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The Challenging Impact of Infection-Related and Unrelated Malignancies in Persons Living with HIV

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INTRODUCTION

The incidence of acquired immunodeficiency syndrome (AIDS)-defining malignancies (ADMs) appears to be on the decline with the advent of highly active antiretroviral therapy (HAART or ART). ART has improved the short and medium-term survival of persons living with HIV (PLWH) and ADM.[1] ART has improved immunity and consequently it has resulted in a dramatic improvement in prognosis. However there still remains the increased risk that PLWH may develop non-AIDS-related mortality and morbidity, including cardiovascular disease, neurocognitive dysfunction, and cancers.[2-4] Non-AIDS defining malignancies (NADMs) are increasingly becoming a major concern. While the lifespan of patients with newly diagnosed HIV/AIDS now is equivalent to that of the general population, the morbidity and mortality associated with NADMS such as head and neck cancers, lung, kidney, liver, gastrointestinal tract, anus, and skin (squamous cell/ basal cell carcinoma, melanoma), Hodgkin lymphoma, and leukemia are significant and continue to increase at a steady and gradual pace.[1-3] There are many studies that suggest an impressive decrease in the rates of ADMs and an increase in the rates of NADMs.[2-3] The greatest risk factor for NADMs appears to be old age and longevity alone, but it is becoming increasingly clear that there are more risk factors that need to be identified.

There is a strong correlational link between lower CD4 cell counts (350–500 cells/μL) and an increased risk of ADMs and/or NADMs. The initiation of ART can decrease the rate of HIV replication resulting in CD4 counts >350–500 cells/μL, and lead to an overall reduction of the incidence of ADMs and even possibly NADMs.[2] Besson et al studied a large French population of PLWH, and they were able to demonstrate that the incidence fell sharply between 1993-1994 (86/10,000 person-years) and 1997-1998 (42.9/10,000 person-years). Epstein Barr Virus (EBV)-related lymphoproliferative disorders were the group in which the most

Table 1. Standard incidence ratios for common AIDS-defining and non-AIDS-defining malignancies in the early and later HAART era and in the context of tumor-associated oncogenic viruses.

HIV-associated malignancies	SIR pre-HAART (1990-1995)	SIR early-HAART era (1996–2002)
ADMs		
Kaposi's sarcoma	22,100	3640
PCNSL	5000	>1020
Burkitt's lyphoma	52	49
DLBCL	64	29
All NHLs	79	22.6
Cervical cancer	4.2	5.3
NADMs		
Hodgkin's lymphoma	8.1	14
Anal cancer	18.3	33
Lung cancer	2.5	2.2-6.6
Head and neck cancer	1.2	1-4
Prostate cancer	N/A	4
Hepatocellular cancer	19	7-35
Melanoma	N/A	3
All ADMs	1.8	1.7-2

ADMs, AIDS-defining malignancies; DLBCL, diffuse large B-cell lymphoma; EBV Epstein–Barr virus; HPV, human papillomavirus; N/A, not available; NADCs, non-AIDS-defining cancers; NHL, nonHodgkin lymphoma; PCNSL, primary central nervous system lymphoma; SIR, standard incidence ratio.

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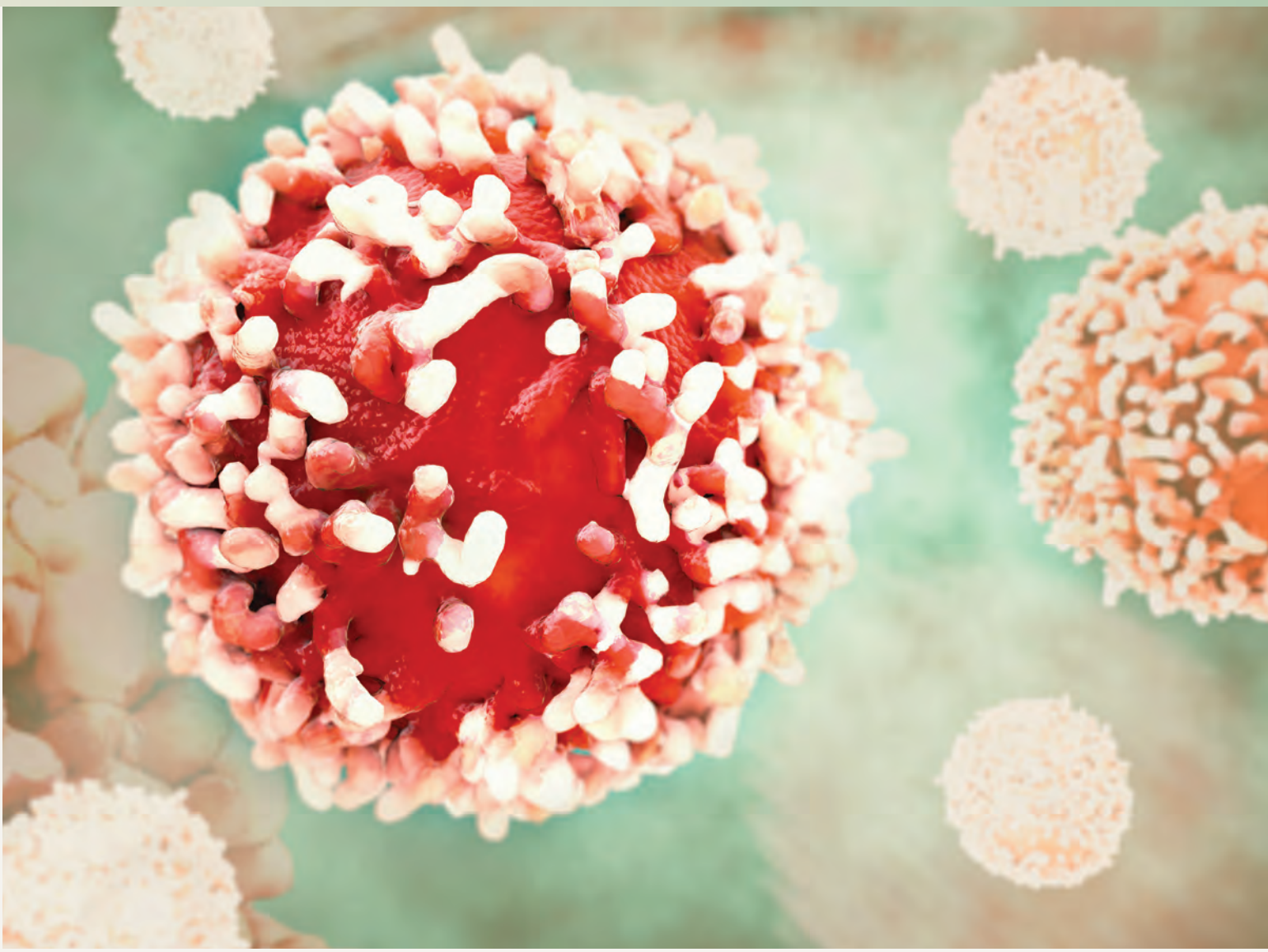


significant changes were witnessed with a dramatic decrease of incidence of primary cerebral and of high grade immunoblastic lymphomas.[4] There is some morbidity associated with opportunistic infections, however, the initiation of ART in addition to chemotherapy in PLWH with malignancies has been shown to not only decrease the rates, but it can also improve the overall survival in patients with ADMs.[5,6]

There is overwhelming data to suggest that the early introduction of ART is essential in the management of PLWH with cancer.[7] However, with the concomitant administration of ART and chemotherapy, there is a concurrent increased risk of complications and toxicity.[8]

In this review, our aim is to closely examine the epidemiology, etiology, treatment and screening of malignancies in PLWH. A more in-depth look at this problem will assist in identifying future treatment modalities.

EPIDEMIOLOGY

AIDS Defining Malignancies

The United States (US) Centers for Disease Control and Prevention recognizes Kaposi sarcoma, primary central nervous system lymphoma (PCNSL), cervical cancer and intermediate grade and high grade forms of non-Hodgkin lymphoma (NHL) to be the classic ADMs by definition.[9] The risk of malignancy in PLWH can be defined by the standard incidence ratio (SIR).[10] For HIV-related malignancies, the SIR compares the rate of malignancies among PLWH to the number expected in the general population at any given time.[9-12] In the ART era, the SIR has substantially decreased for all ADMs, with the exception of invasive cervical carcinoma.[9-12] However, the risk for each of the ADMs is still above that of the general population (Table 1).[9-12] Between 1987 and 1993, there was an increased incidence of Kaposi sarcoma (KS) and NHL in PLWH.[13] The WHO classifies HIV-associated lymphomas based on the intricate epidemiology and histologic interpretation of lymphomas (Table 2).[14-16] Of note, low-grade lymphomas, extra nodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), and Hodgkin's lymphoma

are not considered HIV-associated lymphomas. B-cell NHLs are the most prevalent AIDS-defining NHLs and they typically present at an advanced stage. These AIDS-defining NHLs include PCNSL, Burkitt's lymphoma, diffuse large B-cell lymphoma (DLBCL), plasmablastic lymphoma, and primary effusion lymphoma (PEL).[17] Prior to the advent of ART, DLBCL and PCNSL were the most common NHLs in PLWH.[17] Although the incidence of DLBCLs has decreased since the ART era began, it remains the most common NHL.[12] Burkitt's lymphoma replaced PCNSL as the second most common AIDS-defining NHL.[12] In the pre-ART period, KS and NHL represented 99% of all ADMs.[13] From 1991–1995 to 2001–2005, the number of ADMs cases (especially Kaposi sarcoma and NHLs) decreased by 70% as a result of ART. During this same interval, the incidence of all ADMs decreased by 70%.[13,18] Despite the advent of ART, ADMs still currently account for 15–19% of all deaths in PLWH.[19-21] One of the crucial driving factors for NHL and KS is immune suppression as reflected by a decreased CD4 T-cell count.[22-23]

Non-AIDS Defining Malignancies

Innumerable clinical studies have documented an increased incidence of NADMs in PLWH.[18-21] In the US, the incidence of NADMs increased more than three-fold, from 3,193 to 10,059 cases when comparing the intervals 1991–1995 and 2001–2005.[18] In developing countries where resources to distribute ART are limited or largely unavailable, the incidence of NADMs appears to have likewise increased with the increasing rate of incidence of HIV. NADMs are prevalent among PLWH who are elite controllers, who have undetectable plasma HIV RNA who either do not progress clinically, or progress at very slow rate, or those in developing countries without access to therapy.[24] Several cellular biomarkers have been investigated in PLWH with NADMs, and these include: CD4 lymphocyte count, proteins of various sorts in plasma or serum (cytokines, receptor-derived proteins, immunoglobulins), viral nucleic acids (HIV, EBV, KSHV), and germ line polymorphisms in a variety of genes direct which may have carcinogenic or anti-carcinogenic potential.[25-27] Whether ART may increase the risk of NADMs due to its ability to increase longevity rather than its direct carcinogenicity is not exactly clear. Interestingly enough, statins, through alternative anti-inflammatory modes of action that reduce immune activation, were associated with a 57% decrease in NADMs.[25] This finding suggests that chronic inflammation associated with longevity and/or HIV may play a role in increasing the risk of cancer.

