Chapter 11
Magnetic Resonance Spectroscopy in HIV-Associated Neurocognitive Disorders: HAND

Eva-Maria Ratai

Abstract A significant number of HIV-infected patients develop neurological symptoms ranging from minor cognitive impairment to severe dementia (known HIV-associated dementia, HAD). Without combination antiretroviral therapy (cART) HAD occurs in 20–40 % of HIV positive subjects, with the advent of cART the incident has decreased to 5–10 %, although milder forms of cognitive deficits may occur in 30–50 % of those infected with HIV. It is believed that HIV enters the CNS during the early stages of infection by infected immune cells which initiate an inflammatory cascade which results in neuronal injury and loss. Imaging has been widely used to evaluate the effect of HIV to the brain. Specifically, proton magnetic resonance spectroscopy (^{1}H MRS) is one of the most informative methods employed in patients suffering from HIV-associated neurocognitive disorders (HAND). MRS is able to noninvasively measure metabolic changes pertaining to neuronal injury and inflammation, thus, it can assist in the diagnosis of the disease and measure the severity of injury. In animal models of neuroAIDS, MRS has been proven extremely powerful to assess disease progression and response to treatment. Here we review the literature of preclinical models as well as MRS studies of HIV+ adults and children before and after the advent of cART regiments. In addition, we discuss technical considerations related to the disease and finally talk about future direction in HAND using MRS.

Keywords AIDS (acquired immune deficiency syndrome) • HIV (Human immunodeficiency Virus) • NeuroAIDS • HAND (HIV-associated neurocognitive disorders) • SIV (Simian immunodeficiency virus) • Rhesus Macaque • Brain • MRS (magnetic resonance spectroscopy) • MRSI (magnetic resonance spectroscopic imaging) • cART (combination antiretroviral therapy) • Minocycline • Neuroinflammation

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Background on Disease Pathology

Human immunodeficiency virus (HIV) affects more than 1 million people in the United States of America and ~34 million worldwide. Approximately 1.7 million people have died from AIDS and 2.5 million people were newly infected with the virus in 2011 [1]. Figure 11.1 showed the natural disease progression of HIV/AIDS: During the early phase of infection, the virus replicates extensively, reaching levels of 10^6–10^8 copies of HIV RNA/mL in blood plasma due to the absence of discernible immune responses [2]. Once seroconversion occurs (as determined by ELISA/Western Blot), it is thought that the host's immune response begins to control viral replication, causing the high levels of virus to be quickly reduced within weeks [2]. During acute HIV-1 infection, there is frequently a marked decrease in the $CD4^+$ T cell count [3, 4], followed by an increase toward the end of the acute stage, which typically does not return to preinfection levels in the absence of antiretroviral therapy (ART). Throughout the latent period, there is usually a steady decline in the numbers of $CD4^+$ lymphocytes. A diagnosis of AIDS is made if the $CD4^+$ T-cell count falls below 200 per μL. At these later stages of the disease, viral loads are starting to increase once more, leading to symptoms, opportunistic infections, and death.

Early in the AIDS epidemic, HIV-associated neurocognitive disorders (HAND) were recognized as an important clinical manifestation of the disease [5–9]. Prior to

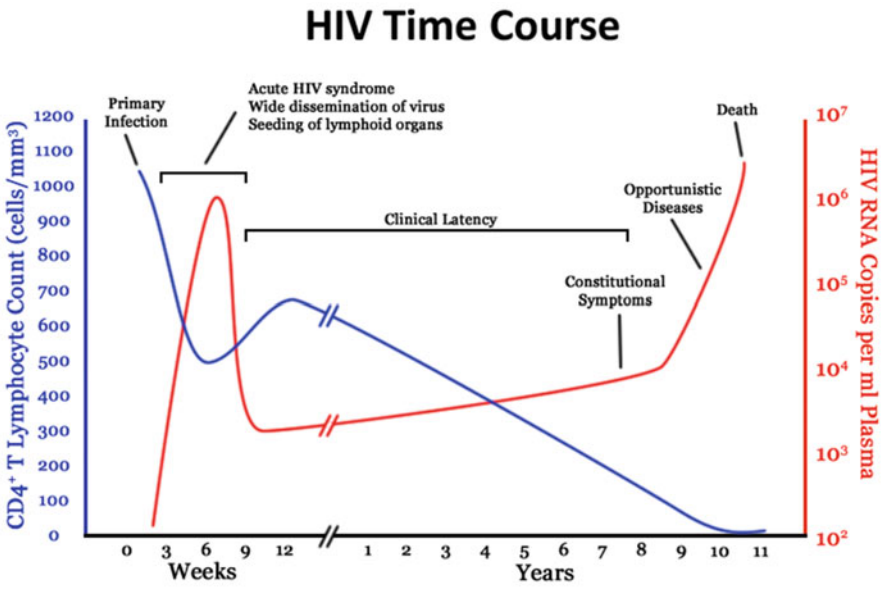

Fig. 11.1 A generalized graph of the relationship between HIV copies (viral load) and $CD4^+$ T cell counts over the average course of untreated HIV infection. This is a file from the Wikimedia Commons. Commons is a freely licensed media file repository. Adapted from Fig. 1 in Pantaleo, G et al. (February 1993). "New concepts in the immunopathogenesis of human immunodeficiency virus infection". *New England Journal of Medicine* 328 (5): 327–335. PMID 8093551

the advent of combination antiretroviral therapy (cART), 20–40 % of HIV-infected patients developed neurological symptoms ranging from minor cognitive impairment to severe dementia (known as HIV-associated dementia, HAD or AIDS dementia complex, ADC). ADC is characterized clinically by severe cognitive, motor, and behavioral abnormalities in the absence of opportunistic infections. Physical symptoms include headaches, generalized seizures, and ataxia. Cognitive symptoms comprise forgetfulness, slowing of thought processes, global dementia, confusion, and disorientation. Abnormalities in motor functions are characterized by unsteady gait, clumsiness, tremor, limb weakness, loss of coordination, and fine motor control. Finally, behavioral changes such as social withdrawal, lethargy, personality change, and hallucinations have been perceived in patients with ADC [7, 10].

Although cART has reduced AIDS-related mortality, HAND continues to be a major problem in patients with HIV. Antiretroviral drugs suppress virus burden in the plasma, CSF, and lymphoid tissue of HIV+ individuals; however, due to their restricted CNS penetration, these drugs exhibit only limited efficacy in the treatment of HAND. While the incidence of more severe neurological symptoms of ADC has been seen to decrease with cART, less severe versions of the disease persist among the infected population [11, 12]. The overall prevalence of HAND and associated morbidity remains high at approximately ~50 % [13–15]. It is projected that the prevalence of HAND is again increasing as life expectancy among patients increases. As the virus gains resistance to ART, the incidence of severe neurodegeneration is predicted to increase [13, 16, 17] and remains a significant independent risk factor for death [18, 19].

