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HIV-Associated Neurocognitive Disorder (HAND)

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Summary

Neurological involvement in HIV is commonly associated with cognitive impairment. While severe and progressive neurocognitive impairment has become rare in HIV clinics in the era of potent antiretroviral therapy, a majority of HIV patients worldwide perform below expectations on formal neurocognitive tests. Co-morbid conditions contribute to impairment, but they are insufficient to explain the frequency of impairment encountered. HIV disease markers like current viral load and CD4 counts are no longer strongly associated with ongoing impairment on therapy, while cardiovascular disease markers and inflammatory markers appear more closely associated. Novel cerebrospinal fluid and neuroimaging biomarkers are needed to detect and follow impairment. Ongoing research to optimize HIV therapy within the central nervous system, and potentially to intervene in downstream mechanisms of neurotoxicity remain important avenues of future investigation. Ultimately, the full control of virus in the brain is a necessary step in the goal of HIV eradication. Weekly searches of English language publications referring to HIV

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neurocognitive impairment, HIV neuropathy, HIV myelopathy, HIV dementia, and HIV from 1988 to August 2013 were performed. In addition, the authors' own files were manually searched.

Keywords

HAND; HAD; dementia; HIV; imaging; HIV therapy; biomarkers

Introduction

Human immunodeficiency virus (HIV) emerged as a major challenge to world health almost thirty years ago, and has challenged scientists and clinicians to combat its vast and devastating impact. While recognized for its direct impact on the cellular immune system through depletion of infected CD4 lymphocytes, it also has had a broad impact on the nervous system, including evidence for direct pathology in the brain, spinal cord, and peripheral nerves. This primary HIV associated neurocognitive disorder (HAND) combined with a unique spectrum of opportunistic infections and malignancy, comprise neuroAIDS.

The landscape of neuroAIDS has rapidly evolved driven by emerging therapeutic options available for care of HIV patients. Development of combined antiretroviral therapy (cART) has changed HIV to a chronic disease with life expectancy approaching population norms for those patients compliant with medications. Leading issues remaining for neuroAIDS include the implications of persistent low level HIV, ongoing inflammatory responses, potential therapeutic toxicity, and interaction between aging and neurodegeneration due to HIV. A functional cure of HIV will require silencing the virus in all body compartments, including the brain.

HIV remains more prevalent in the developing world. Because HIV therapy often is delayed, a heavy burden continues to occur in these settings due to neurologi cal opportunistic infections, particularly cryptococcal and tubercular meningitis, toxoplasma encephalitis, and progressive multifocal leukoencephalopathy. These complications are largely silenced after stable cART is achieved. In addition, peripheral neuropathy can impact the quality of life of HIV patients, but is reduced when therapy that avoids neurotoxic antiretrovirals is started early after infection. These important neuroAIDS topics are reviewed elsewhere. [1-3] We will restrict the focus of this manuscript to HAND.[4-6]

Clinical Manifestations of HIV-Associated Neurocognitive Disorder (HAND) in the cART Era

Far short of the quest for cure, progress toward eliminating HIV associated neurologic disability has been discouraging.[7, 8] Cross sectional studies continue to demonstrate that around half of all treated HIV patients have cognitive impairment. This represents little improvement compared to the pre-cART era. A silver lining of the cART era is that more severe forms of neurocognitive impairment have diminished although milder forms remain. Sorting out the etiology, prognosis and optimal cART regimen for treated HAND patients remains a major incomplete task. Understanding the current HAND definitions is essential. A consensus research definition was articulated in 2006 at Frascati, Italy[9] with HAND sub-

classifications created that include asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV associated dementia (HAD).

HAD—Independent of opportunistic conditions, advanced HIV is associated with cognitive impairment the consequence of HIV infection within the nervous system.[10] AIDS Dementia Complex (ADC), a subcortical dementia. was characterized as a progressive disabling condition that manifested in increasing loss of attention and concentration, marked motor slowing, and variable behavioral components generally leading to death in less than a year. [11] This syndrome was associated with pathologic changes in the brain that include generalized atrophy, changes in white matter causing a leukoencephalopathy,(Figure 1) microglial nodules typical of viral encephalitis, and multinucleated giant cells that appear to be directly infected by HIV as identified by antigen staining.[12, 13] In untreated infection, severity of dementia was more closely associated with inflammatory response markers than viral load, although CSF viral load was modestly associated with clinical manifestations.[14-20] The progressive impairment described as ADC, is now referred to as HIV Associated Dementia (HAD) using recent criteria.

However, confusion may still remain as the term HAD is applied not only to progressive brain disease due to untreated AIDS, but also for persons who have substantial residual HIV associated neurological impairment. It is not unexpected that the significant and growing population who have had brain injury due to HIV, but do not have an obvious progressive disease, will not be helped by the same treatments as those with active virally mediated pathology. Extensive research in neuroAIDS has failed to separate these populations, contributing to disappointing or confusing assessments. Application of current HAND criteria has too heavily rested on making a diagnosis according to severity of neurological impairment on neuropsychological exam. It seems important that the dynamic status of impairment as well as associated pathophysiology be included in diagnostic and therapeutic efforts. This may help the field address remaining issues more effectively.

Mild neurocognitive disease (MND) and asymptomatic neurocognitive impairment (ANI)—The prevalence of HAND currently is driven by ANI and MND. Current categories of MND and ANI are based on neuropsychometric testing abnormalities with or without functional impairment in activities of daily living.(Table 1) It is clear that compared to the best available population norms, around half of HIV patients continue to have lower levels of performance than would be predicted. [7, 8, 21] However current HAND research definitions for ANI and MND may be overly inclusive, resulting in clinically unimportant inflation of impairment figures.[22] Based on neuropsychometric performance that lacks ideally matched norms, knowledge of prior performance, and exclusion of a myriad of confounding issues, the utility of the ANI category remains controversial.

Further confounding the current criteria is the definition of functional impairment, the feature that distinguishes MND from ANI. In practice, assessment of functional impairment proves to be challenging and is likely imprecise. A variety of approaches are permitted to define functional capacity. Typically self-report has been used but this is subjective. If functional impairment is observed it is often difficult to distinguish if changes are caused by HIV infection or other etiologies. Formalized scales for functional impairment (i.e Lawton

Brody[23]) were developed for other neurodegenerative disorders and are quite dated. More quantifiable performance measures have been developed that may be more appropriate for HIV patients. (i.e. Columbia Medication Management Test and the San Diego Finances Test[24]) However, self-report and performance based measures are linked to educational, cultural, and societal biases and do not have the ability to predict who will develop progressive impairment. Further, the ability to discriminate between ANI and MND remains difficult due to the imprecision of these categories such that patients may "wobble" between these two states. While this could be due to biological factors, it seems equally likely that limitation of definition of disorders as they are applied in complex patients over time and testing imprecision substantially contributes to this phenomenon. Long term trajectories of performance are urgently needed to better understand the potential prognostic implications of these categories.

Longitudinal Observations of HAND

The Multicenter AIDS Cohort Study (MACS) studied neurocognitive performance of asymptomatic HIV patients who were either immunologically intact or virologically controlled and HIV seronegative individuals over a five year interval. HIV patients showed no decline on several neuropsychometric tests.[25] This observation is important and reassuring. Testing was sensitive enough to detect the anticipated age related decline, yet failed to demonstrate that there was greater deterioration in performance for asymptomatic HIV+ population, even within individuals with imperfect viral control. This observation is consonant with the authors' impression in the clinics and has been shared by many HIV providers who report little evidence of a widespread deterioration of neurocognitive performance in excess of anticipated ageing or attributable to other co-morbid conditions.

On the other hand, there are numerous reports that some HIV patients continue to experience neurocognitive deterioration despite virologically successful therapy. The ability to assess neurological functions demands careful evaluation, and in busy clinic settings, mild conditions may be overlooked. The CNS HIV Antiretroviral Therapy Effects Research (CHARTER) longitudinal observations of a large US academic clinic cohort, have been reported in a preliminary form.[26] Neurocognitive performance, laboratory measures and neurological exams were performed every 6 months over a 42 month interval. Most (61%) HIV patients remained stable, while 16.5% apparently improved neurocognitive status, and 22.7% declined.[26] Factors associated with risk of progression included the presence of severe co-morbidities (such as other infections, drug abuse, other neurological conditions) or evidence of failure of HIV therapy (off ART and/or low CD4 count). A limitation of this study is that appropriate HIV seronegative controls were not available.

