Hospital and a University of Illinois at Chicago HIV-Malignancy Project (CHaMP)

26. Periodontitis-Specific Pathogens Activate Inflammatory Signaling Pathways Leading to EBV Reactivation
27. Kaposi Sarcoma over Time in Sub-Saharan Africa: The Inexorable Influence of HIV Infection
28. Testing for the Virus to Diagnose the Cancer: Validation of Quantification by PCR of Skin Lesion-Derived KSHV DNA Copy Number for the Diagnosis of Kaposi Sarcoma (KS) in Africa
29. Characterization of Extracellular Vesicles in NHL and AIDS-NHL and Their Role in the Tumor Microenvironment
30. Aquaporin 3 (AQP3) Regulates Oxidative Stress and the Life Cycle of Kaposi Sarcoma Herpesvirus (KSHV) in Its Associated Cancers
31. The Role of eIF5B in Translation Initiation during KSHV Replication and Oncogenesis Is Oxygen-Independent
32. Novel Cereblon-Binding Immunomodulators Are Effective against Cancers Associated with Human Gammaherpesviruses
33. Risk of Non-Hodgkin Lymphoma and Hodgkin Lymphoma Subtypes in People with HIV in the U.S. from 2001 to 2019
34. HIV-Associated Plasmablastic Lymphoma in the Era of ART: Outcomes at a Public Hospital in Johannesburg, South Africa
35. Primary Effusion Lymphoma in People with and without HIV in the United States
36. Immunologic Responses among Participants Receiving Pomalidomide and Liposomal Doxorubicin for Kaposi Sarcoma with or without Other KSHV-Associated Diseases
37. CDK4/6 Inhibitor Abemaciclib Inhibits Growth of KSHV-Infected Endothelial Cells
38. NSUN1/2-Mediated RNA m5C Modification Controls KSHV Viral Infection via Regulating RNA Stability of Host Restriction Factors
39. High-Resolution Antibody Profiling of KSHV-Infected Individuals Presenting with and without Kaposi Sarcoma Reveals Distinct Ab Repertoires

DAY TWO POSTERS

40. Longitudinal Patterns of Survivorship Care in Cervical Cancer Patients Living with or without HIV in Botswana, 2015–2023
41. Premalignant Cervical Lesions among HIV-Infected Women on Care and Treatment at a Tertiary Hospital in Jos, Nigeria
42. Patient Perspectives on Acceptability and Appropriateness of a Navigation Strategy for HIV-Associated Kaposi's Sarcoma: A Mixed Methods Analysis
43. Calendar Trends and Risk of Second Primary Cancers among People with HIV in North America: A Collaborative Cohort Study
44. Social Determinants of Health Influences Stage at Presentation of Cervical Cancer for Women Living with HIV in Zambia
45. Anal Cancer Screening in PLWH: Outcomes in a Rural Medically Underserved Population
46. Cancer Survival among People with HIV Compared with People without HIV in the United States in the Modern ART Era: Results from the MACS-WIHS Combined Cohort Study (1996–2019)
47. Attitudes Toward Healthcare Provider Communication, System Distrust, and HIV Stigma among People with HIV and History of Cancer
48. Human Papilloma Virus Profiles in Healthy Women, Women with Cervical Intraepithelial Neoplasia, and Women with Invasive Cervical Cancer in Botswana
49. Distress among PWH and Cancer Enrolled in Clinical Trials

50. Micro-Costing of Pulsed Community-Based Integrated Campaigns for HPV Vaccination and Cervical Cancer Screening in East Africa
51. HIV and Risk of Breast Cancer: A Case-Cohort Study
52. Barriers and Facilitators to Care for Survivors of Cervical Cancer Living with HIV in Botswana
53. Feasibility of Topical Artesunate for Cervical Precancer Treatment among Women Living with HIV in Kenya: Preliminary Results from a Phase I Trial
54. Multiple Myeloma among People Living with HIV in South Africa, 2004 to 2021
55. Factors Associated with Diagnostic Delays in Lung Cancer in East Africa: The Role of Symptoms and Passive Smoking
56. Population-Level HPV Vaccination Coverage Estimates among Adolescent Girls in Kenya and Uganda Using Community Health Workers and Household Surveys
57. Health-Care Seeking Patterns of Hepatocellular Carcinoma (HCC) Patients and Time to Diagnosis and Death
58. Association Between HIV Status and Demographic Characteristics of Patients with Anogenital-Associated Cancers at Jaramogi Oginga Odinga Teaching and Referral Hospital
59. Survival and Predictors of Mortality among Patients with Virus-Associated Cancers in a High HIV-Prevalence Region in Kenya: A 10-Year Retrospective Study
60. Integration and Availability of Cancer Screening across HIV Treatment Sites in the IeDEA Consortium
61. Anal Cancer Incidence among Privately Insured People with and without HIV in South Africa
62. Incidence of AIDS-Defining Illness by Cancer Status in an Observational Study among Medicaid Beneficiaries Living with HIV in the United States, 2001–2015
63. Establishing a Rapid Autopsy Program for HIV/AIDS-Associated Malignancies: Enhancing the AIDS and Cancer Specimen Resource (ACSR)
64. HPV Viral Loads as a Predictive Marker for Pre-Invasive and Invasive Cervical Cancer: A Literature Review
65. Prostate Cancer Treatment and Outcomes for Veterans with HIV in the Antiretroviral Era
66. Non-Small Cell Lung Cancer Survival, by Tumor Stage and Histology, among People with and without HIV
67. Factors Associated with Increased Mortality among Lung Cancer Patients in Tanzania and Uganda
68. Cancer Mortality among People with HIV in the US, 2001–2019
69. Perceptions of Anal Cancer Risk and Stigma among Black Same-Gender-Loving Men Living with HIV
70. Prostate Cancer Characteristics and Outcomes for Medicare Recipients with and without HIV
71. Inequities in Receipt of Immunotherapy among Advanced Stage Lung Cancer Patients with and without HIV in the US (2015-2020)
72. Nascent Non-AIDS-Defining Skin Cancers among People with HIV: A Cross-Sectional Analysis of the All of Us Database
73. Anal Human Papillomavirus Infection among Transgender Women and Men Who Have Sex with Men from Argentina
74. Cancer Incidence and Trends in People with HIV in the United States, 2001–2019
75. CD4 Count after Cancer Diagnosis and Cancer-Specific Mortality among People with HIV

1: Implementation of Teledermatology to Identify and Expedite Care for Kaposi Sarcoma in East Africa

Authors: *Sonya Ahuja[1], Jeffrey Martin[2], Samson Kiprono[3], David Felker[4], Sigrid Collier[1], Philip Odhiambo[3], Celestine Lagat[3], Martha Nansereko[5], Jane Frances Nalubega[5], Marion Achieng[5], Linda Chemtai[3], Isabel Muraguri[3], Elyne Rotich[3], Patrick Musinguzi[6], Toby Maurer[2,4], and Aggrey Semeere[5]*

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BACKGROUND

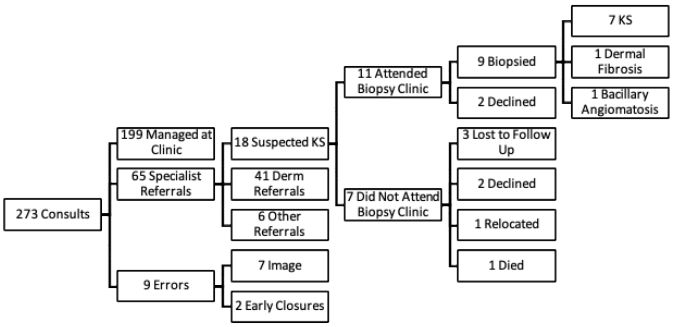
Advanced-stage disease at time of diagnosis, resulting in high mortality, remains an urgent unaddressed issue for HIV-related KS in East Africa. Contributing factors include the lack of expertise among frontline providers in recognizing KS, shortage of dermatologists to aid with differential diagnosis, and limited access to biopsies for diagnostic confirmation. In resource-rich settings, Teledermatology (TD) is increasingly being used to expand access to dermatologists, thereby reducing the time to diagnosis and treatment. In this demonstration project, we sought to evaluate the overall acceptability and feasibility of TD in East Africa and its specific benefits in the detection and management of KS.

METHODS

Several ambulatory clinics providing HIV primary care in Kenya and Uganda were given access to and trained on using MedWeb, a stand-alone, secure commercial TD platform originally developed in the U.S. This platform allows providers to send patient histories and high-resolution skin lesion images via tablets or smartphones to remote dermatologists for consultation. Each clinic was provided with an internet-enabled tablet equipped with MedWeb for communal use, and providers could also install the app on their phones if they were able and willing. Each country had its own consulting dermatologist.

RESULTS

Between February 2023 and February 2024, 273 consultation requests (172 in Kenya, 101 in Uganda) were submitted by 36 providers at 12 HIV clinics. The median patient age was 39 years (IQR: 28-51), and 53% were men. Of these, 73% received treatment recommendations from the consulting dermatologist and were managed at the originating clinic, while 24% were advised to have an in-person consultation with a dermatologist, biopsy at a distal clinic, or care from another type of specialist (Figure). Eighteen patients (6.5%) were suspected to have KS and were referred for biopsy; 11 attended the biopsy clinic, and 9 received a biopsy, with 7 diagnosed with KS. The median time between TD consult and biopsy was four days (IQR: 4-10). Among patients who did not obtain the recommended biopsy, several could no longer be contacted, while others either declined, stated they had relocated, or died.



CONCLUSIONS

In HIV primary care settings in East Africa, TD was adopted by many frontline clinicians and gave access to dermatologic consultation to many patients who otherwise almost certainly would not have had access. Most patients for whom TD was used were managed without traveling to another site. A sizeable number of patients were identified with lesions suspicious for KS, and many had prompt subsequent biopsy for definitive diagnosis, thereby providing proof of concept that TD can assist in timely diagnosis of KS. However, many patients recommended for biopsy did not receive the service, highlighting the need to investigate barriers to care and point-of-care diagnostic methods for KS.

2: Differential Epstein-Barr Virus (EBV) Reactivation by P. Gingivalis Serotypes

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BACKGROUND

Epstein-Barr virus (EBV) is a gammaherpesvirus linked to various diseases and malignancies including oral hairy leukoplakia, nasopharyngeal carcinoma, gastric carcinoma, and lymphomas, and is a recently discovered driver of inflammation. Periodontitis is a bacterially driven inflammatory disease.

Porphyromonas gingivalis (Pg), a key oral pathogenic bacterium, whose different strains are major contributors of periodontitis. We previously demonstrated that patients with periodontitis have high oral EBV viral loads. We hypothesize that oral pathogens differentially contribute to EBV reactivation in latently infected cells. This study aims to determine if pathogenic Pgs differentially reactivate latent EBV.

METHODS

Different types and strains of bacteria: Streptococcus sanguinis (Ss), K1 Pg, K4 Pg, and non-capsulated Pg (K-) were grown in Brain Heart Infusion (BHI) media. Bacterial end products (BEPs) were obtained by centrifugation/filtration. Latently infected cells were treated with 1:20 dilutions of BEPs. 24 hours post-treatment, total RNA and protein were isolated. EBV transcripts were determined by RT-qPCR ($\Delta\Delta$Ct method using GAPDH as a calibrator). Viral and cellular proteins were detected by immunoblot analysis.

RESULTS

K1 and K4 Pg BEP treatment of HEK-293 cells resulted in decreased cell viability (~50%). Pg BEP treatment increased viral transcripts encoded by BRLF1 (10-13X), BMRF1 (22-28X), BILF1 (7-13X), and BXLF2 (2-10X) compared to BHI media. Ss did not result in any fold increase. Pg BEP treatment resulted in the acquisition of H3K9Ac, phospho-erk1/2, and EBVZ protein.

CONCLUSIONS

Factors produced by Pg can effectively induce EBV reactivation in latently infected cells resulting in the expression of all classes of EBV genes representing the full EBV lifecycle, potentially resulting in the production of infectious viral particles that can infect naive cells. K1 and K4 Pg BEP treatments demonstrated higher levels of pathogenicity compared to the K-strain. Pg can promote increased spread of virally infected cells potentially contributing to EBV oncogenicity.

3: Kaposi Sarcoma in Relation to HIV Diagnosis: Which Comes First in East Africa in the "Treat All" Era?

Authors: *Racheal Aida Ayanga[1], Aggrey Semeere[1], Megan Wenger[2], Linda Chemtai[3], Pendo M. Ibrahim[4], Philippa Kadama-Makanga[1], Michael Kanyesigye[5], Matthew Semakadde[6], Bronia Mwine[5], Stella Nabunya[6], Celestine Lagat[3], Martha Nansereko[1], Elyne Rotich[3], Hilda Muwando[1], Zainab Illonga[4], Emmanuel Ochola[7], Charles Kasozi[6], Winnie Muyindike[5], Esther Freeman[8], Elia John[4], Samson Kiprono[3], Miriam Laker[1], Jeffrey Martin[2] and Helen Byakwaga[1]*

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BACKGROUND

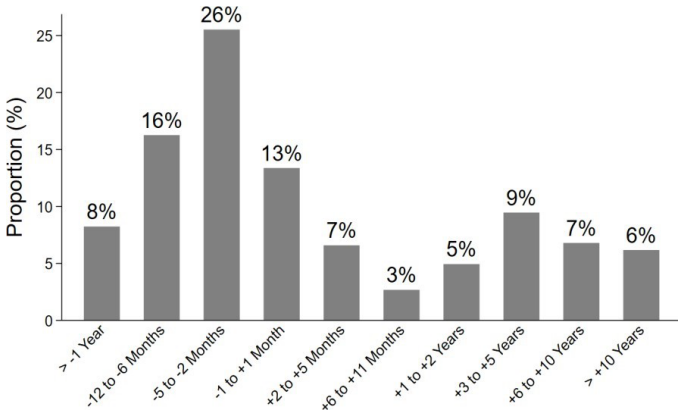
In 2015, the WHO recommended initiation of ART in all persons living with HIV, regardless of CD4 count or clinical stage, the dawning of the "Treat All" era. The intention of "Treat All" is to detect and treat HIV infection in its earliest stages. At the most macroscopic level, "Treat All" has been successful in most resource-limited settings, diminishing all-cause death related to HIV. What is less understood is whether all individual severe HIV-related complications have benefitted equally. We investigated how one oncologic complication—Kaposi sarcoma (KS)—has fared by examining when it develops in relationship to diagnosis of HIV infection.

METHODS

We identified adults (aged ≥ 18 years) with a new diagnosis of KS made between October 2022 and June 2024 in both inpatient and outpatient settings at several sites in East Africa that offer free-of-charge skin biopsy services: Uganda (Infectious Diseases Institute, Masaka and Mbarara Regional Referral Hospitals, and St. Mary's Hospital Lacor); Kenya (Academic Model Providing Access to Healthcare network); and Tanzania (Muhimbili Univ. of Health and Allied Sciences). KS was confirmed by histopathology except in those with lesions that were deemed unsafe to biopsy. We used interviewer-administered questionnaires to collect data on HIV diagnosis and KS history. Using the date that patients reported to have first noticed KS lesions and the date they reported HIV diagnosis was made, we describe the timing of KS lesion development in relation to HIV diagnosis.

RESULTS

Among 501 adults with a new diagnosis of HIV-related KS, 67% were men and the median (IQR) age was 36 (30-42) years. Median monthly household income was <$100 US. Among 482 patients with evaluable dates, 50% first noticed KS lesions one or months prior to HIV diagnosis, 13% noticed lesions within ± 1 month of HIV diagnosis (the exact sequence could not be determined), and 37% noticed lesions ≥ 1 month after HIV diagnosis (Figure).



Duration between First Noticing KS Lesions and HIV Diagnosis

(-) denotes noticing KS lesions before HIV diagnosis, and (+) denotes noticing KS lesions after HIV diagnosis

CONCLUSION

Among adults with newly diagnosed KS in East Africa in the "Treat All" era, half developed KS prior to the health care system's diagnosis of HIV infection. This indicates a need to improve HIV screening strategies in order to have HIV diagnosis made earlier, thus preventing progression to KS. The large proportion of patients developing KS after HIV diagnosis represents another research priority—why is this occurring and how can it be prevented?

4: Systematic Evaluation of the Clinical and Radiographic Manifestations of Pulmonary Kaposi Sarcoma in the Era of the Antiretroviral Rollout in Zimbabwe

Authors: *Margaret Z. Borok[1], Suzanne Fiorillo[2], Felix Manyeruke[1], Tobias Makoni[1], Ivy Gudza[1], Marcia Mutimuri[1], Misheck Phiri[1], Tatenda Nyagura[1], Irene E. White[2], Rick Rapaport[2], Alison M. Bock[3], Angela Nalwoga[2], Thomas W. Campbell[4], Thomas B. Campbell[2]*

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BACKGROUND

The lung is a commonly involved visceral organ in advanced Kaposi sarcoma (KS); however, diagnosis of pulmonary KS in African settings is difficult because of limited diagnostic capabilities and overlapping clinical and radiographic findings with common lung infections such as pulmonary tuberculosis (TB). A longitudinal cohort of Africans with AIDS-KS was established to estimate the prevalence of pulmonary KS, pulmonary TB, and bacterial and fungal pneumonia and evaluate screening for pulmonary KS using clinical findings together with radiographic and laboratory evaluations that are readily available in low resource settings.

METHODS

Persons presenting to the Parirenyatwa Hospital KS Clinic for treatment of AIDS-KS were considered for participation if they met eligibility criteria. Written informed consent was obtained from all participants. Assessments at entry included clinical KS staging, chest x-ray, pulmonary function tests, and bronchoscopy with bacterial, fungal and TB cultures. Vital status was assessed at 2, 4 and 6 months. Chest x-ray abnormalities were scored by radiologists blinded to other participant characteristics. During bronchoscopy, 10 anatomical sites in the lower respiratory tract were visually assessed for KS lesions. Prevalence of pulmonary KS, TB, and bacterial or fungal pneumonia were estimated with confidence intervals (CI). The collective diagnostic performance of combinations of 95 clinical and laboratory attributes was evaluated by training iterative machine learning models using the entire selection of data elements. Attribute importance was evaluated by relative Shapley value analysis. Attributes with high feature importance by cross-validated Shapley value analysis were included in the next iteration of the model. Model performance was evaluated by Area Under Receiver-Operator Characteristic curves (AUROC).

RESULTS

Among 181 participants with cutaneous KS, 113 had KS lesions in the lower respiratory tract (median 3 anatomic sites; range 1-11 sites). Prevalence of pulmonary KS by bronchoscopy was 62.4% (95% CI 55.3, 69.6%). Prevalence of TB and fungal/bacterial pneumonia were 9.4% (95% CI 5.3-13.5%) and 9.4% (95% CI 5.1-13.7%), respectively. Loss-to-follow-up or death at 6 months did not differ by pulmonary KS status (39% vs 38%). A converged set of seven clinical attributes retained in the final machine learning model had improved specificity and sensitivity for predicting pulmonary KS compared to any individual attribute (AUROC 0.70; 95% CI 0.63-0.78).

CONCLUSIONS

Lower respiratory infections with TB, bacteria and fungi were common. Screening for these infections should be included in initial clinical evaluations of AIDS-KS. The presence of gingival KS or raised KS lesions on the palate and high plasma KSHV DNA should increase suspicion for the presence of pulmonary KS.

	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity	AUROC	Relative Shapley Importance Index
Raised KS lesions on palate	0.54	0.10	0.65	0.06	ND	9.01
Plasma KSHV DNA >72 c/mL	0.71	0.56	0.80	0.44	0.66	5.72
KS lesions on gingiva	0.59	0.12	0.79	0.05	ND	2.99
Chest x ray score > 0	0.72	0.54	0.76	0.49	0.64	2.80
Weight ≤ 52 kg	0.61	0.29	0.80	0.14	0.43	2.76
Interstitial infiltrates CXR Q3	0.53	0.29	0.36	0.44	ND	2.67
CD4+ lymphocytes ≤ 83/µL	0.64	0.39	0.80	0.22	0.42	2.59

5: HIV-Related Kaposi Sarcoma in the "Treat All" Era in East Africa: Update on Stage at Time of Diagnosis and Survival

Authors: *Helen Byakwaga[1], Aggrey Semeere[1], Megan Wenger[2], Esther Freeman[3], Miriam Laker-Oketta[1], Elyne Rotich[4], Beatrice Mushi[5], Charles Kasozi[6], Philippa Kadama-Makanga[1], Winnie Muyindike[7], Sigrid Collier[8,9], Toby Maurer[10], Elia Mmbaga[5], Samson Kiprono[11], Andrew Kambugu[1], and Jeffrey Martin[2]*

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BACKGROUND

The stage at diagnosis and survival are critical parameters in the control of any cancer in any geographical setting. Unlike in resource-rich settings where cancer surveillance that includes systems to routinely document every cancer diagnosis and death are publicly funded, data on these parameters are not available through routine means in resource-limited regions. We sought to provide a very contemporary update on stage and survival following a diagnosis of HIV-related Kaposi sarcoma (KS) in East Africa in the "Treat All" antiretroviral therapy (ART) era.

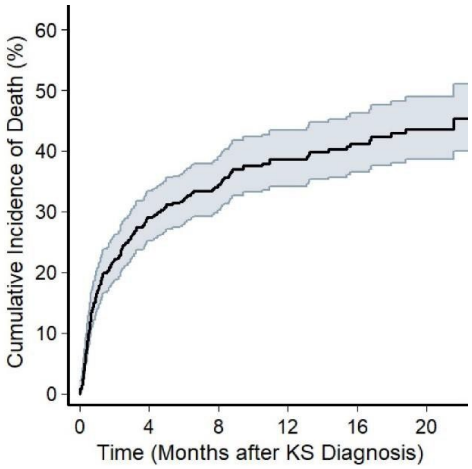
METHODS

Between October 2021 and April 2024, we evaluated HIV-infected adults (age ≥ 18 years) with a new diagnosis of KS in East Africa: in Kenya, (the Academic Model Providing Access to Healthcare network); in Uganda (Infectious Diseases Institute in Kampala, Masaka Regional Referral Hospital, and Mbarara Regional Referral Hospital); and in Tanzania (Muhimbili University of Health and Allied Sciences) using rapid case ascertainment. We confirmed KS diagnosis 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. We subsequently followed participants longitudinally to monitor vital status and use of the health care system.

RESULTS

Among 499 HIV-infected adults identified with a new diagnosis of KS, 66% were men, and the median (IQR) age was 35 (29-42) years. The median (IQR) number of anatomic sites with KS lesions was 8 (4-12); 25% of participants had oral KS lesions that interfered with either eating or speaking, 74% had edema, and 90% had ACTG stage T1 (advanced KS). At the time of KS diagnosis, 95% of the participants were taking ART; 22%, 35%, 33% and 10% had CD4+ T cell count of ≤ 50, 51-200, 201-500 and > 500 cells/mm^3 respectively; 32%, 33%, 10% and 25% had plasma HIV RNA of <40, 40-1000, 1001-10,000 and >10,000 copies/ml, respectively. Over a median follow-up of 7.6 (IQR: 1.3 to 15.5) months, a total of 189 participants died, and 2 were lost to follow-up. The cumulative incidence of death (95% CI), using Kaplan-Meier estimation, at 3, 6, 12 and 18 months were 26% (22%-30%), 32% (28%-36%), 39% (34%-43%),43% (38-48%), respectively (Figure).

Mortality Among Adults with HIV-Related Kaposi Sarcoma in East Africa



CONCLUSIONS

In a very recently assembled community-derived sample of adults with HIV-related KS in the “Treat All” era in East Africa, the majority had advanced disease at the time of KS diagnosis and survival was very poor. These parameters are unchanged from those obtained in the 7 years prior, indicating no improvement in these aspects of the control of KS in the region. Our findings emphasize the need for better control of KS that includes primary prevention, novel approaches for earlier detection, more efficient linkage to oncologic care, and more potent therapeutics.

6: A Rapid Skin Biopsy DNA Extraction for Diagnosing Kaposi's Sarcoma in Sub-Saharan Africa

Authors: *Jason Manning[1], Xinying Chu[1], Juan Boza[1], Aggrey Semeere[2], Racheal Ayanga[2], Hilda Muwando[2], Ethel Cesarman[3], Jeffrey Martin[5], David Erickson[1]*

[1]Cornell University, Ithaca, NY, USA; [2]Infectious Diseases Institute, Kampala, Uganda; [3]Weill Cornell Medical College, New York, NY, USA; [4]University of California San Francisco, CA, USA

BACKGROUND

Kaposi's sarcoma (KS) leads to a high mortality rate in sub-Saharan Africa in part due to insufficient pathological capacity. We hypothesized that KS diagnosis could be made by quantifying KS- associated herpesvirus (KSHV) in suspected skin lesions. Using loop-mediated isothermal amplification (LAMP), we observed favorable diagnostic accuracy compared to histopathologic diagnosis. However, extracting DNA from skin biopsies (DNeasy Blood and Tissue Kit, Qiagen) was the rate-limiting step; due to the 6+ hours required for tissue digestion and DNA purification via spin column membranes, same-day diagnosis was not possible for most cases. To enable same-day results, we have developed a biopsy processing procedure using a simple device ("Slicer") and a rapid DNA extraction ("ColdSHOT").

METHODS

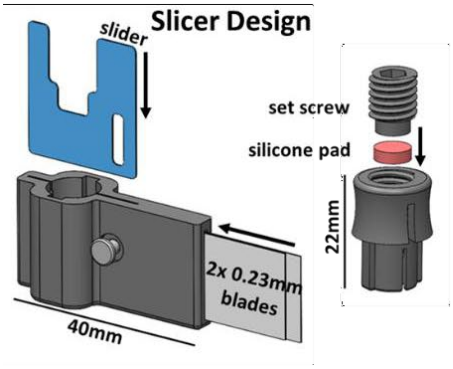
The Slicer is a simple, inexpensive device to safely and quickly cut biopsy samples into two "halves" and a thin cross-sectional slice (Figure). Briefly, two blades are secured in parallel and separated by a slider. After the biopsy is pressed into the blades, the slider is used to retrieve the thin slice. DNA was then extracted from the thin slice using ColdSHOT – an equipment-free version of the alkaline extraction requiring only a 1-hour ambient incubation and a neutralizing buffer. Though the DNA samples were crude, no purification steps were required due to the robustness of the LAMP reaction to impurities. The remaining two "halves" of the patient biopsy enabled standard pathological diagnosis as well as an additional DNA extraction via DNeasy for comparison.

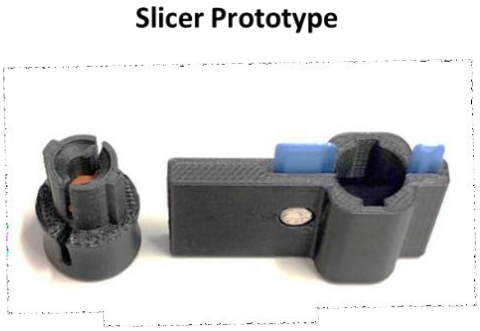
RESULTS

Slicer prototypes were deployed for use at the Infectious Diseases Institute (IDI) in Kampala, Uganda and have been used to cut over 200 patient biopsies at the time of biopsy collection. The ColdSHOT extraction method was similarly implemented at the IDI to extract DNA from 29 of the tissue slices. We compared the results of the ColdSHOT method to the results of the traditional DNA extraction and found that KSHV detection qualitatively agreed for 79% (23/29) of the patient samples. From these initial samples, we learned that simple adjustments to the ColdSHOT formula were needed to increase the DNA yields. We have since observed 100% agreement for 23 patient samples. Additionally, implementing Slicer and ColdSHOT has enabled us to reduce the time to results to as little as 2 hours.

CONCLUSIONS

During deployment, both the Slicer and ColdSHOT were successfully implemented at the IDI to rapidly detect KSHV in patient biopsies. After iterating on the original ColdSHOT formula, we observed 100% concordance in KSHV detection compared to the DNeasy DNA extraction. This data indicate the Slicer and ColdSHOT can yield diagnostic accuracy comparable to our previous work in as little as two hours with less equipment.


Slicer Design
slider
set screw
silicone pad
22mm
2x 0.23mm
blades
40mm


Slicer Prototype


Skin Biopsy after Slicer
Half 1
Slice
Half 2

7: Artificial Intelligence-Based Diagnosis of Kaposi Sarcoma Using Digital Surface Photography in Dark-Skinned Patients in Uganda

Authors: *Sarah Coates[1], Feng Yang[2], Sameer Antani[2], Cody Hill[2], Zhiyun Xue[2], Aggrey Semeere[3], Racheal Ayanga[3], Miriam Laker-Oketta[3], Robert Lukande[3], Matthew Semakadde[4], Micheal Kanyesigye[5], Megan Wenger[1], Philip LeBoit[1], Timothy McCalmont[1], Esther Freeman[6]; Ethel Cesarman[7], David Erickson[7], Toby Maurer[8], and Jeffrey Martin[1]*

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BACKGROUND

Presentation with advanced stage of disease, with resultant high mortality, is among the most urgent and tragic unaddressed issues for HIV-related KS in sub-Saharan Africa. There are many reasons for late-stage KS diagnosis, but lack of access to dermatologists, pathologists, and reagents (e.g., anti-LANA staining) all prominently contribute to delayed diagnosis. We set forth to evaluate whether automated artificial intelligence-based interpretation of digital images of suspicious skin lesions, which has shown diagnostic promise in other skin cancers such as melanoma, could be a possible solution.