There is a consensus that HIV enters the central nervous system (CNS) during the early stages of infection primarily through virally infected/activated monocytes from the blood across the blood–brain barrier (BBB) by a so-called Trojan horse mechanism [20, 21]. Once in the brain, infected monocytes/macrophages and microglia release viral envelope proteins and cytokines, which in turn activate uninfected macrophages and microglia [22–29]. These activated macrophages and microglia release several neurotoxic substances, such as free radicals and glutamate, which lead to neuronal injury and apoptosis [30–34]. In summary, the virus does not directly infect neurons, yet neurons suffer injury due to indirect mechanisms mediated by host proinflammatory and viral proteins [26, 31, 35–37].

Post mortem neuropathological studies have demonstrated that the virus variably affects different regions of the brain. Pre-ART, abnormalities were predominantly found in the white matter and in subcortical structures, with relative sparing of the cortex [5]. Furthermore, higher levels of virus were found in the basal ganglia and hippocampus compared to cerebellar cortex and midfrontal cortical gray matter [38]. However, it appears that the anatomic distribution and temporal progression of neuropathologic changes differ across individuals, thus, it is important to consider both cortical and subcortical brain regions in studies of neuropathogenesis and treatment of HIV-related brain disease [39].

Potential Clinical Utility of MRS in HAND

Imaging has been used widely to evaluate the effect of HIV infection on the brain. Structural neuroimaging methods such as computerized tomography (CT) and magnetic resonance imaging (MRI) are important for the diagnosis of cerebral opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML), Toxoplasmosis, Neurosyphilis, and Cytomegalovirus (CMV) Encephalitis. Morphological alterations detected by MRI include cortical atrophy at later stages of HIV-associated dementia (HAD). Furthermore, hyperintensities in the white matter (WM) and basal ganglia (BG) were observed on T2-weighted images of HIV+ patients. Diffusion tensor imaging (DTI) has been used to study the white matter structural integrity as it is typically more sensitive compared to T2-weighted imaging [40]. More recently, also quantitative morphological MRI has been used for assessing the severity of HAND [41–43]. However, structural imaging techniques were found to be limited in the evaluation of early cognitive changes [44–47]. Thus, neuroimaging techniques that provide functional and biochemical information have proven to be more useful in the evaluation of HAND [48].

SPECT and PET are sensitive to changes related to cerebral perfusion and metabolism. Specifically, PET has been used in patients with HAND and in animal models of neuroAIDS to study glucose metabolism, neuroinflammation, microglial activation, fibrillar amyloid, and dopamine transporters [49–53]. However, nuclear medicine techniques expose the subject to radiation and have therefore limited use for monitoring diseases progression or treatment effects when repeat measurements are needed [54].

Magnetic resonance spectroscopy (MRS) offers the unique ability to measure a wide range of cerebral metabolite levels in a noninvasive manner. Specifically, proton MRS (^{1}H MRS) is one of the most informative methods employed in neuroAIDS research. MRS has been used in HIV-infected patients to understand the cognitive deficits and to establish biomarkers in HAND. To date, more than 80 original studies have been employed to evaluate the effects of HIV infection using MRS. The resonances seen in the brain by ^{1}H MRS are typically low weight molecules related to neuronal injury/loss and inflammation. Specifically, *N*-Acetylaspartate (NAA), an established marker for neuronal density and viability is decreased in patients with advanced neurocognitive symptoms and is of particular value for the in vivo assessment of neuronal integrity [55–58]. The earliest MRS studies of neuroAIDS, published in the early 1990s, reported decreases in NAA/Creatine (NAA/Cr) in patients with advanced neurocognitive symptoms and the decrease in NAA/Cr was found to be associated with disease severity [59–61].

Choline-containing compounds are related to cell/lipid membrane metabolism, thus an increase in Cho or Cho/Cr in HIV-infected patients is possibly associated with an immune response that includes cerebral inflammation or gliosis [61–63]. *Myo*-inositol (mI) is an organic osmolyte which is primarily located in glial cells, thus an increase in mI is associated with gliosis or inflammation [64]. Since HAND is considered a neuroinflammatory disease mI is especially

important in the evaluation of glial response. In fact, MRS studies have found an elevation in mI/Cr as a result of HIV-associated brain injury [65–67].

The total creatine (tCr) resonance consists of the sum of creatine (Cr) and phosphocreatine (PCr), a high energy reservoir for the generation of ATP. Since Cr and PCr are in equilibrium the tCr peak is commonly assumed to remain stable in size despite bioenergetic abnormalities that occur with many pathologies or with age [68]. Consequently, the tCr resonance is often used as an internal standard and is commonly referred to as simply creatine (Cr). However, elevated Cr levels have been reported in the white matter in ART naïve HIV+ ADC stage 3 patients [69] but also in the WM in simian immunodeficiency virus (SIV) infected rhesus macaques during acute infection [70] and in an accelerated macaque model of neuroAIDS a few weeks after infection [71]. In the context of HAND, an elevation in Cr may reflect enhanced high-energy phosphate turnover in activated astrocytes and microglia [71].

Other metabolites of interest include glutamate (Glu), glutamine (Gln), and Glx, which is the sum of Gln and Glu. Glu is an amino acid acting as excitatory neurotransmitter and Gln is its precursor. Even though activated microglia release neurotoxic substances, such as free radicals and glutamate, which result in excitotoxicity and finally to apoptosis [30–34], decreases in Glx levels have been reported during early and chronic HIV infection [72–76]. The observed decrease in Glx may indicate neuronal dysfunction. Furthermore, levels of lactate (Lac), a marker of anaerobic glycolysis and inflammation and lipids, indicators of cell membrane turnover, have been assessed in HIV+ patients. The Lac/Cr ratio in the lenticular nuclei was significantly greater in HIV+ patients with moderate to severe impairment compared to seronegative controls. Moreover, the (Lipids + Lac)/Cr ratio was significantly elevated in both mild and moderate to severe HIV+ patients compared to seronegative controls [77].

Consequently, quantification of these abovementioned metabolite levels can assist in the diagnosis of the disease and measuring the severity of injury. Especially, in animal models where longitudinal scans are common, MRS has been proven extremely powerful to assess disease progression and response to treatment.

