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Neuroimaging of HIV Associated Neurocognitive Disorders (HAND)

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Abstract

Purpose of review—HIV enters the brain after initial infection, and with time can lead to HIV associated neurocognitive disorders (HAND). While the introduction of combination antiretroviral therapy (cART) has reduced the more severe forms of HAND, milder forms are still highly prevalent. The "gold standard" for HAND diagnosis remains detailed neuropsychological performance (NP) testing but additional biomarkers (including neuroimaging) may assist in early detection of HAND.

Recent findings—We review the application of recently developed non-invasive magnetic resonance imaging (MRI) and positron emission tomography (PET) techniques in HIV+ individuals. In particular, magnetic resonance spectroscopy (MRS) may be more sensitive than conventional MRI alone in detecting HIV associated changes. Diffusion tensor imaging (DTI) has become increasingly popular for assessing changes in white matter structural integrity due to HIV. Both functional MRI and PET have been limitedly performed but could provide keys for characterizing neuropathophysiologic changes due to HIV.

Summary—It is hoped that continued progress will allow novel neuroimaging methods to be included in future HAND management guidelines.

Keywords

HIV; neuroimaging; positron emission tomography; volumetrics; diffusion tensor imaging; functional MRI

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Introduction

More than one million individuals in the United States and over forty million people worldwide are infected with the human immunodeficiency virus (HIV). Combination antiretroviral treatment (cART) has transformed HIV from a rapidly fatal disease to a more manageable chronic condition [1–3]. As a result, HIV-infected (HIV+) individuals receiving cART have almost as long a lifespan as HIV-uninfected (HIV−) individuals [4]. A majority of HIV+ patients will be greater than 50 years old by 2015 [5].

Despite these advances, HIV cannot be eradicated from the brain with persistent reservoirs often remaining [6]*. The continued presence of HAND despite cART could result from non-mutually-exclusive factors including irreversible injury prior to initiating cART, persistent HIV-1 RNA in the brain [7], antiretroviral treatment toxicities [8–10], and/or persistent low level inflammation [11]. Currently, the diagnosis of HAND requires neuropsychological performance (NP) testing and self-reported assessment of activities of daily living with the following classifications used: neuropsychologically normal, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), or HIV associated dementia (HAD) [12]. Compared to other neurodegenerative disorders (e.g. Alzheimer's disease (AD)), additional biomarkers have yet to be added to HAND research criteria.

Neuroimaging could have increased utility in the diagnosis and management of HAND. A variety of novel neuroimaging techniques have been developed and are currently performed in the research setting. Of note, magnetic resonance imaging (MRI) techniques (including magnetic resonance spectroscopy (MRS), volumetrics, diffusion tensor imaging (DTI), and functional) and positron emission tomography (PET) have been utilized in HIV+ individuals. This review is not meant to be comprehensive. Instead, it briefly discusses recent results using some of these neuroimaging methods.

Magnetic resonance spectroscopy (MRS)

The most common neuroimaging method for studying neuroHIV in the pre and post cART eras has been MRS [13–16]. MRS detects the signal produced by protons of specific molecules within a volume of brain. Molecules that are typically measured include: 1) n-acetyl aspartate (NAA)- a neuronal marker, 2) choline (Cho)- a marker of cellular proliferation and inflammatory response, 3) creatine (Cr)- a measure of brain energy metabolism and reference marker, and 4) myo-inositol (MI)- a marker of gliosis. MRS can provide key insights into longitudinal changes in brain metabolites as an individual progresses from primary (≤ 1 year since seroconversion) to chronic (> 1 year since seroconversion) infection. Soon after seroconversion, MRS metabolites are affected [14,17–19] with observed neuroimaging changes correlating with inflammation [17] and neuronal injury [19]. Changes seen due to HIV are often observed within both subcortical (basal ganglia) and cortical (frontal grey/white matter and parietal grey matter) compared to HIV− controls. HIV+ patients with chronic infection have reduced NAA and concomitant increased Cho and MI [15,20–23]. MRS metabolite changes in chronically infected HIV+

patients vary according to HAND status with HAD patients showing the greatest changes [15,21].

cART can lead to significant improvements, but not normalization of MRS metabolite levels [23–25]. Early treatment with cART may be neuroprotective and mitigate some of the changes seen soon after seroconversion. However, certain anti-retrovirals may cause mitochondrial toxicity and impair neuronal function [9,26].

HIV+ patients are living longer and growing older due to cART. A number of MRS studies have therefore investigated the interaction between HIV and aging [27]. HIV+ patients have significant changes in brain metabolites with levels measured equivalent to those seen in HIV− controls at least 10–15 years older [28]. In general, no interaction has been observed between HIV and aging [2].

