

**12th INTERNATIONAL
CONFERENCE
ON MALIGNANCIES IN
AIDS AND OTHER
ACQUIRED
IMMUNODEFICIENCIES
(ICMAOI)**

April 26-27, 2010

**Lister Hill Auditorium
NIH Main Campus**

<http://oham.cancer.gov/>



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Acknowledgements

Program Committee for Scientific Input

NCI Office of Communications and
Education for cover art

and

National Institute of Dental and Craniofacial
Research for financial support



Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The George Washington University Medical Center and the National Institutes of Health. The George Washington University Medical Center is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement

The George Washington University Medical Center designates this educational activity for a maximum of **5 AMA PRA Category 1 Credits™**. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Policy on Speaker and Provider Disclosure

The George Washington University Medical Center has a disclosure policy whereby everyone in a position to control the content of an educational activity must disclose all relevant financial relationships with commercial interests. In addition, speakers must also disclose any unlabeled/unapproved uses of drugs or devices that they plan to discuss in their presentation(s). Individuals who fail to disclose potential conflicts of interest are disqualified from participation in planning or implementing this CME activity. Potential conflicts of interest are resolved and documented. Detailed disclosure will be made in the activity handout materials.

Learning Objectives

At the end of this activity, attendees should be able to:

1. Propose trends of specific malignancies that may occur in the context of HIV infection (AIDS defining and non-AIDS defining) and other acquired immunodeficiencies, and identify cofactors (ie. environmental, viral, and behavioral) that may be associated with the development of these malignancies, if known. Describe which populations (geographic, ethnic, racial, sex, age, etc.) may be predisposed to developing specific malignancies.
2. Describe how the use of state-of-the-science information in the epidemiology, pathogenesis, and clinical aspects of malignancies in HIV positive and other immunocompromised patients can lead to more effective prevention, diagnosis and treatment in those that are susceptible to these malignancies.
3. Describe how chronic immunosuppression (either in transplant recipients or HIV positive individuals on HAART) impacts the incidence and types of cancer, and the choice of therapies in those patients who develop malignancies.

12th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies
Lister Hill Auditorium, NIH, Bethesda, Maryland
April 26-27, 2010

PROGRAM CO-CHAIRS*

Robert Yarchoan, MD

Dr. Yarchoan disclosed that he has a Material Transfer Agreement with Johnson and Johnson

Geraldina Dominguez, PhD

Nothing to disclose

PROGRAM COMMITTEE*

Richard F. Ambinder, MD, PhD

Nothing to disclose

Leona Ayers, MD

Nothing to disclose

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Nothing to disclose

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Nothing to disclose

Dirk Dittmer, PhD

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Nothing to disclose

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Nothing to disclose

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Nothing to disclose

Rebecca Liddell Huppi, PhD

Nothing to disclose

Elliott D. Kieff, MD, PhD

Nothing to disclose

Alexandra M. Levine, MD, MACP

Dr. Levine disclosed a consulting relationship with Genentech and a speakers bureau relationship with Abbott Laboratories

Richard Little, MD

Nothing to disclose

Douglas Lowy, MD

Dr. Lowy disclosed that he receives royalties via the NIH for an invention that the NIH licenses to Merck and GlaxoSmithKline

Sam Mbulaiteye, MD

Nothing to disclose

Mostafa Nokta, MD, PhD

Nothing to disclose

Joel Palefsky, MD, FRCP(C)

Dr. Palefsky disclosed that he is a consultant, advisory committee member, and independent contractor with Merck.

C. David Pauza, PhD

Nothing to disclose

Elizabeth Read-Connole, PhD

Nothing to disclose

Isaac R. Rodriguez-Chavez, PhD, MS, MHS

Nothing to disclose

Sylvia Silver, DA

Nothing to disclose

Michael J. Silverberg, PhD, MPH

Dr. Silverberg disclosed that he is an independent contractor with Pfizer and Merck.

Joseph Sparano, MD

Nothing to disclose

*The program chairs and committee were tasked with identifying program content and speakers. The course director conducted the meeting with the best interest of the learning needs in mind. Both chairs and all committee members completed disclosure documents. Any potential conflicts that arose were mitigated by either 1) self-recusal, or 2) concurrence by the committee that the content identified was scientifically sound and without bias and that the speakers identified would deliver balanced scientific presentations on raw data and sound evidence and make no commercial recommendations. It has been determined that no conflicts of interest exist in this role.

12th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies
Lister Hill Auditorium, NIH, Bethesda, Maryland
April 26-27, 2010

Denise Whitby, PhD
Nothing to disclose

Frank Ruscetti, Ph.D.
Nothing to disclose

T-C Wu, MD, PhD
Nothing to disclose

Rengaswamy Sankaranarayanan, M.D
Nothing to disclose

Accredited Faculty

Christopher Buck, Ph.D.
Nothing to disclose

Don Ganem, M.D.
Dr Ganem disclosed a consulting relationship with 3V, Kearny Venture Partners and Novartis. After a review of his presentation it was determined that he will discuss raw data only and make no recommendations.

Clifford Gary Ph.D.
Nothing to disclose

Aisha O. Jumaan, Ph.D., M.P.H.
Nothing to disclose

Ari Melnick, M.D
Nothing to disclose

Eugene Mutimura, Ph.D.
Dr. Mutimura will discuss CareHPV which is under development and for investigational use only. He has no financial relationships to disclose

Robert Newton, M.B.B.S., D.Phil., FFPH
Nothing to disclose

Joel Palefsky, M.D., FRCP(C)
Dr. Palefsky disclosed that he is a consultant, advisory committee member, and independent contractor with Merck. After a review of his presentation it was determined that he will discuss raw data only and make no recommendations.

Groesbeck P. Parham, M.D
Nothing to disclose

*The program chairs and committee were tasked with identifying program content and speakers. The course director conducted the meeting with the best interest of the learning needs in mind. Both chairs and all committee members completed disclosure documents. Any potential conflicts that arose were mitigated by either 1) self-recusal, or 2) concurrence by the committee that the content identified was scientifically sound and without bias and that the speakers identified would deliver balanced scientific presentations on raw data and sound evidence and make no commercial recommendations. It has been determined that no conflicts of interest exist in this role.

Program

April 26

- 8:00 a.m. - 8:15 a.m. **Poster Setup (Day 1 Posters)**
- 8:15 a.m. - 8:30 a.m. **Welcome and Plenary Introduction**
Robert Yarchoan, M.D.
Office of HIV and AIDS Malignancy
National Cancer Institute, NIH, USA
- 8:30 a.m. - 9:00 a.m. **HPV Vaccination in HIV-Positive Men and Women—Challenges and Opportunities**
Joel Palefsky, M.D., FRCP(C)
University of California, San Francisco, USA
- 9:00 a.m. - 10:30 a.m. **Session 1: Cervical Cancer Control in Developing Countries**
Moderators: Joe B. Harford, Ph.D.
National Cancer Institute, NIH, USA

Joel Palefsky, M.D., FRCP(C)
University of California, San Francisco, USA
- 9:00 a.m. - 9:30 a.m. ***Cervical Cancer Control in Developing Countries: Impact of HIV Infection***
Rengaswamy Sankaranarayanan, M.D.
International Agency for Research on Cancer, France
- 9:30 a.m. - 10:00 a.m. ***Cervical Cancer Screening With Point-of-Care Rapid HPV Testing and Visual Inspection With Acetic Acid in HIV-Positive and HIV-Negative Rwandan Women***
Eugene Mutimura, Ph.D.
Women's Equity in Access to Care and Treatment, Rwanda
- 10:00 a.m. - 10:15 a.m. ***UAB/CIDRZ Cervical Cancer Prevention Program in Zambia***
Goesbeck P. Parham, M.D.
University of Alabama at Birmingham, USA
- 10:15 a.m. - 10:30 a.m. ***Factors Impacting Introduction of HPV Vaccination in Low-Resource Settings***
Aisha O. Jumaan, Ph.D., M.P.H.
PATH, USA
- 10:30 a.m. - 10:45 a.m. ***Questions and Answers (directed at all speakers)***
- 10:45 a.m. - 11:00 a.m. **Break: Coffee and Poster Viewing**

11:00 a.m. - 12:30 p.m.	<p>Session 2: KSHV Biology Moderators: Denise Whitby, Ph.D. NCI-Frederick, USA</p> <p>Dirk Dittmer, Ph.D. The University of North Carolina at Chapel Hill, USA</p>
11:00 a.m. - 11:30 a.m.	<p><i>Infection of Primary Lymphoid Cells by KSHV: Novel Mechanisms of Immune Control of KSHV in the Lymphoid Compartment</i> Donald E. Ganem, M.D. University of California, San Francisco, USA</p>
11:30 a.m. - 11:45 a.m.	<p><i>Bim Nuclear Translocation and Inactivation by HHV-8 Interferon Regulatory Factor 1</i> John Nicholas, Ph.D. Johns Hopkins University School of Medicine, USA</p>
11:45 a.m. - 12 noon	<p><i>Hsp90 Is a Viable Therapeutic Target in the Treatment of KSHV-Associated Primary Effusion Lymphoma</i> Utthara Nayar, M.S. Weill Cornell Medical College, USA</p>
12 noon - 12:15 p.m.	<p><i>Upregulation Angiopoietin-like 4 by Viral G Protein-Coupled Receptor Promotes Angiogenesis and Vascular Permeability in Kaposi's Sarcoma</i> Silvia Montaner, Ph.D., M.P.H. University of Maryland, USA</p>
12:15 p.m. - 12:30 p.m.	<p><i>KSHV Regulation of Fibulins in Kaposi's Sarcoma: Implications for Tumorigenesis</i> Donald James Alcendor, Ph.D., M.S. Meharry Medical College, USA</p>
12:30 p.m. - 1:00 p.m.	Lunch (lunch on your own or pre-bought lunch box)
1:00 p.m. - 2:00 p.m.	Poster Viewing (presenters stand by posters)
2:00 p.m. - 3:30 p.m.	<p>Session 3: New and Old Viruses—Impact on Chronic Diseases Moderators: C. David Pauza, Ph.D. Institute of Human Virology, University of Maryland School of Medicine, USA</p> <p>Kishor Bhatia, Ph.D., FRCPath. National Cancer Institute, NIH, USA</p>
2:00 p.m. - 2:30 p.m.	<p><i>Repeated Detection of Infectious Xenotropic Murine Virus-Related Virus (XMRV) in Human Neoplasia and Neuroimmune Diseases</i> Frank Ruscetti, Ph.D. National Cancer Institute, NIH, USA</p>

- 2:30 p.m. - 3:00 p.m. ***Merkel Cell Polyomavirus and Two Novel Polyomaviruses Are Chronically Shed From Human Skin***
Christopher Buck, Ph.D.
National Cancer Institute, NIH, USA
- 3:00 p.m. - 3:15 p.m. ***HIV-Associated Salivary Gland Disease: A Role for BK Virus***
Liesl K. Jeffers, Ph.D.
The University of North Carolina at Chapel Hill, USA
- 3:15 p.m. - 3:30 p.m. ***Bacteria-Mediated Reactivation of Gammaherpesviruses***
Jennifer Webster-Cyriaque, D.D.S., Ph.D.
The University of North Carolina at Chapel Hill, USA
- 3:30 p.m. - 4:00 p.m. **Break: Coffee and Poster Viewing**
- 4:00 p.m. - 5:15 p.m. **Session 4: Clinical Trials Data in HIV/AIDS-Associated Malignancies**
Moderators: Alexandra M. Levine, M.D., M.A.C.P.
City of Hope National Medical Center, USA

Richard F. Little, M.D.
National Cancer Institute, NIH, USA
- 4:00 p.m. - 4:15 p.m. ***Phase II AIDS Malignancy Consortium (AMC) Trial of Imatinib in AIDS-Associated Kaposi's Sarcoma***
Henry B. Koon, M.D.
Case Western Reserve University, USA
- 4:15 p.m. - 4:30 p.m. ***Rituximab Combined With Liposomal Doxorubicin in HIV-Infected Patients With Severe Kaposi Sarcoma-Associated Herpes Virus-Associated Multicentric Castlemans Disease***
Thomas Uldrick, M.D., M.S.
National Cancer Institute, NIH, USA
- 4:30 p.m. - 4:45 p.m. ***The KAART Trial: A Randomized Controlled Trial of HAART Compared to the Combination of HAART and Chemotherapy in Treatment-Naive Patients With HIV-Associated Kaposi Sarcoma in KwaZulu-Natal, South Africa***
Thomas Uldrick, M.D., M.S.
National Cancer Institute, NIH, USA
- 4:45 p.m. - 5:00 p.m. ***Distinct Profiles of Antibodies to Kaposi Sarcoma-Associated Herpesvirus Antigens in Patients With Kaposi Sarcoma, Multicentric Castlemans Disease, and Primary Effusion Lymphoma***
Peter D. Burbelo, Ph.D., M.A.
National Institute of Dental and Craniofacial Research, NIH, USA

5:00 p.m. - 5:15 p.m.

Pooled Analysis of AIDS-Malignancy Consortium Trials Evaluating Rituximab Plus Either CHOP or Infusional EPOCH Chemotherapy in HIV-Associated Non-Hodgkin's Lymphoma

Stefan K. Barta, M.D.

Montefiore Medical Center, Einstein Cancer Center, USA

5:15 p.m.

End of Day One

April 27

8:00 a.m. - 8:15 a.m.

Poster Setup (Day 2 Posters)

8:15 a.m. - 8:25 a.m.

Opening Comments

Geraldina Dominguez, Ph.D.

National Cancer Institute, NIH, USA

8:25 a.m. - 8:30 a.m.

Plenary Introduction

Eric A. Engels, M.D., M.P.H.

National Cancer Institute, NIH, USA

8:30 a.m. - 9:00 a.m.

Epidemiology of HIV-Associated Cancers: New Findings From the Long-Term Followup of Cohorts on HAART

Gary Clifford, Ph.D.

International Agency for Research on Cancer, France

9:00 a.m. - 10:00 a.m.

Session 5: Epidemiology of HPV-Associated Cancers

Moderators: John Brooks, M.D.

Centers for Disease Control and Prevention, USA

Eric Engels, M.D., M.P.H.

National Cancer Institute, NIH, USA

9:00 a.m. - 9:15 a.m.

Cervical Cancer Epidemiology Among HIV-Infected Women in North America

Gypsyamber D'Souza, Ph.D.

Johns Hopkins Bloomberg School of Public Health, USA

9:15 a.m. - 9:30 a.m.

Progression of Cervical Neoplasia in HIV-Seropositive Women With and Without Antiretroviral Therapy in Johannesburg, South Africa

Cynthia S. Firnhaber

Right to Care, USA

9:30 a.m. - 9:45 a.m.

Persistence of Anal Squamous Intraepithelial Lesions and Anal HPV Infection in HIV-Infected Patients Despite Immune Restoration Under cART

Christophe Antoine Piketty, M.D., Ph.D.

Georges-Pompidou Hospital, Paris, France

9:45 a.m. - 10:00 a.m.	<p><i>Risk of Anal Cancer in HIV-Infected Patients and HIV-Uninfected Controls in North America</i> Michael J. Silverberg, Ph.D., M.P.H. Kaiser Permanente Northern California, USA</p>
10:00 a.m. - 10:30 a.m.	<p>Break: Coffee and Poster Viewing</p>
10:30 a.m. - 11:00 a.m.	<p>Plenary Introduction Sam M. Mbulaiteye, M.D. National Cancer Institute, NIH, USA</p> <p>HIV and Cancer in Children Robert Newton, D.Phil., M.B.B.S., FFPH University of York, United Kingdom</p>
11:00 a.m. - 12 noon	<p>Session 6: International Partnerships Moderators: Corey Casper, M.D., M.P.H. Fred Hutchinson Cancer Research Center, USA</p> <p>Sam M. Mbulaiteye, M.D. National Cancer Institute, NIH, USA</p>
11:00 a.m. - 11:15 a.m.	<p><i>Integrative Proteomics and Genomics Supports a Role for Interferon Gamma in the Pathogenesis of Kaposi Sarcoma and Finds Multiple Candidate Diagnostic Proteins for Early Detection or Prevention</i> Lynn M. Amon, Ph.D. Fred Hutchinson Cancer Research Center, USA</p>
11:15 a.m. - 11:30 a.m.	<p><i>Malignant Lymphoma Incidence and HIV-Related Lymphoma Subtypes in the Western Cape of South Africa, 2002-2009</i> Leona W. Ayers, M.D. Ohio State University, USA</p>
11:30 a.m. - 11:45 a.m.	<p><i>HPV Genotype and EGFR Activation in Conjunctival Carcinoma Among HIV Patients in East Africa</i> Scot C. Remick, M.D. West Virginia University, USA</p>
11:45 a.m. - 12 noon	<p><i>Visual Inspection and HPV-Based Cervical Cancer Screening for HIV-Infected Women in Pune, India</i> Vikrant Sahasrabuddhe, Dr.P.H., M.B.B.S. Vanderbilt University, USA</p>
12 noon - 12:30 p.m.	<p>Lunch (lunch on your own or pre-bought lunch box)</p>
12:30 p.m. - 1:30 p.m.	<p>Poster Viewing (presenters stand by posters)</p>

- 1:30 p.m. - 3:00 p.m. **Session 7: EBV Biology and Lymphomagenesis**
Moderators: Elliott D. Kieff, M.D., Ph.D.
Harvard Medical School, USA
- Ethel Cesarman, M.D., Ph.D.
Weill Cornell Medical College, USA
- 1:30 p.m. - 2:00 p.m. ***Epigenetic and Transcriptional Programming and Therapy in B Cell Lymphomas***
Ari Melnick, M.D.
Weill Cornell Medical College, USA
- 2:00 p.m. - 2:15 p.m. ***An ATM/Chk2-Mediated DNA Damage Responsive Signaling Pathway Suppresses Epstein-Barr Virus Transformation of Primary Human B Cells***
Micah Luftig, Ph.D.
Duke University School of Medicine, USA
- 2:15 p.m. - 2:30 p.m. ***TNFAIP3(A20) Genetic Alterations in AIDS-Related Lymphomas***
Lisa Giulino, M.D.
New York Presbyterian Hospital, Well Cornell Medical College, USA
- 2:30 p.m. - 2:45 p.m. ***C/EBPbeta Mediates Bortezomib-Induced EBV and KSHV Lytic Gene Expression***
Courtney O'Farrell
Johns Hopkins University School of Medicine, USA
- 2:45 p.m. - 3:00 p.m. ***Elevated Serum Levels of CXCL13 Precede HIV-Associated Non-Hodgkin's Lymphoma***
Shehnaz K. Hussain, Ph.D.
University of California, Los Angeles, USA
- 3:00 p.m. - 3:30 p.m. **Break: Coffee and Poster Viewing**
- 3:30 p.m. - 4:45 p.m. **Session 8: Cancers in the Era of Combination Antiretroviral Therapy**
Moderators: Richard F. Ambinder, M.D., Ph.D.
Johns Hopkins University School of Medicine, USA
- Joseph Sparano, M.D.
Albert Einstein College of Medicine, USA
- 3:30 p.m. - 3:45 p.m. ***Decreased Risk of Breast Cancer Associated With X4-Tropic HIV***
Nancy A. Hessol, M.S.P.H.
University of California, San Francisco, USA
- 3:45 p.m. - 4:00 p.m. ***HIV-Related Hodgkin Lymphoma in the Era of Combination Antiretroviral Therapy: Incidence, Outcome, and Evolution of CD4+ T Cell Lymphocytes***
Matthias Egger, M.D., M.S., FFPHM DTM & H
Institute of Social and Preventive Medicine, University of Bern, Switzerland

4:00 p.m. - 4:15 p.m.

Risk of HIV-Associated Hodgkin Lymphoma During the First Months After Initiation of Combination Antiretroviral Therapy

Emilie Lanoy, M.D.
INSERM, France

4:15 p.m. - 4:30 p.m.

Non-AIDS-Defining Cancer Mortality Among People With AIDS in Italy

Antonella Zucchetto, Sc.D.
National Cancer Institute Centro di Riferimento Oncologico, Italy

4:30 p.m. - 4:45 p.m.

Phase IIA Trial of 1% Topical Cidofovir for Treatment of High-Grade Perianal Squamous Intraepithelial Neoplasia in HIV-Infected Men and Women (AMC046)

Elizabeth A. Stier, M.D.
Boston Medical Center, USA

4:45 p.m.

Meeting Adjourned

Program Committee

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Isaac R. Rodriguez-Chavez, Ph.D., M.S., M.H.S.

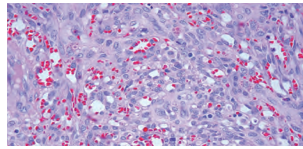
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Sylvia Silver, D.A.

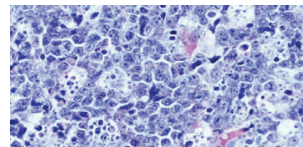
Professor of Pathology
Associate Dean for Health Sciences
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School of Medicine and Health Sciences
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ssilver@gwu.edu

Examples of Specimens:

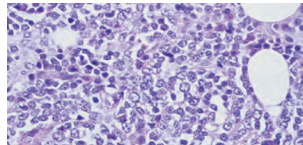
- Kaposi's sarcoma
- Non-Hodgkin's lymphoma
- Hodgkin's lymphoma
- Genito-urinary system dysplasia
- Non-HIV malignancy controls



Kaposi's Sarcoma



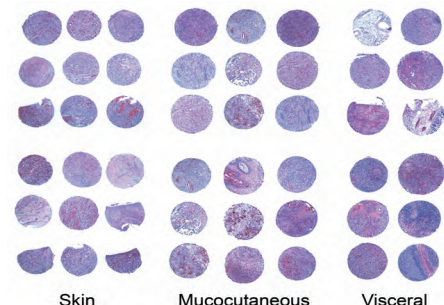
Burkitt's Lymphoma



Large Cell Lymphoma

The ACSR Offers Tissue Micro-Arrays (TMA)

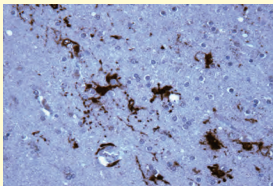
- Hundreds of tissue samples can be assembled into a single TMA
- HIV infected tissues and related malignancies along with non-HIV related controls
- TMA's available include Kaposi's sarcoma and AIDS lymphoma



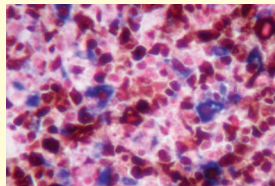
Skin Mucocutaneous Visceral

Kaposi's Sarcoma TMA, H&E stain

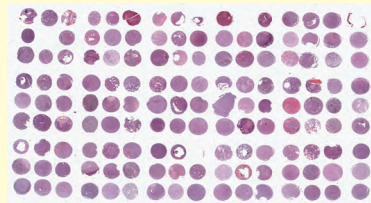
High Quality Specimens Produce Results for Your Research



Frontal cortex with HIV-encephalitis stained with HIV p24



Large cell lymphoma stained with CD68 (blue) and PCNA (brown)



Annotated HIV+ DLBCL TMA

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Case 1																					
Case 2																					
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Plenary Speaker Abstracts

P1. HPV Vaccination in HIV-Positive Men and Women: Challenges and Opportunities

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Background

HIV-positive men and women are at increased risk of anogenital human papillomavirus (HPV) infection, intraepithelial neoplasia, and invasive cancer. Prophylactic vaccination of young women with virus-like particle-based vaccines has been shown to be safe and effective to prevent HPV infection and HPV-associated disease due to vaccine HPV types among women naive to HPV vaccine types pre-vaccination. HPV vaccination therefore has the potential to prevent HPV-associated disease in high-risk HIV-positive individuals. Issues related to vaccinating this population include safety and efficacy of HPV vaccination among men in general; safety and immunogenicity of vaccination in HIV-positive men and women; and the degree to which exposure to HPV prior to vaccination will affect vaccine efficacy.

Materials and methods

Merck 020 was performed to study the safety and efficacy of quadrivalent HPV vaccine (qHPV, HPV 6, 11, 16, and 18) in healthy HIV-negative males aged 16-26 years. The study included 3463 heterosexual men (HM) and 602 men who have sex with men (MSM) with a history of no more than 5 lifetime sexual partners. Prevention of external genital infection and associated lesions was studied in the entire population. Prevention of anal HPV infection and HPV-associated anal lesions was studied in MSM only. AMC 052 was performed to study the safety and immunogenicity of qHPV in HIV-positive MSM.

Results

Data from Merck 020 show that qHPV is effective to prevent persistent external genital HPV 6/11/16/18 infection and external genital condyloma acuminatum in men. qHPV was also effective to prevent persistent anal HPV 6/11/16/18 infection in MSM, anal condyloma acuminatum, and high-grade anal intraepithelial neoplasia (AIN 2+). There were no vaccine-related serious adverse events. AMC 052 showed that qHPV was safe in HIV-positive MSM. More than half were naive to each of the vaccine HPV types individually at baseline, and nearly all seroconverted in response to vaccination. Titers were relatively low in Merck 020 and AMC 052 among MSM, regardless of HIV status, when compared with HM in Merck 020. The relatively low titers among MSM in Merck 020 did not adversely affect vaccine efficacy in this group.

Conclusions

qHPV is effective to prevent anogenital HPV infection and HPV-associated lesions in HIV-negative males. HPV vaccination appears to be safe and immunogenic in HIV-positive individuals. Additional safety studies are in progress in HIV-positive women. Efficacy studies are planned to determine the clinical utility of HPV vaccination in the HIV-positive population.

Acknowledgements

AMC 052 and Merck 020 study teams.

P2. Cervical Cancer Control in Developing Countries: Impact of HIV Infection

Rengaswamy Sankaranarayanan

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Cervical cancer is a major public health problem in developing countries of sub-Saharan Africa, South and Southeast Asia, and Latin America, despite its high preventability by screening and human papillomavirus (HPV) vaccination. Four-fifths of the estimated annual global burden of 500,000 new cases and 280,000 deaths occur in these countries, due to lack of effective screening programs. It is the leading cause of cancer death among women in these countries. Persistent infection with one of the high-risk types of oncogenic HPV infection has been established as a necessary cause of cervical cancer; exposures related to sexual and reproductive behavior such as increasing parity, early age at sexual intercourse, multiple sexual partners, and hormonal contraceptives, as well as smoking, are other established risk factors. Women infected with human immunodeficiency virus (HIV) have an increased risk of cervical cancer precursor lesions such as high-grade cervical intraepithelial neoplasia (CIN 2 and 3 lesions) and cervical cancer. HIV-positive women have higher prevalence of HPV infection, repeated HPV infection and more persistent infection due to immuno-suppression, leading to higher frequencies of cervical neoplasia. The association between HIV infection and invasive cervical cancer (ICC) is complex. Whereas studies in Europe and the United States have shown a 5- to 8-fold increased risk of ICC among HIV-infected women or women suffering from acquired immunodeficiency syndrome (AIDS), such evidence is limited in Africa, where treatment for HIV is limited and the lifespan of HIV-positive women is too short for cervical cancer to develop. Although a high risk of CIN and cervical cancer in HIV-positive women has been demonstrated in Senegal, where a relatively high prevalence of HIV-2 infection occurs, a study from South Africa showed no increased risk of cervical cancer associated with HIV and there have not been significantly higher incidence rates associated with HIV epidemic in developing countries, particularly sub-Saharan Africa. This may be due to the natural progression of HIV disease to opportunistic infections leading to premature death before the onset of ICC in the absence of widespread use of potent antiretroviral treatment. The control of cervical neoplasia among HIV-infected women will be discussed in the context that more than half of the 16 million HIV-infected women in the world are living in sub-Saharan Africa, where they have poor access to both screening and antiretroviral therapy.

Control of cervical neoplasia among HIV-positive women is challenging. The risk of cervical neoplasia has remained high and stable during the last decade in HIV-infected women, and incidence did not decrease with improving CD4 cell counts in women receiving antiretroviral therapy. Although the prevalence of HPV 16 and 18, the two vaccine preventable types, among women with cervical cancer does not differ among HIV-positive and -negative women, the current HPV vaccines will have no impact in HIV-infected women as they have no therapeutic effect. Whether cervical cancer screening is as efficient among HIV-infected women as in the general population is still being debated. The use of HPV DNA tests may be less specific in immuno-compromised women and might not be as efficient as in the general population. No universally accepted consensus exists for primary screening methods, screening intervals, thresholds for proceeding to diagnosis, and treatment or method of treatment. Screening seems to be less effective in preventing cervical cancer among HIV-infected women due to high risk of HPV infection, repeated HPV infection, and high recurrence rates following treatment of CIN, due to immunosuppression. Available evidence on the outcome of treatment for CIN among HIV-infected women is limited, but suggests that standard treatments for CIN are associated with high rates recurrence, despite multiple treatments, ranging from 20% to 70% in HIV-positive women; however, most treatment failures are low-grade CIN. That most HIV-infected women in developing countries have no access to screening and treatment, and the currently available screening approaches are less effective, underscores the importance of searching and establishing optimal screening and treatment approaches to control cervical cancer among them.

P3. Cervical Cancer Screening With Point-of-Care Rapid HPV Testing and Visual Inspection With Acetic Acid in HIV-Positive and HIV-Negative Rwandan Women

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Background

Human papillomavirus (HPV), the cause of cervical cancer, is more common in HIV+ than in HIV- women. Like most sub-Saharan African countries, Rwanda has a dual burden of HIV infection and high cervical cancer rates. We determined the prevalence of high-risk (HR) HPV infection and visible cervical abnormalities in HIV+ and -negative women in urban and periurban Rwanda.

Methods

1303 HIV+ and 1713 HIV- Rwandan women were screened for cervical disease with point-of-care HR-HPV testing (*CareHPV*, Qiagen) and visual inspection with acetic acid (VIA) in a screen-and-treat protocol.

Results

HIV-positive women were more likely than HIV-negative women to test positive for HR-HPV (31.7% vs. 9.1%, $p < 0.0001$) and to test positive by VIA (11.4% vs. 8.1%, $p = 0.003$). Among HIV+ women, CD4 count was associated with testing HR-HPV positive but not VIA+ (figure). In multivariate analyses, factors significantly associated with HR-HPV detection were age ($P < 0.0001$), number of lifetime sex partners (< 0.0001), and HIV status ($p < 0.0001$, OR 4.05, confidence interval (CI), 3.18, 5.14). Only age and HPV infection were associated with VIA positivity, and HIV-infection did not predict VIA+ results (OR 1.04, CI 0.77, 1.43, $p = 0.51$).

Antiretroviral therapy, used by 77% of the HIV+ women, was not associated with testing HR-HPV or VIA positive.

Conclusion

In this study of 3016 Rwandan women previously unscreened for cervical abnormalities, HR-HPV was associated with HIV infection and CD4 count, but VIA was not. Further study with clinically relevant outcomes is necessary to determine whether VIA is an adequate screening methodology for HIV+ women.

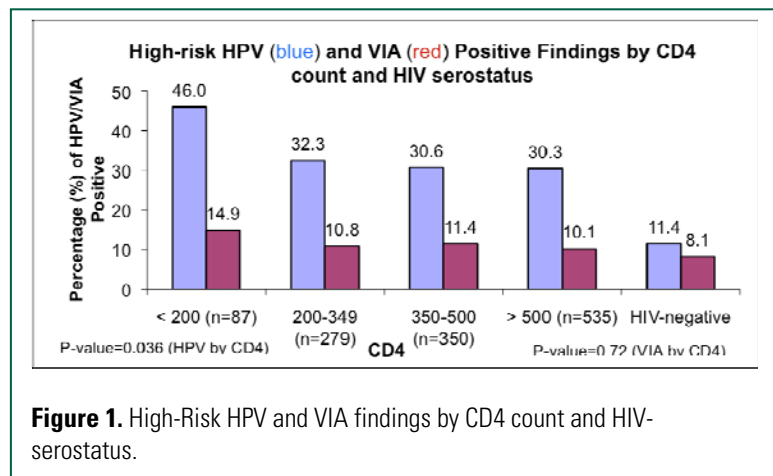


Figure 1. High-Risk HPV and VIA findings by CD4 count and HIV-serostatus.

P4. UAB/CIDRZ Cervical Cancer Prevention Program in Zambia

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Background

Women persistently infected with oncogenic HPV genotypes, severely immunosuppressed from HIV, and without access to effective cervical cancer prevention services are at high risk for developing cervical cancer precursors that, if left untreated, will likely progress to invasive cervical cancer. Such are the circumstances that characterize large numbers of HIV-seropositive women residing in low-income nations whose lifespans are being prolonged because of expanded access to modern HIV care and treatment.

Methods

We implemented nurse-led screen-and-treat services at 15 public-sector sites (11 urban, 4 rural) in Zambia, co-located with ART programs. Nurses evaluated patients using visual inspection with acetic acid (VIA) and digital cervicography. Depending on the surface morphology of acetowhite lesions, patients with VIA positive tests were offered same-visit cryotherapy or referred to the University Teaching Hospital for further evaluation. We estimated program effectiveness by modeling the total number of cervical cancer deaths prevented among the screened population of HIV-seropositive women as a result of our early detection and treatment interventions.

Results

Between January 2006 and December 2008, we screened 21,010 women, of whom 6,572 (31%) were HIV seropositive. In HIV-seropositive women, VIA tests were positive in 3,523 (54%), 2,062 were eligible and offered same-day cryotherapy, and 1,603 underwent the procedure. An additional 1,461 were referred for further evaluation and pathology was available on 715. Clinical, pathologic, and surgical staging of the 715 women revealed 151 with normal/benign histology, 214 with low-grade cervical intraepithelial neoplasia (CIN 1), 235 with high-grade cervical intraepithelial neoplasia (CIN 2/3), and 115 invasive cancers. 69% of the invasive cancers were early stage (stage 1A-1B), and 78% of those were Stage 1A (microinvasive). Using published estimates of disease progression and cure/prevention rates, and assuming all women receive treatment, we estimate that our program prevented 203 deaths from invasive cervical cancer cases among the 6,572 HIV-infected women screened. Overall, one cancer death was prevented for every 32 HIV-seropositive women screened.

Conclusions

A nurse-led, service-oriented VIA-based cervical cancer screening program linked to same-day cryotherapy and referral for excisional biopsy has the potential to prevent deaths from cervical cancer in HIV-seropositive women. Although we face programmatic challenges, low-cost screening saves many lives and should be considered for implementation elsewhere.

P5. Factors Impacting Introduction of HPV Vaccination in Low-Resource Settings

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Introduction

HPV vaccines against HPV types 16 and 18, which are associated with 70 percent of cervical cancer cases, have the potential to reduce cervical cancer if they are used widely among sexually naive girls, especially in developing countries where the disease burden is greatest. However, there are challenges in implementing HPV vaccination within current EPI programs in these countries, including lack of vaccine delivery mechanisms for young adolescent girls, cost associated with and feasibility of delivering the vaccines, and acceptance of vaccines that target sexually transmitted infections. The PATH HPV Vaccines: Evidence for Impact project implemented HPV vaccination in selected areas of three low- and middle-resource countries.

Objective

Evaluate HPV vaccination coverage, feasibility, acceptability, and implementation costs of different delivery strategies.

Methods

Sociocultural research and health system assessment results guided the design of HPV vaccine delivery strategies. Evaluation studies included a modified WHO two-stage cluster survey for coverage; focus groups and key informant interviews for acceptability; vaccination observation, interviews, and focus group discussions for feasibility; and micro-costing using ingredients approach and supplementary expenditure records to estimate costs.

Results

Vaccine delivery included school and clinic-based strategies with HPV vaccines delivered vertically or in combination with other health services. Vaccine coverage varied by region and strategy and ranged from 53 percent to 94 percent. Acceptability was high due to government and EPI support; community trust in vaccines, and comprehensive sensitization and mobilization. Delivery was feasible due to collaboration and planning between health centers and schools for coordinated implementation, and strengthening of cold chain systems. Implementation costs varied by country and strategy used in each country.

Conclusion

Our data suggest that high HPV vaccination coverage can be achieved. Acceptance of the vaccine was also high and the delivery strategies were feasible. Implementation costs are within the range of other vaccination campaign strategies.