Technical Considerations for HAND

Echo Time

As with MRI, the choice of echo time (TE) can have an enormous effect on the appearance of the information obtained in a ^{1}H MRS study. MR spectra obtained with shorter echo times (~30 ms) allow the detection of more metabolites including glutamate, glutamine, and *myo*-inositol. However, the baseline is typically more distorted due to increased lipids and macromolecular background signals. Spectra obtained with longer echo times (135–144 ms) show reduced number of

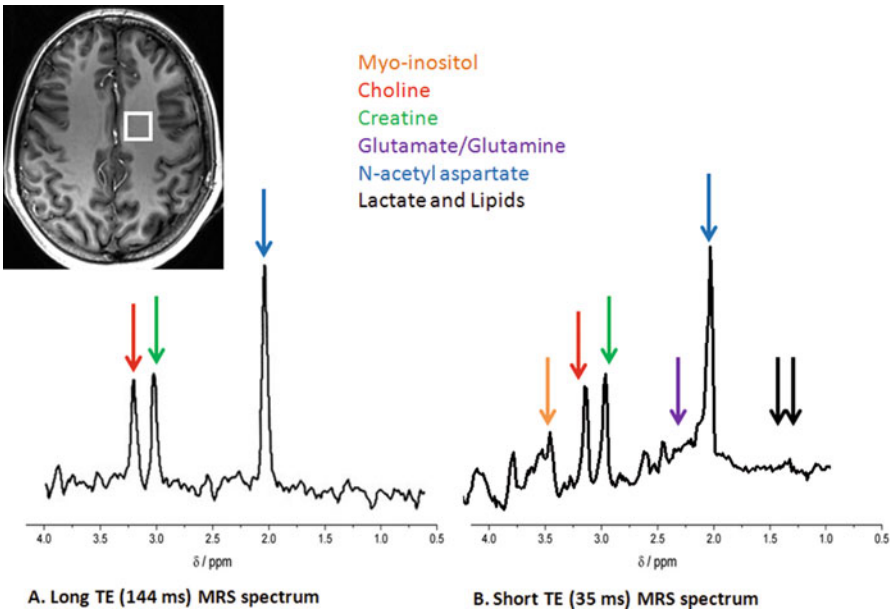

Fig. 11.2 MRS of white matter in a normal brain. (**a**) Long TE spectra have less baseline distortion and are easy to process and analyze but show fewer metabolites than short TE spectra. (**b**) Short TE demonstrates peaks attributable to more metabolites, including lipids and macromolecules, glutamine and glutamate, and *myo*-inositol

metabolites. However, spectra are easier to process and analyze due to the relatively flat baseline. In addition, the lactate (1.3 ppm) doublet is inverted, therefore allowing better differentiation between Lac and lipids. On the other hand, longer TE attenuates the signal-to-noise ratio (SNR) and some metabolites, e.g., mI, Glu, and Gln, which can only be detected at short echo times, would be missed, thus short TE is typically preferred (Fig. 11.2).

Single Voxel vs. MRSI

To measure MR spectra in vivo one has to be able to define the spatial origin of the detected signal. Basically, two methods exist to obtain the spatially localized metabolic information in vivo:

1. Single voxel spectroscopy (SVS) uses selective excitation pulses to localize a voxel of typically 3–8 cm^3. SVS has the advantage of higher SNR and typically shorter acquisition times. However, the accumulative scan time permits acquisition of only a few locations (Fig. 11.3).
2. Magnetic resonance spectroscopic imaging (MRSI) can be obtained in two or three dimensions. MRSI allows one to collect the spectral information from a

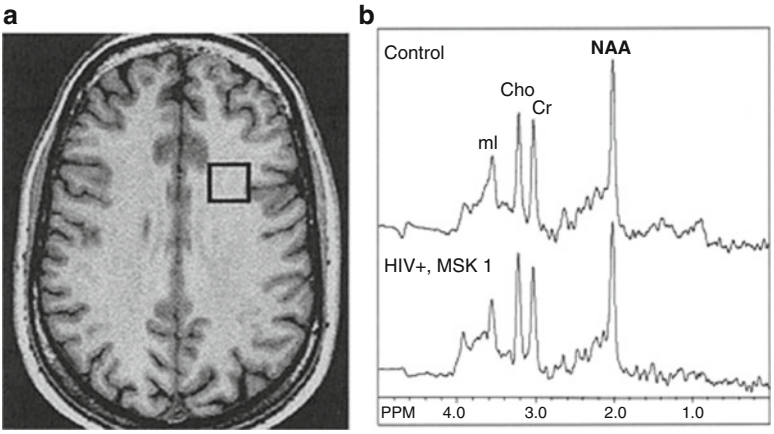

Fig. 11.3 Single-voxel proton magnetic resonance spectroscopy (SV-MRS). (**a**) Voxel locations the left frontal white matter region selected for quantitative spectroscopic analysis using SV MRS. (**b**) Sample spectra obtained in the frontal white matter in an HIV seronegative control and an HIV seropositive individual with mild dementia using SV-MRS. The NAA peak is decreased in the HIV dementia patient. *Reprinted with permission from* [80]

volume consisting of many voxels with individual voxel sizes of typically 0.5–3 cm^3 and most importantly makes it possible to cover large brain areas although spectra are typically characterized by lower SNR compared to SVS (Fig. 11.4).

MRSI is preferred for clinical studies where it is indicated to obtain metabolic information of a large and heterogeneous lesions (e.g., in tumors), and when additional simultaneous spectral information from control regions needs to be obtained. However, HIV is considered a predominantly "global disease" and therefore, most studies have acquired SVS from 1 to 3 brain regions covering frontal white matter (FWM), basal ganglia (BG), and parietal cortex (PC) consistent with recommendations by the HIV MRS Consortium [78, 79]. In a study using both techniques, Sacktor et al. demonstrated that short TE SVS and long TE MRSI offer complementary roles in evaluating individuals with HIV dementia [80] (Fig. 11.4).

Field Strengths

MR spectroscopy inherently suffers from low SNR resulting in voxels with low spatial resolution or long acquisition times. The SNR can be improved by using higher magnetic field strengths. Physics predicts a linear increase in signal with field strength if T1 and T2 relaxation times, coil and system losses, and radiofrequency (RF) penetration effects do not change significantly. In addition,