METHODS

We obtained digital photographs of skin lesions that were being targeted for biopsy among a consecutive sample of dark-skinned patients who were referred to free-of-charge skin biopsy services at several facilities in Uganda because of at least some clinical suspicion of KS. Lesions were photographed from multiple angles using a digital SLR camera, and punch biopsies were subsequently obtained. To obtain gold standard/ground truth, the lesions were determined to be KS or not by a consensus panel of U.S.-based dermatopathologists. Using training (~70% of images) and validation (~10% of images) sets, we developed and fine-tuned a deep convolutional neural network (CNN)-based prediction model using an ensemble of YOLO (You Only Look Once) object detection algorithms. We subsequently assessed the model's accuracy for KS diagnosis in a test set (~20% of images). The accuracy of a board-certified dermatologist's macroscopic interpretation of the images using a 5-category scale (very likely to be KS; likely; not sure; unlikely; very unlikely) was also assessed.

RESULTS

We evaluated 482 participants, of whom 472 (1385 images) had images deemed to be of sufficient quality. Of these, 38% were women, median age was 34 years, and 94% were living with HIV; 332 had KS and 140 had no KS by histopathology. There were 970 images in the training set, 140 in the validation set, and 275 in the test set. In the test set, the CNN model achieved 89% sensitivity and 51% specificity for diagnosing KS (Figure). A dermatologist evaluating the same images achieved slightly less accurate performance (Table).

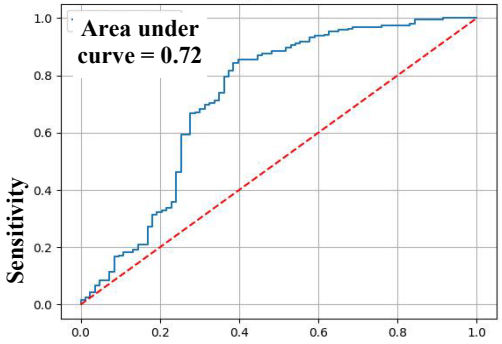

Figure. ROC curve depicting performance of a CNN-based prediction model of digital skin image interpretation for the diagnosis of KS.

CONCLUSIONS

Among patients in Uganda with skin lesions believed to have at least some clinical suspicion of KS, evaluation of lesional surface digital images by a CNN-based prediction model showed moderate success for distinguishing KS from its clinical mimickers. Diagnostic accuracy of the model was comparable if not superior to a dermatologist, but the diagnostic performance of the model in its current state is insufficient for clinical use. Nonetheless, this inaugural assessment (using a modest sample size) is sufficiently promising to justify evaluation

of more numerous image sets and evolving deep-learning technologies to determine if more accurate prediction models can be developed such that, someday, KS diagnostic capability may be available through any healthcare worker's smartphone.

Diagnostic Modality	Sensitivity	Specificity	Pos. Pred. Value	Neg. Pred. Value
CNN prediction model	89%	51%	81%	67%
Dermatologist:				
Very likely/Likely/Not sure vs. Unlikely/Very unlikely	93%	19%	65%	53%
Very likely/Likely vs. Not sure/Unlikely/Very unlikely	55%	59%	75%	36%

8: Development of an Intersectional Stigma Instrument for Individuals Living with HIV and Cancer: Evaluation of Item Acceptability and through Cognitive Debriefing

Authors: *Sigrid M Collier[1], Alexis G Strahan[2], Aggrey Semeere[3], Helen Byakwaga[3], Miriam Laker-Oketta[3], Linda Chemtai[4], Celestine Lagat[4], Ann Pacheco[2], Merridy Grant[5], Laura M Bogart[6], Toby Maurer[7], Ingrid Bassett[2], Jeffrey Martin[8], Samson Kiprono[3], and Esther Freeman[2]*

[1]University of Washington, Veterans Affairs Puget Sound Health Care System, Seattle, USA; [2]Massachusetts General Hospital, Harvard Medical School, Boston, USA; [3]Infectious Disease Institute, Kampala, Uganda; [4]AMPATH, Moi University, Eldoret, Kenya; [5]University of W Australia, Perth, Australia.[6]RAND Corporation, Santa Monica, USA. [7]Indiana University, Indianapolis, USA; [8]University of California San Francisco, San Francisco, USA

BACKGROUND

For people with HIV-associated malignancies the stigma associated with HIV and Cancer likely contribute to compounded negative impacts on their lived experience and health outcomes. Stigma occurs when individuals are labeled as "other" and discriminated against due to sociodemographic, behavioral, or health-related characteristics; intersectional stigma exists with co-occurring stigmatizing conditions. Yet, validated scales assessing HIV and cancer stigma in low-resource settings do not address the experience of intersectional stigma. In this study, we assessed comprehension, acceptability, and equivalence of concept for adapted intersectional scale items and response options in adults living with HIV and Kaposi's Sarcoma (KS).

METHODS

Qualitative data were extracted from semi-structured interviews with adults living with HIV-associated KS in the Academic Model Providing Access to Healthcare (AMPATH) Program in western Kenya. Transcripts were analyzed in an open coding approach to identify emerging themes. Themes were used to develop new items and adapt pre-existing items from validated internalized stigma scales. Member checking and cognitive debriefing were completed with a subset of individuals from a variety of educational backgrounds, disease severity and treatment status. Session transcripts were translated and analyzed to guide further item refinement (Figure 1).

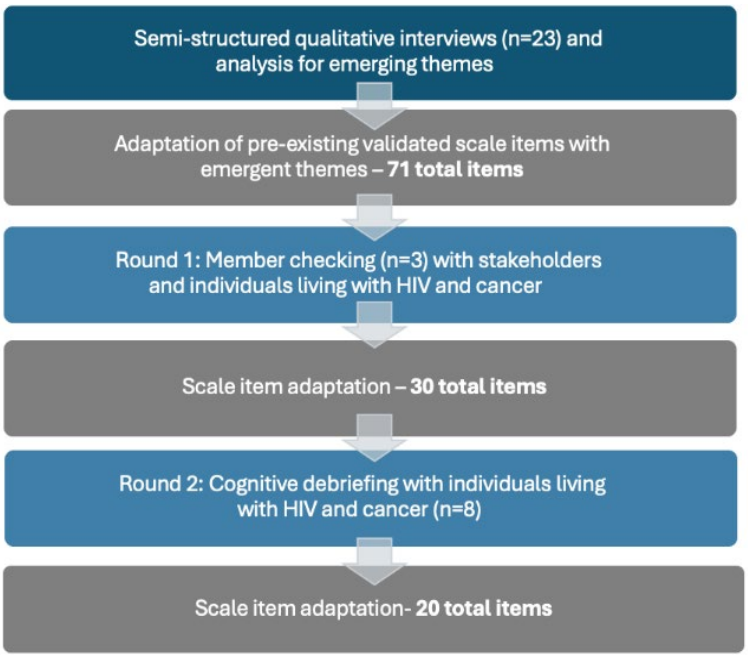

Figure 1: Item refinement methodology

RESULTS

Dominant themes from 27 qualitative interviews (8 women and 19 men), included shame, guilt/failure, burden, self-worth, emotional burden/disgust, self and community acceptance, withdrawal, visibility. For each of these themes we adapted items from pre-existing internalized stigma scales and/or created new items informed by commonly used language from semi-structured interviews to create a preliminary pool of 71 scale questions. Multiple response options with graphic representations of the relative attribution to HIV and cancer were also created (Figure 2). Member checking with community stakeholders further refined the item pool to 30 scale questions and four response options. Cognitive debriefing resulted in 20 scale questions and a single response option measuring intersectional stigma, which was universally and reliably understood (Figure 2). Analysis of cognitive debriefing sessions revealed common themes in item comprehension and acceptability that included influence of cultural customs, item translation, social desirability, offensiveness/shame, and topic sensitivity.

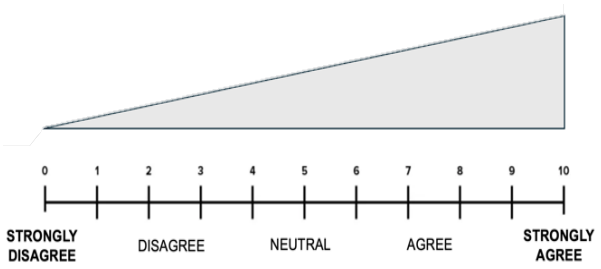

Figure 2: Intersectional Stigma Sample Scale Item & Response:

Item 1. Do you feel ashamed for having developed this [disease]?

a) Point to the place on the depicting how much this is true for [this disease].

b) Point to the place on the image depicting how much you are thinking about HIV when you are thinking about [item 1].

c) Point to the place on the image depicting how much you are thinking about cancer when you are thinking about [item 1].

CONCLUSIONS

Context-specific adapted intersectional, internalized stigma scale items show potential for capturing the unique experience of individuals living with HIV and HIV-associated KS. Future studies will focus on assessing the content validity among other HIV-associated malignancies and quantitative validation of the final scale items.

9: Clinical, Social, and Healthcare System Determinants of Survival among Patients with HIV Diagnosed with Kaposi Sarcoma in the United States (2004–2020)

Authors: *Sarah A. Commaroto[1,2], Anna E. Coghill[1], Zachary Thompson[1], Elizabeth Yu Chiao[3], Jessica Y. Islam[1]*

H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL[1]; University of South Florida, Morsani College of Medicine, Tampa, FL[2]; MD Anderson Cancer Center, Houston, TX[3]

BACKGROUND

Although rates of Kaposi Sarcoma (KS) have declined over time in the US, people living with HIV (PLWH) still have a several hundred-fold higher risk of developing KS compared to the general, HIV-uninfected population. KS remains one of the most prevalent cancers among PLWH. Gaps remain in existing knowledge regarding trends in clinical outcomes for PLWH diagnosed with KS from a multi-level perspective, including individual, clinical, social, and healthcare access factors. Our objective was to evaluate determinants of overall survival among patients with HIV diagnosed with KS from this multi-level perspective, with a focus on chemotherapy receipt, to understand patterns in clinical care among PLWH in the US. We also assess social determinants of health (SDoH), including area-level measures of SES, to understand disparities in real-world overall survival trends among this population.

METHODS

We analyzed PLWH diagnosed with KS (9140 histology code) in the U.S. National Cancer Data Base (NCDB; 2004-2020). PLWH were identified using ICD9 (04200 to 04499, 07953, and V08) and ICD10 (B20 to B24, R75, Z21, B97.35) codes. Our primary outcome was overall survival. Individual-level and clinical determinants considered included sex, age, race and ethnicity, chemotherapy receipt, cancer diagnosis year, and census region. Social determinants considered included area-level measures of SES based on patients' ZIP code at diagnosis segmented into quartiles (Q1 lowest SES - Q4 highest SES): (1) ZIP code-level education, specifically % of adults without a high school diploma, and (2) ZIP code-level income, specifically median household income of adults. Healthcare access factors considered included distance from patient to provider, insurance status of the patient, and type of cancer care facility (e.g., academic/research or community cancer program). We descriptively evaluated our outcome using Kaplan-Meier curves and utilized multi-level cox proportional hazards models clustered by facility ID to identify predictors of overall survival.

RESULTS

Overall, we identified 3628 PLWH diagnosed with KS. KS patients in this US sample were more likely to be less than 40 years of age at diagnosis (52.3%), mostly male (96.1%), 37% NH-Black, 40% residing in the South, one-third Medicaid insured, and 62% treated at an academic/research program. Chemotherapy was received by 38% of patients. The median follow-up time was 14.2 years, with 59% alive at last follow-up. Fifteen-year survival rates were significantly different by sex (49% men vs. 30% women, $p<0.01$), race and ethnicity (52% NH-White, 41% NH-Black, 57% Latinx, $p<0.01$), ZIP code level education (Q1, 44% vs. Q4, 60%, $p<0.01$), ZIP-code level income (Q1 40% vs. Q4 55%, $p<0.01$), insurance status (57% private insurance, 51% uninsured, 44% Medicaid, 36% Medicare, $p<0.01$), and cancer care facility type (academic/research program 51% vs. community cancer program 42%, $p<0.001$). After multivariable analysis, female sex (aHR: 1.31; 95% CI: 1.02-1.68) and NH-Black race (aHR: 1.33; 95% CI: 1.15-1.53) were associated with higher overall mortality. Compared to those who with private health insurance, mortality was higher for PLWH diagnosed with KS living without insurance (aHR: 1.23; 95% CI: 1.03-1.48), on Medicaid (aHR: 1.41; 95% CI: 1.22-1.63), and on Medicare (aHR: 1.69; 1.41-2.02). Receipt of chemotherapy (aHR: 0.74; 95% CI: 0.66-0.83) and residing in a highly educated ZIP code (aHR: 0.69; 95% CI: 0.54-0.87) was associated with lower overall mortality.

CONCLUSION

Multi-level factors are associated with overall survival among KS patients with HIV in the US, suggesting that interventions integrating both the patient and health system factors should be developed to improve outcomes among KS patients with HIV.

10: Characterization of Kaposi Sarcoma-Associated Herpesvirus in an Anaplastic Variant of Gastrointestinal KS

Authors: *Elena M. Cornejo Castro[1], Ramya Ramaswami,[2] Vickie Marshall[1], Stefania Pittaluga[3], Andrew Warner[4], Kathryn Lurain[2], Xiaofan Li[2], Kyle N. Moore[1], Wendell Miley[1], Romin Roshan[1], Nazzarena Labo[1], Laurie T. Krug[2], Robert Yarchoan[2], Denise Whitby[1]*

[1]Viral Oncology Section, AIDS and Cancer Virus Program, Frederick National Laboratory for Cancer Research, Frederick, MD; [2]HIV AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD; [3]Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, MD; [4]Molecular Histopathology Lab, Frederick National Laboratory for Cancer Research, Frederick, MD

BACKGROUND

Kaposi sarcoma (KS) is a vascular tumor caused by Kaposi sarcoma-associated herpesvirus (KSHV/HHV8) that involves the skin, lymph nodes, and visceral organs such as the gastrointestinal (GI) tract. We present here a characterization of KSHV in a 53-year-old cisgender man with a 20-year history of well-controlled HIV and 10-year history of recurrent T1 stage KS, who had received several lines of systemic KS therapy. The patient presented with worsening abdominal pain in 2021. In 2022, he underwent an abdominal resection of his KS to relieve a gastrointestinal obstruction that was unresponsive to systemic therapy. A psoas biopsy demonstrated KS and a jejunal biopsy showed features of anaplastic KS, a rare and aggressive variant of KS characterized by genomic alterations with poor response to standard KS therapies. His HIV VL was 43 copies/mL and his CD4+ T cell count was 154 cells/μL at that time. Genomic instability of the human genome in anaplastic KS was previously linked to its potential transformation from conventional KS, yet alterations in the KSHV genome in such cases were not investigated.

METHODS

Serially sectioned psoas-KS (2021 and 2022) and GI-KS biopsies as well as lymph nodes (2022) were formalin-fixed. Total DNA was isolated from peripheral blood mononuclear cell (PBMC) and KS biopsies. Deep sequencing of KSHV genomes was performed using a target enrichment by hybridization approach and Illumina sequencing platforms. Sequence data were processed using a *de novo* sequence assembly pipeline. KSHV-specific IgG antibody levels in plasma were measured using a multiplexed bead-based immunoassay. KSHV-specific T cell responses were evaluated via KSHV proteome interferon-gamma ELISpot assay.

RESULTS

Pathology confirmed psoas-KS and an anaplastic variant of GI-KS. KSHV genome sequences from one PBMC sample and eight biopsies (one lymph node, two psoas muscle-KS and five GI-KS) were evaluated. The median read depth coverage across all nine samples was 3513 (IQR: 11-16081). Near-full length KSHV genomes (137298 bp) were isolated from two psoas-KS biopsies taken in 2021 and 2022. A previously described nucleotide variant in the microRNA *kshv-mir-K12-10a* (NC_009333:g.118082C>T) was observed in both. Most strikingly, the primary genomes isolated from the GI (KS and lymph node) obtained in 2022 were significantly shorter than the full-length genome, with an average length of 48014 bp. The large deletion in these nonstandard viral genomes (nsVGs) encompassed 61 ORFs, from *K1* to *vIRF-4*. The 5-prime end of the nsVGs was characterized by a chimeric *vIRF-3* sequence composed of *vIRF-3* and the terminal repeat (*TR::vIRF-3*) with a breakpoint at NC_009333:g.89746C>T. The 3-prime end of the nsVGs showed the standard sequence of *K15* into the TR. In addition to the nsVGs region with shared high read depth coverage (median 17891, IQR: 9933-24565), the GI samples also contained low read depth coverage across the full-length genome (median 2, IQR: 0-8). The nsVGs shared 95% sequence identity with the near-full length genomes identified in the psoas-KS. From 2021 through 2023, the patient showed plasma IgG antibody responses against eleven KSHV antigens. In 2022, KSHV-specific T cell responses were evaluated. The number of open reading frame (ORF)-directed interferon-gamma responses was 43 with a median intensity of 80 spot-forming-units/10^6 PBMC [IQR:50-153].

CONCLUSIONS

KSHV-specific B and T cell responses were identified against ORFs across the whole KSHV genome, indicating that much of the systemic immune response is driven by the full-length virus. The previously described KS-specificity of the *kshv-mir-K12-10a* nucleotide variant could not be verified, since the PBMC sample lacked sufficient sequence coverage in the *K12* region. The nsVGs in GI-KS likely originated from a full-length KSHV genome and suggests an etiologic link to the chromosomal instability observed in anaplastic KS, yet an increased pathogenicity of such variants cannot be excluded.

11: Reclassification and Comprehensive Characterization of Lymphoproliferative Disorders in a Mexican HIV-Infected Cohort (1983–2019)

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[1]Pathology and Laboratory Medicine, Weill-Cornell Medicine, NYC, NYC, USA; [2]Department of Anatomical Pathology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, CDMX, Mexico

BACKGROUND

Lymphoproliferative disorders in patients with human immunodeficiency virus (HIV) infection are currently categorized into (1) hyperplasia characterized by preserved tissue architecture and predominantly non-clonal immunoglobulin (IG) rearrangement, (2) polymorphic lymphoproliferative disorders (PLD)/EBV+ mucocutaneous ulcers with disrupted tissue architecture and variable clonality (polyclonal to monoclonal), and (3) lymphomas with disrupted architecture and clonal IG rearrangements, in these context these entities are typically driven by Epstein-Barr virus (EBV) or Kaposi Sarcoma Herpesvirus (KSHV). The diagnosis of some of these entities requires technical tools for virus identification, such as immunohistochemistry (LANA-1) or *in situ* hybridization (EBER), which are often limited in resource-constrained countries like Mexico, leading to underdiagnosis.

METHODS

The clinical, morphological, and immunohistochemical characteristics of a Mexican cohort of HIV-positive patients with lymphoproliferative disorders were retrospectively collected for those with available formalin-fixed, paraffin-embedded material from 1983-2019. Based on the morphological reevaluation, additional immunohistochemical studies and EBER were performed. In all cases, the presence of Kaposi's Sarcoma-Associated Herpesvirus (LANA-1) and EBV (EBER, LMP-1, EBNA-2) was assessed. To examine differences between the groups, Chi-square tests, Student's t-tests, or Mann-Whitney U tests were conducted, depending on the characteristics of the sample.

RESULTS

A total of 188 cases were analyzed, of which 92% were men, with a median age at diagnosis of 37.0±10.9 years. The median age was lower in the group of patients diagnosed with hyperplasia (32.2±9.6 years) compared to those with lymphomas (39.8±10.0 years) ($p<0.01$). A lower CD4 lymphocyte count (154.4±176.4 cells/μL) and higher viral load (1,010,603±1,906,479 copies/mL) were identified in the lymphoma group compared to patients with polymorphic lymphoproliferative disorders (CD4: 210.21±152.6 cells/μL; viral load: 227,571±294,242 copies/mL) and patients with hyperplasia (CD4: 303.9±217.7 cells/μL; viral load: 123,122±184,320 copies/mL) ($p<0.01$). The reevaluation of all cases allowed for the reclassification of approximately 24% of the evaluated cases (Table 1), with 76% of the reclassified cases falling within the hyperplasia group. Additionally, approximately 89% of the reclassified cases were associated with newly performed positive tests for KSHV (LANA-1) or EBV (EBER), while 11% were due to morphological or immunohistochemical features not associated with viruses.

Table 1. Reclassification of Lymphoproliferative Disorders in HIV-Infected Patients: A Mexican Cohort Study at a Reference Center (1983-2019)

Original Diagnosis	Reclassification	Number of cases
Classical Hodgkin Lymphoma	Classical Hodgkin Lymphoma	18
	Subtotal	**18**
Lymphadenopathies / Atypical Hyperplasias	Polymorphic Lymphoproliferative Disorder	22
	Interfollicular polymorphic lymphoproliferative disorder	3
	Diffuse Large B-cell Lymphoma	1
	Extracavitary Primary Effusion Lymphoma	1
	Germinotropic Lymphoproliferative Disorder with Kaposi's sarcoma	1
	Not evaluable	1
	KSHV/HHV8-Associated Multicentric Castleman	5
	KSHV/HHV8-associated multicentric Castleman disease with Polymorphic Lymphoproliferative Disorder	2
	Reactive Lymphoid Hyperplasias	66
	Subtotal	**102**
Diffuse Large B-cell Lymphoma	Diffuse Large B-cell Lymphoma	28
	Extracavitary Primary Effusion Lymphoma	2
	Not Evaluable	4
	EBV+ High-Grade B-cell Lymphoma	1
	Subtotal	**35**
Plasmablastic Lymphomas	Extracavitary Primary Effusion Lymphoma	3
	Polymorphic Lymphoproliferative Disorder	2
	Diffuse Large B-cell Lymphoma	1
	Not evaluable	3
	Plasmablastic Lymphoma	13
	Subtotal	**22**
Burkitt Lymphoma	Burkitt Lymphoma	7
	Diffuse Large B-cell Lymphoma	1
	Subtotal	**8**
T-cell Lymphoma	Dermatopathic Lymphadenitis	1
	Peripheral T-cell Lymphoma, NOS	2
	Subtotal	**3**
Total General		**188**

CONCLUSIONS

Economic limitations and restricted access to techniques such as *in situ* hybridization (EBER) or specific immunohistochemical markers (LANA-1) in Mexico contribute to the underdiagnosis of entities that require these tools for confirmation, a situation that mirrors most of Latin America. The reclassification in this series enabled the extensive identification of underdiagnosed entities in Mexico, such as polymorphic lymphoproliferative disorders, previously unreported entities in the country like extracavitary primary effusion lymphoma, and globally rare conditions such as germinotropic lymphoproliferative disorder. The reclassification of these entities could significantly impact patient prognosis and treatment, as well as the epidemiology of this group of disorders.

12: RBM25 Is a New Restriction Factor against KSHV

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BACKGROUND

Kaposi's sarcoma-associated Herpesvirus (KSHV) is an oncogenic virus characterized by lifelong infection of its host in a quiescent state of latency interrupted by sporadic reactivation events leading to virus production and dissemination. Understanding the mechanisms regulating such events is important to better define druggable antiviral target.

METHODS

We performed a targeted siRNA screening of 597 immune-related genes (IRGs) aiming at discovering new host genes regulating KSHV lytic replication and our study identified RBM25 as a new restriction factor of the KSHV viral life cycle.

RESULTS

RBM25 was shown to restrict both KSHV lytic replication and de novo infection in multiple cell models including primary B cells. Moreover, KSHV lytic reactivation is associated with RBM25 degradation, and data suggests it is mediated through protein ubiquitination. Mechanistically, RNA sequencing analysis in RBM25 depleted cells during immune stimulation indicates that RBM25 is important for the induction of antiviral Interferon-Stimulated Genes (ISGs). Interestingly, RBM25 depletion in KSHV infected B cells inhibited cell proliferation both in vitro and in vivo in the BCBL-1-luciferase xenograft mouse model of KSHV-positive PEL tumor.

CONCLUSION

Altogether, our findings identify RBM25 as a new host restriction factor modulating the antiviral ISG response against KSHV.

13: Travel Time from Cancer Center Is Associated with Disparities in Non-Hodgkin Lymphoma Diagnosis Among People Living with HIV in Malawi

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BACKGROUND

Kamuzu Central Hospital (KCH) in Lilongwe, Malawi, serves a population of around ten million people from the country's Central and Northern regions. As one of just two centers in the country providing pathology and cancer care, the majority of the population are left with the burden of traveling long distances for diagnosis and treatment. HIV-associated non-Hodgkin lymphoma (NHL) is common in sub-Saharan Africa (SSA) due to the high prevalence of HIV in the region. Spatial barriers to care, particularly in relation to travel time, are not well defined in adults with HIV-associated malignancies in Malawi.

METHODS

We included all patients with HIV-associated NHL from the KCH Lymphoma Study, a prospective observational cohort June 2013 to June 2023 (n=117). The location of study patients' residence was mapped using QGIS with further descriptive and survivorship analyses, including demographic and clinical characteristics, conducted in R. AccessMod 5 was used to produce models of travel times to KCH, using assumptions from previous literature.

RESULTS

The diagnoses included in this analysis were DLBCL (n=79), Burkitt (n=22), plasmablastic (n=13), primary effusion (n=3). Estimated travel time to clinic varied significantly (range: 20-618 minutes). 48% of patients are from Lilongwe district which makes up only 10% of the population of the catchment area. We noted a significant negative relationship between mean travel time to KCH and reported incidence of HIV-associated malignancies (correlation= -0.015; p=0.009). Travel time varied significantly when disaggregated by HIV status, with HIV+ART-people tending to be residing closer to the cancer center than HIV- or HIV+ART+ patients (p=0.005). In addition to disparities in diagnosis, HIV-associated NHL patients had worse progression free survival as travel time to clinic increased (p=0.02), which remained significant after controlling for known prognostic markers including stage, performance status, and lactate dehydrogenase.

CONCLUSION

Cancer care in Malawi is centralized, leading to diagnostic and treatment disparities. NHL patients who live further from KCH tend to face more challenges accessing diagnosis and treatment, particularly if they have comorbidities, such as HIV. Interestingly, the HIV+ ART-naïve group tended to come from closer to KCH than other groups, implying that patients with curable lymphomas in more remote parts of the country are likely dying before they can be diagnosed and treated. Implementation science approaches are urgently needed to close the gap on both diagnostic and treatment disparities.

14: Heterogeneity of Oncogenic and Survival Signaling Pathways in Primary Effusion Lymphoma: Implications for Precision Targeting and Combination Therapy

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BACKGROUND

Cancer's inherent heterogeneity presents a major challenge in developing effective therapies. Primary Effusion Lymphoma (PEL), a rare and aggressive lymphoproliferative disorder driven by Kaposi's sarcoma-associated herpesvirus (KSHV) and frequently co-infected with Epstein-Barr virus (EBV), typically manifests as lymphomatous effusions in body cavities. This malignancy primarily affects immunocompromised individuals, such as those with HIV/AIDS, and is associated with poor prognosis and limited therapeutic options, with an average survival rate of less than 6 months. The role of pathway heterogeneity in PEL's poor prognosis and the consequent therapeutic implications remain inadequately explored.

METHODS

To identify potential therapeutic targets for PEL, we analyzed three PEL cell lines including BC3, BCP1, and BCBL1, alongside a control B-cell line, BJAB, and KSHV-infected BJAB cells. Using Western blotting, we assessed the activation patterns of key signaling pathways involved in cell growth, proliferation, and survival, including mTORC1, NF-κB, PI3K/AKT, and FOXOs. We then evaluated the effect of pathway-specific inhibitors on these pathways to determine their roles in PEL cell proliferation and survival.

RESULTS

Our analysis revealed significant heterogeneity in pathway activation among the PEL cell lines. AKT was consistently activated across all PEL lines, while mTORC1, NF-κB, and FOXOs were strongly activated in BC3 and BCBL1 cells but were minimally active in BCP1 cells. BC3 and BCBL1 cells were highly responsive to inhibitors targeting their activated pathways. In contrast, BCP1 cells exhibited resistance to the mTORC1 inhibitor rapamycin; however, this resistance was mitigated by using dual-target inhibitors that address both PI3K/AKT and mTOR.

CONCLUSIONS

The findings highlight significant variability in oncogenic and survival signaling pathways among PEL cell lines, with distinct responses to pathway-specific inhibitors. This heterogeneity suggests that precision medicine approaches tailored to individual PEL patients may be essential for effective treatment. Furthermore, combination therapies targeting multiple pathways offer a promising strategy to improve therapeutic outcomes for PEL.

15: Lack of Evidence for Kaposi's Sarcoma Associated Herpesvirus Association with Osteosarcoma in Sub-Saharan Africa

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BACKGROUND

Osteosarcoma is a common Tanzanian bone tumor that predominantly affects adolescents and young adults in the setting. A previous study, based in a Xinjiang population in China, suggested that osteosarcoma is associated with Kaposi's sarcoma (KS) associated herpesvirus (KSHV) infection. Therefore, in this study, we investigated whether KSHV is associated with osteosarcoma in sub-Saharan Africa, a region endemic to KSHV.

METHODS

We retrospectively analyzed formalin-fixed paraffin-embedded osteosarcoma tissue blocks from diagnoses made between 2021 and 2022 at Muhimbili National Hospital (MNH) in Dar es Salaam, Tanzania. Extracted DNA was tested for KSHV genome detection by PCR and LANA protein expression was detected via immunohistochemistry (IHC).