Table 2. WHO classification of lymphoid malignancies associated with HIV infection. [14-17]

Lymphoma Type	Comments
Burkitt's lymphoma, Burkitt's-like lymphoma	Presents with a higher CD4þ T-cell count; 100% associated with cMYC translocation
Diffuse large B-cell lymphoma	Centroblastic 30% EBV
Centroblastic immunoblastic (associated with PCNSL)	Immunoblastic 90% EBV and associated with primary CNS lymphoma
Extranodal MALT lymphoma	Non-AIDS-defining cancer; rare
Peripheral T-cell lymphoma	Rare
Primary effusion/body cavity lymphoma	Rare; presents in patients in the late stages of HIV; associated 100% with HHV-8 and EBV
Plasmablastic lymphoma of the oral cavity	Rare; associated with HHV-8 50% and EBV 50%
Polymorphic B-cell lymphoma (PTLD-like)	Rare
Hodgkin lymphoma	Non-AIDS-defining lymphoma; may present in patients with elevated CD4 T-cell count; EBV 80–100%

DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; HHV-8, human herpesvirus 8; MALT, marginal zone lymphoma of mucosa associated lymphoid tissue; PCNSL, primary central nervous system lymphoma; PTLD, post-transplant lymphoproliferative disorder.

Etiology

A large number of viruses possess oncogenic potential which in turn causes the development of malignancies in humans. Multiple hypothesis have been proposed to explain how these viruses, through direct and/or indirect mechanisms, may contribute to carcinogenesis. In one case, the virus is able to induce the expression of specific oncogenic protein(s) that then play a direct role in cell transformation; alternatively, the transformation is associated indirectly with the virus-induced chronic infection and inflammation. However, in many instances, it is not possible to elicit or define whether the carcinogenesis is the result of a direct or an indirect oncogenic insult (eg, in the case of hepatitis B virus (HBV), hepatitis C virus (HCV), or human T-cell lymphotropic virus type 1 [HTLV-I]),[1] and, more importantly, it is difficult to distinguish between the 'pro-oncogenic' immune/inflammatory mechanisms and the benign 'anti-oncogenic' mechanism of immunity.[26] Several

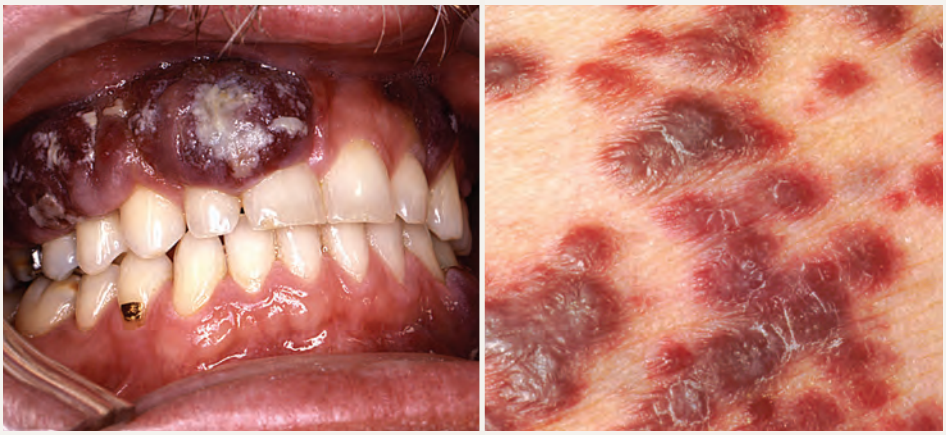
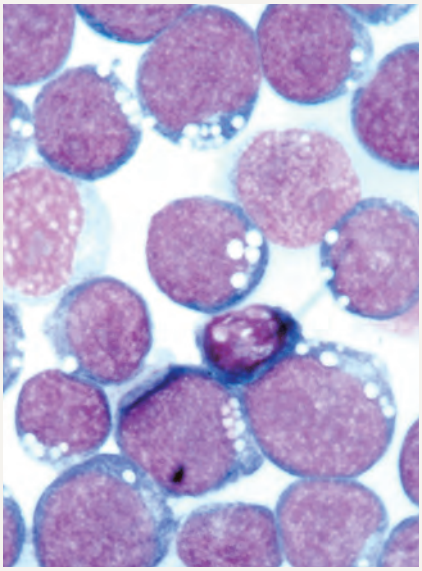


Figure 1a (top left): 1999 Sol Silverman, Jr., DDS. This HIV-positive patient presented with an intraoral Kaposi's sarcoma lesion with an overlying candidiasis infection. This AIDS patient exhibited a CD4+ T-cell count <200, and a high viral load. Initially, the KS lesions are flattened and red, but as they age the become raised, and darker, tending to a purple. https://phil.cdc.gov/phil_images/20040819/5/072.tif. Figure 1b (top right): Kaposi's sarcoma on the skin of an AIDS patient. National Cancer Institute (1985).

viruses with various replication processes have been shown to play a vital role in oncogenesis related to immunosuppression, both directly and indirectly. Among them, the main viruses are as follows: EBV, HBV, HCV, human papillomavirus (HPV), KS herpesvirus (KSHV), HTLV-1, and Merkel cell polyoma virus (MCV) (Table 3). HIV itself has been demonstrated to possess a direct pro-oncogenic effect.



Epstein-Barr Virus (EBV) Stained with Hematoxylin and eosin (HE), is of the Epstein-Barr virus (EBV). Source: National Cancer Institute (1978)

Epstein Barr Virus

In AIDS-associated NHL, viral gene expression is variable.19 In AIDS-related Burkitt's lymphoma, EBV is found in 30–60% of cases.[27] The higher the number of viral genes expressed, the higher the degree to which lymphoma cells depend on EBV. Severe immunosuppression as manifested by low CD4 cell counts and dependence on EBV give rise to malignancies which are associated with higher latency patterns. Recent studies using total RNA-sequencing technology (transcriptome sequencing) and the PathSeq analysis pipeline were carried out in PLWH with lymphoma and no virus other than EBV was discovered in PLWH-related lymphomas treated with ART.[28] More importantly, a highly heterogeneous pattern of viral transcription was found, with many cancer samples showing the restricted type I viral latency, suggesting that EBV latency proteins are under high immunosurveillance.[28,29]

EBV can also cause extensive methylation of both the host genome and the viral genome which can in turn augment cellular functions which drive viral persistence and replication.[30] EBV is a potent oncogenic virus which can mold the microenvironment resulting in cell transformation. EBV regulates the production of soluble factors promoting the growth and/or the survival of lymphoma cells, and acts on a variety of mechanisms favoring escape from antitumor immune responses. There is also evidence that EBV-infected B-lymphocytes actively secrete exosomes, which may contribute to the development and progression of tumors.[29,30]

Table 3. Oncogenic human viruses and viral oncogenes.

Tumor virus	Associated cancer(s)	Viral oncogenes or potential oncogenes*
High-risk HPVs	Cervical cancer, anal cancer, penile cancer, vaginal cancer, oropharyngeal cancer	E6, E7
MCV	Merkel cell carcinoma	T antigens
HTLV-1	Adult T-cell lymphoma	Tax
EBV	Burkitt lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma nasopharyngeal cancer, T-cell and NK lymphoma	LMP1
KSHV	Kaposi's sarcoma, primary effusion lymphoma, multicentric Castleman's disease	LANA, vFLIP, vCyclin, vGPCR, vIRF-1, K1
HBV	Hepatocellular carcinoma	HBx
HCV	Hepatocellular carcinoma	Core protein, NS3, NS4B, NS5A

* For KSHV, HBV and HCV, potential viral oncogenes are presented.

Human Herpes Virus (HHV-8/KSHV)

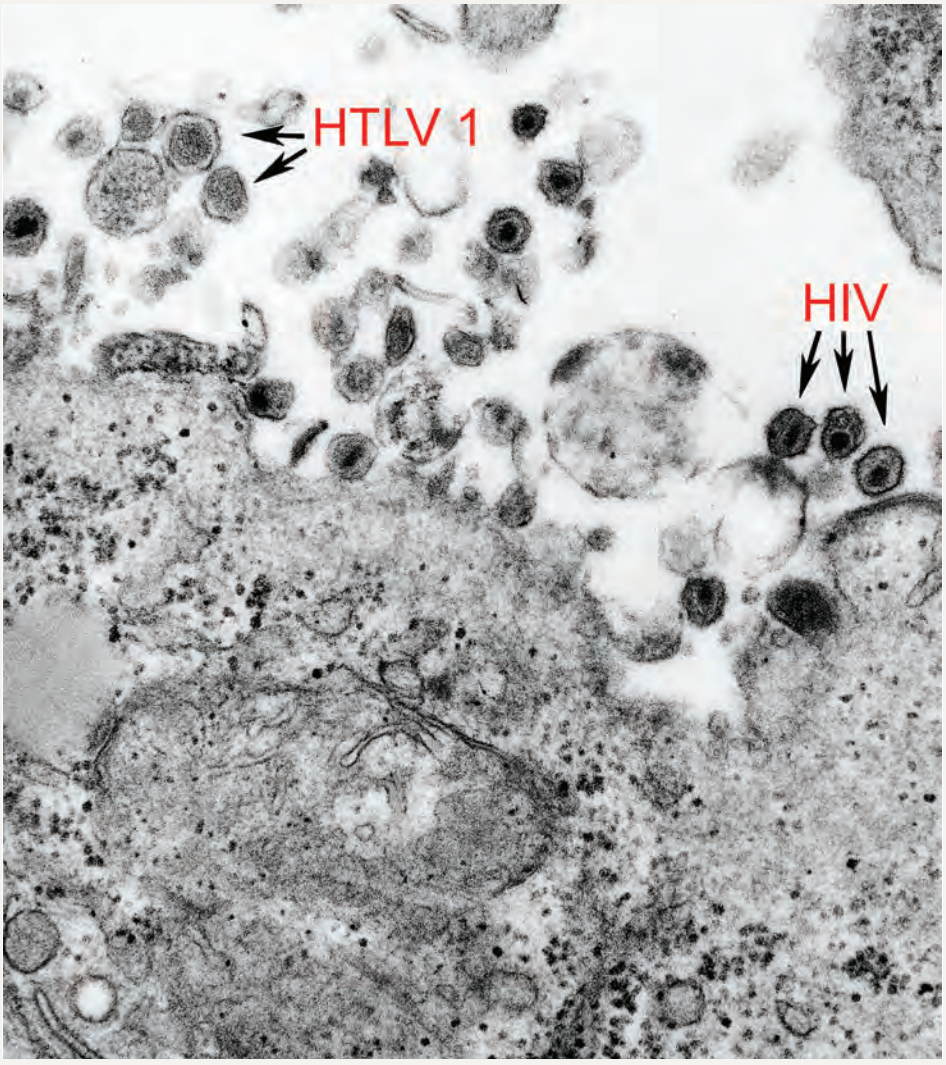
HHV-8 is considered a group I carcinogen, after clinical data revealed a causative relationship with KS, primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD).[31] KS is a multicentric angioproliferative spindle cell tumor resulting from HHV-8-infected endothelial cells and is strongly related to the severity of the HIV-induced immunodeficiency, being 10–50-fold higher PLWH with severe immunodeficiency than in those with early HIV infection.[32] Some PLWH may initially have the indolent form of KS. KS may initially appear clinically as pink or red raised nodules or plaques primarily on the extremities or mucosa [Figure 1]. These lesions may eventually widely disseminate on the skin, and can be associated with visceral lesions and disseminated lymph node involvement.