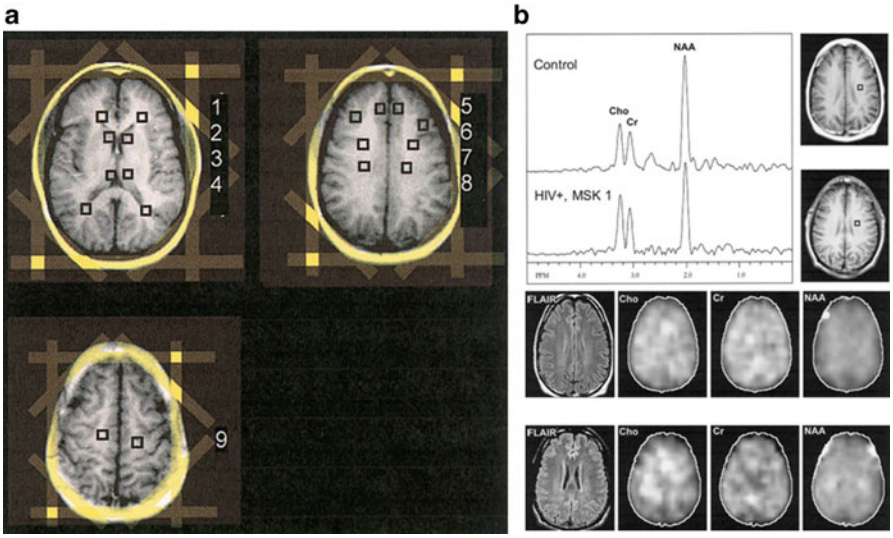

Fig. 11.4 Magnetic resonance spectroscopic imaging (MRSI). (**a**) The MRSI locations include bilateral regions examining the (*1*) forceps minor, (*2*) caudate nucleus, (*3*) thalamus, (*4*) forceps major, (*5*) mesial frontal gray matter, (*6*) dorso-lateral gray matter, (*7*) frontal white matter, (*8*) centrum semiovale, and (*9*) subcortical white matter. The location of octagonal outer-volume saturation bands for lipid suppression is indicated on localizer images in *yellow*. (**b**) Sample spectra, T1-weighted and FLAIR MR images, and spectroscopic images for Cho, Cr, and NAA obtained in the frontal white matter in an HIV seronegative control and an HIV seropositive individual with mild dementia using MRSI. The NAA peak is decreased in the HIV dementia patient. FLAIR MRI scans show no abnormalities; no obvious spatial variations in the metabolic images are apparent between the HIV seronegative control and an HIV seropositive individual. Focal hyperintensity at the edges of the brain in the NAA images is due to lipid contamination from the peri-cranial tissues. *Reprinted with permission from* [80]

the increased chemical shift range at 3 and 7 T relative to 1.5 T results in greater separation of the resonance peaks, and consequently, allows for better quantification of those metabolites that generally overlap with others such as Glu, Gln, and mI. Thus, MRS is preferred at 3 T over 1.5 T. Figure 11.5 shows the spectra from the parietal cortex of a healthy rhesus macaque obtained at three different field strengths, 1.5, 3, and 7 T. The SNR increases at higher fields. In addition, improvements in spectral resolution are evident.

Higher field strength may also result in better reproducibility. For example, in a study at Massachusetts General Hospital, four rhesus macaques underwent repeated (>4 times) SVS scans before infection to access reproducibility of the technique. Data at 1.5 T revealed coefficients of variance (CVs) within the same animals of 7–11 % for NAA/Cr, 13–16 % for Cho/Cr, and 8–12 % for mI/Cr in various brain regions including the FC, WM, and BG [81]. Four additional macaques were scanned a few years later at 3 T and revealed CVs of only 4 % for NAA/Cr, 2–8 % for Cho/Cr, and 3–7 % for mI/Cr in the FC, WM, and BG, respectively.

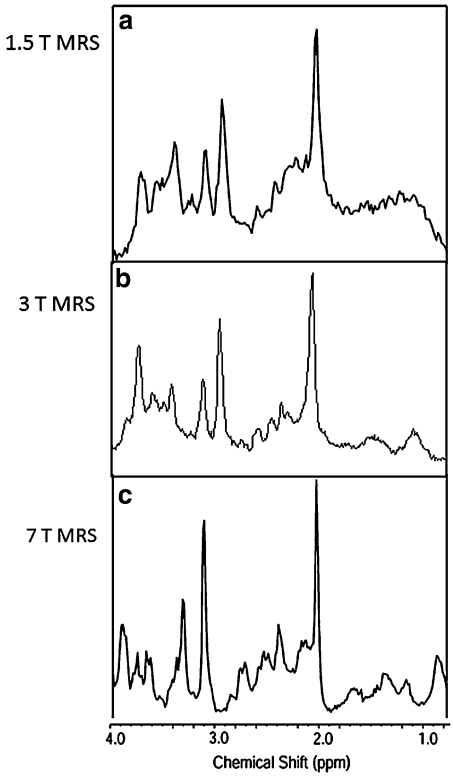

Fig. 11.5 Comparison between MR spectra of rhesus macaques obtained at three different field strengths. (**a**) 1.5 T, (**b**) 3 T, (**c**) 7 T

Ratios vs. Absolute Concentration

There are long-standing discussions on the best way to quantify MRS signals, specifically relative versus absolute quantification. The easiest method is to report metabolite ratios such as NAA/Cr. However, using Cr as an internal standard is often based on the assumption that the Cr concentration does not change during the disease process, which is sometimes, but not always true. Ratios are relatively easy to determine and are more reproducible than absolute concentrations. However, when a change is detected, it may not be possible to determine whether it is due to a change in the numerator, denominator, or both.

Changes in creatine have been reported in patients and an animal model of HAND [69–71]; increasing creatine levels may mask increases in Cho and mI. Absolute quantification of brain metabolites by MRS is more difficult to obtain. They are generally expressed in units of mmol/kg. Methods used for absolute quantification include: (a) phantom replacement techniques [82–84], (b) using the unsuppressed water signal as a reference [85–87], or (c) the use of an external reference [88, 89]. Most studies on HIV-infected patients that reported metabolite concentrations have used the water signal as reference [85].

Overview of MRS in Animal Models of HAND

In the previous chapter, we have established that in vivo MRS is a powerful tool in studying the effect of HIV infection on the brain. Due to its noninvasive nature, in vivo MRS is suitable for both cross-sectional and longitudinal studies. However, studies of HIV-infected individuals present difficulties in interpretation: the time of infection is often unknown; a number of individuals are infected with more than one strain of HIV; alcohol and substance abuse result in comorbidities. Animal models allow for greater flexibility to explore and address the questions concerning HIV neuropathogenesis in a controlled manner. Furthermore, animal models allow access to subsequent *post mortem* neuropathology studies helping define relationships between in vivo biomarkers of neuronal function and inflammation by MRS and *postmortem* histopathology.

Crucial insights into neuroAIDS have emerged from several excellent animal models, including a transgenic HIV mouse model that expresses viral surface protein gp120 in the brain [90]; injection of HIV-1-infected macrophages into the brains of severe combined immunodeficient (SCID) mice [91], which results in the development of pathologic hallmarks for HIV encephalitis (HIVE) and neuroinflammation [92–94]; a feline immunodeficiency virus (FIV) infection of cats [95–102]; and the SIV macaque models [103–107].

MRS Studies of Rodent Models

Rodent models have been applied in elucidating neuropathogenic pathways associated with HIV infection, such as the migration and distribution of monocytes in brain tissue and the neurotoxic effects of specific viral proteins [108–110]. In a SCID mouse model, HIVE was induced focally into the striatum by the unilateral injection of HIV-1ADA-infected human monocyte-derived macrophages. Histology revealed focal giant cell encephalitis, with reactive astrocytes, microgliosis, and neuronal dropout. Metabolite concentrations using in vivo MRSI at 7 T were measured 7 days after injection in infected mice compared to sham-operated and unmanipulated mice. These studies showed significant decreases in NAA in both the ipsilateral and contralateral site of injection in HIVE mice compared to sham-operated mice indicating that a highly focal encephalitis can produce global deficits for neuronal function and metabolism [111].