RESULTS

A total of 23 confirmed osteosarcoma tissue blocks were evaluated. The median age of the cohort was 17 years, (Range= 5 - 42 years), with no significant gender bias. Biopsied lesions were predominantly from the lower limbs and involved the femur. While all the tested osteosarcoma and control KS tissues tested IHC positive, at variable levels, for the cellular proliferation marker Ki-67, none tested positive for KSHV LANA. Additionally, PCR analysis was performed on DNA extracted from 7 FFPE blocks as well as two fresh frozen osteosarcoma tissues with high-quality DNA resulting in amplification of cellular controls. None were found to be positive for KSHV DNA.

CONCLUSIONS

Despite previously reported high KSHV seroprevalence in Tanzania, none of the tested osteosarcoma tissue samples were positive for KSHV. Additional studies are needed to confirm this lack of association and whether contrasting associations are geographically/genetically linked.

16: Human Cerebral Brain Organoids Infected with HIV-1: A New Model for EBV Positive Central Nervous System Lymphomas in HIV-1 Infection

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BACKGROUND

Lymphomas affecting the central nervous system (CNS) occur more frequently in people living with HIV-1 (PLWH) compared to other populations. CNS lymphomas can be primary (PCNSL) or secondary (SCNSL), depending on whether the lymphoma originates in the brain or other peripheral tissues. Regardless of the type, lymphoma cells must infiltrate the brain to form the CNS lymphoma. However, the mechanisms by which the HIV-1-infected CNS recruits either B cells or transformed malignant cells to develop CNS lymphoma remain unclear. Microglia, which are primary reservoirs of HIV-1 in the CNS, play a crucial role in sustaining neuroinflammation. We hypothesized that HIV-1-induced neuroinflammation is a key driver in the recruitment and development of CNS lymphomas in PLWH. Currently, there is no *in vitro* model for the study of CNSL in human cerebral brain organoids (CBO). However, there is a well-established glioma model to study glioblastoma in CBOs. We set out to develop a model to study CNSL in CBOs in HIV-1 infection.

METHODS

We generated microglia from human induced pluripotent stem cells (hiPSC) and infected them with HIV-1. These infected microglia were co-cultured with cerebral brain organoids (CBOs) to create the "M-CBOs HIV-1" model. A control condition with uninfected microglia was also established ("M-CBOs Uninfected"). We assessed neuroinflammation by measuring pro-inflammatory cytokines and phosphorylated NF-κB levels using ELISA and flow cytometry, respectively. The migration of IBL-1 and BCKN-1 lymphoma cell lines in response to supernatants from M-CBOs was evaluated using transwell migration assays. We also assessed the invasion of -1 cells labeled with cell tracker into the M-CBOs with flow cytometry and microscopy.

RESULTS

M-CBOs HIV-1 exhibited elevated levels of pro-inflammatory cytokines such as CCL2 and OPN and increased p-NF-κB in various CNS cells, consistent with HIV-1-associated neuroinflammation. The migration of both lymphoma cell lines was significantly higher in supernatants from M-CBOs HIV-1 compared to M-CBOs Uninfected. Additionally, the percentage of IBL-1 cells invading M-CBOs was significantly higher in the HIV-1-infected condition.

CONCLUSIONS

These findings suggest that HIV-1-infected microglia in CBOs promote a neuroinflammatory state that recruits and enhances the invasion of lymphoma cells into the CNS. The M-CBOs HIV-1 model offers a valuable in vitro system to explore the mechanisms underlying CNS lymphoma development and for developing new therapeutic strategies.

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17: Identifying Cellular Regulators of Latency and Lytic Replication Using the Ubiquitome

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Kaposi sarcoma-associated herpesvirus (KSHV) is an oncogenic virus that is currently without effective treatment and associated malignancies carry a poor prognosis for HIV-positive or otherwise immunocompromised individuals. The virus evades immune response through a latent phase but is dependent on lytic reactivation to replicate and spread. This lytic reactivation is initiated by expression of the Replication and Transcription Activator (RTA). RTA has innate E3 ubiquitin ligase behaviors, as well as the ability to co-opt the ubiquitin proteasome system, to degrade proteins and promote lytic replication. Through analysis of the RTA-dependent ubiquitome, we identified several key proteins as being ubiquitinated in the presence of RTA, including minichromosome maintenance complex component 7 (MCM7) and cyclin dependent kinase 1 (CDK1). Preliminary studies using protein inhibitors supported our hypothesis that these host proteins have regulatory effects on both latency and lytic replication. To further test our hypothesis, we knocked down MCM7 and CDK1 expression in latently infected cell lines and evaluated impacts on latency and lytic replication in latently infected primary effusion lymphoma (PEL) cells. Preliminary knockdown data has indicated increased lytic reactivation in cells expressing protein knockdown when compared to controls, further supporting our hypothesis that CDK1 and MCM7 both have regulatory effects on both latency and lytic reactivation in KSHV infected cells. Our results have the potential to identify novel host proteins as therapeutic targets.

18: WT1 Upregulation by Lytic Induction of Kaposi Sarcoma Herpesvirus

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BACKGROUND

In previous work, we have demonstrated that Kaposi Sarcoma (KS) lesions highly express the WT1 tumor antigen, in particular oncogenic isoforms known to have various functions contributing to tumorigenesis. WT1 has shown promise as an immunotherapeutic target, with multiple WT1 directed therapies demonstrating safety, clinical and immunologic responses in studies for leukemias and solid tumors. Understanding the role of WT1 in both latent and lytic KSHV infection is important to understanding further the role of WT1 in KS oncogenesis. *De novo* KSHV latent infection and in particular vFLIP upregulates WT1. Here we report the expression and functions of WT1 during lytic KSHV infection.

METHODS

Cell culture models of latent and lytic KSHV infection were utilized, including iSLK-BAC16 cells latently infected with KSHV as well as HUVEC E4 and HuARLT-1 endothelial cells that were infected with KSHV. iSLK-BAC16 cells were treated with sodium butyrate and doxycycline for lytic reactivation and HUVEC E4 and HuARLT-1 with TPA or sodium butyrate respectively. WT1 siRNA was transfected in iSLK-BAC16 cells.

RESULTS

Here we have found that upon lytic reactivation, induced by treating iSLK-BAC16 cells with NaButyrate and doxycycline, inducing upregulation of RTA, WT1 is upregulated significantly including its oncogenic isoforms. WT1 upregulation also occurred upon stimulation of *de novo* KSHV infected HUVEC E4 and HuARLT-1 endothelial cells. RTA upregulation alone in uninfected iSLK also leads to WT1 upregulation. Using iSLK-BAC16 cells, we also demonstrate that upon WT1 knockdown during lytic reactivation, there is a further lytic reactivation, demonstrated by increased virus production and secondary infection, as well as an increase in vFLIP, LANA, and K8.1 viral gene expression. We also demonstrate that in both latent and lytic reactivation, WT1 protein appears to be predominantly expressed in the cytoplasm.

CONCLUSION

These findings suggest that latent KSHV infection upregulates WT1, which is further increased upon lytic KSHV infection. In addition, the findings that WT1 knockdown during lytic reactivation leads to marked further lytic reactivation and upregulation of viral gene expression, suggests that WT1 may play a complex role in regulating these two phases of infection, by limiting KSHV reactivation to overall support KSHV latency. This support of maintenance of latency may hence be a role of WT1 in escaping immune surveillance and maintaining persistent infection. Further, cytoplasmic expression of WT1 suggests roles for WT1 in RNA metabolism and regulation of translation, which are being further explored within the KSHV viral life cycle.

19: Suspected Causes of Death among Adults with HIV-Associated Kaposi Sarcoma in East Africa in the "Treat All" Era

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BACKGROUND

In East Africa, one-year mortality following a diagnosis of HIV-associated Kaposi sarcoma (KS) in the "Treat All" era was recently estimated, in a community-derived sample, to be 41%. To date, there is limited information on why these patients die. Understanding causes of death among adults diagnosed with KS might improve management and, hence, survival or suggest other strategies.

METHODS

We identified adults (age ≥ 18 years) who died after a new diagnosis of HIV-associated KS between October 2022 and June 2024 and who were receiving care at one of five clinical sites in Kenya, Tanzania, and Uganda. KS was confirmed by histopathology except where lesions were unsafe for biopsy. Adjudication of each death was performed using information obtained, when possible, from review of medical records and interview of attending clinicians and next of kin. A contributing cause of death was defined as suspicion that the condition mechanistically/causally contributed to death as guided by Rothman's sufficient component cause ("causal pie") model. Certainty of contribution to death was defined as highly (95%–100% certainty), likely (80%–95%) or possibly (50%–80%).

RESULTS

163 deaths were adjudicated. Of these, 63% were men, the median (IQR) age was 36 (29–42) years, and duration from diagnosis to death was 4 (1–14) weeks. Many (40%) deaths occurred outside a health facility, and only 4% had an autopsy. KS was deemed to have at least possibly contributed to all deaths. Other potential causes of death, especially tuberculosis, were also present (Table). In 6% of cases, an unexplained sudden onset of malaise occurred following improvement of KS on chemotherapy, often with fever and respiratory symptoms, which was followed shortly thereafter by death.

CONCLUSION

Among adults who died after a new diagnosis of HIV-associated KS in East Africa in the "Treat All" era, KS was deemed to be at least possibly contributing in all cases. Other causes of death were also suspected, especially TB. Some scenarios beg the question regarding non-KS KSHV-related disease that is difficult to diagnose. Yet, without autopsy, it is impossible to know all causes or sequence of events. The prominence of the contribution from KS per se, combined with the inherent difficulty treating KS, imply that early detection of KS may be the most feasibly achievable intervention to reduce KS mortality.

Table. Suspected Causes of Death among Adults with HIV-Associated KS in East Africa (N=163)

Condition	% of Deaths in which Condition Contributed* % (95% CI)	Certainty of Condition's Presence†			Certainty of Contribution to Death		
		Definite	Likely	Possibly	Highly	Likely	Possibly
Kaposi sarcoma	100% (98%-100%)	99%	--	1%	73%	14%	13%
Tuberculosis	31% (24%-38%)	54%	32%	14%	56%	24%	10%
Anemia	7% (4%-13%)	33%	50%	17%	8%	50%	42%
Cryptococcosis	5% (3%-10%)	50%	50%	--	50%	25%	25%
Renal insufficiency	3% (1%-6%)	75%	--	25%	50%	50%	--
Septicemia	3% (1%-6%)	25%	--	75%	--	--	100%
Pneumonia	2% (1%-6%)	--	--	100%	--	--	100%
Liver disease	1% (1%-4%)	50%	--	50%	--	--	100%
Medication toxicity	4% (2%-8%)	--	--	100%	33%	--	67%

*Only conditions that contributed to death more than once are shown. † Certainty of condition's presence defined as "definite" if histopathology, direct visualization, microscopy, culture or polymerase chain reaction were available; "likely" if based on clinical history, imaging or laboratory markers; and "possibly" if based on only clinical history, signs and symptoms.

20: Frequent Expression of KSHV ORF75, a Lytic Gene, in Kaposi Sarcoma Lesions: Role of Sp1 Transcription Factors

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BACKGROUND

Kaposi sarcoma (KS) lesions typically exhibit KSHV latent gene expression with minimal lytic activity. However, recent studies indicated high expression of ORF75, considered a late lytic gene, in KS lesions. ORF75 encodes a viral pseudo-amidotransferase crucial for lytic replication and immune suppression. This study investigates how ORF75 is constitutively expressed in KS lesions and its implications for viral latency and replication.

METHODS

We used RNAscope to detect ORF75 expression in representative KS lesions and its presence in latency-associated nuclear antigen (LANA)-expressing cells. To explore ORF75 regulation, we analyzed luciferase fusion reporters of the ORF75 promoter and performed electrophoretic mobility shift assays (EMSAs) and chromatin immunoprecipitation (ChIP) assays to study transcription factor interactions, focusing on specificity protein 1 (Sp1). We also examined ORF75's impact on KSHV gene expression during lytic induction.

RESULTS

ORF75 was expressed in most LANA-positive cells in KS lesions. The ORF75 promoter showed high constitutive activity in endothelial cells, driven by a proximal Sp1 element and two distal CCAAT boxes. Sp1, Sp3, and Sp4 bound to the Sp1 element, with Sp1 primarily regulating ORF75 expression. Distinct Sp1 binding patterns in B-cells compared to endothelial and epithelial cells led to differential ORF75 expression. Alternate Sp1 forms accumulated during lytic replication in endothelial cells, differing from those in primary effusion lymphoma (PEL) lines. ORF75 influenced expression of other KSHV genes necessary for lytic induction.

CONCLUSIONS

ORF75 is constitutively expressed in KS lesions due to Sp1 transcription factors, despite being a lytic gene in PEL cell lines. Sp1-mediated regulation explains the high ORF75 levels in KS lesions, indicating a role in both latency and lytic replication.

21: The Impact of B Vitamin Complex Supplementation with Antiretroviral Therapy on Aged HIV-Infected Patients with Malignancies at Hill Top Hospital, Lusaka, Zambia

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BACKGROUND
Aged HIV-infected patients are at heightened risk for malignancies due to immunosenescence and prolonged exposure to immunosuppression. Micronutrient deficiencies, particularly of B vitamins, are prevalent in this population and can exacerbate health complications. This study evaluates the effect of B vitamin complex supplementation alongside antiretroviral therapy (ART) on clinical outcomes in aged HIV-infected patients with malignancies at Hill Top Hospital in Lusaka, Zambia.

METHODS
A prospective, randomized controlled trial was conducted at Hill Top Hospital in Lusaka, Zambia, from January 2023 to June 2024. One hundred HIV-infected patients aged 60 and above, diagnosed with various malignancies, were enrolled and randomly assigned to either the intervention group or the control group. The intervention group received a daily B vitamin complex supplement (including B1, B2, B3, B6, B9, and B12) in addition to their standard ART regimen. The control group received only standard ART. Primary endpoints included changes in CD4 count, viral load, and quality of life (QoL). Secondary endpoints assessed nutritional status, cognitive function, physical function, levels of inflammatory markers, adherence to ART, and incidence of adverse events. Evaluations were conducted at baseline, 3 months, and 6 months.

RESULTS
The malignancies studied included Kaposi's Sarcoma (KS), Non-Hodgkin Lymphoma (NHL), cervical cancer, lung cancer, anal cancer, hepatocellular carcinoma (HCC), Hodgkin's lymphoma, breast cancer, and colorectal cancer. After 6 months, the intervention group showed a significantly greater increase in CD4 count (average increase of 150 cells/μL) compared to the control group (average increase of 100 cells/μL, $p<0.01$). The viral load was undetectable in 80% of the intervention group versus 65% of the control group ($p<0.05$). Quality of life improvements were more pronounced in the intervention group, showing significant gains in physical health, vitality, cognitive function, and mental health domains. Physical function, measured by the Katz Index of Independence in Activities of Daily Living, also improved more significantly in the intervention group. Nutritional status, assessed by BMI and serum B vitamin levels, showed greater improvement in the intervention group. Inflammatory markers (CRP, IL-6, TNF-α) were significantly reduced in the intervention group compared to the control group. Adherence to ART was higher in the intervention group, contributing to better overall outcomes. Adverse events were similar across both groups, indicating the safety of B vitamin supplementation.

CONCLUSIONS
B vitamin complex supplementation with ART significantly improves immune recovery, viral suppression, and QoL in aged HIV-infected patients with malignancies. The study suggests potential benefits in managing HIV-associated malignancies and warrants further research.

22: Using the KSHV Ubiquitome as a Tool to Identify Inhibitors of Latency and Lytic Replication

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Kaposi's Sarcoma-Associated Herpesvirus (KSHV) is the causative agent of Kaposi's Sarcoma (KS) and is often seen in immunocompromised individuals, specifically those with HIV/AIDS. KSHV is also associated with Primary effusion lymphoma (PEL), KSHV Inflammatory Cytokine Syndrome (KICS), and multicentric Castleman disease (MCD). There is a higher occurrence of KSHV in Eastern and sub-Saharan Africa. Patients are diagnosed in the later stages, which results in poor, and sometimes fatal health outcomes. Here, we focus on the KSHV life cycle and the role of cellular proteins in maintaining latency and activating lytic replication. RTA is the transcription activator responsible for lytic gene expression. RTA also acts as an E3 ubiquitin ligase, a SUMO-targeting ubiquitin ligase, and interacts with the cellular ubiquitin-proteasome system. Previously, we identified 40 cellular proteins that display RTA-dependent differential ubiquitination. We observed that RTA decreases the abundance of these proteins, presumably to promote lytic replication. We hypothesize that some of these proteins may be required for latency or lytic replication. Here, we focus on CDK1, EIF4A, and ATR, all of which display RTA-dependent differential ubiquitination. We identified specific inhibitors of these proteins and evaluated the impact of treatment on latency and lytic replication using Vero rKSHV.294 and iSLK rKSHV.219 cells and found differential effects on the viral life cycle. Our results have the potential to inform the development of chemotherapeutics.

23: Human Herpes Virus-8 Shedding Heterogeneity Is Due to Varying Rates of Reactivation from Latency and Immune Containment

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BACKGROUND

Human herpesvirus-8 (HHV-8) is a gamma herpesvirus that causes Kaposi sarcoma (KS), including both epidemic (HIV-associated) and endemic (HIV-negative) KS. HHV-8 shedding occurs in the oral mucosa and is likely responsible for transmission. Viral shedding kinetics provide a window into host-virus interactions and differ significantly between different human viral pathogens as well as the immune status of infected individuals. Mathematical models are a critical tool for the analysis of longitudinal viral load data and account for non-linearity inherent to this data. Models have been applied to capture the timing and intensity of immune responses in tissue, to compare different severity of disease among multiple infected individuals, and to optimize therapeutic and vaccination approaches. Here, we developed the first mathematical models to describe HHV-8 shedding data in the oral cavity to understand observed shedding patterns in a Ugandan cohort of individuals with and without HIV infection and with and without KS.

METHODS

We developed a stochastic mathematical model to understand the basis of observed heterogeneous HHV-8 shedding patterns in the oral mucosa. We fit the model to data from an observational, prospective cohort study of Ugandan adults (age ≥18 years) who were enrolled between October 2007 and May 2010. Participants were divided into 4 groups based on HIV and KS status and were monitored with oral swabs for at least 28 days. Of the 295 participants enrolled, 117 had at least one oral swab positive for HHV-8 DNA as evaluated by quantitative real-time PCR performed by the Uganda Cancer Institute-Fred Hutch Cancer Centre laboratory in Kampala.

Our model simulations were intended to match data from the 117 participants with at least one positive swab: 36 (29%) HIV+/KS-, 16 (21%) HIV-/KS-, 56 (74%) HIV+/KS+, 9 (50%) of HIV-/ KS+. Rather than fit to individual viral trajectories, we attempted to reproduce three summary measures from each person: shedding rate (percentage of swabs positive for HHV8 DNA by PCR), median log HHV-8 viral load per positive swab and peak log HHV-8 viral load.

RESULTS

In all groups, we observed a wide variance of shedding patterns, including no shedding, episodic low viral load shedding, and persistent high viral load shedding. Our model closely replicates patterns in individual data and attributes higher shedding rates to increased rates of viral reactivation, and lower median viral load values to more rapid and effective engagement of cytolytic immune responses and lower viral replication rates in infected cells.

CONCLUSIONS

Many features of HHV-8 oral shedding resemble EBV shedding, with a wide range of HHV-8 shedding phenotypes, including (a) rare and brief episodic shedding, (b) more frequent and prolonged episodic shedding, and (c) continual high viral load shedding. Our model explains this heterogeneity according to variance in key biologic parameters. As with EBV, the rate of viral reactivation from latency is predicted to be highly associated with the observed shedding rate, while median viral load appears to have multi-factorial determinants including viral reactivation rate, rate of viral production from infected cells, and rate of killing by the immune system. In theory, each of these processes would be a viable therapeutic target, but even partial reduction in the rate of viral reactivation from latency might have an outsized effect on shedding and possible transmission likelihood. Future work is needed inform mechanisms of viral latency and immune control, and to establish whether any metric of HHV-8 shedding can be used as a surrogate marker of risk for progression to cancer or treatment response.

24: Preclinical Development of Immunotherapy Combining Anti-CD47 Antibody with KSHV Lytic Inducing Agents for Primary Effusion Lymphoma

Authors: *Georgios Pongas[1], Xavier Emmanuel Weiss[2], Deborah Soon, Ngoc Toomey[1], Noula Shembade[1], and Juan Carlos Ramos[1]*

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Primary effusion lymphoma (PEL) is an aggressive non-Hodgkin lymphoma that most often occurs in immunocompromised patients infected with human immunodeficiency virus (HIV). The main clinical presentation is neoplastic effusions of body cavities without extra cavitary tumor masses. Kaposi sarcoma virus (KSHV) is the etiologic agent of PEL. PEL has a relatively poor prognosis as compared to other aggressive B-cell lymphomas, including in the HIV setting. Therefore, novel therapeutic approaches are needed to improve outcomes in patients with PEL. Our group previously demonstrated that induction of KSVH lytic program could be achieved in PEL cells after combining a proteasome inhibitor (bortezomib) with a histone deacetylase inhibitor (SAHA) resulting in enhanced apoptosis and prolongation of survival in mice carrying PEL xenografts.

To build upon therapies that induce viral expression and innate immunity against PEL, we are investigating blocking CD47, a surface molecule expressed that acts as a “don’t eat me signal” by binding to the signal regulatory protein alpha (SIRPa) on the surface of macrophages and dendritic cells, in order to facilitate phagocytosis of tumor cells. We observed high CD47 expression in our primary and established PEL cell lines and found that an anti-CD47 monoclonal antibody increased phagocytic activity of macrophages against PEL cells *in vitro*. We hypothesized that increased KSHV replication preceding PEL cell death may activate STING (stimulator of interferon genes) in phagocytes resulting in increased production of type I interferon boosting cytotoxic T-cell priming and immune responses against PEL.

We found that PEL cell lines express STING, as well as cyclic GMP-AMP synthase (cGAS), a cytosolic DNA sensor that activates STING. Based on these concepts, we are testing immune-based combinational lytic inducing therapies for PEL with the goal of activating STING signaling in macrophages and augmenting their anti-tumor phagocytotic activity.

25: Characteristics, Survival, Social Factors, and Trends in HIV-Associated Lymphomas: A 23-Year Analysis Since the Implementation of c ART, a County Hospital and a University of Illinois at Chicago HIV- Malignancy Project (CHaMP)

Authors: *Andrew La Valle, William Bae, Michael Rivard, Michelle Nwachukwu, Carlos Galvez, and Paul G. Rubinstein*

BACKGROUND

Stroger Hospital (CCH) and the Ruth M. Rothstein CORE Center (CC) are one of the largest health providers for HIV+ patients in Chicago and one of the largest HIV clinics in the United States. CCH/CC treat approximately 5,000 HIV+ individuals per year and 40 newly diagnosed HIV-associated cancers annually. It represents one of the largest safety net hospitals in the United States. Combined with the University of Illinois, Chicago Medical Center (UIC), both institutions provide care for close to 7,000 persons living with HIV (PWH) yearly. The CHaMP Study was originally a retrospective database from 1990 to 2010 of all clinical, demographic, and cancer characteristics of patients diagnosed with HIV/AIDS at CCH. Since then, the study has compiled data prospectively on all patients with hematological malignancies. This study was recently opened at UIC and has been now combined. In this study, we analyzed various characteristics of patients with HIV-associated lymphomas from stage, outcomes, cd4 count, and onset of HIV-diagnosis with respect to lymphoma, all since the implementation of combined anti-retroviral therapy (ART). While large population studies of HIV and cancer exist, few studies specifically examine the largest growing HIV demographic, the inner-city HIV population.

METHODS

Patients' HIV and cancer clinical, laboratory, and survival data were compiled from the CHaMP database, including time of HIV diagnosis from time of lymphoma diagnosis and treatment. From CCH data from the last 30 years were examined while at UIC from 2010 to present. Survival data were examined using Kaplan-Meier analysis and Cox Proportional Hazards model. Statistical comparisons between different groups were performed via the Fisher's exact test. Analysis focused on Diffuse large B-cell (DLBCL), Hodgkin (HIV-cHL), Plasmablastic (PBL), primary CNS lymphoma (PCNSL), and Burkitt lymphoma (BL).

RESULTS

Between, UIC and CCH, 241 cases of lymphoma were identified: DLBCL (n=101) 40%, HIV-cHL (n=66) 26%, BL (35) 14%, PCNSL (n=20) 8%, and PBL (n=19) 8%. Fifty to 80% of the patients were African American depending on the lymphoma diagnosis, followed by Hispanics 20-35%, and Caucasians 9-18%. The cohort was 87% male. The median age by disease ranged from 30 to 59 years of age. Demonstrating that HIV-associated lymphomas in the inner-city are 80% minority, present young, and present late with advanced disease compared to the HIV-negative population. The CD4+ T-cell count at presentation is consistent with the literature, with cHL and BL presenting with highest median CD4+T-cell count 231 and 240 cells/ul respectively. PCNSL presented with the lowest median CD4+ T-cell count at presentation, with PBL and DLBCL presenting with 150 and 152 CD4+ T-cells cells/ul. Sixty to 100% of the patients presented with stage III/IV disease. Patient diagnosis with DLBCL had a 5-year overall survival (OS) of 78% (n=52) when treated with daEPOCHR versus those treated with RCHOP 62% (P=0.4) (n=32). Stage III/IV HL had a 5-year OS of 81% when treated with ABVD for advanced stage disease (N=32) compared to stage I/II (n=15) 5-year OS of 87% (p=0.3). Most BL cases presented with stage III/IV disease and had a 5-year OS of 62%. However, 15 percent of the patients died within the first month of chemotherapy due to either late presentation or chemotherapy related toxicities. PBL also demonstrated a survival of 64% at 5 years for those treated with da-RPOCHR. Twenty-four percent of all cases of DLBCL were diagnosed with HIV at the time of diagnosis with 61% being Latino compared to just 30% in the African American community (P<0.001).

CONCLUSIONS

HIV/AIDS-associated lymphoma in the inner-city remains an African American, male-dominated disease, a clear disparity compared to the US HIV/cancer population. Late presentations affect outcomes especially in the more aggressive BL, where 15% did not survive beyond the first cycle. Twenty-two percent of DLBCL present with lymphoma without knowing their HIV-diagnosis, making HIV-associated lymphoma in the inner-city not just a medical problem, where better therapies are needed, but a public health problem as well, where better prevention is needed.

26: Periodontitis-Specific Pathogens Activate Inflammatory Signaling Pathways Leading to EBV Reactivation

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BACKGROUND

Epstein-Barr virus (EBV) is a gammaherpesvirus important in human oral and gastric cancers. Viral latency following primary infection is characterized by limited viral gene expression. EBV-associated malignancies are characterized by limited viral gene expression of viral oncogenes. Oral EBV viral loads increase with periodontitis severity, suggesting pathogen-induced viral reactivation. Lytic viral gene expression results in virus production. This study sought to determine signal transduction pathways activated by periodontal pathogens and subsequent EBV reactivation in epithelial and B-cell lines.

METHODS

EBV+ gastric epithelial cells (AGS-EBV) and B-cells (Akata), were treated with bacterial end products (BEP) from pathogenic bacteria (*F. nucleatum* and *P. gingivalis*) culture media. Uninoculated medium and commensal bacteria culture media (*S. sanguinis*) were negative controls. Protein was harvested for phosphokinome analysis by mass spectroscopy. Viral/cellular proteins expressed in cells were detected by immunoblot. Cellular transcripts were determined by RNA-seq. EBV viral gene expression was detected by microplate RT-qPCR. Cells were transfected with EBV-encoded GPCR (BILF1) expression vector.

RESULTS

Pathogen BEP produced specific phospho-kinome profiles in AGS-EBV cells relative to control cells. Thirty-four phosphokinases with statistically significant changes were observed. RNA-seq analysis identified gene expression levels in specific pathways. Pathways associated with inflammation and cancer phenotypes were activated. Pathways resulting in non-canonical NFkappaB activation were observed. Detection of p100/p52 protein confirmed non-canonical NFkappaB activation in pathogen BEP-treated cells. Viral lytic mRNAs and viral lytic proteins were detected in cells treated with pathogen BEP. Ectopic expression of viral-encoded GPCR (BILF1) enhanced BEP-induced lytic gene expression.

CONCLUSIONS

Signal transduction pathways producing inflammation and cancer phenotypes were activated in oral pathogen BEP-treated, EBV+ cells. Ectopic expression of EBV BILF1 enhanced viral reactivation indicated pathogen BEP components engaged GPCRs. Periodontal pathogens produce products inducing inflammation resulting in EBV reactivation. Pathogen BEP-induced lytic reactivation might contribute to EBV spread and increased virus-associated malignancy.

27: Kaposi Sarcoma over Time in Sub-Saharan Africa: The Inexorable Influence of HIV Infection

Authors: *Aggrey Semeere[1], Racheal Ayanga[1], Miriam Laker-Oketta[1], Hilda Muwando[1], Andrew Mulooki[1], Robert Lukande[2], Megan Wenger[3], Celestine Lagat[4], Linda Chemtai[4], Elyne Rotich[4], Samson Kiprono[4], Matthew Ssemakadde[5], Charles Kasozi[5], Bronia Mwine Kwarisiima[6], Winnie Muyindike[6], Michael Kanyesigye[6], Gad Murenzi[7], Sajini S. Souda[8], Bongani Kaimila[9], Tamiwe Tomoka[9], Zainab Illonga[10], Elia Mmbaga[10], John Ngowi[11], Julius Mwaiselage[11], Helen Byakwaga[1], David Erickson[12], Jeffrey Martin[12]*

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BACKGROUND

Incidence of HIV-associated Kaposi sarcoma (KS) is an important metric to monitor the impact of antiretroviral therapy (ART) on KS burden. Given the inconsistent availability of high-quality population-based cancer registries in sub-Saharan Africa, the trend of HIV prevalence among all KS diagnoses could be a proxy indicator of HIV-associated KS incidence changes over time. We evaluate the trend of HIV prevalence among patients with biopsy proven KS in six African countries over 7 years.

