

Role of Neuroimaging in HIV-Associated Neurocognitive Disorders

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Semin Neurol 2014;34:89–102.

Abstract

Human immunodeficiency virus (HIV) enters the brain soon after seroconversion and can cause HIV-associated neurocognitive disorders (HAND). Although the more severe and progressive forms of HAND are less prevalent due to combination antiretroviral therapy (cART), ~ 40% of HIV-infected (HIV+) patients continue to have cognitive impairment. Some HIV+ individuals who have effective plasma HIV-1 RNA suppression with cART still develop HAND. It is often difficult to diagnose HAND in the outpatient setting as detailed neuropsychological performance testing is required. Additional biomarkers that are relatively easy to obtain and clinically relevant are needed for assessing HIV-associated neuropathologic changes. Recently developed noninvasive magnetic resonance imaging (MRI) techniques have great potential to serve as biomarkers. The authors review the application of some of these neuroimaging techniques, magnetic resonance spectroscopy (MRS), volumetric MRI, diffusion tensor imaging (DTI), functional MRI (fMRI), in HIV+ individuals. Each of the neuroimaging methods offers unique insight into mechanisms underlying neuroHIV, could monitor disease progression, and may assist in evaluating the efficacy of particular cART regimens. It is hoped that considerable progress will continue to occur such that some of these neuroimaging methods will be incorporated across multiple sites and included in future HAND guidelines.

Keywords

- ▶ human immunodeficiency virus
- ▶ neuroimaging
- ▶ magnetic resonance spectroscopy
- ▶ volumetrics
- ▶ diffusion tensor imaging
- ▶ functional MRI

Human immunodeficiency virus (HIV) affects more than 1 million individuals in the United States and over 40 million people worldwide.¹ Advances in combination antiretroviral treatment (cART) have transformed HIV from a rapidly fatal disease to a manageable chronic condition.^{2–4} The proportion of older HIV-infected (HIV+) individuals is rapidly growing. More than half of all HIV+ individuals in the United States are expected to be greater than 50 years old by 2015.⁵ HIV infected (HIV+) individuals receiving cART can now expect to live almost as long as HIV-uninfected (HIV-) individuals.⁶

Despite these advances, eradication of HIV from the brain has not occurred. The prevalence of HIV-associated neurocognitive

disorders (HAND) has remained constant (~ 40%) despite more available and effective antiretrovirals.^{7,8} Soon after seroconversion, HIV rapidly spreads throughout the brain. Some HIV+ individuals who have effective plasma HIV-1 RNA suppression with cART still develop HAND.⁹ The continued presence of HAND in the cART era may result from nonmutually-exclusive factors including irreversible injury prior to initiating cART, persistent HIV-1 RNA in the central nervous system (CNS) compartment,¹⁰ antiretroviral toxicities,^{11–13} and/or persistent low-level inflammation in the CNS.¹⁴ A major effort has begun to optimize therapy for HAND by addressing persistent HIV reservoirs and immunologic activation in the brain.

Issue Theme HIV Neurology; Guest Editors, Serena Spudich, MD, MA, and Ana-Claire Meyer, MD, MSHS

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DOI <http://dx.doi.org/10.1055/s-0034-1372346>. ISSN 0271-8235.

HAND is often difficult to characterize in the typical outpatient visit (15–30 min). Multiple connections throughout the brain are often affected leading to the complex series of clinical signs and symptoms.¹⁵ Recent criteria have subdivided HAND into three categories: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV associated dementia (HAD).⁸ These definitions are based upon an individual's performance on neuropsychological performance (NP) testing and self-reported activities of daily living. However, limitations exist with the current HAND criteria.¹⁶ Often NP testing (~3 h) is performed in a research setting at certain sites.⁸ A continuum of HAND may occur instead of set distinctions.¹⁷ Unlike other neurodegenerative disorders (i.e., Alzheimer's disease),¹⁸ additional biomarkers (cerebrospinal fluid [CSF] or neuroimaging) have not been included in the HAND diagnosis. Biomarkers of HAND that are both easy to perform and clinically relevant remain an unmet need.

Neuroimaging techniques may therefore have increased utility in the diagnosis and management of HAND. A variety of novel noninvasive neuroimaging techniques have been developed and hold great promise as they often can be added to conventional sequences. Of note, three magnetic resonance imaging (MRI) techniques have been used in the neuroHIV research setting: metabolic (magnetic resonance spectroscopy [MRS]), structural (MRI volumetrics and diffusion tensor imaging [DTI]), and functional (functional MRI [fMRI]). This review is not meant to be a comprehensive review of all MRI techniques and does not focus on other neuroimaging modalities (e.g., positron emission tomography [PET]).¹⁹

Cerebral Metabolite Imaging using Magnetic Resonance Spectroscopy

MRS has been one of the most consistently used neuroimaging methods during the pre- and post-cART eras.^{20–23} A current PubMed search reveals more than 75 articles that describe studies that have used this technique to detect HIV-associated changes in cerebral metabolites (key search terms: “MRS,” “brain,” and “HIV”). Please see ► **Table 1** for a select list of MRS studies performed in HIV+ patients. MRS detects the signal produced by protons of specific molecules within a volume of brain. Signal amplitude of a particular molecule X (A_X) of interest is proportional to the number of moles of X (N_X) with the brain volume (V_B) interrogated. Typical molecules 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, (4) myo-inositol (MI)- a marker of gliosis, and (5) glutamine (Gln)/glutamate (Glu)- measures of neurotoxicity due to excess N-methyl-D-aspartate (NMDA) receptor activation.