Overall, MRS changes may be more sensitive than conventional MRI alone in detecting changes associated with HIV. MRS could augment current neuroimaging protocols but local implementation of sequences is required. In the future, MRS could be used to evaluate the efficacy of certain therapeutics. However, most MRS studies have been cross-sectional and have primarily focused on specific regions of interest. Additional longitudinal studies that focus on HIV+ patients as they transition across different disease states are needed [29].

Structural Neuroimaging- volumetrics and diffusion tensor imaging (DTI)

Volumetric MRI can assess brain structural differences between HIV+ and HIV− individuals [30]. This technique can concentrate on either specific brain structures or relatively large brain areas [31]. In the pre-cART era, significant volume loss was seen in the basal ganglia, posterior cortex, and white matter of HIV+ patients compared to HIV− controls [32–34]. The greatest changes in volumetrics were seen in more advanced stages of HAND [35]. In the cART era, both subcortical and cortical atrophy have been observed in HIV+ patients [36–38] suggesting that brain volume loss can still occur despite the initiation of effective treatment [20,30]. More recently, volumetric changes have been shown to correlate with the degree of cognitive impairment and virologic markers. Poorer neurocognitive performance has been associated with smaller brain volumes [22,37,39–46] and greater viral burden. In addition, impaired immune response (nadir CD4+ T lymphocyte counts) has been associated with greater atrophy [20,38,40,41,46–49]*. Cortical brain atrophy and expansion of the third ventricle has been observed soon after seroconversion [50].

Diffusion tensor imaging (DTI) technique has become increasingly popular in the assessment of white matter structural integrity in the setting of HIV. This neuroimaging technique measures the diffusion of water molecules [45,51–53]**. In the isotropic state water motion is equal in all directions (e.g. cerebrospinal fluid). In brain tissues the movement of water is anisotropic, with diffusion greater along the length of fiber tracts compared to perpendicular to them [54]. For each voxel, a tensor is calculated that describes the 3-dimensional shape of water diffusion. Fiber direction is indicated by the tensor’s main eigenvector. Mean diffusivity (MD) reflects the average diffusion in three axes. Fractional anisotropy (FA) assesses the general shape of the ellipsoid [55].

Most studies have shown that HIV leads to an increase in MD and a decrease in FA within white matter tracts. However, subtle differences may exist as to where changes are observed depending on the study [56–59]*. To date, no studies have assessed DTI changes soon after seroconversion. Typically HIV+ individuals receiving cART (HIV+/cART+) and those naïve to cART (HIV+/cART−) have been merged and compared to HIV− controls. Conflicting results have been observed in the few studies that have investigated the impact of cART using DTI [60–62]*.

Overall, quantitative volumetric changes may be more sensitive than current conventional MRI evaluation. In the future, DTI could be used to evaluate the efficacy of certain therapeutics but additional longitudinal studies that focus on HIV+ patients soon after seroconversion are needed.

Functional magnetic resonance imaging (fMRI)

Studies are now starting to utilize blood oxygen level dependent (BOLD) fMRI to investigate the effects of HIV on brain function [63]. Changes in the BOLD response for a particular stimulus can indirectly reveal the coupling between neuronal activity and cerebral blood flow (CBF) within certain brain regions [64]. HIV+ patients have greater BOLD activity in the parietal lobes for a simple attention task and greater frontal and parietal activation during more complex attention tasks [65]. These BOLD changes in HIV+ patients may reflect the recruitment of surrounding areas to meet cognitive requirements [24,28,42,65–73]. A recent systematic meta-analysis of BOLD fMRI studies using various functional tasks in HIV+ patients was recently performed using activation likelihood estimation. HIV+ patients had greater functional activation within the left inferior frontal gyrus and caudate nucleus compared to HIV− controls [74]*. Dysfunction in the fronto-striatal network was qualitatively related to degree of neurocognitive impairment. Differences between HIV+ and HIV− individuals can also be seen at rest using BOLD imaging. In particular, functional correlations between brain networks are significantly reduced in HIV+ patients and a signature of the disease may be present that is different than other neurodegenerative disorders. The effects of HIV and aging on BOLD resting state functional correlations were shown to be independent of each other [75]*. However, the effects of cART have not been assessed using BOLD imaging. Additional studies of CBF have nicely complemented existing BOLD studies and have demonstrated a reduction in resting CBF in HIV+ individuals compared to HIV− controls [76,77].

Overall, functional neuroimaging studies have been performed in a limited number of HIV+ patients. Additional longitudinal fMRI studies are needed to determine if these techniques could be used to follow HIV+ individuals. Future BOLD studies could evaluate the efficacy of various treatment regimens for HAND.