Clinical trials involving HIV patients with HAND who receive either a control or intervention have reinforced the impression that cognitive changes due to HIV if present must be slow, since it does not typically occur in control arms over short duration trials.[27-32] Within the AIDS Clinical Trials Group , in one of the longest clinical trials monitored cohorts on cART, no significant decline in performance was observed over 3 years of observation.[30]

Clinical Presentation of HAND

Clinical neuropsychological manifestations of HAND in the cART era differ considerably from the classic descriptions of ADC.[11] In the pre-CART era a progressive subcortical dementia with motor and cognitive slowing was prominent. In the earliest clinical trials, timed motor tasks showed reliable improvement as therapy was initiated, and the patients showed obvious clinical neurological improvement.[33, 34] However, in the cART era more cortical than subcortical involvement is often seen.[21] A comparative analysis evaluating HIV patients and HIV seronegative subjects from the pre and post-cART eras has shown that HIV patients from the pre-cART era had greater impairments in motor skills, cognitive speed and verbal fluency, whereas the HIV patients from the post-cART era patients had more impairments in memory (learning) and executive function.[21] Subtle cognitive changes in HIV patients in the post-cART era are also seen in prospective memory, or the ability to "remember to remember".[35, 36] This may impact function in the workplace as well as problems with medication adherence. Tests of prospective memory need to be performed in the clinical setting as patients may be unaware of their deficits.[37] It is notable that the pattern of cognitive dysfunction now seen with HAND is more similar to other more common degenerative disorders (i.e Alzheimer's disease) than "classic" HAD. This could provide challenges for differentiating these diseases in older HIV patients in the clinic.

Evaluation of HAND

Monitoring for HAND using neuropsychometric performance testing

NeuroAIDS research has relied heavily on neuropsychometric performance testing for both diagnosis and monitoring the course of infection. This worked well in the pre-cART era when obvious progressive HAD could be identified, and when successful intervention with simple zidovudine monotherapy resulted in unequivocal benefits on neurocognitive tests.[34, 38] However, in the cART era use of neuropsychometric performance testing is more challenging since the major concern is to identify patients with more subtle deficits. Detection of mild deficits requires more difficult tests that often take longer compared to simple timed motor administered in the pre-cART era. Seeking short and tolerable screening tests appropriate for busy HIV clinics in both developing and developed countries, has been difficult.[37, 39-41] Commonly used tools include versions of the MiniMental Status Exam (MMSE), the Montreal Cognitive Assessment (MoCA), the composite Z scores of several brief neuropsychometric tests used in the ACTG system (NPZ-4), the International HIV Dementia Screen (IHDS), and portions of CogState tools. In general, these tests are not ideal as they are neither sensitive nor specific for HAND.[37, 40, 42-44] While consensus exists that neuropsychometric performance should be repeatedly measured (at least in research), agreement does not exist concerning the exact battery to be administered.[45] It may be premature to encourage routine repeated implementation of neurocognitive screens in clinic patients. Neurocognitive testing will continue to have a valuable role in longitudinal assessments for research, but additional reliable biomarkers with more pathophysiologic validity are required to transform this field.

Neuropsychometric testing should continue to be utilized to evaluate the efficacy of interventions for performance during therapeutic trials. When patients serve as their own

controls and are compared to other patients similarly monitored by the same investigative team over time, these measures can be sensitive for detection of change relevant to therapeutic interventions. Comparative groups studied with the same sequence of testing can account for the learning effects which may be difficult to detect without concurrent controls. Increasing knowledge about accounting for the impact of practice and familiarity with repeat testing and of the clinical implications of test performance by study of "meaningful change" may further enhance the interpretation of observational data that is more widely available.[46] However, special caution must be used when applying these tests internationally and crossing social and cultural groups. Normative data is greatly influenced by very complex characteristics of administration and the tested population. Careful collection of appropriate controls is necessary. Because HIV is more prevalent in developing countries, and because neuropsychometric tests are substantially influenced by social and economic factors, great effort must be made to develop appropriate local normative assessments. Ideally these norms would be collected in parallel with active data collection for research at developing world sites. However, practical considerations have led to less robust norms for developing world sites than are available for US and European cohorts. Other pathophysiologically based biomarkers are thus of especially great importance in evaluating manifestations of disease in the developing world.

Systemic and Plasma markers

Targeting full systemic control of HIV hardly needs justification based on neurological consequences, since most clinicians now strongly ascribe to the benefits of early and full control of the virus. The preponderance of evidence about HAND reinforces the primary importance of systemic control of HIV to achieve optimal neurological outcomes. However, in the cART era HIV load and CD4 cell counts are no longer closely associated with neuropsychometric performance.[47, 48] Studies suggest that a lower CD4 nadir increases the risk for HAND while a recent study of military patients suggests that early treatment may substantially prevent HAND.[21, 49-53]

Additional blood markers that are associated with HAND or that could identify a population at risk of neurologic progression have been difficult to isolate. One of the more promising areas for potential peripheral biomarkers has been monitoring activation of monocytes. Within the brain, monocytes and macrophages appear to be important cells that not only carry the virus, but also can release potentially deleterious cytokines when activated. Contributions to this inflammatory response may originate outside of the brain and subsequently invade it. Plasma soluble CD14 has potential as a biomarker as it has been linked to impairment in attention and learning in HAND patients.[54] Detection of HIV DNA circulating within mononuclear cells may also identify increased risk for HAND.[55-58] These results are consistent with the theme of increased trafficking of activated monocytes to the brain that may lead to neurocognitive impairment.[54, 59, 60] Another measure of activated monocytes appears to be soluble CD163.This scavenger receptor is up-regulated in activated monocytes. Recent studies suggest that this may remain elevated in HAND patients on stable cART. This observation might allow for the selection of HAND patients whose disease is driven by ongoing systemic cellular activation.[61, 62]

Peripheral inflammatory disease from several potential sources may be relevant to HAND. HIV affects the gut with the potential for microbial translocation driving chronic inflammation leading to HAD.[63, 64] Strategies to reduce such activation might yield neurocognitive benefits. Cardiovascular risk markers which may also be driven by chronic immune activation, were correlated with HAND, and provide a potentially critical modifiable factor. In the MACS study, carotid intima-media thickness (IMT) and glomerular filtration rate were associated with performance speed on neuropsychometric tests, while IMT was also associated with memory impairment. [47] In the SMART study, cardiovascular risks, hypertension and hypercholesterolemia were more associated with baseline neuropsychometric performance results compared to HIV disease markers.[48] A more recent CHARTER study has also demonstrated that the increased presence of metabolic risk factors was associated with HAND.[65]

Cerebrospinal Fluid (CSF) biomarkers

Evaluations of the CSF reflect the biology of the central nervous system more closely than blood. The blood brain barrier limits movement from blood to brain compartments, resulting in a relative physiologic compartment. Often patients and physicians are unduly reluctant to perform a lumbar puncture for CSF collection. In the absence of abnormal clotting, or large asymmetric mass in the brain, lumbar punctures are exceedingly safe and when performed by skilled clinicians generally not as noxious as many other procedures. Use of non-cutting needles vastly reduces the chance of transient orthostatic headaches that sometimes follow lumbar puncture. When unique information can be collected, a lumbar puncture should be performed.

It is clear that occasionally HIV emerges in the CSF heralded by new neurological symptoms or signs, even in the face of continued blood virologic control. [66-68] This phenomenon of viral “escape” is uncommon but should alert the clinician to assess CSF if there are new or active neurological symptoms, not otherwise explained. Rarely, asymptomatic patients also have detectable HIV in low copy numbers when blood viral levels are well controlled.[69-71] At present there is little evidence for CSF viral evolution in successfully treated HIV patients, but additional longitudinal CSF studies of treated patients are needed.

