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Current understanding of HIV-associated neurocognitive disorders pathogenesis

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Abstract

Purpose of review—The present review discusses current concepts of HIV-associated neurocognitive disorders (HAND) in the era of antiretroviral therapy (ART). As the HIV epidemic enters its fourth decade (the second decade of ART), research must address evolving factors in HAND pathogenesis. These include persistent systemic and central nervous system (CNS) inflammation, aging in the HIV-infected brain, HIV subtype (clade) distribution, concomitant use of drugs of abuse, and potential neurotoxicity of ART drugs.

Recent findings—Although the severest form of HAND, HIV-associated dementia (HAD), is now rare due to ART, the persistence of milder, functionally important HAND forms persist in up to half of HIV-infected individuals. HAND prevalence may be higher in areas of Africa where different HIV subtypes predominate, and ART regimens that are more effective in suppressing CNS HIV replication can improve neurological outcomes. HAND are correlated with persistent systemic and CNS inflammation, and enhanced neuronal injury due to stimulant abuse (cocaine and methamphetamine), aging, and possibly ART drugs themselves.

Summary—Prevention and treatment of HAND requires strategies aimed at suppressing CNS HIV replication and effects of systemic and CNS inflammation in aging and substance-abusing HIV populations. Use of improved CNS-penetrating ART must be accompanied by evaluation of potential ART neurotoxicity.

Keywords

antiretroviral therapy; cognitive dysfunction; HIV; HIV-associated neurocognitive disorders; inflammation

Introduction

The term HIV-associated neurocognitive disorders, or HAND, represents a group of syndromes of varying degrees of impairment of cognition and associated functioning in HIV-infected individuals [1,2]. Its clinical severity includes asymptomatic

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neuropsychological impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD), grouped collectively as HAND [1]. ANI is defined by neuropsychological test performance at least one standard deviation below the mean of that in demographic controls, in at least two specific cognitive areas, whereas MND includes those criteria and interference with activities of daily living. The diagnosis of HAD requires test performance at least two standard deviations below the mean in two or more cognitive areas and marked impairment of activities of daily living. The neuropathogenesis of HAND is generally considered to be initiated and driven by HIV invasion and replication within the brain parenchyma, largely through productive infection of brain perivascular macrophages and endogenous microglia, and perhaps to some degree by restricted infection of astrocytes [3,4]. Associated with this infection is neuroinflammation and immune activation of resident glia (macrophages, microglia, astrocytes), which is associated with neuronal injury (both reversible and irreversible). Although the widespread utilization of antiretroviral therapy (ART) has dramatically decreased the prevalence of the severest form of HAND, HAD, the overall prevalence of HAND and associated morbidity remain high (~50%) [5–7,8••]. The persistence of this high risk for HAND in individuals experiencing effective control of systemic HIV viral load is incompletely explained, and suggested factors include effects of aging on brain vulnerability, persistence of HIV replication in brain macrophages, evolution of highly neurovirulent CNS HIV strains, and even long-term CNS toxicity of ART [8••,9••]. This review will discuss several of these key factors implicated in modulating HAND pathogenesis: inflammation, HIV-1 subtype (clade), drugs of abuse, aging, and antiretroviral drug effects. Other important factors, including comorbidity effects of hepatitis C, host genetic susceptibility, viral gene adaptations, and others are discussed elsewhere [4,10•,11•].

Role for inflammation in neuropathogenesis of HIV-associated neurocognitive disorders

Inflammation is associated with HIV replication, both in the periphery and within the CNS where macrophage activation has been correlated with HAND [12,13]. In the last few years, the inflammatory response in the systemic circulation has been recognized as a key driver of HIV pathogenesis, both in the periphery and in the CNS [14••,15,16,17•,18,19•,20,21,22•,23–26]. In the CNS, there is considerable evidence that this inflammatory response drives the development of HAND or worsens it, possibly independently of viral replication [4,27•, 28,29].