PEL is a unique, aggressive form of B-cell NHL, representing 1–4% of all AIDS-related lymphomas.[33] This disease entity is composed of malignant, latently infected B-cells that affect serosal body cavities.[33,34] PEL is a monoclonal population of B-cells, and each cancer cell contains a high HHV-8 copy number, from 50-100 genomes per cell[34]. There is a strong association between HHV-8 and PEL, and in 70–80% of cases the lymphoma cells have coexisting latent infection with EBV.[33,34]

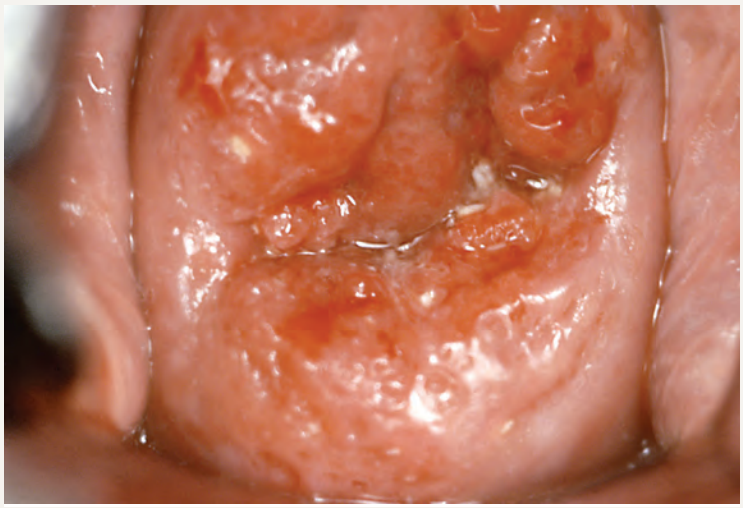
MCD is a disease entity which involves the lymph nodes, and the plasmablastic variant has been associated with HHV-8 infection. HHV-8-associated MCD is typically observed in PLWH with immunosuppression.[32-34] The HHV-8 viral genome has been isolated in almost all HIV-positive MCD cases, whereas HHV-8 is identified in <40% of HIV-negative cases.[33,34] MCD is defined by an abnormal, polyclonal IgM λ proliferation, and atypical cases of monoclonal B-cell expansion have been demonstrated.

Human T-Lymphotropic Virus type I (HTLV-1)

HTLV-1 is an oncogenic retrovirus that is prevalent in the tropics and subtropics, in Japan, sub-Saharan Africa, the Caribbean, and South America.[35-37] In approximately 10% of infected patients, HTLV-1 is associated with severe diseases, such as neoplastic diseases (adult T-cell leukemia/lymphoma [ATL]), inflammatory syndromes (HTLV-1-associated myelopathy/tropical spastic paraparesis), and opportunistic infections (eg, Strongyloides stercoralis hyperinfection).[36] By integrating into the host DNA, HTLV-1 establishes a latent infection, usually characterized by a high proviral load, and it is this latency that contributes to the early phase of oncogenesis of ATL, immortalizing T-lymphocytes in vitro.[37,38] ATL is a malignancy of mature T-lymphocytes, with a heterogeneous clinical course and the effect of HIV-related immunosuppression has not been very clearly defined.



Human T-cell leukemia virus type-1 (HTLV-1), a human oncoretrovirus, is the etiologic agent of adult T-cell leukemia, and of tropical spastic paraparesis/HTLV-1–associated myelopathy. Two closely related retroviruses, HIV-1 and HIV-2, have been identified as causing AIDS in different geographic regions. HIV-1 causes most cases of AIDS in the U.S., with only a few cases of HIV-2 having been found in the U.S. Epidemiologically, HIV-2 has been found to be mostly an infection of persons from West Africa. Courtesy CDC/ Cynthia Goldsmith



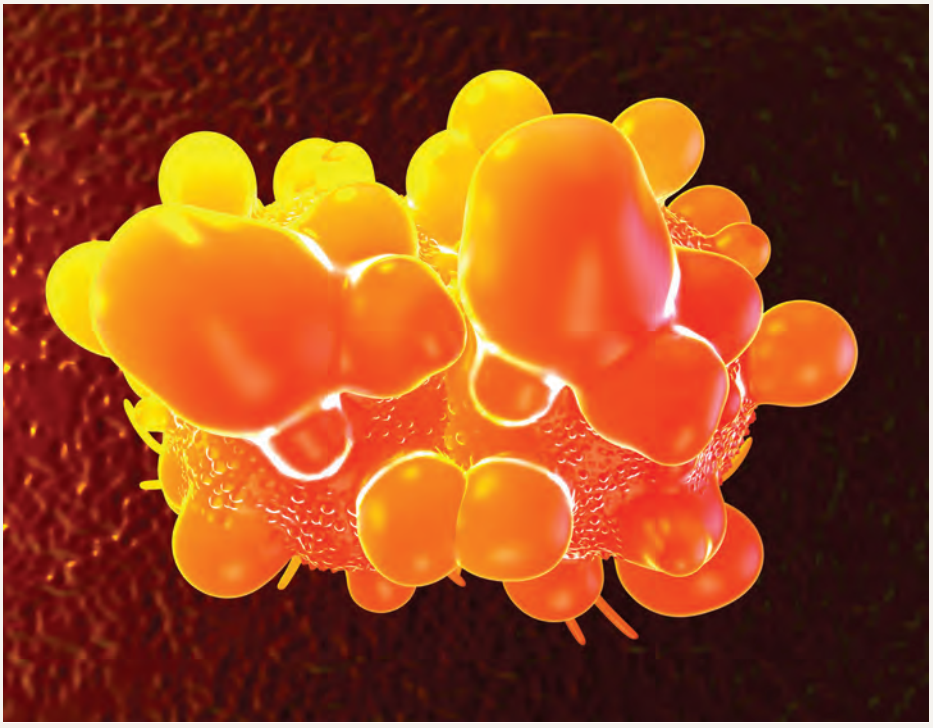
This patient presented with erosion to her cervix due to what turned out to be low grade cervical carcinoma. Courtesy CDC

Human Papillomavirus (HPV)-ASSOCIATED CERVICAL CANCER

HPV is a small double-stranded DNA virus that infects epithelial tissues and 12 high-risk HPVs are classified as type 1 carcinogens by the IARC.[39] HIV-related immunosuppression is associated with an increased risk of malignancies in the anogenital and head and neck regions. In 1993, the CDC decided to classify squamous cell carcinoma (SCC) of the cervix as an AIDS-defining malignancy, owing to the frequent occurrence, estimated to be five times greater, among women with AIDS.[40] This is attributed to the common sexual risk factors for HIV and HPV transmission, the fact that HPV infection increases the efficiency of HIV sexual acquisition,[44] and the impact of immunosuppression on HPV persistence and latency.[40,41]

HPV-ASSOCIATED ANAL CANCER

There is a strong association between HPV and SCC of the anal canal. Anal HPV infection is commonly diagnosed in PLWH, and approximately 90-95% in HIV-positive men who have sex with men (MSM).[42] Most precancerous HPV-associated anal lesions are asymptomatic, but they clearly carry a very high risk of progressing to SCC. It is essential that anal cancer precursors be detected by digital anorectal examination and high-resolution anoscopy. There is clinical evidence to suggest that administration of the quadrivalent HPV (qHPV) vaccine can prevent vaccine associated persistent anal HPV infections as well as anal intraepithelial neoplasia grades 2-3 (AIN2+) in young uninfected MSM. There is additional retrospective data which also demonstrates that qHPV vaccination of older MSM treated for AIN2+ may significantly decrease the risk of recurrence of the AIN2+. The HPV types detected in anal cancer are included in the 9-valent vaccine. Thus, the 9-valent HPV vaccine, when administered to boys and girls prior to the onset of sexual activity, should effectively prevent anal cancer.[42]



Bowel cancer cell

HPV-ASSOCIATED OROPHARYNGEAL CANCER

Forty to eighty percent of oropharyngeal SCCs are associated with HPV infection.[43] HPV-positive SCCs arise predominantly in the tonsils and the base of the tongue, and are associated with a more favorable prognosis.[43] The oncogenicity of HPV-positive oropharyngeal SCC is driven by oral HPV16 infection in 85% of cases, compared to the 60% found in cervical cancer. The high risk of precancerous oropharyngeal lesions in PLWH is linked to high viral loads which contribute to the oncogenesis of HPV-associated oral cancers.[44]

MERKEL CELL CARCINOMA

Merkel cell carcinoma (MCC) is one of the most aggressive skin cancers and hence the second most common cause of cutaneous malignancy death after melanoma.[45] The causative agent is a polyomavirus, named MCV, which was discovered in 2008 as being clonally integrated into MCC cells of infected patients.[46]

Table 4. Drug interactions between chemotherapy drugs and ART. [65]

Chemotherapeutic agents	P450 system responsible for metabolism	Antiretroviral inhibitor [a]	Antiretroviral inhibitor [b]	Associated cancers (being treated)
Vinblastine **Vincristine**	CYP 3A4	Ritonavir, Amprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir, Saquinavir, Darunavir, Conbcistat	Nivarapine Efavirenz	Hodgkin lymphoma ALL, NHL
Paclitaxel **Docetaxel**	CYP 2C8 CYP 3A4	Same as above	Nivarapine Efavirenz	KS, breast, lung, cervical
Etoposide	CYP 3A4 CYP 2E1	Same as above		NHL, lung
Ifosfamide **Cyclophosphamide**	CYP 3A4 CYP2C9 CYP 2B6	Same as above Efavirenz Amprenavir	Nivarapine Efavirenz Etravirine	NHL, lung, breast, sarcoma
Dacarbazine	CYP 2E1	Ritonavir		Hodgkin lymphoma

ALL, acute lymphocytic leukemia; CYP, cytochrome P450; KS, Kaposi sarcoma; NHL, non-Hodgkin lymphoma. [a] Inhibitors increase the concentration of the active metabolite. [b] Inducers decrease the concentration of the active metabolite.