Positron Emission tomography (PET)

Fluorodeoxyglucose (FDG) PET imaging is a commonly used technique that measures the metabolic activity of various cells/tissues, such as in neoplastic diseases. In the brain, evaluation of FDG uptake by neurons has been utilized in multiple CNS disorders such as AD and Parkinson’s disease [78]. In neuroHIV, early FDG-PET studies demonstrated lower

cerebral metabolic rate for glucose consumption in HIV+ patients compared to age-matched HIV− subjects, despite the lack of structural abnormalities on MRI [79]. This probably was the first insight into early metabolic changes can occur with HIV infection without gross structural volumetric loss. Subsequent FDG-PET studies [80–82] have described two unique metabolic signatures of glucose abnormalities associated with HIV infection. The first was a hypermetabolic state, particularly in the striatum, which appeared to provide a disease-specific measure of early central nervous system (CNS) involvement, despite normal motor function on NP testing. This was assumed to reflect abnormal functional connectivity within subcortical areas [82]. A second pattern was seen during chronic stages and was characterized by generalized hypometabolism in both cortical and subcortical regions. These changes correlated with age, cerebral atrophy, and neurocognitive status [81]. A switch from the hypermetabolic to hypometabolic states in subcortical areas (e.g. basal ganglia) was associated with changes in functional deficits and progression to dementia [82].

In the cART era, more subtle FDG-PET changes have been observed [83,84] ** and can still be seen in optimally treated HIV+ patients with virologic suppression. At least half of HIV+ patients on cART can have varying degrees of hypometabolism in the mesial frontal lobes [83]. These abnormalities are accentuated by drug abuse and can lead to extensive cortical hypometabolism [85]. In contrast to some MRI studies, a synergistic interaction has been observed between aging and HIV with changes primarily seen in the frontal regions [84]**.

Ongoing CNS injury observed despite peripheral virologic suppression may reflect persistent low level neuroinflammation. A few studies have attempted to characterize neuroinflammation using PET ligands that specifically target microglia activation. The most commonly used ligand has been ^{11}C-PK11195 which binds to the translocator protein (TSPO), a mitochondrial receptor known to be significantly upregulated in activated microglia [86,87]. Early studies showed significantly higher ^{11}C-PK11195 binding in HIV associated dementia (HAD) patients compared to HIV− controls within five out of eight brain regions of interest. However within a subgroup of non-demented HIV+ patients, no significant increases in binding were seen when compared to HIV− controls [88]. A subsequent larger study using ^{11}C-PK11195 failed to show increases in ligand retention in the brain parenchyma of HIV+ subjects compared to HIV− controls [89]. One possible explanation for observed differences could be due to the variability of the HIV+ patient populations recruited for these studies. While Hammoud and colleagues [88] included cognitively impaired HIV+ who were not receiving cART, Wiley and colleagues [89] only evaluated cognitively normal HIV+ patients receiving treatment [89]. A subsequent study by Garvey and colleagues [90] compared chronically infected HIV+ patients with and without concomitant HCV infection. No significant differences were noted between these two groups. However, HIV+/cART+ individuals had lower ligand binding potentials in the parietal and frontal regions than HIV+/cART− patients. A follow-up paper by the same group compared HIV+/cART+ patients to HIV− controls and showed clusters of increased ligand binding within the corpus callosum, anterior and posterior cingulate gyrus, temporal gyrus, and frontal regions [91]**.

Limitations of ^{11}C-PK11195, including its' high non-specific binding and high lipophilicity, have led some to question the reliability of this ligand. Subsequent attempts have been made

to use second generation TSPO-PET ligands with higher specific to non-specific binding ratios. However, these second generation agents have different binding affinities within HIV − controls. In particular, a genetic polymorphism of the TSPO receptor has been discovered and could affect the binding potential of these various ligands [92,93]**. This discovery has further complicated the analysis of TSPO-PET imaging as patients must be stratified as low-affinity binders (LL), high affinity binders (HH), or heterozygous (HL) [92]. Cross-sectional comparisons, in theory, cannot be done except within the same binding affinity group. Despite these limitations, one study used a second generation TSPO ligand (^{11}C-DPA713) to compare HIV+/cART+ individuals and HIV− controls [94]. Adapting a new method of data analysis based on assessing the volume-of-distribution ratios relative to overall gray matter, HIV+ patients were noted to have higher binding in specific brain regions that may reflect localized rather than diffuse glial cell activation. A novel gray matter normalization approach was employed that improves test-retest reproducibility and may uncover abnormal regional findings not seen using traditional methods [94]. However, additional studies are needed to validate this method for other TSPO ligands.