In general, MRS can be performed on conventional MRI scanners, but technical assistance is needed to ensure good-quality scans are obtained. MRS studies should be carefully performed to ensure homogeneity of the magnetic field and suppression of the water signal.²⁴ Depending on both the institution and time available for scanning, single- or multi-

voxel MRS has been acquired using a variety of acquisition techniques to yield qualitative versus semiquantitative versus quantitative values. Due to quantification limitations, calibration is often performed using a phantom or an internal signal (e.g. water (H_2O) or Cr). This can result in metabolite ratios rather than absolute concentrations (e.g., NAA/Cr).

Though often limited to certain brain regions (e.g., frontal gray, frontal or parietal white matter, and basal ganglia), MRS provides key insights into the dynamic changes in the brain metabolic profile from primary (≤ 1 year since seroconversion) to chronic (> 1 year since seroconversion) infection. Soon after seroconversion, MRS metabolites have been shown to be affected.^{21,25–27} HIV+ patients scanned during the first year of infection have increased Cho/Cr in the frontal and white matter²¹ compared with HIV- controls. A subsequent study confirmed these findings with primary HIV+ individuals having higher Cho/ Cr in the basal ganglia compared with HIV- controls.²⁵ Observed MRS changes are correlated with markers of CNS infection and inflammation (detectable HIV-1 RNA and chemokines)²⁵ and neuronal injury (neurofilament light chain).²⁷ Within chronically infected patients, brain metabolite changes are also evident. Many studies have often observed reductions in NAA and concomitant increases in Cho and MI.^{22,28–31} More recent MRS studies performed at higher magnetic fields using newer analysis methods have demonstrated reductions in Glu³² and Gln.²⁹ Observed MRS changes in chronically infected HIV+ patients are proportional to the degree of cognitive impairment.^{22,29} While increases in MRS markers of inflammation (Cho and MI) are seen in cognitively normal HIV+ patients, greater changes in inflammation (Cho and MI) and neuronal loss (NAA/Cr and Glu/ Cr) are observed in HAND patients.^{22,29,32}

The introduction of cART has dramatically reduced the more severe forms of HAND and can also lead to improvements, but not normalization, of brain metabolites.^{31,33,34} Early treatment with cART may be neuroprotective and mitigate the early inflammatory changes seen in primary HIV+ patients. Commencement of therapy soon after diagnosis normalizes Cho/Cr in the basal ganglia within 6 months.²⁶ Several clinical trials have started to include MRS markers to evaluate the efficacy of adjunctive therapy for HAND.³⁵ This technique may have great potential in future early prevention studies.

Increasing evidence has also suggested that certain antiretrovirals may cause mitochondrial toxicity and lead to neuronal loss.^{12,36} Chronically infected HIV+ patients on cART regimens that included nucleotide reverse transcriptase inhibitors (NRTIs) had significant reductions in NAA in the frontal white matter compared with HIV- controls. HIV+ individuals receiving alternative cART regimens that did not include NRTIs exhibited intermediate decreases in NAA.³⁷ A more recent study has observed that HIV+ patients receiving NRTIs had reductions in parietal and frontal gray matter Glu that were predictive of worse cognitive performance.³²

With a larger proportion of HIV+ growing older with the disease, several studies have started to investigate the interaction between HIV and aging using MRS. HIV+ patients have been shown to have significant reductions in Glu to levels

Table 1 Select citations of magnetic resonance spectroscopy (MRS) in HIV+ patients

Reference	Subjects	% HIV+ on cART	HAND classification	Field strength	Regions of interest	Major findings
Cysique et al, 2013 ²⁰	92 HIV+ (56 y), 30 HIV- (55 y) 100% male	100%	NA	3 T	FWM, caudate, parietal cortex	HIV+ had lower NAA and increased MI in FWM, lower NAA in caudate, and higher Cho/NAA and MI in parietal cortex. HIV and aging interaction in NAA FWM
Valcour et al, 2013 ⁶⁷	61 acute HIV+ (35 y), no HIV-	0%	14 ANI 8 MND 6 HAD	1.5 T	FGM, FWM, BG, occipital gray matter	Blood CD14+ associated with lower NAA and higher MI in FGM, FWM and BG
Sailasuta et al, 2012 ²⁶	31 acute HIV+ (30 y) 26 chronic HIV+ (34 y) 10 HIV- (36 y)	0% Primary HIV+ not on cART, 100% chronic HIV+	NA	1.5 T	FWM, FGM, BG, occipital gray matter	Acute HIV+ had elevated Cho/Cr in BG and occipital gray matter compared with chronic HIV+ and HIV-. cART in acute HIV+ led to normalization of Cho/Cr in BG
Valcour et al, 2012 ²⁵	20 acute HIV+ (31 y, 90% male, no HIV-	0%	NA	1.5 T	FGM, FWM, occipital gray matter, BG	Acute HIV+ had elevated Cho/Cr in occipital gray matter. Higher CSF neopterin was associated with elevated Cho/Cr in occipital gray matter and elevated MI/Cr in FWM.
Harezlak et al, 2011 ²²	240 HIV+ (47 y) 28 HIV- (53 yo)	100%	124 ADC 0 66 ADC 0.5 60 ADC >1	Not stated	BG, FWM, FGM	Increased MI/Cr and Cho/Cr in BG, FGM, FWM in all HIV+ groups compared with HIV-. Decreased Glu/Cr in FWM of ADC 0. Decreased NAA/Cr in ADC > 1 compared with other HIV+ groups.
Lentz et al, 2011 ²¹	9 primary HIV+ (39 y) 9 HIV- (31 y) 100% male	Baseline: 22.2% 2-mon: 44.4% 6-mon: 55.6%	All asymptomatic	1.5T	FGM, FWM, and BG	Cho/Cr increased in FWM and FGM at 2- and 6-mon in primary HIV+. Higher levels of peripheral CD16+ monocytes were associated with lower NAA and higher Cho.
Letendre et al, 2011 ¹	129 HIV+ (42 y, 89% male), no HIV-	91%	30 ADC 0 83 ADC 1 14 ADC 2 2 ADC 3	1.5 T	Parietal cortex, WM (including FWM), BG	Higher CSF IP-10 correlated with lower NAA/Cr in FWM and higher MI/Cr in the parietal cortex, FWM, and BG. Higher CSF MCP-1 correlated with lower NAA/Cr in FWM and parietal cortex.
Ernst et al, 2010 ³²	45 HIV+ (46 y, 93% male) 46 HIV- (43 y, 80% male)	100%	27 cognitively normal 6 ANI 10 MND 2 HAD	3 T	BG, FGM, FWM, parietal cortex	Lower Glu in parietal GM in HIV+ with cognitive deficits. Lower Glu in BG in HIV+ with no cognitive deficits.
Mohamed et al, 2010 ²⁹	86 HIV+ (47 y, 69% male), no HIV-	100%	21 ADC 0 31 ADC 0.5 24 ADC > 1	3 T	FWM and BG	Patients with ADC >1 had decreased Glu, Glu/Cr and increased MI, MI/Cr in FWM and decreased NAA in the BG.

