The changing spectrum of HIV and cancer: risk factors and principles of management

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Introduction

People who are HIV-infected have a higher risk of developing cancer.[1] In the early days of the HIV epidemic, the presence of cancers such as Kaposi's sarcoma (KS), non-Hodgkin lymphoma (NHL), primary central nervous system lymphoma (PCNSL), and invasive cervical carcinoma were designated as AIDS-defining cancers (ADC). After the introduction of anti-retroviral therapy (ART), the spectrum changed; the incidence of KS and NHL decreased while other cancers, referred to as non-AIDS -defining cancers (NADCs), became more common in HIV infected individuals, with a considerable contribution to mortality.[1]

While immunosuppression was the most common risk factor for ADC before the introduction of antiretroviral therapy (ART), other risk factors included co-infection with oncogenic viruses, smoking, substance use, medication use, and HIV-associated metabolic disturbances. Ageing became a more important risk factor, as life expectancy increased considerably after successful ART became available. ART may also be a risk factor as there is a high incidence of KS and NHL shortly after starting ART, possibly in the context of the immune reconstitution inflammatory syndrome (IRIS). However, those patients who do not respond well to ART also have an increased risk of NADCs; these risk factors include the presence of an AIDS diagnosis, a persistent low CD4 count (< 200 cells/μL), and a low nadir CD4 count.[2,3] HIV itself is not oncogenic, but the virus integrates in the host genome as a provirus in the reservoir of infected cells. Co-infection with other oncogenic viruses and severe immunosuppression are important risk factors.[4]

Box 1

Most important Aids defining and non-Aids defining cancers[5]

AIDS-defining cancers

- Kaposi's sarcoma – caused by human herpesvirus (HHV)-8, also known as Kaposi sarcoma-associated herpes virus (KSHV); spectrum varies from indolent to explosive growth; in high-income countries mainly affecting men who have sex with men (MSM). Frequently arises in extra-nodal sites such as oesophagus and stomach. This type of KS is different from other forms of KS (see Box 2).

- Non-Hodgkin lymphoma – Epstein-Barr virus (EBV) related. This includes diffuse large B cell lymphoma, Burkitt's lymphoma, immunoblastic lymphoma, plasmablastic lymphoma, and primary effusion lymphoma.
- Primary central nervous system lymphoma (PCNSL) – strongly related to EBV; there may be focal or non-focal symptoms and signs: confusion, lethargy, memory loss, hemiparesis, aphasia, and seizures.
- Invasive cervical carcinoma – human papilloma virus (HPV).

<u>(Most important) non-AIDS defining cancers</u>

1. Non-virally mediated
   - Lung cancer – 3x increased risk, even when correcting for smoking status. In smokers, sensitization by HIV infection to tobacco has been suggested.[6]
   - Prostate – no increased risk, incidence increases with ageing; outcome worse in HIV/AIDS.
   - Breast – slightly increased risk, worse outcome.
   - Colorectal – occurs at younger age and more aggressive.

2. Virally mediated

   Human Papilloma Virus (HPV)

   - Squamous cell carcinoma of the anus – most common in MSM
   - Squamous cell carcinoma of oropharynx
   - Squamous cell carcinoma of vagina, vulva, penis, conjunctiva
   - Non-melanoma skin cancer: squamous cell carcinoma, basal cell carcinoma.

   In general, there is an increased risk of squamous cell carcinomas in HIV infection with worse outcome compared to non-HIV infected individuals. The incidence increased after the introduction of ART.

   Hepatitis B virus (HBV) and hepatitis C virus (HCV)

   - Hepatocellular carcinoma: low CD4 counts are risk factor; 24% increased mortality in HIV/AIDS.[7]

   Merkel cell polyoma virus

   - Causes Merkel cell carcinoma; poorly differentiated neuroendocrine carcinoma arising in the skin. The incidence increases more than 10-fold in persons with HIV/AIDS.

3. Other microorganisms
   - *Hymenolepis nana*: Malignant transformation of this tapeworm has been described in an HIV infected individual. (8) This is a novel mechanism that needs to be explored further.[8]

Considerations for prevention and management

Prevention

Malignancies in HIV infected individuals occur at an earlier age, with a rapidly progressive clinical course because of high tumour grade and late presentation with advanced disease.

There are opportunities for prevention such as smoking cessation, vaccination for HPV and HBV, and treatment of HBV and HCV disease. There is a need for sensitive and specific biomarkers for early detection and thus better outcome, particularly since the NADCs became more important. Identification of risk groups is important such as HIV patients with HBV or HCV related cirrhosis, and MSM for risk of anal carcinoma. All these factors have implications for outcome including poor response to treatment and recurrent disease.