MRS Studies of FIV Models

Like HIV, FIV is known to infect $CD4^+$ T lymphocytes causing immunosuppression, encephalopathy, and neurobehavioral deficits [112, 113]. The neurological abnormalities are typically more profound when FIV is induced during the

developmental period of brain maturation, making this an ideal model for understanding neurologic complications observed in children infected with HIV [102, 114]. Cats infected with Maryland isolate (FIV-MD) have demonstrated reductions in NAA and NAA/Cho between 8 and 14 months of infection. FIV-infected cats also exhibited a higher proportion of quantitative electroencephalographic relative slow wave activity that correlated to lower NAA in the frontal cortex [102]. Furthermore, cats infected with high viral titers of V1CSF (a neurovirulent FIV strain which was derived from the CSF of a cat with encephalopathy) had increased Cho/Cr and reduced NAA/Cr in the frontal cortex compared to those that received low titers indicating that infectious titers in the brain during the early stages of infection determine the severity of neurovirulence [115]. Like many HIV studies, FIV infection also resulted in reduction in Glu and Glu/Cr in the cortex and white matter [115].

MRS Studies of SIV Macaque Models

The SIV macaque models are arguably the most comparable and informative of CNS disease progression [107]. The SIV-infected rhesus macaque shares very similar pathology with HIV-infected human patients, including the development of AIDS, disease of the CNS, and cognitive or behavioral deficits [103–107]. SIV is the closest known phylogenetic relative of HIV and also infects $CD4^+$ macrophages, lymphocytes, and microglia. Its acute infection parallels that of HIV, with a very rapid change in the blood viral load observed during the first month of infection, usually around 11–12 days after infection [116–118]. Neuroinvasion occurs early in infection for both HIV and SIV [119], and their neuropathology includes gliosis, perivascular cuffing, and neuronal injury [104, 106, 120, 121]. Furthermore, antiretroviral therapy has been successfully applied to SIV-infected macaques [122, 123].

Traditional SIV Model

Acute/Early SIV Infection

Acute HIV infection is the time period from viral infection through seroconversion. It is characterized by high peak in viremia and impairment/destruction of $CD4^+$ T lymphocytes [2, 124, 125] similar to events that are manifest in chronic infection when HIV-related dementia is more likely to occur [126]. In the SIV macaque model peak viremia is typically observed within 2 weeks after inoculation with SIVmac251 (Fig. 11.6a). We found that plasma SIV RNA peaked at 11–12 days postinfection (dpi) at ~10^8 copies/mL. Within days after the peak, the viral load reverted to lower levels ~10^6 copies/mL due to the immunologic response by the macaques. In these studies nearly all macaques had transient reductions in NAA/Cr

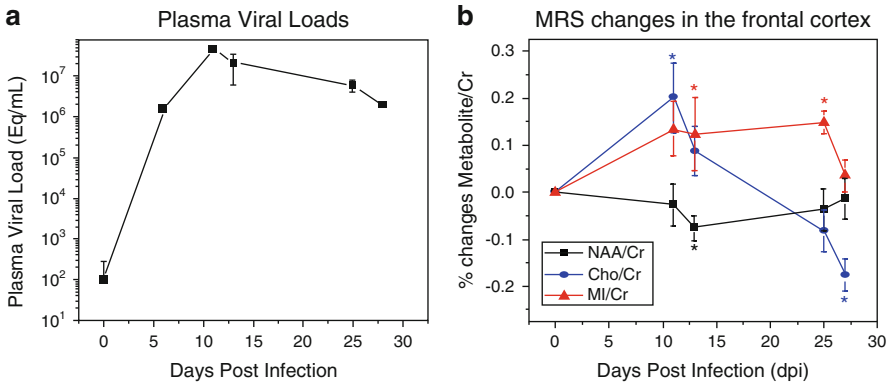

Fig. 11.6 Acute changes in the SIV macaque model of NeuroAIDS. Based on [118] and [70]. (**a**) Plasma viral loads: peak viremia can be detected at 11 days postinfection (dpi). (**b**) Metabolic changes in the frontal cortex: acutely SIV-infected macaques showed a transient decrease in NAA/Cr at 13 dpi; elevated mI/Cr at 11, 13, and 25 dpi; and a dynamic response in Cho/Cr with increases at 11 dpi and decreases below baseline at 27 dpi

by single voxel MRS within the first 2 weeks of infection in the frontal cortex (Fig. 11.6b) but not in the basal ganglia or white matter. Pathology confirmed neuronal dysfunction detected by significant decreases in synaptophysin, a marker for synaptic integrity, while the numbers of neurons were not affected by the virus suggesting that during early infection reversible neuronal injury occurs, but not neuronal loss [127].

Myo-inositol levels were significantly elevated in both the frontal cortex and white matter regions, suggesting stimulation of glial metabolism within the first month of infection [70]. In addition, dynamic changes in choline were observed in the same regions. At the time of peak viremia, both choline and Cho/Cr were significantly elevated; however, between 2 and 4 weeks postinfection (wpi), Cho/Cr ratios underwent a large reduction, resulting in levels below preinfection [118] (Fig. 11.6b). An increase in Cho reflects altered membrane metabolism [128] and in the context of neuroAIDS may be reflective of cerebral inflammation, cell proliferation, recruitment, microgliosis, and/or astrocytosis [61, 63]. Evidence of the association with astrocytosis is given by our observation that during the acute phase changes in Cho/Cr mirror the changes in the astrocyte response by glial fibrillary acidic protein (GFAP) [129]. Decreases in Cho below baseline have rarely been reported in diseases not involving necrosis and still warrant further investigations.

Furthermore, the SIV Model is characterized by elevations in creatine concentrations in the white matter during the acute phase of infection. During that stage, the virus enters the brain through infected monocytes [31], resulting in glial-cell activation and proliferation. These processes may manifest themselves in high tissue metabolism, which would explain an increase in Cr. Energy change as a function of enhanced glial activation is supported by the finding that the greatest increases in mI and Cho are in the same regions as the highest increase in Cr [70].

Chronic SIV Infection

Eight rhesus macaques were infected with SIVmac251 and serially imaged with MRI and ^{1}H MRS to terminal AIDS or the endpoint of the study at 2 years. Due to the low incidence of SIV encephalitis (SIVE), possible diverse viral mutation and the differences in host factors the metabolic response over the time course of infection was variable. However, comparing the same animals we found a positive correlation between frontal cortex Cho/Cr and plasma viral load and a negative correlation between basal ganglia NAA/Cr and plasma viral load [130].

Rapid SIV Model

Untreated SIV^{+}/CD8^{-} Animals

Because of its parallels with HIV pathogenesis, the traditional SIV macaque model is hindered by the low rate of development of SIVE and the long time period for its evolution. Only approximately 25 % of infected macaques develop encephalitis and progression to terminal AIDS may take several years [107, 131]. These factors make it difficult for use in testing potential drug therapies. Therefore, attention has focused on two rapidly progressing SIV macaque models. One model employs pig-tailed macaques that are coinoculated with two SIV strains (SIV/17E-Fr and SIV/DeltaB670), which accelerates SIV CNS disease, producing SIVE in over 90 % of these animals within 3 months [132–135]. The second model retains the use of the SIV-infected rhesus macaques, but uses a monoclonal antibody to deplete the animal of CD8^{+} lymphocytes [136, 137]. In this model, 80 % of persistently CD8-depleted animals develop SIVE, with a course of progression to terminal AIDS within 12 weeks [33, 123, 138]. Modifications in applying the antibody have resulted in >90 % of macaques becoming persistently CD8 depleted with nearly all of them developing SIVE. This model also produces profound neuronal injury detectable within weeks by in vivo ^{1}H MRS [123]. Thus, this accelerated model of neuroAIDS in combination with MRS provides an exceptional opportunity to efficiently explore potentially useful drug therapies that can control or reverse neuronal injury and damage.