P6. Infection of Primary Lymphoid Cells by KSHV: Novel Mechanisms of Immune Control of KSHV in the Lymphoid Compartment

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Kaposi's sarcoma (KS)-associated herpesvirus (KSHV) is a B-lymphotropic herpesvirus whose primary site of replication is the oropharynx, reflecting infection of tonsillar B cells (and possibly oral epithelium). Primary tonsillar explants are infectable in vitro. Although viral entry into both T and B cells is observed in such cultures, T cells do not support either spontaneous or induced lytic replication, while B cells spontaneously produce substantial amounts of infectious virus. When mixed cultures of primary T and B cells are exposed to KSHV, little spontaneous virus production is observed, but virus production can be enhanced by (1) removal of T cells from the mix or (2) treatment of the mixed culture with cyclosporine A. Adding back T cells to purified infected B cells efficiently suppresses KSHV production, and examination of isolated T cell subsets indicates this activity is attributable primarily to CD4-positive T cells. The suppressive activity (1) requires T cell activation, but not prior exposure to KSHV antigen, (2) requires direct cell-cell contact, (3) is not MHC-restricted, and (4) does not result in killing of the target cell. We propose that oropharyngeal T cells activated by a variety of stimuli can recognize ligands on latently infected target cells, leading to signaling events that downregulate lytic reactivation, most likely by promoting latent infection.

P7. Repeated Detection of Infectious Xenotropic Murine Virus-Related Virus (XMRV) in Human Neoplasia and Neuroimmune Diseases

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Background

In 2006, sequences of a novel human retrovirus, XMRV, were identified and reported to be associated with a subset of hereditary prostate cancer. Although the public health implications of this finding were not immediately clear, two recent papers show XMRV is clearly a health concern. One clearly shows that XMRV expression in the proliferating prostate stroma and epithelium of prostate cancer patients [1]. The second describes the detection of XMRV in about two-thirds of patients diagnosed with chronic fatigue syndrome [2]. We will present data that in these and other neuroimmune diseases and cancers, the host mounts a humoral response to XMRV and infected patients are viremic.

Methods

A combination of classical retroviral methods, including RT-PCR, full-length genomic sequencing, immunoblotting of viral expression in activated PBMC, passage of infectious virus in plasma and PBMC to indicator cell lines, and presence of antibodies to XMRV in plasma, allowed XMRV detection in more than 75% of the CFS patients studied. Since then, several publications in Europe using DNA-PCR of blood products failed to detect XMRV sequences in patients with either disease and have created considerable controversy. Reliable methods for the biological and molecular amplification to detect XMRV in unstimulated blood cells and plasma have been developed. Some DNA-PCR negative patient blood samples represent false negatives and molecular analysis using DNA from unstimulated blood cells is not yet sufficient for XMRV identification.

Results

In mice, viruses related to XMRV cause B-cell lymphoma usually by insertional mutagenesis activating a cellular oncogene as well as causing chronic neurological diseases. We will present a case of development of such B cell lymphoma in CFS patients. XMRV-infected individuals with both neuroimmune disease and cancer develop an immune response to XMRV. The isolation of infectious XMRV from prostate cancer patients will be shown for the first time. Pathogenic consequences of this infection will be discussed

Conclusion

XMRV, a retrovirus of unknown pathogenic potential is infectious in humans.

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P8. Merkel Cell Polyomavirus and Two Novel Polyomaviruses Are Chronically Shed From Human Skin

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Background

In the nearly four decades since the human polyomaviruses BKV and JCV were discovered, there have been conflicting reports concerning their possible associations with various forms of human cancer. Although both viruses can cause various forms of cancer in animal model systems, investigation of their possible association with human cancers has been complicated by the fact that nearly all humans harbor chronic kidney infections with one or both viruses. In contrast to BKV and JCV, it is increasingly clear that the recently discovered Merkel cell polyomavirus (MCV) plays a causal role in the development of a rare but highly lethal form of skin cancer called Merkel cell carcinoma (MCC). The discovery of MCV's association with MCC has sparked a resurgence of interest in the possible roles polyomaviruses may play in causing human cancer.

Results

Emerging PCR-based evidence suggests that MCV DNA segments can commonly be detected on various skin surfaces of healthy adult subjects. To investigate the genetic characteristics of commonly circulating strains of MCV, we developed an improved rolling circle amplification technique to clone full-length MCV genomes from skin swab samples contributed by 14/35 (40%) healthy subjects. The results provide the first apparently wild-type full-length MCV isolates and show that commonly circulating MCV strains closely resemble strains found in tumors. The RCA-based analysis also serendipitously revealed the existence of two previously unknown human polyomaviruses, which we have named epsilon polyomavirus-1 (EPV1) and EPV2. The two EPVs occupy a common phylogenetic branch that is distant from MCV and other previously identified human polyomaviruses.

P9. Epidemiology of HIV-Associated Cancers: New Findings From the Long-Term Followup of Cohorts on HAART

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Persons infected with HIV are now known to be at increased risk for all cancers known or suspected to have an infectious cause, an effect believed to be primarily mediated by lowered host immunity via the depletion of CD4+ cells. Whereas Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) were recognised as AIDS-defining illnesses early in the HIV epidemic, the influence of declining CD4+ count on other infection-related cancers has taken longer to establish, undoubtedly because the association is weaker. Following improved survival made possible by combined antiretroviral therapy (cART), however, data from cohorts of PHIV followed up in the cART era are slowly accruing to show that declining CD4+ count both worsens the natural history of infection with carcinogenic viruses, and impacts negatively on the risk for an increasingly wide range of cancers including Hodgkin lymphoma, and cervical, anal, and liver cancer.

Indeed, the introduction of cART has greatly influenced the overall pattern of cancer incidence in people with HIV. The decrease in the prevalence of severe immunodeficiency resulted in a rapid reduction in KS and NHL incidence. Furthermore, there is increasing evidence for a slow increase in the burden of non-AIDS-defining cancers (NADCs) in the cART era. Nevertheless, NADC incidence, even in the immunocompetent population, is strongly associated with increasing age, and the huge shifts in age distribution seen in HIV-positive cohorts make adequately age-standardized comparisons of NADC incidence in the pre- and post-cART periods difficult.

To this end, the latest published epidemiologic research on HIV and cancer risk in the era of cART will be reviewed, and some relevant new data on trends in cancer risk from the Swiss HIV Cohort study will be presented.

P10. HIV and Cancer in Children

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Relative to adults, there are few published data from analytical studies on the risk of cancer in HIV-infected children, primarily because both cancer and HIV infection are less common in children than in adults. It is notable that the spectrum of cancers affecting children in the general population is different from that in adults. Furthermore, unlike adults, the great majority of HIV-infected children acquire the virus in the first months of life, while the immune system is developing and before exposure to many other immunological challenges.

A U.S. study showed that, subsequent to a diagnosis of AIDS, children were at an increased risk of NHL, Kaposi's sarcoma, and leiomyosarcoma. However, the numbers of cases of certain cancer sites or types remain small, hence the need for new and larger studies. Despite the fact that HIV infection is more prevalent in parts of sub-Saharan Africa than elsewhere, there are few data from Africa that indicated the scale of the excess risk of cancer in HIV-infected as compared to uninfected children. The results from studies in Uganda, Malawi, and South Africa indicate that HIV infection increases the risk of Kaposi's sarcoma and lymphoma, although results relating to endemic Burkitt lymphoma are equivocal. Notably, no association between infection with HIV and lymphoid leukemias, for which an underlying infectious etiology has been suggested, has yet been identified.

P11. Epigenetic and Transcriptional Programming and Therapy in B Cell Lymphomas

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Epigenetic deregulation of genes through aberrant DNA methylation has been widely reported in cancer. Epigenetic patterning of genes plays a central role in mediating cell phenotypes. Normal differentiation of stem cells into various terminally differentiated cell types is only possible because of epigenomic programming acquired during the process of cell differentiation. Erasing these epigenomic marks returns cells to a stem cell-like phenotype. Tumor phenotype is equally dependent on epigenomic programming as are normal tissues. Identification of tumor-specific epigenetic programs is crucial to understanding the biology and phenotype and developing specifically targeted therapeutic strategies. In order to identify the epigenetic patterns underlying human tumors we have performed epigenomics profiling studies on cohorts of patients with leukemias and lymphomas. The data demonstrate that aberrant epigenetic programming is a universal event occurring in all tumors, and that epigenetic signatures can identify new subtypes of disease with specific biological and clinical features and serve as biomarkers to predict risk.

Oral Speaker Abstracts

Day 1 Oral Speaker Abstracts

01. Bim nuclear translocation and inactivation by HHV-8 interferon regulatory factor 1

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Viral replication efficiency is in large part governed by the ability of viruses to counteract pro-apoptotic signals induced by infection of host cells. In HHV-8, one group of proteins acting to suppress the host's innate defenses is the set of four viral interferon regulatory factors (vIRFs 1-4), which act to block cellular IRF activities in addition to targeting and inhibiting p53 and other inducers of apoptosis. We observed that in a large proportion of endothelial cells supporting lytic reactivation, the normally cytoplasmic pro-apoptotic BH3-only protein Bim, a negative regulator of HHV-8 productive replication, was localized in the nucleus. Nuclear localization of Bim could be induced in cells cotransfected with vIRF-1, and confocal microscopy identified co-localization of vIRF-1 and Bim in the nuclei of lytically reactivated cells. Physical association of vIRF-1 and Bim was identified in co-precipitation experiments using both transfected cell lysates and purified recombinant vIRF-1 and Bim. In vitro binding studies using a series of truncation and point variants of vIRF-1 enabled precise mapping of the Bim-interacting residues (Bim-binding domain, BBD) of vIRF-1. Wild-type, but not mutated, BBD fused to a nuclear localization signal was sufficient to induce Bim nuclear translocation in transfected cells; BBD-mutated vIRF-1 proteins were unable to do so or to protect cells from Bim-induced apoptosis. Depletion of endogenous vIRF-1 led to reductions in virus production and increased apoptosis in lytically reactivated endothelial cultures, while transduced expression of wild-type vIRF-1 promoted virus production and inhibited apoptosis. Experimental utilization of Bim-refractory vIRF-1 variants revealed the importance of vIRF-1:Bim interaction, specifically, for pro-replication and anti-apoptotic activity of vIRF-1. Furthermore, blocking of the interaction with cell-permeable peptide corresponding to the Bim-binding region of vIRF-1 confirmed the relevance of vIRF-1:Bim association to vIRF-1 pro-replication activity. To our knowledge, this is the first report of an IRF protein that interacts with a Bcl-2 family member and of nuclear sequestration of Bim or any other member of the family as a means of inactivation. Our data reveal a novel mechanism utilized by a virus to control replication-induced apoptosis and suggest that inhibitory targeting of vIRF-1:Bim interaction may provide an effective antiviral strategy.

02. Hsp90 is a viable therapeutic target in the treatment of KSHV-associated primary effusion lymphoma

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Background

Hsp90 is a chaperone protein that binds client proteins involved in the regulation of cell survival and apoptosis signal transduction, including Akt, IKK complex, Apaf-1, survivin, CDKs, and KSHV vFLIP. This binding is necessary to maintain proper protein folding, assembly, transport, and function. A lack of Hsp90 results in protein misfolding, ubiquitination, and degradation. KSHV vFLIP was identified as a viral gene that is responsible for NF- κ B-dependent anti-apoptotic gene expression in primary effusion lymphoma (PEL) cells [1]. In particular, the IKK signaling complex consisting of IKK α , IKK β , IKK γ , vFLIP, and Hsp90 in the case of PEL cells was demonstrated as essential for survival in these cells. As Hsp90 forms part of the IKK signalosome in PEL cells, the Hsp90 inhibitor geldanamycin was previously tested in these cells and has been shown to inhibit activity of this complex in vitro. However, geldanamycin is of limited therapeutic potential due to its undesirable pharmacophysiology. We tested a new purine-scaffold Hsp90 inhibitor with high selectivity for tumor versus normal cell Hsp90, which is water-soluble with high oral bioavailability and excellent therapeutic window [2,3].

Materials and methods

We evaluated the sensitivity of several KSHV infected and uninfected cell lines to treatment with this inhibitor, called PU-H71. We performed viability and NF- κ B reporter luciferase assays. Immunoblot analyses to cellular and viral proteins were done to assess the effect of PU-H71. Finally, we used a mouse PEL xenograft model and in vivo imaging to assess tumor responses to PU-H71.

Results

We found all KSHV-positive PEL cell lines to be exquisitely sensitive when compared to uninfected lymphoma cells, with growth inhibition at IC₅₀s in the nanomolar range. PU-H71 was shown to induce PEL cell death by apoptosis and autophagy within 48 hours of treatment. Western blot analysis indicated that the IKK signaling complex components vFLIP and IKK γ were degraded upon PU-H71 treatment, leading to destabilization of the complex, and inhibition of NF- κ B signaling, as confirmed by reporter luciferase assay. PU-H71 was further tested in a mouse xenograft model of PEL and shown to inhibit progression of tumor spread and confer a significant survival advantage ($p < 0.02$) in these mice.

Conclusions

Our findings suggest that Hsp90 inhibition with PU-H71 is a promising targeted approach for the treatment of PEL and warrants further preclinical and clinical investigation.

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03. Upregulation of angiopoietin-like 4 by viral G protein-coupled receptor promotes angiogenesis and vascular permeability in Kaposi's sarcoma

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Background

Kaposi's sarcoma (KS) is an enigmatic vascular tumor thought to be a consequence of dysregulated expression of the human herpesvirus-8 (HHV-8 or KSHV)-encoded G protein-coupled receptor (vGPCR) [1]. Both human and vGPCR experimental KS lesions are characterized by prominent angiogenesis and vascular permeability attributed to the paracrine release of angiogenic mediators, most notably vascular endothelial growth factor (VEGF). To date, the relative contribution of these paracrine mediators to the angiogenic and exudative phenotype of KS lesions remains unclear. Here we show that vGPCR upregulated angiopoietin-like 4 (ANGPTL4) (Figure 1 A,B,C) plays a prominent role in promoting the angiogenesis and increasing vascular permeability in this tumor. Inhibition of ANGPTL4 effectively blocks vGPCR promotion of angiogenesis and vascular permeability in vitro and tumorigenesis in vivo (Figure 1 D,E,F,G, H).

Conclusion

These observations suggest that ANGPTL4 is a previously unrecognized target for the treatment of patients with KS. As angiogenesis and increased vessel permeability are common themes in all solid tumors, these results may have a broad impact on our understanding and treatment of cancer.

Acknowledgements

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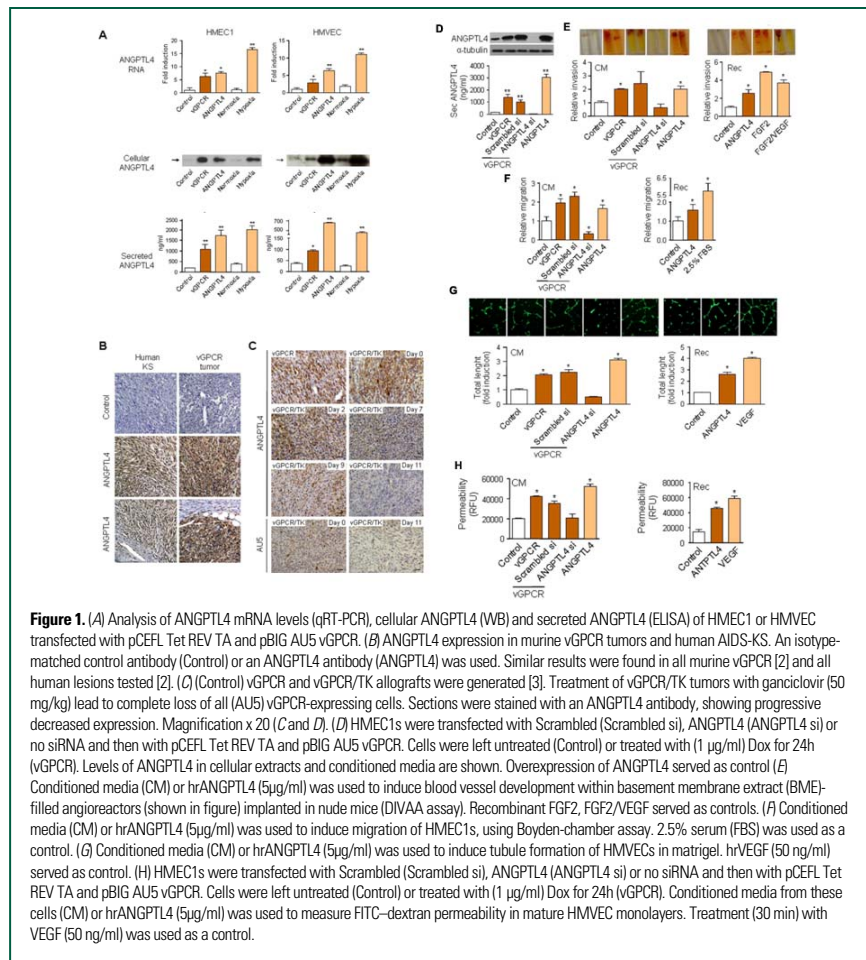


Figure 1. (A) Analysis of ANGPTL4 mRNA levels (qRT-PCR), cellular ANGPTL4 (WB) and secreted ANGPTL4 (ELISA) of HMEC1 or HMVEC transfected with pCEFL Tet REV TA and pBIG AU5 vGPCR. (B) ANGPTL4 expression in murine vGPCR tumors and human AIDS-KS. An isotype-matched control antibody (Control) or an ANGPTL4 antibody (ANGPTL4) was used. Similar results were found in all murine vGPCR [2] and all human lesions tested [2]. (C) (Control) vGPCR and vGPCR/TK allografts were generated [3]. Treatment of vGPCR/TK tumors with ganciclovir (50 mg/kg) lead to complete loss of all (AU5) vGPCR-expressing cells. Sections were stained with an ANGPTL4 antibody, showing progressive decreased expression. Magnification x 20 (C and D). (D) HMEC1s were transfected with Scrambled (Scrambled si), ANGPTL4 (ANGPTL4 si) or no siRNA and then with pCEFL Tet REV TA and pBIG AU5 vGPCR. Cells were left untreated (Control) or treated with (1 μg/ml) Dox for 24h (vGPCR). Levels of ANGPTL4 in cellular extracts and conditioned media are shown. Overexpression of ANGPTL4 served as control (E) Conditioned media (CM) or hrANGPTL4 (5μg/ml) was used to induce blood vessel development within basement membrane extract (BME)-filled angioreactors (shown in figure) implanted in nude mice (DIVAA assay). Recombinant FGF2, FGF2/VEGF served as controls. (F) Conditioned media (CM) or hrANGPTL4 (5μg/ml) was used to induce migration of HMEC1s, using Boyden-chamber assay. 2.5% serum (FBS) was used as a control. (G) Conditioned media (CM) or hrANGPTL4 (5μg/ml) was used to induce tubule formation of HMVECs in matrigel. hrVEGF (50 ng/ml) served as control. (H) HMEC1s were transfected with Scrambled (Scrambled si), ANGPTL4 (ANGPTL4 si) or no siRNA and then with pCEFL Tet REV TA and pBIG AU5 vGPCR. Cells were left untreated (Control) or treated with (1 μg/ml) Dox for 24h (vGPCR). Conditioned media from these cells (CM) or hrANGPTL4 (5μg/ml) was used to measure FITC-dextran permeability in mature HMVEC monolayers. Treatment (30 min) with VEGF (50 ng/ml) was used as a control.

04. KSHV regulation of fibulins in Kaposi's sarcoma: implications for tumorigenesis

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Kaposi's sarcoma (KS) is an angioproliferative tumor of vascular endothelial cells and produces rare B cell lymphoproliferative diseases in the form of primary effusion lymphomas (PELs) and some forms of Multicentric Castleman's Disease (MCD). Kaposi's sarcoma-associated herpesvirus, also known as KSHV or human herpesvirus type 8 (HHV8), is the etiological agent of KS. Fibulins are extra-cellular matrix (ECM) proteins involved in cell adhesion, proliferation, migration, invasion, and angiogenesis, and have been linked to progression of several cancer types. However, to our knowledge, they have not been studied in KS. We examined fibulin-2 because we found it to be significantly downregulated by microarray analysis in KSHV-infected DMVEC cells. Here we demonstrate that fibulin-2 protein expression is downregulated 50-fold in 10 day KSHV-infected dermal microvascular endothelial cells (DMVEC) with a 26-fold reduction in fibulin-2 message. By time-course transcriptional analysis there was consistent reduction of fibulin-2 message accompanied by an increase in KSHV latency associated nuclear antigen (LANA) transcription. Of the fibulins assayed, fibulins -2, -5, and -3 were downregulated over time in KSHV infected DMVEC, while fibulins 1C and 1D were upregulated, with no change in fibulins 4, 6, and 7. In pleural effusion lymphoma cell lines that express different levels of KSHV lytic replication, we observed no detectable fibulin-2 expression. Tissue microarrays representing patch/plaque and nodular forms of KS from 86 different patients were shown to be statistically significant for downregulation of fibulin-2 in virus-infected LANA positive cells by dual labeled immunohistochemical staining. This represents the first study that examines fibulin-2 expression in KSHV-infected DMVEC and KS to determine whether suppression of this ECM protein plays a role in KS tumor progression. Understanding the interactions between KSHV and the fibulin family of extra-cellular matrix proteins that modulate angiogenesis cancer cell proliferation, migration and invasion could lead to development of novel therapies for treatment of KS.

05. HIV-associated salivary gland disease: a role for BK virus

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HIV-associated salivary gland disease (HIV-SGD) is disfiguring and causes significant morbidity in the HIV population. Evidence detailing the epidemiology of HIV-SGD suggests the involvement of a viral opportunist in its pathogenesis, yet the specific etiology of HIV-SGD remains unclear. To determine the role for an opportunistic virus as the etiologic agent of HIV-SGD, we hypothesized that HIV-SGD was a manifestation of primary infection or reactivation with a DNA tumor virus, BKV, during immune suppression. The central hypothesis of this work is that viral pathogenesis is essential to the development of salivary gland disease. Results show for the first time that polyomavirus, BKV, is associated with HIV-SGD. BKV DNA, RNA, and protein were consistently detected in salivary gland biopsies and in the peripheral blood and oral fluids from HIV-SGD patients and not in control subjects. To confirm the *in vivo* findings, an *in vitro* model was created whereby parotid and submandibular salivary gland cells were productively infected with BKV, demonstrating each part of the viral life cycle. Salivary gland tropism was confirmed and the BKV receptor on salivary gland cells was defined. BKV transmission and pathogenesis is not well understood. Importantly, these studies suggest a role for BKV in HIV-SGD and that BKV transmission may occur via the oral route. The long-term goal of this project is to make critical strides toward understanding the etiology of SGD in order to go beyond the ineffective palliative treatment that is currently the standard of care.

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06. Bacteria-mediated reactivation of gammaherpesviruses

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Significant morbidity is associated with the synergistic and inhibitory interactions of bacteria, viruses, parasites, and fungi. The oral cavity, gut, and genitourinary tract are home to many of these organisms and are the site of virus-associated malignancies that affect millions worldwide. Yet little is known with regard to the cellular and molecular interactions of viral pathogens with the normal flora as well as the interactions among pathogens themselves. Our laboratory is interested in understanding the role of factors present within the immediate environment that may influence reactivation of persistent infection and pathogenesis. Our central hypothesis is that viral-bacterial interactions foster enhanced pathogen replication and modulation of the immune response in the mouth, GI tract, and genito-urinary tract. The detection of replicating virus in these tissues has incited investigation into the relationship between bacterial infection and herpesviral reactivation. We hypothesized that bacterial end-products including short chain fatty acids (SCFA), lipopolysaccharide (LPS), and lipoteichoic acid (LTA) secreted by oral bacteria initiate viral reactivation from latency. Latently infected EBV, KSHV, and MHV 68 cell lines were incubated with crude spent media containing secreted SCFA, and components of bacterial pathogens (*E. faecalis*, *Bacteriodes*, *Prevotella*, *Porphomonas*, and *Fusibacterium Nucleatum*). Cells were then assayed for viral promoter activation, promoter-protein interactions, and state of infection. Following incubation with crude spent media, viral immediate early promoters were activated, the viral early genes were upregulated as determined by RT PCR and western blot, and linear genomes were detected. HDAC inhibition activity as well as protein kinase C activity increased significantly following treatment with bacterial spent media. KSHV and EBV were consistently reactivated by bacterial metabolites but the mechanism of reactivation was both bacteria, virus, and cell type specific. Interestingly, EBV was preferentially reactivated following toll like receptor stimulation while KSHV and HSV-1 reactivation occurred following HDAC inhibition. In conclusion, these studies provide significant insights to gammaherpesreactivation that may occur in vivo via pathogen-pathogen interaction.

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07. Phase II AIDS Malignancy Consortium (AMC) trial of imatinib in AIDS-associated Kaposi's sarcoma (KS)

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Background

KS is a disease of multifocal vascular proliferation that requires infection with the KS herpes virus (KSHV/HHV-8). Activation of the c-kit and platelet derived growth factor (PDGF) receptors by autocrine and paracrine mechanisms follows KSHV infection of endothelial cells. Partial KS regression in 5/10 patients was observed in a pilot study using the c-kit/PDGF-R inhibitor imatinib (Novartis Pharmaceuticals), and 3/4 biopsies showed PDGF inhibition, suggesting this agent has activity in AIDS-related KS.

Methods

The primary objective was to estimate the response rate of KS to imatinib in AIDS-related KS. Secondary objectives included investigation of predictors of response and imatinib pharmacokinetics in patients on cART. Patients were treated with imatinib 400 mg/day orally for up to 12 months with the option to dose escalate to 600 mg/day at 3 months if disease was stable. Plasma concentrations of CCL5 (RANTES), IFN γ , IL-6, and FGF- β at baseline, day 8, and day 28 were measured using the Mesoscale platform to assess the utility of these growth factors as biomarkers.

Results

Thirty patients were treated at 12 AMC sites. Median CD4 count was 263 (19-819). 79% had undetectable HIV RNA. Ten (33.3%) showed partial response, 6 (20%) had stable disease, and 7 (23.3%) showed KS progression by modified AIDS Clinical Trial Group response criteria. Treatment was well tolerated. Nine patients completed 52 weeks of imatinib and the median treatment duration was 22.5 weeks (0.3-52.7). Only 5 patients (16.7%) discontinued therapy due to adverse events including grade 3 hypophosphatemia (2), allergic reaction (1), cellulitis (1), depression (1), and grade 4 elevation of CK (1). Pharmacokinetic analysis of the AUC ratios (using day 1 and 15 sampling) demonstrated that actual imatinib AUC levels were significantly higher than predicted ($P=0.036$), but there was no difference between actual and predicted AUC for the active metabolite ($P=0.441$), suggesting the antiretroviral regimens influenced imatinib metabolism. While baseline levels of CCL5 and IFN γ and changes in the levels of IL-6 and FGF-b correlated with response in our pilot study, none of these growth factors predicted response in this larger study.

Conclusion

Imatinib has activity in AIDS-related Kaposi's sarcoma. The potential interactions with antiretroviral drugs did not correlate with increased toxicity. Thirty percent of patients showed long-term clinical benefit and remained on imatinib for the entire year. These results suggest this regimen is well tolerated and may be an alternative to cytotoxic chemotherapy for some patients with AIDS-related KS.

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08. Rituximab combined with liposomal doxorubicin (R-Dox) in HIV-infected patients with severe Kaposi sarcoma-associated herpes virus (KSHV) associated multicentric Castleman disease (MCD)

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Background

MCD is characterized by inflammatory symptoms, splenomegaly, adenopathy, hypoalbuminemia, hyponatremia, and cytopenias. MCD in HIV-infected patients is generally KSHV-associated. No standard therapy exists. Rituximab has activity, but monotherapy may be insufficient in severe disease and can be associated with worsening of Kaposi's sarcoma (KS).

Methods

Patients with symptomatic MCD received rituximab 375 mg/m² plus liposomal doxorubicin 20 mg/m² every 21 days until substantial clinical improvement or disease progression. This regimen is being evaluated prospectively within an MCD natural history protocol. Additional therapy, employing agents with antiviral activity (discussed below), was generally employed to consolidate or maintain responses. Clinical, biochemical, and radiographic responses were evaluated using protocol-defined criteria. Overall complete response (CR) required normalization of all MCD-related abnormalities.

Results

Patient characteristics: 12 (1 woman, 11 men) patients completed R-dox. Median age, 43 (34-55); median number of prior therapies 2 (0-8). Diffuse adenopathy (12); median spleen (cm), 18.5 (12.5-28). Concurrent KS (5). All were receiving concurrent combination antiretroviral therapy. Baseline laboratory values, median (range): CD4 cells/ μ L, 291 (21-1598); C-reactive protein (mg/dL), 9.9 (0.4-21); albumin (mg/dL), 2.7 (1.5-3.3); sodium (mEq/L), 133 (126-136); platelets (K/ μ L), 70 (10-377); hemoglobin (gm/dL), 9.4 (6.8-12.2). Median cycles received 4.5 (3-9).

Table 1. Best response with R-Dox.

Response Category	Complete Response	Partial Response	Stable Disease
Clinical	12 (100%)	-	-
Biochemical	10 (83%)	1 (8%)	1 (8%)
Radiographic	6 (50%)	6 (50%)	-
Overall	3 (25%)	6 (50%)	3(25%)

With 9 patients receiving additional therapy after R-dox; IFN α (6), high-dose zidovudine + valganciclovir (2), additional liposomal doxorubicin (1); 6 additional patients achieved overall CR (total 75%). KS responded in 4/5 (80%). With 31.4 months median potential followup (actual 5.5+ to 47+), estimated 2-year progression-free survival and overall survival are 61.1% and 78.6%, respectively. 8/12 (67%) remain symptom free, while 3 had recurrent MCD flares (months 7, 10, 17) responding to additional R-Dox. One had progressive MCD and worsening KS during cycle 6 and died at month 6. At autopsy, primary effusion lymphoma was discovered. One patient died at month 17 of sepsis unrelated to therapy. Select toxicities: 9 infusion reactions (Gr. 1 = 3, Gr. 2 = 4, Gr. 3 = 2) with the first dose of rituximab; 6/60 cycles complicated by neutropenia (Gr. 2 = 5, Gr. 3 = 1), no infectious complications.

Conclusions

R-Dox is effective in treating severe KSHV-MCD or MCD with concurrent severe KS. Evaluation of R-Dox in KSHV-MCD is ongoing.

09. The KAART Trial: a randomized controlled trial of HAART compared to the combination of HAART and chemotherapy in treatment-naïve patients with HIV-associated Kaposi sarcoma (HIV-KS) in KwaZulu-Natal (KZN), South Africa

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Background

KS is the most common cancer in people with HIV/AIDS, affecting both men and women in sub-Saharan Africa. Without HAART, mortality is high. Given poor access to HAART and prevalent HIV and KS-associated herpesvirus co-infection, advanced HIV-KS is an increasing problem in KZN. This is the first prospective study evaluating the impact of HAART and the role of early chemotherapy in HIV-KS in Africa.

Methods

We performed a randomized, controlled, open-label trial comparing HAART to the combination of HAART and chemotherapy (CXT) in treatment-naïve patients with biopsy-confirmed HIV-KS, recruited from the dermatology clinic at King Edward VIII Hospital, KZN, South Africa. Patients were stratified by ACTG risk group. HAART was stavudine, lamivudine, and nevirapine. CXT consisted of HAART plus bleomycin (10 U/m²), doxorubicin (20 mg/m³), and vincristine (1.4 mg/m²). Responses were evaluated by ACTG criteria. We performed an intention-to-treat comparison between arms of KS clinical responses at month 12 (Fisher exact test), rate of response (Mantel-Haenszel rate ratio), and overall survival (log-rank test). ACTG prognostic criteria were evaluated (Cox proportional hazard regression). Toxicity was monitored using DAIDS criteria. Adherence was assessed by a 7-day recall questionnaire. Toxicities, adherence, and changes in CD4 and HIV-1 viral load were compared between arms (Fisher exact test).

Results

Baseline characteristic: 310 patients were screened, with 112 (62 women, 50 men) randomized; 59 to HAART and 53 to CXT arm. Mean age 34 (20-63 yrs). 89% had advanced disease (T1 disease), 93% poor risk by ACTG criteria, 58% with CD4 <200, 42% had a history of co-morbid infection; commonly tuberculosis (34%). Responses: The overall response rate (complete responses plus partial responses) at month 12 was 39% in the HAART arm and 66% in the CXT arm (p=0.005). The CXT arm had a 2.7 times faster response rate (p<0.001). Overall survival at 12 months was 76%, with no significant differences between arms (p=0.49). ACTG T1S staging was validated (p=0.03), with systemic illness the most significant prognosticator of overall survival. There were no significant differences in CD4 improvement, HIV viral load decay, adverse events, or adherence between arms.

Conclusion

HAART dramatically improves overall survival in African patients with HIV-KS compared to historic controls. Addition of chemotherapy improves response rates in patients with advanced (T1) HIV-KS.

010. Distinct profiles of antibodies to Kaposi sarcoma-associated herpesvirus antigens in patients with Kaposi sarcoma, multicentric Castleman's disease, and primary effusion lymphoma

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Clinical Background

Kaposi sarcoma-associated herpesvirus (KSHV), also called human herpesvirus-8 (HHV-8), is the causative agent of all forms of Kaposi sarcoma (KS), as well as two rare B-cell HIV lymphoproliferative disorders, primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD). Like other herpesviruses, KSHV has two phases of gene expression, latent and lytic. In KS, many of the KSHV-infected spindle cells express only latent genes, while a small percentage express lytic genes. By contrast, a substantial percentage of MCD cells express lytic KSHV genes. The majority of PEL cells express KSHV latent genes, but in addition can show limited expression of certain lytic genes. Given the differential expression of KSHV lytic and latent proteins in KS, PEL, and MCD, we hypothesized that different antibody profiles to KSHV antigens might distinguish these diseases.

Materials and methods

Antibodies were evaluated in sera from patients or volunteers under IRB-approved protocols at the NIH Clinical Center, NIAID, and the NCI including from 35 patients with KS, 14 with both MCD and KS (MCD+/KS+), 6 with MCD but no KS (MCD+/KS-), 5 with PEL, and 34 KSHV-uninfected controls. Luciferase Immunoprecipitation Systems (LIPS) was used for profiling antibodies to latent and lytic KSHV antigens.

Results

Using LIPS, antibodies against the lytic antigen K8.1 were 5-fold higher in MCD than in KS patients. In contrast, markedly higher antibodies to v-cyclin, a latent KSHV gene, were found in the KS and PEL patients compared to the MCD. Antibodies to another latent antigen, LANA, were also markedly higher in the KS compared to the MCD patients. Antibodies to the sum of latent antigens v-cyclin and LANA were 27-fold higher in KS compared to MCD patients ($p < 0.0001$). The sum of anti-v-cyclin and anti-LANA antibody titers discriminated patients with KS without MCD from those with MCD and KS with 93% sensitivity and 83% specificity.

Conclusion

These results suggest that antibody responses to lytic and latent KSHV antigens differ between KS, MCD, and PEL.

Acknowledgements

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011. Pooled analysis of AIDS Malignancy Consortium (AMC) trials evaluating rituximab plus either CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin's lymphoma

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Background

Two consecutively performed randomized studies by the AMC evaluating chemoimmunotherapy for the treatment of HIV-associated NHL include AMC010 [1] (Concurrent Rituximab [R] + CHOP vs. CHOP, N=150) and AMC034 [2] (Concurrent R+EPOCH vs. Sequential EPOCH →R; N=106). In AMC010, the addition of Rituximab to CHOP was associated with an increased risk of infectious death (15% vs. 2%, p=0.035) without a significant improvement in complete response (CR) rate (58% vs. 47%; p=0.147), event-free survival (EFS), or overall survival (OS). In AMC034, the CR rate met its primary efficacy endpoint in the concurrent arm (73%; 95% confidence intervals [CI] 58%, 85%) but not the sequential arm (55%; 95% CI 41%, 68%).

Methods

We performed a pooled analysis of these two consecutive trials including patients treated with R-CHOP and concurrent R-EPOCH in order to determine the influence of the age-adjusted International Prognostic Index (aalPI), CD4 count (<100/μL vs. >100/μL), and treatment (CHOP vs. EPOCH) as variables.

Results

The characteristics and outcomes of the study populations are shown in table 1. Patients treated with R-EPOCH tended to have better outcomes in both the low and high-risk IPI groups.

Table 1. Patient characteristics and outcomes.