HIV-related immunosuppression increases the risk of MCC, and appears to be associated with a more aggressive clinical course and hence worse prognosis.[47] In patients with low CD4 counts, MCC tumors do not arise only in the usual sun-exposed areas, and this suggests that UV exposure may not be a significant contributing risk factor.[46,47] Moreover, in PLWH, MCV DNA has been isolated from the skin, from oral and anogenital mucosa, and from plucked eyebrow hairs, and significantly increased cutaneous MCV DNA loads were identified in those with very low CD4 counts.[48]

LIFESTYLE CHOICES

Cigarette smoking is prevalent in PLWHA with over 50% who smoke compared to just 18% of the US general population older than 18 years of age.[49] There is evidence that PLWH who smoke are at increased overall risk for both ADMs and NADMs.[50-53] However, such an association does not exist between smoking and colon and hepatocellular cancer.[52,53] Alcohol addiction and abuse is also increasing in incidence in PLWH.[51] PLWH who smoke are three times more likely to die from cancer than nonsmokers.[54] In the US, rates of heavy alcohol consumption among PLWH are two times more than the general population.[51] Alcohol consumption is a potent contributor to an increase in risk of developing malignancies of the mouth, esophagus, pharynx, larynx, and liver.[55]

How the various possible etiologic factors which include exposure to oncogenic viruses, degree of immunosuppression and lifestyle choices may influence the pathogenesis of certain malignancies in PLWH needs further investigation. Other factors such as disparities in health care and access to medical care for PLWH may also shed some light in offering an explanation for the incidence of malignancies among PLWH.

Management And Treatment

In the past, chemotherapy was rarely initiated in a patient with an immunocompromising condition such as HIV/AIDS because of the concern of systemic toxicities. The trend used to be that PLWH with malignancy would receive either chemotherapy or ART alone but rarely both treatments simultaneously. There is increasing data to suggest that treating both HIV and the malignancy is crucial to achieve optimal response rates and improve survival outcomes. Since the advent of ART treatment, only a few malignancies such as non-Hodgkin's lymphoma (NHL) and Kaposi sarcoma have decreased in incidence.[56-58] Over the years, the improved safety and toxicity profile of ART therapy has given PLWH more tolerable options and this has resulted in a refinement in the management and treatment of cancer. This factor together with optimal supportive care has played a role in improving the overall survival rate.[59]

It is critical to recognize the drug interactions of chemotherapy drugs and HIV medications (Table 4) so that an ideal and effective regimen can be selected to treat PLWH with malignancies. Some HIV and chemotherapy drugs are metabolized by the cytochrome p450 (CYP) system therefore this can lead to drug-drug interaction.[60-63] Upregulation or inhibition of

Table 5. Major toxicities shared by both ART and chemotherapeutic drugs.[65]

Chemotherapeutic agent	Adverse events	HAART drug
Common with most chemotherapeutic classes. [i.e. anthracyclines, taxanes vinca alkaloids, platinums alkylating agents, camptothecans, etoposide, and antimetabolites (methotrexate and 5FU)] ▪ All taxanes; all vinca alkaloids; oxaliplatin; bortezomib ▪ Cisplatin ▪ Carboplatin ▪ Common with most chemotherapeutic classes. ▪ Vinca alkaloids ▪ Common with most chemotherapeutic classes. (Chemotherapeutic agents that can be administered without any dose reductions in the setting of hepatotoxicity include cisplatin, gemcitabine, and bleomycin) ▪ Irinotecan ▪ Topotecan ▪ Fluorouracil	Bone marrow suppression	Zidovudine
	Neuropathy (motor and/or peripheral) Kidney toxicity	Didanosine; stavudine Tenofovir Indinavir
	Nausea/vomiting	Protease inhibitors; zidovudine
	Constipation Liver toxicity	Protease inhibitors; nucleoside and nonnucleoside reverse transcriptase inhibitors
	Diarrhea	Nelfinovir Lopinavir

the CYP system can lead to increased or decreased drug levels, which can lead to either toxicity or decreased efficacy. On the other hand, there are several HIV and chemotherapy drugs which have a similar toxicity profile. Hence, combining them would lead to a higher risk of drug toxicity.[62-64] Therefore, the potential drug toxicity, drug-drug interaction and combination effects should always be considered prior to the initiation of treatment of malignancies in PLWH. This critical process requires the involvement and collaboration between the pharmacist, oncologist, and infectious disease specialist.

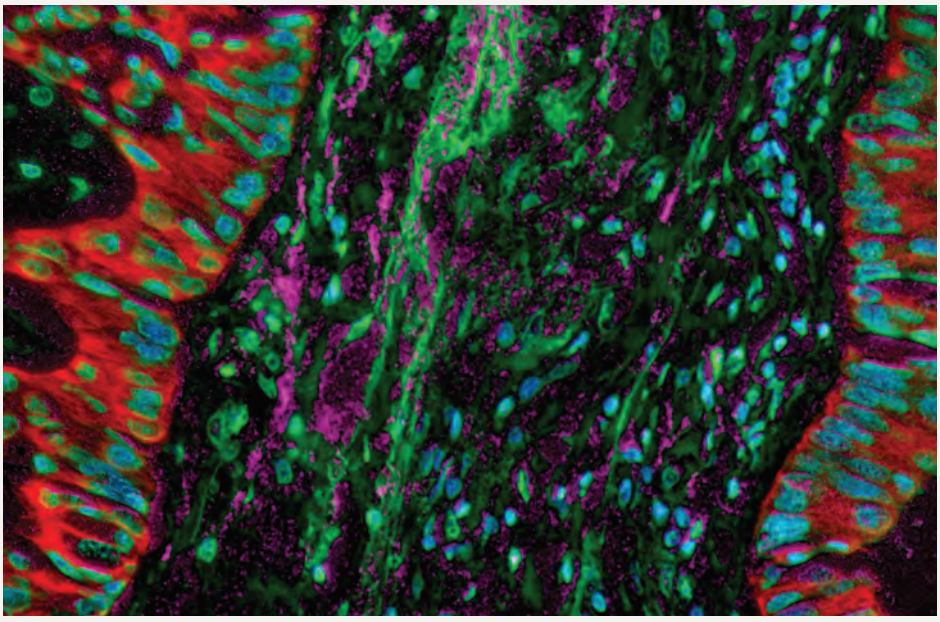
Some of the common drugs initially used in the early ART era included zidovudine, didanosine, and stavudine have overlapping toxicities with chemotherapy drugs (Table 5). About 8% of patients treated with zidovudine developed myelosupression, while didanosine and stavudine caused peripheral neuropathy. Most of the protease inhibitors caused nausea, vomiting and hepatotoxicity.[64,65] The nucleotide analogs, specifically tenofovir disoproxil fumarate (TDF), can cause nephrotoxicity while the non-nucleoside reverse transcriptase inhibitors can cause hepatotoxicity.[63-65] Ritonavir, a protease inhibitor booster, and cobicistat, the only other booster approved for use as a part of ART, are potent CYP inhibitors, and therefore reduce the clearance of vinca alkaloids, taxanes, and alkylating agents.[62-65] Ritonavir can also cause increased neurotoxicity when it is combined with vincristine and vinblastine based chemotherapies.[66-68] Patients with NHL experienced more than a 50% drop in CD4 counts when chemotherapy and ART were given simultaneously, nevertheless they returned to normal within six months to one year.[69] Pelvic radiation for anal cancer can result in

Table 6. General guidelines for the treatment of HIV-associated cancers.[65]

Optimal treatment of patients with HIV-associated malignancies includes input from a multidisciplinary team consisting of a pharmacist, an infectious disease specialist, and a hematologist/oncologist.
HIV medications can inhibit the Cyt p450 system, potentially augmenting toxicities by preventing chemotherapy metabolism.
Multiple overlapping toxicities are seen with HIV medications and chemotherapy agents.
Supportive care medications can also augment chemotherapy toxicities (i.e. azole antifungals and vincristine).
Avoid the use of ritonavir when combined with vinblastine in the setting of Hodgkin's lymphoma.
Rituximab offers substantial benefit when used with combination chemotherapy for treatment of CD20 aggressive B-cell lymphomas.
Rituximab should not be withheld for patients with CD4þ cell counts less than 50 cells/ml. But care should be taken, as patients with low CD4 T-cell counts are more prone to infectious complications.
CD4 T-cell counts can decrease during chemotherapy and/or in the setting of pelvic radiation. Thus, prophylaxis during therapy for opportunistic infections is often warranted despite a normal CD4 T-cell count at therapy onset.
Granulocyte colony-stimulating agents and antibiotic prophylaxis are strongly encouraged to minimize the effects of chemotherapy induced neutropenia during the treatment of AIDS-related lymphomas.

a precipitous decline in CD4 counts and a prolonged myelosuppression which may hinder bone marrow recovery to pre-treatment values.[70]

PLWH who are on chemotherapy for HIV-related malignancies should also be on ART therapy as well unless there is a concern for intolerable side effects most commonly being nausea, vomiting or drug interactions.[65] A National Cancer Institute (NCI) study demonstrated that CD4 counts declined and the viral load increased when ART therapy was stopped during HIV-related lymphoma chemotherapy for about four to six months. In these patients, ART was reinitiated towards the end of antineoplastic therapy and the HIV status returned back to pre-treatment level in six to twelve months.[71-73] The overall survival of this group was 68% at 5 years, and it is comparable to patients received concurrent chemotherapy and ART.[71-74]



Above: Lung Cancer Desmoplasia
As shown here, lung cancer is associated with a vast stromal desmoplastic reaction (the "neighborhood") in which the connective tissue, associated with the tumor, thickens similarly to scars. Cancer is in red; cell nuclei in cyan; stroma/desmoplasia in green; and an active stroma-specific marker in purple.
National Cancer Institute \ Fox Chase Cancer Center (April 11, 2016) https://visualsonline.cancer.gov/details.cfm?imageid=10576

Studies have shown that Rituximab, a chimeric anti-CD20 monoclonal antibody, has tremendous benefit in combination with chemotherapy for CD20+ aggressive B cell lymphoma.[75] Even though, a few studies demonstrated an increase in infection-related deaths, such as fulminant hepatic failure secondary to reactivation of HBV infection, associated with the administration of rituximab, more recent studies have failed to produce the same negative outcomes.[75-77] There is enough conclusive clinical data to support the frontline use of rituximab-based chemotherapy in HIV-related lymphoma.