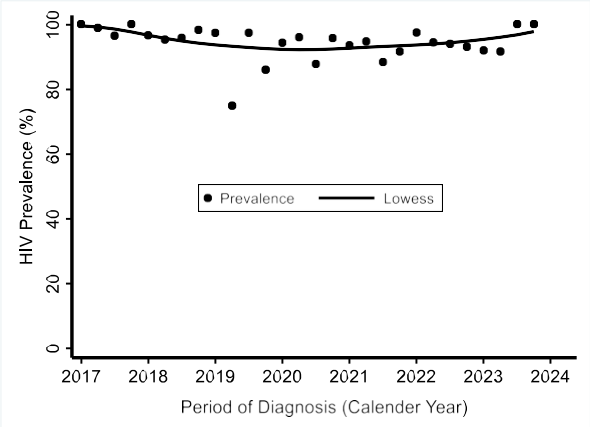
METHODS

At eleven clinical sites in Uganda, Kenya, Malawi, Tanzania, Botswana, and Rwanda, we established and broadly publicized a free punch-biopsy service for all patients suspected to have KS seen between January 1, 2017, and December 31, 2023. Patients had an HIV test with a KS biopsy. We evaluated HIV prevalence, and annual trend among those with biopsy confirmed KS.

Table 1: Annual HIV Prevalence among all patients diagnosed with KS at the study sites

Year	No. Diagnosed with KS	No. Diagnosed with KS and HIV	Prevalence
2017	261	257	99%
2018	383	370	97%
2019	228	218	96%
2020	158	148	94%
2021	203	183	90%
2022	398	354	89%
2023	284	242	85%
Overall	**1,915**	**1,772**	**92%**

Figure 1: Trend of HIV Prevalence among patients diagnosed with KS in Uganda



RESULTS

We studied 1,915 patients with biopsy confirmed KS. Their median age was 35 years (Interquartile range (IQR): 30 to 42), 68% were male, 75% (1446) from Uganda (56% IDI, 11.5% Masaka, 7.4% Mbarara, 0.5% Gulu); 7.1% (136) from Kenya (4.5% AMPATH and 2.6 % from Chulaimbo); 7.5% (144) from Malawi, 6.4% (122) from Tanzania (2.9% MUHAS and 3.5% from ORCI), 2.1% (41) from Botswana, and 1.4% (26) from Rwanda. HIV prevalence was 96% in Uganda, 80% in Kenya, 86% in Malawi, 84% in Tanzania, 78% in Botswana, and 50% in Rwanda. Considering each country there was no change in HIV prevalence for the study period (Figure 1).

CONCLUSION

Majority of KS diagnoses are still among HIV positive patients even with increased ART availability. Prevalence varied by country, and for most it was over 75%. Variability was likely due low numbers (in Botswana and Rwanda) observed. There is need to monitor this trend longer, and also understand why the HIV contribution to KS burden is not changing despite increased ART availability.

28: Testing for the Virus to Diagnose the Cancer: Validation of Quantification by PCR of Skin Lesion-Derived KSHV DNA Copy Number for the Diagnosis of Kaposi Sarcoma (KS) in Africa

Authors: *Aggrey Semeere[1], Jeffrey Martin[2], Racheal Ayanga[1], Andrea Gardner[3], Juan Boza[4], Maite Ibáñez de Garayo[3], Xinying Chu[4], Miranda McGaskey[3], Jason Manning[4], Miriam Laker-Oketta[1], Megan Wenger[2], Charles Kasozi[5], Michael Kanyesigye[6], Esther Freeman[7], Robert Lukande[1], Tim McCalmont[2], Phil LeBoit[2], Toby Maurer[8], Ethel Cesarman[3], David Erickson[4]*

[1]Infectious Diseases Institute, Uganda; [2]University of California, San Francisco; [3]Weill Cornell Medicine; [4]Cornell University; [5]Masaka Regional Referral Hospital, Uganda; [6]Mbarara Immune Suppression Syndrome Clinic, Uganda; [7]Harvard Medical School; [8]Indiana University

BACKGROUND

Inaccessibility and inaccuracies limit histopathologic diagnosis of KS in Africa. We hypothesized that quantification of KSHV DNA from nucleic acid obtained from suspicious skin lesions could distinguish KS from non-KS lesions, thus enabling development of a diagnostic test that would decrease need for histopathologic interpretation. In our earlier training population, quantification of lesional KSHV DNA by qPCR (using sub-optimally transportable Ct values) had high sensitivity and specificity for the diagnosis of histopathologically-confirmed KS. We now assess diagnostic accuracy of qPCR in an external validation population and using a more transportable KSHV copy number readout.

METHODS

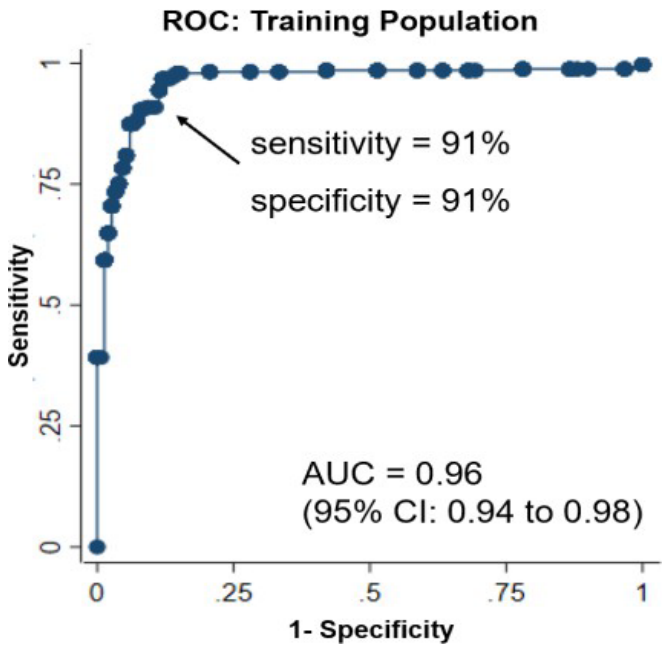
Following identical procedures used in our prior training population in Uganda (n=506 participants), we performed skin punch biopsies among a validation population of consecutive patients referred to free-of-charge skin biopsy services in Uganda because of clinical suspicion of KS. Histopathologic evaluation of one-half of the biopsy was done locally and by up to three US pathologists (including anti-LANA staining). The other biopsy half was stored in RNAlater until it underwent DNA purification in the United State using the QIAGEN DNeasy kit. Purified DNA was standardized to 2 ng/µl followed by testing 5 µl for KSHV ORF 26 DNA in two replicates by qPCR accompanied by a standard curve. With histopathology as gold standard and ROC curves, we assessed the performance characteristics of the mean of the replicates for the diagnosis of KS. An optimal KSHV DNA copy number threshold that was earlier derived in the training population was assessed in the validation population.

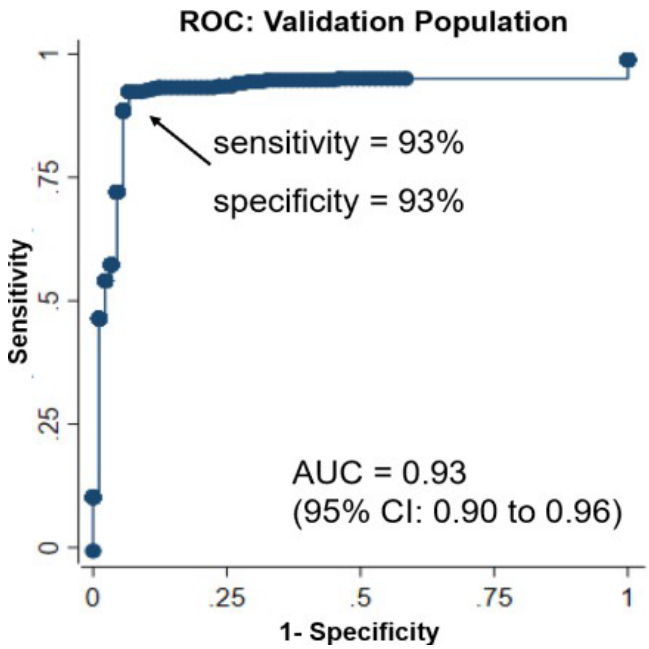
RESULTS

The validation population consisted of 427 participants with skin biopsies. Median age was 33 years (IQR: 29 to 40), 34% were women, and 91% were HIV-infected; 22% of lesions were macules, 61% plaques, and 17% papules/nodules. Gold standard histopathology revealed that 338 biopsies were KS and 89 were not. Using the previously-derived threshold of 161 copies of KSHV DNA per 5 µl input into the reaction, which in our training population yielded 91% sensitivity and 91% specificity for KS diagnosis (accuracy=91% and area under the curve (AUC) = 0.96), qPCR in the validation population yielded 93% sensitivity, 93% specificity, 93% accuracy and an AUC of 0.93 (Figure).

CONCLUSION

In an external validation population of consecutive patients with KS-suspicious skin lesions in Uganda, qPCR of lesional KSHV DNA had high sensitivity and specificity for diagnosis of KS, performing similarly to our training population. Because of ambient endemic KSHV infection in Africa, mere qualitative detection of KSHV DNA in skin lesions is non-specific for KS diagnosis. Instead, precise quantification of KSHV DNA is needed, and a KSHV DNA copy number threshold that balances sensitivity and specificity has now been established. Other thresholds that maximize either sensitivity or specificity may now be evaluated in decision analysis frameworks. This validation of qPCR performance motivates a point-of-care nucleic acid amplification-based diagnostic test for KS, which we are currently developing.


ROC: Training Population
sensitivity = 91%
specificity = 91%
AUC = 0.96
(95% CI: 0.94 to 0.98)
Sensitivity
1- Specificity
0
.25
.5
.75
1


ROC: Validation Population
sensitivity = 93%
specificity = 93%
AUC = 0.93
(95% CI: 0.90 to 0.96)
Sensitivity
1- Specificity
0
.25
.5
.75
1

29: Characterization of Extracellular Vesicles in NHL and AIDS-NHL and Their Role in the Tumor Microenvironment

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BACKGROUND

Non-Hodgkin lymphoma (NHL) encompasses a diverse group of cancers originating from B cells. People living with HIV (PLWH) have a significantly higher risk of developing NHL when compared to people living without HIV (PLWOH). This higher incidence suggests that HIV infection may contribute to B-cell dysfunction, predisposing PLWH to NHL. The tumor microenvironment consists of different cells and molecules that exert an influence on NHL development and progression. Extracellular vesicles (EVs) are small vesicles released by all type of cells, including cancer cells and immune cells, that carry proteins, lipids, RNA, and DNA fragments. EVs can influence recipient cells either locally or systemically by releasing their content or interacting with their surface receptors in recipient cells, making EVs an important means of intercellular communication. This way, EVs can impact the function of target cells through reprogramming signaling pathways and influencing physiological and pathological processes. EVs may facilitate an important role in tumor development by transporting molecular cargoes playing a critical role in cellular communication, immune modulation, angiogenesis, and microenvironmental remodeling. Given their potential integral role in the tumor microenvironment, we hypothesize that EVs may contribute to B-cell dysfunction potentially leading to NHL development. Therefore, our study aims to explore the role of EVs in both NHL and AIDS-NHL development in a mouse model system.

METHODS

We injected 1x106 cells of NHL (Ramos, OY6) or AIDS-NHL (2F7) cell lines in NSG mice. Mice inoculated with either NHL or AIDS-NHL cell lines were monitored for any signs of illness and survival. Tumors that developed in mice injected with either NHL or AIDS-NHL cell lines were dissociated into single cells for flow cytometry analysis to determine whether the tumors were of human B cell origin and expressed markers characteristic of NHL and AIDS-NHL (CD71, CD27, PD-L1, CD10, CD11c, and T-bet). EVs were isolated from serum and tumor cell supernatants using the SBI ExoQuick Exosome isolation kit, and characterized by the presence of EV specific markers (CD63, HSP70, CD81, TSG101) by western blot, including the absence of calnexin, a non-EV marker. Additionally, molecules (CD30, gp-130, TRAIL, CD27, CD25, CD40, CD40L, IL-1R1, TNF-RII, IL-6Rα, B7-H3, ICAM-1, and FasL) that are associated with risk of NHL and AIDS-NHL development were quantified in serum and tumor-derived EVs using Luminex immunometric assay.

RESULTS

Mice implanted with NHL and AIDS-NHL cell lines developed multiple lymphoma-like tumors composed of human CD19+ B-cells, and notably exhibited expression of molecules associated with lymphomagenesis (CD71, CD27, PD-L1, CD10, and CD11c). Tumor derived human CD19+ B-cells also expressed T-bet, which is a transcription factor expressed in a subset of B-cell lymphoproliferative disorders. These molecules were expressed at higher levels in tumor cells compared to the original NHL and AIDS-NHL cell lines they were implanted with. Furthermore, tumor-derived EVs expressed CD63, CD81, HSP70, and TSG101, and lacked calnexin, confirming their isolation from tumor cell supernatants. Moreover, EVs also expressed human cell surface markers implicated in lymphomagenesis such as CD30, gp-130, TRAIL, CD27, CD40, CD40L, TNF-RII, IL-6Rα, and B7-H3. These markers were expressed in the EVs derived from tumors that originated from both NHL and AIDS-NHL cell lines.

CONCLUSION

Mice implanted with NHL or AIDS-NHL cell lines develop tumors that contain human CD19+ B cells that express markers of B cell activation that are important in NHL development. These tumors release EVs bearing cell surface markers associated with lymphoma growth and immune modulation, highlighting their potential role in the tumor microenvironment. This mouse model offers a promising avenue to investigate how tumor-derived EVs influence the tumor microenvironment in NHL and AIDS-NHL.

30: Aquaporin 3 (AQP3) Regulates Oxidative Stress and the Life Cycle of Kaposi Sarcoma Herpesvirus (KSHV) in Its Associated Cancers

Authors: *Olivia Powrozek, Warren Nakazawa, Melanie Klemond, Alexander Van Den Avont, Christopher Kywe, Xiaomeng Shao, Serdar Gayybov, Lindsay Holic, Morgan Mroz, and Neelam Sharma-Walia*

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BACKGROUND

Kaposi's sarcoma-associated herpesvirus (KSHV) is a gammaherpesvirus linked to Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), multicentric Castleman's disease (MCD), and KS Inflammatory Cytokine Syndrome (KICS). Current treatments struggle to target dormant KSHV-infected cells. Aquaporin 3 (AQP3) is a protein that transports water, glycerol, and hydrogen peroxide (H2O2), contributing to cellular functions and inflammation-associated responses, making it a potential therapy target.

METHODS

We used HMVEC-d and TIVE cells as *in vitro* models for KS and BCBL-1 and BC-3 cells to model PEL. We investigated the role of AQP3 in KSHV latent and lytic replication using iSLK cells infected with RGB-BAC16. We also examined AQP3 inhibition using an inhibitor and DMSO as solvent control and validated AQP3's role through AQP3 silencing. We employed qRT-PCR, Western blotting, cytotoxicity assays, antioxidant arrays, oxidative stress assays, RNA-seq analysis, and latent and lytic gene expression assays.

RESULTS

Here, we demonstrate that the levels of AQP3 in KS skin are higher than the sections from healthy controls. KSHV infection of human primary endothelial cells upregulates the AQP3 gene expression. KSHV-infected PEL cells exhibit a higher AQP3 gene expression and protein level than control uninfected BJAB cells. KSHV-infected PEL cells are more sensitive to low doses of AQP3 inhibitor than BJAB. Targeted inhibition of AQP3 reduces intracellular ROS in KSHV-infected PEL compared to BJAB cells. Silencing AQP3 increased the expression of antioxidant genes in KSHV-infected PEL cells. Additionally, inhibiting AQP3 reduced the expression of the KSHV latent ORF73 and increased the expression of the lytic ORF50 gene.

CONCLUSIONS

Targeting AQP3 has a similar effect on KSHV-positive cells as the FDA-approved antioxidant NAC, balancing ROS levels and reducing KSHV latent gene expression. AQP3 may regulate viral latency and lytic replication by maintaining the redox balance, suggesting it is a potential approach for antiviral therapy.

31: The Role of eIF5B in Translation Initiation during KSHV Replication and Oncogenesis Is Oxygen-Independent

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Kaposi's Sarcoma (KS) herpesvirus (KSHV) infection precedes the development of KS, an AIDS-related cancer, and is also responsible for the initiation of primary effusion lymphoma, a lymphoproliferative disease. While antiretroviral therapy has helped to reduce the global prevalence of AIDS-KS, this endothelial malignancy is refractory to treatment and continues to be a significant burden for HIV patients. Patients with KS have lesions all over their bodies, but they are most common in hypoxic regions. Recent research has revealed an interplay between KSHV infection and the hypoxic cellular response mechanisms.

Our research has shown that KSHV infection can usurp the hypoxia translation machinery. Specifically, work from our laboratory has demonstrated that KSHV infection is able to facilitate the formation of the HIF2a-dependent hypoxic translation initiation machinery for the synthesis of viral proteins. Our current research aims to understand the role of eIF5B, another crucial component of the hypoxia translation machinery. This translation factor acts as a hypoxic surrogate for translation initiation during hypoxia over the canonical eIF2. We use two cell models in normoxic conditions to explore the role of eIF5B in the hypoxic translation machinery usurped by KSHV. Collectively, this study implicates a critical role for eIF5B in normoxic conditions during KSHV lytic replication in our models.

Findings from this research will provide more insight into how the hypoxia translation machinery plays a role in viral oncogenesis and KS disease progression after KSHV infection and contributes to a larger body of knowledge on how KSHV induces a hypoxia-like environment in the infected cell.

32: Novel Cereblon-Binding Immunomodulators Are Effective against Cancers Associated with Human Gammaherpesviruses

Authors: *Prabha Shrestha, Emma N. Treco, David A. Davis, and Robert Yarchoan*

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BACKGROUND

Pomalidomide (Pom) is a cereblon-binding immunomodulator (CBI) that is FDA-approved for use in Kaposi Sarcoma, a malignancy caused by Kaposi sarcoma herpesvirus (KSHV). Pom also shows *in vitro* efficacy against primary effusion lymphoma (PEL), another KSHV-associated malignancy, and Burkitt lymphoma (BL), which is often associated with Epstein-Barr virus (EBV). Pom exerts its anti-cancer effects by binding to a cellular E3-ubiquitin ligase, cereblon, and altering its substrate specificity, leading to the downregulation of oncogenes IRF4 and cMyc. Pom also upregulates immune-activating surface markers ICAM-1, B7-2, and/or MHC-1 in these tumors, restoring their recognition by immune cells. Golcadomide (Golc) and iberdomide (Iber) are two new-generation CBIs designed to have increased affinity to cereblon and are currently being examined for use in various lymphomas. Here, we performed preclinical analysis of these novel CBIs to assess their anti-cancer activity against PEL and BL.

METHODS

Several PEL and BL-derived cell lines were used to test the *in vitro* anti-tumor activities of Golc and Iber, obtained from Selleck Chemicals. Their effects on growth suppression were measured using an ATP viability assay and western blotting for downstream target proteins. The ability of the CBIs to alter the levels of immune surface markers was assessed by flow cytometry. To gain mechanistic insight into the activity of these drugs, pomalidomide-resistant PEL and BL cell lines (PomR cells) were developed by exposing cells to increasing concentrations of Pom.

RESULTS

Both Golc and Iber led to significant growth suppression of PEL and BL cell lines with IC_{50} concentrations 100 and 10-fold lower, respectively, than that of Pom. Consistent with this finding, these CBIs induced a larger decrease in IRF4 levels than Pom in PEL cell lines. Additionally, survivin, an anti-apoptotic protein shown to be necessary for the survival of PEL and BL, was identified as a novel target of the CBIs. Golc and Iber downregulated survivin and increased apoptosis (as shown by PARP cleavage) substantially better than Pom. Both Golc and Iber were also able to upregulate surface ICAM-1 and B7-2 levels in latent PEL and BL cells, and prevent the downregulation of MHC-1 in lytic PEL cells at lower concentrations than Pom. PomR PEL and BL cells, which had substantially decreased levels of cereblon, no longer showed suppression of growth, decreases in survivin, or increases in surface immune marker expressions upon treatment with Golc or Iber, suggesting that these novel CBIs also depend on cereblon for these functions.

CONCLUSIONS

These results show that the newer CBIs are more potent and effective than Pom at inhibiting the growth of BL and PEL cells while also potentially enhancing immune recognition of BL and PEL, and therefore, should be investigated as therapeutic options for patients with these tumors.

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33: Risk of Non-Hodgkin Lymphoma and Hodgkin Lymphoma Subtypes in People with HIV in the U.S. from 2001 to 2019

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BACKGROUND

People with HIV (PWH) have significantly elevated risks of both non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), though risk varies by histologic type. There has been a 70% decline in the incidence of lymphoma among PWH since the adoption of antiretroviral therapy. However, the trends of NHL and HL risk have not been fully investigated among PWH in the United States from 2001 to 2019.

METHODS

We used data from the HIV/AIDS Cancer Match (HACM) Study, which is a US registry-based cohort of PWH linked to cancer registries. We estimated the risk of each lymphoma type in PWH compared to the general population overall and across calendar periods during 2001-2019. Standardized incidence ratios (SIR) were estimated by dividing the observed number of NHL and HL subtypes in PWH by the expected case number in the general US population adjusting for age, sex, race/ethnicity, year and registry. P for trend across calendar year periods was estimated with Poisson regression adjusted for categorical age groups from 20-84 years.

RESULTS

We observed 6,452 NHL and 1,748 HL cases among 818,091 PWH. Diffuse large B cell lymphoma (DLBCL) was the most common NHL with 3989 cases and classical HL was the most common HL with 1284 cases. The relative risk of all NHL and HL subtypes among PWH compared to the general population declined from 2001 to 2019 (P-trend<.01). The SIRs (95%CIs) for total NHL and HL from 2015 to 2019, the most recent period, were 2.3 (2.2, 2.5) and 6.2 (5.6, 6.8), respectively. In 2015–2019, the risks of several histologic subtypes of NHL and HL remained elevated among PWH, including Burkitt lymphoma (SIR: 14.5, 95%CI: 12.1-17.3), DLBCL (5.3, 4.9-5.7), peripheral T-cell lymphoma (1.7, 1.2-2.2), classical HL (8.8, 7.8-9.8), and nodular sclerosis HL (4.0, 3.2-5.0). In contrast, in the most recent time period, the risk of some lymphomas was significantly lower among PWH, including follicular lymphoma (SIR: 0.7, 95%CI: 0.6-1.0), marginal zone lymphoma (0.8, 0.5-1.1), and chronic lymphocytic leukemia/small lymphocytic lymphoma (0.2, 0.1-0.3).

CONCLUSION

Although the relative risk of most NHL and HL subtypes among PWH compared to the general population declined in the United States during 2001-2019, the risks of DLBCL, Burkitt lymphoma, peripheral T-cell lymphoma, classical HL, and nodular sclerosis HL remained significantly elevated among PWH in the most recent time period.

Table 1. Standardized incidence Ratio for lymphoma subtypes in people with HIV in the US from 2001–2019

Lymphoma Type	N	2001-2004	2005-2009	2010-2014	2015-2019	*P-trend*
All NHL	6452	7.2 (6.8, 7.6)	5.4 (5.1, 5.6)	3.7 (3.5, 3.8)	2.3 (2.2, 2.5)	<.0001
DLBCL	3994	13.5 (12.5, 14.5)	10.8 (10.2, 11.4)	8.0 (7.5, 8.4)	5.3 (4.9, 5.7)	<.0001
Burkitt lymphoma	775	26.5 (22.2, 31.4)	23.4 (20.6, 26.5)	20.8 (18.4, 23.5)	14.5 (12.1, 17.3)	<.0001
Peripheral T-cell lymphoma	290	5.2 (4.0, 6.7)	3.6 (2.9, 4.4)	2.5 (2.0, 3.0)	1.7 (1.2, 2.2)	<.0001
Follicular lymphoma	202	1.5 (1.0, 2.1)	1.2 (1.0, 1.6)	0.8 (0.6, 1.0)	0.7 (0.6, 1.0)	0.0143
MZL	146	1.7 (1.0, 2.7)	2.0 (1.5, 2.6)	1.1 (0.8, 1.4)	0.8 (0.5, 1.1)	0.0045
CLL/SLL	110	0.9 (0.6, 1.4)	0.4 (0.3, 0.6)	0.3 (0.2, 0.4)	0.2 (0.1, 0.3)	0.0004
NHL, other/unspecified	789	8.6 (7.3, 10.0)	5.1 (4.4, 5.8)	3.3 (2.9, 3.8)	2.3 (2.0, 2.7)	<.0001
All HL	1748	8.5 (7.5, 9.6)	7.8 (7.2, 8.6)	7.7 (7.1, 8.3)	6.2 (5.6, 6.8)	0.0002
HL, Classical, other	1284	13.3 (11.5, 15.4)	12.0 (10.7, 13.3)	11.0 (10.0, 12.1)	8.8 (7.8, 9.8)	0.0004
HL, Nodular sclerosis	442	5.1 (4.0, 6.3)	4.9 (4.1, 5.8)	4.9 (4.1, 5.7)	4.0 (3.2, 5.0)	0.0603

Abbreviations: CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma, DLBCL: diffuse large B cell lymphoma, HL: Hodgkin lymphoma, MZL: marginal zone lymphoma, NHL: non-Hodgkin lymphoma.

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34: HIV-Associated Plasmablastic Lymphoma in the Era of ART: Outcomes at a Public Hospital in Johannesburg, South Africa

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BACKGROUND

Plasmablastic lymphoma (PBL) is a rare, aggressive lymphoma that carries a strong association with HIV and EBV infection. PBL occurs predominantly in extra-nodal sites with a predilection for the oral and gastrointestinal tract. Treatment includes concurrent chemotherapy and ART in HIV-associated PBL. We describe the presenting characteristics and outcomes in a cohort of HIV-associated PBL in Johannesburg, South Africa.

METHODS

We enrolled 12 people living with HIV (PLWH) with a pathologic diagnosis of PBL in an IRB-approved observational prospective cohort study at Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa from January 2021 to September 2023. History was obtained at the time of enrollment and a retrospective chart review was performed from the National Health Laboratory Service (NHLS) database, hematology charts, and mortuary files.

RESULTS

Among 12 patients with HIV-associated PBL, presenting characteristics at time of lymphoma diagnosis include median age of 39 (IQR 34-45), male-predominance (83%; 10/12 male), median CD4 count of 153 (IQR 92-379), VL undetectable in 27% (3/11), self-reported adherence to ART at time of diagnosis was 50% (6/12), B-symptoms were present in 92% (11/12), and extra-nodal involvement in 100% (12/12) including bone marrow involvement in 25% (3/12). Majority of tumors were EBER positive (81%; 9/11) and had a high Ki67 of $\geq$80% (92%; 11/12). The median time to treatment initiation was 1.3 months, however 1 patient died prior to treatment initiation. First line therapy was CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone) in all patients treated with chemotherapy and patients received a median of 5.5 cycles. One year mortality was 50% with a median overall survival of 2.9 months in those who died.

CONCLUSIONS

Despite improved access to ART, HIV-associated PBL remains prevalent in Johannesburg, South Africa. PBL is associated with poor survival outcomes and early demise. A comprehensive approach including prioritized lymphoma diagnosis, prompt initiation of treatment, improved access to infusional regimens and targeted agents is needed.

35: Primary Effusion Lymphoma in People with and without HIV in the United States

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BACKGROUND

Primary effusion lymphoma (PEL) is a rare subtype of large B-cell non-Hodgkin lymphoma (NHL) caused by Kaposi sarcoma (KS)-associated herpesvirus. This study describes the incidence and survival of PEL in the US among people with (PWH) and without HIV.

METHODS

PEL cases diagnosed during 2001–2019 were identified in the HIVAIDS Cancer Match (HACM) Study, which links population-based cancer and HIV registries in 14 US regions. We tabulated demographic characteristics stratified by HIV status and used multivariable negative binomial regression to examine PEL risk factors among PWH. We summarized the CD4 counts of PWH in the five years before PEL diagnosis. We compared survival after PEL diagnosis according to HIV status and survival between PEL and other NHLs among PWH using Cox regression.