	R-CHOP	R-EPOCH
No.	99	51
CD4<100/μL	41%	31%
High aalPI risk (2-3 factors)	59%	69%
Mean age (years +/- standard deviation)	43.5 (± 8.3)	42.6 (±8.4)
CR rate		
Low risk aalPI (0-1 factors)	76% (60%, 88%)	88% (62%, 98%)
High risk aalPI (2-3 factors)	45% (32%, 58%)	60% (42%, 76%)
2 year EFS		
Low risk aalPI (0-1 factors)	57% (36%, 73%)	81% (51%, 93%)
High risk IPI (2-3 factors)	30% (18%, 43%)	59% (41%, 74%)
2 year OS		
Low risk aalPI (0-1 factors)	66% (43%, 82%)	87% (57%, 97%)
High risk aalPI (2-3 factors)	36% (23%, 50%)	62% (44%, 76%)

In a multivariate analysis that included pooled data from both consecutive studies, features that were significantly associated with improved EFS, OS, and CR rate included low aalPI score and baseline CD4 count of at least 100/μL. Additionally patients treated with concurrent R-EPOCH exhibited improved EFS and OS even when adjusted for prognostic covariates including aalPI score and CD4 count (Table 2).

Table 2. Multivariate analysis regarding the outcomes event-free survival (EFS), overall survival (OS) and rate of complete or unconfirmed complete remission (CR/CRu).

	EFS p-value HR (95% CI)	OS p-value HR (95% CI)	CR/CRu p-value OR (95% CI)
aaIPI score (0-1 vs. 2-3)	<0.001 0.32 (0.17, 0.57)	<0.001 0.28 (0.14, 0.56)	<0.001 4.58 (1.96, 10.69)
CD4 (≥ 100 vs. $< 100/\mu\text{L}$)	<0.001 0.42 (0.26, 0.69)	<0.001 0.37 (0.22, 0.63)	<0.05 2.70 (1.26, 5.79)
R-EPOCH vs. R-CHOP	<0.01 0.40 (0.23,0.69)	<0.01 0.38 (0.21, 0.69)	0.117 1.90 (0.85, 4.22)

Conclusions

These findings suggest that treatment outcomes may be superior with concurrent R-EPOCH compared with R-CHOP, and support the design of an ongoing Phase III trial comparing concurrent R-EPOCH with R-CHOP in immunocompetent patients with diffuse, large B-cell lymphoma (NCT00118209). This analysis provides additional level 2 evidence supporting the use of concurrent R-EPOCH in patients with HIV-associated lymphoma.

Acknowledgements

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Day 2 Oral Speaker Abstracts

012. Cervical cancer epidemiology among HIV-infected women in North America

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Background

Initial studies suggest immunosuppression may be associated with the increased rates of precancerous cervical lesions observed in HIV-infected compared with HIV-uninfected individuals, but few studies have large enough populations to study the effect on invasive cancer. To characterize the incidence of cervical cancer among HIV-infected women in the HAART era, we examined data from the NA-ACCORD HIV cohort collaboration of IeDEA.

Materials and methods

This analysis includes data from 13 North American cohorts of HIV-infected women that collected clinically confirmed or cancer registry-linked data on invasive cervical cancer. Cervical cancer-free women were followed from the first HAART era CD4+ measurement (1996 onwards) until the earliest of: cervical cancer diagnosis, lost to followup, death, or December 2007. Incidence rate overall, by calendar period, and by first CD4+ cell count after 1995 (baseline) were standardized for age using the 2000 U.S. standard population.

Results

Among the 16,467 HIV-infected women free of disease at baseline, 102 cases of invasive cervical cancer were reported, yielding an age-standardized incidence rate of 114 per 100,000 person-years (95% CI: 88–139). Of those cases, 40 (39%) were HAART-naïve at the time of diagnosis. Among women ≤39, 40-49, and ≥50 years of age the incidence rates were 122, 142, and 89 per 100,000 person-years, respectively. The age-standardized incidence rates by calendar periods for 1996-1999, 2000-2003, and 2004-2007 were 133, 152, and 87 per 100,000 person-years, respectively, showing no trend. The age-standardized incidence rates by baseline CD4+ categories of >350, 200-350 and <200 cells/μL were 68, 113, and 185, respectively, indicating an increasing rate with declining CD4+ cell count ($P_{\text{trend}} < 0.001$). Among 13,716 HIV-negative women free of disease in these cohorts, there were 10 invasive cervical cancers for an incidence of 12.3 per 100,000 person-years (95% CI 6.6-23), similar to the age-adjusted SEER population incidence of 8.2 per 100,000 person-years.

Conclusions

In this large collaboration of North American HIV cohorts, the estimate of cervical cancer incidence was almost 10-fold higher among HIV-infected than uninfected women in these cohorts. Although an effect of increased sexual risk-taking in HIV-infected women and/or differences in screening cannot be excluded, the strong association with lower baseline CD4+ cell count suggests a single low CD4 measurement may predict increased cervical cancer risk. It is unclear whether improvements in HIV-therapies during the HAART era have influenced cervical cancer rates; although no significant trend in incidence was observed over time, a decrease was observed in 2004-07.

Acknowledgement

This work is presented on behalf of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA.

013. Progression of cervical neoplasia in HIV-seropositive women with and without antiretroviral therapy in Johannesburg, South Africa

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Background

HIV-seropositive women have a higher risk of oncogenic HPV infection, cervical neoplasia, and cervical cancer than HIV-seronegative women. As HIV-seropositive women begin to live longer due to effective highly active antiretroviral therapy (HAART), their risk of developing cervical cancer may increase. Little data exist regarding the progression of cervical neoplasia in HIV seropositive women from sub-Saharan Africa.

Methods

A longitudinal observational study of 2,106 HIV-seropositive women was performed to determine progression rates of cytological outcomes in a government HIV clinic in Johannesburg, South Africa, stratified by use of HAART. The 2001 Bethesda grading system was to classify conventional Pap smear diagnoses. The effect of HAART use at initial visit on rate of progression of cervical neoplasia was determined using multivariate Poisson regression to obtain incidence rate ratios (IRRs) adjusted for age, CD4 count, history of STDs, use of hormonal contraception, parity, number of lifetime sex partners, and age at first sexual contact.

Results

The cohort comprised 741 HIV-seropositive women with at least two visits more than 6 months apart. Mean followup time among these women was 565 days (median 449 days; intraquartile range 382-698 days). Among women with a normal baseline Pap (n=326), 76 (23%) progressed to LSIL or HSIL, at a rate of 16.0 (95% CL 12.8, 20.0) per 100 woman-years. Among women with LSIL at baseline Pap (n=275), 46 (17%) progressed to HSIL at a rate of 10.8 (95% CL 8.1, 14.4) per 100 woman-years. Of the remaining 140 women with HSIL at baseline Pap who not assessed treatment before repeat Pap smear, none progressed to cancer. In multivariate Poisson regression, women receiving HAART at baseline visit were less likely to progress than women not receiving HAART at baseline (IRR=0.60, 95% CL 0.41, 0.87). Results were similar regardless of baseline Pap result, and using multivariate Cox proportional hazards models (hazard ratio, 0.55, 95% CL 0.38, 0.80). In addition, lower CD4 counts were associated with higher rates of cervical neoplastic progression, although results were imprecise.

Conclusion

This is one of the first reports of progression rates of cervical neoplasia among HIV-positive women. These rates among women from South Africa are concerning. There is an urgent need for broad-reaching screening/treatment in Africa.

014. Persistence of anal squamous intraepithelial lesions and anal HPV infection in HIV-infected patients despite immune restoration under cART

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Background

A high prevalence of anal squamous intraepithelial lesions (ASIL) and HPV infection have been observed in HIV-infected MSM in the pre-cART era. To date, the impact of cART on the natural history of HPV infection and ASIL is poorly documented.

Methods

94 HIV-infected MSM naïve of cART were enrolled in a longitudinal study before starting a first-line regimen of cART. Each patient provided anal samples for cytology, histology, and HPV DNA testing at baseline, month 12, and month 24 of cART. HPV DNA was detected by real-time PCR and Roche Linear Array assay. Anal cytologic was processed by the Thin Prep™ method (Hologic). CD4+ and CD8+ T cell responses to HPV-16 E6 and E7 proteins were measured in a subgroup of individuals exhibiting HPV-16 anal infection at inclusion.

Results

Table 1. The median age of the patients was 39.7 years (33.2-43.5). Baseline and month 12 cytologic and/or histologic results.

	CD4/mm ³ median (Q1-Q3)	Plasma HIV RNA log ₁₀ copies/mL	VL <50	Prior AIDS event	Visible lesion	Presence of condyloma	Anal SIL	Low-grade SIL; High-grade SIL
Baseline	299 (242 – 342)	4.8 (4.17 – 5.26)	1%	4 (4%)	40/94 (43%)	23/94 (25%)	51 (54%)	30 (32%); 8 (9%)
M12	500 (411 – 575)	1.6 (1.6 – 1.6)	93%		25/71 (35%)	5/71 (7%)	41 (58%)	24 (34%); 10 (14%)

Prevalence of low-grade SIL, high-grade SIL, and HPV infection was similar at M12 compared to baseline. Among patients with normal cytology and/or histology at baseline, 44% progressed to SIL at M12 whereas 31% of patients with ASIL at baseline exhibited a regression at M12. Specific anti-HPV CD4 T cell responses were mostly undetectable both at baseline and M12.

Table 2. Baseline and month 12 virological results.

	Number of HPV	Number of high-risk and low-risk type	High risk HPV	HPV-16	HPV-18	HPV-16 DNA log ₁₀ copies/10 ⁶ cells
Baseline	5 (2 – 7)	3 (2 – 5); 2 (1 – 4)	83 (90%)	49 (53%)	28 (30%)	6.1 (5.3 – 7.1)
M12	5 (2 – 6)	3 (1 – 4); 2 (1 – 4)	59 (87%)	28 (41%)	15 (22%)	6.1 (2.0 – 7.2)

At month 12, prevalence of anal HPV DNA detection was similar than at baseline. High-risk HPV was detected at month 12 in 92% of the patients with high-risk HPV infection at baseline. Low-risk HPV was detected at month 12 in 91% of the patients with low-risk HPV infection at baseline. HPV-16 and HPV-18 were detected at month 12 in 13% and 3.7% of patients with no HPV-16 and HPV 18 infection at baseline, respectively. HPV-16 was detected in 100% and 70% of high-grade SIL at baseline and month 12, respectively.

Conclusion

Our results demonstrate a high prevalence and incidence of ASIL and anal HPV infection in HIV-infected MSM despite CD4 reconstitution under cART. These data suggest that all HIV-positive MSM, even under antiretroviral therapy, remain at risk of anal SIL.

015. Risk of anal cancer in HIV-infected patients and HIV-uninfected controls in North America

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Background

Studies have provided conflicting data for calendar trends in anal cancer among HIV+ individuals, one of the most frequent cancers in this population. Our objective here was to compare the risk of anal cancer between HIV+ and HIV- individuals in North America, and how this relationship has changed over time.

Methods

We conducted a cohort study involving 12 cohorts from North America followed between 1996 and 2007. Anal cancer incidence rates were compared between HIV+ men who have sex with men (MSM), HIV+ non-MSM (including women), and HIV- individuals. We calculated rate ratios (RRs) using multivariable Poisson regression with adjustment for age, sex, race/ethnicity (26% imputed), and calendar era. We next determined whether the adjusted RR for HIV+ compared with HIV- controls has changed over time. Since only a subset of cohorts contributed HIV- controls, we also computed age- and sex- and race-standardized incidence ratios (SIR) using national U.S. SEER rates.

Results

Cohort-specific HIV+ anal cancer incidence rates ranged across cohorts from 0 to 154 cases per 100,000 person-years. The cohort-specific prevalence of MSM explained 58% of the total variability in rates. Overall, there were 111 anal cancer diagnoses among 15,907 HIV+ MSM, 38 diagnoses among 18,239 HIV+ non-MSM, and 79 diagnoses among 115,469 HIV- individuals. The corresponding adjusted RRs were 66.6 (95% CI: 36.9-120.2) for HIV+ MSM and 23.4 (95% CI: 11.9-46.1) for HIV+ non-MSM compared with the HIV- control group. For both HIV+ MSM and non-MSM, the RR was highest in 1999-2002, but the RR decreased for both groups in the most recent calendar era, 2003-2007 (Table), although the differences were not statistically significant ($p>0.2$) comparing RRs across eras. Inferences were similar for SIRs.

Table. Anal cancer RR (95% CI) for HIV+ MSM and HIV+ non-MSM compared with HIV- controls (reference) and national US SEER rates.

	RR (MSM)	RR (non-MSM)	SIR (MSM)	SIR (non-MSM)
1996 to 1998	97.7 (12.3-774.3)	12.0 (0.7-195.5)	63.5 (29.0-120.6)	10.2 (0.3-56.9)
1999 to 2002	114.7 (35.3-372.8)	35.2 (9.8-126.5)	117.3 (84.5-158.5)	26.4 (11.4-52.0)
2003 to 2007	48.1 (23.6-98.2)	19.7 (8.8-44.1)	77.7 (59.3-100.0)	26.4 (14.8-43.5)

Conclusions

Despite an aging HIV+ population with presumed longer exposure to the oncogenic effects of human papillomavirus, the relative incidence of anal cancer among HIV+ individuals in the most recent calendar era has not increased. It is possible that improvements in immune function resulting from effective antiretroviral therapy contributed to this result.

Acknowledgements

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016. Integrative proteomics and genomics supports a role for interferon gamma in the pathogenesis of Kaposi sarcoma and finds multiple candidate diagnostic proteins for early detection or prevention

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Background

Kaposi sarcoma (KS) is a common and morbid condition among persons with HIV infection. Strategies for preventing KS or designing better treatment regimens would be aided by the identification of biomarkers for development or progression of KS. Due to the vascular and often disseminated nature of KS, proteomic signatures detected from and specific to KS tumors may yield viable candidate diagnostic protein markers and insights into the pathogenesis of KS.

Methods

Flash-frozen punch biopsies from cutaneous samples of tumor and normal skin of individuals having epidemic (HIV-positive) or endemic (HIV-negative) KS were profiled using tandem mass spectrometry. Protein data were integrated with previously existing databases relevant for prioritizing diagnostic marker candidates, including plasma proteome data of cancer-free individuals, normal endothelial cells, and microarrays profiling the mRNA of KS, normal skin, KSHV-infected endothelial cells, and uninfected cells.

Results

In a comparison of 13 HIV+ tumor punch biopsies to 5 HIV+ normal samples, 5100 total proteins were identified. We have identified proteins abundant in the majority of tumor samples and absent from normal skin and plasma of cancer-free individuals that may serve as candidate diagnostic markers. Aligning the data with KS tissue expression data produced 72 proteins that were over-abundant in KS samples in both proteomic and transcriptomic datasets. Most notably, a third of those proteins (24 total) are known to interact with interferon gamma (IFN γ) (enrichment p-value < 10⁻⁸). Gene symbols are shown in Figure 1. This finding is consistent with previous observations on the importance of IFN γ in endothelial cell proliferation and expression in KS tumors. We are currently evaluating these results further, including conducting other experiments intended to compare the KS proteomics signatures that distinguish 6 HIV+ and 6 HIV- KS tumors. Preliminary results from these analyses will be presented as well.

Conclusions

The combined use of genomic and proteomic interrogation of biopsy material from KS tumors has revealed a large set of proteins that are overexpressed in KS compared to normal skin and provides a set of candidate diagnostic proteins for the prevention or early detection of KS. These data are also useful in exploring hypotheses regarding the pathogenesis of KS and relating those mechanisms to their role in endemic and epidemic disease.

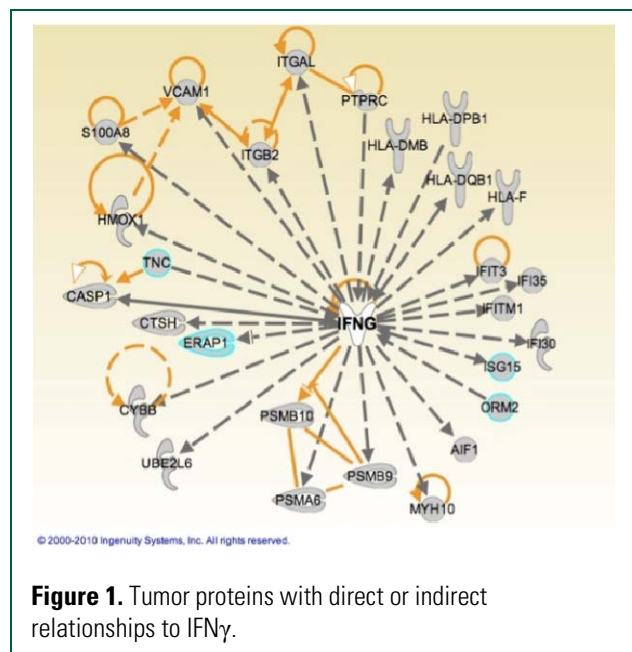


Figure 1. Tumor proteins with direct or indirect relationships to IFN γ .

017. Malignant lymphoma incidence and HIV-related lymphoma subtypes in the Western Cape of South Africa, 2002-2009

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Background

The incidence of malignant lymphomas (ML) in the Western Cape, a province of South Africa (SA), with a population of 5 million and an estimated HIV prevalence of 15% (census report 2002) has not been previously documented. Highly active antiretroviral therapy (HAART) was introduced into the public patient sector in 2004, with 28% estimated coverage by 2007 (UNAIDS/WHO 2008). People living with HIV (PLWH) have 60-200 times increased risk of developing HIV-related lymphoma (HRL). Therefore, based on HIV prevalence, HRL would be expected to increase but is undocumented.

Materials and methods

We reviewed all patients diagnosed with ML from the Tygerberg Academic Hospital catchments area in the Western Cape of SA for years 2002-2009. In this timeframe 606 cases of ML were identified, of which 488 were HIV-negative and 118 HIV-positive. ML were subtyped according to WHO classification (2008) based on cell or tissue morphology and molecular and immunophenotypic platforms.

Results

ML cases increased each year from 2002 to 2005 and remain elevated in both the HIV-negative and HIV-positive patients through 2009. HRL increased from 5% in 2002 to 30% in 2009 with a profile of subtypes differing from the HIV-negative cases. ML subtypes of HIV-negative (488) and HIV-positive (118) cases are shown in Table 1.

Table 1. Percentages of ML subtypes by HIV status.

Subtype	%HIV-	%HIV+
Burkitt lymphoma		35
Diffuse large B-cell lymphoma	44	33
Plasmablastic lymphoma		16
Follicular lymphoma	12	
Hodgkin's lymphoma	11	5
Small cell lymphoma	4	1
Mucosa-associated lymphoid tissue (MALT)	4	1
Anaplastic large cell lymphoma	3	3
Marginal zone lymphoma	3	
Cutaneous T-cell lymphoma	3	
T-cell lymphoma	2	1
Primary effusion lymphoma and Castleman's disease		2
Other	13	4
<i>Total</i>	<i>100</i>	<i>100</i>

Conclusions

ML cases increased from 2002 to 2009 including a dramatic increase in HRL, currently at 29% of all cases. This changing pattern of subtypes in PLWH presents new challenges to histopathology diagnosis as well as a clinically more therapeutically difficult patient population. Burkitt lymphoma, the most common HRL, is among emerging subtypes, along with plasmablastic lymphoma, not previously seen in this geographic region. We anticipate the continued rise in HRL cases as PLWH live longer with HAART. Emergence of more aggressive lymphoma subtypes inevitably poses a major strategic health concern in the region. We participate in the Sub-Saharan Africa Lymphoma Consortium [<http://www.ssalc.org>] to expand the understanding of HRL in this region of the world.

018. HPV genotype and EGFR activation in conjunctival carcinoma among HIV patients in East Africa

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Purpose

There is a substantial growth in the number of HIV patients with conjunctival squamous cell carcinoma in East Africa. However, the etiologic mechanism is unclear and therapeutic options are very limited. We hypothesized that this unique AIDS-associated malignancy would harbor human papillomavirus and involve activation of the EGFR signaling pathway. Positive findings would identify etiologic causes and provide clinical guidance to improve treatment.

Experimental design

Expression of p-MAPK/MAPK, p-Akt/Akt, and p-EGFR/EGFR in cell nucleus and cytoplasm of 38 FFPE specimens was assessed by immunohistochemistry; HPV genotype was detected by qPCR; EGFR mutation was assessed by DNA sequencing; and EGFR mRNA expression was measured using relative qPCR. Statistical analyses included two-sided Fisher exact test or chi-square test, Spearman correlation coefficient, and ANOVA.

Results

HPV 18 was found in 23 of 38 (61%) samples, with HPV 16 double-genotype in 6 patients. Immunohistochemistry and qPCR data suggest that activation and expression of the EGFR signaling pathway are related to disease progression of conjunctival cancer. The associations of cytoplasmic p-MAPK and cytoplasmic p-Akt with tumor invasiveness were significant ($p = 0.05$ and 0.028 , respectively). Nuclear p-EGFR appeared only in invasive tumors. A significant positive association between EGFR expression and disease invasiveness was observed ($p=0.01$). A SNP in 10 patients and one missense mutation were found within EGFR tyrosine kinase domain. Statistical analysis indicates that patients with measurable EGFR expression more likely harbor EGFR mutations, compared to those with negative EGFR expression (35.3% vs. 0%).

Conclusions

Our data indicate a relationship between HPV infection and EGFR signaling in patients with AIDS-associated squamous cell carcinoma of the conjunctiva. HPV infection and EGFR activation/alteration may contribute to and sustain the high prevalence of the cancer in East Africa. Our findings support clinical trials that involve HPV vaccination, with application of therapeutic agents that target the EGFR pathway. These clinical strategies may reduce the incidence of conjunctival carcinoma among HIV patients in equatorial Africa.

Acknowledgements

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019. Visual inspection and HPV-based cervical cancer screening in HIV-infected women in Pune, India

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Background

Visual inspection with acetic acid (VIA) and human papillomavirus (HPV) testing are being explored as alternatives to cervical cytology (Pap smears) for cervical cancer screening in India and other resource-limited settings. However, there are limited data on utility and acceptability of these screening approaches for detection of cervical intraepithelial neoplasia (CIN) among HIV-infected women.

Methods

We conducted a cross-sectional study among n=303 consenting non-pregnant HIV-infected women in Pune, India. All participants underwent independent and simultaneous screening with VIA, cytology, and collection of HPV samples [by both self-collected samples and clinician collected samples, analyzed using Digene Hybrid Capture-2™ (HC2) assay]. Independent diagnostic assessment by colposcopy was conducted in the same visit and histopathology was performed if clinically indicated. We compared the measures of test performance for VIA-positive test results and “cytology-positive” detection of any squamous intraepithelial lesions (SIL), at the \geq CIN2 diagnostic threshold. We also performed multiple imputation analysis to derive predictions for missing values of histopathology to account for potential verification bias, using data from VIA, cytology, and colposcopy results and compared simulated measures of screening test performance. We compared patient preferences, HPV detection rates, and measures of agreement between two HPV sample collection approaches (self-sampling versus sample collection during pelvic examination).

Results

The median age of the HIV-infected participants was 30 years (interquartile range, IQR: 27-34), and their median CD4+ cell count was 343/ μ L (IQR: 244–495). VIA was positive in 84/303 (27.7%). Cytology revealed normal results in 131 (53%), ASCUS in 11 (4.5%), LSIL in 87 (35.2%), and HSIL in 18 (7.3%) of the 247 evaluable slides. VIA has higher sensitivity compared to cytology: 80% vs. 60% (based on conventional gold standard) and 70% vs. 69% (based on multiple imputations for missing histopathology). The specificity of VIA was also higher than cytology (83% vs. 65% and 82% and 70%, based on the conventional and imputation methods, respectively). The detection rates of HR-HPV positive test results were comparable in self versus clinician collected samples overall [44.1% (130/295) vs. 41.8% (124/297), p=0.6]. The pair-wise agreement between the two HPV sampling approaches was high [88.1%] and the kappa statistic of 0.76 (95% C.I.: 0.68-0.83) denoted substantial agreement beyond chance. A higher proportion of women found self-sampling to cause absolutely no discomfort (61% vs. 51%, p=0.01) and no pain (59% vs. 42%, p=0.01) than pelvic examination.

Conclusions

VIA performed similar to or better than cytology among HIV-infected women in Pune, India. With sensitivity for \geq CIN2 lesions consistently at or above 70%, and with the ability to link screening and testing in the same visit, VIA can be a useful independent primary screening test for HIV-infected women in low-resource settings. Clinic-based self-collection of HPV compared favorably in comparison to sample collection through clinic-based pelvic examination, signifying importance of further research to explore field acceptability and operational aspects of HPV-based screening.

Acknowledgements

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020. An ATM/Chk2-mediated DNA damage responsive signaling pathway suppresses Epstein-Barr virus transformation of primary human B cells

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Epstein-Barr virus (EBV) infection of primary B cells leads to the outgrowth of indefinitely proliferating lymphoblastoid cell lines (LCLs). However, the efficiency of immortalization is less than 10% of infected cells. We hypothesize that a robust innate tumor suppressor response prevents long-term outgrowth of the majority of infected cells. In this study we identify the DNA damage response (DDR) as a major component of this response. EBV infection of primary B cells activated hallmarks of the DDR including phosphorylated ATM, Chk2, γ -H2AX, and 53BP1 foci. DDR activation was not due to lytic viral DNA replication nor did its marks co-localize with latent viral episomes. Rather, EBV induced a period of hyper-proliferation early after infection responsible for DDR activation. Microarray data supported the transient activation and subsequent attenuation of proliferation and DDR-associated mRNAs during LCL outgrowth. Importantly, activation of this pathway suppressed transformation as small molecule antagonism of the DNA damage responsive kinases ATM and Chk2 increased EBV transformation efficiency. Thus, we propose a model whereby EBV infection initially drives aberrant cellular DNA replication activating an anti-proliferative DNA damage response. Long-term outgrowth depends on attenuation of this hyper-proliferative signal through full latency III gene expression.

021. TNFAIP3(A20) genetic alterations in AIDS-related lymphomas

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Background

AIDS-related lymphomas (ARLs), which include Burkitt lymphoma and diffuse large B cell lymphoma (DLBCL), are a heterogeneous group of lymphoproliferative disorders that occur in the setting of HIV-mediated immune suppression. A subset of cases are associated with Epstein-Barr virus (EBV) infection. EBV expresses latent viral oncoproteins that constitutively activate the transcription factor NF- κ B, a potent inducer of genes involved in promoting B cell survival and proliferation [1].

In immunocompetent individuals, lymphomas that are not associated with EBV can also display increased NF- κ B activity, and recent reports have described mutations in regulators of NF- κ B. One of the frequently mutated regulatory genes is TNFAIP3, which encodes A20, a ubiquitin modifying enzyme involved in the termination of NF- κ B signaling. Mutations resulting in the inactivation of A20 have been found in a significant proportion of marginal zone lymphomas [2], classical Hodgkin's lymphomas and primary mediastinal B cell lymphomas [3], and DLBCLs [4]. In ARL the role of NF- κ B activation and the incidence of mutations in A20 have not been described.

Materials and methods

We evaluated archival formalin-fixed paraffin-embedded tissue samples of AIDS-related lymphoma for genetic alterations in A20. Tissue was collected through an international collaboration between Weill Cornell Medical College in New York, NY, and Siena University in Siena, Italy. A tissue microarray with 48 cases of ARL was prepared, and characterization of viral status and lymphoma subtype were determined by immunohistochemistry and in situ hybridization for Epstein-Barr encoded RNA (EBER). Fluorescent in situ hybridization (FISH) was used to evaluate for genomic deletions in A20, and translocations of cMYC, BCL-2, and BCL-6. Direct sequencing of the coding region of A20 was performed to evaluate for additional mutations.

Results

FISH was performed on 48 cases of ARL. Of 21 cases with successful hybridization loss of heterozygosity at the A20 locus was observed in 6 cases (28%). Cases with A20 deletion included three diffuse large B cell lymphomas, two Burkitt lymphomas, and one Burkitt-like lymphoma. Two cases were positive for EBER but all were negative for latent membrane protein-1 (LMP-1). Partial sequencing of approximately 70% of the A20 coding regions in 23 cases did not reveal additional mutations.

Conclusions

A20 may represent a tumor suppressor gene in a subset of AIDS-related lymphomas. Inactivation of A20 may be an alternative mechanism of NF- κ B upregulation in the absence of LMP-1.

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022. C/EBPbeta mediates bortezomi b-induced EBV and KSHV lytic gene expression

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Bortezomib is a proteasome inhibitor used clinically for the treatment of multiple myeloma and mantle cell lymphoma and is being evaluated for the treatment of AIDS-related lymphoma and Kaposi's sarcoma in the AIDS Malignancy Consortium. Activation of herpes zoster infection is a well-recognized complication of bortezomib therapy. In previous work, we have shown that bortezomib is a potent inducer of EBV and KSHV lytic gene expression and demonstrated a novel approach to therapy that leverages this activation to facilitate tumor imaging and treatment.

In an effort to better understand the relevant pathways, we confirmed that bortezomib at 20 nM concentrations induces expression of EBV and KSHV immediate early genes (EBV ZTA, KSHV RTA) as assessed by immunoblot and by reverse transcriptase PCR for the associated transcripts. Bortezomib activates EBV ZTA promoter expression and KSHV RTA promoter expression in reporter assays. C/EBPalpha and beta protein family members are recognized activators of EBV ZTA and KSHV RTA expression. Bortezomib does not alter C/EBPalpha protein level as assessed by immunoblot but does lead to increased C/EBPbeta. C/EBPbeta includes activating isoforms (LAP) and an inhibitory isoform (LIP). In reporter assays, we show that C/EBPbeta LAP activates the EBV promoters whereas LIP is inhibitory. In ChIP assays we show that bortezomib treatment leads to increased C/EBPbeta binding to the ZTA promoter. Mutation of the binding sites abolishes activation of the promoter associated with bortezomib treatment. In order to determine whether C/EBPbeta expression simply tracks with lytic viral gene expression or plays a key role in mediating such expression, we created a tet-regulated C/EBPbeta knockdown. In the presence of doxycycline, C/EBPbeta is suppressed, and bortezomib lytic induction of EBV as measured by increases in ZTA mRNA, ZTA protein, and viral DNA copy number are all blunted. Induction of lytic viral gene expression in EBV Akata cell lines by anti-Ig treatment is also blunted.

These results suggest that C/EBPbeta family members play a key role in mediating activation of EBV and KSHV lytic infection following bortezomib and other inducers.

Acknowledgements

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023. Elevated serum levels of CXCL13 precede HIV-associated non-Hodgkin's lymphoma

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Introduction

CXCL13 (BCA-1, BLC), a chemokine constitutively expressed by cells in secondary lymphoid organs, promotes the chemotaxis of B cells to secondary lymphoid organs. There is accumulating evidence that CXCL13 is aberrantly expressed in a variety of lymphomas; thus we sought to define the longitudinal expression pattern of CXCL13 preceding a non-Hodgkin's lymphoma (NHL) diagnosis in the setting of HIV.

Methods

A nested case-control study was conducted in the setting of two large prospective cohort studies of the natural and treated history of HIV and AIDS, the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS). Archival, pre-cancer diagnosis serum specimens from NHL cases (180 MACS and 30 WIHS) and HIV-seropositive matched controls (180 MACS and 109 WIHS) were assayed for CXCL13 by ELISA. Visit-matched sera from case-control pairs were obtained when available from three time windows preceding NHL diagnosis in the case: 3-5 years pre-NHL (closest to 4 years), 1-3 years pre-NHL (closest to 2 years), and 0-1 year pre-NHL (closest to 0.5 year). These data were analyzed using multivariate conditional logistic regression models to obtain adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for each unit increase in log-transformed CXCL13 for each of the three study visits.

Results

CXCL13 levels were significantly elevated at all three time points preceding the clinical recognition of NHL, 3-5 years: OR=3.66 (95% CI, 2.34-5.74); 1-3 years: OR=6.62 (95% CI, 3.78-11.6); and 0-1 year: OR=3.68 (95% CI, 2.27-5.98). Subgroup analyses revealed that CXCL13 was more strongly associated with systemic NHL compared to central nervous system NHL, and EBV-negative compared to EBV-positive tumors.

Conclusions

These data suggest that CXCL13 may be a biomarker for NHL in the setting of HIV, and is more strongly associated with systemic, EBV-negative tumors. Studies are currently under way to further characterize the role CXCL13, and its receptor CXCR5, in lymphomagenesis.

024. Decreased risk of breast cancer associated with X4-tropic HIV

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Background

HIV envelope (env) protein binds to CCR5 and/or CXCR4 chemokine receptors on lymphocytes, resulting in cell infection and death. CXCR4 is also commonly and highly expressed on neoplastic breast duct cells. Binding of X4-env protein, but not R5-env protein, can induce apoptosis of neoplastic breast cells. We hypothesized that CXCR4-tropic HIV may account for the reduced breast cancer incidence observed in HIV-infected women in the United States before widespread use of effective antiretroviral therapy.

Methods

This was a retrospective case-control study of women who developed breast cancer during 1993-2008 in the WIHS and HERS longitudinal studies. Cases were HIV-infected women who had stored plasma samples within 24 months (before or after) of a confirmed breast cancer diagnosis and who had HIV viral load ≥ 500 copies/mL. Three HIV-infected women controls, without breast cancer, were matched to each case based on age (± 2 yrs) and date (± 6 months) of plasma specimen collection. The Monogram Biosciences Trofile assay was used to classify women who had X4-tropic (including X4/R5-tropic) versus exclusively R5-tropic HIV. Unadjusted and adjusted conditional logistic regression models were used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for breast cancer associated with tropism, contemporaneous HIV viral load and CD4 count, antiretroviral therapy, and classical breast cancer risk factors.

Results

22 breast cancer cases and 66 matched controls met the inclusion criteria and had valid HIV tropism results. Only 2 (9.1%) breast cancer cases had CXCR4-using HIV, compared to 19 (28.8%) of the matched controls. In unadjusted analysis of 19 variables, breast cancer was inversely associated with CXCR4-using HIV ($p=0.05$), and marginally associated with menstrual status ($p=0.08$). In multivariate analysis adjusted for CXCR4-using HIV and menstruation in the past 12 months, both variables were significantly associated with reduced odds of breast cancer (CXCR4-tropic HIV $OR_{adj}=0.10$, 95% CI 0.01-0.93; menstruation in the past 12 months $OR_{adj}=0.07$, 95% CI 0.005-0.92). Other classical breast cancer risk factors, HIV viral load, CD4 cell count, antiretroviral therapy, and race/ethnicity had no detectable impact on these associations.

Conclusions

These results support the hypothesis that the low breast cancer incidence observed in women with HIV/AIDS is specifically tied to circulating variants of HIV that bind to and signal through CXCR4, a receptor that is commonly expressed on hyperplastic and neoplastic breast duct cells. These findings suggest novel pathogenic interactions between viral proteins and neoplastic breast cells in vivo and invite new approaches for treating CXCR4-expressing malignancies.

These results will be presented as a poster at the 101st Meeting of the American Association for Cancer Research, Washington, DC, April 17-21, 2010, and the abstract will be published in the 2010 Proceedings of the American Association for Cancer Research.

025. HIV-related Hodgkin lymphoma in the era of combination antiretroviral therapy: incidence, outcome, and evolution of CD4+ T cell lymphocytes

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Clinical background

HIV-infected patients are at increased risk to develop Hodgkin lymphoma (HL). We examined the incidence and risk factors for HL, the evolution of CD4 cell counts before HL diagnosis and prognosis of patients with HIV-related HL and in the era of combined antiretroviral therapy (cART) in the Collaboration of Observational HIV Epidemiological Research Europe (COHERE).

Patients and methods

40,168 adult HIV-1 infected patients who started cART in one of 16 prospective cohort studies in Europe were included. Incidence rates per 100,000 person-years, Kaplan-Meier estimates of cumulative incidence and survival, and adjusted hazard ratios from Weibull random-effects models, with 95% confidence intervals (CIs), were calculated. CD4 counts over time were compared between patients who were free of AIDS, on cART and developed HL (cases), and control patients. Cases and controls were matched 1:5 for cohort, age, sex, risk group, CD4 cell count at start of cART, and HIV-1 RNA at reference date, defined as HL diagnosis (cases), or at identical length of followup since start of cART (controls). We used multilevel linear regression to model changes in CD4 cell counts after start of cART and during the year before reference date and tested for differences between slopes in cases and controls. The analysis was repeated for patients with non-Hodgkin lymphoma (NHL).