(Continued)

Table 1 (Continued)

Reference	Subjects	% HIV+ on cART	HAND classification	Field strength	Regions of interest	Major findings
Paul et al, 2008 ³⁰	22 HIV+ (38 y, 86% male) 20 HIV- (35 y, 47% male)	> 50%	6 ADC 0 16 ADC 1	1.5 T	BG	Cho/Cr higher and NAA/Cr lower in HIV+ vs. HIV-. MRS measures correlated with NP testing
Schwensburg et al, 2005 ³⁷	18 HIV+ (32 y), 17 HIV- (28 y)	67%	NA	1.5 T	FGM and FWM	HIV+ patients on NRTIs had lower NAA in the FWM compared with HIV-. HIV+ patients not receiving NRTIs had intermediate NAA levels.
Chang et al, 2004 ⁹⁶	100 HIV+ (40 y) 37 HIV- (34 y) Cohort 77% male	100%	61 cognitively normal 39 cognitively impaired	1.5 T	FWM, BG, parietal cortex	MJ/Cr increased in WM of cognitively normal HIV+ MJ/Cr increased in WM and BG of cognitively impaired HIV+ Cho/Cr increased in WM and BG of cognitively impaired HIV+ NAA/Cr decreased in WM and BG of cognitively impaired HIV+ CSF viral load correlated with increase MJ/Cr and Cho/Cr in WM and decreased NAA/Cr in parietal cortex Aging and HIV infection have additive effect on increased MJ/Cr and Cho/Cr in BG and WM
Yiannoutsos et al, 2008 ³¹	100 HIV+, no HIV-	NA	NA	1.5 T	FWM, FGM, BG, parietal cortex	Three metabolic patterns: (1) inflammatory (elevated MJ/Cr in all regions and elevated Cho/Cr in the FWM and parietal cortex); (2) basal ganglia (elevated NAA/Cr and Cho/Cr); (3) neuronal (reduced NAA/Cr in FGM and parietal cortex).

Abbreviations: ADC, AIDS dementia complex; BG, basal ganglia; cART, combination antiretroviral therapy; Cho, choline; Cr, creatine; FWM, frontal white matter; FGM, frontal gray matter; Glu, glutamate; Gln, glutamine; HIV, human immunodeficiency virus; MJ, myoinositol; NAA, N-acetyl aspartate; NA, not available; WM, white matter.

equivalent to those in HIV- controls a decade older.³² Another study confirmed these findings by demonstrating that HIV+ patients exhibited age dependent declines in NAA and Gln, such that the metabolic profile of a 30-year-old HIV+ patient was equivalent to a 56-year-old HIV- control.²² In both instances, though HIV and aging effects were observed, no interaction was present.

Overall, MRS offers a valuable method for monitoring HIV-associated neuropathologic changes. Observed MRS changes may be more sensitive than conventional MRI alone and could augment current neuroimaging protocols. MRS measures may detect subtle early changes associated with HIV infection, and concentrations or ratios of cerebral metabolites measured by MRS could be used as a quantitative indicator of cerebral involvement. In addition, MRS could be used to evaluate the efficacy of therapeutics directed against HIV infection within the CNS during early stages of infection. Some limitations exist in the current MRS HIV research literature, including mostly cross-sectional studies, as well as analyses restricted to specific regions of interest. However, MRS results suggest that contributions of inflammation, aging, and drug toxicity could all contribute to the continued prevalence of HAND. Additional studies that include more HIV- controls are needed. Longitudinal studies, with a focus on repeated imaging of HIV+ patients as they transition through different stages of infection, as well as prior to and after stable cART, are needed. In addition, the impact of comorbidities (e.g., hepatitis, substance abuse, etc.) on MRS measurements should be more fully characterized in HIV+ patients.