Characteristics of virus recovered in CSF or from the CNS may reflect unique characteristics of a neurotrophic virus.[72] Interest in changes in tat sequences across viruses has suggested the possibility that variation in clade neurotropism might relate to tat sequence differences.[73,74, 75] Mutations can occur at specific sequences of the viral genome, and can affect the ability of the virus to successfully bind and enter macrophages.[76-78] The HIV epidemic has resulted in subtypes of HIV evolving throughout the world. The possibility that these also diverge in neurological manifestations has been an area of active research. Differing prevalence of HAD between Subtype A and D in Uganda suggested differing pathogenicity,[79] but overall comparisons of different HIV clades using neuropsychometric performance have shown mostly similar results across regions .[80] There is little evidence connecting specific viral characteristics to ultimate development of milder HAND. HIV RNA and DNA found in the brain at post mortem are most highly associated with

multinucleate cell encephalitis with HAD. Pathological findings and viral recovery are not associated with mild forms of HAND. Indeed, it is notable that ANI and MND do not have specific neuropathological correlates.[81, 82]

The clinical utility of inflammatory markers in the CSF has been limited, but these measures could potentially identify patients at risk for developing HAND. Even patients on long term suppressive cART have mildly elevated CSF neopterin and IgG index.[83] Persistent immune activation markers including IL-6, IL-8, CCL2 (MCP-1) remain present in successfully treated cART patients.[84] Another situation in which dysregulated immune response may drive impairment and symptoms is during immune reconstitution, particularly in the rare, but dramatic CD8 encephalitis cases that are reported during treated HIV infection.[85-87]

Markers of neuronal injury may also be associated with more advanced cognitive impairment.[88-92] In particular, neurofilament light protein (NFL) is elevated in untreated HAND patients and declines with successful treatment. Tau may be elevated in HAD but not ANI or MND patients although data remain inconsistent for this potential biomarker.[91-94]

Neuroimaging

Neuroimaging techniques are continuing to evolve and may have increased utility in the diagnosis and management of HAND. At least three modalities of neuroimaging have been used in the research setting: metabolic, structural, and functional. Many of these neuroimaging techniques hold great promise as they can be easily added to conventional scans that are often obtained of HIV+ patients.

Metabolic imaging using magnetic resonance spectroscopy has been performed both in the pre and post cART eras.[95-98] These studies measure metabolite ratios reflecting either neuronal function (n-acetyl aspartate, NAA) or inflammation (choline or myoinositol) compared to a reference marker (creatine, Cr). In the pre cART era decreases in NAA/Cr and increases in Cho/Cr were seen with HIV.[99] However, these measures may be normalized after cART administration.[100] In addition, this technique may be limited as only certain brain regions or voxels are studied. Other metabolic studies, such as positron emission tomography (PET), have primarily been performed in the pre-cART era. A biphasic response was observed with early increases followed by progressive declines with more advanced cognitive impairment.[101] Large studies using PET imaging in the post-cART era are needed. More recently, PET imaging using ligands specific for microglial activation have been investigated in hopes of quantifying and localizing brain inflammation. [102-104]

In regards to structural neuroimaging two techniques have been of particular interest: volumetric analysis and diffusion tensor imaging. Structural neuroimaging has demonstrated changes not only within subcortical areas but also cortical areas.[105-108] These changes can accrue early after seroconversion and continue to persist even after administration of cART.[109] Diffusion tensor imaging has been used to measure diffusion of water molecules in white matter tracts, specifically within the corpus callosum, a white matter tract connecting the two hemispheres. A decrease in mean diffusivity (MD) and an increase in fractional anisotropy (FA) have typically been associated with HIV. These measures can improve after starting cART[110-113] and have considerable promise.

More recently, functional neuroimaging measures have been employed using magnetic resonance imaging (MRI) for blood oxygen level dependent imaging (BOLD) and arterial spin labeling (ASL). For relatively simple functional tasks, increased recruitment of additional areas may occur in HIV+ patients to meet cognitive demands.[114, 115] When assessed at rest, functional connections between brain networks may be compromised in HAND, in ways that are similar to aging.[116] ASL allows for non-invasive measurement of cerebral blood flow (CBF) which is a time linked measure of brain metabolism. A decrease in CBF has been seen soon after seroconversion with HIV+ patients having CBF values equivalent to HIV seronegative individuals 15-20 years older.[117] Administration of cART can lead to an improvement in CBF but CBF values do not completely normalize.[117, 118] These results suggest that this technique may be a good measure to evaluate the efficacy of new therapies. With the development of new methods, multi-center trials that use common neuroimaging sequences are needed.

Antiretroviral therapy for HAND—Introduction of cART therapy has resulted in clear benefits. As a result of immune reconstitution, opportunistic conditions have become rare, and HAD now rarely develops. However, variability exists in the penetration and transport of antiretroviral drugs across the blood brain barrier. This has led to serious concerns about the brain serving as a nidus of infection that could smolder with partial control. In theory, resistant virus could evolve in the central nervous system and re-seed the body. Clearing of the virus from the central nervous system (CNS) will be required to achieve a cure for HIV. The practical evidence of long term successful suppression of HIV in the cART era with only rare CNS escape is reassuring that virtually all of the drug combinations serve to control the virus in the CNS compartment. However, this theoretical risk along with recognition of ongoing HAND has appropriately inspired intensive consideration and monitoring of therapy. Indeed, one explanation for the continued prevalence of HAND is that low level viremia in the CNS can continue, driving neurodegeneration either by toxic inflammatory activation and/or toxic viral products such as the tat protein.

The concept of CNS penetration effectiveness (CPE) of drug regimens was formalized to encourage study of the association of efficacy of antiretrovirals with their ability to enter and function in the CNS. A ranking scale was constructed based on available information about current antiretrovirals including the physicochemical properties, known CSF drug levels, and effectiveness in clearing virus in CSF. Each drug in a regimen was given a score for relative effectiveness, and the summed score for the regimen monitored. The model appears to have validity supported by some observations that CSF viral loads are more likely to remain controlled when the CPE is higher.[119] However, the impact of CPE appears inconsistent across studies, imperfectly linked to degree of cognitive impairment or survival in treatment studies.[31, 52, 120-122] A prospective test of the validity of the current concept of CPE was recently reported.[123] A randomized trial compared treatment of mild to moderate HAND patients with participants randomly assigned to receive either higher or lower CPE regimens that were otherwise expected to be active against the virus. Accrual was challenging, and eventually the study was terminated short of study goals. However, with 49 evaluable patients randomized, no significant differences between high and low CPE regimens were seen based on neuropsychometric performance. At this point, there seems no

reason to use this strategy to select cART routinely. However, continued research on variable effectiveness of therapy should be performed. It is possible that as more information is acquired about drug activity and distribution, ongoing revisions of CPE might enhance its power. If viral breakthrough in CNS is discovered, viral drug sensitivity should be tested and therapy should be changed to the most potent, tolerable and simple regimen available for that viral isolate. CPE might also inform the relative possibility of drug toxicity. While unproven, in vitro and some in vivo observations would be consistent with chronic drug toxicity contributing to neurologic impairment.[31, 124, 125]

An alternative therapeutic strategy has emphasized that monocytes and macrophages appear to be the primary cellular reservoir affecting the CNS, representing resident cells with proliferative infection in untreated brain, and potentially harboring the virus in circulating monocytes even during effective therapy.[56] When therapy was graded by effectiveness for monocyte infection, cognitive outcomes appeared correlated with this index. Further investigation of this strategy deserves consideration.[58, 126]

The demonstration of ongoing viral breakthrough in some CSF samples, as well as recognizing that very low levels of virus are detected in the CSF if ultrasensitive assays are used, has also spurred consideration of treatment intensification regimens that include newer classes of medications. CCR5 antagonists would be predicted to contribute uniquely to CNS isolates, while integrase inhibitors deserve further evaluation for potency in the CNS. While small intensification trials have been disappointing to date, larger multi-center trials could better address this possibility.[127, 128] Application of nanoparticles to augment delivery of antiretrovirals to the brain is also under investigation, with the caveat that more effective delivery might also increase intrinsic toxicity.[129]

