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Effect of AIDS on Women Who Have Sex-Determined Health Issues

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Worldwide, women account for a growing percentage of human immunodeficiency virus (HIV)–infected patients and more than half of all HIV infections. For many years, morphologic imaging methods were the main approaches employed to investigate HIV and its complications. However, during the past decade, advancements in PET and SPECT imaging technologies opened new possibilities for improved understanding of the pathophysiological processes in HIV. Diagnosis of early HIV-associated neurocognitive disorders (HAND) is important, as many of its symptoms can be caused by other conditions common to people with HIV/AIDS. Presently, there are no PET and SPECT tracers or combination of markers for HAND, hence novel HAND-specific tracers are needed if nuclear medicine is to play a role in solving the problem of the HAND "epidemic." As both highly active antiretroviral therapy (HAART)–induced lipoatrophy and cardiovascular diseases are characterized by ongoing inflammation, FDG-PET/CT imaging may represent an important imaging technique for better understanding the metabolic risk in HIV-infected women on HAART. HIV-infected women are at increased risk for the development of human papilloma virus–associated neoplasms such as cervical and anal carcinomas; these aggressive tumors could be treated better with integration of FDG-PET as part of the standard pretreatment workup. A similar value of FDG-PET may be realized in women with HIV-associated Kaposi sarcoma, as they have more extensive cutaneous disease than men do. In the era of HAART, the incidence and local invasiveness of breast cancer may change, thus creating a need to redefine the pathophysiology of breast cancer in HIV-positive women. Finally, mammary tuberculosis, occasionally the presenting symptom in HIV-infected women, may present with nonspecific clinical, radiological, and histologic findings. In these women, FDG-PET can be of value to detect the lesion for a representative biopsy, staging to exclude pulmonary and other extrapulmonary lesions, and also for therapy monitoring.
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Introduction

After more than 30 years since the discovery of human immunodeficiency virus (HIV), women continue to endure the most owing to the epidemic than men. Furthermore, young women are infected almost 10 years earlier compared with their male counterparts. Epidemiologic evidence suggests unacceptably high HIV prevalence and incidence rates among women,[1,2] with more than half of the 33 million people living with HIV worldwide being women.[3] This number increases to 60% in sub-Saharan Africa, where young women under the age of 24 years are 2-4 times more likely to become infected with HIV than their male peers are.[3] It is reported that every minute, a young woman becomes infected with HIV.[4] The disproportionate effect of the HIV epidemic on women can be attributable to several factors including biological, social, behavioral, cultural, economic, and structural.[2]

Some of the sex-specific differences in people living with HIV are conditions such as HIV-associated neurocognitive

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disorders (HAND), lipodystrophy, cardiovascular disease (CVD), and human papilloma virus (HPV)–related cervical and anal cancers.

Being an HIV-positive woman is an identifiable risk factor for HAND, with older HIV-positive women appearing to be more likely to show neurocognitive progression. While in lipodystrophy; lipoatrophy, which affects both peripheral and central sites, predominates in HIV-infected women and has been previously linked to insulin resistance and cardiovascular risk.[5,6] HIV-infected women are at significantly higher risk for CVD in association with abnormal fat distribution; more noncalcified, potentially vulnerable plaque; and increased immune activation.[7-9]

Women with HIV infection have an increased risk of developing certain malignancies. These malignancies are commonly HPV related, reflecting the high rate of coinfection with HPV in women with underlying HIV infection.[10] In this regard, both cervical and anal cancers stand out. HIV-associated Kaposi sarcoma (KS) and breast cancer still remain a focus of future research particularly among women.

Tuberculosis (TB) of the breast is a rare disease with nonspecific manifestations. It should be included in the differential diagnosis of breast lesions in HIV-infected women especially in TB endemic areas.

Globally, one of the significant challenges to the success of achieving universal access to HIV prevention, treatment, care, and support is the optimization of imaging HIV. In this regard, nuclear medicine with both PET and SPECT is an integral part of imaging. More recent developments rely on PET with FDG, based on increased (though nonspecific) accumulation of this agent at sites of abnormally enhanced metabolism (such as tumors or infection).