Structural Neuroimaging

Volumetric Analysis of MRI

Volumetric MRI examines particular regions of interest and assesses if abnormal structural changes are present in affected individuals compared with healthy controls.³⁸ This method provides a useful tool to rule out alternate etiologies and can support a diagnosis of HAND. Specific structures or general brain regions (e.g., white and gray matter) are analyzed.³⁹ A PubMed search using keyword search terms “MRI,” “volume,” “brain,” and “HIV” identifies more than 60 articles. Please see ► **Table 2** for a select list of MRI volumetric studies performed in HIV+ patients. Typically, higher field MRI (initially 1.5 T and now 3 T) has been used to acquire high resolution T1-weighted images. In particular, a magnetization prepared rapid acquisition gradient echo (MPRAGE) image provides the greatest contrast for segmenting gray matter, white matter, and CSF. Although not typically acquired with conventional imaging sequences, the MPRAGE sequence can be obtained on most MRI scanners.

Early volumetric work concentrated on measuring ratios of subcortical (e.g., caudate) to intraventricular volumes. This technique could not isolate the location of atrophy and missed brain regions not within the field of view.⁴⁰ Semi- or fully automated methods have been developed for segmenting the brain based on voxel signal intensity properties of tissues.^{41–43} Currently, a variety of preprocessing pro-

grams are available, but some experience is needed for analysis.

In the pre- and early antiretroviral era, significant volume loss was observed in the basal ganglia, posterior cortex, and total white matter of HIV+ patients compared with age-matched HIV- individuals.^{44–46} Atrophy was greatest in more advanced stages of infection, but changes were seen even in cognitively normal HIV+ individuals.⁴⁷ Subsequent studies in the cART era have demonstrated subcortical and cortical atrophy in HIV+ patients^{42,48–50} (see ► **Fig. 1**). HIV+ individuals, especially those with an acquired immunodeficiency syndrome- (AIDS-) defining event, have thinner cortical thickness (primary sensory, and motor),⁴⁹ smaller cortical volumes,^{28,42,49,51,52} and larger total ventricular size.^{49,52} Ongoing brain volume loss occurs despite initiation of cART.^{28,50} Changes in brain volume may commence early as cortical atrophy and expansion of the third ventricle are observed in primary HIV infection.⁵¹

Volumetric changes also correlate with NP testing and clinical measures. Several studies have reported structure-function relations with poorer cognitive or motor performance associated with smaller brain volumes.^{30,49,53–60} Both greater viral burden (plasma HIV-1 RNA, CSF HIV-1 RNA, peripheral monocyte DNA) and immune response to the virus (nadir CD4+ T lymphocyte counts) are associated with greater volume loss.^{28,42,52,54,55,60–62}

Common comorbidities may also contribute to volume abnormalities in HIV+ patients. Hepatitis C coinfection,⁴² alcoholism,⁵⁵ cigarette smoking,⁶³ and small-vessel disease⁶⁴ may exacerbate brain atrophy in the setting of HIV infection. Furthermore, characteristic volume loss associated with aging may independently affect certain brain structures in older HIV+ individuals.^{50,55,65,66} Older HIV+ individuals suffering from multiple comorbidities may experience greater cumulative volume losses, increasing their risk for HIV-induced neurocognitive impairment.⁶⁷

Overall, MRI volumetric analysis demonstrates that brain structure abnormalities begin early and progress throughout the course of HIV infection. Brain structural integrity in HIV likely reflects dynamic effects of current immune status and active viral replication, superimposed on possible residual effects associated with severe prior immunosuppression and other comorbidities. Though most MRI volumetric studies have been performed cross sectionally, additional longitudinal studies could assess for risk factors for developing HAND and response to therapy. Future studies should include more HIV- controls for comparison.

Diffusion Tensor Imaging

More recently, diffusion tensor imaging (DTI) has become a popular method for studying white matter structural integrity.^{59,68–70} A PubMed search including the keywords “DTI,” “brain,” and “HIV” identified more than 30 articles. Please see ► **Table 3** for a select list of DTI studies performed in HIV+ patients. DTI measures the diffusion of water molecules in white matter. Movement of water can be anisotropic with diffusion greater along the length of the fiber (longitudinal direction) than perpendicular to it (radial or transverse

Table 2 Select citations of magnetic resonance imaging (MRI) of volumetrics in HIV+ patients