Results

During 159,133 person-years of followup, 78 patients were diagnosed with HL. The crude incidence rate of HL was 50.4 per 100,000 person-years for patients who developed HL before starting cART (17 cases) and 48.7 per 100,000 person-years in patients who were already on cART (61 cases). Age, gender, CDC clinical stage, CD4 cell count, and HIV-1 RNA viral load at baseline (start of observation) were not significantly associated with the risk of HL. During a median followup of 18 months (IQR 4.8-34.8 months) 12 of 78 patients with HL died. Survival was 88% (95% CI 77-94) at 1 year and 81% (95% CI 68-89) at 2 years. A total of 18 HL patients were matched to 79 controls. At HL diagnosis, 16 of 18 cases (89%) had undetectable viral loads (<500 copies/ml). The evolution of CD4 cell counts before reference date differed: in HL patients the CD4 cell count increased after start of cART (+126 cells per year) but declined during the year before the HL diagnosis (-99 cells per year). In controls the CD4 cell counts increased throughout (+57 cells per year). Slopes differed significantly during the year before the HL diagnosis ($p=0.003$), but not after start of cART ($p=0.944$); see Figure 1. In NHL patients, the CD4 cell count increased after start of cART (+131 cells per year) and remained stable during the year before the NHL diagnosis (-16 cells per year). In controls CD4 cell counts increased throughout (+ 38 cells per year).

Conclusions

HL incidence rates were similar in cART treated and untreated patients. CD4 cells declined before HL diagnosis in patients on cART, despite undetectable viral load. In contrast, in NHL patients CD4 cell counts did not sharply decrease in the year before NHL diagnosis. Patients on successful cART who experience a sudden decline of CD4 counts should be investigated for HL.

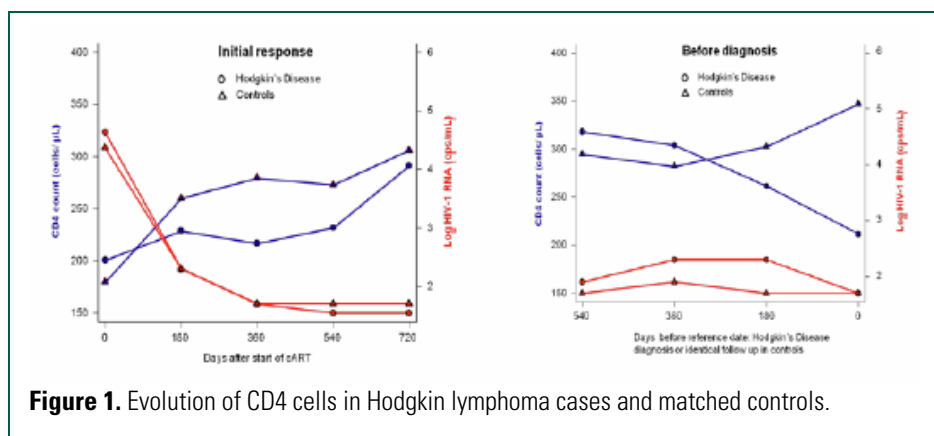


Figure 1. Evolution of CD4 cells in Hodgkin lymphoma cases and matched controls.

O26. Risk of HIV-associated Hodgkin lymphoma during the first months after initiation of combination antiretroviral therapy

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Background

Since the advent of combination antiretroviral therapy (cART), several studies have described an increase in the incidence of Hodgkin lymphoma (HL). This increase has been postulated to be linked with immunologic mechanisms occurring at cART initiation. Relationships between the CD4 cell count and the risk of HL have also been investigated. Our study aimed to evaluate the risk of HL by use of cART and its duration.

Materials and methods

From the French Hospital Database on HIV (FHDH-ANRS CO4), a large prospective hospital cohort, we studied the incidence of HL in 1992-2007 according to the duration of cART exposure: no cART and year < 1996, no cART and year ≥ 1996, [0;1], [1;2], [2;3], [3;6] and ≥ 6 months. Relative rates (RR) of HL were estimated using Poisson regression models for the duration of cART exposure, adjusted for age, period of followup, sex and exposure group, migration from sub-Saharan Africa, AIDS stage, and CD4 cell count.

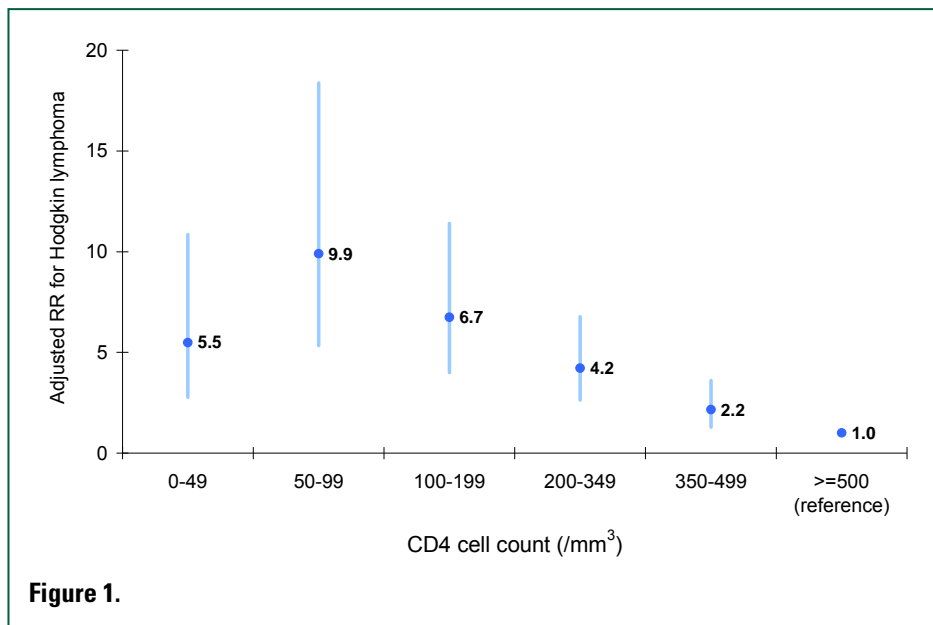
Results

Our study included 286,806 person-years (PY) of followup and 187 HL cases. The incidence of HL was not associated with the period: 0.79, 0.60, and 0.64 per 1000 PY before 1996, in 1996-1999, and since 2000, respectively (p=0.55). Risk of HL was significantly related to cART (p=0.008), being especially high during the first 3 months of use (Table 1). The association remained after adjustment for age, sex and exposure group, migration, and AIDS stage (p=0.006), but not in the model accounting for CD4 cell count (p=0.058). A peak of HL incidence was observed for 50-99 CD4 cell count and the association between risk of HL and CD4 cell count remained significant in the multivariate model (Figure 1, p<10⁻⁶).

Table 1.

	No of diagnoses	Incidence per 1000 PY	Crude RR 95%CI	Adjusted RR Model 1* 95%CI	Adjusted Model 2** 95%CI
no cART and year < 1996	43	0.58	1.35 [0.84;2.18]	1.14 [0.7;1.85]	0.68 [0.4;1.17]
no cART and year ≥ 1996	28	0.79	1	1	1
[0;1]	6	2.01	3.48 [1.48;8.17]	3.09 [1.31;7.28]	1.75 [0.73;4.19]
[1;2]	2	0.68	1.19 [0.29;4.89]	1.05 [0.25;4.33]	0.30 [0.04;2.23]
[2;3]	7	2.35	4.11 [1.85;9.13]	3.62 [1.62;8.08]	2.17 [0.96;4.92]
[3;6]	8	0.94	1.63 [0.76;3.46]	1.43 [0.67;3.05]	0.90 [0.41;1.94]
≥ 6	93	0.58	1.00 [0.69;1.43]	0.83 [0.57;1.2]	0.75 [0.51;1.10]

*adjusted for age, sex and exposure group, migration for sub-Saharan Africa, AIDS stage. **adjusted for variables in model 1 and CD4 cell count.



Conclusion

Our results support that the early cART effect on the risk of HL is largely explained by CD4 count.

Acknowledgement

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027. Non-AIDS-defining cancer mortality among people with AIDS in Italy

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Background

Mortality due to non-AIDS-defining cancers (NADCs) among HIV-positive patients, in the era of highly active antiretroviral therapies, has yet to be completely defined. To estimate the excess risk of death for each NADC among people with AIDS (PWA), in comparison with the general population, we conducted a population-based study in Italy.

Materials and methods

Between 1999 and 2006, 10,391 Italian citizens (≥ 15 years of age) had been diagnosed with AIDS in Italy. These PWAs constituted the population included in our study. Death certificates were retrieved through a record-linkage with the mortality databases at the National Institute of Statistics. This allowed the extraction of information about PWA dates of death, up to December 31, 2006. The underlying cause of death, for each deceased PWA, was identified following the International Classification of Diseases, 10th revision (ICD-10), applied also for the general population. The excess risks of death for each NADC were therefore estimated through standardized mortality ratios (SMRs) with 95% confidence intervals (CIs), in comparison with the Italian general population.

Results

Among 3,209 deceased PWA, 7.4% had died of NADCs, with an SMR of 6.6 (95% CI 5.8-7.5). Significantly elevated excess risks of death were found for a broad range of cancers, notably for Hodgkin lymphoma (SMR=174), cancers of liver (SMR=11.1), brain (SMR=10.0), head and neck (SMR=8.2), lung (SMR=5.9), and myeloma and leukemias (SMR=5.9). SMRs were higher among injecting drug users (IDUs) (SMR=15.5 for all NADC) than among other HIV-transmission categories (SMR=4.8), above all for liver cancer (SMR=65.2 among IDUs; SMR=2.8 among non-IDUs).

Conclusions

We found particularly elevated SMRs for NADCs among PWA, with several excess risks of death that were higher than those expected, based on NADC incidence recorded in Italy [1]. This finding could be explained by the joint effect of an increased incidence of some malignancies, markedly those related to smoking and viral infections, and of their poorer prognosis among PWA versus the general population.

Reference

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028. Phase IIA trial of 1% topical cidofovir for treatment of high-grade perianal squamous intraepithelial neoplasia in HIV-infected men and women (AMC046)

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Objective

Treatments for high-grade perianal intraepithelial neoplasia (PAIN 2-3), include surgical ablation/excision and have significant morbidity and recurrence rates. Cidofovir, a cytidine nucleotide analogue, has broad-spectrum antiviral activity. This multicenter study prospectively evaluated the efficacy, safety, and tolerability of topical cidofovir for treatment of PAIN 2-3 in HIV-positive individuals.

Methods

HIV-positive patients with biopsy-proven PAIN 2-3 ≥ 3 cm² were eligible. Subjects applied 1% topical cidofovir for 6 two-week cycles consisting of 5 consecutive days of treatment and 9 days without treatment. Subjects were evaluated every 2 weeks. High-resolution anoscopy and biopsy were performed 6 weeks after the last cycle. Results were scored as stable disease (SD), partial response (PR) (> 50% reduction in size), complete response (CR), or progressive disease (PD) based on size and histology.

Results

24 men and 9 women were enrolled. Mean age was 33 years, median HIV RNA level was <75 copies/ml, and mean CD4 count was 440/ μ l. HPV DNA was detected in intra-anal swabs of 31 of 32 (97%) subjects with analyzable specimens. The most common type was HPV16 (44%).

27 (82%) subjects completed treatment per protocol—CR: 4 (15%); PR: 12 (44%); SD: 9 (33%); PD: 2 (7%) (1 with a superficially invasive cancer and 1 with new PAIN 2-3). Six subjects did not complete treatment because of discomfort (1), poor compliance (4), and CR after 4 cycles (1).

26 of 33 subjects (79%) reported adverse events likely related to treatment. Most were mild or moderate, including self-limited, localized, superficial ulcerations in the disease area (2 mild, 19 moderate, 1 severe), discomfort (4 mild, 14 moderate), itching (1 mild, 3 moderate), and bleeding (6 mild). Seven (21%) had mild transient proteinuria.

Conclusions

Topical cidofovir is a well-tolerated and effective treatment for PAIN 2-3 in HIV-positive patients. A larger study is warranted.

Poster Abstracts – Day 1

1. A proportion of germinal center and memory B cells express the latency-associated nuclear antigen (LANA) throughout chronic infection in vivo

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An integral feature of gammaherpesvirus infections is the ability to establish lifelong latency in B cells. During latency, the viral genome is maintained as an extrachromosomal episome, with stable maintenance of the episome in dividing cells mediated by the critical viral proteins LANA for Kaposi's sarcoma-associated herpesvirus (KSHV) and EBNA-1 for Epstein-Barr virus (EBV). Although EBNA-1 is known to be expressed in multiple B cell subsets, it is believed that the expression of episome maintenance proteins is turned off in the predominant long-term latency reservoir of resting memory B cells, suggesting that chronic gammaherpesvirus infection is maintained in a primarily dormant state. However, the kinetics of LANA/EBNA-1 expression in individual B cell subsets throughout a course of infection has not been previously examined. The infection of mice with murine gammaherpesvirus 68 (MHV68, HV68) provides a useful small-animal model to determine the specific cellular and molecular events that occur in vivo during the establishment of lifelong gammaherpesvirus latency. In work presented here, we describe the use of a heterologously expressed enzymatic marker to define the types of B cells that express the LANA homolog mLANA during chronic MHV68 infection. Our data demonstrate that mLANA is expressed in a stable proportion of infected B cells throughout chronic infection. Expression of mLANA was detected in naïve follicular B cells, germinal center B cells, and memory B cells throughout infection, with germinal center and memory B cells accounting for more than 80% of the mLANA expressing cells during the maintenance of latency. These findings suggest that the maintenance phase of latency is an active process involving proliferation of latently infected germinal center and memory B cells.

2. **AIDS-related Kaposi's sarcoma: outcomes after initiation of highly active antiretroviral therapy under routine conditions in Zimbabwe**

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Background

Additional information on the outcomes of patients with AIDS-related Kaposi's sarcoma (AIDS-KS) on highly active antiretroviral therapy (HAART) in resource-limited settings is needed. This study evaluated outcomes in AIDS-KS patients after initiation of HAART in Zimbabwe.

Methods

A retrospective cohort of 124 patients from the Parirenyatwa Hospital Kaposi's Sarcoma and Opportunistic Infections (OI) Clinics was studied. 31 patients with AIDS-KS were matched 1:3 to 93 non-KS AIDS patients based on date of initiation of HAART, gender, and age. The primary endpoint was loss to care, defined as failure to attend clinic or refill prescriptions for 3 months or longer. Secondary endpoints were weight gain at 6 months, change in CD4+ count within 1 year, and final CD4+ count within 1 year of initiating HAART. Eligibility criteria included a minimum of 6 months of followup in the OI Clinic and less than 2 months of previous HAART prior to beginning therapy through the OI Clinic. A two-step model-selection strategy using KS status, gender, age, WHO performance status, OI disease burden, medical aid, employment, education, pre-treatment cotrimoxazole use, pre-treatment weight, and pre-treatment CD4+ count was used to identify factors associated with loss to care. On the initial univariate analysis, KS status, medical aid, and pre-treatment cotrimoxazole use had a $p < 0.15$ and were included in the final multivariate analysis.

Results

AIDS-KS and non-KS patients did not differ significantly in baseline characteristics except for pre-treatment CD4+ count (196 vs. 92 cells/mm³, $p = 0.005$). On the multivariate analysis, KS status ($p = 0.016$, HR: 4.11, CI: 1.31-12.92) and having medical aid were significant predictors of loss to care ($p = 0.048$, HR: 3.84, CI: 1.02-14.44). At a median followup of 632 days, 37.5% of AIDS-KS patients were lost to care compared to 16.1% of non-KS patients. AIDS-KS patients had significantly worse weight gain than non-KS patients (+0.78% vs. +4.18%, $p = 0.023$). Change in CD4+ count ($p = 0.149$) and final CD4+ count ($p = 0.729$) were not significantly different between study groups. Amongst AIDS-KS patients, retained patients ($n = 20$) had significantly higher pre-treatment CD4+ counts than patients lost to care ($n = 11$) (232 vs. 122 cells/mm³, $p = 0.048$).

Conclusions

After initiating HAART, AIDS-KS patients experienced greater loss to care and poorer weight gain than matched non-KS patients, suggesting that, under routine conditions in Zimbabwe, AIDS-KS patients have worse intermediate- and long-term clinical outcomes than non-KS AIDS patients. AIDS-KS patients retained in care had higher pre-treatment CD4+ counts than patients lost to care, indicating that early intervention with HAART may improve outcomes in AIDS-KS patients.

3. Caspase-7 cleavage of Kaposi sarcoma-associated herpesvirus ORF57 confers a cellular function against viral lytic gene expression

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Background

Host persistent infection by Kaposi sarcoma-associated herpesvirus (KSHV) is etiologically linked to the development of Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. Like other gammaherpesviruses, KSHV establishes a long-term latency in infected cells upon primary infection. The latent infection can be reactivated in a small proportion of latently infected cells, leading to limited production of infectious virus. However, factors which restrict KSHV reactivation from latency and lytic replication remain unknown.

Results

We found that virus reactivation in KSHV latently infected B cells derived from cavity-based B-cell lymphoma by various inducers is associated with induction of apoptosis. We also showed that virus reactivation leads to a specific activation of initiator caspase-8 but not caspase-9. The activation of caspase-8 pathway in infected cells results in cleavage of KSHV ORF57, a viral early protein essential for KSHV multiplication. ORF57 is cleaved at the aspartate residue at position 33 from the N-terminus by caspase-7 in the cytoplasm of infected cells. Caspase-7 cleavage of ORF57 is prevented by pan-caspase inhibitor z-VAD, caspase-3 and caspase-7 inhibitor z-DEVD, and caspase-7 siRNAs. Interestingly, the caspase-7 cleavage site 30DETD33 in ORF57 is not cleavable by caspase-3, although both enzymes use DEXD as a common cleavage site. B cells with lytic KSHV infection and caspase-7 activation exhibit a greatly reduced level of ORF57. In a majority of the cells expressing active caspase-7 no detectable ORF57 appeared. Upon cleavage with caspase-7, ORF57 is deficient in promoting the expression of viral lytic genes. In contrast, the inhibition of caspase-7 cleavage of ORF57 in KSHV⁺ BCBL-1 cells by z-VAD, z-DEVD, or caspase-7 siRNA increased expression of viral lytic genes and production of cell-free virus particles.

Conclusion

Collectively, our data provide the first compelling evidence that caspase cleavage of an essential viral protein ORF57, as a result of apoptosis triggered by virus reactivation, may represent a cellular defense mechanism against lytic KSHV infection.

4. Characterization of lytic human herpesvirus-8 gene expression in Kaposi sarcoma tumor tissue and its clinical correlates

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Background

Human herpesvirus 8 (HHV-8) replication is necessary for KS tumor growth and maintenance, and the detection of replicating HHV-8 in the peripheral blood predicts the development of KS [1]. Quantities of HHV-8 lytic and latent mRNA vary in KS biopsy tissue [2,3], suggesting that differences in lytic gene expression may be important in tumor pathogenesis and could have clinical significance. We evaluated lytic and latent mRNA transcripts in KS tumors from Ugandans with epidemic KS, and examined associations between HHV-8 gene expression in tumors, KS morphology, and systemic viral replication.

Methods

KS biopsy specimens were obtained from 13 treatment-naive, HIV-positive Ugandans with histologically confirmed KS. Participants also collected oral swabs daily and plasma samples weekly over 4 weeks to quantify HHV-8 replication. HHV-8 mRNA gene transcripts, including 2 lytic genes (K8 and ORF50) and 1 latent gene (ORF73), and GAPDH were quantified in biopsy specimens using RT-PCR; total RNA was determined by optical density. Only specimens with total RNA >10 ng and GAPDH threshold cycle (Ct) <35 were included in the analysis. HHV-8 mRNA log copies were normalized to the total ng of RNA in samples.

Results

HHV-8 mRNA gene transcripts were detected in all 13 KS biopsy samples. In all samples, the quantity of mRNA from lytic genes (K8 or ORF50) exceeded that of ORF73 when adjusted for total RNA recovered, though in two samples the amount of ORF73 mRNA exceeded the amount of ORF50 mRNA. The quantity of HHV-8 mRNA detected was highly correlated within samples (K8 and ORF50 Spearman coefficient (Sp)=0.92; K8 and ORF73 Sp=0.78; ORF50 and ORF73 Sp=0.84). Tumors of nodular morphotype had a lower proportion of lytic genes detected compared to macular morphotype (K8/ORF73 p=0.04; ORF50/ORF73 p=0.07). The quantity of K8, ORF50, and ORF73 mRNA in KS biopsies was positively associated with the detection of oral HHV-8 (K8 p=0.003; ORF50 p<0.001; ORF73 p=0.002). The quantity of lytic K8 and ORF50 mRNA, but not latent ORF73 mRNA, was also positively associated with the quantity of HHV-8 detected in saliva (K8 p=0.06; ORF50 p=0.06).

Conclusions

KS tumors in our cohort express a preponderance of lytic HHV-8 gene products. The quantity of lytic HHV-8 mRNA detected in KS tumors is associated with tumor morphotype and the detection of replicating HHV-8 in the oropharynx. Quantification of HHV-8 mRNA from KS tissue may provide insight into the pathophysiology of KS and could help predict disease progression and response to treatment.

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5. Concurrent human herpesvirus 8 and 6a viremia in end-stage AIDS as uncovered by NextGen sequencing

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Kaposi sarcoma-associated herpesvirus (KSHV) cancers are AIDS defining, but high-level viremia is infrequent. We observed plasma viral load of 5,300,000 copies/ml, the highest yet, despite <5 skin lesions and no lymphoma. NextGen sequencing uncovered HHV6a. This is the first report of systemic HHV6a/KSHV co-viremia. Epstein-Barr virus loads (EBV) and human cytomegalovirus loads (HCMV) were negligible at <250 copies/ml and 647 copies/ml, respectively. We therefore conclude that the patient died of acute KSHV/HHV6 reactivation disease.

Acknowledgements

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6. Current epidemiology of KSHV infection in American men who have sex with men

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Background

The introduction of highly active antiretroviral therapy (HAART) has resulted in a dramatic decline in the incidence of AIDS-associated Kaposi sarcoma (KS) among men who have sex with men (MSM). The decline had been associated with increased CD4+ cell counts; however, the effect of HAART on the epidemiology of the Kaposi sarcoma-associated herpesvirus (KSHV) has not been investigated. We describe here the prevalence of KSHV in HIV infected and uninfected MSM across time periods of different prevailing HAART usage.

Subjects, materials, and methods

The serostatus of 4159 participants in the prospective Multicenter AIDS Cohort Study (MACS) was ascertained using two ELISAs, detecting antibodies against the latently associated nuclear antigen (LANA) and the lytic antigen encoded by ORFk8.1, respectively. KSHV seropositivity was defined as positivity in either assay. The calendar period between 1984 and 1990 was defined as untreated era, while the periods 1990-1995 and 1995-2001 were defined as pre-HAART era and HAART era, respectively. Because the last wave of enrollment in the MACS that occurred in 2001 involved a distinct change in study demographics, a fourth period, 2001-2009 was defined as current era.

Results

The study population was composed of 2920 HIV-positive and 1239 HIV-negative subjects. The prevalence of KSHV was 54.6% overall (95% CI: 53.0-56.1%), 67.8% (95% CI: 66.0-69.5%), in HIV+ and 23.5% (95% CI: 21.1-25.9%) in HIV- subjects. When examining the cohort by calendar time, the prevalence was 52.9% (95% CI: 51.2-54.6%) in the untreated era, 67.5% (95% CI: 59.3-75.1%) in the pre-HAART era, 52.7% (95% CI: 35.4-69.9%) in the HAART era, and 59.7% (56.0-63.4%) in the current era.

Conclusions

The overall prevalence of KSHV in MSM enrolled in the MACS did not vary significantly from 1984 through 2009, indicating that the decline in incidence of KS seen over the same calendar periods in this population is not associated with a decline in KSHV prevalence. The observation is significant because of the potential excess morbidity risk associated with KSHV in an aging population, particularly among HIV/ KSHV co-infected individuals, notwithstanding effective anti-HIV treatment. To elucidate the mechanisms sustaining the high prevalence of KSHV amongst MSM, KSHV incidence in time and risk factors associated with KSHV infection are being investigated.

7. Cytosine methylation in the HPV16 3' L1/ 5'LCR region characterized from anal epithelia of HPV-HIV coinfecting men

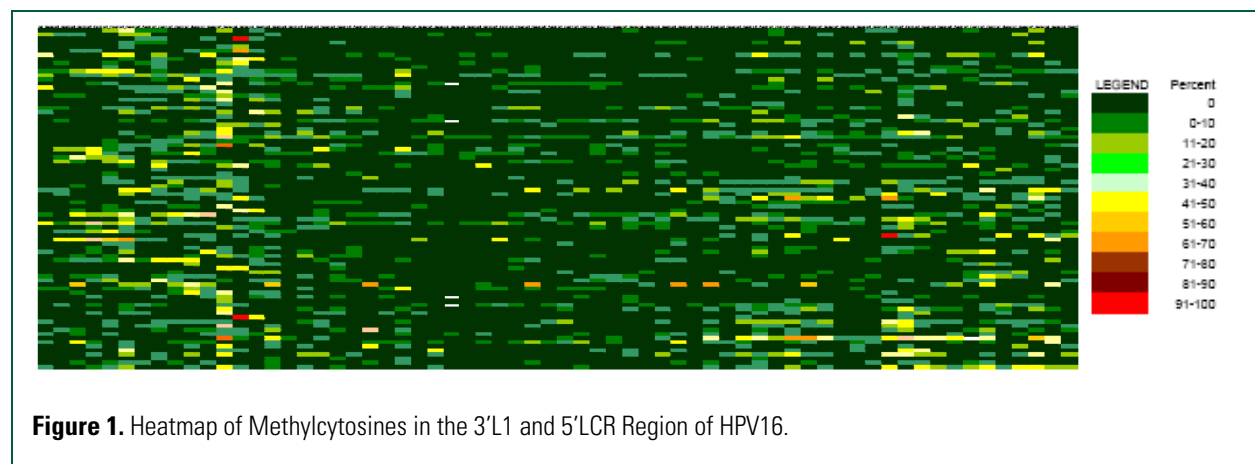
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Anal specimens derived from 83 HIV-HPV16 co-infected men were analyzed for cytosine methylation using bisulfite modification, PCR amplification, cloning, and sequencing. Data were processed using the ClustalW alignment algorithm within BiQ Analyzer Software and input into SAS 9.2 to generate heat maps and histograms. Approximately 10 clones were characterized for each specimen across 81 CpA, CpT, CpC (denovo methylation) and 10 CpG sites within the 3'-L1 and 5'LCR region of HPV16 genomes. Analyses were confined to 64 denovo cytosine residues and 10 CpGs outside the primer annealing regions. Clinical outcome evaluation by a single examiner showed seven men with no anal intraepithelial neoplasias (AIN), 26 with AIN-1, and 50 with AIN-2. Data showed the average prevalence (standard deviation) of methylcytosines was 11% (0.3) across 7,553 bases/residues and did not vary across maintained or denovo cytosine groups, i.e., 6,723 denovo sites and 830 CpGs. Evaluation by a single examiner using cytology and histology showed 7 with no anal intraepithelial neoplasias (AIN), 26 showed AIN-1, and 50 showed AIN-2. Mean and median prevalence of denovo and CpG methylation were closely approximated across AIN groups. Maxima were observed in two regions: 7111 to 7119, and 7505 to 7514 that showed a methylcytosine prevalence of 24% (0.4), and 18% (0.4), respectively. Logistic regression suggests that with each year of age, risk for moderate-severe methylation $\geq 30\%$ at each site decreases; however, among smokers risk for $\geq 30\%$ methylation increases. Specifically, moderate cytosine-methylation decreased by 5% (OR=0.95, 95% CI, (0.92, 0.99) for each year of age, centered around the mean of the sample. Smokers were nearly twice as likely to show moderate cytosine methylation overall (OR=1.9, (1.1, 3.3) and these estimates did not vary across CpG-denovo sites. Although not statistically significant, moderate cytosine methylation was inversely associated with grade of AIN in these data (when compared to high-grade, low-grade and no AIN showed OR=1.5 (0.8, 2.7) and 2.0 (0.9, 4.5), respectively, $p=0.2$).



8. Detection and quantitation of HPV in anogenital and oral tissues and fluids of HIV-positive individuals by real-time PCR

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Human papillomaviruses (HPV) remain a serious world health problem due to their association with anogenital and oral cancers and warts. While over 100 HPV types have been identified, only a subset is associated with malignancy. HPV16 and 18 are the most common oncogenic types, while HPV6 and 11 are the most common types responsible for anogenital warts. These four types cause up to 90% of HPV-associated disease. While other quantitative PCR (qPCR) assays can be used to detect oncogenic HPV, there is no single tube assay that distinguishes the most frequent oncogenic types and the most common types found in warts. A qPCR assay was developed that allowed for detection and quantitation of these 4 HPV types. Type-specific primer pairs and TaqMan probes allowed single tube multiplex reactions to be performed. Each HPV type was detected over a range from 2×10^1 to 2×10^6 copies/reaction, providing a reliable method of quantitating type-specific HPV. A Sybr Green-based qPCR assay was developed that utilizes degenerate primers targeting the E1 region of all HPVs. These assays were run in parallel with PCR/sequence gold standard on 76 oral cancers from HIV-negative individuals. Cervical and oral washes were collected from 25 HIV-positive women and 90 HIV-positive men, respectively, being screened for anogenital neoplasia. Samples were analyzed using the newly developed assays. Of the 115 samples, 16% were HPV positive. Cervical washes contained HPV types 44, 67, 35, and 68 and oral specimens contained HPV types 16, 11, 32, 6, 55, 73, and 70. These results indicate that these assays can be used to detect and quantitate HPV in clinical samples obtained by noninvasive measures.

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9. Development of a proteomic platform for EBV and KSHV serological screening

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In the context of HIV infection, there is an increased susceptibility to EBV- and KSHV-associated malignancies. Evaluating a possible role for specific humoral responses to individual viral proteins in the control of viral load and prevention of EBV or KSHV related disease development in this population has been hampered by the limited availability of suitable screening reagents.

We have developed a protein array platform that can be utilized for EBV and KSHV serological screening. The array consists of EBV and KSHV proteins printed onto glass slides. All eighty-four EBV open reading frames and eighty-six KSHV open reading frames were cloned into bacterial vectors and the inserts validated by DNA sequencing in both directions. Authenticated inserts were transferred to a yeast vector that expresses proteins as N-terminal GST-fusions. Seventy-nine EBV proteins and eighty-one KSHV proteins were successfully purified from yeast. First-generation EBV/KSHV protein arrays have been printed with these proteins plus a variety of control proteins that include GST, and human IgG, IgM, and IgA.

Glycosylation of viral proteins may affect immunogenicity. To evaluate this aspect, EBV and KSHV virion glycoproteins are being expressed in insect cells modified with the human glycosylation machinery. Once purified, these proteins will be added to the EBV/KSHV protein arrays.

The ability to compare serological responses to the complete repertoire of individual EBV and KSHV encoded proteins should provide new insight into B cell mediated immune regulation of these viruses.

10. DNA ploidy, cell proliferation, and HIV/EBV association in Tanzanian malignant lymphomas

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Background

Malignant lymphomas (ML) are increasingly important causes of morbidity and mortality in sub-Saharan Africa including Tanzania, possibly due to HIV and AIDS. However, the biological characterization ML including their HIV and Epstein-Barr virus (EBV) association as well as DLBCL subtypes in Tanzania is still sketchy. This prevents diagnostic/prognostic comparison as well as application of established therapeutic protocols.

Materials and methods

Selected archival, diagnostic ML biopsies (N=60) collected at Muhimbili National Hospital (MNH), Dar es Salaam, Tanzania, between 1996 and 2006 and their corresponding clinical/histopathological notes were analyzed by histopathology; immunohistochemistry (IHC) using CD20, CD3, CD30, CD10, MUM1p, BCL-6, BCL-2, and Ki-67 cell markers; flow-cytometry (FC) for DNA ploidy; and in situ hybridization (ISH) (n=25) for EBV-encoded RNA (EBER). Available sera (N=35) were screened by ELISA for HIV antibodies.

Results

Out of the evaluated cases, 27 were diffuse large B-cell lymphoma (DLBCL) of which a slight majority (55.6%, n=15/27) had activated B cell-like (ABC) and 44.4% (12/27) had germinal center B cell-like (GCB) immunophenotype, although this was not statistically significant (p-value 0.547, Chi² Test). Overall, 40% (24/60) ML were aneuploid mostly (63.0%, 17/27) the DLBCL and T-cell lymphoma (TCL) [54.5%, 6/11] which differences were not statistically significant (p-value 0.06, Chi² Test). DNA index (DI) of FC-analyzed ML ranged from 1.103 to 2.407 (median=1.51) and most (75.0%) aneuploid cases showed high (>40%) cell proliferation by Ki-67 reactivity (p-value 0.031, statistically significant, Fisher's Exact Test). The majority (51.4%, 19/37) of EBER ISH analyzed lymphoma biopsies were positive (p-value 0.87, not statistically significant, Chi² Test). Of the serologically tested lymphomas 40.0% (14/35) were HIV positive, mostly with high (≥40.0%) Ki-67 reactivity [p-value=0.05, statistically significant, Pearson Correlation].

Conclusions

Lymphomas at MNH appear to have frequent aneuploidy and EBER positivity as well as high DNA indices and tumor proliferation (Ki-67). DLBCL phenotype heterogeneity was similar to that observed in other countries suggesting applicability of established intervention approaches. HIV was apparently associated with high lymphoma cell proliferation but extended studies are needed to clarify this.

11. EBV-induced miR-34a functions to stimulate transformed B cell growth

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Background

Epstein-Barr virus (EBV) is a member of the γ -herpesvirus family estimated to infect 90% of the world's population. Despite the high prevalence of infection, EBV-associated malignancies are largely kept in check by a strong cytotoxic T cell immune response. However, EBV causes lymphoproliferative disease in immune-deficient individuals and plays a role in the pathogenesis of African Burkitt lymphoma, Hodgkin's disease, and nasopharyngeal carcinoma. In vitro, EBV infection of B cells results in proliferation and outgrowth of indefinitely proliferating lymphoblastoid cell lines (LCLs). Thus, LCLs represent a viable model for the pathogenesis of EBV-associated malignancies.

microRNAs are small noncoding RNAs that post-transcriptionally regulate gene expression to control a variety of processes including development, cell cycle, and immunity. Their role in EBV transformation and lymphomas is currently not well understood.

Results

Using a miRNA microarray, we identified a number of cellular miRNAs that were over- or under-expressed comparing resting CD19+ B cells to EBV-infected, proliferating B cells and immortalized LCLs. In particular, we focused on miR-34a, whose expression was induced by EBV. This miRNA has been previously reported to be a pro-apoptotic target of p53 implicated in the response to DNA damage. Surprisingly, contrary to its regulation in other cell types, miR-34a was not found to be p53 responsive in LCLs. In order to understand the functional role of this miRNA in EBV transformation, we constructed a miRNA sponge. miR-34a knockdown in LCLs showed that these cells depend on normal miR-34a expression to proliferate and to aggregate.

Conclusions

miR-34a is important for efficient growth and survival of EBV-transformed cells, in contrast to its tumor suppressive role in carcinoma and sarcoma-derived cell lines.

12. Efficacy of a latency-deficient gamma-herpesvirus as a vaccine strategy

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Background

Human gamma-herpesviruses, Epstein-Barr virus (EBV or HHV-4), and Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8), are associated with several malignancies, especially in persons with immunodeficiency conditions, such as human immunodeficiency virus (HIV) infection and AIDS. Tumorigenesis of gamma-herpesviruses is associated with the persistence of infection. Thus, vaccination to inhibit viral infection will reduce the frequency of virus-associated cancers. However, currently there are no effective vaccines available for KSHV or EBV.