Opportunistic infections are a known complication in immunosuppressed (low CD4 cell counts) PLWH. Appropriate prophylaxis treatment is imperative when treating the malignancies in PLWH. Rubinstein et al[65] recommends that prophylaxis for Pneumocystis *jirocevi* should be started regardless of the CD4 counts during the initiation of chemotherapy. The same authors also advocate prophylaxis therapy targeting other opportunistic infections such as herpes simplex virus and thrush should also be started.[65] Fluconazole is another agent that can potentially result in toxicity because it can inhibit the CYP3A4 system when administered in combination with vinca alkaloid thus causing neutropenia and neuropathy. Granulocyte colony-stimulating agents, on a risk assessment basis, can safely be used to prevent and treat chemotherapy-induced neutropenia in patients with HIV-related lymphomas or other cancers receiving chemotherapy.[71-73] Table 6 outlines the general guidelines and

principles for the treatment of HIV-associated malignancies.[65]

Screening Guidelines

The most common NADM among PLWH is lung cancer. It is also the leading cause of cancer-related mortality. Among PLWH with a history of smoking, immediate smoking cessation or within the past 15 years increases the risk of **lung cancer** compared to non-smokers.[78] Randomized trials have looked at the screening tools such as chest radiography with or without sputum cytology. The results essentially concluded that screening tools did not lead to a significant reduction in lung cancer mortality. However, a study done by The National Lung Screening Trial (NLST), evaluated the difference between chest radiography versus low-dose helical chest computerized tomography (LDCT) as a screening tool for detecting lung cancer.[79] There were 53,454 participants with 30 pack-years history of smoking, actively smoking or quit within 15 years, and who are in the age range of 55-74 were followed for six and a half years.[80] A 20% relative reduction in lung cancer-related mortality and 6.7% reduction in all-cause mortality was identified when comparing the LDCT screening to chest radiography.[81] It is important to note that the study done by the NLST may not represent the community population since the trial participants were highly motivated and engaged individuals who received multidisciplinary coordinated medical care including strict preventative screening methods along with necessary treatment interventions.[80,81] The age for inclusion into the NLST trial was 55–74 years, older than the median age at lung cancer diagnosis among PLWH. Additionally, most study participants were Caucasians (91%), in contrast to the largely minority demographics of PLWH in the US. Although the NLST did not exclude PLWH, it is not clear exactly how many participants had HIV infection. As a result, it is unclear whether we can apply the findings of NLST to the HIV-infected population. In December 2013, the US Preventive Services Task Force (USPSTF) released an updated guideline which recommends adults of age 55-80 with 30 pack-year smoking history, currently smoking or quit within the past 15 years to be screened annually with LDCT.[81] Further research, incorporating the traditional and emerging immunologic risk factors, is needed to conclude that HIV-infected smokers will benefit from lung cancer screening at younger ages.

Table 7. Cervical Cancer Screening Guidelines: Women with HIV ≥30]

Women with HIV ≥30	
▪ If Pap smear testing only ▪ If Pap and HPV cotesting	Annually x 3, if 3 consecutive normal, then every 3 years
	Pap and HPV negative→co-test in 3 years Pap normal, HPV+ →co-test in 1 year and if either are abnormal→ colposcopy Genotype testing is not recommended here, however if done, 16 or 16/18+, then colposcopy

Moyer, Virginia A. "Screening for cervical cancer: US Preventive Services Task Force recommendation statement." Annals of internal medicine 156, no. 12 (2012): 880-891.

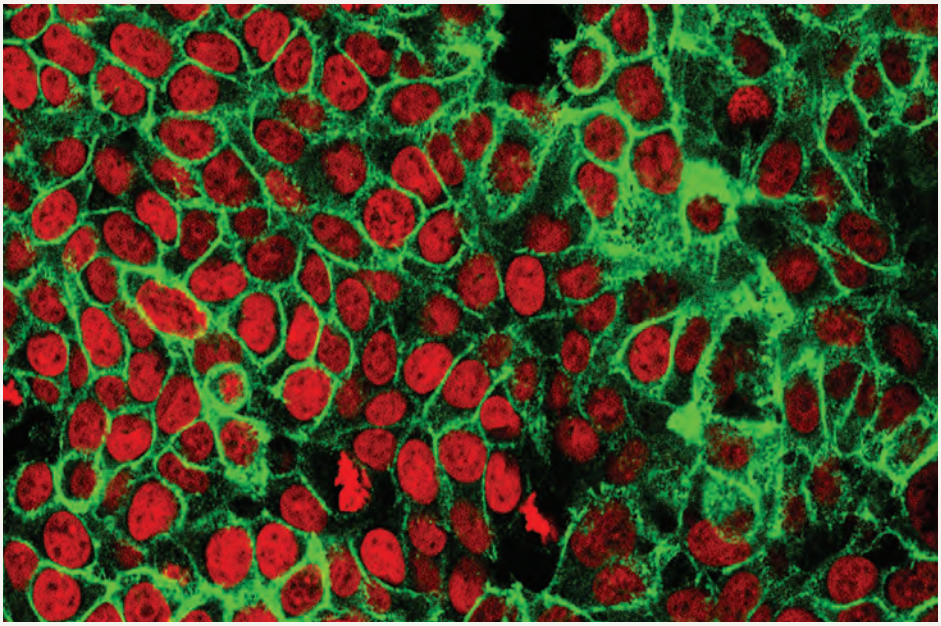
Hepatocellular carcinoma (HCC) is more common among PLWH than the general population due to the increased prevalence of co-infection with HBV and/or HCV which increases the risk for hepatocellular cancer. Data indicates the AIDS patient population has a four-fold increase in risk of HCC compared to the general population.[82] PLWH should get a baseline testing for HBV surface antigen (HBsAg), HBV surface antibody (HBsAb or anti-HBs), and hepatitis B core antibody (HBcAb or anti-HBc) to differentiate immunity versus infection.[83] The vaccine is indicated if the patient does not have infection and does not have serological evidence of immunity. Due to the nature of HIV, PLWH may not develop a positive immunity from vaccination, therefore methods such as increasing the number of vaccines given and even increasing the doses have been implemented to ameliorate the response.[84] At the time of HIV diagnosis, PLWH should be screened for HCV infection as well since one third of PLWH are co-infected with HCV, and at least annually thereafter.[87] The HCV serology is not as sensitive in PLWH with extremely low CD4 counts and therefore these patients in addition to those with past history of intravenous drug use, abnormal liver function test and thrombocytopenia, should undergo HCV RNA testing.[86] The rate of reinfection is high even after successful HCV for some patient populations should still be screened continuously and monitored closely despite successful treatment.[86] Infection with HCV increases the risk of liver cirrhosis and fibrosis[88]; however, compared to PLWH who are not on ART, PLWH on ART have demonstrated decreased rates of progression to cirrhosis. There is a strong correlational relationship between low CD4 cell counts (<200 cells/dl), presence of cirrhosis, and cumulative HIV viremia and increased risk of HCC.[89-91] It is important to note that persistent HIV viremia is significant only in the cirrhotic population and that correction of cirrhosis with ART treatment does not increase the risk of HCC.[91]

Table 8. Treatment Options for Anal Dysplasia[101-102]

Biopsy Findings	Treatment Options
Low-grade lesions (AIN 1)	▪ Monitor via HRA every 6 months until normal twice in succession, then annual Pap smear. ▪ Topical treatment (see below) may be indicated for symptoms such as bleeding, itching, or burning; or for discrete lesions.
High-grade lesions (AIN 2 or 3)	**Topical therapy** For small lesions (<1 cm^2 at the base): Local application of bichloroacetic acid or 80-90% trichloroacetic acid (well-tolerated but occasionally painful) ▪ Liquid nitrogen ▪ Other topical, self-applied options studied in small cohorts include: ▪ Topical imiquimod applied for 6-10 hours then washed off, TIW for 16 weeks ▪ Topical 5% 5-fluorouracil applied BID for 16 weeks *These sometimes are used to treat diffuse lesions* **Infrared coagulation (office based)** ▪ For lesions too large for topical therapy ▪ Followed by debridement of destroyed tissue using biopsy forceps *Note: this treatment is not yet FDA approved* **Surgery and CO2 laser ablation** ▪ For large (>1 cm^2) or extensive lesions, or for patients unable to receive infrared coagulation ▪ Surgical excision with a scalpel for discrete lesions with or without laser ablation ▪ Large lesions may require multiple, staged procedures to reduce risk of bleeding, anal stenosis, sphincter compromise, and infection ▪ Referrals should be made to surgical centers with experience in treating anal dysplasia *Follow-up HRA should be done every 6 months*

A study found a 37% mortality reduction in PLWH who are co-infected with HBV by screening with serum alpha-fetoprotein (AFP) and biennial liver ultrasonography.[80] Most patients with HCC will require surgical resection and a liver transplantation. Several recent reports from Europe have raised concern that there may be an increased risk of HCC or more diffuse HCC recurrence after successful treatment with direct-acting antiviral (DAA) therapy. In these studies, a higher rate of recurrence or more diffuse HCC was observed in HCV patients who were cured than the rate expected in untreated control patients.[93] In this study, positive outcomes were identified in PLWH who underwent liver transplant with effective short term treatment for the HCV/HIV co-infection.[93] A largely accepted surveillance method for high risk patients is to obtain liver ultrasound every 6 months and to follow up any abnormalities with a four-phase multidetector computed tomography or a dynamic contrast-enhanced magnetic resonance imagining.[95]