Reference	Subjects	% HIV+ on cART	HAND classification	Field strength	Regions of interest	Major findings
Bonnet et al, 2013 ¹⁰⁴	400 HIV+ (47 y, 79% male), no HIV-	89%	21% ANI 31% MND 7% HAD	1.5 T	GM and WM	MND or HAD had lower WM and GM than ANI.
Fennema-Notestine et al, 2013 ¹⁰⁵	75 HIV+ (45 y, 83% male), no HIV-	79%	NA	1.5 T	Total cerebral WM, abnormal WM, subcortical and cortical GM, and ventricular and sulcal CSF	Greater plasma CD4 recovery associated with increased abnormal WM and subcortical GM volumes. Virologic suppression was independently associated with increased GM volume.
Kallianpur et al, 2013 ⁶¹	135 HIV+ (54 y, 91% male), 12 HIV-(54 y, 100% male)	100%	NA	3 T	Caudate, amygdala, hippocampus, thalamus, nucleus accumbens, putamen, globus pallidus, subcortical and cortical GM, cerebral WM, cerebellar GM, cerebellar WM, brainstem, lateral ventricles	HIV+ subjects with detectable viral load in the periphery had decreases in cerebellar and subcortical GM compared with HIV+ subjects with undetectable viral load. HIV+ subjects with detectable viral load had ventricular enlargement and reduction of caudate, putamen, thalamus, hippocampus, nucleus accumbens, brainstem, total cortical GM, and cerebral WM compared with HIV-
Ances et al, 2012 ⁵⁰	52 HIV+ (36 y, 91% male), 26 HIV- (35 y, 77% male)	50%	NA	3 T	Amygdala, caudate, thalamus, hippocampus, putamen, corpus callosum, cerebral GM and WM	HIV+ subjects had reduction in amygdala, caudate, and corpus callosum compared with HIV-. Both HIV and aging were independently associated with volume reductions
Becker et al, 2012 ⁶⁵	84 HIV+ (38 y) 76 HIV- (39 y) 100% male	NA	NA	3 T	GM and WM	HIV+ subjects had greater GM loss in posterior and inferior temporal lobe, parietal cortex, and cerebellum compared with HIV-. Both aging and HIV affect WM and GM volumes. Cardiovascular disease risk factors were not associated with brain volume loss.
Pfeifferbaum et al, 2012 ⁵⁵	127 HIV+, (45 y, 70% male), 218 HIV- (47 y, 69% male)	87%	NA	1.5 T	Lateral frontal, medial frontal, temporal, parietal, occipital, caudate, putamen, globus pallidus, hippocampus, amygdala, thalamus	HIV+ subjects had reduced thalamic and frontal volumes compared with HIV-. Volume loss correlated with CD4 nadir and history of AIDS.
Ragin et al, 2012 ⁵¹	43 HIV+ (33 y, 88% male) 21 HIV- (31 y, 76% male)	47%	NA	3 T	Total brain volume, cortical and subcortical GM, WM, ventricular volume	HIV+ subjects had reductions in total and cortical GM and increase in the ventricular volume compared with HIV-
Thames et al, 2012 ⁵⁷	20 HIV+ (53 y, 60% male), no HIV-	100%	50% had HAND	1.5 T	Putamen and caudate	Impaired word generation significantly predicted reduction in caudate volume
Towgood et al, 2012 ⁶⁶	40 HIV+ (47 y), 42 HIV- (45 y) 100% male	100%	NA	3 T	Total GM and WM	HIV+ subjects had reduced GM volume in the medial and superior frontal gyri compared with HIV-. HIV and aging were independently

Table 2 (Continued)

Reference	Subjects	% HIV+ on cART	HAND classification	Field strength	Regions of interest	Major findings
Jernigan et al, 2011 ⁴²	251 HIV+ (44 y, 82% male), no HIV-	76%	37% neurocognitively impaired	1.5 T	Total WM, abnormal WM, subcortical and cortical GM	associated with reduced frontotemporal GM and WM volumes. Lower CD4 nadir and higher current CD4 cell counts were associated with lower total WM and subcortical GM volumes. Detectable HIV in the CSF correlated with total WM volume loss. Longer cART exposure correlated with reduced WM volumes and increased ventricular volumes.
Ragin et al, 2011 ⁶²	8 HIV+ (51 y, 75% male), no HIV-	100%	NA	3 T	Cerebral cortex, cerebral WM, caudate, putamen, pallidum, accumbens, amygdala, hippocampus, thalamus, cerebellar cortex, cerebellar WM	MMP-7 significantly correlated with brain atrophy in multiple brain regions.
Cohen et al, 2010 ⁵²	82 HIV+ (46 y, 52% male), no HIV-	80%	16% ADC >1	1.5 T	Cortical and subcortical GM; WM: total ventricular volume; frontal, parietal, temporal, and occipital lobes	HIV+ subjects with cognitive impairment had greater reductions in GM and parietal cortical volumes and increased ventricular volumes. Nadir CD4 and duration of infection correlated with volumetric reductions in WM, GM, parietal, temporal, and frontal lobes; and hippocampal volume.
Cardenas et al, 2009 ²⁸	39 HIV+ (45 y), 30 HIV- (42 y) 100% male	100%	NA	1.5T	Total, frontal, temporal, parietal, and occipital WM and GM	HIV+ subjects had greater WM volume loss than SN controls. Greater rates of WM and GM volume loss were found in HIV+ subjects with detectable plasma HIV viral loads.
Castelo et al, 2007 ⁵⁶	22 HIV+ (43 y) 22 HIV- (43 yo)	77%	NA	3 T	Hippocampus, caudate nucleus, putamen, globus pallidus	HIV+ subjects had putamen hypertrophy compared with HIV-. Enlarged putamen correlated with increased CD4 cell counts.
Thompson et al, 2005 ⁴⁹	26 HIV+ (47y, 96% male) 14 HIV- (38 yo, 57% male)	50%	NA	1.5 T	Cortical GM	HIV+ patients had volumetric loss within primary sensory, motor, and premotor cortices compared with HIV-. Volumetric loss in frontopolar areas correlated with nadir CD4+ cell counts.
Patel et al, 2002 ⁵³	20 HIV+, NAS (36 y, 77% male), no HIV-	94%	8 ADC 0 5 ADC 0.5 2 ADC 1	1.5 T	Total GM volume	Greater cognitive impairment was associated with greater volume loss.

Abbreviations: ADC, AIDS dementia complex; AIDS, acquired immunodeficiency syndrome; ANI, asymptomatic neurocognitive impairment; cART, combination antiretroviral therapy; GM, gray matter; HAND, HAD, HIV-associated dementia; HIV-associated neurocognitive disorders; HIV, human immunodeficiency virus; MND, mild neurocognitive disorder; NA, not available; WM, white matter.