In the SIV^{+}/CD8^{-} model plasma viral RNA was detectable 6 days after infection with ~10^{7} copies Eq./mL and approached a plateau by 4 weeks after infection at ~5×10^{8} copies Eq./mL (Fig. 11.7a). CSF viral loads were found to be approximately 3 orders of magnitude lower than plasma. SIV^{+}/CD8^{-} animals were euthanized at 4, 6, and 8 weeks after infection and the amount of viral RNA in the frontal cortex was found to be ~10^{6} copies Eq./g at all three time points (Fig. 11.7b).

The neuronal marker NAA/Cr steadily declined following SIV infection and CD8 depletion, reaching levels as low as 20 % below baseline by 8 wpi in untreated animals (Fig. 11.7c). The decrease in NAA/Cr following infection is due to both decreases in neuronal NAA and increases in creatine, which most likely reflects the

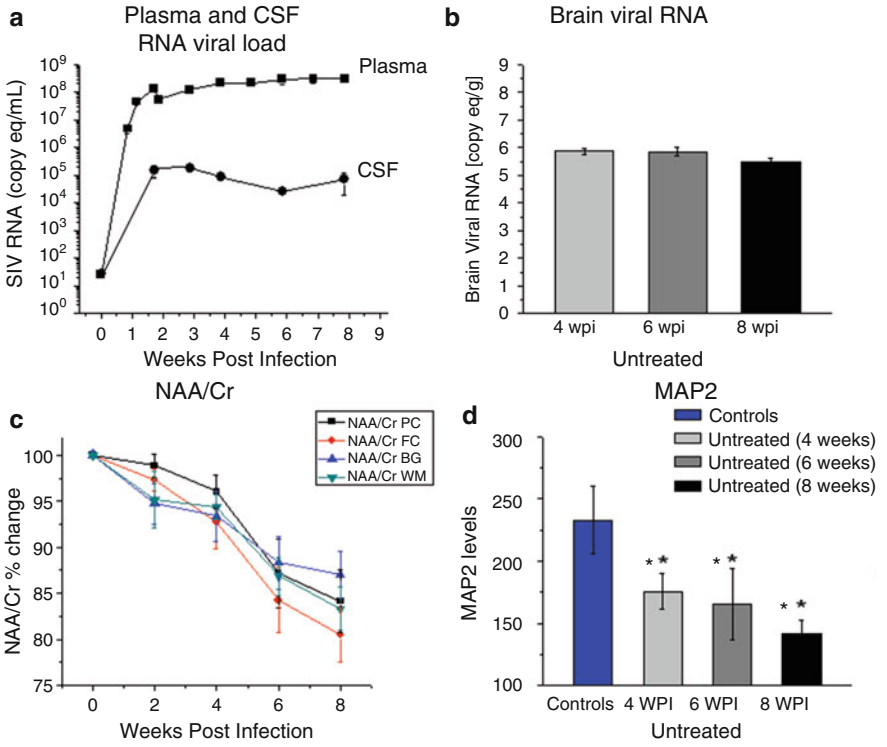

Fig. 11.7 (**a** and **b**) Viral RNA and neuronal injury following SIV infection and CD8 depletion. Based on [148] and [71]. (**a**) Viral RNA was detectable in plasma 6 days after infection (~10^7 copies Eq./mL) and the viral load approaches a plateau by 4 weeks after infection. The mean plasma viral load in infected animals was 4.9×10^8 copies Eq./mL 8 weeks after infection. CSF viral loads were found to be approximately 3 orders of magnitude lower than plasma in all animals. (**b**) Animals were euthanized at 4, 6, and 8 weeks after infection. The amount of viral RNA in the frontal cortex of untreated animals was 7.5×10^5, 9.2×10^5, and 3.0×10^5 copies Eq./g at 4, 6, and 8 weeks after infection, respectively. (**c**) The neuronal marker NAA/Cr steadily declined following SIV infection, reaching decreases as low as 20 % below baseline by 8 weeks postinfection (wpi) in the parietal cortex (PC). (**d**) Neuronal injury is confirmed by decreases in Microtubule-associated protein 2 (MAP2), a marker of dendritic integrity

cumulative effects of altered metabolic states of neurons and glial cells, respectively (for further discussion, see Ratai et al. [71]). Neuronal injury was confirmed by decreases in microtubule-associated protein 2 (MAP2), a marker of dendritic integrity (Fig. 11.7d).

CART and Minocycline-Treated SIV$^+$/CD8$^-$ Animals

To gain further insights into the neuropathogenesis of AIDS we modulated disease progression with treatments. In total, 11 SIV$^+$/CD8$^-$ rhesus macaques were treated. Seven received minocycline (MN), an antibiotic, which easily crosses the BBB, and

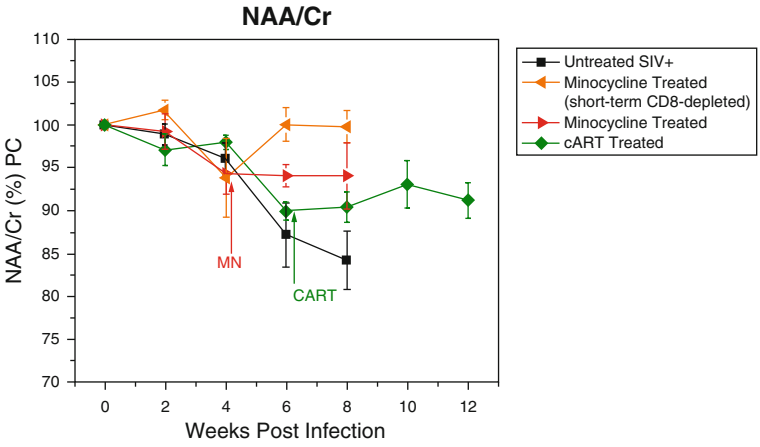

Fig. 11.8 Amelioration of neuronal injury with combination antiretroviral therapy (cART) and minocycline. Based on [147, 148]. NAA/Cr steadily declined following SIV infection in all animals, reaching levels as low as 20 % below baseline by 8 wpi in untreated animals (*black squares*). The decline in NAA/Cr was arrested with the cART (*green diamonds*) and minocycline treatment (*red triangles*) resulting in higher NAA/Cr levels when compared to untreated animals sacrificed at 8 wpi. Animals that were MN treated and had partial immune reconstitution of the $CD8^+$ T cell population had the most complete recovery (*orange triangles*)

has been found to have anti-inflammatory, neuroprotective, possibly antiviral effects [139–146]. Four of the seven MN-treated animals had persistent depletion of $CD8^+$ lymphocytes. However, three of the MN-treated animals had partial recovery of $CD8^+$ lymphocytes. This latter cohort was distinct from the long-term depleted cohorts in respect to its 1 order of magnitude lower viral loads and was thus grouped into a separate cohort of MN-treated short-term depleted animals. All seven animals were treated at 4 wpi for 4 weeks.