RESULTS

During 2001–2019, 92 (53%) of the 174 PEL cases in the HACM Study were among PWH, comprising 1.15% of NHLs among PWH. PEL incidence among PWH was 1.36 cases per million person years, representing greatly increased incidence compared with the general population (standardized incidence ratio=712, 95% CI: 553–883). Median time between HIV diagnosis to PEL diagnosis was 7 years (range: 0–26 years). Compared to PEL cases without HIV, PWH were more likely to be male (96% vs. 81%), younger (median age at diagnosis: 45 vs. 78 years), Hispanic (33% vs. 17%) or non-Hispanic Black (28% vs. 18%), and to have had prior KS (30% vs. 12%). Among PWH, MSM had the highest PEL risk compared to males with other HIV transmission routes, and females. Prior KS diagnosis increased PEL risk 59-fold in PWH, while AIDS without KS increased risk 1.8-fold compared to PWH without AIDS. There was an increase in the proportion of PWH with CD4 counts below 200 cells/mm^3, reaching 68.7% in the six months before PEL diagnosis (Figure 1). Among PEL patients, HIV was associated with 45% lower mortality (hazard ratio [HR]=0.55, 95% CI: 0.38–0.81), but this association was not longer significant (HR=0.76, CI: 0.47–1.23) after adjusting for age-group. Among PWH, in a model adjusted for sex, age-group, and race/ethnicity, Burkitt lymphoma and diffuse large B-cell lymphoma exhibited similar mortality to PEL (HR=1.00, CI: 0.91–1.10, and 1.14, 0.86–1.52, respectively) but central nervous system lymphoma mortality was worse (HR=1.68, CI: 1.52–1.85) (Figure 2).

CONCLUSIONS

PWH have greatly elevated risk for PEL. While a disproportionate number of cases arise in PWH, there is a sizeable proportion of cases among older individuals without HIV. KS is an extremely strong risk factor for development of PEL. The age difference between PEL cases with and without HIV accounted for the lower mortality associated with HIV.

Figure 1. Distribution of CD4 counts among people with HIV in the five years leading to primary effusion lymphoma diagnosis

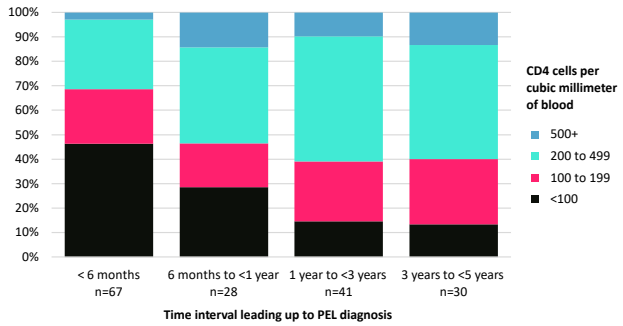
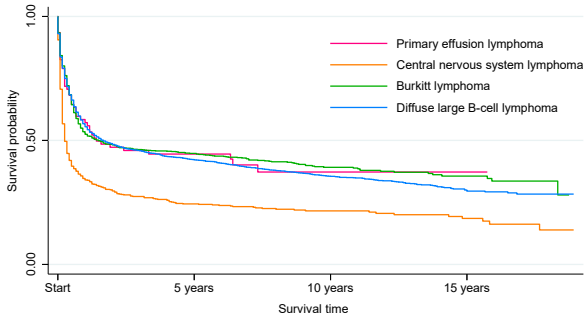


Figure 2. Overall survival following non-Hodgkin lymphoma

diagnosis among PWH



36: Immunologic Responses among Participants Receiving 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 plasmablastic form of multicentric Castleman disease (MCD), and KSHV-associated inflammatory cytokine syndrome (KICS). KS can occur alone or concurrently with MCD or KICS. Liposomal doxorubicin (DOX), a chemotherapy, and pomalidomide (POM), an immunomodulatory drug, are FDA-approved therapies for KS alone. A phase I/II study combining POM/DOX led to a response rate (RR) of 71% in participants with KS alone. However, in participants with KS and MCD or KICS, the KS RR was 45% and POM/DOX was less well-tolerated. Evaluating the immunologic response may further our understanding of the differences in the treatment groups of KS alone as compared with KS with concurrent MCD or KICS.

METHODS

There were 51 participants enrolled in the POM/DOX study in 2 groups of participants with KS requiring systemic therapy: Group I (G1)- 37 participants had KS alone; Group II (G2)- 14 participants had KS with concurrent active MCD or KICS. Participants received DOX at 20 mg/m^2 intravenously on day 1 combined with POM once daily on days 1 to 21 of a 28-day cycle. After adjusting for quality control aspects, we analyzed T-cell subset among 23 participants using flow cytometry of peripheral blood mononuclear cells (PBMCs) at baseline and cycle 1 day 28 (C1D28). We evaluated markers of T-cell activation (CD38 and HLA-DR), exhaustion (PD-1), and senescence (CD57). KSHV-specific T-cell responses were evaluated via a whole KSHV proteome interferon-gamma ELISpot assay employing ~7,500 overlapping 15mer peptides into peptide pools that represented 83 KSHV open reading frames. Assays were performed using fresh PBMCs collected and analyzed at baseline and at cycle 4 day 28 (C4D28) among 47 participants. A response was considered positive if $\geq$ 40 spot-forming units (SFU)/10^6 cells were detected. The breadth of T-cell responses was determined by the number of antigens eliciting interferon-gamma responses, and the intensity of responses was determined by the total SFU/10^6 cells at each time point. Wilcoxon tests were used to analyze significant differences between groups and changes across time points for flow cytometry and KSHV-specific T-cell responses.

RESULTS

In the POM/DOX study, 49 participants (96%) had HIV and 38 (75%) had prior systemic therapy for KS. There were no significant baseline differences in the percentage of CD4 (P=0.3) or CD8 T-cells (P=0.2) between G1 and G2. Overall, among all participants, there was an increase in the percentage of CD4 T-cells from baseline to C1D28 (P=0.0004) and a decrease in the percentage of CD8 T-cells from baseline to C1D28 (P=0.0009). The percentage of PD-1$^+$ CD4 T-cells and PD-1$^+$ CD8 T-cells were higher at baseline in G2 compared to G1 (P=0.01, P=0.007, respectively). Among the effector memory (CD45RO$^+$CD27$^-$) T-cell population, G2 had higher percentages of PD-1$^+$ CD4 T-cells (P=0.03), CD38$^+$HLA-DR$^+$ CD4 T-cells (P=0.02), CD38$^+$HLA-DR$^+$ CD8 T-cells (P=0.02), and CD38$^+$ CD8 T-cells (P=0.03) than G1 at baseline. Among the naïve (CD27$^+$CD45RO$^-$) T-cell population, G1 had higher levels of CD38$^+$HLA-DR$^-$ CD4 T-cells (P=0.007) and CD38$^+$ CD4 T-cells (P=0.007) compared to G2. On assessing baseline to C1D28 changes between the groups, only the percentage of CD38$^+$HLADR$^-$ central memory (CM, CD45RO$^+$CD27$^+$) CD4 T-cells increased and HLADR$^+$CD38$^-$ CM CD4 T-cells decreased between G1 compared to G2 (P=0.05, P=0.02). At baseline, there were no differences in the KSHV-specific T-cell responses in the breadth (P=0.4) and intensity (P=0.2) between G1 and G2. There were also no differences observed in the changes of breadth (P=0.8) and intensity (P=0.9) of KSHV-specific T-cell responses from baseline to C4D28 between G1 and G2.

CONCLUSION

Phenotypic differences at baseline in T-cells may account for the differences observed in treatment response by group. Increased expression of exhaustion markers in effector memory subsets among participants in G2 may account for differences in treatment response as compared to participants in G1. The T-cell differences did not correspond to KSHV-specific T-cell responses between the groups.

37: CDK4/6 Inhibitor Abemaciclib Inhibits Growth of KSHV-Infected Endothelial Cells

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BACKGROUND

Kaposi sarcoma-associated herpesvirus (KSHV) is the etiological agent responsible for several malignancies, including Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD). KSHV downregulates immune surface molecules such as MHC-I, ICAM-1, and B7-2, thereby enabling the virus to evade T-cell and natural killer cell-mediated immunity. Previous studies have demonstrated that CDK4/6 inhibitors can inhibit growth of PEL cells and also induce the expression of surface immune markers in KSHV-infected PEL cell lines, counteracting virus-induced immune evasion, and these findings have informed an ongoing trial of abemaciclib in KS. The current study seeks to investigate other mechanisms by which abemaciclib may be active in KS.

METHODS

The immortalized endothelial lines TIME, iTIME.219 (KSHV-infected), TIVE, and TIVE.219 (KSHV-infected) cells were treated with 1 μM abemaciclib (MedChemExpress, Cat. #: HY-16297A) for 3 days. The number of viable cells was assessed and quantified using the Celigo Image Cytometer. Supernatants from treated cells were collected for cytokine analysis using the Proteome Profiler Human Cytokine Array Kit. IL-6 expression was further evaluated using ELISA. RNA expression of various cytokines was analyzed by qPCR. A tube formation assay was employed to determine cell proliferation in response to abemaciclib treatment.

RESULTS

Cell counting showed that abemaciclib inhibited cell growth in mock-infected TIME cells (69% inhibition) and KSHV-infected endothelial cells iTIME.219 (79% inhibition) without inducing the lytic cycle of KSHV in iTIME.219 cells. Additionally, abemaciclib inhibited tube formation, a measure of angiogenesis, in TIME cells. Treatment with abemaciclib altered the cytokine profile in the culture supernatant, notably reducing IL-6 and CXCL1 levels, as confirmed by ELISA. A decrease in IL-6 RNA expression was also observed.

CONCLUSIONS

Abemaciclib inhibited cell growth and proliferation of KSHV-infected endothelial cells (iTIME.219) without inducing lytic infection. In addition, it reduced expression of IL-6, which may help reduce KS growth and also reduce the inflammatory cytokine symptomatology seen in some patients with KS. Coupled with its immunomodulatory effects, these findings provide a rationale for the assessment of CDK4/6 inhibitors in the treatment of Kaposi sarcoma.

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38: NSUN1/2-Mediated RNA m5C Modification Controls KSHV Viral Infection via Regulating RNA Stability of Host Restriction Factors

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BACKGROUND

Kaposi's sarcoma-associated herpesvirus (KSHV) has the capability to establish a persistent infection in humans and is associated with the development of various tumors. The lytic reactivation of KSHV can be leveraged to eliminate tumor cells containing latently infected viruses. NSUN1/2 serve as crucial methyltransferases responsible for RNA m5C modification, a prevalent RNA alteration in the realm of epi-transcriptomics. This modification is known to govern RNA stability, splicing, nuclear-cytoplasmic RNA export, and mRNA translation efficiency. The implications of epi-transcriptomic regulation provide a novel lens through which to explore the intricate interplay between host and virus.

METHODS

We determined the impact of KSHV lytic reactivation on NSUN1/2 expression by measuring their mRNA (RT-qPCR) and protein (immunoblotting) levels. We also employed an RNAi approach to determine the impact of NSUN1/2 knockdown on KSHV lytic reactivation and *de novo* infection rate by fluorescence microscopy, as well as by quantifying KSHV lytic gene transcription and protein. To gain molecular insight on how NSUN1/2 regulates KSHV viral gene expression, we performed RNA-Bisulfite sequencing to identify transcripts that were differentially methylated before and after KSHV reactivation. To narrow down the candidate pool by overlap our RNA-Bis-seq results with differentially expressed gene we identified from public RNA-seq datasets analysis. We then validated the NSUN2-TRIM25 mRNA interaction by RNA immunoprecipitation (RIP). We predicted six transcription factors as NSUN1/2 regulators through re-analyzing public chromatin immunoprecipitation(ChIP)-seq datasets and confirmed the binding of C-MYC to NSUN2 promoter using ChIP-qPCR.

RESULTS

In our study, we unveil a previously undocumented mechanism wherein NSUN1/2 regulates the expression of host restriction factors by RNA stability via RNA m5C modification. This regulatory pathway facilitates the expression of KSHV lytic genes during lytic reactivation. Initially, we confirmed that both *de novo* infection and lytic reactivation of KSHV substantially decrease the expression of NSUN1/2, leading to a reduction in the overall m5C modification levels of mRNAs. In return, the depletion of NSUN1/2 was found to enhance the rate of KSHV de novo infection and promote KSHV lytic reactivation. KSHV lytic reactivation led to the significant reduction of m5C methylation and mRNA stability of TRIM25, while TRIM25 depletion indeed promoted KSHV lytic replication. Further investigations unveiled C-MYC as a transcription factor governing the expression of NSUN1/2.

CONCLUSIONS

Our results demonstrated that KSHV downregulates NSUN2-mediated m5C methylation of TRIM25 mRNA, thus reducing its stability, which benefits its lytic replication. These findings indicate that the m5C RNA writers NSUN2/1 may play a profound role in regulating viral infection and antiviral immunity by targeting host and viral mRNAs, which would generate a distinct impact in the milieu of unique host cell types for individual viral species. And our findings imply that inhibition of host RNA m5C methylation may benefit such KSHV viral oncolytic strategies for immune clearance of tumor cells.

39: High-Resolution Antibody Profiling of KSHV-infected Individuals Presenting with and without Kaposi Sarcoma Reveals Distinct Ab Repertoires

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BACKGROUND

Kaposi sarcoma-associated herpesvirus (KSHV) is the etiologic agent of Kaposi sarcoma (KS). Immune suppression in addition to KSHV infection is thought to drive KS development. We have recently demonstrated the utility of phage display in facilitating highest-resolution epitope mapping of the KSHV proteome to date and found that antibody (Ab) responses against a subset of KSHV epitopes are associated with symptomatic KS. Here, we extended our approach to profile and quantify the breadth and magnitude of Ab responses of the same SSA cohort against 554 viral organisms with known human tropism and determine whether the responses against these other viruses can also be associated with KS, since co-factors such as prior/co- infections may also contribute to KS disease pathogenesis.

METHODS

A phage library expressing systematically derived linear 56-amino acid peptides with 28-amino acid overlap that tile all pathogens with known human tropism (VirScan) was coupled to patient sera phage immunoprecipitation and sequencing (PhIP-Seq). Ab repertoires were derived from high throughput sequencing of patient-barcoded immunoprecipitated phage DNA. Recognition of each viral protein or organism was determined by quantifying the collection of reactive peptides (breadth) and the frequency with which those reactive peptides were targeted (magnitude). Our approach supported intra- and inter- individual/group repertoire comparisons across the entire virome.

RESULTS

We have first analyzed the Ab responses against EBV since it a common co-infection with KSHV in most pleural effusion lymphomas and generated the first comprehensive linear epitope map of EBV using serum samples (n=106) derived from (1) KSHV seronegative (n=25), (2) KSHV seropositive (n=22), and (3) KS (n=59) groups. While we have reported that there was an increase in KSHV-specific Ab recognition in KS compared to asymptomatic KSHV infection (ASY), EBV Ab responses showed noticeable increase in the context of HIV-1 co-infection but were reduced in KS compared to ASY controls. This suggests both gain and loss of Ab recognition against a subset of viral epitopes, which can be utilized as a potential discriminative Ab signature for KS. In addition, the presence of antibodies against a subset of hCMV and HHV6B peptide antigens were significantly higher among symptomatic KS patients. We also detected significantly higher breadth of Ab responses in KS patients against hepatitis B, C, and E viruses. Pattern recognition and network analyses highlighted co-occurring Ab responses against other viruses, which suggest being synergistic to the previously reported reactivity against the discriminative KSHV peptides that were associated with KS.

CONCLUSIONS

Overall, comparison of organism-level breadth between KS and ASY subjects revealed >1,000 peptide-level Ab responses from >50 potential prior/co-infections that exhibited unique exposure signatures for KS and ASY. Elucidation of humoral Ab repertoire is vital to discern host-pathogen interactions, and to define diagnostic and prognostic biomarkers. Future longitudinal studies will evaluate the predictive, prognostic, and therapeutic value of these discriminative Ab signatures.

40: Longitudinal Patterns of Survivorship Care in Cervical Cancer Patients Living with or without HIV in Botswana, 2015–2023

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BACKGROUND

The number of cancer survivors living in low-and-middle income countries is rapidly growing, but the vast majority of research has been conducted in developed countries, leaving a critical gap in our current understanding of survivorship practices and needs. Drawing from a longitudinal cohort of patients treated for cervical cancer (CaCx) in Botswana, we aimed to assess adherence to the recommended survivorship care overall and by HIV status and to prospectively evaluate factors associated with adherence to care in this population to help fill this gap.

METHODS

Between 2015–2023, CaCx patients (stages IA-IVB), with or without HIV, were prospectively enrolled in an observational cohort study at Princess Marina Hospital (PMH). Short-term (first 2 years post-treatment) and long-term (3–5 years post-treatment) adherence were assessed based on the number of recommended visits (per the Botswana National Cervical Cancer Guidelines) completed before known death. For this analysis, patients who completed definitive or curative intent CaCx treatment (surgery-based or radiation-based) before January 1, 2024 were included to allow for at least 6 months of follow-up care. Clinical, demographic, and temporal factors (e.g., COVID-19) associated with optimal adherence (defined as completing at least 75% of recommended visits) for each care period were analyzed using multivariable logistic regression modeling, adjusting for potential confounders (aOR).

RESULTS

Between 2015–2023, 1181 patients initiated and completed CaCx treatment at PMH. The median age of patients was 48.2 years (IQR, 41.9-58.7 years), and 67.3% (n=795) were living with HIV. Over half of patients (53.9%, n=637) received chemoradiation as their primary form of treatment and at treatment completion, the majority of patients had stage II (37.1%, n=438) or stage III (28.8%, n=340) CaCx. Among those eligible for short-term survivorship care (n=1161), 35.1% (n=407) completed 100% of recommended visits with 14.9% (n=173) completing 50%, 15.7% (n=182) completing 25%, and 34.4% (n=399) completing no follow-up visits. On multivariable analysis, patients who traveled ≥100 km for treatment (aOR 0.51, p<0.001), were living with HIV (aOR 0.70, p=0.022), and had advanced disease (stage III-IV CaCx) (aOR 0.54, p<0.001) were less likely than their counterparts to reach optimal adherence to short-term survivorship care. Among the subset of 851 patients eligible for long-term survivorship care, 15.5% (n=132) completed all recommended visits with 12.5% (n=106) completing 67%, 13.0% (n=111) completing 33%, and 59.0% (n=502) completing no follow-up visits. Similar to short-term survivorship care, patients who traveled ≥100 km for treatment (aOR 0.43, p<0.001) and had advanced disease (aOR 0.43, p<0.001) were less likely to reach optimal adherence for long-term survivorship care. Additionally, those who completed treatment during the COVID-19 pandemic (aOR 0.04, p<0.001) compared to before the pandemic were less likely to reach optimal adherence, but patients treated with surgery were more likely (aOR 1.99; p=0.010) than those treated with radiation. Unlike short-term care, HIV status was not significantly associated with optimal adherence to long-term survivorship care.

CONCLUSIONS

Our results indicate that adherence to recommended survivorship care in Botswana is suboptimal both in the short- and long-term care periods. Strategies to help patients achieve optimal adherence, particularly for those traveling long distances for treatment and with advanced disease, are needed to decrease CaCx mortality and ensure high quality of care for all CaCx survivors.

41: Premalignant Cervical Lesions among HIV-Infected Women on Care and Treatment at a Tertiary Hospital in Jos, Nigeria

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BACKGROUND
High-risk Human Papillomavirus (hrHPV) is the major risk factor for cervical cancer (CC) which is the fourth most frequent cancer among reproductive women in Low- and Middle-income countries. The risk of CC increases with HIV infection resulting in higher incidence and prevalence of cervical intraepithelial neoplasia lesions. We aimed to assess the prevalence and factors associated with premalignant cervical lesions among HIV-infected women on antiretroviral therapy (ART) at Jos University Teaching Hospital, Jos, Nigeria.

METHODS
A cross-sectional study was employed to enroll 131 HIV-infected women aged 20-65 years on ART between November 1, 2020 to April 30, 2021 using a convenient sampling technique. Ethical approval was obtained from Jos University Teaching Hospital. Semi-structured interviewer-administered questionnaire was used to collect demographic, behavioural and clinical data from consented women. The cervical smear was collected using Cytobrush during the gynaecologic examination, stained by the Papanicolaou staining technique, and the results classified. Frequency, percentage, and Chi-square were conducted using SPSS, P<0.05 was considered statistically significant.

RESULTS
Results: Of 131 women the mean age was 41.2 ±10.5 years. The overall prevalence of premalignant cervical lesions was 26.0%; 3.1% had Atypical Squamous Cells of Undetermined Significance; 6.1% had Atypical squamous cells that cannot exclude HSIL; 6.1% had Low-Grade Squamous Intraepithelial Lesion and 12.2% had High-Grade Squamous Intraepithelial Lesion. Intraepithelial abnormality was highest among those between 50 and 59 years (9.9%); married had 11.5%, separated had 1.5%; tertiary education status had (11.5%), primary education (3.8%). For the occupation category: self-employed had the highest prevalence (9.9%). Factors associated with premalignant lesions were: age (X2=29.63, p=0.02) and occupation (X2=29.45, p=0.02).

CONCLUSION
The prevalence of premalignant lesions was high, and increased age and self-employed occupation were risk factors, this suggests the need for massive screening services beyond the risk population and early detection is key to timely intervention.

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42: Patient Perspectives on Acceptability and Appropriateness of a Navigation Strategy for HIV-Associated Kaposi's Sarcoma: A Mixed Methods Analysis

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BACKGROUND

In sub-Saharan Africa, most people with HIV-associated Kaposi's Sarcoma (KS) are diagnosed at advanced stages of disease, requiring chemotherapy, yet less than 50% receive chemotherapy, contributing to persistently poor outcomes. Based on evidence that patient navigation can improve timely access to cancer treatment among underserved populations, in July 2021, a multicomponent patient navigation strategy was developed and implemented within the Academic Model Providing Access to Health (AMPATH) health system in Eldoret, Kenya. The strategy comprises (1) physical navigation, (2) video-based education, (3) travel stipend, (4) health insurance enrollment assistance, (5) health insurance stipend, and (6) peer mentorship. We evaluated the implementation of this multicomponent navigation strategy, including patient-reported acceptability and appropriateness.

METHODS

This study is nested within a longitudinal cohort study of adults (18+) with newly diagnosed HIV-associated Kaposi's sarcoma within AMPATH. From October 2021 until July 2024, we evaluated service penetration, dose, acceptability, and appropriateness of the navigation strategy using structured questionnaires and logs of navigation activities (Table 1). We also conducted semi-structured interviews among a purposive subset of adults with HIV-associated Kaposi's sarcoma who were eligible to participate in the multicomponent patient navigation strategy. We used a theory-based, framework approach to qualitative data analysis. Interviews were independently coded by three researchers trained in qualitative data analysis supported by NVivo qualitative data analysis software.

RESULTS

A total of 175 participants were enrolled in the parent study; 33.9% were female (N=58) and 66.1% (N=113) were male, with a median age of 39 years (IQR: 33, 48). Service penetration was 73.1% (N=128), and on average participants had 18.6 interactions (SD=13.8) with the patient navigator and 6.1 interactions (SD 5.5) with the peer mentor. The multicomponent navigation strategy was acceptable (Median: 20, IQR 20,20) and appropriate (Median: 20, IQR 20,20). Among 27 purposively selected participants in semi-structured interviews, all described the multicomponent navigation strategy overall as acceptable and appropriate. Most participants stated the transportation and health insurance stipends were the most important components of the strategy, but a few participants expressed that the video about KS diagnosis was "frightening" and the least acceptable component.

CONCLUSIONS

Overall, the implementation of a multicomponent patient navigation strategy for HIV-associated Kaposi's sarcoma was successful in western Kenya, with high levels of service penetration and dose. Importantly, in our mixed-methods evaluation the strategy was also acceptable and appropriate.

Outcome Measures	Expected
Service Penetration: Proportion of clients who qualify for patient navigation who have at least one contact with a patient navigator or peer mentor within 90 days after receiving a KS diagnosis.	100%
Dose (Patient Navigation): Total number of interactions with the patient navigator within the first year among clients engaged in patient navigation	9 interactions
Dose (Peer Mentorship): Total number of interactions with the peer mentor within the first year among clients engaged in patient navigation	7 interactions
Acceptability: Acceptability of multicomponent patient navigation strategy on adapted questionnaire (AIM); Semi-structured Interview*	20
Appropriateness: Total scores of appropriateness of multicomponent patient navigation on adapted questionnaire (IAM); Semi-structured Interview*	20

*Summative composite score for 4 questions can range between 4 and 20, with 20 representing the highest level of acceptability and/or appropriateness.

43: Calendar Trends and Risk of Second Primary Cancers among People with HIV in North America: A Collaborative Cohort Study

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BACKGROUND

Increased longevity and prolonged immunosuppression among people with HIV (PWH), combined with ongoing risk factors such as infections, obesity, tobacco, and alcohol use, may contribute to increasing the risk of second primary cancers (SPCs). Trends in SPC incidence and risk among PWH remain unclear.

METHODS

Using data from the North American AIDS Cohort Collaboration on Research and Design (NA- ACCORD), we examined SPC incidence trends and risks in the United States and Canada. PWH were followed from January 2000, enrollment date or cohort inception date (or initial cancer diagnosis for SPC analysis) until the earliest time-to-event (initial cancer diagnosis, occurrence of SPC, death) or administratively censored at December 2016 or the cohort-specific close date. We estimated age-adjusted SPC incidence rates and calendar trends. We calculated sex, age, race/ethnicity, and calendar year-adjusted standardized incidence ratios (SIRs) to estimate SPC risk among PWH compared with the general population with a history of first primary cancer, using the Surveillance, Epidemiology, and End Results cancer registry data. We further calculated SIRs for three different periods: 2000–2003 (pre-tenofovir), 2004–2009 (early integrase era), and 2010-2016 (second integrase era).

RESULTS

A total of 113,006 PWH contributed 1,002,304 person-years of follow-up. We identified 9,113 cancer cases among 8113 PWH (31,325 person-years), of which 515 (5.7%) were SPCs. The incidence rates per 100,000 person-years were 751 (95% CI=734-768) for first primary cancers and 1,412 (95% CI=1,214-1,633) for SPCs. From 2000 to 2016, annual percentage change was -13.4%/year (95% CI=-19.8% to -6.5%) for AIDS-defining SPCs and -1.7%/year (95% CI=-5.8% to 2.4%) for non-AIDS-defining SPCs. The SPC risk was elevated among PWH compared to cancer patients in the general population (SIR, 1.3; [1.2-1.4]). The highest SIRs for specific SPCs included Kaposi Sarcoma (26.6, [17.2-38.0]), anal cancer (17.7, [13.2-23.0]), cervical cancer (10.7, [2.8-23.8]), and liver cancer (3.5, [2.4-4.8]). For AIDS-defining SPCs, SIRs decreased from 10.3 (95% CI=5.5-16.6) during 2000-2003 to 4.7 (95% CI=3.1-6.8) during 2004-2009 and 1.3 (95% CI=0.8-2.0) during 2010-2016. For non-AIDS-defining SPCs, SIRs were 1.5 (95% CI=1.0-2.0) during 2000-2003, 1.3 (95% CI=1.1-1.6) during 2004-2009, and 1.1 (95% CI=1.0-1.2) during 2010-2016.

CONCLUSION

The incidence of SPCs, particularly AIDS-defining cancers is decreasing among PWH in North America. The elevated risk for certain SPCs necessitates enhanced preventive measures and regular monitoring among PWH with a history of cancer.

44: Social Determinants of Health Influences Stage at Presentation of Cervical Cancer for Women Living with HIV in Zambia

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BACKGROUND

Socioeconomic, cultural, and healthcare disparities can impact the accessibility of oncologic care in Southern Africa. Women living with HIV (WLWH) and cervical cancer are particularly vulnerable due to the multi-level socio and biological factors that may impact their stage at presentation and access to care.

METHODS

Newly diagnosed patients with cervical cancer who presented to the Cancer Diseases Hospital in Lusaka, Zambia were enrolled on a prospective cohort study. Standard epidemiologic data was collected along with a survey adapted from the Accountable Health Communities Health-Related Social Needs Screening Tool, administered by research coordinators in their native language. Descriptive statistics and logistic regression analyses were conducted using R version 4.3.0.

RESULTS

A total of 177 women with newly diagnosed cervical cancer were enrolled, of which 55% (n=98) were WLWH. There was no difference in cervical cancer stage at presentation between WLWH and HIV-negative women (HIVNW) (p=0.972). WLWH were significantly younger than HIVNW (48 vs. 53 years, respectively), had less travel time (median 5 [IQR 1-7] vs. 7 [IQR 2-8] hours), were more likely to own a smartphone (37% vs. 21%), and had greater knowledge about cervical cancer risks and symptoms (35% vs. 16%) (all p<0.050). However, WLWH were more likely to report feeling lonely and isolated as “always/often/sometimes” vs. “rarely/never” (p=0.031). HIVNW who were knowledgeable about risks and symptoms of cervical cancer had significantly reduced odds of advanced stage presentation compared to WLWH who also reported to have knowledge about cervical cancer risks and symptoms (OR=0.14, p=0.034).

CONCLUSIONS

We observed differing impacts of patient knowledge of risks and symptoms of cervical cancer between WLWH and HIVNW. Social isolation and/or other unmeasured factors may be among the barriers to early-stage presentation of cervical cancer in Zambia in WLWH and should be explored in future studies.

45: Anal Cancer Screening in PLWH: Outcomes in a Rural Medically Underserved Population

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BACKGROUND

The incidence of anal cancer has been increasing in the United States since 1990 [1] and is an emerging concern in people living with HIV (PLWH), particularly in high-risk groups such as men who have sex with men (MSM) and transgender women. The Department of Health and Human Services guidelines updated July 2024 emphasize the importance of High Resolution Anoscopy (HRA) for early detection of anal cancer [2]. However, limited availability of HRA, especially in rural settings remains a challenge to effective implementation of these guidelines. We report the outcomes of anal cancer screening in a community HIV practice catering to rural medically underserved population in Northwestern Wisconsin.