Evidence for persistent inflammation in central nervous system in antiretroviral therapy-experienced patients

The era of ART is associated with changes in the neuropathology of HIV infection, which reflects the partial efficacy of ART drugs in suppressing, though incompletely, CNS virus replication and associated inflammation [30–32]. Before the introduction of ART, robust neuroinflammation was frequently observed in brain autopsies from HIV-infected patients and the severity of inflammation generally increased throughout clinical disease progression from the early asymptomatic stage to AIDS to severe HAND [33–36]. Although inflammation is less severe since ART inception, it nonetheless persists within the macrophage/microglial populations, which represent the primary reservoir for HIV in the brain [37–38]. Perivascular monocyte-derived macrophages (MDMs) and microglia are the primary CD4+ cells in the CNS and the major sources of productive HIV infection in the brain [39–42] and clinical disease severity correlates more strongly with the amount of monocyte infiltration and MDM/microglia activation than with the quantity of infected cells or viral load [12,13]. This suggests that MDM/microglia play a predominant role in the neuroinflammation and neurodegeneration seen in HAND. Immune activation of MDM/

microglia is demonstrated by expression of CD14 [lipopolysaccharide (LPS) receptor], CD16, CD68, and major histocompatibility complex (MHC) class II *in vivo* [34,43–45]. Furthermore, cerebrospinal fluid (CSF) markers of immune activation and inflammation are commonly detected in individuals with HAND. These markers include CCL2 [46,47], β2-microglobulin [48–51], quinolinic acid [52–55], arachidonic acid metabolites [56,57], oxidative stress markers [58,59], and platelet activating factor [60].

Although ART has limited the severity of pathological changes characteristic of HAND, it has not eliminated them. These persistent pathological findings in ART-experienced individuals include neuronal loss with apoptosis, astrocytosis, myelin pallor, and at least some activated microglia and perivascular macrophages, although the neuropathological hallmarks of HIV encephalitis (HIVE), multinucleated giant cells, and microglial nodules, are typically absent [37]. Persistent CNS immune activation has also been documented in pediatric AIDS patients, as evidenced by detection of sCD14 and an elevated CSF IgG index, despite prolonged (>4 years) ART use and undetectable serum viral loads [61]. Thus, despite some ART effectiveness in limiting the infiltration of infected cells (monocytes/macrophages) into the CNS, neuroinflammation still persists. Nonetheless, the primary sites of neuroinflammation are different; the characteristic involvement of the basal ganglia in pre-ART specimens is less commonly seen in post-ART specimens, which display inflammation in the hippocampus and in adjacent parts of the entorhinal and temporal cortices [32,38,62]. Overall, these studies confirm the notion that neuroinflammation continues to be associated with HIV CNS infection in ART-experienced individuals [63].

Chronic systemic inflammation and microbial translocation in the gut as a driving force for central nervous system inflammation and HIV-associated neurocognitive disorders

Chronic systemic inflammation has been tightly linked to morbidity and mortality in HIV-infected patients receiving ART, which suggests that adjunctive anti-inflammatory drug therapy is needed to improve outcomes [14••,15,16,17•,18,19•,20,21,22•,23–26]. Studies have correlated systemic inflammation (elevated plasma sCD14, LPS), CNS inflammation and HAND [64] and persistence of CSF immune activation (sCD14, elevated IgG index), despite ART use and undetectable serum viral loads [61]. A strong association between the early and persistent damage caused to gut-associated lymphoid tissue (GALT) by HIV infection [simian immunodeficiency virus (SIV) infection in macaques], increased microbial translocation resulting in systemic immune/ monocyte activation, and disease progression has been established [21,22•,24–26,65]. An association between this systemic immune activation and HAND has also been established, and a causal relationship between increased systemic monocyte activation, increased transendothelial migration of activated monocytes into the brain, and neurocognitive decline secondary to neurodegeneration has been proposed [64]. Furthermore, the persistence of HAND (~50% prevalence) despite prolonged ART use is associated with not only neuropathologic but also neuroradiologic evidence of persistent CNS inflammation [7,61,66•,67,68]. Persistent systemic and CNS inflammation in ART-treated individuals are, thus, clear targets for adjunctive therapies against disease progression.

Association of HIV-1 clades/subtypes and risk of HIV-associated neurocognitive disorders

Until recently, HAND has been studied nearly exclusively in developed countries (United States and Europe), where a single HIV clade or genotypically defined subtype predominates (HIV clade B). The distribution of HIV-1 clades varies worldwide, and differences in phenotypic characteristics, including induction of immune responses, viral fitness, drug resistance, coreceptor utilization, antibody neutralization sensitivity, and

neurovirulence among HIV clades have been described [69–76]. Several recent publications have suggested that HAND prevalence varies among populations based upon clade predominance, thus representing an independent risk factor for HAND [77,78]. The majority of clinical studies have been performed in cohorts infected with clade B, and the neuropathogenesis of HAND has, until recently, been exclusively described in these populations. Furthermore, HIV clades can be further modified through genetic recombination events, which could alter their pathogenic potential. Early studies in Uganda (where clades A and D predominate) have shown that prevalence of some HAND features is comparable to that observed in the United States during the pre-ART era, and that advanced age and low CD4+ T-cell count are major risk factors [79•]. Other investigators observed a greater prevalence of HAND in antiretroviral-naive HIV-positive individuals in Uganda who are infected with clade D strains in comparison with individuals infected with clade A strains (89 vs. 24%) [80•]. Notably, the use of ART can significantly improve neurocognitive function in these individuals within a few months [81].