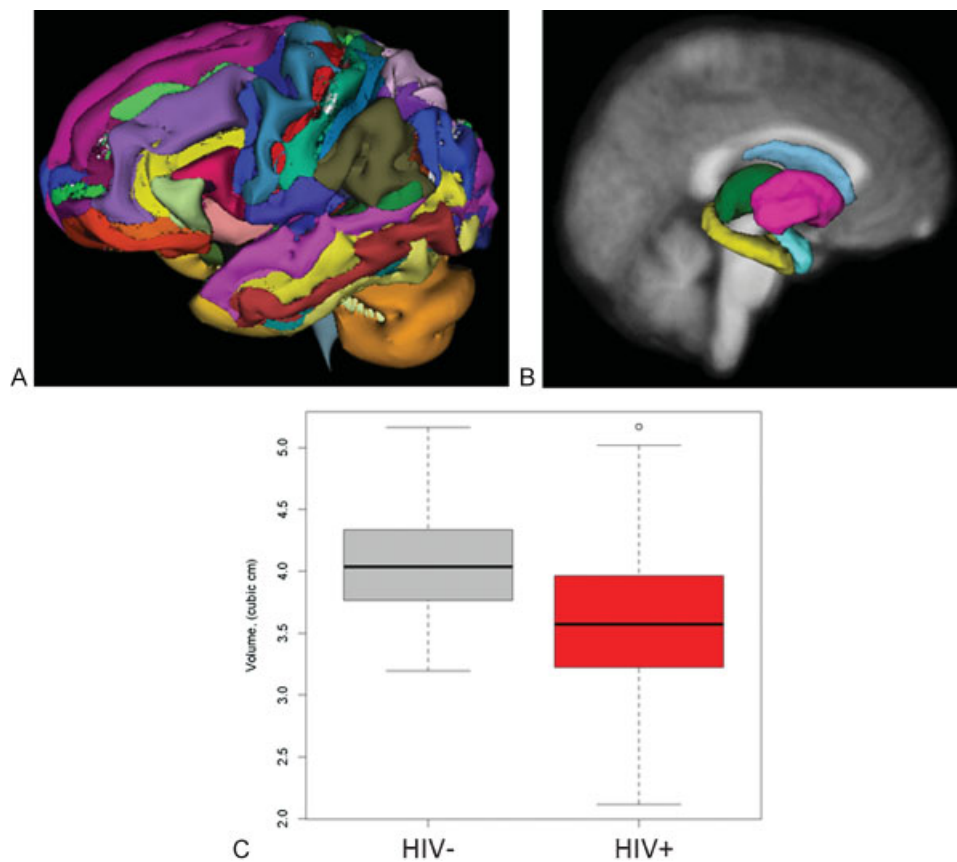


Fig. 1 Freesurfer segmentation of cortical (A) and subcortical (B) regions of the brain. (C) Comparison of volumes from the right caudate for human immunodeficiency virus-negative (HIV-) controls and HIV+ patients. Overall, HIV+ patients had significantly smaller volumes ($p < 0.05$).

direction), as myelin may restrict diffusion.⁷¹ For each voxel, a tensor is calculated that describes the three-dimensional shape of diffusion of water. The fiber direction is indicated by the tensor's main eigenvector. Diffusion along the major axis is assumed to reflect diffusivity parallel to the white matter tract. Mean diffusivity (MD) reflects the average diffusion in the major axis and the two minor axes. Fractional anisotropy (FA) is a value between zero and one and provides a measure of the general shape of the ellipsoid.⁷²

In general, DTI can be performed on conventional MRI scanners, but technical assistance is required. Depending on both the institution and time available for scanning, DTI with either single or multiple diffusion sensitivity parameters ("b values") can be performed. A minimum of six directions is acquired. Conventional preprocessing packages exist, but experience is required for analysis.

Variable results have been observed when DTI has been used to study the effects of HIV on white matter integrity.^{60,66,68,73-83} In general, many studies have shown that HIV leads to an increase in MD and a decrease in FA within white matter tracts (including the corpus callosum [CC] and centrum semiovale [CSO]) (see ►Fig. 2). However, subtle differences exist in the location of these changes depending on the study.⁸⁴⁻⁸⁷ For example, Filippi and colleagues showed a decrease in FA and an increase in MD in the genu and splenium of the CC of HIV+ patients.⁸⁰ Thurnher and colleagues observed a reduction in FA within

the genu of the CC of HIV+ patients.⁷⁵ Wu and colleagues reported a reduction in FA within the splenium of the CC in HIV+ individuals. This reduction in FA was associated with worsening motor speed performance.⁷⁴ However, Wright and colleagues observed a reduction in MD throughout the CC and CSO of HIV+ patients compared with HIV- controls.⁸⁸ Instead of region of interest analyses, a voxelwise analysis can also be performed. Gongvtana and colleagues showed significantly higher MD and lower FA throughout the white matter of HIV+ individuals compared with HIV- controls.⁷³

Typically, comparisons have been performed between HIV+ and HIV- controls. HIV+ individuals receiving cART (HIV+/cART+) and those naïve to cART (HIV+/cART-) have often been merged into a single group. The few studies that have investigated the effects of cART on DTI parameters in HIV+ individuals have shown conflicting results. Pfefferbaum and colleagues demonstrated that HIV+/cART- individuals had significantly higher MD values in the inferior cingulate bundle, occipital forceps, and superior longitudinal fasciculus compared with HIV- controls or HIV+/cART+.⁸³ However, Chen and colleagues noted no significant differences in DTI parameters between HIV+/cART- and HIV+/cART+ patients.⁸⁹ A decrease in FA was seen in the temporal lobes of HIV+/cART+ compared with HIV+/cART- individuals,⁷³ suggesting possible neurotoxicity. More recently, Wright and colleagues demonstrated that initiation of cART led to