METHODS

We performed retrospective chart review of all PLWH cared for in our infectious diseases clinic who were eligible for anal cancer screening for patterns of anal pap smear collection, high risk human papillomavirus (HPV) positivity, pathology findings, referral to colorectal surgery (CRS) and completion of HRA among these individuals. Routine anal pap screening was performed and referral to CRS was requested for those with abnormal pathology and/or HPV 16/18 strains positive. Outcomes were individually assessed for concordance by multiple providers experienced in the care of PLWH. Numeric results are reported since our numbers were too low to perform statistical analysis.

RESULTS

Eighty-five PLWH were screened for eligibility, nine were excluded as they were yet to establish longitudinal care with us. Of the 76 eligible PLWH included, 13% were cisgender females. Median age was 54 years. 53/76 (69.73%) PLWH underwent anal pap smear. Only 20% of females underwent anal pap smear, even when offered. 25/53 (47%) had positive high-risk HPV strains, of these 60% were non-16/18 strains and 40% HPV 16/18. 23/53 (43%) had abnormal pathology; of these 65% were ASCUS, 17% LSIL, 8.5% each HSIL and AIN. 26 individuals were referred to CRS for HRA. HRA was completed in 16 (49%). Four in 10 individuals declined referral without any specified reason. Distance to the referral facility was the most common reason (3/10) for declining referral when a reason was provided.

CONCLUSIONS

Our abstract highlights challenges in completing guideline directed anal cancer screening when resources for HRA are not available locally. The nearest center with HRA facility is a 2-hour drive from our center. The rate of offering and completing anal pap smear was significantly lower in women. Providers caring for PLWH should offer anal cancer screening to individuals of all gender identities.

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46: Cancer Survival among People with HIV Compared with People without HIV in the United States in the Modern ART Era: Results from the MACS-WIHS Combined Cohort Study (1996–2019)

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BACKGROUND
People living with HIV (PLHIV) are more likely to die after a cancer diagnosis compared to people without HIV (PWOH). Limited evidence exists characterizing the role of immunosuppression and HIV-related clinical factors in these observed disparities. We examined survival after a cancer diagnosis to identify associated predictors of survival among PLHIV and PWOH.

METHODS
Participants diagnosed with invasive cancer between 1996 and 2019 within the MACS/WIHS Combined Cohort Study were included. Survival after a cancer diagnosis was descriptively assessed using Kaplan-Meier curves. We evaluated clinical, sociodemographic, and behavioral predictors of survival using Cox-proportional hazard models.

RESULTS
There were 653 cases of cancer identified, including 324 men and 329 women (483 PLHIV and 170 PWOH). The median follow-up time was 3.9 years. Sixty-three unique cancer sites were identified and grouped using SEER program codes. The most frequently observed cancers included AIDS-defining cancers (20%), prostate (14%), lung (13%) and breast (10%) cancers. Survival after a cancer diagnosis was poorer among PLHIV than PWOH ($p<0.001$) and the probability of survival was poorer among those with a detectable HIV viral load compared to those with an undetectable viral load and PWOH ($p<0.001$). Among PLHIV, the hazard of death was highest among those with a HIV viral load >100,000 copies/mm^3 (aHR:1.72; 95% CI:1.08-2.72), with lower CD4+ count [201-499 or ≤ 200 cells/mm^3 vs. ≥ 500 cells/mm^3 (aHR:1.71; 95% CI:1.19-2.44 and aHR:2.62; 95% CI:1.76-3.89, respectively)], and an ever AIDS diagnosis (aHR:1.39; 95% CI:1.05-1.84). PLHIV using antiretroviral therapy (ART) at the time of cancer diagnosis had a lower risk of death compared to those not using ART (aHR:0.69; 95% CI:0.50-0.95).

CONCLUSION
Following cancer diagnosis, we observed higher all-cause mortality among those with uncontrolled HIV and who did not report ART use. Our findings underscore the importance of HIV treatment in improving cancer outcomes among PLHIV.

Key words: HIV, MACS/WIHS Combined Cohort Study, Cancer, Survival, HIV Viral Load

47: Attitudes toward Healthcare Provider Communication, System Distrust, and HIV Stigma among People with HIV and History of Cancer

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BACKGROUND

People with HIV (PWH) are more likely to develop cancer and have higher cancer mortality compared to those without HIV. Attitudes toward healthcare providers and the healthcare system more broadly differ among patients with HIV and cancer, which could impact cancer treatment adherence and outcomes. However, prior studies have been conducted within academic healthcare practices, which may differ from community clinics that predominantly serve PWH with intersectional marginalized identities, such as lesbian, gay, bisexual, transgender, and queer (LGBTQ+). To address this gap, this study aimed to: (1) assess patient attitudes toward communication with healthcare providers and trust in the healthcare system among PWH, patients with a history of cancer, or both, and (2) examine HIV-related stigma among PWH with and without cancer.

METHODS

Through a partnership between Moffitt Cancer Center and CAN Community Health (a multi-center provider network predominantly serving PWH and LGBTQ+ individuals), we conducted a survey between April and June 2024 among patients aged 18+ who received care at a CAN Community Health clinic during 2022–2023. The primary outcomes were assessed using an adapted Healthcare Communication Scale (which measures patients' attitudes about communication with healthcare providers), the Health Care System Distrust Scale, and the HIV Stigma Scale short form. The scales were recoded into binary variables (positive vs. non-positive attitudes) for analysis. The independent variables of interest included whether participants had been diagnosed with HIV, cancer, or both. Adjusting for age, race/ethnicity, sex, other sociodemographic and health characteristics, and financial situation, we computed adjusted differences using multivariable linear probability models to assess the impact of HIV and cancer diagnoses on the measured outcomes.

RESULTS

Study participants (N=987) were on average 42.2 years old, were 66.5% male assigned at birth, and had a racial/ethnic makeup of non-Hispanic (NH)-White (39.9%), NH-Black (28.7%), Hispanic/Latinx (22.8%), other (7.5%), and unknown (1.1%). Most (62.3%) participants identified as LGBTQ+. HIV and cancer were diagnosed in 55.5% and 8.3% of study participants, respectively, and 7.2% of participants were diagnosed with both HIV and cancer. Adjusting for participant characteristics, PWH were 9 percentage points more likely than patients without HIV to rate communication with their healthcare providers positively (p=.007) but 3 percentage points more likely to report greater distrust toward the healthcare system overall (p=.048). Being diagnosed with both HIV and cancer was not associated with patient attitudes about healthcare provider communication or system distrust. Among PWH, patients with a history of cancer were 17 percentage points less likely to report stigma surrounding HIV disclosure concerns (p=.026) compared to patients without a history of cancer; no associations between cancer diagnosis and overall HIV stigma or other HIV stigma subscales were found.

CONCLUSIONS

PWH were found to have a more positive attitude toward healthcare providers while having higher distrust toward the healthcare system as a whole. Our findings can facilitate intervention development to provide more inclusive care for PWH and LGBTQ+ individuals. Our future work will explore PWH identity-based (e.g., Black or Hispanic/Latinx race and ethnicity) facilitators and barriers to patient-provider relationships to assess the effects of patient attitudes on cancer outcomes.

48: Human Papilloma Virus Profiles In Healthy Women, Women With Cervical Intraepithelial Neoplasia, And Women With Invasive Cervical Cancer In Botswana

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BACKGROUND

Botswana has a high prevalence of HPV and HIV that contribute to the high rate of cervical cancer (CaCx). This study characterizes the patterns of HPV subtypes between healthy, unvaccinated university- aged women (Cohort 1), women with CIN II/III (Cohort 2), and women with invasive CaCx (Cohort 3) with and without HIV.

METHODS

Patients were enrolled into the Ipabalele study in Gaborone, Botswana, between 2016 and 2020. Baseline demographic data, clinical treatment characteristics, and HPV cervical swabs were collected. Cohort 1 repeated swabs at 3 time points between baseline and 3-20 months after enrollment. PathoChip was used to determine hybridization signal intensity (HSI), a surrogate for viral burden, and prevalence for HPV subtypes.

RESULTS

This study enrolled 414 participants (Cohort 1: 43, Cohort 2: 212, Cohort 3: 159). Median age was 19, 39, and 46, respectively. All patients were HPV-unvaccinated. Women living with HIV (WLWH) accounted for 0%, 76%, and 72%, respectively. High-risk (HR) HPV prevalence increased across Cohort 1 over time. In Cohorts 2 and 3, at least 1 HR subtype was present in >98% and >88% of samples, respectively. All low- risk (LR) subtypes were represented in at least 88% and 80% of samples in Cohorts 2 and 3, respectively. Cohort 2 had a significantly higher prevalence of HR HPV 18, 26, 34, 53, and 30 LR subtypes when compared to both Cohort 1 and 3. HIV status did not correlate with HR subtype prevalence or HSI. Among the WLWH subgroup, Cohort 2 had a significantly higher prevalence of HPV 18, 26, 34, and 53 when compared to Cohort 3. Among women without HIV, Cohort 2 had a significantly higher prevalence of HPV 26, 34, and 53 when compared to Cohorts 1 and 3. Cohort 1 did not have significantly lower HSI for any HPV subtypes compared to Cohorts 2 and 3. HSI of HPV 26 was the highest among the HR subtypes for Cohort 1. HSI of HPV 16 was the highest among the HR subtypes for both Cohorts 2 and 3. Among WLWH, HSI of all HR and all LR subtypes were not significantly different between cohorts.

Among women without HIV, Cohort 2 had significantly higher HSI of HR subtype HPV 34 and 9 LR subtypes when compared to Cohort 3.

CONCLUSIONS

Women with CIN/invasive CaCx have increased prevalence of high- and low-risk HPV subtypes compared to healthy women. Overall, women with CIN had the highest burden and prevalence of HR and LR HPV subtypes. HR HPV HSI was not associated with HIV status. These findings suggest that after the diagnosis of CIN, further increases in the subtypes of HPV in the cervical microenvironment or HPV viral burden do not impact the progression to cervical cancer. Given that several HR subtypes identified are not covered by available HPV vaccination, it is critical to continue to augment screening efforts for HPV-related cervical malignancies in Botswana.

49: Distress among PWH and Cancer Enrolled in Clinical Trials

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BACKGROUND

Distress is common among patients with cancer and may negatively impact quality of life and survival outcomes. The association between distress and enrollment in a clinical trial, particularly among people with HIV (PWH) has not been studied. We evaluated patient-reported distress using a validated tool among PWH enrolled and not enrolled in Phase I/II interventional cancer clinical trials.

METHODS

We conducted a cross-sectional survey between August 2020 and May 2024 of 58 PWH receiving cancer treatment in the HIV and AIDS Malignancy Branch at the National Cancer Institute. They were screened for distress using the National Comprehensive Cancer Network tool during their first cycle of cancer therapy for either a clinical trial or standard of care (SOC) treatment options. The tool consisted of a pictorial thermometer to represent their level of distress from 0-10 and 5 concern categories (physical, emotional, social, practical, spiritual/religious). Patient and cancer characteristics were analyzed using Fisher's exact test and Wilcoxon-Mann-Whitney test to compare groups. The association between patient-reported distress or concern and clinical trial enrollment status was evaluated using linear regression with distress and concern measures assessed as continuous variables and using logistic regression with clinically relevant distress (score ≥ 4), or at least one concern or more represented as binary variables.

RESULTS

Among the 58 patients with HIV, the median age was 41 years, 97% were male, 52% were Black, 83% had advanced disease, 74% received prior cancer therapy, and 69% had less than 6 months of experience with the oncology team. All but one patient had a virus-associated cancer diagnosis. Thirty-six patients (62%) were enrolled in clinical trials at the time of the distress assessment. The baseline characteristics between patients in the clinical and SOC groups were similar.

The median distress score among patients enrolled in clinical trials (0.5; IQR, 0-3.5) was significantly lower as compared to those receiving SOC (3; IQR, 1-7) (p=.03). However, linear regression models did not identify an association between distress scores and status of clinical trial enrollment (p=.06). Clinically relevant distress (distress score ≥ 4) was evident in 33% (n=19) of all patients. There was a trend towards a lower proportion of patients with clinically relevant distress among patients enrolled in clinical trials (25%) as compared to those receiving SOC (46%), but the difference was not statistically significant (p=.15). There was no statistically significant association between clinically relevant distress and patient enrollment in clinical trials in the logistic regression model (OR, 0.40; 95% CI, 0.13-1.24, p=.11).

Overall, 43 PWH (74%) reported experiencing at least one concern; this included 26 of 36 (72%) who were enrolled in clinical trials, and 17 of 22 (77%) who were receiving SOC treatment. Of the five concerns, patients most frequently reported a physical concern (62%) as a priority prior to cancer therapy, and this was not different by type of treatment received at baseline. The median number of concerns were not different by clinical trial enrollment vs. SOC (1, IQR= 0-3 vs. 2, IQR= 0-3, p=.53). There was no statistically significant association between having at least one or more concerns and enrollment in a clinical trial in the logistic regression analysis (OR, 0.76; 95% CI, .22- 2.63, p=.67).

CONCLUSION

Distress is reported among PWH and cancer and enrollment in clinical trials is not associated with the likelihood of experiencing distress. While the demands of clinical trial participation and involvement in testing an agent with unknown activity and/or toxicity could conceivably contribute to distress, we did not see this in our cohort. It is possible that the clinical trial structure, support and framework may offer mechanisms to address distress among patients with cancer and increase clinical trial enrollment.

50: Micro-Costing of Pulsed Community-Based Integrated Campaigns for HPV Vaccination and Cervical Cancer Screening in East Africa

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BACKGROUND

Resource-limited countries bear the brunt of the world's incidence and mortality from cervical cancer, due, historically, to the lack of cervical cancer screening and, more recently, HPV vaccination. Facilities-based cervical cancer prevention services, the approach used in resource-rich settings, have largely failed to reach the general population of eligible women in resource-limited areas. Even where facilities-based screening has had the most success among women living with HIV, reach is limited by women needing to know their HIV status (and be in care) and many HIV programs are seeking to decentralize care and reduce the need for visits. Therefore, it is increasingly recognized that more omnibus community-based approaches—particularly pulsed campaigns that integrate cervical cancer screening and HPV vaccination—are needed. Yet, community-based approaches could be implemented in various ways, and, ultimately, the most cost-efficient will be the most compelling to funders.

METHODS

In rural and low-density areas of Kenya and Uganda, we recently demonstrated the feasibility of a pulsed multi-component campaign featuring (a) Community Health Worker-led mobilization of residents to attend centrally located Health Fairs; (b) implementation of the Fairs that offer self-collected HPV-based screening for adult

women (irrespective of HIV infection) and catch-up HPV vaccination for girls; (c) notification of HPV test results; and (d) provision of thermoablative therapy at a Mobile Treatment Unit for women found to have HPV. To assess the costs of the activities, we took a health system perspective and developed a micro-costing tool based on review of expense records, staff interviews, and time and motion logs which record the duration of completing different tasks.

RESULTS

We have, to date, undertook observation of and micro-costing related to all activities leading up to and including 6 full-day Health Fairs (Figure) in rural Kenya that provided cervicovaginal HPV- screening to 652 women and HPV vaccines to 267 girls. Costing related to notification of test results and therapy is still ongoing. We interviewed the program leadership to identify personnel, recurrent goods, capital goods, and services. For items not currently

procured by the program, reference price from WHO or UNICEF is used. For items shared across different programs, we discounted the value based on the share of time attributing to this program. Thus far, 1,336 time and motion logs were collected from the Health Fairs, documenting time spent at each step in the process. The program spent a mean of 12 and 27 minutes, respectively, to serve one adolescent girl and one adult woman at the Fair. We plan to report (1) the total implementation cost of the program, (2) total costs per woman served, disaggregated by the four campaign components (mobilization, Health Fair, notification, and Mobile Treatment, and 3) fixed and variant cost to estimate the potential cost of scaling up the program.

Figure. Representative Health Fair in rural Kenya providing HPV vaccines & cervical cancer screening.

CONCLUSION

In East Africa, we have begun to create a micro-costing tool to understand the total and per-component costs needed to provide, in the context of a pulsed campaign, HPV vaccination to each community-dwelling adolescent girl and cervical cancer screening to each adult woman. This tool will subsequently allow estimation of the costs of scaling the program to a region or nation. In addition to formal costing of our distinct formulation of a community-based campaign, we expect that the tool will be a useful foundation for others to cost their permutations on the process, thus allowing formal comparison and ultimately determining the most cost-efficient approach.

51: HIV and Risk of Breast Cancer: A Case-Cohort Study

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BACKGROUND

Breast cancer is the leading cause of cancer-related death among women globally, and the burden is growing among people with HIV (PWH) as the population ages. Analyses using US registries identified a 37% lower risk of breast cancer risk among people with HIV,[1] but PWH were more likely to present with advanced cancer stages[2] raising possibly that differential access to screening and diagnosis could bias risk estimates. We sought to estimate the effect of HIV infection on breast cancer incidence in the context of a generalized HIV epidemic without population breast cancer screening.

METHODS

We conducted a case-cohort study in Botswana involving female citizens aged 20 to 65, born between 1947 and 1998. Adults with breast cancer were prospectively enrolled in a cancer cohort ("Thabatse") from February 2012 to July 2024 at the principal cancer treatment centers in Botswana. The population was sampled in a subcohort drawn from the Ya Tsie trial, which consisted of a random 20% household sample of 30 communities (2013-2015) and a random 80% sample in 6 communities (2017) in Botswana. We estimated the marginal relative risk of breast cancer incidence by HIV status using G-computation of quasibinomial regression models with inverse probability of treatment weights (IPTW), to account for possible associations between HIV status and access to cancer treatment: 5-year age strata, geographic region, time period, parity, education level, and household resources. Secondarily, we examined the effect of ART duration (0-2 years vs. 2+ years) on breast cancer risk relative to people without HIV.

RESULTS

A total of 12,388 participants were enrolled, including 1,027 cancer cases. Of the cancer cases, 39.9% had HIV infection compared to 35.0% of the sub-cohort. The median age of breast cancer diagnosis was 47 years (IQR: 39.5-54.5 years). Following IPTW, baseline characteristics were balanced between groups with a standardized mean difference (SMD) below 0.05 for all included covariates and advanced cancer stage at diagnosis. People with HIV (PWH) had a similar risk of breast cancer compared to HIV-negative individuals (adjusted relative risk (ARR), 1.10, 95% CI 0.98 to 1.23). Additionally, HIV infection was not associated with an increased risk for triple-negative (ARR, 1.02, 95% CI, .72 – 1.46) or HER2-positive cancer (ARR .96, 95% CI, .74-1.26). However, PWH on ART for less than 2 years were at greater risk of breast cancer (ARR, 1.24, 95% CI, 1.01-1.53).

CONCLUSIONS

In a population with a generalized HIV epidemic, women with and without HIV have similar risk of invasive breast cancer.

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52: Barriers and Facilitators to Care for Survivors of Cervical Cancer Living with HIV in Botswana

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BACKGROUND

The number of cancer survivors living with HIV in low- and middle-income (LMIC) is rapidly growing, but most survivorship research has been conducted in developed countries, leaving a critical gap in understanding survivorship practices and needs globally. This is particularly true for cervical cancer, where the vast majority of cases and deaths occur in LMICs. Knowledge about the current state of survivorship care in LMICs is crucial for ensuring optimal support and quality of life for all women. This NCI-funded study (P30CA016520-45s7) aims to fill this lacuna by assessing contextual determinants—such as resource access and care delivery strategies—that influence patient experiences and adherence to survivorship care in Botswana. The long-term goal is to develop and adapt interventions for survivors of cervical cancer with HIV living in Botswana and other LMICs.

METHODS

Between March and June 2023, we conducted a mixed-methods study of women treated for cervical cancer at an oncology clinic in Botswana. Participants completed a semi-structured interview and survey to assess patient characteristics, cancer attitudes and beliefs, cervical cancer stigma, treatment pathways, and barriers and facilitators to survivorship care. Qualitative data were analyzed using a modified grounded theory approach guided by the Consolidated Framework for Implementation Research (CFIR). Survey data were analyzed descriptively and triangulated with qualitative findings.

RESULTS

Thirty-two patients enrolled in the study, with median age 52 years. Among the participants, 60% were living with HIV and 33% had advanced disease (stage III or IV). Half of participants (54%) had completed secondary school or higher. At the time of the interview, 37% of women had completed treatment less than one year prior, 23% between 1 and 3 years prior, and 40% more than 3 years prior.

In surveys, participants reported financial burden as a primary barrier to care adherence, with 26% describing it as significant and 23% as catastrophic. Bus was the primary mode of transport for 81% of the sample and patients noted that transport cost and travel time were barriers made worse by treatment side effects. Overall, experiences of cervical cancer stigma were low, with the most common issues being job loss (15.6%), relationship breakdown (12.5%), and familial rejection (9.4%). Only two participants reported high levels of stigma, including losing friends and becoming socially isolated. While beliefs about cancer and treatment were predominantly positive, 36% reported fear of dying and 22% reported, at some point, having lost hope in fighting their illness. Finally, in interviews, several patients reported not having enough information or understanding about the importance of survivorship care.

Patients identified several facilitators of adherence, including support from government, family, community, and their care team. All participants had treatment covered by the state and 44% had requested a governmental transport allowance. Overall, social support was high, with patients relying on their families and friends to overcome barriers to adherence. A significant majority reported having someone accompany them to the hospital (97%), assist in discussions with doctors (100%), help with housework (94%), and share their feelings (97%). In interviews, patients described the importance of the care team in helping them understand the importance of survivorship care, alleviating fear and anxiety, and providing emotional support. Patients also recognized telehealth visits as a valuable tool to save time and resources while facilitating ongoing contact and support from their care team.

CONCLUSIONS

Achieving optimal adherence to survivorship care is challenging, but support from external support such as family, friends, and governmental resources can help patients overcome barriers. Developing effective strategies (e.g., telehealth) to increase the reach of care and reduce patient burden is critical to ensuring high-quality care for cervical cancer survivors living with HIV across LMICs.

53: Feasibility of Topical Artesunate for Cervical Precancer Treatment among Women Living with HIV in Kenya: Preliminary Results from a Phase I Trial

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BACKGROUND

Women living with HIV (WLWH), a majority of whom reside in low- and middle-income settings (LMICs), face the highest risk of cervical cancer. In LMICs, access to provider-administered precancer treatment is severely limited due to a shortage of trained healthcare providers and inadequate health infrastructure. An effective and accessible self-administered precancer treatment could be transformative for secondary prevention of cervical cancer in LMICs, particularly for WLWH. Recent Phase I studies in high-income settings have shown promising safety and early efficacy of topical artesunate in treating HPV-associated anogenital lesions, primarily in HIV-negative individuals. We are conducting a Phase I trial to evaluate the feasibility of self-administered intravaginal artesunate for treatment of biopsy-confirmed high-grade precancer among HIV-positive and negative women in Kenya (ClinicalTrials.gov ID NCT06165614).

METHODS

Eighteen HIV-negative and HIV-positive women with biopsy-confirmed cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) with a visible lesion will self-administer a 5-day course of 200 mg artesunate vaginal inserts on weeks 1, 3, 5, and 7. The primary objective is safety, assessed using a standardized grading scale. Secondary outcomes are adherence, change in lesion size, histologic regression to CIN1 or less, and acceptability. Interim colposcopy will be performed at week 8, and clinical regression will be evaluated at week 14 with colposcopy and biopsy. Participants with persistent CIN2/3 at week 14 will have excision, and those with regression to CIN1 or less will be followed closely for two years. Correlative outcomes will include type-specific HPV clearance and the impact of the cervicovaginal microbiome on treatment response. The trial opened to accrual in March 2024.

RESULTS

Fourteen eligible participants are enrolled in the trial so far, with a mean age of 41 years. Thirteen, 92.9%, participants are HIV-positive, all of whom are on antiretroviral therapy, with a mean CD4 count of 599.5 cells/mm^3. Most participants, 58%, were married, and 73% had some secondary education as the highest level of education attained, with no participant having a college education. All 14 reported at least one grade 1 adverse event (AE) from artesunate use, with vaginal discharge and pruritis being the most common AEs. No grade 2 or worse AEs have been reported. Excellent adherence has been demonstrated so far, using self-report and return of pessary covers. Of seven participants who have had a week 14 visit thus far, five (71.4%) had persistent CIN2/3 and had loop excision, while two had regression to CIN1 or less and are undergoing observation. Study visits are ongoing, and samples have been stored for correlative studies, including HPV genotyping and characterization of the microbiome.

CONCLUSIONS

Topical artesunate is a generic and accessible treatment in LMICs, where the burden of cervical cancer is greatest. Early studies in the United States have indicated its potential efficacy for HPV-related anogenital lesions, including cervical precancer. However, in our ongoing Phase I study of topical artesunate for treating CIN2/3 in WLWH in Kenya, preliminary findings suggest lower response rates compared to those observed in HIV-negative women. Further analyses are planned to investigate the influence of HPV genotype, the presence of single versus multiple HPV infections, the microbiome, and the cervical immune activation on treatment response.

54: Multiple Myeloma among People Living with HIV in South Africa – 2004 to 2021

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BACKGROUND

The role of HIV infection on the incidence of Multiple Myeloma (MM) has not been fully established due to inconsistent data[1]. With the introduction of ART in South Africa (SA) in 2004, eligibility criteria for initiation have evolved from CD4 count <200 cells/µl to CD4 count <350 cells/µl to universal test and treat. We aimed to describe MM epidemiology in the context of HIV in SA.

METHODS

We conducted a cohort study of histologically diagnosed MM cases from 2004 to 2021 in the SA HIV Cancer Match (SAM) study. This nationwide cohort comprises linked HIV-related laboratory records (HIV tests, CD4 counts, viral load) from the National Health Laboratory Services and cancer diagnoses from the National Cancer Registry. Cancers were classified using the International Classification of Diseases for Oncology, third edition (ICD-O-3). Cox regression, Age-standardized incidence rate (ASIR) using Segi world standard population, midyear population estimates from Statistics SA and the annual percentage change (APC) using Joinpoint regression were estimated.

RESULTS

Of the 9,891,285 PLHIV who contributed 57,079,459 person years, there were 321 MM incident cases who had a median observation time of 2.91 (Interquartile Range [IQR] 0.6-7.3) person years. Their median age was 52 years (IQR: 45-59). The median baseline CD4 count was 277 (IQR: 169-446). Males were more likely than females to be diagnosed with MM (Adjusted Hazard ratio [aHR] =1.8; CI: 1.4 – 2.2). There was an initial decline in MM incidence from the mid-2000s (APC=-24.7; CI: -41.1 to -11.6 in males and APC=-12.6; CI: -33.1 to -2.4 in females) and from about 2013, there has been a steady rise in the incidence (Males-APC=11.5; CI: 5.3 to 22.7; Females-APC=11.3; CI: 4.4 to 28.1) (Figure 1).

CONCLUSION

There was no association between baseline CD4 count and risk of MM. The SA ART program has not decreased MM risk.

Key words: myeloma, HIV, antiretrovirals, CD4 count

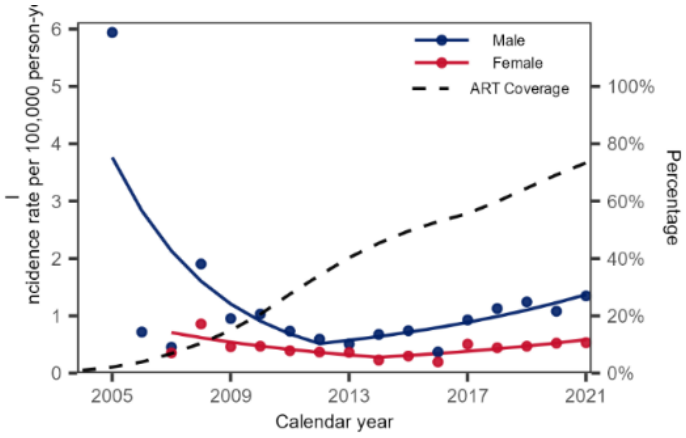

Figure 1: Trends in Multiple Myeloma by Gender and through the ART Roll-Out

55: Factors Associated with Diagnostic Delays in Lung Cancer in East Africa: The Role of Symptoms and Passive Smoking

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BACKGROUND:
Lung cancer remains the leading cause of cancer-related deaths worldwide, with 1.8 million fatalities annually. In sub-Saharan Africa, the incidence and mortality rates are significantly high. Screening often relies on symptom presentation and diagnostic imaging, yet many symptoms are nonspecific, leading to potential misdiagnoses and delays. This study aims to identify factors contributing to delayed lung cancer diagnosis in Uganda and Tanzania.

METHODS
Adults (≥18 years) with biopsy-confirmed lung cancer were enrolled from cancer clinics in Uganda and Tanzania. Sociodemographic, clinical, diagnostic, and treatment data were collected. Logistic regression analyzed factors associated with diagnostic delays stratified by HIV status.

RESULTS
From 2022, 528 potential lung cancer cases were screened; 227 (43.0%) were confirmed. The median age was 59 years (IQR: 49-68), with a majority of females (55.0%) and (7.9%) infected with HIV-1. Out of the 18 HIV-1 infected individuals, only two had detectable viral loads. Current and passive smokers comprised 26.4% and 18.5% of the cohort, respectively. Adenocarcinoma was the most common type (50.2%), with advanced-stage presentation (III and IV) in 89.3% of cases. Diagnostic delay, defined as seeking care after 90 days from symptom onset, occurred in 30% (95% CI: 25.1%-37.2%). Significant factors included cough (OR=3.7, 95% CI: 1.23-11.41, P=0.020), hemoptysis (OR=1.5, 95% CI: 1.03-2.10, P=0.034), household smoking (OR=1.5, 95% CI: 1.03-2.25, P=0.036), and history of chest radiation (OR=1.9, 95% CI: 1.33-2.70, P<0.001). HIV status and socio-demographic characteristics were not statistically significant.