More studies have focused on clade C, as it is the most common HIV clade and it accounts for approximately 50% of HIV infections worldwide. Clade C is linked to growing epidemics in sub-Saharan Africa and parts of Asia, including China and India [79•]. Some studies have associated infection with clade C with a low risk for HAND (in Ethiopia), whereas others (performed by Australia-Pacific Neuro AIDS consortium in many countries in the Pacific Rim) associate it with a higher risk. Studies in India, where clade C accounts for 95% of HIV infections, have produced conflicting results. In southern India, approximately 60.5% of ART-naive HIV-positive individuals in one study (n=119) were found to have neuropsychological test impairments without clinically identifiable neurological symptoms (consistent with asymptomatic HAND, ANI), whereas another study indicated a higher than expected prevalence of clinically symptomatic HAND [77,78]. A study of HIV-positive individuals (clade C) in China showed that the prevalence, pattern, and severity of some HAND deficits were comparable to those reported for (clade B) in western countries. Finally, a recent study of clade C-infected ART-experienced (average 2 years on ART) individuals in Botswana demonstrated a prevalence of neurocognitive impairment detected by neuropsychological testing and a modified International HIV Dementia Scale (IHDS) of greater than 33%, which exceeds the expected prevalence of HAD, even in the pre-ART era [82•]. Thus, several studies in distinct clade C cohorts worldwide suggest a potentially high risk for moderate-to-severe HAND complications with clade C infection. Notably, despite possible different risks for HAND among these different HIV clades, beneficial effects of ART have been demonstrated worldwide (reviewed in [83•]).

Association of drugs of abuse and risk for HIV-associated neurocognitive disorders

Although the strict definition of HAND requires the exclusion of other comorbid conditions (besides HIV infection) as the cause of neurocognitive dysfunction, the contribution of drugs of abuse as a major comorbidity risk for neurocognitive dysfunction in HIV-positive individuals is a major concern worldwide [84,85•,86,87•]. Among the major drugs of abuse contributing to HIV pathogenesis are opiates (morphine) and stimulants [cocaine, methamphetamine (METH)]. In developed countries, approximately 30% of HIV-positive individuals are intravenous drug abusers, and the risk for HAND is clearly greater among these individuals [87•]. The neuroinflammation associated with HAND appears to be exacerbated by drugs of abuse, as demonstrated by brain autopsy studies revealing a higher prevalence of HIV encephalitis [microglia activation, presence of multinucleated giant cells, and blood–brain barrier (BBB) disruption] in drug-abusing HIV-positive individuals in comparison with non abusing HIV-positive controls [88–90]. These findings suggest that

drug abuse exerts an additive (if not synergistic) effect with HIV within the CNS. However, the inherently heterogeneous nature of drug-abusing patient populations confounds the specific effects of drugs of abuse on neuronal function and survival *in vivo*.

Both in-vitro and in-vivo studies, however, clearly implicate drugs of abuse in exacerbating neuronal injury induced by HIV (or the primate homologue, SIV), although conflicting evidence for certain drugs of abuse has been presented [91,92•,93–97]. Enhanced HIV replication in MDM and T lymphocytes through opioid exposure has been demonstrated [98–100] as has enhancement of MDM-associated inflammation and oxidative stress [101]. Opiates (methadone) also activate HIV replication in latently infected macrophages *in vitro* [102]. In nonhuman primate models of SIV infection (the primate homologue of HIV infection), carefully controlled studies show that chronic morphine administration markedly increases viral loads in the plasma and CSF [103]. Interestingly, activation of mu opioid receptors, which are expressed in neurons, MDM, and T lymphocytes, can increase the expression of some of the chemokine receptors (CCR3, CCR5, and CXCR4) that serve as HIV coreceptors for HIV in susceptible cells (MDM and T lymphocytes) [104,105]. Furthermore, activation of kappa opioid receptors (MDM and T lymphocytes) can decrease CCR5 expression and, thus, decrease cell susceptibility to HIV infection [106,107]. Nonetheless, a role for opiates in exacerbating neurodegeneration in HAND remains controversial [85•,108].