Table 3 Select citations of diffusion tensor imaging (DTI) in HIV+ patients

Reference	Subjects	% on cART	HAND classification	Field strength	Findings
Zhu et al., 2013 ⁸⁷	50 HIV+ (48 y, 65% male) 13 HIV- (51 y, 23% male)	100%	86% neurologically asymptomatic 14% mild cognitive impairment	1.5 T	Compared with controls, HIV+ neurologically asymptomatic individuals showed increased MD in the posterior hemispheres. HIV+ individuals with mild cognitive impairment showed additional increased MD in prefrontal areas and decreased FA compared with HIV- controls and HIV+ neuroasymptomatic individuals. These findings correlated with duration of infection and multiple cognitive domains.
Du et al., 2012 ⁸⁶	10 HIV+ (53 y, 80% male), 24 HIV- (49 y, 67% male)	100%	NA	1.5 T	FA was affected most in HIV+ patients compared with HIV- controls
Hoare et al., 2012 ⁸⁴	128 HIV+ (29 y, 33% male), 32 HIV- (25 y, 39% male)	0%	NA	3 T	Lower FA values correlated with poorer prospective memory performance in HIV+ individuals
Stubbe-Drger et al., 2012 ⁸⁵	19 HIV+ (41 y, 100% male) 19 HIV- (41 y, 79% male)	68%	NA	3 T	FA was reduced in HIV+ subjects compared with HIV- controls
Gongvatana et al., 2011 ⁷³	85 HIV+ (45 y, 67% male), no HIV-	81%	48% neurocognitively impaired	3 T	Higher current CD4 cell count correlated with higher FA in parietal lobes. Initiation of cART correlated with higher FA in temporal lobes.
Muller-Oehring et al., 2010 ¹⁰⁶	21 HIV+ (43 y, 76% male) 19 HIV- (42 y, 58% male)	71.00%	NA	1.5 T	HIV+ participants showed poor fiber integrity in posterior portion of the corpus callosum compared with HIV- controls. In HIV+ subjects compromised callosal fiber integrity was correlated with poorer neuropsychological performance
Pfefferbaum et al., 2009 ⁸³	42 HIV+ (43 y, 69% male) 88 HIV- (45 y, 48% male)	79%	NA	1.5 T	HIV+ participants exhibited higher MD than HIV- controls in the posterior corpus callosum, internal and external capsules, and superior cingulate bundles.
Chen et al., 2009 ⁸⁹	29 HIV+ (35 y, 75% male) 18 HIV- (40 y, 50% male)	62%	28% HAD	3 T	HIV+ participants with HAD exhibited significantly MD in the parietal white matter. Widespread FA and MD abnormalities were present in HIV+ patients compared with HIV- controls.
Stebbins et al., 2007 ⁷⁸	30 HIV+ (45 y, 53% male), 30 HIV- (41 y, 43% male)	77%	NA	1.5 T	HIV+ patients had lower whole brain FA and higher whole brain MD compared with HIV- controls. Whole-brain FA and MD did not significantly correlate with cognitive performance measures in HIV+ patients.
Pfefferbaum et al., 2009 ¹⁰⁷	94 HIV+ (43 y, 74% male) 130 HIV- (45 y, 54% male)	68%	NA	N A	HIV+ subjects with a history of an AIDS-defining event, CD4+ cell count < 200, or alcoholism had greater abnormalities in MD and FA compared with HIV- controls.
Wu et al, 2006 ⁷⁴	11 HIV+ (49 y, 82% male) 11 HIV- (42 y, 82% male)	91%	6 MSK 0.5 4 MSK 1 1 MSK 2	1.5 T	HIV+ patients exhibited significantly reduced splenium FA values compared with HIV- controls. Changes in FA in HIV+ patients correlated with neuropsychological performance. Increases in MD in the splenium in HIV+ patients correlated with neuropsychological performance.
Thurnher et al., 2005 ⁷⁵	60 HIV+ (42 y, 80% male) 30 HIV- (40 y, 73% male)	NA	NA	1.5 T	In HIV+ patients FA was significantly decreased in the genu of the corpus callosum compared with HIV- controls.

(Continued)

Table 3 (Continued)

Reference	Subjects	% on cART	HAND classification	Field strength	Findings
Ragin et al., 2005 ⁷⁹	11 HIV+ (49 y, 82% male), 11 HIV- (42 y, 82% male)	91%	NA	1.5 T	HIV+ subjects had increased MD in the putamen and centrum semiovale compared with HIV- controls. MD values in putamen correlated with neuropsychological performance in HIV+ patients.
Pomara et al., 2001 ⁷⁶	6 HIV+ (40 y, 67% male), 9 HIV- (43 y, 78% male)	83%	NA	NA	In HIV+ subjects, FA was increased in the internal capsule and decreased in the FWM compared with HIV- controls.