Materials and methods

Mouse infection with murine gamma-herpesvirus 68 (MHV-68) has been used as an experimental model to explore and test proof-of-principle vaccination strategies. In this model, vaccines targeting individual viral proteins or based on heat inactivated MHV-68 confer only modest protective effects. A live attenuated virus, which allows for the presentation of the full repertoire of viral antigens, will effectively elicit both humoral and cellular immunity. However, the primary concern using a live virus as a vaccine for EBV and KSHV is the tumorigenicity associated with the persistent infection. Therefore, we constructed and tested the protective efficacy of a live attenuated MHV-68 virus (AC-RTA) that is deficient in latency using the mouse infection model. AC-RTA was generated by replacing the genes required for persistent infection with a constitutively expressed viral transcription activator, RTA, which dictates the virus to lytic replication.

Results

We have shown that AC-RTA undergoes lytic infection without establishing latency in mice. More importantly, this latency deficient virus, AC-RTA, is able to prevent challenge infection of the wild-type virus. Next, we aim to genetically modify AC-RTA to reduce its lytic replication capacity without compromising the immunogenicity. The strategy is to delete a group of viral immune evasion genes that inhibit the type I interferon responses and block the MHC class I antigen presentation. This new vaccine virus, DIP (**d**eficient in **i**mmune evasion and **p**ersistent infection), will be evaluated for its preventive and therapeutic efficacy.

Conclusions

DIP represents a vaccine strategy for preventing infection of human gamma-herpesviruses. The "proof-of-concept" study in the mouse infection model is necessary to provide fundamental insights into the development of vaccines for the tumor-associated human herpesviruses.

13. Elevated serum levels of heat shock protein 70 precede the development of AIDS-non-Hodgkin lymphoma in carriers of the common and highly conserved HLA-B8-DR3 haplotype

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Background

Polymorphisms in the tumor necrosis factor (*TNF*) and lymphotoxin alpha (*LTA*) genes, by themselves or in combination with nearby specific human leukocyte antigen (*HLA*) loci, have been associated with classical and AIDS-related non-Hodgkin lymphoma (NHL). However, whether those gene variants represent true etiologic factors remains uncertain because they are part of the conserved and extended HLA-B*08-containing AH8.1. Building on recent observations linking the MHC-encoded heat shock protein 70 (Hsp70) to lymphomagenesis, we hypothesized that concomitant carriage of presumably high *TNF* and Hsp70 producing gene variants on AH8.1 may predispose HIV-infected individuals to AIDS-NHL. To test this hypothesis, we have compared Hsp70 serum levels in the years preceding the diagnosis of AIDS-NHL in carriers vs. non-carriers of AH8.1.

Materials and methods

A Caucasian case-control sample (n=169 pairs) was nested in the Multicenter AIDS Cohort Study (MACS). Cases are participants diagnosed with AIDS-NHL prior to April 2002, matched 1:1 with HIV+ NHL-free controls on duration of HIV infection and availability of serum samples at time points 3-5 years; 1-3 years; and <1 year prior to NHL diagnosis. Typed loci are HLA-B, HLA-DRB1, and 6 MHC class III single nucleotide polymorphisms (SNPs) from *TNF* and complement factor gene clusters. Hsp70 levels were measured by an ultra-sensitive ELISA. Extended MHC haplotypes were estimated via the EM-algorithm and were modeled as fixed main and interaction (with time) effects in a mixed linear model with adjustment for the CD4+ counts at the time of NHL diagnosis separately in cases and controls. A random model was fitted to account for the different levels of Hsp70 at the earliest time point.

Results

No MHC haplotype was associated with a change in Hsp70 levels in cases or controls during the 5 years preceding NHL. However, when the study was restricted to the subset of cases who developed NHL as their AIDS-defining condition (vs. NHL subsequent to another AIDS-defining condition), carriage of AH8.1 haplotypes was significantly ($p=0.0002-0.006$) associated with increasing Hsp70 levels in the cases but not in the matched controls. Conversely, the common HLA-B7-DR15 haplotype appears to be protective and associated with decreasing Hsp70 levels.

Conclusion

An altered level of Hsp70 may be a component of the AH8.1-mediated pathogenetic pathway in AIDS NHL, perhaps through the action of Hsp70 as a B-cell stimulatory molecule. Investigation of *Hsp70* promoter variants in AIDS-NHL is a worthy undertaking, especially if the association can be replicated in larger studies.

14. Epigenetic deregulation of *IGF2* and cervical cancer precursors in HIV+ and HIV- patients

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Introduction

Early detection and aggressive treatment programs to prevent cervical carcinoma in situ (CIS) and invasive uterine cervical cancer (ICC) have been available for more than 30 years with more than 80% population coverage. Despite this, 11,000 cases of ICC and 40,000 cases of CIS continue to be diagnosed in the United States annually. Women of African descent are at >2-fold higher risk of invasive cervical cancer death compared to other ethnic groups.

Objective

The overarching goal is to develop epigenetic biomarkers that can be used for early identification of aggressive cases likely to result in invasive cervical cancer and death.

Methods

We conducted a hospital-based, case-control study comprising 26 women with ICC, 18 with CIN2/3/HSIL and 41 with normal cytology, at Kilimanjaro Christian Medical Center in Moshi, Tanzania. We analyzed methylation of three regions in the *IGF2/H19* imprinted domain known to regulate the expression of imprinted *IGF2*. Aberrant methylation is associated with *IGF2* deregulation, including changes in expression, loss of imprinting, and neoplasia.

Results

At the *IGF2/H19* imprint center upstream of *H19*, methylation profiles for all women with no evidence of cervical abnormality or those with CIN2-CIN3 were within normal ranges (40%-60%), while 23% with invasive cancer had hypermethylation. In contrast, 25% of the CIN2/3 cases were abnormally hypomethylated at the *IGF2* DMR in *IGF2* intron 2, and the methylation profile worsened in the invasive cervical cancer cases with 64% having an abnormal methylation profile. A similar trend was found for the regulatory region in *IGF2* intron 6. Stratifying these analyses by HIV status in ICC revealed that aberrant intragenic *IGF2* hypomethylation was observed only among women without HIV. These associations persisted after adjusting for HPV genotype.

Conclusion

Our findings suggest that regulation of *IGF2* is substantially altered in CIN2 or worse via epigenetic alterations. DNA methylation profiles of these regions may be markers of risk of progression especially in HIV- women. The findings support our hypothesis that epigenetic deregulation of this imprinted gene could be useful in discriminating women with dysplasia likely to progress.

15. Epstein-Barr virus (EBV)-associated miRNAs are important for the maintenance of EBV transformed B cells

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The human oncogenic gamma-herpesvirus, Epstein-Barr virus (EBV), infects approximately 95% of the adult human population and causes B-cell lymphomas in immune-compromised individuals, such as AIDS patients. EBV transforms primary human B cells into indefinitely proliferating lymphoblastoid cell lines (LCLs) in vitro, which represents an important model system for the transformation of B cells by EBV. EBV encodes 25 viral miRNAs, but their role in virus replication and pathogenesis is unclear. Three of these miRNAs, miR-BHRF1-1, miR-BHRF1-2, and miR-BHRF1-3, are expressed during the latency III stage of EBV, the EBV gene expression pattern observed in AIDS-associated B cell lymphomas and LCLs. We have performed functional studies examining the roles of the three BHRF1 miRNAs during the transformation of primary B cells by EBV in vitro as well as in the maintenance of the transformed state in established LCL cultures. Our preliminary data suggest that at least one EBV miRNA is necessary for LCL outgrowth. EBV is also known to up-regulate a number of cellular microRNAs, including miR-155, and our preliminary data also suggest a role of miR-155 in the maintenance of LCLs. We are currently examining the mechanisms by which EBV and cellular microRNAs contribute to the growth and maintenance of LCLs. Together, our data point to a role for EBV-encoded and EBV-induced miRNAs in EBV-induced cell transformation.

16. Gamma-tubulin and 53BP1 as candidate biomarkers of human papillomavirus-associated anal dysplasia

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Background

HIV+ men who have sex with men (MSM) are at increased risk of developing anal squamous cell carcinoma. High-grade anal intraepithelial neoplasia (HG-AIN or AIN2/3) is the consequence of persistent infection with high-risk human papillomaviruses and is a precursor to cancer. No biomarkers exist to identify patients with HG-AIN at risk of malignant progression. We investigated two candidate biomarkers of genomic instability, gamma-tubulin and 53BP1, in a series of anal biopsies from HIV+ MSM by immunofluorescence microscopy. Gamma-tubulin staining is used to assess centrosome abnormalities as a potential source of cell division errors and aneuploidy, while staining for 53BP1 nuclear foci reflects the presence of DNA double strand breaks.

Materials and methods

Anal biopsies were obtained from HIV+ MSM undergoing high-resolution anoscopy and reported using the Bethesda 2001 classification system as AIN1 through 3 or carcinoma. Normal colonic tissue served as controls. The percentage of cells with abnormal centrosome number (more than two per cell) and DNA damage-associated 53BP1 foci was assessed and correlated with the histopathological diagnosis. Eighty-eight biopsies were stained for gamma-tubulin, and ninety biopsies were stained for 53BP1.

Results

The mean percentage of cells with abnormal centrosomes was 1.5% in AIN1, 1.3% in AIN2, and 0.9% in AIN3. No controls showed centrosome aberrations. A single biopsy diagnosed as carcinoma contained 16.1% cells with abnormal centrosomes. The mean percentage of cells with abnormal 53BP1 foci was 2.5% in controls, 17% in AIN1, 18.5% in AIN2, and 5.2% in AIN3. Higher levels of abnormal 53BP1 foci were seen in AIN1 and AIN2 compared to controls based on pair-wise comparisons between control and AIN1 ($p=0.0008$) and control and AIN2 ($p=0.0030$) using the Mann Whitney test. Lower levels of 53BP1 foci were seen in AIN3 compared to AIN1 and 2 based on pair-wise comparisons between AIN1 versus AIN3 ($p=0.0034$) and between AIN2 versus AIN3 ($p=0.0056$).

Conclusion

The levels of centrosome aberrations were generally low in AIN1 through 3 and were increased in carcinoma, suggesting that centrosome abnormalities may not occur until malignant progression. DNA damage-associated 53BP1 foci were increased in AIN1 and 2 when compared to controls, whereas AIN3 showed lower levels of 53BP1 foci. These results are consistent with previous studies suggesting that the DNA damage response represents an early barrier against malignant progression. Further prospective studies assessing the predictive value in particular of 53BP1 as a biomarker in HPV-associated anal neoplasia are warranted.

17. Human herpesvirus type 8 variants in Kaposi's sarcoma before and after AIDS era

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Background

Human herpesvirus 8 (HHV- 8) variants have been found heterogeneously distributed among human populations living in diverse geographic regions, but their differential pathogenicity in Kaposi's sarcoma (KS) development remains controversial. The aim of the present study was to analyze variations of HHV-8 genomes in tumor biopsies collected before and in the course of HIV epidemic (1971 - 2008), from patients with classic, iatrogenic, endemic as well as epidemic KS living in Africa, Europe, and North America.

Materials and methods

DNA samples have been extracted from cutaneous KS lesions of 68 patients living in Africa (n=23, Cameroon, Kenya and Uganda), Europe (n=34, Greece and Italy), and North America (n=11). The identification and characterization of HHV-8 variants has been based on PCR amplification followed by direct nucleotide sequencing and phylogenetic analysis of the highly conserved ORF 26 and T0.7, the hypervariable ORF K1, as well as on the analysis of P and M alleles of the K14.1/15 locus.

Results

Among the 23 African samples, the majority of HHV-8 ORF 26 variants clustered with the subtype R (n=12) and B (n=5). Conversely, the viral sequences obtained from 45 European and North European tumors belonged mainly to subtype A/C (n=36). In general HHV-8 and K1 variant clustering paralleled that of ORF 26 and T0.7. Genotyping of the K14.1/15 loci revealed a large predominance of P subtype in all tumors.

Conclusions

Although the virus has genetic regions of high variability, approaching that of HIV-1 env gene, the HHV-8 subtypes remained stably distributed before and after the AIDS epidemic. These results suggest that the increased incidence of epidemic KS in low-incidence countries was not related to the spreading of high pathogenic HHV-8 variants, furthermore, suggest the presence of other cofactors in high risk KS countries pre-existing in pre-AIDS era [1].

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18. Inhibition of KSHV-associated lymphoma engraftment in SCID mouse by morpholino oligomers

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Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8, is associated with several malignant disorders, including Kaposi's sarcoma, primary effusion lymphoma (PEL), and multicentric Castleman's disease. We have explored peptide-conjugated antisense phosphorodiamidate morpholino oligonucleotides (PPMOs) against KSHV and found effective PPMOs in inhibition of KSHV gene expression in cell culture. PPMOs are single-stranded DNA analogues that have a modified backbone and penetrate cells readily. In this study, we further tested the PPMOs in a SCID mouse model to assess their effect on engraftment and growth of PEL cells. PEL cells were engrafted into SCID mice via intraperitoneal route. PPMO was administered at the same time and repeated every other day for 10 doses. The mice were observed and scored for ascites development. The tumor cell burden was assessed by flow cytometry. Administration of anti-vIL-6 PPMO protected the mice from lymphoma development, while those mice receiving a control PPMO developed ascites and had high ratio of PEL cells in peritoneal lavage. The results demonstrate that PPMO against key KSHV genes can potently reduce KSHV replication and growth of PEL cells in SCID mice. Further exploration of PPMOs in the animal model is warranted.

19. Kaposi's sarcoma-associated herpesvirus (KSHV) serum DNA not associated with subsequent non-Hodgkin's lymphoma (NHL) risk

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Background

Non-Hodgkin's lymphoma (NHL) is a diverse group of cancers, elevated in HIV-infected individuals. Kaposi's sarcoma-associated herpes virus (KSHV) is found in a subset of NHL tumors, and could therefore be a cause of NHL. However, antibody testing for KSHV has limited sensitivity and specificity and studies have not associated KSHV antibodies with NHL odds. KSHV DNA in serum is a more specific marker of KSHV infection.

Methods

We performed a nested case-control study in the Multicenter AIDS Cohort Study, including 155 incident NHL cases occurring between 1984 and 2006 and non-cancer controls matched by study entry and time at risk. KSHV DNA was tested in pre-diagnostic serum from within 5 years before diagnosis using real-time quantitative PCR. Risk factors for NHL were evaluated with conditional logistic regression models.

Results

NHL cases were significantly more likely to have Kaposi sarcoma, and had more advanced HIV disease as indicated by lower CD4 cell count at study baseline and greater reduction in CD4 from baseline to HAART era than their matched controls (each $p < 0.01$). Detection of KSHV DNA in pre-diagnostic serum was more common among NHL cases than controls (14% vs. 6.5%, $p = 0.03$). However, among cases and controls who had detectable KSHV DNA, the median KSHV viral load (406 vs. 324, $p = 0.39$) was comparable. After adjusting for age, baseline CD4 cell count, and CD4 change, KSHV serum DNA was no longer significantly associated with odds of NHL (OR=1.5, 95% CI=0.53-3.9). Similarly null associations were observed among the subset of participants with serum within 1 year before diagnosis, by NHL sub-type, and when stratified by history of Kaposi sarcoma (Table 1). To better match for stage of disease, we performed a second analysis among 76 NHL cases who developed NHL after AIDS diagnosis, matching these cases to controls by time since AIDS diagnosis. KSHV serum DNA prevalence was similar among these AIDS NHL cases and matched controls (14% vs. 9.2%, $p = 0.32$). KSHV seroprevalence was also not associated with odds of NHL.

Conclusions

We found no significant independent association between KSHV DNA in pre-diagnostic serum with overall odds of NHL in this nested case control study. This research suggests that, similar to KSHV antibodies, KSHV serum DNA does not have predictive value for NHL risk and KSHV is not a primary cause of NHL in HIV-positive men who have sex with men.

Table 1. Comparison of KSHV DNA and KSHV seropositivity among 155 HIV-positive incident NHL cases compared to 155 HIV-positive matched controls.

	N	OR (95% CI)	
		Univariate	Multivariate
KSHV serum DNA: ≥ 1 copy detected	310	2.3 (1.1-5.1)	1.5 (0.53-3.9)
Among subset with serum within 1 year before diagnosis	130	1.2 (0.37-3.9)	0.81 (0.14-4.7)
Among subset without Kaposi sarcoma diagnosis	216	4.0 (1.13-14)	1.9 (0.37-9.6)
Among those developing NHL after AIDS	152	2.0 (0.60-6.6)	2.0 (0.55-7.0)
KSHV antibodies: seroprevalent	252	1.3 (0.68-2.5)	0.85 (0.36-2.0)

20. Kaposi's sarcoma-associated herpesvirus ORF57 promotes escape of viral and human IL6 RNAs from microRNA-mediated suppression

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Cancerous cells transformed by KSHV infection manifest an increased expression of both viral and human interleukin 6 (IL6). Although increased IL6 appears important to maintain cancer cell proliferation, what causes IL6 increase in the tumor cells by KSHV infection remains largely unknown. KSHV mRNA transcript accumulation protein (MTA or ORF57) has been characterized as a multifunctional protein in regulation of viral gene expression.

In seeking for genome-wide RNA targets of MTA by the CLIP assay, we identified viral IL6 (vIL6) as an MTA target which contains an MTA response element (MRE). MTA enhanced both vIL6 and human IL6 (hIL6) expression and cells with a MTA-null KSHV genome displayed a deficiency in vIL6 expression during virus lytic induction. Mutations in the vIL6 MRE identified its role in translational enhancement of vIL6, suggesting that vIL6 is translationally regulated in a sequence-specific manner. Unexpectedly, Ago2 which is a major component in RISC was found in RNA-protein pulldown assays by using MRE-RNA oligomers. Bioinformatics analysis showed that the identified vIL6 MRE contains a functional seed match to miR-1293. Ectopic expression of miR-1293 prevented vIL6 expression. Mutation of the miR-1293 seed match in the MRE or by ectopic expression of MTA could diminish the translational repression of vIL6 mediated by miR-1293 in vitro and in vivo, resulting in enhancement of vIL6 expression. Furthermore, we demonstrated that hIL6 expression is also under control by miR-608 binding to a similar MRE in the corresponding region. Through interaction with a RISC component Ago2, MTA prevents miRNA-mediated recruitment of IL6 mRNA into RISC, thereby relieving the translational repression.

Together, our results suggest the existence of a highly conserved miRNA pathway in cells in prevention of cytokine-induced cell proliferation and compelling evidence of how an oncogenic virus invades this pathway to induce cell proliferation and tumorigenesis during virus infection.

21. **KSHV activation, human and viral IL-6 production, and other cytokine dysregulation: Association with the symptomatology of KSHV-associated multicentric Castleman's disease**

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Background

KSHV-associated multicentric Castleman's disease (MCD) is a frequently fatal lymphoproliferative disorder characterized by inflammatory flares of fever, cytopenias, hypoalbuminemia, hyponatremia, and splenomegaly. Most cases occur in HIV-infected patients. KSHV viral interleukin-6 (vIL-6), human IL-6 (hIL-6), and possibly other proinflammatory cellular cytokines are believed to contribute to the pathophysiology of MCD flares.

Methods

We identified MCD patients with clinical flares. KSHV viral load (VL) in peripheral blood mononuclear cells, vIL-6, and the cellular cytokines IL-6, IL-1b, IL-8, IL-10, IL-12p70, interferon gamma, and tumor necrosis factor alpha were measured during flares and remissions to identify parameters best characterizing flares. The assay for vIL-6 was modified from Aoki Y. et al., Blood, 97, 2526, 2001; the cutoff of detection was 1560 pg/ml. Factors statistically associated with flares ($p < 0.01$) were explored in relationship to common disease manifestations with multiple linear regression models.

Results

20 patients (18 male, 2 female) were studied during 33 flares (range 1-3 per patient) and, in 18 patients, remission with therapy. Median (range) values of key parameters during flares included hemoglobin 9.9 mg/dL (6.8-14.4); platelet count 97 K/ μ L (6-377); sodium 133 mEq/L (127-143); albumin 2.7 mg/dL (1.2-3.9); spleen size 14.5 cm (9-28); temperature 38 °C (36.1-40.5); CD4 count 240 cells/ μ L (24-1319); HIV VL <50 copies/mL (<50-64100). Flares were associated with elevated KSHV VL (median 23448 copies/mL; range 0-3913043; $p < 0.0001$ compared with remission), vIL-6 (2575 pg/mL; <1560-20497; $p = 0.0039$), hIL-6 (24.2 pg/mL; 1.4-171.5; $p = 0.0034$), hIL-10 (783.9 pg/mL; 2.8-26021; $p = 0.0027$), and hIL-1b (1.3 pg/mL; 0-11.3; $p = 0.0074$). In two of the 33 flares vIL-6 was elevated but hIL-6 was not; in 14 hIL-6 was elevated but vIL6 was undetectable; and in 15 both were elevated. Neither was initially elevated in 2 flares, but hIL-6 later became elevated in both. Disease manifestations did not differ among flares with differing vIL-6/hIL-6 profiles. In multiple regression analysis, elevated KSHV VL was the strongest predictor of level of hemoglobin ($p < 0.0001$), sodium ($p < 0.0001$), albumin ($p < 0.0001$), and spleen size ($p = 0.0002$); hIL-6 the strongest predictor of thrombocytes ($p = 0.0011$), and KSHV and hIL-6 together the strongest predictors of body temperature ($p < 0.0001$). For hemoglobin, but not other parameters, vIL-6 and hIL-6 in combination were stronger predictors than either independently ($p = 0.0002$), though less strong than KSHV VL alone.

Conclusions

KSHV activity, vIL-6 production, and associated human hIL-6 dysregulation are key determinants of the clinical manifestations of MCD. vIL-6 and hIL-6 each appear sufficient to induce flares without the other. hIL-10 and hIL-1 β are also elevated in MCD flares, but their contribution to symptomatology remains to be determined.

22. KSHV interaction with Langerhans and dermal dendritic cells through C-type lectins

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The skin contains two types of dendritic cells (DC), Langerhans cells (LC), which reside in the epidermis in close contact with keratinocytes, and dermal dendritic cells (DDC), resident in the dermis. LC and DDC process cutaneous antigens and migrate out of the skin into the draining lymph nodes to present antigens to T and B cells. Recent reports showed that LC and DDC play an important role in certain virus infections, such as HIV-1 and HSV. Because of the strategic position of LC and DDC at mucosal sites of infection and the ability of these cells to capture pathogens, we hypothesized that these cells could be infected with KSHV and have an important role in the development of Kaposi's sarcoma. We have previously shown that KSHV enters monocyte-derived dendritic cells (MoDC) through DC-SIGN, resulting in a nonproductive infection. We have now generated LC and DDC from pluripotent cord blood CD34+ precursors by culture with GM-CSF, TNF, and TGF- β to obtain LC, and GM-CSF, TNF, and IL4 to generate DDC. These expressed the typical phenotype of LC, i.e., CD207^{pos}, CD14^{pos}, CD11b^{neg}, CD1a^{pos}, HLA-DR^{pos}, DC-SIGN^{neg}, and dermal DC, i.e., DC-SIGN^{pos}, CD14^{neg}, CD11b^{pos}, CD1a^{pos}, HLA-DR^{pos}, langerin^{neg}. We found that both LC and DDC supported productive infection with KSHV. Strikingly, while the level of viral DNA replication increased only 4-fold in infected DDC by 24h, we observed a $>1 \log_{10}$ increase in levels of viral DNA in LC. Anti-DC-SIGN mAb inhibited viral infection of DDC as detected by expression of viral proteins and viral DNA, while blocking of langerin on LC did not interfere with viral entry and replication. Infection with KSHV did not alter cell surface expression of langerin on LC, but downregulated expression of DC-SIGN on DDC, as we previously reported for MoDC. Cytokine production in infected LC and DDC was also altered compared to uninfected cells, with an increase in the levels of IL-8, IL-6, and IL-10 in the infected cells. These results indicate that KSHV can target both LC and DDC for productive infection and alter their function, supporting a role for these dermal DC in KSHV infection and pathogen.

23. KSHV-mediated ROS induction defines novel therapeutic targets in Kaposi's sarcoma

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Background

Kaposi's sarcoma herpesvirus (KSHV) is the etiological agent of Kaposi's sarcoma (KS). Understanding the interplay of viral and host factors in KS carcinogenesis is critical for the rational development of new therapies. Reactive oxygen species (ROS) have a recognized broad function in oncogenesis mediated by signaling cascades leading to the Rac1 activation of NADPH oxidases (Nox) [1]. ROS play a role in cell cycle regulation and angiogenesis, yet the specific molecular events linking ROS and these cancer hallmarks are still elusive. KSHV encodes a constitutively active G protein-coupled receptor (vGPCR) [2], which triggers KS-like sarcomagenesis via Rac1 [3]. It has been shown that Rac1-activated mutant induces tumors resembling Kaposi's sarcoma by a ROS-mediated mechanism in transgenic mice [4,5]. Moreover, Rac1 is overexpressed in AIDS-KS lesions and in KSHV-infected mECK36 tumors, pointing to a role for KSHV-induced Rac1-mediated production of ROS in KS pathogenesis [5]. The current study explored the induction of oxidative stress pathways in the KSHV-induced mouse model mECK36.

Results

vGPCR expression led to the upregulation of the c-sis/PDGFB oncogene in a dose-dependent manner in mECK36. PDGFB upregulation was dependent on Rac1 and ROS since it was suppressed by the Rac1 inhibitor EHT1864 and the ROS scavenger N-acetyl cysteine (NAC). PDGF activated oxidative signaling in a Rac/Nox/ROS-dependent manner in latently infected cells, leading to the upregulation of important genes for proliferation and angiogenesis, such as c-Myc and VEGFA through the activation of the STAT3 transcription factor. Treatment with antioxidant NAC and PDGF receptor inhibitors (imatinib and sunitinib) proved effective in inhibiting KSHV-induced tumorigenesis in the mECK36 mouse model.

Conclusions

Our results show a novel KSHV-driven oncogenic mechanism mediated by PDGF-B, whereby KSHV infection induces and exploits ROS production. ROS can be targeted therapeutically by using the NAC antioxidant or FDA-approved PDGF receptors inhibitors. Imatinib clinical responses in AIDS-KS could be due to PDGF-receptor inhibition of ROS production and warrant further clinical trials and molecular exploration of these new molecular therapeutic and prevention targets in AIDS-KS.

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24. MicroRNA analysis in human papillomavirus (HPV)-associated cervical neoplasia and cancer

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MicroRNAs (miRNAs) are ~22 nt single-stranded, non-protein-coding RNAs that generally negatively regulate their target mRNAs at a posttranscriptional level. Differential expression of miRNAs has been observed in many human cancers. To study their potential role in the pathogenesis of human papillomavirus (HPV) type 16-associated cervical neoplasia and cancer, we analyzed miRNA expression in cervical tissue from the normal cervix, moderate/severe dysplasia, and invasive squamous cell carcinoma. Using RNA from 6 cervical cancers, 3 dysplasias, and 4 normal samples and the TaqMan[®] MicroRNA Arrays, we found that 18 miRNAs were overexpressed and 2 underexpressed in cervical cancer compared to the normal cervical tissue ($p < 0.05$). We further found that 9 miRNAs (miRs-16, 21, 106b, 124, 135b, 223, 301b, 449a, and 141) were consistently overexpressed and 2 miRNAs (miRs-218 and 433) were consistently underexpressed in cervical cancer compared to the normal tissue. MiRNA expression in dysplasia samples was most similar to the normal tissue, with the exception of the overexpression of miR-16, miR-141, and miR-449a, and the underexpression of miR-218 and miR-433. Our results suggest that five miRNAs may have potential as markers for progression of dysplasia to invasive cervical disease.

25. Phase II AIDS Malignancy Consortium (AMC) trial of topical halofuginone in AIDS-associated Kaposi's sarcoma (KS): clinical and biological effects using a novel intra-patient control design

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Background

KS is a disease of multifocal vascular proliferation. Matrix metalloproteinases (MMPs) and type I collagen play critical roles in angiogenesis and are potential targets. Halofuginone (TempostatTM), a synthetic quinazolinone alkaloid derivative, induced anti-angiogenic, anti-metastatic and anti-proliferative effects in preclinical studies. It inhibits several essential stages of angiogenesis: endothelial cell proliferation, MMP2 expression, BM invasion, ECM deposition by newly formed vessels, synthesis of type I collagen during angiogenic sprouting, and bFGF-induced neovascularization. These data suggested that halofuginone might have activity in KS.

Methods

The AMC developed a novel trial design with a blinded intra-patient vehicle control. Halofuginone was supplied by Collgard Biopharmaceuticals Ltd (Atlanta, GA) to the NCI-DCTD under a CRADA as a 0.01% w/w ointment. Twelve KS lesions were divided into two groups of six, designated Group A and Group B. Tubes designated A and B containing either halofuginone or matching placebo ointment were supplied in a blinded fashion. Ointment A was applied to Group A lesions and ointment B to Group B lesions twice daily. Lesion response was assessed every 4 weeks for Group A and Group B lesions individually, and global response assessed both treated and untreated disease. Tumor biopsies obtained at baseline and from both Group A and B lesions during treatment were studied for expression of type I collagen by ISH and of MMP2 and VEGF by IHC. A patient subset had blood sampling after 8 weeks to evaluate systemic absorption.

Results

Twenty-three patients were treated. Median CD4 count was 322 (2-693); 68% had undetectable HIV RNA. Treatment was well tolerated. Of 14 patients who completed 12 weeks of treatment, 26% (95% CI, 10%-48%) showed partial response in halofuginone-treated lesions and 17% in placebo-treated lesions (95% CI, 5%-39%), (P=0.689). Global response was 30% (95% CI, 13%-53%). None of 10 subjects showed detectable blood levels. Type 1 collagen message decreased significantly in halofuginone-treated lesions at week 4, whereas vehicle-treated lesions showed no change. VEGF protein expression decreased significantly in vehicle-treated lesions at week 4, whereas halofuginone-treated lesions showed no change. There were no differences in levels of MMP2 or VEGF protein between halofuginone- and vehicle-treated lesions. No changes in HIV RNA levels or CD4 counts were observed.

Conclusion

Although topical halofuginone appears ineffective for KS treatment, this study presents a novel design that could be applied to future studies using the patient as his own control to test a topical, non-absorbed agent.

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26. Preventing HHV-8 transmission and Kaposi's sarcoma (KS) risk prediction and prognostication in resource-poor countries

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Background

Kaposi's sarcoma (KS) is the now most important AIDS-defining malignancy in sub-Saharan Africa including Tanzania, and human herpesvirus-8 (HHV-8) is necessary for its development. Detecting HHV-8 in biopsies and its antibodies in sera allows the confirmation of KS diagnosis and predicts its risk among blood transfusion (BT) and organ transplant recipients but this is not yet routine in most African countries. This impedes the provision of safe BT/organ donation as well as KS prevention. A cost-effective HHV-8 serological assay for routine use will help improve blood/organ safety and lower iatrogenic KS incidence in resource-poor countries.

Materials and methods

Consecutive archival (1990-2001) biopsies and their corresponding sera from African patients with KS, non-KS tumors, and non-neoplastic (reactive) lesions at Muhimbili National Hospital (MNH) were evaluated by histopathology, immunohistochemistry (IHC) for the HHV-8 latency-associated nuclear antigen (LANA), and serology for HIV and HHV-8 (ELISA) as well as for HHV-8 [immunofluorescence (IFA)].

Results

A total of 184 biopsies and corresponding sera from 120 KS (65%), 24 non-KS tumors (13%), and 40 non-neoplastic lesions (22%) were evaluated. Most sera (89.0%, 164/184) were HHV-8+ by either IFA or ELISA ($p < 0.001$, highly statistically significant, Chi² Test) and as expected the majority (68.3%, 112/164) were KS. HHV-8 serology tests by IFA and ELISA were mostly (92.4%, 73/79) concordant. Sensitivity, positive predictive value (PPV), and specificity were 98.6%, 93.5%, and 16.7% for IFA and 93.5%, 98.6%, and 50.0% for ELISA, respectively. All patients with early-stage KS were HHV-8 seropositive but two late-stage cases were seronegative despite LANA expression in their corresponding biopsies.

Conclusions

HHV-8 frequency at MNH appears to be very high and necessitates routine screening of blood/organ donors and recipients to prevent viral transmission and lower risk of iatrogenic KS development. IFA and ELISA serology tests appeared highly concordant and ELISA showed higher PPV and specificity in detecting anti-HHV-8 antibodies. Thus ELISA might allow affordable HHV-8 screening in resource-poor countries like Tanzania, with most lacking the cell culture and fluorescence microscopy facilities needed in IFA. The apparent tissue (LANA)-serum HHV-8 antibodies discrepancy in late-stage KS suggests that serum HHV-8 might not be a good indicator of this tumor's development.

Acknowledgement

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27. Relationship between salivary shedding and seropositivity for Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV) among South African children and adults: insights on why EBV infection is ubiquitous and KSHV is not

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Background

In a recent population-based study of South African children, we found KSHV seroprevalence in children to be low (7%) and not associated with age, but EBV infection was nearly ubiquitous (96%). While saliva is known to be the main conduit for transmission of both KSHV and EBV, little is known about the comparative patterns of KSHV and EBV salivary shedding in Africa. To address whether differences in salivary shedding may account for the difference in seroprevalence, we assessed KSHV and EBV shedding in children and their caregivers in South Africa.

Methods

Participants were children ages 1.5 to 8.9 years and their primary female caregivers in a population-based sample in a rural and an urban community in KwaZulu-Natal Province, South Africa. KSHV antibody testing utilized a previously established algorithm featuring two enzyme immunoassays and one indirect immunofluorescence assay. Viral DNA in unstimulated saliva was detected by PCR targeting ORF25 for KSHV and the EBNA gene for EBV.

Results

Among 458 children, 33 (7%) were KSHV antibody-positive, of whom 30 had saliva available for testing. Of these 30, 70% were female, and median age was 4.3 years (IQR 2.5-8.2). Among the female caregivers, 84 (17%) were KSHV antibody-positive, of whom 80 had saliva available for testing. Of these 80, the median age was 34 years (IQR 26-51). Among KSHV-seropositive individuals, KSHV DNA was detected in saliva of 1/30 children (3.3%) and 9/80 (11.3%) adults ($p=0.20$). KSHV DNA was not detected in the saliva of any KSHV antibody-negative or -equivocal individual. EBV DNA was detected in the saliva of 83% (25/30) of children ($p<0.001$ compared to KSHV) and 60% (48/80) of adults ($p<0.001$ compared to KSHV). There was no association between viral shedding of EBV and KSHV in saliva ($p=0.83$). Examination of the determinants of salivary shedding found that both younger age (odds ratio=0.97 per year of age, $p=0.01$) and HIV infection (OR=4.0, $p=0.01$) were independently associated with EBV shedding but not with KSHV shedding.

Conclusions

EBV is present in saliva substantially more often than KSHV among KSHV/EBV-infected South African children and adults. The much higher prevalence of EBV in saliva may, at least in part, explain why EBV infection is ubiquitous and KSHV is not. Attention next needs to turn to comparative mechanisms of host control of viral salivary shedding. The effect of HIV on herpesvirus salivary shedding suggests yet another reason why widespread therapy of HIV infection would be useful.

28. T cell immunosenescence is associated with the presence of Kaposi's sarcoma in antiretroviral treated human immunodeficiency virus-infected persons

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Background

We reported an atypical cohort of antiretroviral-treated patients who developed or had unremitting Kaposi's sarcoma (KS) despite having undetectable viral loads and high CD4 cell counts. The KS course of these patients is indolent, resembling elderly or classical HIV- KS. Since HIV infection is associated with accelerated immunologic aging ("immunosenescence"), and since classical HIV- KS of the elderly may be related to age-associated T cell dysfunction, we hypothesized that T cell immunosenescence would be associated with the presence of this atypical KS.

Materials and methods

We identified 19 individuals on antiretroviral therapy (ART) who developed or had unremitting KS after an interval of at least 24 months with viral loads <75 copies RNA/mL and peripheral CD4 cell counts >300 cells/mm³. We also recruited 47 HIV+ KS- controls on ART with viral loads <75 copies RNA/mL and peripheral CD4 cell counts >300 cells/mm³. Global immunosenescence markers CD28 and CD57, as well as naïve cell phenotypic coexpression of CD27+/CD28+/CD45RA+, were examined in peripheral blood via flow cytometry.