A third use of PET imaging in the setting of neuroHIV is the evaluation specific neurotransmitter systems. The first system to be evaluated was the dopaminergic system. Significantly lower dopamine transporters (DAT) availability was seen in the putamen of HIV+ patients with HAD compared to non-demented HIV+ patients. In addition, lower DAT levels were seen in the ventral striatum of HIV+ patients when compared to HIV− subjects [95]. These findings suggested dopaminergic terminal injury occurs in HIV+ patients with significant cognitive impairment. Within the HIV+ demented group, higher plasma viral load correlated with lower DAT binding in the caudate and putamen. This inverse relationship between plasma viral burden and DAT availability further support an HIV mediated neurotoxicity within dopaminergic nerve terminals [95]. A subsequent DAT imaging study assessed the cofounding effects of drug abuse (specifically cocaine) and HIV infection [96]*. While HIV+ patients showed lower DAT binding in the putamen compared to HIV− subjects, irrespective of drug abuse, HIV+ patients with a previous history of drug abuse problems had the lowest DAT values in the caudate. These results further support the theory of drug abuse contributing to CNS injury observed in HIV+ patients. Previous cocaine use may increase the release of dopamine, resulting in microglial activation, and possibly increases in viral replication [97]. Besides the dopaminergic system, only one study has targeted the serotonergic system in HIV+ patients. Using a serotonin transporter ligand, ^{11}C-DASB, Hammoud and colleagues [98] showed dysregulated serotonergic transmission in HIV+ patients with depression compared to non-depressed HIV+ subjects. This observation may reflect increased density of serotonin, leading to increased clearance of this neurotransmitter from the synapse, which could subsequently lead to depressive symptoms [98]. However, additional longitudinal studies using these compounds and other recently developed ligands are needed in HIV+ patients.

A fourth approach to using PET in neuroHIV has investigated the role of amyloid. Previous pathological studies have shown increases in diffuse plaques in HIV+ patients [99–101]. With a greying of the HIV+ population, increasing concerns have arisen as to whether older HIV+ patients are at increased risk for developing Alzheimer's disease (AD). PET imaging using the amyloid-binding agent ^{11}C-labeled Pittsburgh Compound B (^{11}C-PiB) has

demonstrated amyloid deposition in preclinical AD [102]. However, ^{11}C-PiB studies in HIV + individuals failed to show increased amyloid accumulation, even in symptomatic (HAND) patients [103,104]. A more recent study looking at HIV+ patients across a range of ages also did not show significant increases in amyloid typically seen with AD [105]. Observed differences between HAND and AD could potentially reflect variances in amyloid metabolism between the two disease entities or the lack of affinity of current amyloid ligands for more diffuse amyloid plaques. Additional studies using more recently developed amyloid agents (e.g. florbetapir) are needed.

Conclusion

In conclusion, PET imaging has been used rather limitedly in neuroHIV. However, PET methods have great potential for further characterizing the neuropathophysiological changes associated with HIV, especially in the setting of optimal cART. Evaluation of various neurotransmitter systems besides the dopaminergic and serotonergic systems might shed more light on selective vulnerability of various neuron subtypes to the virus. Evaluation of the effect of drug abuse on the course of neuroHIV is needed. Most importantly, PET imaging might help finding reliable non-invasive biomarkers of neuronal injury in HIV that could potentially be used in the evaluation of response to treatment and/or neuroprotective measures.

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Abbreviations

ANI	asymptomatic neurocognitive impairment
cART	combination antiretroviral therapy
Cr	creatine
DTI	diffusion tensor imaging
FA	fractional anisotropy
fMRI	functional magnetic resonance imaging
HAD	HIV associated dementia
HAND	HIV associated neurocognitive disorders
HIV	Human immunodeficiency virus
HIV+	HIV-infected
HIV−	HIV-uninfected
MD	mean diffusivity
MI	myoinositol

MND	mild neurocognitive disorder
MRS	magnetic resonance spectroscopy
NAA	n-acetyl aspartate
PET	positron emission tomography
DAT	dopamine transporter
NP	neuropsychological performance
AD	Alzheimer's disease
FDG	fluorodeoxyglucose
CBF	cerebral blood flow
CNS	central nervous system
TSPO	translocator protein

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Key points

- The effects of HIV in the brain can be non-invasively assessed by structural (e.g. volumetrics and diffusion tensor imaging) and functional (e.g. blood oxygen level dependent imaging) magnetic resonance imaging (MRI).
- Positron emission tomography (PET) of glucose metabolism, neurotransmitter systems' abnormalities, or amyloid deposition could provide additional understanding of the neuropathophysiological changes associated with HIV.
- Novel neuroimaging methods could be added to current criteria for defining HIV associated neurocognitive disorders (HAND). These methods may also help in evaluating the efficacy of combination anti-retroviral therapy (cART) regimens.
- Neuroimaging studies that are longitudinal; have larger sample sizes of both HIV infected (HIV+) and HIV uninfected (HIV−); and include HIV+ patients of different disease durations are needed.