Management

As HIV-infected patients often use multiple drugs, chemotherapy may lead to drug-drug interactions including increased immunosuppression. Depending on the treatment that needs to be given for a certain malignancy, ART may have to be stopped temporarily. Newer ART drugs such as integrase inhibitors may be more suitable for combined administration with other drugs. A multidisciplinary approach is needed (infectious disease specialist, HIV/aids specialist, oncologist).

Other factors to be considered in outcome are the presence of co-morbidities that are common in HIV/AIDS. In addition, as reactive lymphadenopathy is common in HIV/AIDS, this may complicate accurate staging of the cancer and decision making on the best approach. Patients with advanced AIDS may be at risk of postoperative complications in case surgery is needed in the treatment of cancer.

Treatment consists of two pillars: adequate treatment for the malignancy (that should be confirmed by biopsy) and antiretroviral therapy. Successful anticancer therapy necessitates the elimination of all cells with tumour regenerating potential. In parallel to cancer therapy, all the infected cells that can regenerate new infectious HIV-1 particles need to be removed.

Research and treatment capacity

While in the past, HIV infected individuals were excluded from most clinical trials, there is a pressing need for such trials specifically directed towards this group of individuals. In addition, there is a need for trial sites and availability of treatment modalities, such as chemotherapy and radiotherapy, in LMICs.

References

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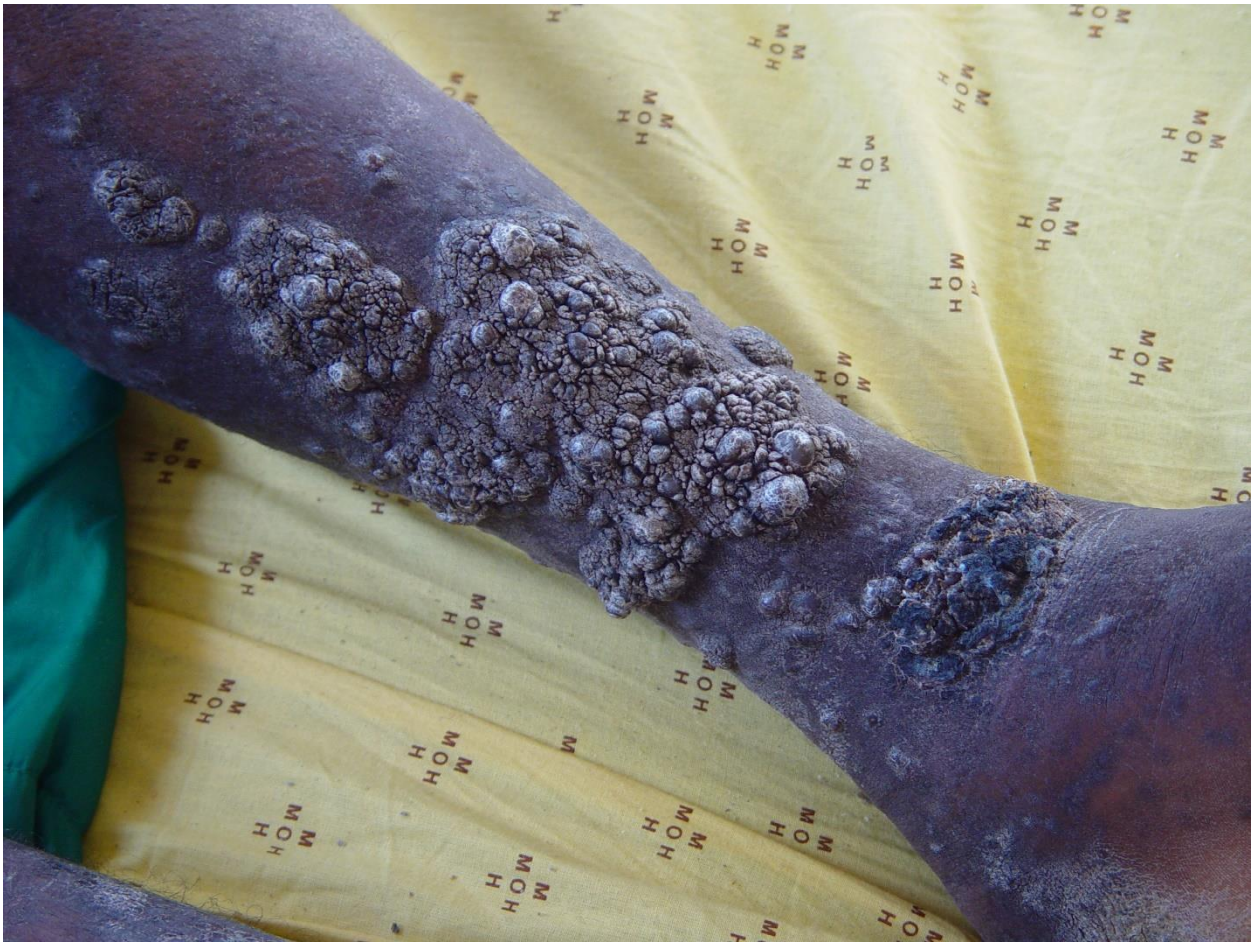