Results

All cases and controls were men. Cases and controls were not significantly different with regard to CD4 or CD8 cell count and viral load, though age was significantly different ($p < 0.001$, Table 1). Cases had a higher proportion of CD57+CD8+ T cells vs. controls (median of 41.5% vs. 27.7%, age-adjusted $p = 0.005$). There was a trend suggesting that cases had a higher frequency of CD57+CD4+ T cells than controls (median of 7.4% vs. 3.7%, age-adjusted $p = 0.07$). Cases also had a higher proportion of CD28-/CD4+ cells (median of 9.1% vs. 4.8%, age adjusted $p = 0.030$) and CD28-/CD8+ cells (median of 60.5% vs. 51.3%, age adjusted $p = 0.044$) vs. controls. Cases had a lower proportion of CD27+/CD28+/CD45RA+ naïve CD8+ T cells vs. controls (median of 11.3% vs. 20.7%, age adjusted $p = 0.022$). There was a trend suggesting that cases had a lower frequency of CD27+/CD28+/CD45RA+ naïve CD4+ cells vs. controls (median of 23.0% vs. 32.2%, age adjusted $p = 0.11$).

Table 1. Age and Markers of HIV Infection in HIV+ KS+ Cases and HIV+ KS- Controls.

	Number of Subjects (N)	Median Age (years)*	Median CD4 cell count (cells/mm ³)	Median CD8 cell count (cells/mm ³)	Median Viral Load (copies RNA/mL)
HIV+ KS+ Cases	19	54*	701	933	<75
HIV+ KS- Controls	47	43*	521	1200	<75

* $p < 0.05$

Conclusion

The indolent KS observed among antiretroviral-treated patients is associated with a higher frequency of immunosenescent T cells, characterized by global immunosenescence markers and decreased numbers of naïve cells. These markers provide more evidence that KS in these patients may be a consequence of enduring HIV-associated T cell dysfunction and T cell immunosenescence. This association of immunosenescence in otherwise well-treated HIV infection with an AIDS-defining malignancy may provide important insights into the role of immune dysfunction as a cause of premature morbidity commonly observed in the HIV+ cohorts.

29. The angiogenic properties of Kaposi's sarcoma-associated herpesvirus encoded G-protein coupled receptor are reduced by flavopiridol, an inhibitor of cyclin-dependent kinase 9

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Kaposi's sarcoma-associated herpesvirus (KSHV/HHV8) has been identified as the etiologic agent of Kaposi's sarcoma (KS), a multifocal highly vascularized neoplasm that is the most common malignancy associated with AIDS. Although highly active antiretroviral therapy has decreased the incidence of KS, it remains an incurable tumor for which there is no established treatment. Due to the vascular nature of KS, an anti-angiogenic therapeutic approach is attractive. The KSHV-encoded G-protein-coupled receptor (vGPCR) is required and sufficient to initiate angiogenesis and tumorigenesis. Recent evidence suggests that inhibition of P-TEFb, a transcriptional elongation factor composed of cyclin dependent kinase 9 (CDK9) and its regulatory partner cyclin T, is anti-angiogenic.

We hypothesized that flavopiridol, a novel inhibitor of CDK9, would inhibit vGPCR-induced angiogenesis by downregulating expression of angiogenic growth factors and/or Bcl-2. To test this hypothesis, *in vitro* and *in vivo* angiogenesis assays were carried out using primary human umbilical vein endothelial cells (HUVECs) transduced with either a control or a vGPCR-expressing retroviral vector and then treated with flavopiridol. Our results show that CDK9 activity is increased in vGPCR-expressing HUVECs and that pretreatment with 50 nM flavopiridol inhibited vGPCR-induced migration and capillary tubule formation. These results correlated with a significant decrease in expression of genes encoding the angiogenic factors VEGF-A and VEGF-C and the pro-survival factor Bcl-2. Initial studies to determine the molecular mechanisms by which CDK9 affects angiogenesis demonstrated that HUVECs treated with bFGF and VEGF had increased CDK9 activity as well as increased expression of the major isoform of Cdk9₄₂ and cyclin T. Although Cdk9 was described in the literature as a general transcription factor, we have observed that inhibition of CDK9 by flavopiridol decreased the expression of Bcl-2 but not p21 in HUVEC. Together these results suggest that CDK9 plays a role in mediating transcriptional regulation of vGPCR responsive genes and implicate CDK9 as a potential target to reduce vGPCR-enhanced endothelial cell survival, angiogenesis, and tumorigenesis. Experiments are currently under way to determine whether CDK9 is directly activated upon vGPCR expression and whether inhibition of CDK9 activity suppresses KSHV-enhanced angiogenesis and tumorigenesis *in vivo*.

30. The Kaposi's sarcoma-associated herpesvirus E3 ubiquitin ligase K5 acts as a novel oncogene, altering cellular metabolism and signaling: implications for tumorigenesis

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While it is clear that Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8) is the causative agent of a number of malignancies including multicentric Castleman's disease, primary effusion lymphoma, and Kaposi's sarcoma (KS), the molecular mechanisms of tumor induction by this virus are still unclear. In part, KS lesion presentation is thought to be driven primarily through paracrine mechanisms and is mainly observed in immunocompromised patients. Monocyte subsets, including dendritic cells and macrophages, are crucial to immune system functionality and are also skewed in KS patients. The goals of this study were to investigate a potential role for the E3 ubiquitin ligase K5 of KSHV, which plays a role in viral immune evasion, in altering monocyte functionality, thereby contributing to KSHV-driven tumorigenesis.

A series of wild-type (WT) and mutant K5-expressing stable cell lines were generated in THP-1 monocytic cell line and examined. Surprisingly, these cells demonstrated a serum-dependent increased growth rate and a propensity to acidify the growth medium as compared to vector-THP-1 cells. Biochemical examination indicated that K5 induced aerobic glycolysis and other hallmarks of the "Warburg Effect," including increased lactate production and glucose uptake. Observed increases in Akt and total cellular tyrosine phosphorylation, combined with the serum-dependence, suggested a role for receptor tyrosine kinases (RTKs). A human-RTK array demonstrated increased activation of the Flt-3, Axl, PDGFR- β , and Flt-4 receptors in K5-expressing versus vector cell lines. Subsequent testing demonstrated increased sensitivity of K5-expressing THP-1 cells to growth arrest and apoptosis by sunitinib and increased ligand-dependent signaling. Dynamin inhibitor studies showed that K5 can target these RTKs from the surface to increase intracellular signaling. Additional molecular details will be presented.

Overall, our studies demonstrate that the KSHV K5 protein is acting as a novel oncogene – the first viral protein of its kind – to drive monocyte subset expansion and alter cellular metabolism, contributing to a pro-tumorigenic microenvironment. Intriguingly, the metabolic changes observed are caused by a single KSHV protein and thus serve as a useful model to study different aspects of KS pathology and its overall regulation of cellular metabolism. These studies also provide additional rationale for the currently ongoing clinical trials of sunitinib, Gleevec, and rapamycin for the treatment of KSHV-driven neoplasias. Finally, the ability of this viral E3 ubiquitin ligase to drive metabolic changes provides the tantalizing suggestion that a cellular ligase may be acting in a similar, either physiologic or oncogenic, manner.

31. The HIV nef protein within ARL is genetically and structurally distinct from those in the brain of patients with HAD

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Background

Despite antiretroviral therapy, macrophages remain significant cellular reservoirs for HIV infection. Two fatal macrophage-mediated diseases still occur at a much higher rate in the HIV-infected and HAART-treated population: (1) AIDS-related lymphoma (ARL), a noninflammatory disease, and (2) HIV-associated dementia (HAD), an inflammatory disease. The frequency of HIV-infected macrophages in ARL is 50%. Macrophages are the primary HIV-infected cells in the brain. The mechanisms that lead to the development of these diseases are not understood. Because certain subtypes of HIV are associated with a higher prevalence of HAD, a viral genetic determinant for HAD development is likely. On the other hand, ARL development occurs fairly consistently across multiple HIV subtypes and genetic analysis has clearly differentiated ARL tissue-associated HIV from non-ARL tissue HIV within individuals. These facts raise two questions: (1) Are there tumor-specific genetic differences among HIV proteins that could influence the macrophage to accelerate ARL development? (2) How might HAD-associated and ARL-associated viruses differ at the genetic and structural levels? Our goal was to analyze HAD and ARL viral sequences and determine whether a disease association could be identified within viral proteins.

Methods

The AIDS and Cancer Specimen Resource (ACSR) archives tissue samples derived from well-documented cases of both ARL and HAD. Multisite autopsies of 7 patients with ARL, HAD, and other neurological and systemic disorders were identified at the ACSR. More than 20 sequences from each of 5 to 7 tissues from each patient were sequenced. The HIV nef sequence was used in multiple genetic analyses, including a neural net signature pattern analysis, a tertiary structural analysis, and an analysis of the stability of an HIV viral microRNA associated with apoptosis.

Results

Signature pattern analysis clearly separated ARL from HAD viruses and identified positions that may in concert produce specific pathological outcomes. HIV subtype D viruses are known to be associated with a high rate of HAD. Comparative tertiary structural analysis of nef showed that HAD viruses were more similar to HIV subtype D viruses than ARL viruses. ARL viruses were either missing or possessed a less stable miR-H1 structure compared to HAD viruses.

Conclusions

Our results show that HIV-associated diseases are likely related to specific viral genetic signatures and structures. Discovery of an ARL virus would enable the development of diagnostic tools and identify subsets of viruses to be targeted with drugs or vaccines.

32. The use of high-dose azidothymidine in combination with chemotherapy upfront is an effective treatment approach for gamma-herpes virus-related non-Hodgkin's lymphomas

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Background

Azidothymidine (AZT), a thymidine analogue, is an excellent substrate for gamma-herpes virus thymidine kinases (TKs). Our group previously demonstrated that AZT alone can inhibit NF- κ B and disrupt EBV latency in primary low-passage Type I latency EBV+ Burkitt lines. The addition of hydroxyurea, which increases the intracellular levels of AZT monophosphate, synergized with AZT in Type III latency EBV+ immunoblastic lymphoma cell lines. The use of AZT in targeting gamma-herpes virus lymphomas is an attractive concept given that this drug is preferentially phosphorylated by EBV and HHV-8 TKs as compared to non-thymidine nucleoside analogues. The drugs methotrexate (MTX) and doxorubicin (DOX) also induce lytic expression of gamma-herpes viruses. MTX inhibits thymidylate synthase, thus blocking de novo synthesis of dTMP and increasing the likelihood of AZT incorporation into DNA. We have found that the combination of high-dose AZT with MTX, used alone or with alternating standard chemotherapy, can result in dramatic clinical responses and even cures in patients with poor prognosis gamma-herpes virus-related lymphomas.

Materials and methods

Ten patients with EBV-positive (9 HIV-positive) non-Hodgkin's lymphoma (NHL) were treated with first-line MTX (3.0-4.5 g/m² IV on day 1) and AZT 1.5 g IV infusion q12 hours (days 1-4) every 3 weeks or alternated with other chemotherapy regimens, including EPOCH, or hyper cVAD between 2004-2009 at the discretion of the treating physician (Table 1). One patient (solid PEL) received AZT and MTX initially, and upon relapse 31 months later received DOX 20 mg/m² (Day 1), MTX 5 g/m² (Day 2), and AZT 750 mg twice daily with hydroxyurea 1 g daily (Days 2-5) under our new clinical trial.

Results

Clinical characteristics, response, and survival data of patients are summarized in Table 1. All patients were treated with high-dose AZT and MTX. Three patients with plasmablastic lymphoma (PBL) and 1 patient with BL also received alternating EPOCH; 2 BL patients received alternating hCVAD. Seven patients achieved CR. Two patients developed neutropenic fever. Median PFS in this cohort of patients has not been reached. Median OS was 31 months (95% CI: 0.0-84.8).

Table 1.

Age	Lymphoma type	Stage	PS	HIV	CD4	Alternating regimen	RT	Sustained Response (months)	Progression (months)	Death (months)
34	DLBCL	IVB	3	+	4	-	-	PD	1.0	1.3
49	BL	IVB	2	+	91	EPOCH	-	CR (50)	-	-
40	BL	IIA	2	-	-	hCVAD	+	CR (57)	-	-
51	DLBCL	IVB	2	+	47	EPOCH	-	CR (65)	-	-
40	BL	IVB	2	+	214	hCVAD	-	PD	2.0	-
34	PBL	IVB	2	+	16	-	-	PD	1.0	4.5
33	PBL	IIA	1	+	166	EPOCH	-	CR (18)	-	-
44	PBL	IVA	1	+	458	EPOCH	-	CR (19)	-	-
52	PBL	IIB	1	+	57	EPOCH	+	CR (20)	-	-
51	Solid PEL	IVB	2	+	113	-	-	CR (31), 2 nd CR (10)	After 1st line: 31.1	-

PS: ECOG performance score; RT: radiotherapy; DLBCL: diffuse large B-cell lymphoma; PEL: primary effusion lymphoma; PBL: plasmablastic lymphoma. EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; hyper cVAD: dexamethasone and fractionated vincristine, doxorubicin cyclophosphamide; CR: complete remission; PR: partial remission; PD: progressive disease.

Conclusions

The combination of high-dose MTX/AZT is a promising and tolerable treatment for gamma-herpes virus-related lymphomas. A Phase II clinical trial with low-dose doxorubicin, MTX, AZT, and hydroxyurea for relapse EBV+ NHL is currently recruiting participants. Interim results and supporting laboratory data for using this gamma-herpes virus lytic approach will be presented at the meeting.

33. Upregulation of p18Ink4c expression by HPV E6 via p53-miR-34a pathway

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Binding of p53 to miR-34a promoter activates the expression of tumor suppressive miR-34a. Our previous study demonstrated that oncogenic HPV infection downregulates miR-34a expression through degradation of p53 mediated by E6. In searching for miR-34a targets, we found that miR-34a mainly downregulates p18Ink4c, a CDK4/6 inhibitor induced by E2F transactivation. HPV18+ HeLa cells with ectopic miR-34a expression or by E6 siRNA knockdown-induced expression of miR-34a had a substantially reduced expression of p18Ink4c in a dose-dependent manner, but had no effect on p16Ink4a, another member of CDK4/6 inhibitor family. Further investigation showed an increased p18Ink4c level in cervical cancer tissues by western blotting as compared to normal cervix. By immunostaining of tissue arrays, an increased expression of p18Ink4c was found in 68% of cervical cancer tissues, but only in 6.6% of normal cervical tissues. Moreover, specific inhibition of miR-34a expression in CaSki cells promoted the expression of p18Ink4c. Raft cultures with HPV16 or HPV18 infections also showed an increased p18Ink4c expression. In a reporter assay, we demonstrated that disruption of the miR-34a seed match from p18Ink4c promoted luciferase activity in the presence of ectopic miR-34a. As a cell cycle regulatory protein in normal cells, the increased p18Ink4c expression by E6-induced p53 destabilization and miR-34a reduction in cervical cancer would lead to suppress cell cycling and proliferation. However, viral E7 expressed in cervical cancer cells inactivates pRB and disassociates E2F from pRB, resulting in disruption of normal G1 checkpoint. Thus, an increased p18Ink4c in the cervical cancer cells would not affect the cell growth. To test this hypothesis, we knocked down p18Ink4c expression by siRNA in both HPV18-positive HeLa cells and HPV-negative HCT116 cells, a colon cancer cell line that contains an intact G1 checkpoint. As we predicted, knocking down p18Ink4c expression promoted the growth of HCT116 cells but had no effect on HeLa cells. Altogether, our data indicate that p18Ink4c is a miR-34a target and its increased expression in cervical cancer tissues can be used as a new biomarker for cervical cancer diagnosis and prognosis.

Poster Abstracts – Day 2

34. A higher proportion of squamous intraepithelial lesion of the cervix in symptomatic HIV-infected women at a tertiary health center in Tanzania

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Background

Many study reports have associated cervical squamous intraepithelial lesion (SIL) and HIV infection [1,2]. In Tanzania, however, there are limited and conflicting published reports on the association between HIV infection and SIL [3]. A study was conducted to determine the proportion and severity of SIL in HIV-infected women attending a cervical cancer screening clinic at Kilimanjaro Christian Medical Center (KCMC) in Tanzania. A total of 214 women 18 to 60 years old, among whom 99 (46.3%) and 115 (53.7%) were HIV-seropositive and HIV-seronegative, respectively, were recruited in the study. Blood samples were taken to associate SIL and degree of HIV infection by CD4+ T lymphocyte counts. Structured questionnaires with socio-demographic characteristics were administered while cervical smears were taken from all women to determine and grade the degree of SIL. High-grade and low-grade squamous intraepithelial lesions were regarded as abnormal smear. Overall proportion of SIL was 17%. Proportion of SIL among HIV-seropositive subjects was 32% versus 4% in seronegative subjects (OR=13.3, 95% CI=4.2-46.4) (see Table 1). Low CD4+ T lymphocyte cell count was associated with higher proportion of SIL (p=0.001) (see Table 2). The relationship between CD4+ T lymphocyte cell counts and the severity of cervical SIL was significant (p=0.007) (see Table 3). Marital status and number of lifetime sex partners were risk factors significantly associated with SIL (p=0.004 and 0.005, respectively). There was no association between SIL with age, education level, parity, or age at sex debut.

Table 1. Relationship between HIV serostatus and cervical SIL (n, 214).

Variable	Total	Pap results		Chi-square	p-value	OR (95% CI)
		SIL	Normal			
		No (%)	No (%)			
HIV-seropositive	99	32 (32.3)	67 (67.7)			
HIV-seronegative	115	4 (3.5)	111 (96.5)	31.5	<0.001	13.3 (4.2-46.4)

Note; Pap = Papanicolous smear; SIL = Squamous Intraepithelial Lesion.

Table 2. Relationship between SIL and HIV disease progression according to CD4+ T lymphocyte count (cells/microl).

Variable	Total	PAP smear results		Chi-square	p-value
		SIL	Normal		
		No. (%)	No. (%)		
CD4+ T lymphocyte cell Count (cells/microliter):					
Less than 200	31	18 (58.1)	13 (41.9)		
200-499	49	32 (32.3)	38 (77.6)		
500 or more	19	4 (3.5)	16 (96.5)	13.9	0.001

Note: PAP = Papanicolous; SIL = Squamous Intraepithelial Neoplasia.

Table 3. Relationship between degree of SIL and degree of HIV progression (n=99).

Variable	Total	PAP smear results			Chi-square	p-value
		HGL	LGL	Normal		
		No. (%)	No. (%)	No. (%)		
<i>CD4+ T lymphocyte cell Count (cells/microliter):</i>						
Less than 200	31	7 (22.6)	11(35.5)	13 (14.9)		
200-499	49	4 (8.2)	7 (14.3)	38 (77.6)		
500 or more	19	1 (5.3)	2 (10.5)	16 (84.2)	14.0	0.007

Note: PAP = Papanicolous; HGL = High-Grade Squamous Intraepithelial Lesion; LGL = Low-Grade Squamous Intraepithelial Lesion.

Conclusion

SIL diagnosis was significantly associated with HIV infection with inverse relationship between HIV disease progression and degree of SIL. These findings underscore the need for HIV screening among women with SIL, and the need for cervical cancer screening in HIV-infected women. Marital status and number of lifetime sex partners were significant risk factors associated with SIL.

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35. Nonlinear Burkitt lymphoma risk patterns with age and CD4 lymphocyte count among persons with AIDS in the United States

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Background

Trimodal age-specific incidence rates for Burkitt lymphoma (BL) were observed in the U.S. general population, particularly among men. Because BL is AIDS-related, it is not known whether trimodal incidence peaks occur independently of immunosuppression. We therefore investigated age-specific BL incidence in persons with AIDS (PWA).

Methods

Crude and adjusted incidence rates, rate ratios (IRR), and 95% confidence intervals (95% CI) for BL and other non-Hodgkin lymphomas (NHLs) diagnosed during 4-60 months following AIDS diagnosis in the United States HIV/AIDS Cancer Match study (1980-2005) were assessed by age and CD4 lymphocyte counts using Poisson regression models. Two-tailed p -values < 0.05 were considered statistically significant.

Findings

We analyzed 306 incident cases (22 cases per 100,000 person-years) diagnosed among 567,865 PWA. The adjusted incidence rate ratio for BL among males was 1.6 times that among females and among non-Hispanic Blacks 0.4 times that among non-Hispanic Whites, but it was unrelated to HIV-transmission categories. The age-specific incidence rates for BL revealed at least two and perhaps three peaks during the pediatric and adult/geriatric years, whereas the incidence rates for other NHLs increased from childhood to adulthood. Compared to PWA aged 32-39 years, the adjusted incidence rate ratio (IRR) for BL was significantly elevated among PWA aged 0-19 years (2.3, 95% CI 1.2-4.4). The adjusted IRR for BL among PWA aged 20-31 years was significantly decreased (0.6, 95% CI 0.4-0.8), but the adjusted IRRs for BL among PWA aged 40-51 years, 52-59 years, and aged 60 years or older were not significantly different (1.0, 95% CI 0.8-1.3), (0.8, 95% CI 0.4-1.4), and (1.4, 95% CI 0.7-2.7), respectively. The risk for BL among PWA with <50 CD4 lymphocytes/ μ L was 0.3 (95% CI=0.2-0.6) of those with \geq 250 CD4 lymphocytes/ μ L, whereas the incidence for other NHLs rose with decreasing CD4 lymphocyte counts.

Interpretation

Our findings strengthen the notion that bi/trimodal BL may occur independently of immunosuppression. The deficit of BL at low CD4 lymphocyte counts suggests that functional CD4 lymphocytes may be required for BL to develop.

36. AIDS-related lymphomas in Nigeria an emerging phenomenon

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Background

In comparison to the western world, aggressive non-Hodgkin's lymphoma (NHL) including primary central nervous system (CNS) lymphoma, as AIDS-defining disease, is less common in sub-Saharan Africa even with its high HIV/AIDS prevalence. We studied the occurrence of HIV/AIDS-related lymphomas in Nigerian patients with a view toward highlighting the incidence.

Patients and method

Consecutive cases of histologically and/or cytologically confirmed lymphoma screened for HIV (after appropriate counseling) and seen between January 2003 and December 2009 were the subjects. Types and treatment outcome of lymphoma in the HIV-positive group were further studied. Data were analyzed using appropriate descriptive and inferential statistics.

Results

There were 161 cases comprising NHL, 42 (25.5%); HL, 15 (9.3%), and BL, 104, (64.6%). Seven (4.3%), aged 2-49 (median = 41) years were retroviral positive. Of these, 4 (3 males, 1 female, aged 28-49 (median = 38.5) years) had NHL, 2 (both females) HL, and 1 case, a 2-year-old boy with HIV since birth, had Burkitt's and an HIV-positive mother. All, except one female with stage 1 HL, presented late (at least clinical stage IIIb). Three patients with NHL and 1 with late-stage HL succumbed to their disease within 1-3 weeks of hospital admission. The remaining 3 patients had been responding satisfactorily to chemotherapy (CHOP for NHL, ABVD for HL, and COM for Burkitt's lymphoma.)

Conclusion

Compared to earlier reports from Nigeria, the AIDS-related lymphomas rate of 4.3% in the series indicated rising incidence. AIDS-associated BL of 0.1%, in spite of high background prevalence of Burkitt's lymphoma (>60% of lymphomas), supported its relative rarity. With longer survival and longer immunosuppression, closely following up AIDS patients on HAART would be justified, as more cases of AIDS-related lymphomas may possibly emerge in the future.

Acknowledgements

AIDS-Associated Malignancies Management Team, OAUTHC ILE-IFE Nigeria.

37. Attitude of health care providers in Abia State, Nigeria, to people living with HIV and AIDS

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Background

In pursuit of the global commitment of universal access to HIV services, there has been rapid scale up of HIV programmes including care and support in Nigeria in the past few years. Consequently, more health care providers are increasingly being involved in the provision of HIV services; this however increases their risk of exposure to HIV infection. Most people accessing HIV services are also at risk of developing malignancies because they often present late as a result of stigma. Care providers attitude towards PLWHA has been shown to be the most important factor influencing uptake of HIV services [1]. The objective of this study is to ascertain health care workers knowledge of HIV and their attitude towards PLWHAs in Abia State, Nigeria.

Methodology

A cross-sectional, descriptive study, involving a total of 300 health care workers selected using stratified sampling technique from the list of registered health care workers in the State. Responses were elicited from them using semi-structured self-administered questionnaire on socio-demographic characteristics, knowledge of HIV/AIDS and attitude towards PLWHAs. Data collected was analyzed using Epi-info 3.5.1 version. IRB approval was obtained from Abia State University.

Result

The respondents included 135 nurses (52%), 56 doctors (21.7%), others were pharmacists, laboratory scientists and medical records officers. Almost all know that HIV is a blood transmissible infection. Over 50% believe that HIV transmission in health care settings is predominantly by sexual intercourse, while 40% of them consider recapping of needles as an important measure in preventing HIV transmission. 13% of them feel that their work do not expose them to the risk of acquiring HIV, and 40% do not think that increased uptake of HIV services increases their chance of acquiring HIV. Majority of them provide one form of HIV services in their facility or the other, but their facilities lack enough provisions to protect them from HIV infection. However, most health workers in the state expressed willingness to care for PLWHAs, admit them into their facility, as well as work with an HIV positive colleague. However, less than 35% are not willing to share a meal with HIV person, buy food from a HIV positive shopkeeper.

Conclusion

These findings underscores the need to further educate health care providers in Abia State Nigeria on the risk of occupational exposure to HIV transmission, so as to improve their attitude towards PLWHA, which in turn may result in increased uptake of HIV services.

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38. Cancer in HIV patients in Latin America and the Caribbean: characteristics in seven sites from the CCASAnet Cohort (IeDEA Region 2)

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Background

Cancer in the Latin American and Caribbean HIV+ population has not been comprehensively studied. CCASAnet includes sites from Argentina, Brazil, Chile, Haiti, Honduras, Mexico, and Peru [1]. With support from NIH and NCI, CCASAnet established a region-wide registry of cancer-related information on HIV+ individuals.

Methods

Retrospective cancer data from HIV+ patients was collected between 2007 and 2009. Cancer cases were identified by review of clinical charts and preexisting databases. A standardized case report form was developed by the Vanderbilt data coordination center. Data were entered via a secure online Web interface. Cancers were categorized as AIDS-defining and non-AIDS-defining cancers (ADC and NADC). Time relations between HIV diagnosis, ARV initiation, and cancer diagnosis were established. For computing cancer incidence after HAART initiation, we used data from HAART starters in the CCASAnet cohort [2]. Haiti's data were analyzed separately considering available information.

Results

Of 463 cancers reported, 357 were ADC: 242 Kaposi's sarcoma, 98 non-Hodgkin lymphoma, and 17 invasive cervical cancers. Most frequent NADC were Hodgkin lymphoma (16), breast cancer (15) (most from Haiti), skin cancer (11), anal cancer (6), and in situ cervical carcinoma (6). About half of the cancers were diagnosed prior to or within 1 year of HIV diagnosis. However, 73% of NADC and 45% of ADC were found >1 year after HIV diagnosis. ADC occurred more commonly prior to initiation of ARV therapy. Among patients previously exposed to ARV, time from ARV start until cancer diagnosis was longer for NADC than ADC (median: 2.48 vs. 0.5 years, $p < 0.001$). Survival probability for people with ADC was lower than for those with NADC but risk of death did not differ among both groups ($p = 0.51$).

Among 3372 HAART recipients, 158 (4.7%) were diagnosed with 165 cancers during the followup period: 136 ADC and 29 NADC. 85 cases were diagnosed prior to or at HAART initiation (77 ADC, 8 NADC). Incidence of cancer after HAART initiation in 8080 person-years of followup (median=1.9, IQR=1-3.2 years) was 7.3 (95% CI=5.7-9.4) for ADC 47.6 (95% CI=32.2-70.5) in the first 2 months], and 2.6 (95% CI= 1.7-4) for NADC. For a 100-cell increase in CD4 at HAART initiation, relative risk of cancer decreased 31% (95% CI 13-45%).

Conclusions

Our findings on incidence and type of cancer in this cohort are consistent with reports from other regions, with variations among sites. Early HIV diagnosis and treatment should be improved considering the high number of ADC and concomitant cancers with HIV diagnosis or HAART initiation.

Acknowledgements

CCASAnet, leDEA Region 2: Caribbean, Central and South America.

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39. Challenges in integrating cervical cancer screening in HIV care clinics in West Africa: A pilot study in Abidjan, Côte d'Ivoire

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Background

The ongoing scale-up of antiretroviral therapy (ART) in low-resource settings continues to improve the prognosis of HIV-infected individuals, necessitating a focus on long-term case management especially in women. Facing the particularly high burden of cervical cancer in sub-Saharan Africa, preventive measures are therefore becoming an integral component of a comprehensive approach to the management of patients. We describe here some of the operational aspects of a cervical cancer screening procedure based on visual inspection among HIV-positive women attending ART clinics in Abidjan.

Methods

A cross-sectional study is being conducted in two HIV clinics of Abidjan, since August 2009. A mobile team composed of three trained midwives and a senior gynecologist is in charge of proposing cervical screening based on visual inspection to all HIV-infected women attending participating clinics. Midwives are in charge to perform visual inspection of the cervix with acetic acid (IVA) and lugol's iodine (IVL). Exclusion criteria are following: no previous cervical cancer or total hysterectomy, aged <25 or >59 years, pregnancy over 20 weeks. They refer positively screened women (IVA+ or IVL+), to a gynecologist in charge of the colposcopy examination (and biopsy if needed). Women with confirmed lesions are proposed an adapted treatment according to local available resources.

Results

Of the first 1,653 HIV-positive women, who attended the cervical screening consultations, 49 were not eligible and 103 were not assessable because of a prevalent cervical infection. The median age of the 1,501 screened women was 37 (IQR 32-43) years, and 1171 (78%) were on ART. 133 (9%) women were positively screened for cervical pre malignancy and referred for medical examination. 69 (4.6%, 95% CI 3.5-5.6) were confirmed by colposcopy and had histological investigation. Results of the 69 biopsy performed were as follows; 48 cervical intraepithelial neoplasia (CIN) of grade 1, 8 CIN grade 2 or 3, 2 invasive carcinoma and 10 nonmalignant findings. 22 patients were treated with cryotherapy, 16 were referred for surgical excision, and 31 were proposed a gynecological followup.

Conclusion

Several barriers were identified as limiting the ability of visual inspection used as a cervical screening method such as a high rate of cervical infection or a high rate of false-positive cervical lesions. Health care systems in West African countries cannot afford the financial and structural burdens of a conventional cervical screening program. Strategies adapted to HIV-infected women and relying on visual inspection appear feasible despite stated limitations and should be further evaluated.

Acknowledgement

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40. Clinical presentation and outcome of epidemic Kaposi sarcoma in Ugandan children

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Background

Kaposi sarcoma (KS) is one of the most common pediatric cancers in sub-Saharan Africa. Few data are available about the clinical presentation or response to treatment of children with epidemic (HIV-associated) KS.

Methods

Medical records of all children with KS and HIV infection referred to the Uganda Cancer Institute from October 2004 to June 2007 were reviewed. Charts were abstracted for age, sex, location of KS lesions, biopsy results, CD4 T-cell counts, and KS treatment and outcome.

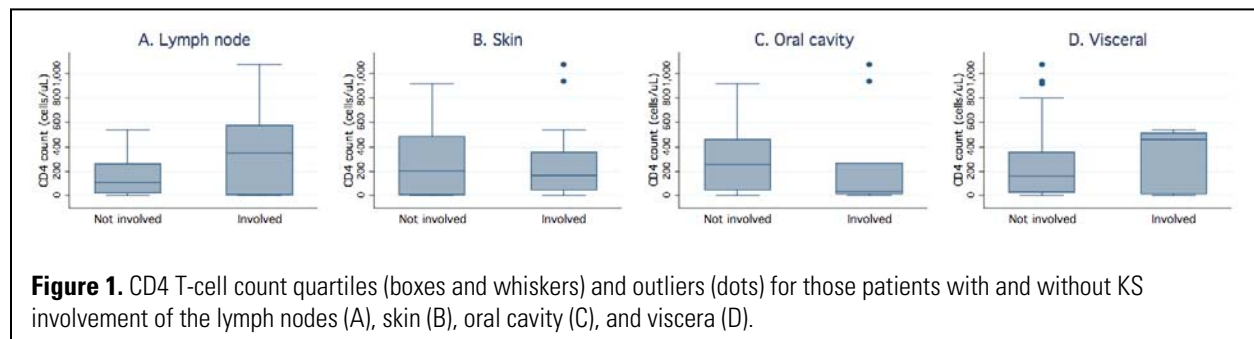
Table 1.

	Total	Males	Females
KS cases, n (percent)	73 (100%)	37 (50.7%)	36 (49.3%)
Age in years, median (range), n=56	10.1 (2 – 18)	9.3 (2 – 16)	11.0 (2 – 18)
CD4 T-cells/uL, median (IQR) n=36	210 (21 – 482)	165 (16 – 538)	263 (26 – 464)
Location of lesions n=42*			
Skin involvement	20 (47.6%)	10 (45.5%)	10 (50.0%)
Oral cavity involvement	9 (21.4%)	4 (20.0%)	5 (22.7%)
Viscera involvement	5 (11.9%)	3 (15.0%)	2 (9.1%)
Lymph node involvement	25 (59.5%)	11 (55.0%)	14 (58.3%)

*Categories of lesion location not mutually exclusive.

Those children with lymphadenopathic KS were younger (mean difference 3.7 years; $p = 0.01$), and had higher CD4 T-cell counts (mean difference 242 cells/ μ L; $p = 0.03$) than those without lymph node involvement. CD4 T-cell count was not associated with KS presentations other than lymph node involvement (Figure 1).

Twenty children (62.5%) of the 32 patients with outcome data available had a complete resolution of KS. Eleven patients had a partial response, and only one patient had a documented lack of response. No association was apparent between outcome and age, sex, or type of KS presentation. Thirty (93.8%) of the 32 patients with outcome data available received cancer chemotherapy (10 with vincristine, 20 with vincristine plus bleomycin). No difference was observed in outcome with respect to whether cancer chemotherapy was used, or whether one or two drugs were given. Of those patients with a known outcome, a higher proportion had a complete resolution of KS among those who received any antiretroviral therapy (ART) regimen compared to those who did not receive ART (19 of 26 vs. 1 of 6; $P=0.02$).



Conclusions

Compared to skin involvement, lymph node involvement of epidemic KS occurs at younger ages and at higher CD4 levels. This presentation may reflect recent infection with human herpesvirus 8 followed by a rapid progression to malignancy. Favorable response to treatment was observed in some cases, but the observed response rate was almost certainly biased by the large number of children lost to followup, among whom we expect disproportionately poor outcomes. Prospective studies are needed to determine optimal management.

41. Comparison of self-collected versus nurse-collected samples for detection of HPV-DNA among HIV-infected women in Pune, India

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Background

Self-collection of samples for papillomavirus (HPV)-DNA testing may represent a noninvasive and discreet method for cervical cancer screening, especially among HIV-infected women whose screening options are often compromised by the dual burden stigma of HIV and gender and lack of health care access.

Methods

We conducted a cross-sectional study in Pune, India among n=303 consenting HIV-infected women who underwent a brief informational session about high-vaginal self-collection for HPV samples. The participants then undertook self collection using a Digene cervical sampler in a private room in the clinic. This was followed by collection of cervical samples by a pelvic examination (along with other screening tests) conducted by a female nurse. Participants also answered a brief acceptability survey after the screening examination. High-risk (HR) HPV-DNA detection was conducted using Digene Hybrid Capture-2™ (HC2) assay. We calculated detection rates and measures of agreement between the two tests and compared survey responses for acceptability of self-sampling versus sample collection during pelvic examination.

Results

The median age was 30 years (interquartile range, IQR: 27–34) and the median CD4+ T-cell count was 343/μL (IQR: 244–495). The detection rates of HR-HPV positive test results were comparable in self versus clinician collected samples overall [44.1% (130/295) vs. 41.8% (124/297), p=0.6], and did not statistically differ by age (i.e., >30 vs. ≤30 years) (44% vs. 41%, p=0.5), CD4+ cut-off (i.e., <200/μL vs. ≥200/μL) (43% versus 41%, p=0.6) or antiretroviral treatment (ART)-status (i.e., on ART vs. never on ART) (45% vs. 49%, p=0.6).