The incidence of **cervical cancer** is higher in women living with HIV than the general population of women by 26 per 100,000 vs. 8 per 100,000, respectively, and women living with HIV have a higher incidence of precancerous cervical lesions like low-grade squamous intraepithelial lesion and high-grade squamous intraepithelial lesion (HSIL).[7,96-98] Additionally, women living with HIV have a higher recurrence rate from cervical HSIL post treatment. The USPSTF recommends that women living with HIV have a cervical Pap test every 6 months during the first year of diagnosis and annually following normal results.[7] An abnormal result needs further workup with colposcopy and visual inspection with acetic acid (VIA). Treatment with cryotherapy, laser or loop electrosurgical procedure (LEEP) should be followed up in these patients. Women on ART have the following benefits: lower risk of precancerous lesions, regression of previously identified precancerous lesions, decreased recurrence, and increased clearance of HPV.[96-98] However, rates of screening among women living with HIV is suboptimal with identification as African American, drinking, increased number of cigarettes smoked per day, smoking risk perception, and younger age were related to Pap smear screening non-adherence in one study.[99] The American College of Obstetricians and Gynecologists (ACOG) recently updated the practice guidelines for cervical cancer

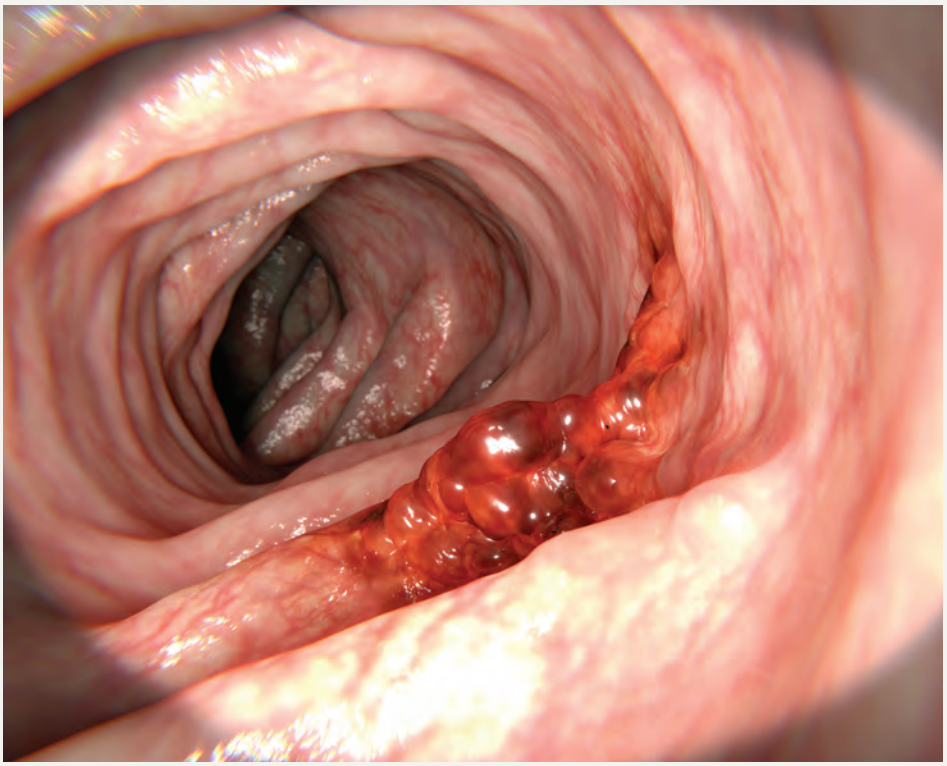


Above: Lung Cancer Desmoplasia
As shown here, lung cancer is associated with a vast stromal desmoplastic reaction (the "neighborhood") in which the connective tissue, associated with the tumor, thickens similarly to scars. Cancer is in red; cell nuclei in cyan; stroma/desmoplasia in green; and an active stroma-specific marker in purple.
National Cancer Institute \ Fox Chase Cancer Center (April 11, 2016) https://visualsonline.cancer.gov/details.cfm?imageid=10576

screening and prevention (Table 7). Women living with HIV younger than 30 years can undergo cytology testing once every 3 years instead of annually if they have had three consecutive normal annual cytology tests. ACOG recommends against co-testing for women younger than 30 years. Women with HIV who are aged 30 years or older can undergo either testing with cytology alone or cotesting. Patients with three consecutive normal annual cytology tests can then be screened annually, and those with one normal cotest result can also be screened annually.[98] The Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents recommend to: (a) commence screening patients if younger than age 21, known to be HIV-infected or newly diagnosed with HIV, and sexually active, within 1 year of onset of sexual activity regardless of mode of HIV infection, (b) conduct Pap test on HIV-infected women aged 21–29 following initial diagnosis of HIV for women who are 21 to 29, (c) if initial baseline Pap test Is negative then it should be repeated in 12 months, (d) if results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years and (e) co-testing (Pap test and HPV test) is not recommended for women younger than 30.[99]

Anal cancer incidence is higher among PLWH than the general population, especially higher in men who have sex with men (MSM). Incident rate is 46/100,000 in MSM.[101] In women, the rate of anal cancer is also increased due to HPV infection compared to non-HIV women.[101,102] HPV infection, especially serotype 16, in PLWH and severe immunosuppression is the most important risk factor for HSIL and anal cancer. Although there are no national guidelines for anal cancer screening, the New York State Department of Health AIDS institute recommends an annual digital anorectal exam (DARE) with additional screening for patients at high risk such as MSM, those with a previous history of anogenital condylomas, and women with abnormal cervical or vulvar histology.[102] Anal Pap and HPV testing are used, followed by high resolution anoscopy (HRA) if the anal Pap test is abnormal. Treatment options for management of anal dysplasia are outlined in Table 8.

Colorectal cancer (CRC) is the third most common type of cancer in men and second most common type in women world-wide.[102] A cohort study indicated that PLWH develop CRC at a lower median age in comparison to the general population. Interestingly, they also have a higher incidence of right-sided cancer than the general population.[104] The



Above: Intestinal tumor

USPSTF recommends CRC screening with a high-sensitivity Fecal Occult Blood Test (FOBT) every year, sigmoidoscopy every 5 years with FOBT every 3 years or colonoscopy every 10 years, for patients age 50-75.[105]

Incidental cancer that is not associated with HIV infection needs to be evaluated and screened for in HIV patient populations. Cancers such as breast, prostate and colon should be screened same as the general population guidelines since HIV patients are at higher risk of developing cancer.[106].

Conclusion

Moving forward, a comprehensive schema for HIV-associated malignancies should now be possible just as it has been for HIV, and updated agendas should replace old fashioned ones. The trend to differentiate ADM and NADM predates the modern ART era and based on this review, is clearly losing its scientific relevance. This concept is archaic and needs to be discarded when conducting any epidemiological study which focuses on malignancies among PLWH. Instead, the spotlight of research should be individual malignancies or, when necessary, classifying and defining these malignancies by the biologic and oncogenetic processes which initiate and drive them. In the search for optimal treatment strategies, molecular studies should be implemented to identify specific subset populations, as is typically done in non-HIV associated malignancies. The amelioration of cancer screening and prevention strategies for populations of PLWH is of valuable importance. Focusing all these efforts in areas of the world that's most affected by HIV-related malignancies can provide valuable knowledge and information which can lead to scientific and medical progress. The culmination of these endeavors will be a world in which PLWH with malignancies can benefit fully and safely from ART and chemotherapy and live longer healthy lives. ❖

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Diagnosing/Assessing Neurocognitive Issues in Adults Living with HIV

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INTRODUCTION

Neurocognitive impairment (NCI) is one of the most common sequelae of HIV-1 and is considered one of the most feared symptoms of HIV among patients.[1] Unlike other neurodegenerative diseases (eg, Alzheimer's and Parkinson's disease), the course of HIV-associated NCI can fluctuate and improve depending on disease and other non-HIV factors.[2] Typical symptoms of NCI include: mild memory problems, slowed thinking, concentration/attention problems, planning difficulties, and difficulties with multitasking.[1] Mild impairment is most common in HIV, even among those people living with HIV (PLWH) who have well-controlled viremia.[1,2] Prevalence of mild NCI ranges from 22%-70% depending on the population sampled and diagnostic criteria used.[2-5] Prevalence of severe NCI (HIV-associated dementia) is much lower, ranging from 2%-9%.[2-5] Compared to younger PLWH, those 50 years of age and over have been shown to have higher rates of NCI and be at greater risk for developing it.[6] Rates of non-HIV-associated NCI are also high among PLWH, ranging in prevalence from 7%-33%.[4,7]

Among PLWH, having even mild or asymptomatic NCI has been associated with an increased risk for developing more severe NCI and mortality.[8] Research has also established a strong relationship between NCI and worse ART adherence,[9-12] further jeopardizing positive health outcomes. NCI among PLWH is also associated with work difficulties, impaired activities of daily living, (eg, planning, driving, finance management), worse overall quality of life, and need for more social services.[13-17] Neurocognitive deficits have been associated with poor decision-making and greater HIV transmission risk behaviors (eg, unprotected sex).[18,19]

HIV and the Brain

HIV has an affinity for and invades the central nervous system (CNS) soon after infection, as it is able to cross the blood brain barrier.[20,21] Once in the CNS it infects and depletes specific immune cells, including CD4 lymphocytes and macrophages, contributing to initial CNS damage.[22] Subsequent to infecting CNS immune cells, proinflammatory cytokines and chemokines are upregulated in the CNS and peripheral nervous system (PNS) which contribute to various diffuse and focal neuropathological changes.[23]

These neuropathological changes correlate with diffuse neuroanatomical deficits, such as HIV encephalitis, leukoencephalopathy, diffuse poliodystrophy, and vacuolar myelopathy. Focal neuroanatomical changes also occur in the temporal and frontostriatal regions (eg, hippocampus and basal ganglia).[24,25] HIV infection appears to be associated with a 50-90% reduction of neurons in the hippocampus and basal ganglia.[25] Studies have also found an overall 40% decrease in brain density in frontal and temporal regions.[26,27] These neuropathological and neuroanatomical changes are thought to cause neurocognitive impairment.[23] Impaired processing