A role for stimulants such as cocaine and METH in exacerbating the risk for HAND is more strongly established by in-vivo and in-vitro studies [109]. Enhancement of HIV replication in MDM by stimulants (cocaine and METH) has been consistently demonstrated *in vitro*, and the expected consequence of enhanced HIV replication in MDM is enhanced neurodegeneration through enhanced production of neurotoxic factors from infected and activated macrophages within the CNS [3,84]. Cocaine can also increase HIV replication in monocytes, and even astrocytes *in vitro* [110,111]. The later observation could be significant, as restricted infection of astrocytes *in vivo* has been demonstrated in several studies, suggesting that this could be a second HIV reservoir (in addition to the primary HIV reservoir, macrophages/microglia) [112–114]. In addition, cocaine can facilitate HIV infection by upregulating dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), another HIV coreceptor, in dendritic cells, through dysregulation of mitogen-activated protein kinases [115]. METH can increase macrophage HIV infection in association with increased expression of CXCR4 and CCR5, and perhaps by downregulation of extracellular-regulated kinase (ERK) and the upregulation of p38 mitogen-activated protein kinase [116]. METH can also enhance HIV replication in monocyte-derived dendritic cells [116].

Alterations in BBB integrity by cocaine and METH are another proposed mechanisms for enhancing neurodegeneration through enhanced monocyte entry and disruption of cellular homeostasis. *In vitro*, cocaine can enhance monocyte transendothelial migration, induce the expression of adhesion molecules on endothelial cells, and disrupt intercellular junctions [117–119]. METH and the HIV envelope protein gp120 can modulate tight junction expression in brain endothelial cells, leading to decreased transendothelial resistance across the BBB and enhanced transendothelial migration of monocytes [120]. Morphine alone, on the other hand, does not appear to alter the integrity of the BBB, although in combination with the HIV transactivator protein Tat it can alter tight junction expression in brain endothelial cells *in vitro*. Interestingly, although morphine by itself is not toxic to striatal neurons in culture, it can significantly potentiate Tat toxicity in striatal neurons [121]. Thus, the ability of HIV-derived proteins and cocaine and METH to alter endothelial cell function and/or disrupt the BBB *in vitro* suggests potential additive effects of HIV infection, cocaine, and METH *in vivo*.

Evidence for in-vivo neuropathologic effects of cocaine and METH in HIV-positive individuals is also accumulating [85•]. Disruption of the BBB in such individuals has been demonstrated in neuropathologic studies, and this disruption correlates with early inflammatory changes in the CSF, particularly with increased monocyte chemoattractant protein-1 (MCP-1/CCL2) levels [122]. However, whether BBB integrity is even further compromised in individuals abusing cocaine or METH is unknown. Autopsy studies of adult METH abusers have demonstrated neuronal loss within the substantia nigra and structural and metabolic changes within the brain have been detected in children after prenatal exposure [123,124]. Injury to dopaminergic pathways and the basal ganglia also occurs in HIV-positive individuals in the presence and absence of abuse of cocaine, which can result in profound clinical symptoms of basal ganglia dysfunction [125]. Thus, drugs of abuse, particularly cocaine and METH, are strongly associated with enhanced brain injury in HIV-positive individuals, which is expressed as enhanced risk for HAND and other neurologic complications.

Aging and HIV-associated neurocognitive disorder

The long-term prognosis for ART-treated HIV-positive individuals continues to improve as the incidence of many AIDS-related complications declines, and by 2015 more than 50% of the HIV-positive population in the United States will be over 50 years of age [14••]. Nonetheless, life expectancy for treated HIV-positive individuals remains 10–30 years less than that of uninfected individuals [14••]. ART-treated patients are at increased risk for systemic and CNS diseases associated with aging: renal failure, osteoporosis, cancer, cardiovascular disease, and cognitive decline, which can be associated with Alzheimer's disease and Parkinson's disease-like pathology [14••,126•]. This suggests that the aging brain might be more vulnerable to neuronal injury associated with HIV infection, although comorbidity factors in aging patients complicate establishing a causal relationship between age and HAND risk.