Adjuvant Therapy for HAND

Recognizing that HIV in the brain is necessary but not sufficient for manifestations of HAND, application of adjuvant therapies based on potential downstream pathologic mechanisms has also been considered.[130] Most of the hypotheses tested are derived from in vitro or animal model results. To date, despite numerous Phase 2 human trials, none have had demonstrated convincing evidence for significant activity when compared to control treated subjects. A recent trial tested minocycline, which is thought to inhibit microglial activation and have antioxidative and neuroprotective properties. In a simian immunodeficiency virus model of encephalitis, minocycline reduced brain inflammatory disease.[131] No benefit in neurocognitive status or in disease markers could be seen in antiretroviral treated[32] or untreated[132] populations with HAND. A current trial is investigating fluconazole and a serotonin reuptake inhibitor(SSRI) based on animal models of HAND and cohort data associated with SSRI.[133] Use of drugs approved for Alzheimer's disease has been considered. Memantine, an NMDA antagonist with neuroprotective properties in vitro, failed to demonstrate neuroprotection or cognitive improvement, while a recent small trial of an acetyl cholinesterase inhibitor appeared to provide slight symptomatic improvement.[134-137] Valproic acid has been a drug of interest for HIV, most recently as a histone deacetylase inhibitor that might be used as a tool for cellular activation in a cure strategy. It has also been reported to have neuroprotective properties. A small study

showed a trend towards cognitive improvement using neuropsychometric tests and neuroimaging measures. However, this was not substantiated in another trial.[138-140] At present, anti-inflammatory strategies are the most often discussed adjuvant therapy for HAND. Upcoming evaluations of low dose methotrexate, as well as large trials evaluating statins may provide opportunities to probe the impact of inflammation on neurocognitive function further.

Aging population

Research into special interactions between anticipated changes of aging and chronic HIV infection have drawn attention, most prominently surrounding possible interactions of immunosenesce. [141] The possibility that HIV neurocognitive impairment results from earlier expression of degenerative brain disorders such as Alzheimer's disease (AD) driven by HIV has been considered. While HAD in the pre-cART era was characteristic of subcortical dementia unlike Alzheimer's disease, current clinical presentation of HAND can be similar to Alzheimer's disease. Some reports support pathologic findings consistent with Alzheimer's disease, but a fully consistent pathologic confirmation has not been described.[142, 143] Some reports suggest at least a partial overlap in CSF biomarkers for Alzheimer's disease and HAND. However, differences in CSF biomarkers do exist between the two neurodegenerative disorders.[94, 144, 145] Years before the onset of AD, changes in amyloid metabolism in the brain are reflected by amyloid plaque deposition that can be detected with amyloid with positron imaging markers. [146] Recently amyloid imaging scans have also been performed in HIV+ patient with no increases in amyloid deposition seen in HAND patients.[147] Further, a genetic predisposition for Alzheimer's disease has been observed with the APOE ε4 allele. Within the CHARTER study presence of at least one APOE ε4 allele was not associated with increased incidence of HAND.[148] However, prior studies have reported some impact of APOE4 generally in advanced disease or older patients.[148-153] Ongoing attention to interactions of HIV with aging processes, especially in the brain, will continue to be an important focus of research as the HIV population ages.[141]

Conclusions

Neurological involvement during HIV infection remains an important aspect of the infection requiring continued study. Both objective tests of neurological function and the witness of patients confirm that cART, while immensely improving outcomes, has not accomplished full functional protection of the nervous system. Because changes are now subtle, and in general slowly changing, HAND remains challenging to study, but the importance of brain function to independence and quality of life demand that ongoing efforts be directed to optimize this aspect of care for HIV patients. It is almost certain that multiple mechanisms contribute, and thus multiple therapeutic interventions will need to be rationally employed to achieve success.

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References

1. Tan IL, McArthur JC. HIV-associated neurological disorders: a guide to pharmacotherapy. CNS Drugs. 2012; 26(2):123–34. [PubMed: 22201342]
2. Harrison TB, Smith B. Neuromuscular manifestations of HIV/AIDS. J Clin Neuromuscul Dis. 2011; 13(2):68–84. [PubMed: 22361691]
3. Kranick SM, Nath A. Neurologic complications of HIV-1 infection and its treatment in the era of antiretroviral therapy. Continuum. 2012; 18(6):1319–37. Infectious Disease. [PubMed: 23221843]
4. McArthur JC, Steiner J, Sacktor N, Nath A. Human immunodeficiency virus-associated neurocognitive disorders mind the gap. AnnNeurol. 2010; 67:699–714.
5. Schouten J, Cinque P, Gisslen M, Reiss P, Portegies P. HIV-1 infection and cognitive impairment in the cART era: a review (editorial). AIDS. 2011; 25(5):561–75. [PubMed: 21160410]
6. Spudich S, Gonzalez-Scarano F. HIV-1-related central nervous system disease: current issues in pathogenesis, diagnosis, and treatment. Cold Spring Harbor perspectives in medicine. 2012; 2(6):a007120. [PubMed: 22675662]
7. Simioni S, Cavassini M, Annoni JM, et al. Cognitive dysfunction in HIV patients despite longstanding suppression of viremia. AIDS. 2010; 24:1243–50. [PubMed: 19996937]
8. Heaton RK, Clifford DB, Franklin DR Jr. et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy. CHARTER study. Neurology. 2010; 75:2087–96. [PubMed: 21135382]
9. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69(18):1789–99. [PubMed: 17914061]
10. Snider WD, Simpson DM, Nielsen S, Gold JWM, Metroka CE, Posner JB. Neurological complications of acquired immune deficiency syndrome: Analysis of 50 patients. AnnNeurol. 1983; 14:403–18.
11. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. AnnNeurol. 1986; 19:517–24.
12. Navia BA, Cho ES, Petito CK, Price RW. The AIDS dementia complex: II. Neuropathology. AnnNeurol. 1986; 19:525–35.
13. Petito CK, Cho ES, Lemann W, Navia BA, Price RW. Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. JNeuropatholExpNeurol. 1986; 45:635–46.
14. Glass JD, Fedor H, Wesselingh SL, McArthur JC. Immunocytochemical quantitation of human immunodeficiency virus in the brain: correlations with dementia. AnnNeurol. 1995; 38:755–62.
15. Brew BJ, Bhalla RB, Paul M, et al. Cerebrospinal fluid neopterin in human immunodeficiency virus type 1 infection. AnnNeurol. 1990; 28:556–60.
16. McArthur JC, Nance-Sproson TE, Griffin DE, et al. The diagnostic utility of elevation in cerebrospinal fluid β_2-microglobulin in HIV-1 dementia. Neurology. 1992; 42:1707–12. [PubMed: 1355286]
17. Wesselingh SL, Power C, Glass JD, et al. Intracerebral cytokine messenger RNA expression in acquired immunodeficiency syndrome dementia. AnnNeurol. 1993; 33:576–82.
18. Johnson RT, Glass JD, McArthur JC, Chesebro BW. Quantitation of human immunodeficiency virus in brains of demented and nondemented patients with acquired immunodeficiency syndrome. AnnNeurol. 1996; 39:392–5.
19. McArthur JC, McClernon DR, Cronin MF, et al. Relationship between human immunodeficiency virus-associated dementia and viral load in cerebrospinal fluid and brain. AnnNeurol. 1997; 42:689–98.
20. Ellis RJ, Hsia K, Spector SA, et al. Cerebrospinal fluid human immunodeficiency virus Type 1 RNA levels are elevated in neurocognitively impaired individuals with acquired immunodeficiency syndrome. AnnNeurol. 1997; 42:679–88.

21. Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011; 17(1):3–16. [PubMed: 21174240]
22. Gisslen M, Price RW, Nilsson S. The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? BMC InfectDis. 2011; 11:356.
23. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969; 9:179–86. [PubMed: 5349366]
24. Gandhi NS, Skolasky RL, Peters KB, et al. A comparison of performance-based measures of function in HIV-associated neurocognitive disorders. JNeurovirol. 2011; 17(2):159–65. [PubMed: 21437751]
25. Cole MA, Margolick JB, Cox C, et al. Longitudinally preserved psychomotor performance in long-term asymptomatic HIV-infected individuals. Neurology. 2007; 69(24):2213–20. [PubMed: 17914066]
26. Heaton RD,R, Franklin D, Woods S, Collier A, Clifford D, Gelman B, McArthur J, Simpson D, Grant I, the CHARTER Group. Prevalence and predictors of neurocognitive decline over 18 to 42 months: A CHARTER longitudinal study. 19th Conference on Retroviruses and Opportunistic Infections -Seattle, WA. 2012:246.
27. Clifford DB, McArthur JC, Schifitto G, et al. A randomized clinical trial of CPI-1189 for HIV-associated cognitive-motor impairment. Neurology. 2002; 59(10):1568–73. [PubMed: 12451199]
28. Evans SR, Yeh T, Sacktor N, et al. Selegiline transdermal system (STS) for HIV-associated cognitive impairment: open-label report of ACTG 5090. HIV Clinical Trials. 2007; 8(6):437–46. [PubMed: 18042509]
29. Schifitto G, Zhang J, Evans SR, et al. A multicenter trial of selegiline transdermal system for HIV-associated cognitive impairment. Neurology. 2007; 69:1314–21. [PubMed: 17652642]
30. Clifford DB, Evans S, Yang Y, et al. Long-term impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals (ACTG 5097s). HIV Clinical Trials. 2009; 10(6):343–55. [PubMed: 20133265]
31. Marra CM, Zhao Y, Clifford DB, et al. Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. AIDS. 2009; 23(11):1359–66. [PubMed: 19424052]
32. Sacktor N, Miyahara S, Deng L, et al. Minocycline treatment for HIV-associated cognitive impairment: results from a randomized trial. Neurology. 2011; 77(12):1135–42. [PubMed: 21900636]
33. Schmitt FA, Bigley JW, McKinnis R, et al. Neuropsychological outcome of zidovudine (AZT) treatment of patients with AIDS and AIDS-related complex. NEnglJMed. 1988; 319:1573–8.
34. Sidtis JJ, Gatsonis C, Price RW, et al. Zidovudine treatment of the AIDS dementia complex: Results of a placebo-controlled trial. AnnNeurol. 1993; 33:343–9.
35. Woods SP, Weber E, Weisz BM, Twamley EW, Grant I. Prospective memory deficits are associated with unemployment in persons living with HIV infection. RehabilPsychol. 2011; 56(1): 77–84.
36. Jacqueline H, Jenny WT, Jean-Paul F, et al. A diffusion tensor imaging and neuropsychological study of prospective memory impairment in South African HIV positive individuals. Metab Brain Dis. 2012; 27(3):289–97. [PubMed: 22569999]
37. Valcour VG. Evaluating cognitive impairment in the clinical setting: practical screening and assessment tools. TopAntivirMed. 2011; 19(5):175–80.
38. Yarchoan R, Brouwers P, Spitzer AR, et al. Response of human-immunodeficiency-virus-associated neurological disease to 3′-azido-3′-deoxythymidine. Lancet. 1987:132–5. [PubMed: 2879972]
39. Ellis R, Robertson K, Moo L, et al. NARC007: clinical validation of the AACTG neuroscreen. 11th Conference on Retroviruses and Opportunistic Infections. 2004:242.
40. Overton ET, Kauwe JS, Paul R, et al. Performances on the CogState and standard neuropsychological batteries among HIV patients without dementia. AIDS and behavior. 2011; 15(8):1902–9. [PubMed: 21877204]

41. Sacktor NC, Wong M, Nakasujja N, et al. The International HIV Dementia Scale: a new rapid screening test for HIV dementia. AIDS. 2005; 19:1367–74. [PubMed: 16103767]
42. Overton ET, Azad TD, Parker N, et al. The Alzheimer's disease-8 and Montreal Cognitive Assessment as screening tools for neurocognitive impairment in HIV-infected persons. J Neurovirol. 2013; 19(1):109–16. [PubMed: 23345074]
43. Chalermchai T, Valcour V, Sithinamsuwan P, et al. Trail Making Test A improves performance characteristics of the International HIV Dementia Scale to identify symptomatic HAND. J Neurovirol. 2013; 19(2):137–43. [PubMed: 23483520]
44. Ellis RJ, Evans SR, Clifford DB, et al. Clinical validation of the neuroscreen. JNeurovirology. 2005; 11:503–11. [PubMed: 16338744]
45. Mind Exchange Working G. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2013; 56(7):1004–17. [PubMed: 23175555]
46. Cysique LA, Franklin DJ, Abramson I, et al. Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change. Journal of Clinical and Experimental Neuropsychology. 2011; 33(5):505–22. [PubMed: 21391011]
47. Becker JT, Kingsley L, Mullen J, et al. Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men. Neurology. 2009; 73(16):1292–9. [PubMed: 19841381]
48. Wright EJ, Grund B, Robertson K, et al. Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons. Neurology. 2010; 75:864–73. [PubMed: 20702792]
49. Ellis RJ, Badiee J, Vaida F, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS. 2011; 25(14):1747–51. [PubMed: 21750419]
50. Valcour V, Yee P, Williams AE, et al. Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection - The Hawaii aging with HIV cohort. Journal of NeuroVirology. 2006; 12:387–91. [PubMed: 17065131]
51. Munoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Nadir CD4 cell count predicts neurocognitive impairment in HIV-infected patients. AIDS Research & Human Retroviruses. 2008; 24(10):1301–7. [PubMed: 18844464]
52. Smurzynski M, Wu K, Letendre S, et al. Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. AIDS. 2011; 25(3):357–65. [PubMed: 21124201]
53. Crum-Cianflone NF, Moore DJ, Letendre S, et al. Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons. Neurology. 2013; 80(4):371–9. [PubMed: 23303852]
54. Lyons JL, Uno H, Ancuta P, et al. Plasma sCD14 is a biomarker associated with impaired neurocognitive test performance in attention and learning domains in HIV infection. Journal of Acquired Immune Deficiency Syndromes: JAIDS. 2011; 57(5):371–9.
55. Valcour VG, Shiramizu BT, Sithinamsuwan P, et al. HIV DNA and cognition in a Thai longitudinal HAART initiation cohort. The SEARCH 001 Cohort Study. Neurology. 2009; 72:992–8. [PubMed: 19289739]
56. Shiramizu B, Williams AE, Shikuma C, Valcour V. Amount of HIV DNA in peripheral blood mononuclear cells is proportional to the severity of HIV-1-associated neurocognitive disorders. The Journal of neuropsychiatry and clinical neurosciences. 2009; 21(1):68–74. [PubMed: 19359454]
57. Valcour VG, Shiramizu BT, Shikuma CM. HIV DNA in circulating monocytes as a mechanism to dementia and other HIV complications. [Review] [72 refs]. Journal of Leukocyte Biology. 2010; 87(4):621–6. [PubMed: 20130221]
58. Shiramizu B, Ananworanich J, Chalermchai T, et al. Failure to clear intra-monocyte HIV infection linked to persistent neuropsychological testing impairment after first-line combined antiretroviral therapy. J Neurovirol. 2012; 18(1):69–73. [PubMed: 22207583]