HIV-Associated Neurocognitive Disorders

HIV is a neurotropic virus that directly invades the brain shortly after infection. HIV replicates in brain macrophages and microglia, causing inflammatory and neurotoxic host responses. HIV may cause neurologic sequelae such as HAND with some of the identifiable risk factors including female sex, high HIV viral set point, and lower CD4 cell counts.[11] HAND (formerly known as AIDS dementia complex) remains among the most common clinical disorders encountered in people infected with HIV despite widespread use of antiretroviral therapy. HAND encompasses a hierarchy of progressively more severe patterns of central nervous system (CNS) involvement, ranging from asymptomatic neurocognitive impairment to minor neurocognitive disorder, to the most severe HIV-associated dementia.[12]

HAND can develop at almost any stage of HIV infection, although it is more common as immunosuppression advances. Importantly, female sex and age appear to be predictive of neurologic progression.[13]

Since the introduction of highly active antiretroviral therapy (HAART), the incidence of moderate or severe dementia has fallen from approximately 7% in 1989 to only 1% in 2000, and the severity of neurologic disease appears to have been attenuated.[14] Despite this remarkable effect on incidence rates, the prevalence of HAND continues at very high rates. For example, in 1 cohort (CNS HIV Antiretroviral Therapy Effects Research), 53% of the total sample had neurocognitive impairment, with increasing rates in those with more comorbid illnesses.[15] Prevalence estimates were 33% for asymptomatic neurocognitive impairment, 12% for minor neurocognitive disorder, and 2% for HIV-associated dementia. In fact, the recent review on the subject calls HAND "a hidden epidemic."[16] The persistence of this high risk for HAND in individuals experiencing effective control of systemic HIV viral load is incompletely explained, and suggested factors include effects of aging on brain vulnerability, persistence of HIV replication in brain macrophages, evolution of highly neurovirulent CNS HIV strains, and even long-term CNS toxicity of ART.[15,17] Recently, Maki et al[18] demonstrated that verbal episodic memory deficits are evident in HIV-positive women and may be associated with hippocampal dysfunction at both encoding and retrieval.

A variety of PET agents such as FDG, ^{11}C-PiB, and [^{11}C]-R-PK11195 as well as SPECT agents ^{99m}Tc-hexamethylpropyleneamineoxime, ^{123}I-FP-CIT, and ^{123}I-iodobenzamide have been investigated for the diagnosis of HAND, for distinguishing between demented and nondemented HIV-infected patients, for differentiation between HAND and non–HIV-related dementia, as well as for assessing the influence of coinfection with the other viral pathogens on the brain functionality.[19] In spite of some encouraging results, none of these tracers are specific for HIV disease (Fig. 1). Obviously, novel HAND-specific tracers are needed if nuclear medicine is to play a role in solving the problem of the HAND "epidemic." Another possible and no less important application of nuclear medicine methodologies to neuro-HIV is actually eliminating the HIV-infected cells in the CNS that are causing HAND. This approach will help to address evolving factors in HAND pathogenesis, which may include persistent inflammation associated with HIV replication. Our laboratories have been developing radioimmunotherapy targeting viral gp41 antigen on the infected cells as a backbone for HIV cure.[20,21] Recently, we also demonstrated that the same radiolabeled antibody to gp41 was capable of penetrating the in vitro human blood-brain barrier and specifically killing HIV-infected peripheral blood mononuclear cells and monocytes behind the barrier.[22] We are now working toward moving this promising strategy into clinical trials in HIV-infected patients.

Cardiovascular Disease

CVD is increased approximately 2-fold in HIV infection,[23] and recently few studies have shown that the relative increases in myocardial infarction rates are higher in HIV-infected vs non–HIV-infected women than in HIV-infected vs non–HIV-infected men.[7,8] HIV-infected women demonstrate significantly increased risk factors for CVD in association with abnormal fat distribution, as elaborated in the lipodystrophy section.