Four additional animals were treated with combination antiretroviral therapy (cART) consisting of 9-*R*-2-Phosphonomethoxypropyl adenine (PMPA), 5-Fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-[1,3]oxathiolan-5-yl]cytosine (FTC), and 2′-3-′-didehydro-2′-3′-dideoxythymidine (Stavudine, Zerit®) starting at 6 wpi for 6 weeks. Both treatments, MN and cART, resulted in a moderate decline of plasma, CSF, and brain viral levels [147, 148]. During minocycline as well as cART treatment, a significant reduction of circulating activated $CD14^+CD16^+$ monocytes was observed. Without treatment, SIV progression is characterized by the expansion of these monocytes in the periphery, which play a major role in trafficking virus across the BBB into the brain [149]. More importantly, the decline in NAA/Cr was arrested with MN and cART (Fig. 11.8, here shown for the parietal cortex, NAA/Cr) resulting in higher NAA/Cr levels when compared to untreated animals sacrificed at 8 wpi. Animals that were MN treated and had partial immune reconstitution of the $CD8^+$ T cell population had the most complete recovery. Thus, we hypothesize that possibly the best strategy to treat neuroAIDS is by the use of combination therapies targeting pathogenic factors in both the periphery and CNS [148].

Overview of Clinical MRS in HAND

Early HIV Infection

Until recently the effect of HIV to the brain during the early stages of HIV infection (less than 1 year of seroconversion) remained relatively unknown. However, a few studies show that soon after infection brain metabolism is affected by the virus as detected by in vivo MRS. In a study by Lentz et al., eight subjects were examined by SVS MRS within 3 months of their evolving Western blot and subsequently at

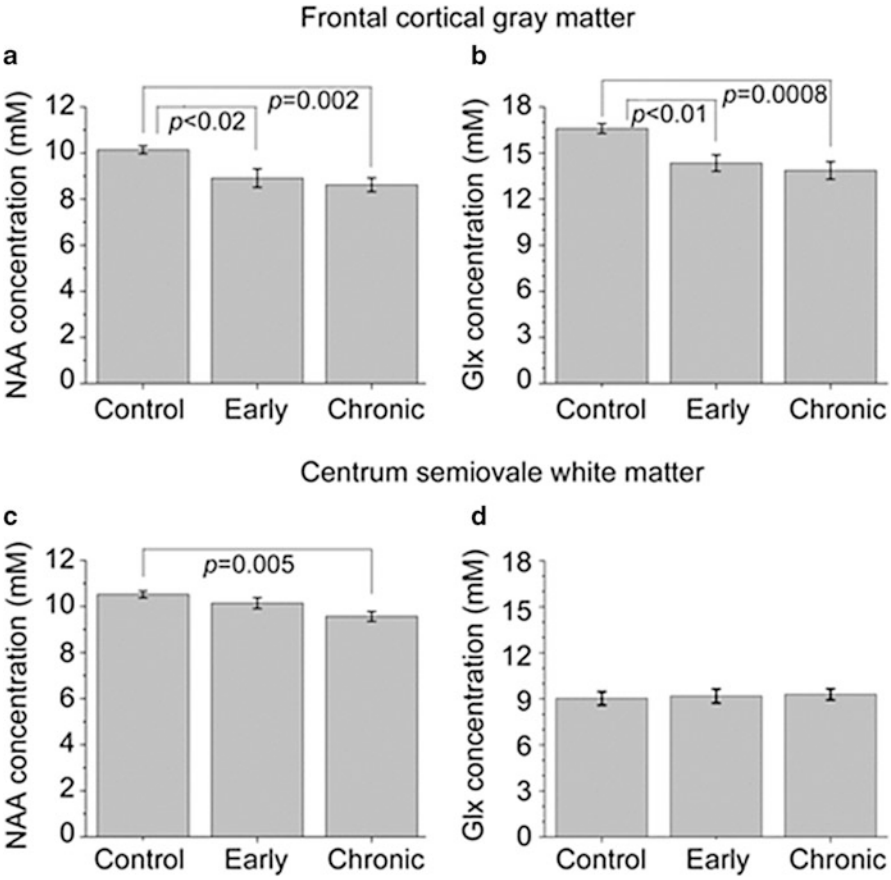

Fig. 11.9 Metabolic changes in NAA and Glx in the frontal cortex and white matter centrum semiovale during early and chronic infection. In the frontal cortical gray matter *N*-acetylaspartate (NAA) (**a**) and glutamate + glutamine (Glx) (**b**) levels are reduced in subjects during the first few months of infection, similar to subjects with chronic infection who are neurologically asymptomatic. Within the white matter of the centrum semiovale, NAA (**c**) was found to be reduced in chronically infected patients with HIV, but not in those during early infection. No changes from control levels for Glx in the white matter were observed (**d**). *Reprinted with permission from* [76]

2 and 6 months after their initial scan. Initially, a decrease in NAA and Glx were observed in the frontal cortex but not in the white matter semiovale compared to controls suggesting that frontal cortical gray matter to be more susceptible to early neuronal injury [76] (Fig. 11.9). Further longitudinal evaluation of this cohort showed increases in choline metabolism in the FC and WM indicative of lipid membrane turnover and glial metabolism [150]. These findings were confirmed by Sailasuta and Valcour who found increases in Cho/Cr in the WM and BG, respectively, in HIV+ patients being scanned during the first year of infection (median 2 weeks after infection) compared with HIV− controls [151, 152]. Recently, MRS markers have been correlated with markers of inflammation and neuronal injury suggesting early neuronal injury in a subset of participants with primary HIV infection through mechanisms involving central nervous system inflammation [153, 154].

Chronic HIV Infection

Observed MRS changes in chronically HIV-infected patients typically show reduction in NAA or NAA/Cr and elevations in Cho and mI or their respective ratios over Cr. The first case report of MRS studies in HIV-infected patients appeared in 1990 and discussed the strength of MRS in providing a marker of neuronal loss in patients with normal MRIs [155]. The first larger study of MRS in more than 100 HIV+ patients showed decreased NAA/Cr and elevated Cho/Cr [61]. Subsequently, it was found that Cho/Cr was elevated even in asymptomatic HIV+ patients and in patients with AIDS dementia complex while NAA/Cr was only decreased in symptomatic ADC patients [156] confirming that brain choline-containing compounds are elevated in HIV+ patients before the onset of ADC [157]. The decrease in NAA seems to correlate with the degree of neuronal dysfunction. Decreases in NAA/Cr of ~10 % have been observed in HIV+ patients with minor cognitive or motor dysfunction [67], while reductions of 15–28 % been reported in HIV+ patients with severe cognitive impairment or AIDS dementia complex compared to HIV− controls [63, 156, 158, 159].