Figure 1. Verrucous lesions on the lower leg – AIDS-related Kaposi sarcoma

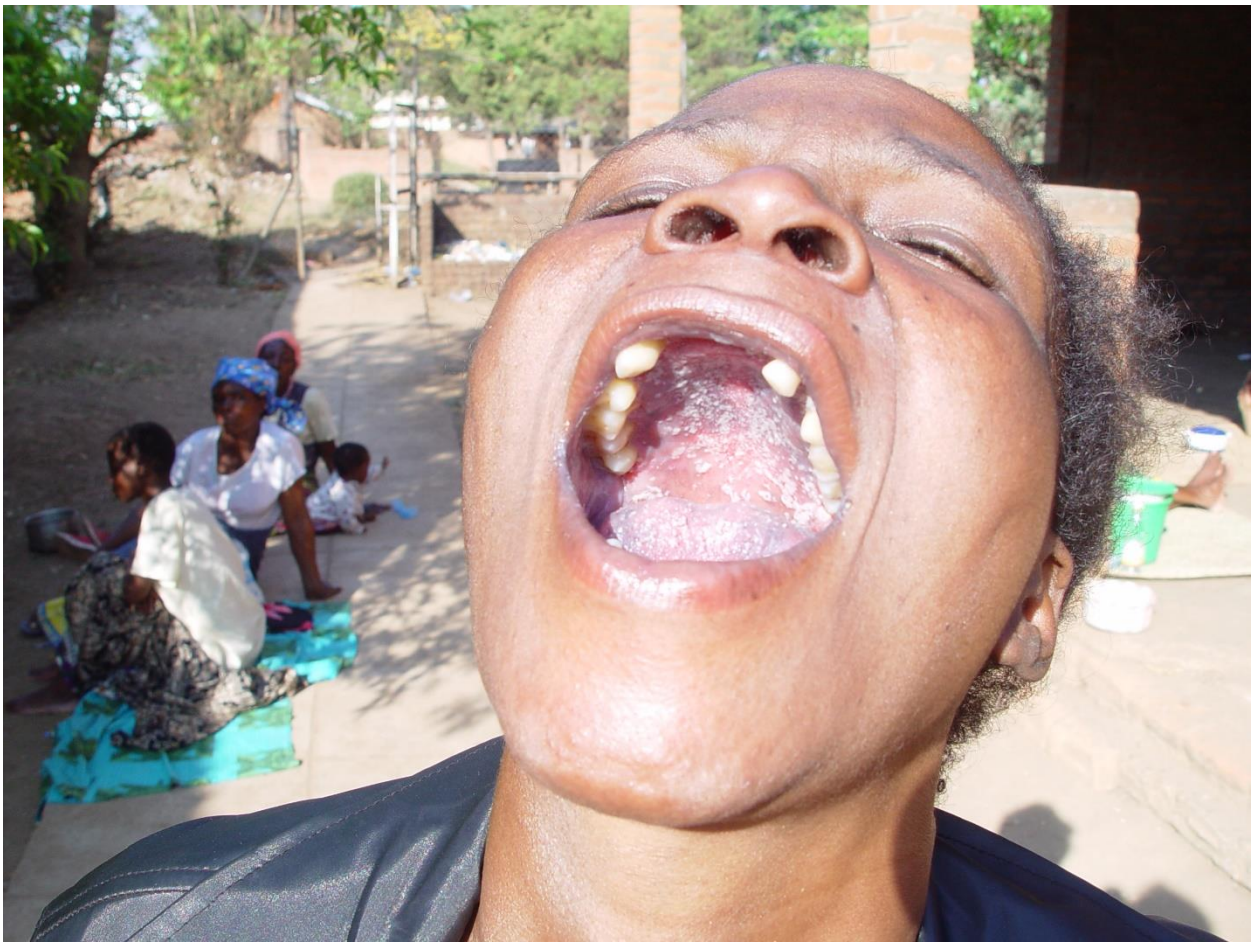

Figure 2. Prominent oral thrush, and in the background on the palate and laterally, multiple blueish flat lesions of Kaposi's sarcoma