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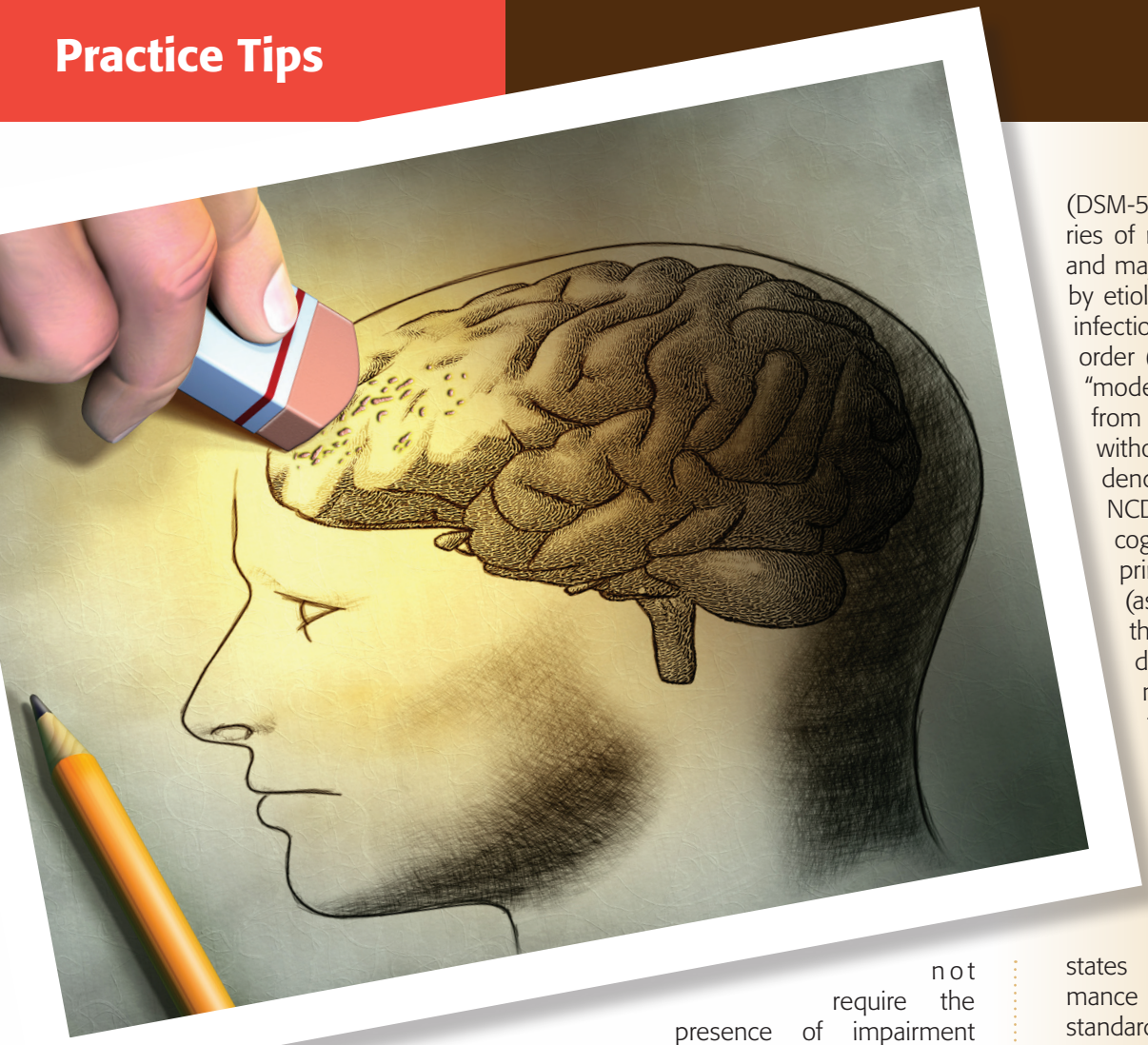

speed, learning, memory, motor ability, executive functioning, and attention/working memory are the hallmark neurocognitive domains affected by HIV.[2]

HIV-associated neurocognitive disorder (HAND), the nomenclature used to diagnose NCI in PLWH, typically uses the "Frascati criteria" to classify individuals for research purposes. Increasing in severity are: Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV-associated Dementia (HAD).[28] Both ANI and MND are defined by impaired performance in at least two neurocognitive domains (eg, attention/working memory, learning, memory, processing speed, motor abilities, and executive functions) falling a minimum of one standard deviation below the mean of demographically corrected (eg, age, education) norms. ANI does not require the presence of impairment in everyday functional abilities (eg, work, home life, social functioning), nor does it require any patient report of neurocognitive problems. MND, however, requires at least mild impairment in daily functioning and neurocognitive difficulties as described by self-report or as observed by knowledgeable collateral sources. HAD is characterized by moderate to severe neurocognitive decline in two or more neurocognitive domains as evidenced by at least a two standard deviation disparity between the patient's scores and demographically adjusted norms. HAD is also defined by the presence of marked interference in everyday functional abilities. To diagnose HAND, clinicians must establish that the observed NCI and functional decline are not due to a comorbid condition (eg, substance use, psychosis, etc) or delirium.

Unlike the Frascati criteria for research, the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5), provides only two categories of neurocognitive disorder: mild and major, which are further defined by etiological subtype, including HIV infection.[29] Mild neurocognitive disorder (NCD) due to HIV requires a "modest" neurocognitive decline from a prior level of functioning without interfering with independence of functional abilities. Mild NCD due to HIV involves neurocognitive decline in one or more primary neurocognitive domains (as opposed to two domains in the Frascati criteria). Major NCD due to HIV requires significant neurocognitive decline and interference in independence of everyday functional abilities. Major NCD due to HIV also only requires neurocognitive decline in at least one domain. Although not explicitly stated in the diagnostic criteria, the DSM-5 states that neurocognitive performance should be below one to two standard deviations in mild NCD and two standard deviations below the mean in major NCD. Finally, DSM-5 criteria for NCD due to HIV requires that the NCD not be better explained by delirium or non-HIV conditions (eg, neurological, medical, psychiatric, and substance use).

The International Classification of Diseases, 10th revision (ICD-10) Classification of Mental and Behavioural Disorders,[30] also has categories for Dementia in HIV disease, and Mild NCD (due to HIV), though it does not require formal neuropsychological testing to determine either diagnosis. The ICD-10 describes the main feature of Mild neurocognitive disorder as a decline in cognitive ability, such as memory, learning and/or concentration. To diagnose dementia in HIV disease, the general ICD-10 criteria for dementia must be met.

Although the Frascati criteria are considered the gold standard for diagnosing HAND, some debate exists

as to whether the one standard deviation cutoff to define impairment in ANI and MND is appropriate, and if using a cut-off of 1.5 standard deviations might provide more accurate diagnoses (ie Gisslén criteria).[31] Hence, prevalence rates of HAND vary depending on the specific classification and cut-off scores used. In a large sample of HIV-infected adults Heaton et al[4] found the following HAND prevalence rates according to Frascati criteria: 32.7% for ANI, 11.7% for MND, and 2.7% for HAD. However, in another study using a cut-off of 1.5 standard deviations, prevalence rates of 4% and 1% of ANI and MND were observed, respectively.[31] A very recent study comparing the Frascati, Gisslén, and DSM-5 criteria to diagnose HAND found the highest rates of HAND using DSM-5 criteria followed by the Frascati criteria; the Gisslén criteria yielded the lowest rates.[32]

Making a HAND Diagnosis: Assessment and Screening Tools

Regardless of the specific criteria used, to make a HAND diagnosis the clinician must observe or formally assess domains of neurocognitive functioning known to be sensitive to HIV infection (eg, processing speed, learning and memory, motor skills, executive functioning, and attention/working memory). Ideally, neurocognitive domains would be assessed via a comprehensive neuropsychological/neurocognitive evaluation using demographically corrected normative data and conducted by a neuropsychologist or clinical psychologist. However, formal HAND criteria do permit use of shorter screening measures and increased reliance on clinical judgment.

Two commonly used, reliable, and valid approaches to diagnose HAND using a comprehensive neurocognitive test battery include: the global deficit approach and clinical ratings approach.[33,34] After completing a test battery, raw scores are converted to demographically adjusted ***T***-scores, with a mean of 50 and standard deviation of 10 (a ***T***-score of 40 would indicate performance one standard deviation below the mean). Both approaches

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require review of the ***T***-scores across at least seven domains of neurocognitive functioning: speed of information processing, attention/working memory, executive functions, learning, memory, verbal fluency, and motor skills. The clinical ratings approach requires clinicians to convert the ***T***-scores from each individual test to a "clinical rating" based on the following algorithm:

Clinical Ratings *T*-scores [35]	
≥55=1	54-45=2
44-40=3	39-35=5
34-30=6	29-25=7
24-20=8	≤19=9 [35]

A clinical rating of 4 is typically assigned in neurocognitive domains where performance on one measure receives a clinical rating between 1 and 3 and another measure from the same domain receives a clinical rating of 5. Finally, a global clinical rating is typically assigned according to the most impaired domain (See Heaton et al [1994] for complete procedures). The global deficit approach is similar to the clinical rating approach, but with the following different score ranges:

Global Deficit *T*-score [33]	
≥40=0	35-39=1
34-30=2	29-25=3
24-20=4	≤19=5

The global deficit score is assigned based on the average ***T***-scores across all neurocognitive tests included in the battery.

According to Frascati HAND criteria, when formal neurocognitive testing is not available (eg, in resource-limited settings) shorter neurocognitive screening measures may be used to make a diagnosis.[28] These screening tools should assess the same neurocognitive domains as the longer batteries described above (eg, information processing, attention/working memory, executive functions, learning, memory, verbal fluency, and motor skills). Antinori et al[28] recommends using: the Folstein Mini-Mental Status Examination,[36] the HIV Dementia Scale (HDS),[37] the International HIV Dementia Scale,[38] or the Mattis Dementia Rating Scale.[39] However, a recent systematic review found that these screening tests were less accurate at detecting the more common milder impairments and suggested that screening tools incorporate either a short neurocognitive battery of tests (ie, two to four individual measures) and/or a computerized neurocognitive screening battery to detect all forms of HAND.[40] A few studies have provided evidence that the Montreal Cognitive Assessment (MoCA) has moderate ability to detect HAND.[41-43] Newer screening tools administerable on mobile devices by a wide range of personnel may soon be available.[44]

Another recent review of screening tools for HAND[45] concluded that currently available screening tools alone may not be sufficient to detect impairment, decline, or improvement of neurocognitive functioning in PLWH. Kamminga et al[45] suggest that screening tools be used in conjunction with the patient clinical history including relevant neuropsychiatric factors and current mood to determine if a formal neurocognitive evaluation is warranted. Finally, these researchers caution that future research is required to validate these tools with non-United States populations.

Characterizing the presence or absence of declines in everyday functioning allows clinicians to differentiate ANI, MND, and HAD. In addition to neurocognitive testing using a comprehensive battery or short screening measure, clinicians should use an independent measure of activities of daily living.[40] Although there is currently no gold standard measure of everyday functioning, this area is often assessed by using self-report questionnaires (eg, Lawton & Brody's modified Activities of Daily Living scale, the Patient's Assessment of Own Functioning) and patient/caregiver reports.[46,47] Given the high prevalence rates of depression observed among PLWH,[48] and that individuals with depression can report neurocognitive symptoms (eg, memory disturbances and concentration difficulties), it is commonly recommended that psychiatric symptomatology be assessed during any formal, comprehensive neuropsychological evaluation or in conjunction with screening tools.