Elevated mI or mI/Cr has been reported at various stages of HIV dementia and has been shown to increase with dementia severity [54, 65–67, 160]. Elevated Cr levels have been reported in the frontal white matter of chronic HIV patients [69]. Further changes in chronically infected patients include decreases in glutamate or Glx in the frontal white matter [72, 73]. Lower brain glutamate levels are associated with poorer cognitive deficits in HIV patients [74, 75].

Post Post-cART

As previously stated with the advent of ART, the incidence of severe neurological symptoms of HAD has been seen to decrease; however, less severe versions of the

disease persist among the infected population [11, 12]. The characteristic involvement of the basal ganglia in pre-ART specimens is less commonly seen in post-ART specimens, which display neuroinflammation in the hippocampus and in adjacent parts of the entorhinal and temporal cortices [15, 161, 162].

Longitudinal studies in HIV+ patients with mild dementia showed improvement of CD4 counts and HIV Dementia Scale score when treated with cART. The initially increased Cho/Cr levels reversed in the midfrontal cortex and in the basal ganglia and the initially elevated mI/Cr and mI levels in the basal ganglia also decreased [163]. Another study that followed HIV+ patients before and after cART showed no significant improvement in Cho or mI after 3 months of treatment, but only after 6–9 months [54].

Clinical Trials Using MRS

A few clinical trials have included MRS as one of the outcome measures for neuroprotective drugs in HIV+ patients. In a Phase II randomized, double-blind, placebo-controlled, multicenter trial within the Adult AIDS Clinical Trials Group, 140 HIV-infected patients with mild to severe ADC receiving stable antiretroviral therapy were enrolled to assess the safety and efficacy of memantine, an *N*-methyl-D-aspartate receptor antagonist as treatment of HIV-associated cognitive impairment. While no significant differences in cognitive performance (neuropsychological z score (NPZ)-8) were shown 16 weeks later, the MRS data suggested that memantine may ameliorate neuronal metabolism, an important step to stabilizing or preventing neuronal injury. These results underscore the need for longer studies to assess the full potential of neuroprotective agents [164]. On the other hand, a study that assessed the effectiveness of selegiline transdermal system (STS) in reversing HIV-induced neurologic injury revealed no effect on either MRS metabolites, oxidative stress, or NPZ-8 scores [165].

Comorbidities

HAND is exacerbated by several comorbidities. Numerous studies have shown that neuronal injury is enhanced by both licit (alcohol) and illicit drugs (methamphetamine) [43, 166, 167]. As the HIV-infected population ages, other age-related neurological disorders will likely affect HIV+ patients. Several studies started to investigate the relationship between HIV and age [79].

Of note, increasing evidence suggests that certain antiretrovirals may be neurotoxic [168]. Nucleoside reverse transcriptase inhibitors (NRTIs) suppress HIV replication but are often associated with mitochondrial toxicity. Chronically infected HIV+ patients on long-term cART regimens that included NRTIs such as didanosine and/or stavudine revealed significant reductions in NAA in the FWM

compared with HIV− controls while HIV+ individuals receiving alternative cART regimens that did not include NRTIs exhibited only intermediate decreases in NAA [169].

HIV-Infected Children

Overall, fewer MRS studies have been performed on the brains of HIV-infected children. Most HIV+ children under the age of 13 are infected during pregnancy, childbirth, or breastfeeding. A study by Keller et al. showed that while healthy children showed an increase in NAA with age in the frontal WM and hippocampus, HIV+ children did not show the age-related increase. Furthermore, HIV+ children with high plasma viral loads had lower Cho, mI, and Cr in the basal ganglia but higher Cho in the midfrontal gray matter compared to children with lower viral loads [170].

A study by Mbugua et al. imaged a cohort of 5-year-old HIV+ children in South Africa and found lower CD4/CD8 ratio in early infancy (mean age $= 8 \pm 2$ weeks old) to be significantly associated with lower NAA and Cho levels in the basal ganglia [171]. Furthermore, a longitudinal study by Holmes et al. compared HIV uninfected, exposed (HEU) and HIV unexposed, uninfected (HUU) young children; they found a significant increase in NAA levels with age in HUU only as well as significantly higher mean Cho levels in HEU children at age 7 years [172].

Summary and Future Perspectives

In summary, MRS offers a valuable imaging technique to assess disease status and response to therapeutics in patients with HAND. Since MRS changes are sensitive to early subtle neuropathogenic changes MRS studies certainly add information to conventional MRI exams. In animal models MRS has successfully been utilized to understand the neuropathogenesis of the disease. Specifically, the combination of MRS with immunology, virology, and pathology in animal models has led to a greater understanding of the inflammatory and neuronal events caused by the virus.

To date most human studies have been cross sectional; however, MRS is especially powerful when applied longitudinally to monitor individual patients. Thus, the next step in neuroimaging studies should include standardized MRS protocols in multicenter clinical trials to evaluate potential treatments for patients suffering from HAND. Significant effort has been made by the AIDS Clinical Trial Group (ACTG) using the same imaging paradigm at multiple sites [154].

Furthermore, most studies performed single voxel spectroscopy on either 1.5 or 3 T. However, more novel MRS techniques have been developed to more accurately measure metabolites that show overlapping peaks in the regular one-dimensional (1D) MRS spectra. For instance, using 2D localized chemical

shift correlated spectroscopy (L-COSY) enables converting a crowded, overlapping 1D MR spectrum to a better resolved 2D spectrum through the addition of a spectral dimension [173] and allows for better detection of metabolites at lower concentrations and delineation of the components of otherwise overlapping peaks such as glutamate/glutamine, *myo*-inositol, aspartate (Asp), gamma-aminobutyrate (GABA), taurine, glutathione (GSH), threonine, and macromolecules [174].

In addition, GABA and GSH can specifically be detected with so-called editing techniques either using double-quantum coherence (DQC) [175, 176] or difference editing techniques, e.g., MEGA PRESS [177, 178]. Specifically, the quantification of GSH levels may be of pertinence in HIV-infected patients. HIV is associated with substantial oxidative stress [179]. Glutathione is thought to be an extremely important antioxidant for HIV-infected patients, because it appears to interfere with HIV's entry into its target cells [180].

Greater signal-to-noise ratio, spatial and spectral resolution can also be gained from higher field strengths. 7 T MRS in combination with LCModel [181] allows for the quantification of 17 metabolites [182]. 7 T MRS has successfully been employed in the CD8-depleted macaque model of neuroAIDS [183]. In addition, Gonen et al., have successfully implemented a 3D MRSI sequence with 0.05 cm^3 isotropic spatial resolution at 7 T [184].

Other technical advances include motion- corrected MR spectroscopy exams. For children between 2 months and 7 years of age, motion artifact and patient cooperation often limit the feasibility of MRI and MRS [185]. Using image-based navigators, it is possible to correct motion in structural imaging, single-voxel and multivoxel spectroscopy prospectively [186–192].

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