59. Pulliam L, Gascon R, Stubblebine M, McGuire D, McGrath MS. Unique monocyte subset in patients with AIDS dementia. Lancet. 1997; 349:692–5. [PubMed: 9078201]
60. Kusdra L, McGuire D, Pulliam L. Changes in monocyte/macrophage neurotoxicity in the era of HAART: implications for HIV-associated dementia. AIDS. 2002; 16:31–8. [PubMed: 11741160]
61. Burdo TH, Weiffenbach A, Woods SP, Letendre S, Ellis RJ, Williams KC. Elevated sCD163 is a marker of neurocognitive impairment in HIV infection. AIDS. 2013
62. Burdo TH, Lackner A, Williams KC. Monocyte/macrophages and their role in HIV neuropathogenesis. Immunol Rev. 2013; 254(1):102–13. [PubMed: 23772617]
63. Ancuta P, Kamat A, Kunstman KJ, et al. Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. PLoS ONE. 2008; 3(6):e2516. [PubMed: 18575590]
64. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nature Medicine. 2006; 12(12):1365–71.
65. McCutchan JA, Marquie-Beck JA, Fitzsimons CA, et al. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. Neurology. 2012; 78(7):485–92. [PubMed: 22330412]
66. Soulié C, Tubiana R, Simon A, et al. Presence of HIV-1 R5 viruses in cerebrospinal fluid even in patients harboring R5X4/X4 viruses in plasma. JAcquirImmune DeficSyndr. 2009; 51(1):60–4.
67. Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2010; 50(5):773–8. [PubMed: 20100092]
68. Wendel KA, McArthur JC. Acute meningoencephalitis in chronic human immunodeficiency virus (HIV) infection: putative central nervous system escape of HIV replication. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2003; 37(8):1107–11. [PubMed: 14523776]
69. Edén A, Fuchs D, Hagberg L, et al. HIV-1 viral escape in cerebrospinal fluiud of subjects on suppressive antiretroviral treatment. Journal of Infectious Diseases. 2010; 202(12):1819–25. [PubMed: 21050119]
70. Bingham R, Ahmed N, Rangi P, Johnson M, Tyrer M, Green J. HIV encephalitis despite suppressed viraemia: a case of compartmentalized viral escape. IntJSTD AIDS. 2011; 22(10):608–9.
71. Peluso MJ, Ferretti F, Peterson J, et al. Cerebrospinal fluid HIV escape associated with progressive neurologic dysfunction in patients on antiretroviral therapy with well controlled plasma viral load. AIDS. 2012; 26(14):1765–74. [PubMed: 22614889]
72. Power C, McArthur JC, Johnson RT, et al. Demented and nondemented patients with AIDS differ in brain-derived human immunodeficiency virus Type 1 envelope sequences. JVirol. 1994; 68:4643–9. [PubMed: 8207838]
73. Mishra M, Vetrivel S, Siddappa NB, Ranga U, Seth P. Clade-specific differences in neurotoxicity of human immunodeficiency virus-1 B and C tat of human neurons: significance of dicysteine C30C31 motif. AnnNeurol. 2008; 63(3):366–76.
74. Clifford DB, Mitike MT, Mekonnen Y, et al. Neurological evaluation of untreated human immunodeficiency virus infected adults in Ethiopia. Journal of Neurovirology. 2007; 13:67–72. [PubMed: 17454450]
75. Choi JY, Hightower GK, Wong JK, et al. Genetic features of cerebrospinal fluid-derived subtype B HIV-1 tat. J Neurovirol. 2012; 18(2):81–90. [PubMed: 22528397]
76. Dunfee RL, Thomas ER, Gorry PR, et al. The HIV Env variant N283 enhances macrophage tropism and is associated with brain infection and dementia. Proc Natl Acad Sci U S A. 2006; 103(41):15160–5. [PubMed: 17015824]
77. Dunfee RL, Thomas ER, Wang J, Kunstman K, Wolinsky SM, Gabuzda D. Loss of the N-linked glycosylation site at position 386 in the HIV envelope V4 region enhances macrophage tropism and is associated with dementia. Virology. 2007; 367(1):222–34. [PubMed: 17599380]

78. Olivieri KC, Agopian KA, Mukerji J, Gabuzda D. Evidence for adaptive evolution at the divergence between lymphoid and brain HIV-1 nef genes. AIDS Res Hum Retroviruses. 2010; 26(4):495–500. [PubMed: 20377428]

79. Sacktor N, Nakasujja N, Skolasky RL, et al. HIV subtype D is associated with dementia, compared with subtype A, in immunosuppressed individuals at risk of cognitive impairment in Kampala, Uganda. Clinical Infectious Diseases. 2009; 49(5):780–6. [PubMed: 19622045]

80. Joseph J, Achim CL, Boivin MJ, et al. Global NeuroAIDS roundtable. J Neurovirol. 2013; 19(1): 1–9. [PubMed: 23354550]

81. Everall I, Vaida F, Khanlou N, et al. Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. Journal of NeuroVirology. 2009; 15:360–70. [PubMed: 20175693]

82. Gelman BB, Lisinicchia JG, Morgello S, et al. Neurovirological correlation with HIV-associated neurocognitive disorders and encephalitis in a HAART-era cohort. J Acquir Immune Defic Syndr. 2013; 62(5):487–95. [PubMed: 23242157]

83. Eden A, Price RW, Spudich S, Fuchs D, Hagberg L, Gisslen M. Immune activation of the central nervous system is still present after >4 years of effective highly active antiretroviral therapy. Journal of Infectious Diseases. 2007; 196(12):1779–83. [PubMed: 18190258]

84. Kamat A, Lyons JL, Misra V, et al. Monocyte activation markers in cerebrospinal fluid associated with impaired neurocognitive testing in advanced HIV infection. J Acquir Immune Defic Syndr. 2012; 60(3):234–43. [PubMed: 22569268]

85. Gray F, Lescure FX, Adle-Biassette H, et al. Encephalitis with Infiltration by CD8+ Lymphocytes in HIV Patients Receiving Combination Antiretroviral Treatment. Brain Pathol. 2013

86. Riedel DJ, Pardo CA, McArthur JC, Nath A. Therapy insight: CNS manifestations of HIV-associated immune reconstitution inflammatory syndrome. Nature Clinical Practice Neurology. 2006; 2:557–65.

87. Langford TD, Letendre SL, Marcotte TD, et al. Severe, demyelinating leukoencepahlopathy in AIDS patients on antiretroviral therapy. AIDS. 2002; 16:1019–29. [PubMed: 11953468]

88. Mellgren A, Price RW, Hagberg L, Rosengren L, Brew BJ, Gisslén M. Antiretroviral treatment reduces increased CSF neurofilament protein (NFL) in HIV-1 infection. Neurology. 2007; 69(15): 1536–41. [PubMed: 17923616]

89. Abdulle S, Mellgren A, Brew BJ, et al. CSF neurofilament protein (NFL) - a marker of active HIV-related neurodegeneration. Journal of Neurology. 2007; 254:1026–32. [PubMed: 17420923]

90. Gisslén M, Hagberg L, Brew BJ, Cinque P, Price RW, Rosengren L. Elevated cerebrospinal fluiud neurofilament light protein concentrations predict the development of AIDS dementia complex. Journal of Infectious Diseases. 2007; 195:1774–8. [PubMed: 17492593]

91. Gisslén M, Krut J, Andreasson U, et al. Amyloid and tau cerebrospinal fluid biomarkers in HIV infection. BMC Neurology. 2009; 9:63. [PubMed: 20028512]

92. Letendre S, Rosario D, Ellis R, Potter M, Woods SP. Higher levels of phosphorylated tau in CSF are associated with HIV infection, older age, antiretroviral use, and worse prospective memory. 18th Conference on Retroviruses and Opportunistic Infections. 2011:222.