Diagnosing HIV infection in its early stages, prescribing antiretroviral regimens that fully suppress viral load, helping patients optimize strategies for adhering to life-long medication regimens, and effectively managing co-morbidities that contribute to NCI are the most effective approaches to reducing the incidence of NCD and exploring whether improvement of a given patient's HIV-related NCD is possible. Helping patients manage NCIs that occur and/or do not improve despite these measures is an important component of HIV care and treatment. ❖

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Update


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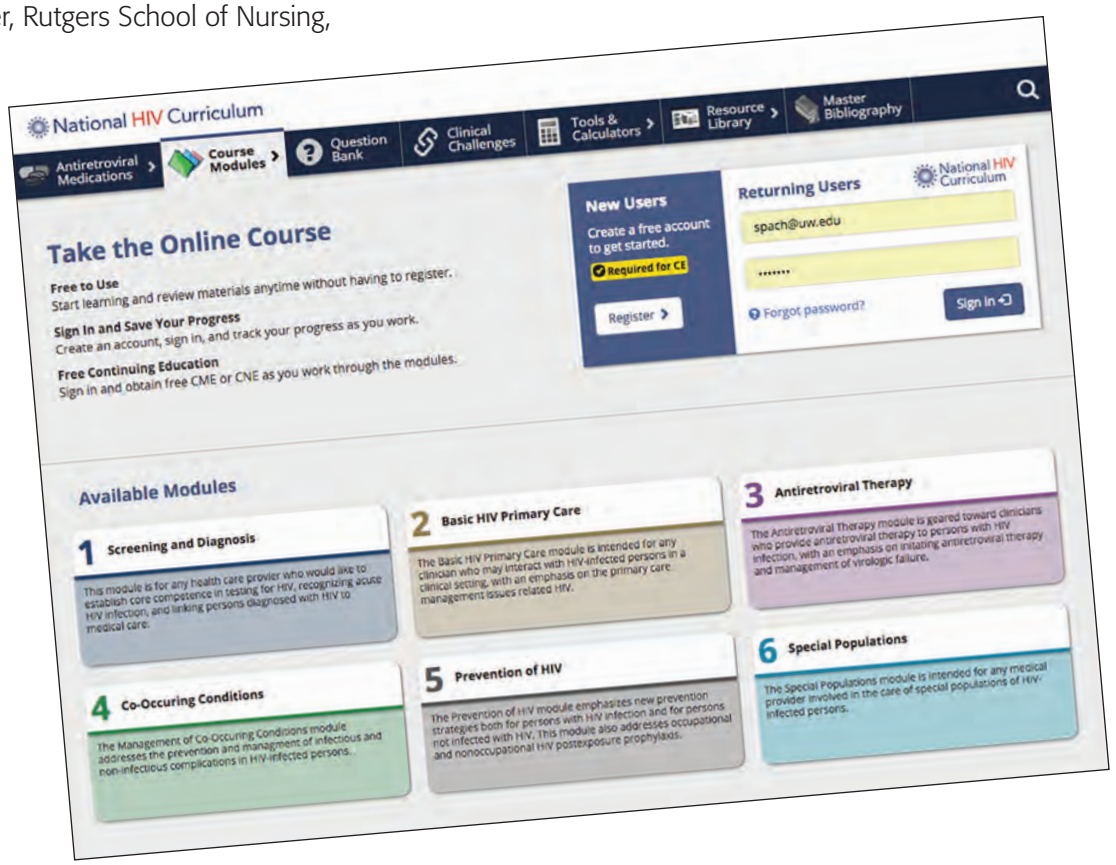

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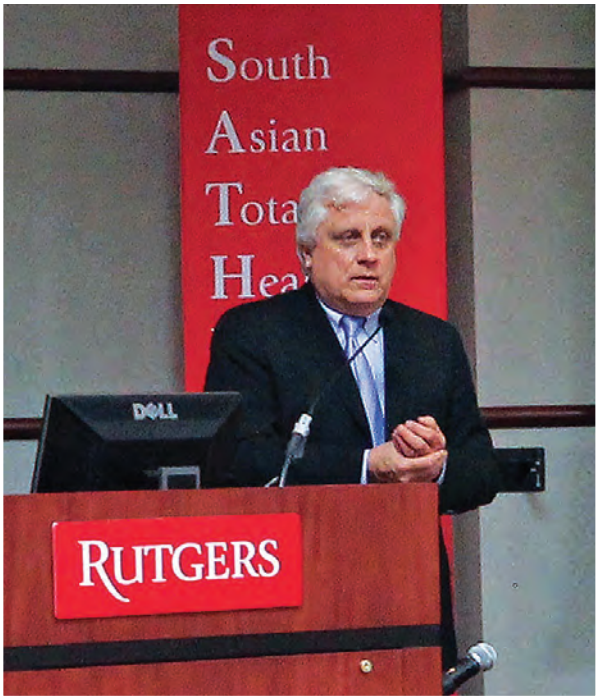
From left to right: Dr. M. Carolyn Daniels presents Dr. Sunanda Gaur, Dr. Sneha Jacob, Bishakha Ghoshal, Christina Varghese, Shailja Mathur, and Vanessa Rios with a proclamation from Governor Chris Christie in observance of Minority Health Month.

Global Crossroads Seminar



Above: Dr. Richard Marlink welcomes the conference attendees and discusses the new Global Health Institute at Rutgers.

Author: Bishakha Ghoshal

April 4, 2017

The Global Crossroads Seminar Series was established in 2013. The seminars probe the socio-cultural and environmental determinants of health in the global South Asian community. This year's seminar was entitled "Breaking Barriers: Promoting HIV Awareness in the South Asian Community". The main objectives of the program were to address HIV awareness in the South Asian community, complexities of reaching this population, and prevention programs offered by the New Jersey Department of Health (NJDOH). In addition to learning the importance of HIV testing, the participants learned about the best practices for outreach and advocacy tailored to South Asian LGBT and other South Asian at-risk populations to engage in HIV prevention practices, care and treatment. Nearly 100 people of multidisciplinary backgrounds attended the event.

The welcome address were given by:

- Sunanda Gaur, MD (Director, South Asian Total health Initiative [SATHI])
- Richard Marlink, MD (Rutgers Professor of Global Health, Director of Global Health Institute at Rutgers Biomedical and Health Sciences [RBHS], RBHS Chancellor)
- M. Carolyn Daniels, MED, DHSc (Executive Director, NJ, Office of Minority and Multicultural Health Trenton, NJ)

An overview of programs provided by the NJDOH was discussed by Steven Saunders, MS (Director, HIV Prevention and Education NJDOH-Division of HIV, STD and TB Services, Trenton, NJ). A lecture on HIV epidemic and the South Asian American community was given by Dr. Sneha Jacob, Director HIV Clinical Services, and Rutgers Eric B. Chandler Health Center, New Brunswick, NJ. Dr. Jacob also shared data from a study that was conducted at Rutgers Robert Wood Johnson Medical School to assess attitudes and knowledge surrounding HIV among South Asians living in NJ.

Mr. Haran Vijaynathan (Executive Director, Alliance for South Asian AIDS Prevention [ASAAP], Toronto, Canada) explained about outreach and advocacy in the South Asian community.

One of the highlights of the event was the panel discussion. Three individuals of South Asian origin infected/affected with HIV presented their experiences.

This conference was one of the first in the US on this topic and we hope will serve as a starting point to catalyze further work that urgently needs to be done in this community. ❖

New Jersey HIVLinks Summer 2017
HIV, STD, and TB news and information for health professionals

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HIV Case Study Day and Perinatal Update
Tuesday, September 26, 2017 ◆ RWJ Clinical Academic Building (CAB) Conference Center

28th Annual HIV Medical Update
Wednesday, December 6, 2017 ◆ Crowne Plaza, Cherry Hill

For more information contact: Michelle Thompson at ccthomps@sn.rutgers.edu or (973) 972-1293.

NJDOH-DHSTS The New Jersey AIDS Drug Distribution Program (ADDP) and Social Media for Agencies, Centers and Academic Institutions http://hpcpsdi.rutgers.edu/training/main.php

HIV/AIDS Training & Information Resources

New Jersey Department of Health–Division of HIV, STD, and TB Services (NJDOH-DHSTS) (609) 984-5874 ▪ www.state.nj.us/health/aids

- NJ HIV/AIDS statistical reports, regulations, forms, and links to HIV care, prevention programs, and training
- New Jersey rapid testing site: www.state.nj.us/health/aids/rapidtesting
- New Jersey AIDS/STD Hotline: (800) 624-2377

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- HIV/AIDS MEDICAL UPDATE SERIES: with funding from NJDHSS
- Free on-site HIV medical education for healthcare sites. **Contact** Michelle Thompson at (973) 972-1293 or ccthomps@sn.rutgers.edu

AIDS Education and Training Center (AETC) Program

- National Coordinating Resource Center: www.aidsetc.org
- Northeast/Caribbean AETC: necaaetc.org
- National Clinician Consultation Center: http://www.nccc.ucsf.edu/
  HIV Warmline: (800) 933-3413
  Post-Exposure Prophylaxis Hotline/PEPline: (888) 448-4911
  Perinatal HIV Hotline: (888) 448-8765
  Pre-Exposure Prophylaxis Hotline (PrEPline): 888-HIV-PREP
  Substance Use Warmline: (855) 300-3595

AIDSinfo: a service of the US Department of Health and Human Services, offers access to the latest, federally approved HIV/AIDS medical practice guidelines, HIV treatment and prevention clinical trials, and other research information. http://www.aidsinfo.nih.gov/

US National Institutes of Health: a registry and results database of publicly and privately supported clinical studies conducted around the world. http://clinicaltrials.gov

US Centers for Disease Control and Prevention (CDC): http://www.cdc.gov/hiv/default.html

Health Resources and Services Administration (HRSA): http://www.hrsa.gov

FDA MedWatch: (800) FDA-1088; Subscribe to **e-bulletin:** www.fda.gov/medwatch/elist.htm

National Quality Center: no-cost, technical assistance for Ryan White funded grantees to improve the quality of HIV care nationwide. www.nationalqualitycenter.org

TARGET Center: technical assistance and training resources for the Ryan White HIV/AIDS Program community. www.careacttarget.org

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