CONCLUSION
A significant proportion of lung cancer patients experienced diagnostic delays, influenced by specific symptoms and passive smoking. Enhancing public awareness about key symptoms and the risks of passive smoking is crucial. Future interventions should focus on public health education and training for early symptom recognition among healthcare providers.

56: Population-level HPV Vaccination Coverage Estimates Among Adolescent Girls in Kenya and Uganda Using Community Health Workers and Household Surveys

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BACKGROUND

HPV vaccination represents the ultimate primary prevention tool for HPV-related cancer, and this is especially true for adolescent girls in resource-limited settings who later acquire HIV infection. Given the importance of HPV vaccination, it is axiomatic that public health leadership understand local HPV vaccine coverage. However, current understanding of the extent of vaccination in resource-limited settings largely comes from administrative data collected during routine public health practice. Such vaccination coverage estimates have been widely criticized for problems in numerators, denominators, and non-reproducible interpretation. In short, many countries have scant knowledge of their vaccination progress. We hypothesized that an existing resource—the network of Community Health Workers (CHWs, aka Village Health Team members) that exists in most countries—could be leveraged to derive low-cost, accurate, and interpretable estimates of HPV vaccination coverage.

METHODS

As part of an evaluation of the penetrance of recent community-based health campaigns in rural/peri-urban Kenya and Uganda, we randomly selected 25% of the households that we encountered within the borders of two participating communities. At each household approached, local CHWs introduced the purpose of the visit (Figure), which included surveying parents/guardians of residing girls ages 10 to 14 years old about the girls' HPV vaccination status.

RESULTS

We approached 628 households, of which 262 (42%) had age-eligible girls. Almost all (99%) approached parent/guardians were willing to respond. HPV vaccination status was ascertained for

330 girls (Kenya=237, Uganda=93; Table). Overall, by age 14 years, 74% (95% CI: 64-83%) of girls had received at least one HPV vaccine dose (Kenya=75%, Uganda=73%), while two-dose HPV vaccine coverage was 49% (95% CI: 39-59%) (Kenya=52%; Uganda=42%).

CONCLUSION

In rural/peri-urban communities in Kenya and Uganda, household surveys utilizing local CHWs are a feasible and low-cost approach to estimate accurate population-level HPV vaccination coverage. Importantly, this approach estimates "coverage by age 14 (or 15)", which is a more interpretable and standardized metric across countries. In our demonstration communities, vaccination coverage remains below WHO target, indicating need for more innovation to close the gap.

Figure. Parent/guardian being interviewed at a community residence about HPV vaccination status of all residing girls ages 10 to 14 years.

Table. Distribution of HPV vaccine doses received among girls according to age in Kenya (KE) & Uganda (UG).

	10 years		11 years		12 years		13 years		14 years		Unknown but within 10 to 14 yrs	Overall	
No. of HPV doses	KE (n=30)	UG (n=16)	KE (n=32)	UG (n=13)	KE (n=58)	UG (n=19)	KE (n=46)	UG (n=17)	KE (n=71)	UG (n=26)	UG (n=2)	KE (n=237)	UG (n=93)
None	12 (40%)	4 (25%)	6 (19%)	6 (46%)	14 (24%)	6 (32%)	7 (15%)	3 (18%)	15 (21%)	5 (19%)	1 (50%)	54 (23%)	25 (27%)
1	7 (23%)	8 (50%)	12 (38%)	5 (38%)	18 (31%)	3 (16%)	9 (20%)	5 (29%)	16 (23%)	8 (31%)	0	62 (26%)	29 (31%)
2	9 (30%)	3 (19%)	13 (41%)	2 (15%)	24 (41%)	8 (42%)	29 (63%)	8 (47%)	37 (52%)	11 (42%)	1 (50%)	112 (47%)	33 (35%)
Not sure	2 (6.7%)	1 (6.0%)	1 (3.1%)	0	2 (3.5%)	2 (11%)	1 (2.2%)	1 (5.7%)	3 (4.2%)	2 (7.7%)	0	9 (3.8%)	6 (6.5%)

57: Health-Care Seeking Patterns of Hepatocellular Carcinoma (HCC) Patients and Time to Diagnosis and Death

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BACKGROUND
Hepatocellular carcinoma (HCC) patients are often diagnosed with advanced-stage disease. We aimed to identify healthcare-seeking patterns, assess correlates of earlier diagnosis, and determine the impact of diagnostic delay on mortality among HCC patients in Uganda.

METHODS
Cross-sectional study, enrolled (March 2015 to August 2020), HCC patients in three Ugandan tertiary care hospitals. HCC diagnosis time was the duration between onset of the first reported pertinent symptom(s) and ultrasound-based HCC diagnosis dates. Incidence ratios (IR) from negative binomial models identified correlates of time to HCC diagnosis. Kaplan-Meier survival curves assessed time to death by diagnosis time status.

RESULTS
Of 651 HCC patients, 442 (67.9%) were male with median age of 43 years (IQR 32-56 years). Almost all patients sought health care for HCC related symptoms prior to study enrolment (248 [38.1%] once, 388 ([59.6%], two or more times. Prior encounters reported included public health facilities (442, 69.4%), private facilities (493, 77.5%) and traditional health providers (140, 22%); 45 patients (6.9%) reported visiting all three types at least once. Female patients (60.3%) reported multiple visits to facilities and had a longer time to diagnosis (p 0.001). 442 (68%) patients had an ultrasound scan-based HCC diagnosis before study enrolment. Median time from reported symptom onset to ultrasound-based HCC diagnosis was 90 days (IQR 58-173 days). Factors independently associated with duration of HCC diagnosis include: age older than 50 years (IRR 1.28;95% CI 1.00-1.64), alcohol use (IRR 1.22; 95%CI 1.03-1.44), chronic hepatitis B (IRR 0.80; 95%CI 0.67-0.96), and HIV infection (IRR 0.64; 95%CI 0.51-0.80). There was no difference in disease prognosis according to diagnosis time.

CONCLUSIONS
Improving early diagnosis of HCC is crucial for better outcomes. Public health strategies should enhance surveillance of high-risk patients and promote better healthcare-seeking behaviour. Standardized diagnostics and treatment practices are necessary to optimize the existing pluralistic healthcare system.

58: Association Between HIV Status and Demographic Characteristics of Patients with Anogenital-Associated Cancers at Jaramogi Oginga Odinga Teaching and Referral Hospital

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BACKGROUND
Anogenital cancers, including anal, penile, vaginal, and vulvar, occur 2 to 5 times more frequently among people with HIV compared to the general population, primarily due to shared risk factors and the immunosuppressive effects of HIV. This study aims to investigate the association between HIV status and the demographic characteristics of patients diagnosed with anogenital cancers.

METHODS
This retrospective cohort study included all patients diagnosed with anogenital-associated cancers (anal, penile, vaginal, vulvar) and receiving care at the Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) between January 2014 and December 2023. Demographic and HIV data were extracted from patient records. Descriptive analyses were conducted to examine the socio-demographic characteristics of participants and the presence of comorbidities such as HIV. A generalized linear model with a Poisson distribution was employed to analyze factors associated with patient mortality.

RESULTS
Out of 3,456 patients at JOOTRH's oncology clinic, 139 (4.0%) were identified with anogenital-associated cancers. The majority were female (54.0%) and married (75.5%), with 61.9% having more than one comorbidity (HIV/diabetes/hypertension/other), and 60.4% were people with HIV. Additionally, 7.9% were current or former smokers, while 9.3% had a history of alcohol use. The most common types of anogenital cancer were penile cancer (41.7%), followed by vulvar cancer (31.3%), anal cancer (19.4%), and vaginal cancer (3.6%). The mean age at diagnosis was 49 years. A significant proportion of patients (70.5%) were lost to follow-up, 3.5% were alive and active in care, 13.0% had transferred out, and 13.0% were deceased. Smoking history was associated with a significantly higher risk of mortality (relative risk = 4.302, p = 0.017).

CONCLUSION
HIV prevalence was high among patients with anogenital cancers at JOOTRH, with penile cancer being the most common type among these cases. This highlights the need to promote early detection efforts in this population.

59: Survival and Predictors of Mortality among Patients with Virus-Associated Cancers in a High HIV-Prevalence Region in Kenya: A 10-Year Retrospective Study

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BACKGROUND

Virus-associated cancers significantly contribute to cancer-associated mortality in Africa. Understanding risk factors for mortality in patients with these cancers is crucial for effective prevention and treatment strategies. We aimed to conduct the first comprehensive analysis of the demographic and clinical characteristics of people with virus-associated cancers in Kisumu County, western Kenya—a region with a high HIV prevalence of 14.5%—and evaluate factors associated with mortality.

METHODS

We conducted a retrospective cohort study of all adult patients who presented for cancer care at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) in western Kenya between January 2014 and December 2023. We included all cases where viral infection is causally associated to cancer (cervical, anal, Kaposi sarcoma) and all cases where persistent viral infection is the strongest risk factor for cancer (penile, vaginal, vulvar). We extracted data from paper-based patient records. We used the Kaplan-Meier method to estimate survival rates and competing risk regression to determine the association between baseline characteristics and mortality, with loss to follow-up (LTFU, defined as >6 months late for the last appointment) and transfer-out considered as competing events.

RESULTS

Among 3,437 patients, 1,073 (31%) met eligibility criteria. Median age at diagnosis was 47 years (inter-quartile range 39-59), with 933 (87%) being female, and 553 (51.5%) people with HIV. Cervical cancer was the most prevalent (n=823, 76.7%), followed by Kaposi sarcoma (n=112, 10.4%), penile (n=57, 5.3%), vulva (n=48, 4.5%), anal (n=28, 2.6%), and vaginal (n=5, 0.5%). One year after enrolling in cancer care, 538 (62%) were lost to follow-up. Median overall survival was 6% (95% CI: 5%-7%). In multivariable analyses, age <20 years and advanced stage at diagnosis (stage III and IV) were associated with increased risk of death. HIV status was not significantly associated with mortality (subhazard ratio 1.29, 95% CI: 0.83-2.01; p=0.3)

CONCLUSION

Virus-associated cancers are highly prevalent in western Kenya, with high rates of loss to follow-up and low overall survival among these patients. Older age and early-stage diagnosis were associated with a lower risk of death. Notably, HIV status did not significantly affect mortality. Urgent strategies are needed to encourage early cancer detection and referral to treatment, improve patient retention in care, and develop interventions to reduce mortality risk among young patients. To better characterize all virus-associated cancers, future research should consider testing for viral infections or the presence of viral genomes within tumor cells to attribute carcinogenicity for cancer types excluded in this analysis, such as nasopharyngeal carcinoma (Epstein-Barr virus), other head and neck cancers (human papillomavirus), gastric cancer (Epstein-Barr virus), Burkitt lymphoma (Epstein-Barr virus), diffuse large B-cell lymphoma (Epstein-Barr virus), Hodgkin lymphoma (Epstein-Barr virus), and hepatocellular and intrahepatic bile duct cancers (hepatitis B and C viruses).

60: Integration and Availability of Cancer Screening across HIV Treatment Sites in the IeDEA Consortium

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BACKGROUND

Cancer remains a leading cause of morbidity and mortality in people with HIV (PWH). The importance of cancer screening, diagnosis, and prevention is increasing as this population ages. We aimed to describe current cancer screening practices as well as cervical and anal cancer screening trends over time at HIV care sites internationally.

METHODS

In 2017, 2020, and 2023, standardized cross-sectional surveys were conducted at HIV care sites within the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium. We described the reported availability and barriers to cervical, anal, breast, liver, colon, lung, and prostate cancer screening in 2023. We assessed the change in availability on site of cervical cancer screening by cytology or visual inspection and anal cancer screening by cytology between 2017 and 2023. We used generalized estimating equations with a logit link function to account for site clustering, rurality, and country income based on the World Bank classification.

RESULTS

The 2023 survey included 220 sites providing care for adult PWH with 75% of sites from low- and middle-income countries. Overall, 88% (194/220) of sites reported cervical cancer screening by visual inspection, cytology, or HPV testing on site. HPV testing was available at 45% (98/220) of sites. At sites serving predominantly rural populations, 9% (4/47) had HPV testing, and 62% (29/47) exclusively performed screening by visual inspection. Overall, 45% (100/220) of sites offered routine screening for anal cancer in 2023. Anal cytology was available on site at 23% (50/220) of all sites, at 4% (2/47) of sites serving rural populations, and at 2% (1/55) of sites in low-income countries. Almost all (45/50) sites with anal cytology on site had access to follow-up high-resolution anoscopy either on site or by referral. Breast cancer screening by physical exam was performed at 81% (179/220) of sites. Screening for cancer of the liver, colon, lung, prostate, or breast (by imaging) were each available at less than 43% of sites. Lack of trained staff was the most frequently reported barrier to cancer screening, followed by lack of equipment. After adjusting for country income and rurality, the odds of cervical cancer screening availability multiplicatively increased by 16% annually from 2017 through 2023 (OR=1.16, 95% CI: 1.07-1.27), while the relative odds of anal cancer screening availability decreased by 9% annually between these periods (OR=0.91, 95% CI: 0.84-0.99).

CONCLUSIONS

Cervical cancer screening has increased over time and is reported to be widely available to PWH at IeDEA sites. However, there is less availability of screening for other cancers. Understanding of current practices and capacity is essential to the continued integration of cancer screening in HIV care.

61: Anal Cancer Incidence among Privately Insured People with and without HIV in South Africa

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BACKGROUND

People with HIV (PWH) have a higher incidence of anal cancer than the general population. Although most PWH live in sub-Saharan Africa, data about the association between HIV and anal cancer in this region are scarce. We examined anal cancer incidence rates among privately insured people with and without HIV in South Africa.

METHODS

We did a retrospective cohort study using reimbursement claims data from a South African medical insurance scheme (01/2011-07/2020) to assess anal cancer rates among people with and without HIV aged ≥18 years. We defined anal cancer diagnoses as ≥2 claims with ICD-10 codes for anal cancer (C21). Using flexible parametric survival models, we estimated adjusted hazard ratios (aHRs) for the association between HIV and incident anal cancer. The multivariable model included sex, HIV status, age, population group, calendar year, history of genital warts, and history of other sexually transmitted infection (STIs). Among women, we also estimated aHRs for the association between past cervical pre-cancer and an incident anal cancer diagnosis.

RESULTS

We included 1,068,915 people of whom 557,717 were women (52%) and 69,985 (7%) were living with HIV. The median age at the start of time-at-risk was 39.7 years (interquartile range [IQR] 33.4-47.3) in PWH and 36.3 years (IQR 26.1-49.9) in people without HIV. During 3,933,145 person- years, 122 incident anal cancers were diagnosed for a crude incidence rate of 3.1 per 100,000 person-years (95% confidence intervals [CI] 2.6-3.7). PWH had a four-fold higher risk of an incident anal cancer diagnosis than people without HIV (aHR 4.43; 95% CI 2.44-8.04). Anal cancer rates increased with older age, being highest among those aged 65 years and above compared with individuals aged 45-54 years (aHR 5.01; 95% CI: 2.94-8.53), and they did not differ by sex (female vs. male: aHR 0.97; 95% CI: 0.68- 1.38). While a history of genital warts was associated with a substantially higher risk of an incident of anal cancer diagnosis (aHR 7.56; 95% CI: 2.28-25.07), we did not find a clear association between a history of other STIs and the risk of developing anal cancer (aHR 1.46; 95% 0.44-4.80). Among women, a prior diagnosis of cervical pre-cancer was associated with an almost six-fold increased risk of developing anal cancer (aHR 5.70; 95% CI 1.75-18.58).

CONCLUSIONS

We found that PWH in South Africa had considerably higher anal cancer rates than people without HIV. Older individuals, people with a history of genital warts, and women with a prior diagnosis of cervical pre-cancer were also at increased risk of developing anal cancer. These population groups may benefit from prioritized access to anal cancer screening and treatment of pre-cancerous lesions.

62: Incidence of AIDS-Defining Illness by Cancer Status in an Observational Study among Medicaid Beneficiaries Living with HIV in the United States, 2001–2015

Authors: *Yiyi Zhou[1], Bryan Lau[1,2], Jacqueline E. Rudolph[1], Xueer Zhang[1], Xiaoqiang Xu[2], Karine Yenokyan[1], Eryka L. Wentz[1], Keri L. Calkins[1,3], Corinne E. Joshu[1]*

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BACKGROUND

In the modern era of antiretroviral therapy (ART), the burden of cancers not traditionally associated with AIDS among people with HIV (PWH) is increasing, and malignant neoplasms remain one of the leading causes of death among PWH. In addition to the possibility that a cancer diagnosis could be disruptive to routine HIV care, prior research suggests that certain cancer treatments may have a deleterious effect on the immune system. However, to our knowledge, the relationship between a cancer diagnosis and incidence of an AIDS-defining illness (ADI) has not previously been examined. Thus, we sought to quantify the association between non-AIDS defining cancers (NADCs) and the development of a new ADI among Medicaid beneficiaries living with HIV in the United States (US).

METHODS

We used enrollment, inpatient, outpatient, and prescription claims Medicaid data for beneficiaries aged 18–64 who enrolled between 2001 and 2015 in 14 US states. We subset our analysis to individuals who had evidence of HIV, no evidence of a prevalent ADI, and no evidence of cancer at baseline (defined as 6 months following the start of their Medicaid enrollment). We then followed beneficiaries from baseline until incidence of a new ADI, disenrollment from Medicaid, death, or administrative censoring at age 65 or in 2015, whichever came first. At-risk person-time was allocated based on whether the time was accrued before or after an NADC diagnosis. We then estimated crude incidence rates of first ADI and adjusted incidence rate ratios (IRR) comparing rates by NADC status, estimated using Poisson regression and controlling for sex, race/ethnicity, state of residence, age at baseline, and calendar year at baseline. We examined all NADCs combined, as well as lung, colon, breast, and prostate cancers separately. We ran analyses overall and stratified by calendar period and a time-updated indicator of whether the beneficiary had initiated ART.

RESULTS

154,493 Medicaid beneficiaries with HIV contributed 409,157 person-years of follow-up, 3,843 incident NADCs, and 28,875 incident ADIs. We estimated crude incidence rates of 7.06 ADIs per 100 person-years (95% confidence interval (CI): 6.98, 7.14) overall, 6.9 ADIs per 100 person-years (95% CI: 6.82, 6.98) among those without an NADC, and 15.52 ADIs per 100 person-years (95% CI: 14.66, 16.43) following an NADC diagnosis. The adjusted IRR comparing rate of first ADI after NADC diagnosis to before NADC diagnosis was elevated for all NADCs (2.82, 95% CI: 2.63, 3.02) and all specific cancers examined. While the overall rate of ADIs decreased across calendar time, the rate of ADI following an NADC diagnosis remained consistently elevated in all calendar periods (IRR: 2.69 (95% CI: 2.39, 3.02) in 2001-2005; 3.02 (95% CI: 2.71, 3.36) in 2006-2010; 2.83 (95% CI: 2.53, 3.17) in 2011-2015). The IRR was stronger in beneficiaries within 6 months of ART initiation, relative both to those who had not yet initiated ART and those who had been on ART longer than 6 months, for NADCs overall and lung cancer.

CONCLUSIONS

Incidence of new ADIs was elevated following a cancer diagnosis among adult Medicaid beneficiaries living with HIV. PWH with cancer and undergoing cancer treatment may require careful observation for ADI development and potentially warrant consideration of immune sparing cancer treatment regimes.

63: Establishing a Rapid Autopsy Program for HIV/AIDS-Associated Malignancies: Enhancing the AIDS and Cancer Specimen Resource (ACSR)

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BACKGROUND

Autopsies have historically provided insights into disease progression and pathology, but traditional methods may not reliably capture the dynamic and multifaceted nature of HIV and HIV-related malignancies. Rapid autopsy programs (RAP), designed to collect high-quality tissue and body fluid samples shortly after death (usually within six hours of passing), offer a powerful tool to overcome these limitations. The AIDS and Cancer Specimen Resource (ACSR) is establishing a Rapid Autopsy Program (RAP) at the University of São Paulo (USP) in Brazil. The proposed RAP aims at collecting and preserving, within 6 hours of death, high-quality postmortem samples to address a critical need in HIV and HIV-malignancy research: i.e., preserving cellular and molecular integrity by minimizing the postmortem degradation (e.g., autolysis) that may impact subsequent downstream applications. This project will facilitate the acquisition, storage, and distribution of unique biospecimens from individuals who consent to tissue and body fluid donations at the time of death.

METHODS

The RAP will be implemented at the Autopsy Service affiliated with USP within the Hospital das Clínicas Complex. The service conducts around 500 autopsies annually and an additional 1,400 cases are referred from other hospitals across the São Paulo metropolitan area. The substantial autopsy volume provides an opportunity to enroll participants from diverse racial and ethnic backgrounds and collect a wide array of biospecimens. The Cancer Institute (ICESP) will serve as the primary source for these samples, ensuring a steady and reliable flow of cases. The biorepository will monitor the ICESP healthcare information system (TASY) to identify potential participants. The infectious diseases team will flag cases entering into the intensive care unit where a biorepository assistant physician/nurse will apply the autopsy consent. The RAP team will be notified about the death and body availability for sample collection, and the rapid autopsy team will be mobilized and prepared for sample collection. The study will focus on collecting tissues and fluids, including but not limited to spleen, cavitary lymph nodes, ileum, heart, kidney, liver, lung, bone marrow, tumor sites, blood, and cerebrospinal fluid samples. For each tissue type, a total of 10 aliquots will be collected, fixed, and stabilized, following three conditions: (i) 1 cm^3 in formalin solution; (ii) 0.25 x 1 cm in RNAlater; (iii) 1 cm^3 flash-frozen in LN_2. For tumor samples, specimens will be collected from primary and metastatic sites, as well as from control sites. Storage will be performed at ambient temperature (18-25ºC), -80ºC after overnight fixation at 2-8ºC, and at -180ºC, respectively.

RESULTS

In total, at least 300 aliquots will be collected per rapid autopsy. To ensure the successful implementation of the RAP, the ACSR is collaborating closely with investigators from the University of California San Diego's Last Gift Study, a pioneering program in prospective autopsy tissue collection. The implementation of this RAP will significantly enhance the ACSR's mission to support HIV-related cancer research.

CONCLUSIONS

The RAP will offer a unique collection of biospecimens from a racially and ethnically diverse population, including HIV-1 subtypes B and F which will be critical for identifying viral reservoirs across the human body and advancing the science of HIV/AIDS-associated malignancies through a rare opportunity to access and study critical tissues that would otherwise be inaccessible via routine clinical biopsies.

64: HPV Viral Load as a Predictive Marker for Pre-invasive and Invasive Cervical Cancer: A Literature Review

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BACKGROUND

Cervical cancer is the fourth leading cause of cancer and cancer-related mortality in women worldwide[1]. Persistent infection of human papillomavirus (HPV) is strongly associated with cervical intraepithelial neoplasia, which, without early management and treatment can progress to invasive cervical cancer[2]. Characteristics of HPV infection, such as the quantity of viral genetic material present, also known as viral load (VL), may be predictive of cervical lesion development, disease severity, and treatment response. Many studies have shown varying correlations between high-risk HPV subtypes, their viral load content, and the grade of intra-epithelial lesions. We aimed to summarize data on the association of HPV viral load and association with pre-invasive and invasive cervical cancer and its outcomes.

METHODS

On June 2, 2021, we conducted a review of electronic databases, including PubMed, Ovid, and Embase, using specific key phrases to extract relevant titles. We then screened the abstracts and subsequently the full texts pertinent to HPV viral load and pre-invasive and invasive cancer. Studies not in English, non-primary literature, or published before 1994 were excluded. Data was collected and analyzed on literature available on pre-invasion and invasive cervical cancer and its association with HPV viral load.

RESULTS

Of the 41 articles published between years 1994–2022 included in the final study, most were conducted in Asia and 23 focused on pre-invasive cervical cancer, 11 focused on invasive cervical cancer, and 7 included both. The studies reported the association between HPV viral load and development of pre-invasive cervical cancer (n= 30) or invasive cervical cancer (n= 18), disease recurrence (n= 5), disease progression (n=7) or survival outcomes (n=6). Additionally, many of the studies commented on the value of HPV viral load as a prognostic marker (n=31) and that patients with higher HPV viral load had better response with radiotherapy (5%). Eight out of 11 invasive cervical cancer studies, eighteen out of 21 pre-invasive cervical cancer studies, and six out of 7 studies that included both pre-invasive and invasive cervical cancer stated that HPV viral load can be used as a prognostic biomarker in the setting of cervical cancer. Across the literature, there was much heterogeneity in measurement technique, such as measuring through serum biobanking, HPV 16 antibodies, biopsies, and hybrid capture assays, as well as in reporting units of viral load, such as copies/mL, copies/scrape, copies/cell, relative light units/positive cut off and relative light units/ cut off. Among the pre-invasive studies using a common unit (log 10 of viral load), avg viral load in CIN 2/3 group was 4.22 vs CIN 1 was 3.36. Among invasive studies using a common unit (RLU/CO), average viral load for cancer patients was 575.14 . For the studies in the pre-invasive group, CIN 2/3 had higher reported viral loads than CIN 1, HSIL had higher reported viral loads than LSIL, and HPV strain 16 had the highest viral load, followed by HPV strain 18. For the studies in the invasive group, HPV strains 16 and 18 had the highest viral load and were associated with invasive SCC. Additionally, SCC had higher HPV viral load counts than CIN 1/2/3. Of note, higher viral load titers were associated with increased lymphovascular invasion and deep stromal invasion when compared to patients with lower viral load titers.

CONCLUSION

Data suggests that higher HPV viral load is associated with oncogenic disease, superior response to radiation therapy, and better prognosis. These results suggest establishing an HPV viral load threshold to identify patients at higher risk of developing cervical lesions. This threshold would facilitate increased surveillance and prompt referral for radiotherapy upon disease progression.

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65: Prostate Cancer Treatment and Outcomes for Veterans with HIV in the Antiretroviral Era

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BACKGROUND

Prostate cancer is the leading cancer diagnosis among veterans with HIV. There has been limited national data on prostate cancer outcomes for people with HIV (PWH) despite the substantial burden. Therefore, we studied prostate cancer characteristics, treatment patterns, and survival by HIV status in the Veterans Aging Cohort Study (VACS)-HIV, a national cohort of Veterans with HIV and demographically similar Veterans without HIV infection.

METHODS

In VACS-HIV (2001-2018) we identified a cohort of men with prostate cancer, 791 were previously diagnosed with HIV and 2,778 were not. We compared patient demographics, HIV disease characteristics, comorbid disease burden, and prostate cancer clinical characteristics by HIV status. Using linked registry data, we identified treatments (surgery, radiotherapy and/or hormonal therapies), comparing the use of these modalities by HIV status, adjusting for age, prostate cancer risk group, and comorbid burden. We then compared D'Amico prostate cancer risk group distribution and prostate cancer-specific and overall survival by HIV status, stratified by risk group using age adjusted Cox regression models.

RESULTS

VACS-HIV patients with prostate cancer had a median age of 62 years, which did not differ by HIV status. Race/ethnicity proportions were also similar, with non-Hispanic Blacks being the most common group diagnosed with prostate cancer. Comorbid burden, measured by modified Charlson comorbidity index, was not different by HIV status for prostate cancer patients (p=0.52). HIV infection was associated with higher prostate specific antigen (median 6.8 vs. 6.3; p=0.005) but no difference in Gleason grade. PWH were more likely to be diagnosed with D'Amico intermediate/high risk localized prostate cancer (p= 0.02) and advanced prostate cancer (either nodal involvement or metastatic disease) than PWoH (p=0.04). PWH were less likely to be treated with surgery even after adjustment for age, D'amico risk, and comorbid burden (p<0.001). There were no differences in the use of radiotherapy or hormonal therapies by HIV status in unadjusted or adjusted analyses. HIV was significantly associated with worse all-cause mortality for intermediate-, high-risk localized, and advanced cancers adjusting for age and comorbid burden. PWH did not have higher age adjusted prostate-cancer specific mortality in any cancer risk group compared to PWoH.

CONCLUSIONS

PWH were diagnosed with higher risk prostate cancers more frequently than those without HIV and were less likely to receive surgical therapy. Higher non-cancer mortality seen in those with HIV infection may impact the benefits of aggressive prostate cancer treatment strategies versus active surveillance for appropriate patient groups.

Table. Prostate cancer treatment, risk groups and death risk by HIV status

First-line Prostate Cancer Treatments, n (%)	PWH N=759	PWoH N=2,703	p
Surgery	135 (18)	678 (25)	<0.001
Radiotherapy	312 (41)	1030 (38)	0.13
Hormonal	194 (26)	592 (22)	0.03
D'Amico risk groups, n (%)			
Low risk	241 (31.8)	984 (36.4)	
Intermediate	358 (47.2)	1219 (45.1)	
High Risk	160 (21.1)	500 (18.5)	
All-cause death, n (%)			
Low risk	46 (19.1)	153 (15.5)	0.11
Intermediate	76 (21.2)	192 (15.8)	<0.001
High Risk	41 (25.6)	123 (24.6)	0.013
Prostate cancer death, n (%)			
Low risk	1 (0.42)	5 (0.51)	0.92
Intermediate	5 (1.4)	26 (2.2)	0.80
High Risk	11 (7.0)	37 (7.5)	0.41

*age adjusted

66: Non-Small Cell Lung Cancer Survival, by Tumor Stage and Histology, among People with and without HIV

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BACKGROUND

Among people with lung cancer, having HIV is associated with poorer survival. Few studies have evaluated the HIV survival gap by tumor histology and stage.