93. Ellis RJ, Seubert P, Motter R, et al. Cerebrospinal fluid tau protein is not elevated in HIV-associated neurologic disease in humans. Neuroscience Letters. 1998; 254:1–4. [PubMed: 9780077]

94. Clifford DB, Fagan AM, Holtzman DM, et al. CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease. Neurology. 2009; 73:1982–7. [PubMed: 19907013]

95. Cysique LA, Moffat K, Moore DM, et al. HIV, vascular and aging injuries in the brain of clinically stable HIV-infected adults: a (1)H MRS study. PLoS One. 2013; 8(4):e61738. [PubMed: 23620788]

96. Lentz MR, Kim WK, Kim H, et al. Alterations in brain metabolism during the first year of HIV infection. J Neurovirol. 2011; 17(3):220–9. [PubMed: 21494901]

97. Harezlak J, Buchthal S, Taylor M, et al. Persistence of HIV-associated cognitive impairment, inflammation, and neuronal injury in era of highly active antiretroviral treatment. AIDS. 2011; 25(5):625–33. [PubMed: 21297425]

98. Descamps M, Hyare H, Stebbing J, Winston A. Magnetic resonance imaging and spectroscopy of the brain in HIV disease. Journal of HIV therapy. 2008; 13(3):55–8. [PubMed: 19039299]

99. Cohen RA, Harezlak J, Gongvatana A, et al. Cerebral metabolite abnormalities in human immunodeficiency virus are associated with cortical and subcortical volumes. J Neurovirol. 2010; 16(6):435–44. [PubMed: 20961212]

100. Chang L, Ernst T, Witt MD, et al. Persistent brain abnormalities in antiretroviral-naive HIV patients 3 months after HAART. Antivir Ther. 2003; 8(1):17–26. [PubMed: 12713060]

101. Rottenberg DA, Moeller JR, Strother SC, et al. The metabolic pathology of the AIDS dementia complex. AnnNeurol. 1987; 22:700–6.

102. Venneti S, Lopresti BJ, Wang G, et al. PET imaging of brain macrophages using the peripheral benzodiazepine receptor in a macaque model of neuroAIDS. JClinInvest. 2004; 113:981–9.

103. Garvey LJ, Pavese N, Politis M, et al. Increased microglia activation in neurologically asymptomatic HIV-infected patients receiving effective ART; An 11C-PK11195 PET study. AIDS. 2013

104. Wiley CA, Lopresti BJ, Becker JT, et al. Positron emission tomography imaging of peripheral benzodiazepine receptor binding in human immunodeficiency virus-infected subjects with and without cognitive impairment. J Neurovirol. 2006; 12(4):262–71. [PubMed: 16966217]

105. Heaps JM, Joska J, Hoare J, et al. Neuroimaging markers of human immunodeficiency virus infection in South Africa. J Neurovirol. 2012; 18(3):151–6. [PubMed: 22528474]

106. Thompson PM, Dutton RA, Hayashi KM, et al. Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. PNAS. 2005; 102:15647–52. [PubMed: 16227428]

107. Jernigan TL, Archibald SL, Fennema-Notestine C, et al. Clinical factors related to brain structure in HIV: the CHARTER study. JNeurovirol. 2011; 17(3):248–57. [PubMed: 21544705]

108. Ances BM, Ortega M, Vaida F, Heaps J, Paul R. Independent effects of HIV, aging, and HAART on brain volumetric measures. J Acquir Immune Defic Syndr. 2012; 59(5):469–77. [PubMed: 22269799]

109. Fennema-Notestine C, Ellis RJ, Archibald SL, et al. Increases in brain white matter abnormalities and subcortical gray matter are linked to CD4 recovery in HIV infection. J Neurovirol. 2013

110. Wu Y, Storey P, Cohen BA, Epstein LG, Edelman RR, Ragin AB. Diffusion alterations in corpus callosum of patients with HIV. AJNR American journal of neuroradiology. 2006; 27(3):656–60. [PubMed: 16552012]

111. Nakamoto BK, Jahanshad N, McMurtray A, et al. Cerebrovascular risk factors and brain microstructural abnormalities on diffusion tensor images in HIV-infected individuals. J Neurovirol. 2012; 18(4):303–12. [PubMed: 22585287]

112. Wright PW, Heaps JM, Shimony JS, Thomas JB, Ances BM. The effects of HIV and combination antiretroviral therapy on white matter integrity. AIDS. 2012; 26(12):1501–8. [PubMed: 22546990]

113. Gongvatana A, Cohen RA, Correia S, et al. Clinical contributors to cerebral white matter integrity in HIV-infected individuals. J Neurovirol. 2011; 17(5):477–86. [PubMed: 21965122]

114. Melrose RJ, Tinaz S, Castelo JM, Courtney MG, Stern CE. Compromised fronto-striatal functioning in HIV: an fMRI investigation of semantic event sequencing. Behavioural brain research. 2008; 188(2):337–47. [PubMed: 18242723]

115. Ernst T, Chang L, Jovicich J, Ames N, Arnold S. Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients. Neurology. 2002; 59:1343–9. [PubMed: 12427881]

116. Thomas JB, Brier MR, Snyder AZ, Vaida FF, Ances BM. Pathways to neurodegeneration: effects of HIV and aging on resting-state functional connectivity. Neurology. 2013; 80(13):1186–93. [PubMed: 23446675]

117. Ances BM, Sisti D, Vaida F, et al. Resting cerebral blood flow: a potential biomarker of the effects of HIV in the brain. Neurology. 2009; 73(9):702–8. [PubMed: 19720977]

118. Ances BM, Leontiev O, Perthen JE, Liang C, Lansing AE, Buxton RB. Regional differences in the coupling of cerebral blood flow and oxygen metabolism changes in response to activation: implications for BOLD-fMRI. NeuroImage. 2008; 39:1510–21. [PubMed: 18164629]

119. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. ArchNeurol. 2008; 65(1):65–70.
120. Garvey L, Winston A, Walsh J, et al. Antiretroviral therapy CNS penetration and HIV-1-associated CNS disease. Neurology. 2011; 76(8):693–700. [PubMed: 21339496]
121. Lanoy E, Guiguet M, Bentata M, et al. Survival after neuroAIDS: Association with antiretroviral CNS Penetration-Effectiveness score. Neurology. 2011; 76(7):644–51. [PubMed: 21248274]
122. McManus H, Li PC, Nolan D, et al. Does use of antiretroviral therapy regimens with high central nervous system penetration improve survival in HIV-infected adults? HIV Med. 2011; 12(10): 610–9. [PubMed: 21819527]
123. Ellis, RVF.; Letendre, S.; Haubrich, R.; Heaton, R.; McCutchan, A.; Cherner, M.; Umlauf, A.; Sacktor, N.; Clifford, D. A randomized, controlled trial of a central nervous system-targeted ART strategy for HIV-associated neurocognitive disorders.. 20th Conference on Retroviruses and Opportunistic Infections - Atlanta, GA; 2013. p. 3
124. Robertson KR, Su Z, Margolis DM, et al. Neurocognitive effects of treatment interruption in stable HIV-positive patients in an observational cohort. Neurology. 2010; 74(16):1260–6. [PubMed: 20237308]
125. Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. J Neurovirol. 2012; 18(5):388–99. [PubMed: 22811264]
126. Shikuma CM, Nakamoto B, Shiramizu B, et al. Antiretroviral monocyte efficacy score linked to cognitive impairment in HIV. Antivir Ther. 2012; 17(7):1233–42. [PubMed: 23018140]
127. Dahl V, Lee E, Peterson J, et al. Raltegravir treatment intensification does not alter cerebrospinal fluid HIV-1 infection or immunoactivation in subjects on suppressive therapy. J Infect Dis. 2011; 204(12):1936–45. [PubMed: 22021620]
128. Yilmaz A, Verhofstede C, D'Avolio A, et al. Treatment intensification has no effect on the HIV-1 central nervous system infection in patients on suppressive antiretroviral therapy. J Acquir Immune Defic Syndr. 2010; 55(5):590–6. [PubMed: 20847699]
129. Wong HL, Chattopadhyay N, Wu XY, Bendayan R. Nanotechnology applications for improved delivery of antiretroviral drugs to the brain. [Review] [194 refs]. Advanced Drug Delivery Reviews. 2010; 62(4-5):503–17. [PubMed: 19914319]
130. Clifford DB. Human immunodeficiency virus-associated dementia. ArchNeurol. 2000; 57(3): 321–4.
131. Zink MC, Uhrlaub J, DeWitt J, et al. Neuroprotective and anti-human immunodeficiency virus activity of minocycline. JAMA. 2005; 293:2003–11. [PubMed: 15855434]
132. Sacktor N, Nakasujja N, Miyahara S, et al. Minocycline treatment for HIV-associated cognitive impairment in Uganda. Neurology. 2011; 76(9):A23.
133. Letendre S, Marquie-Beck J, Ellis RJ, et al. The role of cohort studies in drug development: clinical evidence of antiviral activity of serotonin reuptake inhibitors and HMG-CoA reductase inhibitors in the central nervous system. JNeuroimmune Pharmacol. 2007; 2:120–7. [PubMed: 18040835]
134. Navia BA, Yiannoutsos CT, Change L, et al. ACTG 301: a phase II randomized, double-blind, placebo-controlled trial of memantine for AIDS dementia complex (ADC). American Academy of Neurology 53rd Annual Meeting. 2001; 56:A474–A5.
135. Anderson ER, Gendelman HE, Xiong H. Memantine protects hippocampal neuronal function in murine human immunodeficiency virus type 1 encephalitis. Journal of Neuroscience. 2004; 24:7194–8. [PubMed: 15306653]
136. Zhao Y, Navia BA, Marra CM, et al. Memantine for AIDS dementia complex: open-label report of ACTG 301. HIV Clinical Trials. 2010; 11(1):59–67. [PubMed: 20400412]
137. Simioni S, Cavassini M, Annoni JM, et al. Rivastigmine for HIV-associated neurocognitive disorders: a randomized crossover pilot study. Neurology. 2013; 80(6):553–60. [PubMed: 23345635]
138. Schifitto G, Peterson DR, Zhong J, et al. Valproic acid adjunctive therapy for HIV-associated cognitive impairment: A first report. Neurology. 2006; 66:919–21. [PubMed: 16510768]