Abbreviations: ADC, AIDS dementia complex; AIDS, acquired immunodeficiency syndrome; ANI, asymptomatic neurocognitive impairment; cART, combination antiretroviral therapy; FA, fractional anisotropy; HAD, HIV-associated dementia; HAND, HIV-associated neurocognitive disorders; HIV, human immunodeficiency virus; MD, mean diffusivity; MND, mild neurocognitive disorder; MSK, Memorial Sloan Kettering scale; NA, not available.

significant increases in MD, but not FA in the CC and CSO of HIV+ patients.⁸⁸

In summary, DTI may be a more sensitive method than conventional T2-weighted imaging for detecting subtle changes despite the presence of normal appearing white matter in HIV+ patients. Most DTI studies have been cross sectional, and studied changes in chronic or advanced HIV infection. The effects of early HIV infection or of cART initiation on the white matter have not been systematically assessed by DTI. Furthermore, few DTI studies have included enough HIV- controls. Additional studies comparing DTI parameters to CSF biomarkers and assessing the potential impact of comorbidities need to be performed.

Functional Magnetic Resonance Imaging

A nascent literature has started to develop utilizing blood oxygen-level dependent (BOLD) fMRI to investigate the effects of HIV on brain function.⁹⁰ A PubMed search using “fMRI,” “BOLD,” and “HIV” as keyword search terms yielded nine articles. Although the BOLD sequence can be performed on conventional MRI scanners, additional technical assistance is required for designing functional task paradigms. Preprocessing programs are available, but significant experience is needed.

Fluctuations in the BOLD response within specific brain regions indirectly reveal the coupling between changes in neuronal activity and cerebral blood flow for a particular stimulus.⁹¹ Increases or decreases in brain activation during a task, as compared with rest or a neutral task, are assumed to be related to the cognitive function that is under investigation.⁹² HIV+ patients have greater parietal activation for a simple attention task and greater frontal and parietal activation during more complex attention tasks.⁹³ These BOLD changes in HIV+ patients may reflect increased recruitment of additional areas to meet cognitive demands^{32,33,56,93–101} A recent systematic meta-analysis of BOLD fMRI studies using various functional tasks in HIV+ patients was performed using an activation likelihood estimation (ALE). HIV+ patients had greater functional activation within the left inferior frontal gyrus and caudate nucleus compared with HIV- controls.¹⁰² Dysfunction in this frontostriatal network was qualitatively related to neurocognitive impairment. When assessed at rest, functional connections between brain networks may be compromised in HAND, in ways that are similar to aging.¹⁰³

To date, most BOLD fMRI studies have been performed in a limited number of HIV+ patients with most receiving cART. Only a few studies have started to assess the impact of comorbidities such as methamphetamine use. A common task paradigm has not been developed across studies or sites. Additional BOLD fMRI studies are needed to evaluate the efficacy of novel therapies.

The Future of Advanced Neuroimaging

Considerable progress has been made in applying MRI methods to understand neuroHIV. However, most studies have compared HIV+ individuals to HIV- controls with secondary comparisons concentrating on HAND diagnosis or certain

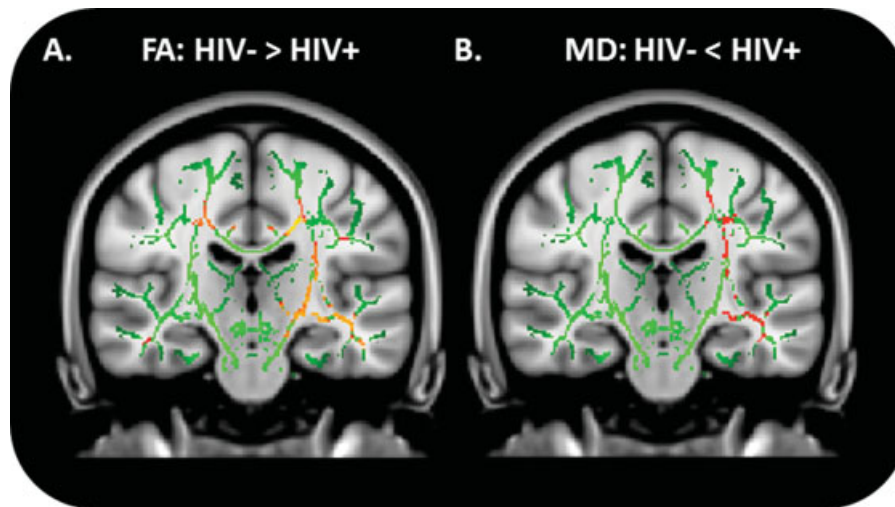


Fig. 2 Voxelwise comparisons for fractional anisotropy (FA) (A) and mean diffusivity (MD) (B) between HIV- controls and HIV+ patients using Tract-Based Spatial Statistics (TBSS). Red: $p = 0.05$; Orange: $p = 0.03$; Yellow: $p = 0.01$.

laboratory measures or comorbidities. Further studies that investigate the pathophysiology of spread of the disease throughout the brain are needed. These studies could help predict which HIV+ patients are at increased risk for developing HAND.

For neuroimaging to take the next step, these techniques need to be included not only within research criteria for HAND, but also in the evaluation of therapeutics. This can be accomplished by using a common protocol at multiple research sites. This protocol should include multiple MRI modalities. A first attempt has been made by the AIDS Clinical Trial Group (ACTG) with multiple sites scanning HIV+ patients using the same imaging paradigm. Results from this pilot study were encouraging and it is hoped that a similar protocol can be rolled out to more sites. Cross-modality comparisons within the same HIV+ individual will provide us a more complete understanding of the HIV pathophysiology.

Acknowledgments

This work was supported by grants R01NR014449, R01NR012657, R01NR012907, R21MH099979, and the Alzheimer's Association (B.M.A.).

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