The pair-wise agreement between the two sampling approaches was high [88.1%] and the kappa statistic denoted substantial agreement beyond chance [kappa: 0.76 (95% C.I.: 0.68-0.83)]. Survey responses about acceptability between the two approaches revealed that in comparison to screening by pelvic examination, a higher proportion of women found self-sampling to cause absolutely no discomfort [51% vs. 61%, p=0.01] and absolutely no pain [42% vs. 59%, p=0.01]. However, over half (50.2%) still preferred screening through pelvic examination, a third (35.2%) preferred self-collection as the favored method for screening, while 14.3% had no preference of one sampling method over the other.

Conclusions

Clinic-based self-collection of HPV compared favorably in comparison to sample collection through clinic-based pelvic examination among HIV-infected women in Pune, India. Further research needs to be undertaken to explore acceptability of home-based versus clinic-based collection of HPV samples, and operational challenges that may be encountered in these approaches.

42. Cutaneous squamous cell carcinoma in HIV-infected patients: a report of two (2) cases.

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Cutaneous squamous cell carcinoma (SCC) is a malignant neoplasm of the keratinizing epidermal cells and it accounts for 20% of all cases of nonmelanoma skin cancer. Important etiologic factors to the development of SCC are host characteristics, such as male gender, age, skin pigmentation, and environmental elements, the most important being long-time exposure to sunlight. Other predisposing factors include ionizing radiation, exposure to UV light, exposure to chemical carcinogens and chronic immunosuppression which is not HIV-associated. Though cutaneous SCC had been reported in several regions of the body, we are reporting two cases of cutaneous squamous cell carcinoma in the penile shaft and left gluteal region.

43. Delay in anal cancer diagnosis as a non-AIDS-defining malignancy

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Background

Anal cancer is not considered an AIDS-defining malignancy (ADM). Nevertheless, the frequency of both anal intraepithelial neoplasia and invasive squamous cell carcinoma of the anus continues to increase in the HIV/AIDS population. As in cervical cancer, an ADM, numerous studies have established a causal relationship between high-risk types of human papillomavirus (HPV) infection and anal cancer [1]. In cervical cancer, the diagnosis is typically established at or near the time of HIV diagnosis [2]. The goal of this study was to evaluate and ascertain the interval from HIV diagnosis to anal cancer diagnosis.

Materials and methods

Medical records were retrospectively reviewed in 25 HIV+ patients with documented anal cancer. Cases were selectively analyzed using preexistent diagnosis dates of HIV infection. Surgical pathology reports were examined to corroborate the diagnosis of anal cancer.

Results

In all 25 patients, anal cancer was biopsy-proven between 1 and 25 years after a diagnosis of HIV infection, with a mean of 11.43 years (Table 1). Greater than 95% of patients were compliant on antiretroviral therapy at the time of cancer diagnosis. This study identified a considerable delay in anal cancer diagnosis in all cases (Figure 1).

Table 1.

Years elapsed from HIV diagnosis to anal cancer diagnosis	# of patients/ Years elapsed	Cumulative number of patients
1	1	1
2	1	2
3	0	2
4	1	3
5	2	5
6	0	5
7	2	7
8	2	9
9	1	10
10	1	11
11	2	13
12	0	13
13	2	15
14	2	17
15	2	19
16	2	21
17	1	22
18	0	22
19	0	22
20	0	22
21	2	24
22	0	24
23	0	24
24	1	25
25	0	25

Conclusions

The frequency of anal cancer within the HIV/AIDS population continues to increase despite effective antiretroviral therapy. This study reveals that unlike cervical cancer as an ADM, there is a frequent lag in identifying anal cancer among HIV patients. Given the known progression of HPV to cancer despite anti-retroviral therapy, it is imperative that health care providers include a closer examination of the perianal area on a regular and continuing basis. We believe that increased awareness of anal cancer in the setting of HIV/AIDS will lead to earlier recognition, timely treatment, as well as improved outcome and long-term survival.

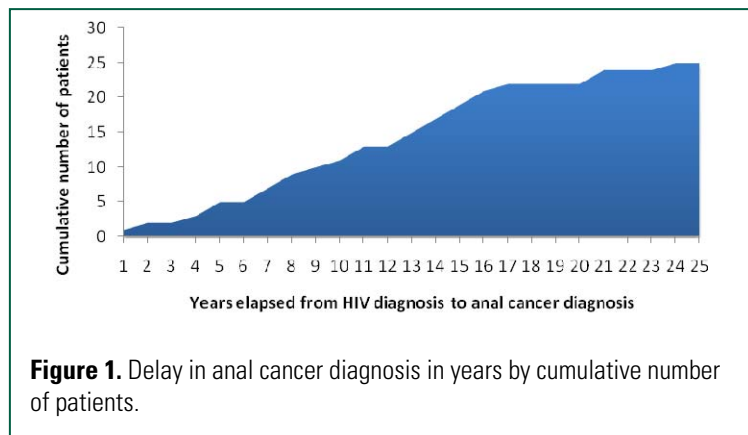


Figure 1. Delay in anal cancer diagnosis in years by cumulative number of patients.

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44. Diagnosis of HIV-related malignancies in resource-constrained settings of sub-Saharan Africa, a cautionary tale for non-Hodgkin's lymphoma

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Background

Non-Hodgkin's lymphoma (NHL) subgroups, immunophenotypes, and genotypes have been defined in developed countries but how that information translates to resource-constrained sub-Saharan Africa medical settings is undocumented. Local published data on NHL subgroups come largely from retrospective clinical biopsy study sets of paraffin-embedded tissues filed in local pathology archives. Relatively poorer representation of the rural and low socioeconomic populations is likely in such data. Prospectively identified NHL subgroups using immunologic and molecular techniques in consecutive presentations of patients would best clarify NHL subgroups and confounding diagnoses.

Materials and methods

Approximately 456 cases of malignant lymphoma (ML) from both the sub-Saharan African Lymphoma Consortium and Mid-region AIDS and Cancer Specimen Resource (ACSR) projects in East Africa were examined for microscopic morphology and 30 monoclonal antibodies for common NHL antigens; Lana-1 for HHV-8 (immunohistochemical, IHC); in situ hybridization (ISH) for EBV-encoded RNA, kappa/lambda light chains (Ventana, Tucson, AZ); and fluorescent in situ hybridization (FISH) c-myc t(8;14) (Abbott/Vysis, Downer's Grove, IL).

Results

There was a small but consistent population of other tumors that reduced the accuracy of both the clinical and histopathology diagnosis of NHLs including those given in Table 1.

Table 1. Confounding tumor look-alikes.

Tumor	Subtype examples/confounding factors	Presentation or clinical classification
Fungal infections	African histoplasmosis	Kaposi's sarcoma
	Entomophthoromycosis – <i>Basidiobolus ranarum</i>	NHL
Viral lymphadenopathy	HIV-1 lymphadenopathy, follicular hyperplasia	NHL
	EBV lymphadenopathy or lymphoproliferative disorders	NHL
	HHV-8 lymphoblastic lymphoma	Burkitt lymphoma
	Castleman's disease	Atypical hyperplasia
Pediatric small round cell tumors	Undifferentiated neuroblastoma	Burkitt lymphoma
	Primitive neuroectodermal tumors (PNET)	Burkitt lymphoma
Hodgkin's disease	Lymphocyte predominant	Burkitt lymphoma
Carcinomas	Poorly differentiated	NHL

Conclusions

Clinical diagnosis of NHL is complicated by other pathological entities that lead to inaccuracies. Histopathology diagnosis based on hematoxylin and eosin (H&E) stained tissue morphology alone improves accuracy (vs. clinical diagnoses alone) but can provide additional inaccuracies due to tumor look-alikes. Caution is warranted in considering either clinical diagnosis or local histopathology diagnosis in a resource-constrained medical setting as accurate in the conduct of clinical treatment trials or epidemiology studies.

45. Do people with AIDS develop cancer at younger ages than the general population?

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Background

Previous studies have reported that age at cancer diagnosis is far younger among persons with HIV than in the general population, suggesting that cancer development is “accelerated” in persons with HIV. However, these estimates were influenced by differences in population age structures, since there are fewer older people with HIV at risk for developing cancer. We compared ages at cancer diagnosis among people with AIDS and the general population, after adjusting for underlying population age differences.

Methods

The HIV/AIDS Cancer Match study links 15 U.S. HIV/AIDS and cancer registries. Using data from 338,349 persons with AIDS from 1980-2006, we compared observed cancers in persons with AIDS and the general population, and expected cancers calculated by applying general population rates from the cancer registry to followup time of persons with AIDS. Expected cancers represent cases that would occur in the general population if it had the same structure as the AIDS population, defined by age, sex, race, year, and registry. Median age at cancer diagnosis was estimated for each cancer.

Results

The proportion of person-time contributed by older persons (65+ years) was far smaller in the AIDS (1%) than in the general population (13%). Reflecting this difference, the median observed age at diagnosis for most cancers was ~15-30 years younger among people with AIDS than in the general population. However, after accounting for differences in age structure, observed and expected ages at diagnosis did not differ for most cancers. Observed ages at diagnosis were younger than expected ($p < 0.001$) only for Kaposi sarcoma (median 37 vs. 44 years), non-Hodgkin lymphoma (39 years vs. 43 years), lung cancer (49 years vs. 53 years), and anal cancer (42 years vs. 45 years), and older for Hodgkin lymphoma (41 years vs. 38 years; $p < 0.001$).

Conclusions

For most cancers, age at diagnosis is similar between people with AIDS and the general population, after accounting for the ages of the populations at risk. After controlling for differences in population structure, age at diagnosis remained slightly younger for only a few cancers among people with AIDS. These differences may reflect the effects of HIV in accelerating the development of some cancers where immunosuppression plays an important role. Alternatively, some age differences might reflect earlier exposure to other cancer risk factors among HIV-infected people (e.g., HPV infection, tobacco).

46. Epidemiology of malignancies in HIV patients at Kamuzu Central Hospital in Lilongwe, Malawi

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Clinical background

Malawi lacks an operational cancer registry, thus reliable epidemiological data to develop evidence-based care and focused research. HIV, infecting approximately 20% of urban Malawians [1], contributes to the pathogenesis of cancers, particularly AIDS-defining malignancies (Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer) [2,3,4]. As antiretroviral use expands and life expectancy increases, malignancies will become a more significant cause of morbidity and mortality in this population. To gain understanding about malignancies in Malawians, we designed a database to collect clinical data for all presenting cancer patients at Kamuzu Central Hospital (KCH) in Lilongwe, Malawi.

Methods

Patients with histologically confirmed or clinically diagnosed malignancies were identified at Kamuzu Central Hospital's departments of Medicine, General Surgery, Gynecology, Dental, Pediatrics, and Ophthalmology. From September 2009, patients underwent interviews and medical chart reviews to complete database questionnaires. Collected information included demographic data (age, sex, race, home village), family history of malignancy, exposure to potential carcinogens (tobacco, alcohol, and marijuana use, water source, cooking materials, and insecticide exposure), past medical history (including HIV, malaria, tuberculosis, and schistosomiasis), tumor location, histology diagnosis, stage, and treatment received. The questionnaire data were entered into a Web-based metaclinics database and extracted into Microsoft Excel. Calculations and analysis were performed with Excel. The cancer database will continue until at least 2013.

Results

Thus far, 315 cancer patients have been identified, with 152 (48.3%) HIV positive, 36 (11.4%) ignorant of their HIV status, and 127 (40.3%) HIV-negative. For representation from different departments, there were 155 patients from Medicine, 62 from Surgery, 48 from Pediatrics, 32 from Gynecology, 13 from Ophthalmology, and 5 from Dental. Of the HIV-positive patients, 107 (70.4%) had Kaposi's sarcoma, 14 (9.2%) had lymphoma, 13 (8.6%) had cervical cancer, 4 (2.6%) had breast cancer, 2 (1.3%) had esophageal cancer, 2 (1.3%) had squamous cell carcinoma of the penis, and 2 (1.3%) had conjunctival squamous cell carcinoma. More HIV patients with Kaposi's sarcoma used tobacco and alcohol than HIV patients with other malignancies (Table 2). Among HIV-positive patients, 126 (82.9%) had a history of malaria infection, and 34 (22.4%) had a history of TB infection.

Table 1. HIV status, sex, and mean age for KCH cancer database patients.

	Total Cases	Male Cases	Current Age (mean in years)	Age Range (years)
HIV-positive	152	95	38.5	6 to 77
HIV-negative	127	67	40.5	3 to 96
All patients	315	178	39.8	1 to 96

Table 2. Distribution of malignancies, infectious disease history, and substance use of HIV patients.

	Kaposi's sarcoma	Lymphoma	Cervical Cancer	Other
Total	107	14	13	18
Tobacco	37	2	0	1
No Alcohol	51	11	13	16
Light Alcohol	12	0	0	1
Heavy Alcohol	44	3	0	1
TB	21	6	2	5
Malaria	92	8	12	14

Conclusions

The majority of registered patients came from the Medicine Department, suggesting possible under-reporting from other departments. Almost half of the diagnosed malignancies registered occurred in known HIV-positive patients with Kaposi's sarcoma as the most common malignancy. Analysis of broader epidemiological data about malignancies of HIV patients in Malawi will aid future efforts for prevention and treatment.

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47. HAART and response to therapy improve quality of life (QOL) of African patients with advanced HIV-associated Kaposi's sarcoma (HIV-KS): a prospective analysis of QOL in the KAART trial

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Background

Quality of Life (QOL) assessment is important in oncology studies. Effect of therapy on QOL is important in HIV-KS, as decreasing morbidity is a goal of therapy. This is the first prospective study to evaluate the effect of HAART, +/- chemotherapy, on QOL in African patients with HIV-KS. Within the KAART study, we assessed the impact of HAART over 12 months in all patients, differences in QOL between arms, as well as associations between QOL and several clinical parameters.

Methods

KAART is a randomized, controlled, open label trial of HAART vs. HAART plus chemotherapy (CXT) in treatment-naive South African patients with HIV-KS. QOL outcomes were assessed prospectively in English or isiZulu using EORTC-QOL30. We evaluated intra-group changes between baseline and month 12 QOL scores (Wilcoxon rank sign test), changes between baseline and month 12 QOL scores between the two groups (Mann-Whitney test), and the relationship between clinical responses and global QOL (Kruskal-Wallis test). Given multiple comparisons, p-values <0.01 are considered statistically significant; 0.01 < p < 0.05 represent important trends.

Results

111 participants had QOL information. Median global health score (perfect score = 100) was 50 at baseline, improving to 67 at month 12 (p<0.001). Significant improvements in median scores from baseline to month 12 were seen in emotional, cognitive, and social scales, but not physical function and role function. Most symptom scales (fatigue, pain, dyspnea, insomnia, appetite, diarrhea, and constipation) showed significant improvement over time. Improvement in nausea was borderline (p=0.03). There were no statistically significant changes over time between arms; however role function (p=0.011) trended toward greater improvement in the CXT arm. Complete or partial response was associated with increased global health scores (p<0.001), while number or severity of adverse events, adherence, HIV viral load, or CD4 count were not.

Conclusion

African HIV-KS patients benefit significantly in their overall global health status, functioning and symptoms from HAART. Partial and complete responses to therapy are significant predictors of global health, and the role of early chemotherapy in advanced HIV-KS merits further investigation. Improving QOL is an important goal in the treatment of advanced KS in resource-limited settings. QOL results from this study inform treatment paradigms for management of African patients with HIV-KS.

48. High acceptance rate of anal pap screening despite limited knowledge about anal dysplasia among HIV+ MSM

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Background

Anal cancer in the general population is more prevalent in women, but in most HIV populations, MSM have the highest risk. Data suggest that screening can prevent invasive carcinoma. Use of routine cervical pap smears resulted in an 80% reduction in cervical cancer rates. The current study examines the effectiveness of a clinical intervention designed to increase anal dysplasia education, screening, and treatment for HIV+ MSM.

Methods

To assess anal dysplasia knowledge, sexual history/behavior, and attitudes about health care, a convenience sample of HIV+ MSM (≥ 18 years, English-speaking) being seen for routine care were asked to complete a questionnaire. The questionnaire assessed anal dysplasia knowledge and acceptance of screening anal pap utilizing a 5-point Likert-scale. Subjects were categorized as having anal dysplasia knowledge and accepting of anal pap smear if they answered "agree" or "strongly agree." A chi-square analysis was conducted to determine whether those with anal dysplasia knowledge significantly differed from those who did not in terms of anal pap screening. Clinical information was abstracted from medical records.

Results

Of 142 subjects, 56% were Caucasian, 39% were African American, and 5% were of other ethnicities with a mean age of 44 years (SD 10.74 years) and eighth grade or higher reading level (88%). Most (92%) subjects were on ART with median HIV RNA < 48 copies per mL and median CD4 534 cells/UL. Although less than half (39%) of the participants felt their current knowledge of anal dysplasia was sufficient to make decisions about detection and treatment, acceptance of anal pap smear screening was close to universal (93%). One-third of subjects (50) had undergone anal pap testing and of these, 44% had dysplasia. Knowledge of dysplasia was not significantly correlated with anal pap screening ($p=.37$).

Conclusions

We found a high acceptance rate of anal pap smear despite low rates of knowledge about anal dysplasia. Importantly, anal dysplasia knowledge did not differ between patients who had been previously screened for anal dysplasia and those who had not. These results suggest that the clinical intervention to increase anal dysplasia screening and treatment must also focus on patient education and awareness. The high acceptance rate of the anal pap test indicates that, if implemented effectively, anal dysplasia screening should be well received by patients.

49. HIV-associated primary lung cancer (LC) in the era of highly active antiretroviral therapy (HAART): a multi-institutional collaboration

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Background

HIV-infected individuals are at increased risk for primary LC. We wished to compare the clinico-pathologic features and treatment outcome of HIV-LC patients with HIV-negative LC patients. We also sought to compare smoking habits and immunologic features of HIV-LC patients with HIV-positive patients without LC.

Methods

A database of 75 HIV-positive patients with primary LC in the HAART era was established from an international collaboration. These cases were drawn from the archives of contributing physicians who subspecialize in HIV malignancies. Patient characteristics were compared with registry data from the Surveillance Epidemiology and End Results (SEER, n=169,091 participants) Program and with HIV-positive individuals without LC from the Adult and Adolescent Spectrum of HIV-related Diseases (ASD, n=36,569 participants) Project.

Results

The median age at HIV-related LC diagnosis was 50 years compared to 68 years for SEER participants ($p<0.001$). HIV-LC patients, like their SEER counterparts, most frequently presented with stage III (29% vs. 32%) and stage IV (55% vs. 48%) cancers, usually with adenocarcinoma (41% vs. 37%) or squamous carcinoma (32% vs. 20%) histologies. HIV-LC patients and ASD participants had comparable median nadir CD4+ cell counts (138 vs. 160 cells/ μ L). HIV-LC patients were, however, more likely to be smokers (99% vs. 76%; $p<0.001$) with a higher median pack-year history of cigarette consumption (41 vs. 14 pack-years; $p<0.001$). At LC diagnosis, their median CD4+ count was 340 cells/ μ L and 86% were receiving HAART. Sixty-three (84%) HIV-LC patients received cancer-specific treatments, but chemotherapy-associated toxicity was substantial. The median survival among HIV-LC patients and SEER participants both measured 9 months.

Conclusions

Smoking was tightly associated with the risk of HIV-LC. Most HIV patients were receiving HAART and had substantial immune reconstitution at time of LC diagnosis. They were able to receive LC treatments; their tumor types and overall survival were similar to SEER LC participants. However, HIV-LC patients were diagnosed with LC at a younger age than their HIV-negative counterparts. Future research should explore how screening and diagnostic and treatment strategies directed toward the general population may apply to HIV-positive patients at risk for LC.

50. HPV genotypes and association with cervical cytology and immune status in HIV-infected women in India

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Background

Knowledge about HPV genotypes may inform rational design of prevention strategies for HIV-infected women in India and other developing country settings.

Methods

We analyzed cervical cytobrush samples using Linear Array HPV genotyping assay among n=267 non-pregnant HIV-infected women in Pune, India, and evaluated the association between high-risk (HR) HPV genotypes, cervical cytology status, and current CD4+ cell counts.

Results

The median (IQR) age was 31 (29-35) years and CD4+ cell count was 392/ μ L (242-581). HR-HPV genotypes were present in 106 [39.7% (95%CI: 33.8-45.6)], low-risk/unknown-risk HPV genotypes in 97 [36.3% (95%CI: 30.6-42.1)] women, while no HPV genotypes were detected in 126 [47.2% (95%CI: 41.2-53.1)] participants.

Among women with HSIL, HPV 16 (44%), HPV 53 (22%), and HPV 33 (22%) were the most common HR-HPV genotypes. HR-HPV genotypes were present in 100% of 9 women with HSIL, 77.1% in 35 with LSIL, 45% in 40 with ASCUS, and 26.6% in 169 women with normal cytology (Chi-square for trend: $p < 0.001$). Severely immune-compromised women [CD4+ $< 200/\mu$ L] had higher HR-HPV prevalence [OR: 2.5 (95%CI: 1.2-5.5)], higher prevalence of LSIL/HSIL on cytology [OR: 2.5 (95%CI: 0.9-6.9)] and higher prevalence of HPV 16 [OR: 3.9 (95%CI: 1.3-12.0)] compared to HIV-infected women with CD4+ $\geq 500/\mu$ L. No significant difference was noted in HR-HPV prevalence among women currently on ART versus those never on ART [OR: 1.2 (95%CI: 0.7-2.0)].

Conclusions

The burden of HR-HPV infection, including HPV 16, correlated directly with severity of cytology and level of HIV-related immune suppression among HIV-infected women in India. HPV prevention strategies for HIV-infected women in India and other developing country settings should take into account the unique HPV type composition and the impact of immune suppression.

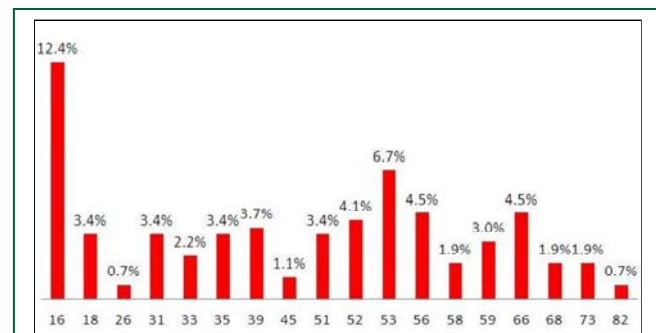


Figure 1. Prevalence of “high-risk” HPV genotypes in HIV-infected women (n=267) in Pune, India.

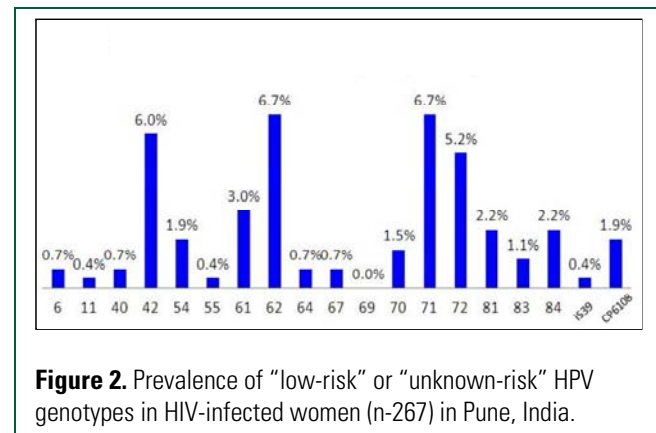


Figure 2. Prevalence of “low-risk” or “unknown-risk” HPV genotypes in HIV-infected women (n=267) in Pune, India.

51. Immunoglobulin abnormalities and monoclonal gammopathy of undetermined significance in uninfected and HIV-infected men

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Background

Multiple myeloma (MM) is a non-AIDS related malignancy of an immunoglobulin (Ig)-secreting B cell (plasma cell) usually associated with older age. MM is characterized by the presence of a high concentration monoclonal Ig protein in serum, and excretion of free light chains (FLC) in urine. In the years preceding MM diagnosis, a small monoclonal Ig develops that may be detectable upon serum protein electrophoresis, resulting in a premalignant condition known as monoclonal gammopathy of undetermined significance (MGUS). In an individual with MGUS, there may also be abnormal levels of FLC. Increased circulating levels of Ig, other indicators of B cell hyperactivation, and B cell lymphoma are well-recognized features of HIV infection. There have also been several reports of increased prevalence of MGUS and a meta-analysis showing increased risk of MM among HIV-infected (HIV+) individuals. There are, however, little or no longitudinal data on HIV-associated Ig abnormalities, B cell activation, and MGUS. We have initiated a pilot study within the Multicenter AIDS Cohort Study (MACS), a prospective study of untreated and treated HIV infection and AIDS in the United States, to begin to examine Ig abnormalities associated with MGUS in HIV-uninfected (HIV-) and HIV+ homosexual men.

Materials and methods

Archived serum samples from the Los Angeles site of the MACS were obtained from 172 long-term HIV+ (8.1-18 years), HAART-naïve subjects at the latest visit before initiating HAART, and from 166 HIV- subjects of similar age (31-62 years) and ethnicity (88% White, 8% Hispanic, 2% Black). Serum protein electrophoresis and quantitative IgG, IgM, IgA, kappa FLC, and lambda FLC assays were performed on all samples, followed by immunofixation when possible monoclonal protein or abnormal kappa/lambda FLC ratios were observed.

Results

Increased mean serum concentrations of IgG, IgA, IgM, kappa FLC, and lambda FLC ($p < 0.001$) were seen in HIV+ subjects compared to HIV- subjects. Kappa/lambda FLC ratios were higher in HIV+ men (1.16 vs. 1.04, $p < 0.01$), with a clear increase in the frequency of elevated (> 1.65) ratios (11.0% vs. 1.8%). MGUS prevalence (defined as a monoclonal peak confirmed by immunofixation) was 0/166 ($< 0.6\%$) in HIV- and 4/172 (2.3%, $p < 0.05$) in HIV+ MACS subjects.

Conclusions

MGUS is uncommon but increased among untreated HIV+ MACS subjects under 65 years of age. FLC levels and/or abnormal ratios may be more sensitive indicator(s) of Ig abnormalities associated with MGUS or MM. Longitudinal MACS studies are planned to examine FLC, MGUS, and B cell activation.

52. Immunohistochemically confirmed HHV-8-related lymphoproliferative disorders in Uganda

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Background

Human herpesvirus-8 (HHV-8) infection is endemic in Uganda and has an estimated 36%-60% seroprevalence. This virus is in the oropharynx and peripheral blood of Ugandans with Kaposi's sarcoma, and viremia is increased in those with HIV-1. While Kaposi's sarcoma is widely recognized as both endemic and with HIV epidemic, HHV-8 associated lymphoproliferative disorders have not been previously reported in Uganda. Evidence for these disorders was sought in lymphoma surveys conducted by sub-Saharan African Lymphoma Consortium (SSALC) consortium members in Uganda.

Materials and methods

Samples of 456 malignant lymphoma and adenopathy cases in formalin-fixed paraffin-embedded (FFPE) blocks from the Uganda SSALC and the Uganda AIDS and Cancer Specimen Resource (ACSR) were examined for morphology and LANA-1 (immunohistochemical, IHC) for diagnosis of HHV-8 lymphoproliferative disorders. Samples were also tested (IHC and in situ hybridization, ISH) using 20 monoclonal antibodies for common NHL antigens, ISH for EBV-encoded RNA, and kappa/lambda light chains (ISH, Ventana, Tucson).

Results

Many but not all of reported HHV-8-related proliferative disorders were identified in this sample population. Those identified and remaining to be identified are listed in Table 1.

Table 1. Subtypes.

Subtype		N
Castleman's disease	Unicentric varieties	Hyaline vascular variant 2
	Multicentric varieties	Plasma cell variant 1
		Plasmablastic variant 1
		Lymphocyte depleted 1
Plasmablastic lymphoma (HHV-8 negative and positive)		2
Primary effusion lymphoma		
Peripheral T-cell lymphoma		
Diffuse large B-cell lymphoma		
Plasmacytic lymphoproliferative disorder		1
Total		8

Conclusions

HHV-8 proliferative disorders excluding Kaposi's sarcoma are present but generally not recognized by Ugandan clinicians and pathologists. Disorders are present in Uganda, especially in HIV-positive patients, in association with the high infection rates of both HIV-1 and HHV-8. Recognition is important because HHV-8 infection in HIV-1-positive patients associates with poor prognosis. Familiarity with the clinical presentation and tissue morphology of these disorders will likely result in recognition of the full range of reported HHV-8 proliferative complications. HHV-8-related lymphoma has increased prevalence in the HIV-1 infected. It arises and progresses in the face of highly active antiretroviral therapy immune reconstitution, making recognition of these disorders critical to patient care. We participate in the Sub-Saharan Africa Lymphoma Consortium [<http://www.ssalc.org>] to expand the understanding of HIV/AIDS-related malignancies and viral proliferative disorders in this region of the world.

53. Initial experience with topical fluorouracil (5-FU) for treatment of anal intraepithelial neoplasia (AIN) in HIV-positive patients

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Background

Exposure to certain strains of human papilloma virus (HPV) promotes dysplasia in cells of the anal canal epithelium, leading to AIN, which is in turn a precursor to squamous cell carcinoma of the anus (SCCA). Patients with HIV infection who have anoreceptive intercourse are at heightened risk for acquiring HPV, AIN, and SCCA. The use of topical 5-FU to prevent the progression of lower genital tract neoplasia to invasive cervical carcinoma has been studied in both HIV+ and HIV- women. Although intravenous 5-FU is also commonly used for treatment of invasive SCCA, there has been little experience with the use of topical 5-FU as therapy for AIN.

Materials and methods

We retrospectively reviewed medical records from our anal dysplasia clinic. Our study population comprised 11 HIV+ men with biopsy-proven AIN who were treated with topical 5-FU. All patients were initially instructed to apply a pea-sized amount of topical 5-FU to the anus each night, to wash their hands afterwards, and to wipe away excess 5-FU in the morning. Patients reduced the frequency of application if they experienced undue local irritation.

Results

Patient data are summarized in Table 1. 6 of 11 (55%) patients showed improvement in clinical appearance. Anoscopy images for one of these patients before and after treatment are shown in Figures 1 and 2, respectively; note the diffusely verrucous appearance in Figure 1 (arrows).

While all patients had biopsies of the areas with the most clinically severe dysplasia pre-treatment, only 6 had biopsies post-treatment, and of those only 2 showed improvement in pathologic grade on biopsy. 6 (55%) patients decreased frequency of 5-FU application due to mild to moderate perianal irritation.

Conclusions

Patients tolerated topical 5-FU without significant side effects. Our results are preliminary, but suggest a role for topical 5-FU in reducing disease burden in anal dysplasia. While this therapy may not eliminate areas with the worst dysplasia, reducing disease burden may facilitate the use of destructive modalities to treat residual areas of high-grade dysplasia.

Age range in years (median)	32-67 (45)
On HAART (%)	9 (82%)
CD4+ cell count/μL range (median)	35-730 (416)
HIV viral copies/mL range (median)	<75-172,966 (<75)
Treatment duration range (median)	7 wks-6 mo (20 wks)
Clinically improved (%)	6 (55%)
Perianal irritation (%)	8 (73%)
Anal fissure (%)	1 (9%)
Perianal HSV (%)	1 (9%)
Decreased dosing frequency (%)	6 (55%)
Discontinued (%)	1 (9%)

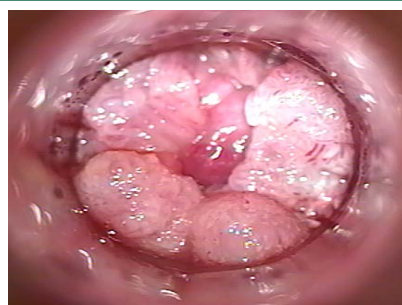


Figure 1. Before Topical 5-FU.

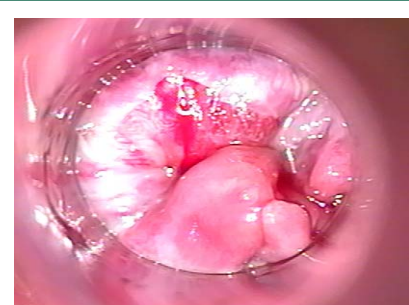


Figure 2. After Topical 5-FU.

54. Kaposi sarcoma in South African children

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Background

The AIDS epidemic has contributed to an abrupt increase of the incidence of Kaposi sarcoma, especially in Sub-Saharan Africa, to values tens of times higher than in the pre-epidemic era. There is, however, very little literature concerning the clinical features of this disease and its management and outcome in HIV-positive children in Africa.

Aim

To examine retrospectively a series of 70 HIV-positive children with Kaposi sarcoma, from several centers in South Africa, in order to describe the usual clinical presentation as well as the management and its impact on the course of the disease.

Patients and methods

Data were analyzed from tumor registries and patient records in four South African hospitals from January 1998 to December 2009.

Results

The average age in this series was 73 months. The ratio of males to females was 1,65. The lesions were present on skin in 32 out of 63 cases (50.79%), alone or in combination with other sites. In 8 cases (12.69%) the tumor was localized exclusively in the mouth, in a further 8 patients (12.69%) exclusively in the viscera, and in 6 patients (9.52%) only in the lymph nodes. Tuberculosis was associated with Kaposi's sarcoma in 9 cases out of 38 (23.68%). The mean CD4+ lymphocyte count was 440 (SD=385). Only 38 patients (54.28%) were taking combined antiretrovirals at the time of diagnosis. Twenty-nine cases (41.42%) received chemotherapy with Bleomycine, Vincristine, and Adriamycin, alone or in combination. While 32 patients (45.71%) died after an average of 4 months, the average followup period for the remaining children was 16 months, with a maximum of 57 months.

Conclusions

Most of the time the clinical diagnosis was suggested by the skin lesions; however, in a large percentage of cases the tumor was hidden in the mouth, viscera, or lymph nodes. The CD4+ lymphocyte count was not a predictor of Kaposi sarcoma. The mortality remains high in South Africa in spite of antiretroviral drugs and chemotherapy.

55. Knowledge of HPV and cervical cancer among HIV-positive women in Lagos, Nigeria

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Background

Cervical cancer is the second most common cancer among women in the world. In parts of Africa it is the most common cancer among women. The age-specific incident rate is in some parts of Africa. Persistent infection with high-risk human papillomavirus (HPV) is a necessary cause of cervical cancer and HIV is a known co-factor that enhances the oncogenic potential of HPV. Sub-Saharan Africa has the highest number of people living with HIV. In Nigeria there are about 4.5 million people living with HIV/AIDS; more than half are women. Women infected with HIV are at greater risk of persistent HPV infection and consequently at greater risk of the associated premalignant disease and cervical cancer. The objective of this study was to determine the knowledge of HIV-positive women on HPV and cervical cancer.

Materials and methods

Two-hundred women who attended an HIV clinic in Lagos in January 2010 and who consented to participate in the study were randomly selected. They were given self-administered questionnaires. The questionnaire sought to determine their sociodemographic characteristics and their knowledge of HPV, cervical cancer, and the HPV vaccine.

Results

183 completed the questionnaire. The mean age was 33.0±6.1 years (range 23-52 years). About one third (32.1%) had had post-secondary school education and almost a third were single. 117 (71.1%) had never been on any form of contraception. 127 (69.3%) had had the HIV test because they were very sick; only 16.7% had voluntary testing. The awareness of cervical cancer was poor. 74.4% had never had any form of cervical cancer screening. About 90% had never heard of HPV and 92.3% did not know that HPV causes cervical cancer, 82.1% did not know that HPV is contracted via sexual intercourse, and only 17.1% knew cervical cancer can be prevented by a vaccine.

Conclusion

The overall knowledge of cervical cancer and HPV in this high-risk population was very poor. There is a need to improve the knowledge of this disease among this population. Cervical cancer screening should be made available at little or no cost to them.

56. Liver cancers and other hepatic disease from the Adult/Adolescent Spectrum of HIV-related Diseases (ASD) Project

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Background

As individuals with HIV infection live longer due to highly active antiretroviral therapy (HAART), co-morbid conditions and infections, including liver cancers and viral hepatitis, warrant increased attention and action.

Materials and methods

The multisite ASD Project followed 29,491 HIV-infected individuals receiving medical care in 11 U.S. metropolitan areas for an average of 2.4 years and a total of 69,487 person-years. ASD collected data on the presentation, treatment, and outcomes related to HIV infection, including viral hepatitis screening and liver-specific complications including hepatic neoplasms. Data were restricted to the HAART era, 1998-2004.