139. Ances BM, Letendre S, Buzzell M, et al. Valproic acid does not affect markers of human immunodeficiency virus disease progression. Journal of NeuroVirology. 2006; 12:403–6. [PubMed: 17065134]

140. Routy JP, Tremblay CL, Angel JB, et al. Valproic acid in association with highly active antiretroviral therapy for reducing systemic HIV-1 reservoirs: results from a multicentre randomized clinical study. HIV Med. 2012; 13(5):291–6. [PubMed: 22276680]

141. High KP, Brennan-Ing M, Clifford DB, et al. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. J Acquir Immune Defic Syndr. 2012; 60(Suppl 1):S1–18. [PubMed: 22688010]

142. Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, Achim CL. Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. AIDS. 2005; 19:407–11. [PubMed: 15750394]

143. Rempel HC, Pulliam L. HIV-1 Tat inhibits neprilysin and elevates amyloid β. AIDS. 2005; 19:127–35. [PubMed: 15668537]

144. Brew BJ, Pemberton L, Blennow K, Wallin A, Hagberg L. CSF amyloid β42 and tau levels correlate with AIDS dementia complex. Neurology. 2005; 65:1490–2. [PubMed: 16275845]

145. Gisslén M, Blennow K, Brew B, et al. CSF neural marker profile distinguishes AIDS dementia complex from Alzheimer's disease. 15th Conference on Retroviruses and Opportunistic Infections. 2008:196.

146. Mintun MA, LaRossa GN, Sheline YI, et al. [^{11}C]PIB in a nondemented population. Potential antecedent marker of Alzheimer disease. Neurology. 2006; 67:446–52. [PubMed: 16894106]

147. Ances BM, Benzinger TL, Christensen JJ, et al. 11C-PiB imaging of human immunodeficiency virus-associated neurocognitive disorder. ArchNeurol. 2012; 69(1):72–7.

148. Morgan EE, Woods SP, Letendre SL, et al. Apolipoprotein E4 genotype does not increase risk of HIV-associated neurocognitive disorders. J Neurovirol. 2013; 19(2):150–6. [PubMed: 23408335]

149. Corder EH, Robertson K, Lannfelt L, et al. HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. Nature Medicine. 1998; 4:1182–4.

150. Burt TD, Agan BK, Marconi VC, et al. Apolipoprotein (apo) E4 enhances HIV-1 cell entry in vitro, and the APOE ε4/ε4 genotype accelerates HIV disease progression. PNAS. 2008; 105(25): 8718–23. [PubMed: 18562290]

151. Joska JA, Combrinck M, Valcour VG, et al. Association between apolipoprotein E4 genotype and human immunodeficiency virus-associated dementia in younger adults starting antiretroviral therapy in South Africa. Journal of NeuroVirology. 2010; 16(5):377–83. [PubMed: 20825268]

152. Chang L, Andres M, Sadino J, et al. Impact of apolipoprotein E epsilon4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. Neuroimage. 2011; 58(4): 1017–27. [PubMed: 21803164]

153. Valcour V, Shikuma C, Shiramizu B, et al. Age, apolipoprotein E4, and the risk of HIV dementia: the Hawaii Aging with HIV Cohort. Journal of Neuroimmunology. 2007; 157:197–202. [PubMed: 15579298]

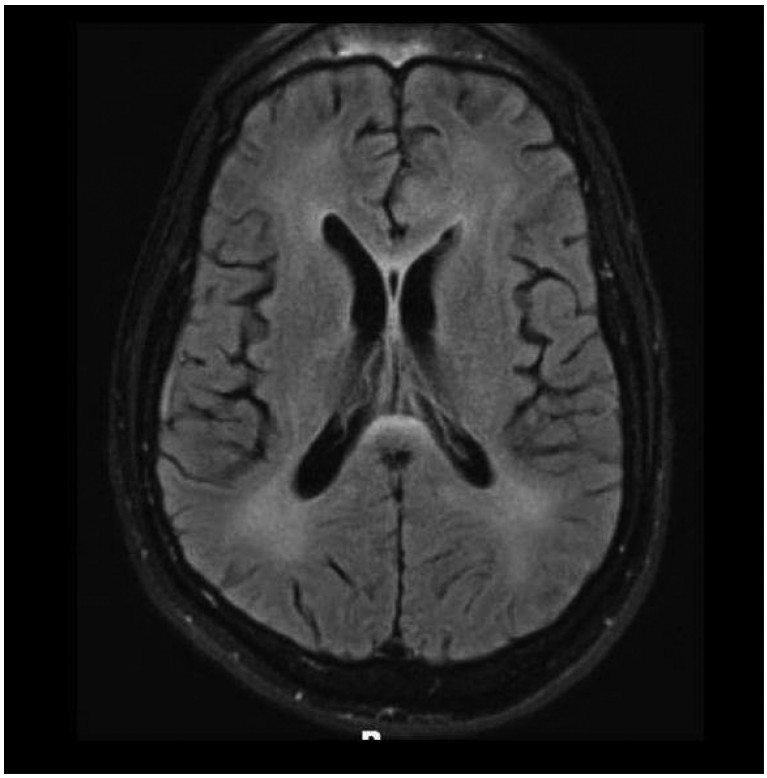

Figure 1.

Characteristic magnetic resonance imaging findings of an HIV patient with HAND. A fluid level attenuated inversion recovery (FLAIR) image was obtained and demonstrates prominent white matter changes throughout the brain. These changes are typically seen only in more advanced disease and relatively rare in the post combination antiretroviral therapy (cART) era.

Table 1

Categories of HIV-Associated Neurocognitive Disorder (HAND), Frascati Criteria[9]

	Neurocognitive Status[#]	**Functional Status**[*]
Asymptomatic Neurocognitive Impairment (ANI)	1 SD below mean, 2cognitive domains	No Impairment in activities of daily living
Mild Neurocognitive Disorder (MND)	1 SD below mean, 2cognitive domains	Impairment in activities of daily living
HIV Associated Dementia (HAD)	2 SD below mean, 2 cognitive domains	Marked impairment in activities of daily living

Of note, for HAND diagnosis other etiology of dementia must be ruled out and confounding effect of substance use or psychiatric illness must be considered.

[#]Neurocognitive testing should include evaluating at least five domains including attention-information processing, language, abstraction-executive, complex perceptual motor skills, memory (including learning and recall) simple motor skills or sensory perceptual skills. Appropriate norms must be available to determine the number of domains in which performance is below 1 standard deviation (SD).

[*]Functional status is typically evaluated by self report but may be corroborated by a collateral source. No agreed upon measures exist for HAND criteria.