METHODS

A retrospective cohort of people with HIV (PWH) and people without HIV (PWoH) with newly diagnosed non-small cell lung cancer (NSCLC), identified between 2008-2020 from the US Department of Veterans Affairs and Kaiser Permanente. Hazard ratios for HIV status associated with survival up to 5 years were estimated from Cox models stratified by histological subtype (adenocarcinoma, squamous) and TNM stage (I, II/III, IV), adjusting for baseline factors and cancer treatment (see Table). Separate models stratified PWH by CD4 and HIV RNA levels at diagnosis.

RESULTS

There were 515 NSCLC cases diagnosed in PWH (61% adenocarcinoma, 39% squamous cell; 97% men; 49% non-Hispanic Black, 46% non-Hispanic White). There were 72,432 NSCLC cases diagnosed among PWoH (62% adenocarcinoma, 38% squamous cell; 83% men; 14% non-Hispanic Black, 76% non-Hispanic White). For PWH, 25% were stage I, 15% stage II, 19% stage III, 41% stage IV. For PWoH, 27% were stage I, 12% stage II, 22% stage III, 40% stage IV. PWH had 30-50% higher mortality across most of the analyzed histologic and stage subgroups, except for adenocarcinoma stages II/III (Table). Mortality differences (vs PWoH) were attenuated when restricting to PWH with higher CD4 or lower HIV RNA levels, but not eliminated (data not shown).

CONCLUSIONS

After accounting for HIV severity, cancer stage, histologic subtype, and cancer treatment, there are only moderate differences in survival following an NSCLC diagnosis by HIV status. The similar survival by HIV status for stage II or III adenocarcinomas, but not squamous cell cancers, requires further investigation.

Table. Adjusted hazard ratios (95% confidence intervals)[1] for association of HIV status (reference: PWoH) with mortality risk up to 5 years after NSCLC diagnosis

All NSCLC[2]			Adenocarcinoma		Squamous cell	
TNM Stage	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
I	1.46	(1.14, 1.87)	1.52	(1.08, 2.14)	1.35	(0.94, 1.93)
II or III	1.25	(1.05, 1.49)	1.03	(0.79, 1.33)	1.48	(1.16, 1.88)
IV	1.35	(1.18, 1.56)	1.37	(1.16, 1.61)	1.29	(0.99, 1.69)

[1]From Cox regression models with terms for HIV status (PWoH as reference), baseline age, sex, race/ethnicity, organization, diagnosis year, Deyo Charlson index, smoking, alcohol and/or substance use disorders, low education and income census tracts, cancer stage (for model including all stages), histology (for model including all NSCLC), and time-updated cancer treatment within first six months after NSCLC diagnosis.

67: Factors Associated with Increased Mortality among Lung Cancer Patients in Tanzania and Uganda

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BACKGROUND
Lung cancer is the most prevalent cancer globally and the leading cause of cancer-related deaths, accounting for 1.8 million deaths worldwide. In sub-Saharan Africa, incidence and mortality rates are approximately 128.2 and 87.2 per 100,000 people respectively. Mortality rates vary due to multiple factors, including HIV. Understanding these determinants is crucial for creating targeted interventions in Tanzania and Uganda. This study aims to identify factors associated with increased mortality among lung cancer patients in these countries focusing on the impact of HIV co-infection.

METHODS
This cohort study involved prospective data collection from lung cancer patients. Individuals ≥ 18 years with biopsy-proven lung cancer were enrolled since April 2022. Sociodemographic, clinical and comorbidities, and diagnostic and treatment outcome data were recorded. Kaplan Meier was used to assess for difference in survival rates by HIV status, and Cox hazard proportion regression for assessing factors associated with increased mortality among these patients in Tanzania and Uganda.

RESULTS
A total of 227 patients were enrolled, representing 44.9% of the lung cancer biopsy-confirmed cohort. Majority, 128 (56.4%) were under 60 years of age, 124 (54.9%) women, 99 (43.6%) peasant 59.5% non-smokers and 19 (8.37%) were HIV positive. Firewood/logs 109 (48.2%) and charcoal 77 (34.1%) were the major cooking fuels. Coughing was the most common symptom reported by both groups. Majority cases were adenocarcinomas stages (III and IV). This study revealed that, education level, weight loss, stage at diagnosis and HIV positive were the major causes of death among lung cancer patients in Tanzania and Uganda.

CONCLUSION
Early detection, increasing awareness of the disease, and targeted interventions addressing these factors are essential to reduce lung cancer mortality. Further research should investigate the impact of socioeconomic factors on lung cancer outcomes in HIV-positive populations to develop region- specific guidelines for lung cancer management in the context of HIV.

68: Cancer Mortality among People with HIV in the United States, 2001–2019

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BACKGROUND

People with HIV (PWH) face a higher risk of death, including cancer-related death. We examined the leading causes of death among PWH in the United States during 2001-2019, with a focus on cancer mortality.

METHODS

Underlying cause of death data for PWH aged 20 or older who died during 2001–2019 were obtained from DC, Puerto Rico, and 11 states participating in the HIV/AIDS Cancer Match Study. To compare mortality rates in PWH to the general population, we calculated standardized mortality ratios (SMRs), adjusted for sex, age-group, race/ethnicity, and calendar year.

RESULTS

Over 5.3 million person-years of follow-up, there were 131,120 deaths among PWH. HIV was the leading cause of death, responsible for 51.4% of deaths, followed by cancer (9.1% of deaths), heart disease (7.6%), and accidents and adverse events (4.4%). Overall, PWH had 4.4-fold higher risk of death compared to the general population (SMR: 4.44). Cancer mortality was 70% higher in PWH than the general population (SMR: 1.7, see Table). While SMRs were significantly increased for all groups examined, cancer death was especially elevated among males and females who inject drugs (SMRs: 1.93 and 2.72, respectively), and individuals aged 20 to 39 years old (SMR: 4.02). The SMRs for cancer steadily decreased with more recent calendar periods, from 2.21 in 2001–2004 to 1.46 in 2015–2019.

CONCLUSIONS

Following HIV, cancer was the second leading cause of death among PWH in the US during 2001–2019. Despite improvements over time, cancer mortality remained approximately 50% higher among PWH during 2015–2019. Elevated cancer mortality rates in PWH reflect increased risk of certain cancer types, notably infection-related cancers, as well as inadequate cancer treatment and poorer survival after a cancer diagnosis. Strategies to improve cancer mortality include earlier HIV diagnosis, increased access to cART, cancer prevention and screening, and equitable access to appropriate cancer treatment.

Standardized mortality ratios (SMR) for cancer, by demographics and calendar period			
Characteristic	**Cancer deaths**	**% of all deaths due to cancer**	**SMR (95% CI)**
Overall	11,897	9.1	1.70 (1.67–1.73)
Sex and HIV risk group			
Men who have sex with men	4,191	10.7	1.66 (1.61–1.71)
Male: person who injects drugs	2,204	7.8	1.93 (1.85–2.01)
Male: other	2,464	9.1	1.41 (1.36–1.47)
Female: person who injects drugs	809	7.5	2.72 (2.54–2.91)
Female: other	2,229	8.7	1.73 (1.66–1.80)
Age group, years			
20–39	952	3.6	4.02 (3.77–4.28)
40–59	7,306	9.1	1.97 (1.92–2.01)
60+	3,639	15.3	1.19 (1.15–1.23)
Race and ethnicity			
Hispanic	1,808	7.3	1.89 (1.80–1.97)
Non-Hispanic Black	5,686	8.4	1.50 (1.46–1.54)
Non-Hispanic White	3,884	11.4	1.86 (1.81–1.92)
Other or unknown	519	10.0	3.00 (2.75–3.27)
Calendar period			
2001–2004	1,569	5.5	2.21 (2.10–2.32)
2005–2009	3,279	7.6	1.97 (1.90–2.03)
2010–2014	3,970	10.9	1.58 (1.53–1.63)
2015–2019	3,079	13.4	1.46 (1.41–1.51)

69: Perceptions of Anal Cancer risk and Stigma among Black Same Gender-Loving Men Living with HIV

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BACKGROUND

HPV-related anal cancers occur in excess rates in persons with HIV/AIDS. The incidence of anal cancer occurs in remarkable excess particularly in same gender-loving (SGL) men who experience a 20- to 40-fold increase in risk. Furthermore, Black SGL are at significantly increased risk for anal cancer compared to non-Black SGL. Thus, we explored perceptions of anal cancer risk and stigma among SGL Black men living with HIV.

METHODS

A secondary analysis was performed to examine stigma and its relationship to anal cancer perceptions among a subsample of participants who self-reported as Black and same gender loving. The Champion Health Belief Model Scale is a 41-item Likert scale questionnaire with five subscales that were adapted to measure perceived susceptibility to anal cancer, perceived seriousness of anal cancer, perceived benefits of anal Pap tests, and perceived barriers to anal Pap testing. The responses result in a summative score for each subscale where a higher score is indicative of higher levels of that perception. Internalized AIDS-Related Stigma Scale is a 7-item instrument that assesses self-defacing beliefs and negative perceptions of people living with HIV/AIDS with higher scores representing greater internalized stigma. P-values were calculated by parametric or non-parametric tests where appropriate.

RESULTS

The mean age of the subsample (n=67) was 44.6 years (SD=9.3) where 78.1% of the sample reported a history of receiving an anal pap test. Mean stigma score was 4.67 (SD=1.97). The mean perceived susceptibility score for anal cancer was 15.12 (SD=5.93, range 6-30); mean score for perceived seriousness of anal cancer was 34.71 (SD= 9.69, range 12-60); mean score for perceived benefits of anal Pap tests was 20.14 (SD= 4.86, range 5-25); mean score for perceived barriers to anal Pap tests was 18.90 (SD= 7.21, range 8-40). Stigma was not significantly correlated to the perceptions of anal cancer subscales. Perceived barriers to anal cancer screening was related to perceived susceptibility to anal cancer (r= .372; pvalue= .002) and perceived seriousness of anal cancer (r= .289, pvalue= .031).

CONCLUSIONS

Our sample of Black same gender-loving men living with HIV reported moderate HIV-related stigma. Although HIV-related stigma was not related to perceptions of anal cancer, perceived barriers to anal cancer screening was associated with increased perception of anal cancer susceptibility and seriousness of anal cancer. Next steps include examining how stigma and perceptions relate to cancer screening behaviors and uptake.

70: Prostate Cancer Characteristics and Outcomes for Medicare Recipients with and without HIV

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BACKGROUND

Prostate cancer is a leading cancer diagnosis in people with HIV (PWH) and a growing source of morbidity for this group. Despite the rising burden of prostate cancer among PWH, limited research on prostate cancer clinical characteristics, treatment, and outcomes has hindered HIV-specific management guidance. Therefore, we studied prostate cancer characteristics at diagnosis, treatment, and mortality by HIV status using data from the Surveillance, Epidemiology and End Results registry linked to Medicare claims (SEER-Medicare).

Table. Prostate cancer first-line treatment and NCCN/D'Amico risk group by HIV status

Prostate cancer treatment, %	PWH (n=449)	PWoH (1,794)	p
Androgen deprivation therapy	29	27	0.40
Chemotherapy	<5	<5	0.33
Radiation	37	35	0.60
Surgery	39	36	0.25
No Treatment	29	29	0.92
D'Amico risk groups, n (%)			0.03
Low risk	69 (15)	235 (13)	
Intermediate risk	155 (35)	740 (41)	
High risk	225 (50)	819 (46)	

METHODS

Using SEER-Medicare data (2004-2017), we identified PWH with prostate cancer (n=449) and an age at diagnosis- and race/ethnicity-matched comparator group of prostate cancer patients without HIV (PWoH; n=1,794). We then compared D'Amico prostate cancer risk group characteristics, treatment, and prostate cancer-specific causes of death by HIV status, adjusting for age and stratified by risk group. Last, as some prostate cancer treatments have been linked to adverse cardiovascular events, we compared the risk of these long-term events by HIV status and treatment modality using age-adjusted logistic regression models.

RESULTS

PWH with prostate cancer had a median age of 65 (IQR: 57-69); despite matching PWoH were older with a median age of 67.5 (IQR: 61-72). Proportions of White (44%) and Black (43%) participants did not differ by HIV status. HIV infection was not associated with higher prostate specific antigen (p=0.13) but was associated with higher Gleason scores at diagnosis (p<0.001). PWH had different distributions of D'Amico and National Comprehensive Cancer Network risk scores at diagnosis with more high-risk cases than PWoH (see Table; both p<0.05) but no significant difference in the proportion of cases that were metastatic. There were also no differences in the use of first-line treatment modalities by HIV status (see Table); 29%, 37%, 39% and 29% of PWH received androgen deprivation therapy, radiotherapy, surgery or no treatment, respectively. HIV was not significantly associated with worse all-cause or cancer-specific mortality for any NCCN-risk group localized cancers in the matched cohort. We also did not find any difference in the long-term risk of incident cardiovascular events by HIV status in any treatment group in adjusted regression models.

CONCLUSIONS

In a population-based cohort, PWH were diagnosed with higher risk tumors than PWoH although this did not translate into worse mortality outcomes. There were also no major differences in prostate cancer treatment patterns by HIV status. This study was limited by a potential lack of representativeness in the PWoH comparison group (younger Medicare recipients often have disability or end-stage renal disease), and future work will explore alternative data sources for comparison. Nonetheless, our findings are similar to contemporary data from other large cohorts.

71: Inequities in Receipt of Immunotherapy among Advanced Stage Lung Cancer Patients with and without HIV in the US (2015–2020)

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BACKGROUND

Lung cancer is the leading cause of non-AIDS death among people with HIV (PWH) in the United States. Compared to those without HIV, PWH have worse lung cancer survival due to multifactorial factors, such as chronic immunosuppression. Inequities in cancer treatment delivery to PWH is a contributor to elevated mortality rates among PWH. PWH have historically been excluded from cancer clinical trials, and often continue to be excluded, particularly for immunotherapies given chronic immunosuppression of HIV. Nonetheless, phase II data among PWH suggests safety and tolerability of immunotherapy. In spite of this, there are limited studies examining real-world immunotherapy utilization in the years since this therapy has been widely used for stage III and IV lung cancer. Our objective was to investigate immunotherapy receipt and outcomes in lung cancer patients with and without HIV.

METHODS

We used data from the 2015–2020 National Cancer Database (NCDB) to represent the current immunotherapy era and included patients aged 18-89 years diagnosed with lung cancer (ICD-0-3 codes: C340-C349). PWH were identified using ICD9 (04200 to 04499, 07953, and V08) and ICD10 (B20 to B24, R75, Z21, B97.35) codes. We included those with stage III and stage IV cancer diagnosis and excluded those with unknown HIV status. Sociodemographic and clinical factors were descriptively compared separately in people with and without HIV to determine differences in immunotherapy receipt. Multilevel hierarchical logistic regression models clustered by facility ID were used to investigate the association of HIV status with immunotherapy receipt and identify predictors of immunotherapy use among PWH. Kaplan-Meier curves investigated survival after diagnosis among PWH and without HIV (PWoH).

RESULTS

We identified 432,477 patients with stage III (30%) or stage IV (70%) lung cancer and an identifiable HIV status—of which 1,485 (0.3%) were living with HIV. Of all participants, 90,258 (21%) received immunotherapy during the first course of cancer treatment—with a higher proportion of receipt among PWoH (20% vs 18% of PWH). Most PWH were non-Hispanic Black (51%) and either 50-59 years old (41%) or 60+ years old (49%) while most of those without HIV were non-Hispanic White (82%) and over the age of 60 (81%). After adjustment for age group, sex, stage, year of diagnosis, insurance status, and census region, PWH were significantly less likely to receive immunotherapy (aOR: 0.73; 95% CI: 0.62-0.86) compared to people without HIV. Among PWH, those with stage IV cancers (vs. stage III: aOR:1.86; 95% CI:1.23-2.81) were more likely to receive immunotherapy, and PWH who receive care at comprehensive community cancer programs (vs. academic/research: aOR: 0.54; 95% CI:0.33-0.89) and were diagnosed in earlier years (2019 vs. 2015: aOR: 0.10; 95% CI: 0.05-0.21) were less likely to receive immunotherapy. Median survival was longest for patients without HIV who did not receive immunotherapy (42 days) compared to PWoH who received immunotherapy (31 days) and PWH regardless of immunotherapy use (with immunotherapy use: 30 days; without immunotherapy: 32 days).

CONCLUSIONS

PWH diagnosed with advanced stage lung cancer were less likely to receive immunotherapy than people without HIV, and there was no difference in median survival by HIV status. As immunotherapy indications continue to grow, additional work is needed to investigate possible underlying factors impacting receipt of immunotherapy use in PWH and cancer.

72: Nascent Non-AIDS-Defining Skin Cancers among People with HIV: A Cross-Sectional Analysis of the *All of Us* Database

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BACKGROUND

With the prolonged survival of people with HIV (PWH) due to effective antiretroviral therapy, the development of nascent non-AIDS-defining skin cancers (NADSC) have become more concerning. This study aims to characterize the prevalence and types of nascent NADSC among PWH, using the extensive and diverse data available in the *All of Us* (AoU) Database.

METHODS

We conducted a descriptive cross-sectional study utilizing the AoU Database, which contains health data from over 1 million participants across the United States. PWH who developed a nascent NADSC after HIV diagnosis were identified through a combination of AoU condition, procedure, drug, and observation codes. We calculated the prevalence of nascent NADSC among PWH and categorized the types of skin cancers identified. Descriptive statistics were used to summarize the findings.

RESULTS

Among the 13,033 PWH identified in the *All of Us* Database, 436 (3.35%) were diagnosed with a nascent NADSC. Of the NADSCs queried, the most prevalent types among PWH included basal cell carcinoma at 47.94% (209 cases), squamous cell carcinoma at 29.36% (128 cases), and melanoma at 16.97% (74 cases). Most PWH who developed nascent NADSC were older than 65 years of age (55.04%). White individuals accounted for 73.39% of cases. Males accounted for 73.62% of cases.

CONCLUSIONS

This study highlights a concerning prevalence of skin cancers among PWH, with basal cell carcinoma being the most common type. The findings emphasize the need for routine skin cancer screening and prevention efforts in the HIV-positive population. These data provide a foundation for future research aimed at understanding the underlying factors and mechanisms contributing to increased skin cancer risk in PWH and developing targeted prevention strategies and guidelines.

73: Anal Human Papillomavirus Infection among Transgender Women and Men Who Have Sex with Men from Argentina

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BACKGROUND

Men who have sex with men (MSM) and transgender women (TGW) are the populations at the highest risk of HIV in Argentina and also at high risk for HPV infection and associated cancers. Gender neutral HPV vaccine was introduced in 2017, providing HPV vaccine at no cost for children at 11 years and for immunocompromised people aged 11 and 26. A cohort was organized to study HPV epidemiology. Data on baseline anal HPV and cytology is presented.

METHODS

Individuals were recruited between April 2018 and August 2022. Anal samples were collected for conventional cytology and HPV genotyping. DNA was purified using Qiagen DNA purification kits. HPV genotyping was done by BSGp5+6+ PCR combined with Reverse Blotting Hybridization, which allows the identification of 13 high-risk (HR) and 24 low-risk (LR) HPV genotypes.

RESULTS

A total of 208 MSM and 148 TGW were included. Median age was 32 years old (IQR 27-40); 63% lived with HIV (69% MSM, 53% TGW). Among them, the median CD4 cell count was 647 cells/ml (IQR 418-902) and 69% had undetectable viral load. No or irregular condom use was reported by 72% of those participants with steady partners and 40.7% of those with non-steady partners, 88.5% of TGW and 13.9% of MSM were current or former sex workers; 28.4% of MSM and 73.6% of TGW had more than 100-lifetime sexual partners. Only 5.1% of the participants had 3 doses of HPV vaccine and 4.8% received 1-2 doses. The available vaccine at the time of evaluation was the quadrivalent vaccine.

Anal cytology results were: negative (51.4%), low-grade squamous intraepithelial lesion (LSIL) (39.3%), high-grade squamous intraepithelial lesion (HSIL) (5.7%), ASCUS (3.4%) and invasive cancer (0.3%), similar among both groups. HPV was detected in 90% of the anal samples (78% HR-HPV), with 60% of the samples positive for at least one of the HPV genotypes in the quadrivalent and 65% for at least one of the HR-HPV genotypes in the nonavalent vaccine. The most frequent HR genotypes were HPV-16, HPV-58, HPV-18 and LR genotypes, HPV-6, HPV-42 and HPV-11. HR-HPV was more frequent in HSIL. HPV-16 was detected in 55% of HSIL, 27.4% of LSIL and 17.4% of negative cytology samples. Abnormal cytology was associated with HIV diagnosis ($p<0.001$), no or irregular condom use with steady partners ($p=0.031$) and anal HR-HPV ($p<0.001$) for TGW. Among MSM, abnormal cytology was associated with having >100 lifetime sexual partners ($p=0.046$), anal HR-HPV ($p=0.001$) and having non-steady sexual partners ($p=0.007$). HR-HPV presence was associated with having non-steady partners among MSM ($p=0.005$) and having HIV among TGW ($p=0.035$).

CONCLUSIONS

Anal HPV infection was frequent in this population with a few vaccinated participants, probably related to the extension of the current national vaccination program. Although anal cancer screening programs tend to expand, knowing and understanding more about local epidemiology becomes critical to improve prevention, both by promoting anal screening and by expanding the target population that benefits from HPV vaccination in Argentina. Funding: NIH2P30AI073961-06/ U54CA221208

74: Cancer Incidence and Trends in People with HIV in the United States, 2001–2019

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BACKGROUND

Cancer risk and burden in PWH in the United States have evolved over time with widely available ART, resulting in declining incidence rates of some cancer types and a growing burden of age-related cancers. We provide essential estimates on the incidence of cancers using recent linkages and updates from HIV and cancer registries with data through 2019.

METHODS

We utilize data from 14 regions in the HIV/AIDS Cancer Match (HACM) Study from 2001 to 2019, calculate age-standardized incidence rates (IR per 100,000 person-years) for 2010–2014, 2015–2019, and 2019, and estimated incidence rate ratios (IRR) comparing calendar periods using adjusted Poisson regression. We also provide age group specific estimates of incidence rates for 2010–2019. We calculate standardized incidence ratios (SIRs) in 2010–2014 and 2015–2019, then estimate the change in SIR between periods using adjusted Poisson regression.

RESULTS

Comparing 2015–2019 to 2010–2014, incidence declines for non-Hodgkin lymphoma (NHL), lung cancer, Kaposi sarcoma (KS), Hodgkin lymphoma (HL), and liver cancer (**Table**). For PWH ages 30–39 years, cancer incidence was highest for NHL (IR=79.9), KS (70.4), and cervical cancer (49.0). Among those ages 60-69 years, the incidence was highest for prostate (IR=351.6), lung (216.1), and female breast (191). Risk remained significantly elevated in 2015–2019 compared to the general population for several cancer types, including KS (SIR=213.9), anal (17.1), vulva (11.4), HL (7.8), NHL (6.1), liver (1.9), and lung (1.6). Elevated risk comparing PWH to the general population declined by 33% for NHL, 25% for KS, 13% for liver, and 17% for HL but was unchanged for the other most common cancers in PWH.

CONCLUSIONS

Recent updates to cancer incidence estimates are essential to understanding the evolving needs of an aging population of PWH in the United States. We present data showing continued declines in cancer rates in the most recent decade for some cancer types and stagnant rates for others and among specific age groups. These estimates may provide insight into the priorities for prevention and early detection of cancer as the population of PWH enters ages with greater risk for cancer.

Table. Age-standardized incidence rates (standard error) of cancer in people with HIV in the United States by calendar period and incidence rate ratios (IRRs), 2010–2019.

	2010–2014	2015–2019	IRR 2015–2019 to 2010–2014 (95% CI)
Female Breast	98.6 (3.9)	101.6 (4.5)	0.98 (0.87-1.10)
Prostate	76 (2.0)	68.5 (1.8)	0.95 (0.88-1.03)
Non-Hodgkin lymphoma	91.8 (2.0)	67.2 (2.0)	0.70 (0.65-0.76)*
Lung	65.5 (1.6)	47.7 (1.4)	0.83 (0.77-0.90)*
Cervix Uteri	45.3 (2.7)	47.1 (3.2)	1.08 (0.91-1.29)
Anus, Anal Canal and Anorectum	46.5 (1.4)	44.9 (1.5)	1.01 (0.92-1.10)
Kaposi sarcoma	49 (1.5)	39.5 (1.5)	0.76 (0.69-0.84)*
Vulva	23.4 (1.9)	28.3 (2.5)	1.26 (1.00-1.59)
Oral Cavity and Pharynx	26.3 (1)	25.3 (1.1)	0.94 (0.83-1.05)
Hodgkin lymphoma	26.2 (1.1)	19.9 (1.1)	0.75 (0.65-0.86)*
Liver	29.3 (1.1)	19.8 (0.9)	0.75 (0.67-0.84)*
Colon	17.3 (0.8)	16.5 (0.9)	0.94 (0.82-1.08)
Rectum and Rectosigmoid Junction	14.7 (0.8)	12.6 (0.8)	0.86 (0.72-1.01)

Incidence rates were standardized to the 2010 age distribution of people with HIV. Poisson regression estimates for IRRs adjusted for age, sex, and HIV acquisition risk group, race and ethnicity, and region.
*P-value < 0.001

75: CD4 Count after Cancer Diagnosis and Cancer-Specific Mortality among People with HIV

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BACKGROUND

People with HIV (PWH) have greater cancer-specific mortality following a cancer diagnosis compared to cancer patients without HIV, which may reflect the effects of immunosuppression on cancer control. For PWH and cancer, markers of immune function that indicate risk of HIV progression, such as CD4 count (cells/mm^3), may also be informative for cancer prognosis.

METHODS

We used linked data from participating US HIV and cancer registries to study six common cancers in PWH. We restricted analysis to calendar years 2007–2019 during which laboratory data are available for at least 80% of individuals in the state HIV registries. We used a 3-month landmark analysis in which the last CD4 count within the first 3 months after cancer diagnosis was used to categorize patients (<50, [50–100), [100-200), and 200+ CD4 cells/mm^3). Follow-up started 3 months after diagnosis and ended at the earliest of a cancer specific death, other death, or 3 years after cancer diagnosis. We used Cox regression to estimate hazard ratios (HRs) for cancer-specific mortality associated with CD4 counts and tested for trend per increase in categorical CD4 count, adjusted for demographic and clinical factors related to cancer mortality. We also provide Kaplan-Meier estimates for 3-year cancer-specific mortality according to CD4 count category among those who survived 3 months past cancer diagnosis and present estimates for lung and colorectal cancers because of their high mortality in this population.

RESULTS

We analyzed 763 individuals with colorectal cancer, 1,248 anal, 1,407 lung, 1,681 prostate, 2,311 non-Hodgkin lymphoma (NHL), and 1,423 individuals with Kaposi sarcoma (KS). Cancer-specific survival was statistically significantly worse for individuals with a last CD4 count within the first 3 months of less than 50 compared to 200 or greater for colorectal cancer, lung cancer, prostate, NHL, and KS (**Table**). The 3-year cancer-specific mortality estimates for PWH with colorectal cancer with a CD4 of 200 or greater and less than 50 were 32% and 67%, respectively. The 3-year cancer-specific mortality estimates for PWH with lung cancer with a CD4 of 200 or greater and less than 50 were 67% and 84%, respectively.

CONCLUSIONS

We show significant differences in cancer-specific mortality among PWH according to CD4 count within the first 3 months of cancer diagnosis, even for prostate cancer, which is not typically associated with immunosuppression. For lung cancer, a cancer with high mortality in PWH, CD4 count was a strong determinant of cancer-specific mortality. These estimates provide evidence for the potential role of immunity in controlling cancer and support efforts to strengthen immune function to improve cancer outcomes.

Table. Cox proportional hazard ratios for cancer-specific mortality associated with CD4 count using a 3-month landmark analysis.

	CD4 Count Hazard Ratio (95%CI) (Ref=200+)			
Cancer site	<50	[50-100)	[100-200)	p-trend
Colon & rectum	3.05** (1.72-5.39)	0.67 (0.32-1.38)	1.31 (0.89-1.93)	0.02
Anus	1.19 (0.81-1.75)	1.41 (0.94-2.12)	1.50* (1.10-2.03)	0.11
Lung	1.65** (1.30-2.09)	1.58* (1.2-2.09)	1.15 (0.95-1.38)	<0.001
Prostate	4.49* (1.75-11.49)	1.63 (0.39-6.87)	0.91 (0.41-2.05)	0.01
Non-Hodgkin lymphoma	1.81** (1.30-2.52)	1.16 (0.76-1.78)	1.20 (0.86-1.66)	0.002
Kaposi sarcoma	4.05* (1.45-11.31)	0.69 (0.13-3.64)	1.54 (0.46-5.19)	0.01

Adjusted for sex, age, race and ethnicity, stage at diagnosis, and cancer treatment, including radiation, chemotherapy, and surgery. *p-value<0.05; **p-value <0.01

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