Results

There were 25 participants with liver malignancies in the ASD cohort corresponding to a rate of 8.5 cancers/10,000 people living with HIV. Twenty two (88%) participants died and the remaining 3 were lost to followup. Fifteen (60%) of the 25 had hepatocellular carcinoma; 6 had metastatic adenocarcinoma, 1 each had lymphoma, hepatoblastoma, sarcoma, and poorly differentiated carcinoma. Thirteen of 25 (52%) individuals with liver malignancies were diagnosed with hepatitis C virus (HCV) and 10 (40%) with chronic hepatitis B virus (HBV) infection (including 2 participants with HBV and HCV co-infection). This corresponds to a relative risk of liver cancer among HCV and HBV infected individuals of 12.8 (95% confidence interval [CI] = 4.1-40.2) and 26.8 (95% CI = 8.1-88.9), respectively (relative to those without HBV or HCV diagnoses). The risk of malignancy in HIV-infected individuals with both HBV and HCV co-infection, relative to those with neither co-infection, was 16.8 (95% CI = 3.1-91.8). Four individuals did not undergo HBV or HCV screening, and their viral hepatitis serostatus remained undefined. Twelve percent of liver cancer patients also had a diagnosis of cirrhosis, relative to a 1 percent prevalence of cirrhosis overall (relative risk of liver cancer for those with cirrhosis = 10.2, 95% CI = 3.1-33.9). Incident liver disease and chronic HBV and HCV were diagnosed in 0.9, 1.8, and 4.7 per 100 person-years. HBV and HCV screening increased from fewer than 20% to over 60% during this period of observation ($p < .001$). Deaths occurred in 57% of those diagnosed with liver disease relative to 15% overall ($p < .001$). Overall, 10% of deaths occurred among individuals with a diagnosis of liver disease.

Conclusions

Despite care guidelines promoting screening for HBV and HCV, screening was not universally conducted or, if conducted, not documented. Due to elevated risks of liver cancer and other liver diseases, HCV and HBV screening and treatment of viral hepatitis among HIV-infected individuals should be a priority in the HAART era.

57. Malignancies in HIV

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We identified all known cases of malignancy among HIV-infected patients admitted to the AIDS Center hospital in Saint Petersburg in 2004-2009 via statistical cards completed for each discharged or dying case with a final clinical and/or autopsy diagnosis. From a total of 19,410 patients admitted during this period, we identified 38 cases (0.2%). We randomly selected 42 patients without malignancy, also using statistical cards. The cancer cases included 15 (39.5%) AIDS-defining malignancies (ADMs) (9 cases of non-Hodgkin's lymphoma [including one case of brain lymphoma], 3 cases of Kaposi's sarcoma, and 2 cases of invasive cervical cancer), and 23 (60.5%) non-ADMs [Hodgkin's disease (7 cases), lung cancer (3 cases), breast, rectal, larynx, and brain cancer (2 cases each), oral, stomach and penis cancer (1 case each), and cancer of unknown primary site (2 cases)]. All cases were confirmed histologically; the two brain tumors were diagnosed as oligodendroglioma and ependymoma.

Most of the cancer patients were men (73.7%), consistent with the population of patients visiting the AIDS Center. Most cases were diagnosed when patients sought medical care for cancer-related symptoms. About 60% of the subjects with malignancy died. Patients with ADMs were younger and had lower CD4 cell counts and lower HIV RNA loads than those with non-ADMs. There was no significant difference between the two groups in (a) the interval between HIV diagnosis and development of malignancy, (b) cancer survival, (c) HIV survival, and (d) frequency of death. The majority (55%) of the patients had stage III-IV malignancies; over half of the ADM cases and about one-third of non-ADM cases were untreated. When comparing patients who had malignancy with those who had no cancer, the latter were younger, less likely drug users and smokers, and had higher CD4 cell counts and lower frequency of death.

Conclusion

The small number of malignancies we identified suggests that malignancies, especially ADMs, in HIV-infected patients are under-diagnosed in Saint Petersburg. The majority of cancers were diagnosed at their end stages, and almost half of cancers remained untreated. Patients with malignancy had more risk factors and a more severe clinical picture than those with no malignancy. It is imperative that we conduct further research on malignancies in HIV-infected persons in Saint Petersburg, with a focus on determining whether under-diagnosis is occurring and, if so, reasons for under-diagnosis. Programs to enhance cancer screening interventions in HIV-infected patients in Saint Petersburg may be needed.

58. Malignant lymphoma subgroups from Zaria, Nigeria, reveal absence of HIV/AIDS-related plasmablastic lymphomas and HHV-8-related lymphoproliferative disorders

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Background

Prevalence of non-Hodgkin's lymphoma (NHL) subgroups throughout Africa, particularly among persons with HIV/AIDS, is unknown but increases in Burkitt lymphoma, plasmablastic lymphoma, and HHV-8 proliferation disorders have been noted. SSALC, an AIDS and Cancer Specimen Resource (ACSR/NCI) project, seeks to define indigenous sub-Saharan NHL subtypes using WHO classification (2008). Omoti (Univ. Benin 2007) defined an overall malignant lymphoma (ML) rate: 13.4/100,000 (1990s) including 17% Hodgkin's disease and 83% NHL but subgroups were not defined. Because regional HIV/AIDS prevalence is high, we subgrouped NHL and reviewed lymph node hyperplasia using stored material from Ahmadu Bello University Teaching Hospital in Zaria, Nigeria, to look for HIV/AIDS-associated lymphoid malignancies.

Materials and methods

Fifty-seven paraffin blocks were used to construct a tissue microarray (TMA), and whole tissue sections were H&E stained for morphology. TMA sections were stained using 30 monoclonal antibodies for common NHL antigens and Lana-1 for HHV-8 (immunohistochemical, IHC); in situ hybridization (ISH) for EBV-encoded RNA, kappa/lambda light chains (Ventana, Tucson, AZ), and fluorescent in situ hybridization (FISH) c-myc t(8;14) (Abbott/Vysis, Downer's Grove, IL).

Results

There were 43 ML and 14 hyperplastic lymph nodes or reactive tissues. One lymph node was suspected for Castleman's disease but Lana-1 was negative. Table 1 lists ML subgroups.

Table 1. Cases by diagnostic subgroup.

Subgroups		N	%NHL		
ML	NHL	Burkitt lymphoma	19	51	
		Lymphoblastic lymphoma: (pre-B)	1	3	
		Angioimmunoblastic T-cell lymphoma	1	3	
		Follicular lymphoma	6	16	
		Marginal zone lymphoma	1	3	
		Lymphoma not otherwise specified (NOS)	2	5	
		B-cell lymphoma, EBV+	1	3	
		Diffuse large B-cell lymphoma	Activated B cell	4	11
			NOS	1	3
	Malignant infiltrate (HHV-8 negative)	1	3		
Hodgkin's disease	5				
Reactive/normal tissue		15			
Total		57			

Conclusions

Subgrouping ML with Hodgkin's disease (12%) and NHL (88%) is similar to the 2007 report from nearby Benin University. Burkitt lymphoma was the most common NHL at 51% followed by follicular lymphoma 16% and diffuse large B-cell lymphomas 14%. With the exception of Burkitt lymphoma, which is endemic in Nigeria, other NHL commonly associated with HIV/AIDS such as plasmablastic lymphoma and HHV-8 lymphoproliferative disorders were not identified.

59. Mortality after cancer diagnosis among HIV-infected individuals in the CFAR Network of Integrated Clinical Systems (CNICS)

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Background

Increased cancer risk has been well established in several HIV-infected populations. However, studies investigating mortality after a diagnosis of cancer have been limited in size, scope, and HIV-specific risk factors.

Materials and methods

CNICS is a cohort of over 20,000 HIV-infected adults in clinical care at eight U.S. sites. We included patients with chart review verified incident cancer diagnoses between 1996 and 2009. Non-AIDS defining cancers (NADC) were categorized as infection (HPV, EBV, or HBV/HCV)-related [1]: squamous cell anal, squamous cell oral cavity/pharynx, penis, vagina/vulva, Hodgkins, and liver; or non-infection-related: all other NADCs. Death was confirmed by the National Death Index and/or state death certificate data. We examined independent predictors of mortality by employing Cox proportional hazards regression models.

Results

918 adults with HIV and cancer were included in this analysis. 55% had AIDS-defining cancer (ADC), 15% had infection-related NADC, and 30% had non-infection related NADC. At cancer diagnosis, median age was 43 years, 50% were white, 86% male, 19% IDU, 21% HBV/HCV, 46% current smokers, and 56% current alcohol drinkers. Median CD4+ cell count was 192 cells/mm³ and HIV RNA was 3.6 log₁₀ copies/ml. There were 395 deaths in 2,393 person-years of follow-up for a crude mortality rate of 16.5 per 100 person-years (95% CL: 15.0, 18.2). Adjusted hazard of mortality was significantly increased among individuals who were older, non-white, IDU, current or former smokers, had lower CD4+ cell count, higher HIV RNA, and non-infection related NADC (see Table 1). Figure 1 shows cumulative mortality after cancer diagnosis stratified by type of cancer.

Table 1.

	Mortality Hazard Ratio*	95% Confidence Limits
Age, per 10 years	1.23	1.09, 1.40
White	0.77	0.62, 0.95
Male	1.06	0.78, 1.44
HBV/HCV	1.11	0.86, 1.43
IDU	1.31	1.00, 1.70
Smoking:		
Never	1	-
Former	1.51	1.08, 2.12
Current	1.45	1.04, 2.02
Alcohol intake:		
Never	1	-
Former	0.99	0.72, 1.36
Current	0.78	0.58, 1.04
HIV RNA, per log ₁₀ copies/ml	1.09	1.01, 1.17
CD4 count:		
> 500 cells/mm ³	1	-
200–500 cells/mm ³	1.11	0.77, 1.59
< 200 cells/mm ³	1.57	1.10, 2.26
Summary cancer type:		
ADC	1	-
Infection-related NADC	0.78	0.55, 1.11
Non-infection-related NADC	1.38	1.05, 1.82

*Adjusted for all variables in the table.

Conclusions

In the era of ART, unique independent predictors of mortality among individuals with HIV and cancer were level of immune suppression, degree of HIV RNA replication, and non-infection-related type of cancer. These data highlight the need to improve prevention and management of NADC in this population.

Acknowledgements

These findings are presented on behalf of the CNICS. Funding for this study was provided by NIAID and NCI.

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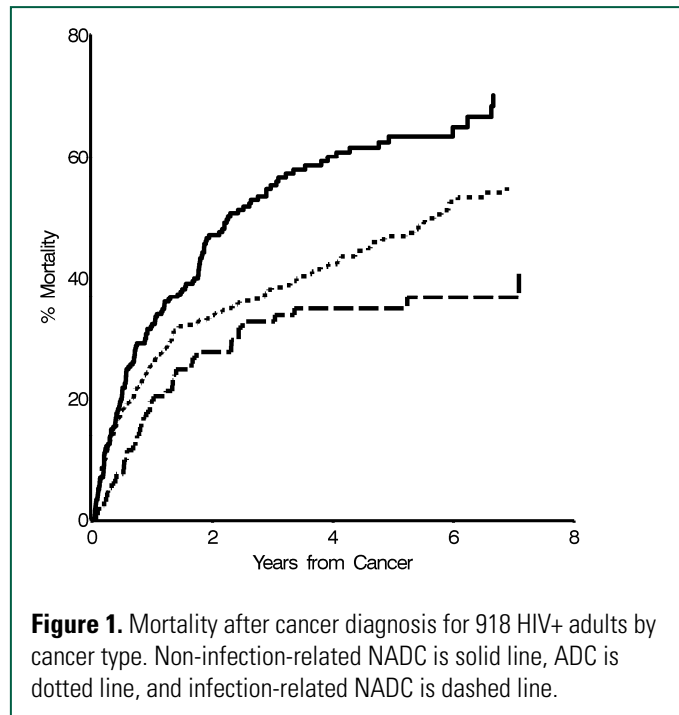


Figure 1. Mortality after cancer diagnosis for 918 HIV+ adults by cancer type. Non-infection-related NADC is solid line, ADC is dotted line, and infection-related NADC is dashed line.

60. Multiple oncogenic viruses identified in ocular surface squamous neoplasia in HIV-1 patients from a developing country outpatient clinic

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Background

Ocular surface squamous neoplasia (OSSN) is a conjunctival or corneal neoplastic growth that encompasses the conditions of simple dysplasia to conjunctival intraepithelial neoplasia (CIN) to invasive squamous cell carcinoma. Prior to the HIV pandemic, OSSN was noted to occur predominantly in the elderly, for whom it is the third most common oculoorbital tumor after melanoma and lymphoma. In Africa, OSSN is becoming more common, more aggressive, and more likely to affect young people. Several countries have noted a sharp rise in the incidence of OSSN in HIV-infected individuals such that OSSN, in parallel with the rise in HIV infection, is currently the most common ocular tumor among adults in Africa. The underlying cause of this cancer in HIV-infected patients from Botswana is not well defined.

Method

DNA was extracted from 28 OSSN and 8 pterygia tissues, a benign neoplasia that may go on to develop into OSSN. The samples were analyzed for the presence of a number of human viruses including the tumor viruses HPV, EBV, KSHV, JC, and BK by PCR using consensus sequence primers. Type specific primers and sequencing using consensus GP5+ primers of HPV were used for the determination of HPV types. Tissues were further analyzed using in situ hybridization with specific viral probes and immunohistochemistry with antibodies against specific antigens encoded by these tumor viruses.

Results

DNA was extracted from the 28 OSSN tissues and the results showed that 83% were EBV positive, 75% were HPV positive, 70% were KSHV positive, 75% were HSV-1/2 positive, and 61% were CMV positive by PCR. Of the 8 pterygia tissues, 88% were EBV positive, 75% were HPV positive, 50% were KSHV positive, and 60% were CMV positive. None of the patients were JC or BK positive by PCR analysis. Furthermore, in situ hybridization and immunohistochemistry analyses identified HPV, EBV, and KSHV in the tissue samples. Of particular interest was the fact that greater than 50% of the patients were co-infected with more than one type of HPV as well as with EBV and KSHV.

Conclusion

We identified the known oncogenic viruses HPV, KSHV, and EBV in OSSN and pterygia tissues. The presence of these tumor viruses in OSSN in the HIV population suggests that they may be involved in the development of this malignancy. Further studies are necessary to characterize the molecular mechanisms associated with viral antigens and their potential role in development of SSN.

61. Prevalence of HIV among general surgical patients in southeastern Nigeria

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Background

With the advent of HAART, many HIV patients are now living longer. It is expected that the incidence of HIV-related malignancies will increase, with additional burden of operating on HIV patients in areas of chronic severe shortages where minimum basic precautions may not always be feasible. We decided to assess the HIV prevalence in surgical patients and compare the periods 2001-04 and 2008-09.

Aim

To determine HIV seropositivity among elective general surgical patients at Nnamdi Azikiwe University Teaching Hospital, Nnewi.

Patients and methods

All surgical patients were sent for HIV screening as part of their workup for surgery. Patients testing positive were sent for further confirmatory tests.

Results

During the period 2008/09, 75 out of 2350 (3.25%) patients tested were positive for HIV. This compares with 78 out 2208 in the 3-year period 2001-04.(3.5%). Of this number, only 30.4% of these seropositive patients are receiving antiretroviral treatment. Males were affected more than the females and the reproductive age group [30-40] was the most affected.

Conclusion

The prevalence of HIV seropositivity among general surgical patients has remained the same over the past 10 years. The prevalence of 3-3.5% is significantly lower than the figures quoted from sentinel studies in Nigeria.

62. Prevalence of HIV-associated malignancies among PLWHAs accessing HIV services in Abia State, Nigeria

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Background

Malignancies are features of late HIV presentation. In Nigeria the eligibility criteria for enrollment into ART programme is CD4 cell count ≤ 200 cells/mm³ or stage of IV of HIV/AIDS. Studies linking HIV/AIDS databases to cancer registries have shown a decrease in AIDS-related malignancies and an increase in non-AIDS-defining malignancies. However, in Nigeria, pattern and prevalence of malignancies among PLWHAs are understudied. The objective of this study was to determine the pattern and prevalence of HIV-associated malignancies among PLWHAs in Abia State, Nigeria.

Methodology

This was a retrospective review of records of PLWHAs assessing care in 3 selected ART centers in the State. The 3 centers which comprised 2 tertiary, and a secondary, health care facilities were purposely selected because they accounted for about 70% of the total client load of PLWHAs in the State. All records of patients who have accessed care in the facilities since 2007, when ART programme commenced in the State, were reviewed. Relevant data such as sex, age, CD4 cell count at first visit, clinical stage of HIV disease, year of enrollment, presence of OIs, and presence of malignancies were collected. Data collected were analyzed using SPSS version 15.

Results

Of the 896 patient's record so far reviewed, 68% were females and 32% males. Mean age was 32.5 ± 9.6 years for females and 44.9 ± 11.7 years for males. 80% of them had their CD4 cell count at first visit recorded in their treatment card. The mean CD4 cell counts at presentation were 365.9 ± 299.8 for females and 285 ± 262.9 for males. 33.8% and 48.1% of the females and males, respectively, were eligible for ART based on CD4 cell count of ≤ 200 cells/mm³. The mean CD4 cell count at presentation for males eligible for ART was 78.1 ± 64.5 cells/mm³ compared with 91.7 ± 60.5 cells/mm³ for females. No case of malignancy has been reported among those reviewed so far.

Conclusion

Although with CD4 cell count of < 500 cell/mm³ one would have expected increasing prevalence of malignancies among the patients, none was so far reported. This is probably because the ART card/proforma used in capturing the data from enrolled patients has no provision to capture malignancies or HIV care providers and lacks resources required for diagnosis of cancers. There is therefore a need for health care providers to be properly trained to detect malignancies in PLWHA and also increase their indices of suspicion.

63. Reasons for not adhering to cervical cancer screening guidelines and HPV knowledge among HIV indeterminate midlife women (50-64 years old) whose last Pap test was >6 years ago

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Background

Oncogenic human papillomavirus (HPV) infection is a main cause of cervical cancer. Annual Pap tests are recommended for HIV-positive women because their risk of developing cervical cancer, an AIDS defining illness, is increased [1]. Poor uptake of routine HIV testing combined with poor adherence to recommended Pap test screening guidelines among midlife women (50-64 years old) with late-diagnosed HIV infection increases their risk of being diagnosed with cervical cancer [2]. Women who miss opportunities for early initiation of effective antiretroviral therapy and early detection of precancerous cells face a double jeopardy of being diagnosed with HIV/AIDS and cervical cancer in late disease stages, when treatment is less successful.

Materials and methods

National Health Interview Survey (NHIS) 2008 data were analyzed to describe reasons for not adhering to recommended cervical cancer screening guidelines and HPV knowledge of midlife women who had never been tested for HIV and whose last Pap test was more than 6 years ago. Frequencies and weighted percents are reported.

Results

The sample included 224 midlife women. Of the 20% who had an abnormal Pap test (n=42), only 1 (<1%) reported having a previous diagnosis of HPV infection. A third (33%) did not have a Pap test in the past 6 years (n=65) because they had a hysterectomy, including 11% who had an abnormal Pap test (n=20). Only 12% (n=14) of those who did not have a hysterectomy (n=115) were planning to get a Pap test within a year. Most of these women (40%) had no specific reason for not having a more recent Pap test (Table 1). For many other women (32%), poor adherence was attributed to health care access issues (Table 1). HPV knowledge: 60% had heard of HPV (n=129); 64% knew HPV caused cervical cancer (n=82); 60% knew HPV was spread through sexual contact (n=79); and 85% did not think that HPV would go away without treatment (n=111).

Table 1. Reasons for not having a Pap test in the last 6 years, NHIS 2008 (n=115)^a.

Reasons	Abn Pap		No Abn Pap		Total
	n	% ^b	n	% ^b	% ^b
No reason/didn't think about it/put it off/didn't get to it/don't know	2	1.2	35	38.8	40.0
Cost was too expensive/no insurance/didn't have a doctor	6	4.4	32	27.8	32.2
Didn't need/doctor didn't order it/not having any problems	2	3.7	17	11.5	15.2
Too painful, unpleasant, or embarrassing	1	0.9	4	2.6	3.5
Other	1	1.5	8	7.5	9.0

^amissing (n=7); ^bweighted percent

Conclusions

Despite increased prevalence of HIV/AIDS, routine HIV testing is underutilized. Older adults are disproportionately burdened with late-diagnosed HIV infection. Early diagnosis of HIV and precancerous cervical cells due to HPV infection improves health outcomes for women. Dual HIV and cervical cancer prevention messages that target midlife women are needed.

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64. Role of TP53 polymorphisms in sub-Saharan mucosal cancers

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Background

The most common TP53 gene polymorphism, which alters amino acid sequence of the oncosuppressor p53 protein, is located at the codon 72, resulting in either Pro72 or Arg72 p53 variant. Several studies have associated, with controversial results, the prevalence of the Arg allele with different types of cancer. The aim of this report is to analyze the role of p53 polymorphisms in two mucosal (conjunctival and genital) HPV-associated cancers during HIV epidemic.

Distribution and role of TP53 Arg72 and Pro72 alleles in conjunctival neoplasia

Method

The study included 41 invasive conjunctival squamous cell carcinoma (ICSCC), 33 conjunctival intraepithelial neoplasia of grade 3 (CIN3), 33 of moderate grade (CIN1 and CIN2), and 115 controls from Uganda, a sub-Saharan country with the highest incidence rate of conjunctival neoplasia in the world, particularly in the era of AIDS.

Results

The TP53 Arg/Arg codon 72 genotype was detected in 21.9% of ICSCC and in 18.2% of CIN3 but only in 6% of CIN1-2 and in 5.2% of controls ($P < 0.05$). These data show an increased risk of ICSCC (odds ratio (OR)=6.2, 95% confidence interval (CI): 1.6-24.6) and CIN3 (OR=4.1, 95% CI: 1.0-18.0) associated with TP53 Arg homozygosity, not observed in CIN1-2 lesions (OR=0.8, 95% CI: 0.1-5.1). Moreover, the frequency of the Arg homozygosity was similar in HIV-positive and HIV-negative groups.

Discussion

The results suggest that TP53 Arg/Arg codon 72 genotype is a relevant risk factor for invasive squamous cell carcinoma of the conjunctiva and for CIN3 in the Ugandan population.

Distribution and role of TP53 Arg72 and Pro72 alleles in cervical neoplasia

Method

In the genital mucosal study, 78 penile squamous cell carcinoma biopsies ($n = 17$ from Uganda, $n = 61$ from Italy) and blood samples from 150 healthy controls ($n = 57$ from Uganda, $n = 93$ from Italy) have been analyzed for the arginine and proline allele distribution

Results

Among Ugandan cases the heterozygous, proline homozygous and arginine homozygous genotype frequency was 41.2%, 52.9%, and 5.9%, respectively, and among controls was 40.3%, 54.4%, and 5.3%, respectively ($P = 0.9917$). Conversely, among Italian cases, genotype distribution was 42.6%, 4.9%, and 52.5%, and among controls was 34.4%, 7.5%, and 58.1%, respectively ($P = 0.5343$).

Discussion

No significant differences in arginine and proline allele distribution were observed when the cases were stratified by HPV status. Therefore, no evidence of association between homozygosity for p53 arginine and HPV-related or HPV-unrelated penile squamous cell carcinoma was observed.

Conclusions

The overall results from the combined data of these studies strongly suggest that (1) Arg homozygosity represents a relevant risk factor for low-risk HPV β -related cancers, for which further co-carcinogenic factors are needed. (2) Arg homozygosity does not represent a significant risk factor for high-risk HPV α -related cancers, such as penile cancers.

65. The approach to individualized prediction of human papillomavirus (HPV) infection persistence/clearance in HIV-1-positive adolescent girls based on dynamics of CD4+ counts, viral load, and HAART

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Background

Several studies suggest that CD4⁺ T-cell count (CD4) is important in pathogenesis of human papillomavirus (HPV) infection in HIV-positive patients including HPV clearance. CD4 dynamics as well as other co-factors such as highly active antiretroviral therapy (HAART), HIV-1 RNA viral load (VL), demographics, behavioral risks and, clinical diagnosis allows for predicting the absolute probabilities of HPV clearance/persistence. The modeling approach allows for the utilization of complete datasets and does not require any additional essential assumptions about missing information and possible violations in study design.

Materials and methods

We analyzed 266 HIV-1 positive adolescent girls from the Reaching for Excellence in Adolescent Care and Health (REACH) cohort. At enrollment and every 6 months thereafter, cervical lavage samples were tested for HPV using MY09/MY11/HMB01-based PCR and 30 HPV type-specific probes. HIV-related clinical data and risk factors were recorded every 3 months. For analytic purposes, HPV types were categorized according to phylogenetic patterns into (1) 16/16-like, (2) 18/18-like, (3) other high risk (56/56-like), and (4) low risk. HPV clearance was defined by the absence of type-specific infection for two subsequent visits after infection. Maximum likelihood estimates based on the logistic-type model were developed for 3-month reconstructed probabilities of HPV clearance/persistent with CD4, VL, and HAART as the main predictors at the moment of examination.

Results

Figure 1A presents the clearance probability for HIV-positive patients depending on CD4 for HPV16/16-like, HPV18/18-like, HPV56/56-like, and low-risk HPV. HPV16/16-like infection has the lowest chance to be cleared by host at low CD4 levels. The probability of 3-month clearance was less than 20% for patients with CD4 <200, but increased gradually with CD4 increase but overall was slower than for HPV18/18-like, other high-risk, and low-risk HPV. Additionally, the 3-D plot in Figure 1B describes CD4 and log (VL) as predictors of probability of HPV16/16-like clearance: the lowest CD4 levels together with the highest VL were significant predictors for HPV persistence. The multiplicative effect of HAART showed tendency to decrease on HPV16/16-like clearance probability with increasing CD4 levels.

Conclusion

This approach could extend opportunities to understand the associations between CD4, VL, and HAART to develop the comprehensive approach to individualized prediction of HPV infection persistence/clearance in HIV-positive patients.

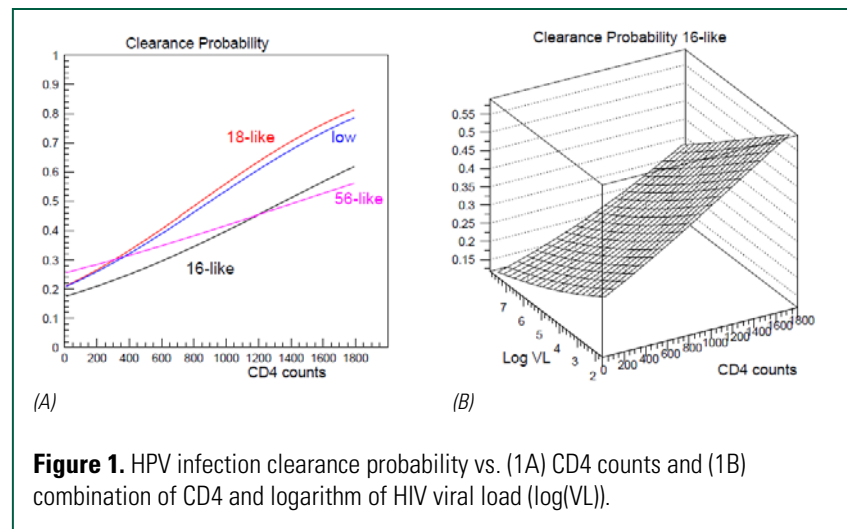


Figure 1. HPV infection clearance probability vs. (1A) CD4 counts and (1B) combination of CD4 and logarithm of HIV viral load (log(VL)).

66. The impact of aging on cancer burden in people with HIV/AIDS

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Background

People with HIV/AIDS (PWHA) have higher risk of some cancers compared to the general population, with an approximately 2-fold increase for all non-AIDS-defining cancers (NADC). The widespread use of highly active antiretroviral therapy (HAART) has improved life expectancy of PWHA, exposing them to both aging and the prolonged exposure to cancer risk factors. A linkage study was therefore conducted to evaluate the impact of aging on the burden of cancer in this population.

Materials and methods

We performed an anonymous record linkage between Italian AIDS (21,951 cases) and Cancer Registries (17.3 million people, covering 30% of the general population). Crude incidence rates (IR), IRs directly standardized by sex and age, and age-specific IRs were estimated for NADCs in the pre-HAART (1986-1996) and in the HAART (1997-2004) periods.

Results

Crude IRs of NADCs increased 78% from pre-HAART to HAART period (IRs: 287 and 496 per 100,000, respectively). However, when aging of PWHA was taken into account through standardization, no difference emerged (standardized IRs: 352 and 379 per 100,000, respectively). Concerning specific cancer site/type, standardized IRs revealed an increase of liver (from 6 to 26 per 100,000; IR ratio: 4.6, 95% confidence interval, CI: 1.3-17.0) and lung cancers (from 37 to 65 per 100,000; IR ratio: 1.8, 95% CI: 1.0-3.2). No significant variation across periods emerged for Hodgkin lymphoma (IRs: 83 and 69 per 100,000 in pre- and HAART period; IR ratio: 0.8, 95% CI: 0.5-1.3). IRs of NADCs increased with age from 147 per 100,000 in PWHA aged 25-34 years to 1396 per 100,000 in those aged 55-69 years (Figure 1); however, the rise was smoother than in the general population. As a consequence, the excess of NADCs risk declined with age, peaking in PWHA aged 25-44 years (IRs ratio: 2.7) and disappearing in the oldest age group (IRs ratio: 1.1; 95% CI: 0.8-1.5).

Conclusions

The lack of any change in standardized IRs of NADCs across periods highlights the strong influence of PWHA aging on the observed upward trends of crude IRs. The aging of PWHA in HAART period, together with the age-related increase of cancer incidence, points to cancer as an increasing medical priority for this population in the near future. This calls for the intensification of cancer prevention strategies, notably smoking cessation and screening programs.

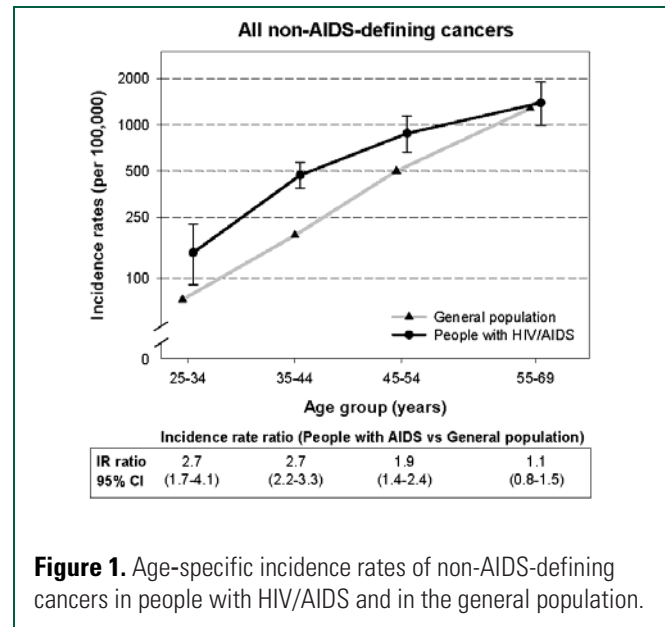


Figure 1. Age-specific incidence rates of non-AIDS-defining cancers in people with HIV/AIDS and in the general population.

Table 1. All non-AIDS-defining cancers.

Age Group (years)	Incidence Rates (per 100,000)	General Population People With HIV/AIDS	Incidence Rate Ratio (people with AIDS vs. general population) IR Ratio
25-34	100	2.7 (1.7-4.1)	95% CI
35-44	250	2.7 (2.2-3.3)	
45-54	500	1.9 (1.4-2.4)	
55-69	1000 2000	1.1 (0.8-1.5)	

67. Type distribution of human papillomavirus in HIV-infected women with cervical intraepithelial neoplasia (CIN) stages 2 and 3 in Botswana

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Background

Human papillomavirus (HPV) vaccines containing types 16 and 18 are remarkably effective in preventing cervical cancer associated with these HPV types. No information currently exists in Botswana concerning the HPV types causing precancerous or cancerous lesions.

Methods

The goal of this pilot project was to determine the HPV types causing precancerous cervical intraepithelial neoplasia (CIN) stages 2 and 3 in HIV-infected women in Gaborone, Botswana. HIV-infected women referred to our clinic with high-grade intraepithelial lesion (HSIL) on the Pap smear were enrolled in the study. Two specimens were obtained on all subjects, one for histopathology and the other for HPV typing. HPV typing was performed only if the histopathology results demonstrated CIN stage 2 or 3 disease. Histopathology results were corroborated at two sites: Lancet Laboratories (Johannesburg, South Africa) and University of Pennsylvania (Pennsylvania, United States). HPV typing was performed using linear array genotyping (CE-IVD, Roche Diagnostics).

Results

This is an interim analysis of an intended sample size of 100 women. We identified 30 HIV-infected women with CIN stages 2 or 3 between August 11, 2009, and January 29, 2010. The median age was 36 (interquartile range [IQR], 33 - 38) and the median CD4 cell count was 427 cells/mm³ (IQR, 360-560 cells/mm³). Of the 30 women enrolled, 28 (93%) had co-infection by multiple HPV types. HPV type 52 was found in the 2 (7%) women carrying a single type. 15 (50%) had HPV types 16, 18, or both. 25 (83%) women, including all the ones not carrying the 16 or 18 types, carried other high-risk HPV types. Among the other high-risk types, HPV types 33, 35, and 58 were the most prevalent, accounting for 7 (23%), 8 (27%), and 10 (33%) cases, respectively.

Conclusion

HPV 16 and 18 are the most common types in HIV-infected women with CIN 2 or 3 in Gaborone, Botswana. However, other high-risk HPV types may account for a significant number of advanced CIN lesions in this population.

68. Use of mobile telemedicine for cervical cancer screening of HIV-positive women in Gaborone, Botswana

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Introduction and aims

Throughout the developing world, delivery of women's health care, specifically cervical cancer screening, is limited by cost and access to trained personnel. Visual inspection with application of 4% acetic acid (VIA) is a practical, inexpensive alternative to cytology-based screening in areas where resources are limited. Mobile telemedicine using a cellular phone to photograph the cervix after VIA allows clinicians in "see and treat" cervical cancer screening clinics to capture high-quality images of the cervix, which can then be transmitted through the cellular network to a gynecology specialist located remotely. We present results of a prospective case-control study evaluating the accuracy of offsite (remote) expert diagnosis using mobile telemedicine photographic images of the cervix with VIA (PIA) in HIV-positive women in Gaborone, Botswana.

Methods and design

ClickDiagnostics has developed software (ClickDoc) specifically for remote diagnosis with the Samsung Soul U900 phone, which comes equipped with a 5 Megapixel camera. Ninety-five women presenting to Bontleng Clinic were enrolled and had (1) VIA evaluation by an onsite clinician, (2) an HPV (human papillomavirus) sample taken for PCR (polymerase chain reaction), (3) cervical photos taken with the Samsung phone camera, and (4) photos evaluated by original onsite clinician and by a remote gynecology specialist blinded to the initial visit. VIA and PIA results were categorized as "positive," "negative," or "indeterminate." Percent agreement will be calculated for each pair of diagnostic impressions: (1) offsite gynecologist PIA to onsite clinician using VIA, (2) onsite clinician PIA to the same onsite clinician using VIA, (3) offsite gynecologist PIA to onsite clinician PIA. The HPV PCR results will also be compared to VIA findings of the onsite clinician and the PIA findings of the offsite gynecologist.

Results

All 95 subjects have been enrolled and final data analysis is currently under way. Preliminary concordance data will be presented, along with HPV correlation and prevalence data from PCR testing. We hypothesize that there will be significant concordance in the diagnosis of cervical lesions in HIV patients, when comparing the diagnosis of the onsite clinician to the diagnosis of the clinician evaluating the photos through telemedicine.

Conclusions

Women in sub-Saharan Africa often present with advanced cervical cancer, which is a result of poor screening, lack of appropriate referral, and HIV-HPV co-infection. In order to improve the availability of cervical cancer screening in Botswana, we propose the use of mobile telemedicine as an adjunct tool to visual screening techniques for cervical cancer. We aim to show that mobile telemedicine technology is a reliable method for diagnosing cervical lesions compared to in-person gynecological evaluation and that use of this technology has the potential to connect resource-poor cancer screening centers to remotely located gynecologists.

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