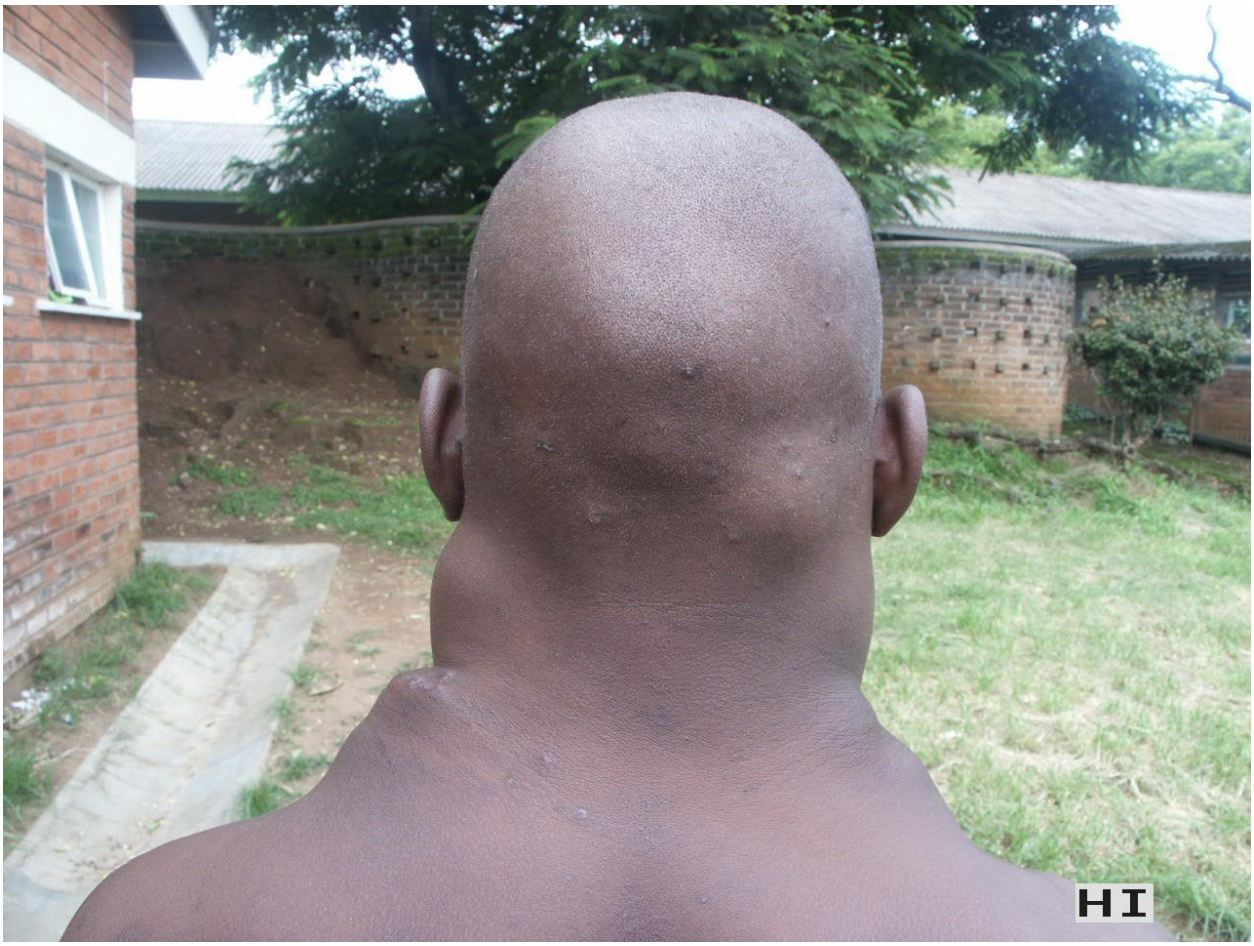

Figure 3. Multiple lymph node swelling in the neck in HIV/AIDS; a biopsy showed non-Hodgkin lymphoma.

Type	Characteristics	Clinical	Course
Classic (sporadic)	Age > 60 yrs Mediterranean, Eastern/central Europe, Middle East	Lower legs, feet	Indolent usually
AIDS associated	HIC: MSM LMICs: heterosexual males and females (Africa); low CD4 counts Co-morbidity, ART start and use of corticosteroids may unmask KS	Common in legs, feet; oral cavity; visceralization common: frequent manifestations: pleural effusion, pericardial effusion, ascites, lymphadenopathy, intrapulmonary	Indolent or aggressive; may respond to ART and chemotherapy
Endemic (African)	Male adults, in children male and female Equatorial Africa Common before HIV era	Variable, lymphoedema legs	Indolent to aggressive (children)
Iatrogenic	Older patients with transplants or other immunosuppression	Lower legs, feet; may disseminate	

Box 2. Types of Kaposi's sarcoma (KS)

ART antiretroviral therapy

LMICs low- and middle-income countries

MSM men who have sex with men