Several published neuroimaging and neurobehavioral studies have suggested an increased risk for cognitive impairment with increased age in HIV-positive individuals [66•,127,128], although an additional study has suggested that the effects of HIV infection and aging on the brain might act independently [129]. Ernst and Chang [127] used brain proton magnetic resonance spectroscopy (MRS) to demonstrate that the combined effects of HIV-positive serostatus resulted in a greater than five-fold acceleration of aging effects (rather than additive effects) in the basal ganglia, in a cohort of 46 HIV-positive individuals in comparison with HIV-negative controls. Cherner *et al.* [128] showed that an HIV-positive individual cohort with an age greater than 50 years and detectable CSF viral loads had a two-fold higher prevalence of neuropsychological impairment in comparison with a younger cohort (less than 35 years of age) showing undetectable viral loads. Notably, this relationship was not found in those individuals less than 50 years of age. These studies suggest that older adults are at higher risk for neurocognitive dysfunction because of age-related brain vulnerability; however, whether this dysfunction reflects accelerated neuropathological processes associated more specifically with HAND or processes more specifically associated with other familiar neurodegenerative diseases, or neither, remains to be determined.

Some recent studies have begun to address the underlying neuropathology of age-related neurocognitive dysfunction in HIV-positive individuals. Alzheimer's disease and Parkinson's disease-like pathological changes observed in ART-treated patients [130•,131] include elevated levels of hyperphosphorylated Tau (p-Tau) in the hippocampus and beta-amyloid deposition, both intracellular and extracellular, in the frontal cortex and hippocampus [132–135]. Recent evidence has also shown increased levels of alpha-

synuclein in the substantia nigra and increased risk for Parkinson's disease in aging HIV-positive patients on ART [131]. Although accumulation of neurodegeneration-related proteins might be accounted for by the increased lifespan associated with ART, possible toxic effects of ART in the CNS are now being considered as a contributing factor in HAND [11•,136•]. One study demonstrated that pre-ART individuals who lived up 15 years with HIV infection did not express excessive levels of hyperphosphorylated Tau or beta-amyloid, nor were they associated with HAND [38]. Other studies have demonstrated increased levels of amyloid precursor protein in damaged axons in brain specimens from ART-naive patients without evidence for elevated p-Tau expression or neuritic plaque formation [137,138]. Thus, studies utilizing neuropsychological performance testing, neuroimaging, and neuropathological analyses strongly support a correlation between accelerated neurocognitive decline and aging in HIV-infected individuals, even in those with what is considered 'effective' suppression of systemic HIV replication. These studies further emphasize the need for developing new strategies involving current ART and possibly adjunctive therapies for protecting the brain against injury in the aging HIV-positive population.

Possible role for antiretroviral therapy drugs in HIV-associated neurocognitive disorders

The persistent high prevalence of less severe forms of HAND, including ANI and MND, after widespread implementation of ART was not anticipated, and several causes have been suggested, including effects of aging and associated comorbidity factors on the brain [9••, 39,66•]. Antiretroviral drugs, particularly nucleoside reverse transcriptase inhibitors (NRTIs), are highly neurotoxic, and ART drug-induced neuropathy is a major complication of HIV treatment [10•]. In addition, some clinical studies have also suggested a role for direct and/or indirect neurotoxic effects of ARTdrugs in the CNS[139,140•,141]. In addition to direct neurotoxicity, ART has been linked to multiple risk factors for neurodegenerative disease, such as insulin resistance, lipodystrophy, atherosclerosis, coronary artery disease, and immune reconstitution syndrome [142–149]. These studies suggest possible direct and indirect effects of ART drugs in the CNS that could be linked to impaired neurocognitive performance.

However, other studies have demonstrated beneficial effects on neurocognitive functioning by ART regimens ranked according to their predicted effectiveness (termed CNS penetration-effectiveness ranking, CPE) in suppressing HIV replication within the CNS [8••, 150•,151,152]. Better neurocognitive performance was observed over a 15-week period in adult individuals beginning ART with regimens of higher CPE [151], and improved survival rates over more than 6 years of follow-up of pediatric HIV encephalopathy patients receiving higher CNS-penetrating regimens were also observed [153••,154••]. A cross-sectional study of 2636 adults [AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT cohort)] on effective ART (less than 50 HIV RNA copies/ml) also demonstrated better neurocognitive performance in those receiving higher CPE ART [150•]. Another recent study utilized MRS brain imaging and neurocognitive testing to demonstrate partial reversal of neuronal injury in patients and greater improvements in neurocognitive functioning in other patients receiving different ART regimens over a 48-week period, which might relate to CNS drug penetrance [155•]. These studies suggest a neuroprotective effect of ART based upon use of higher CPE regimens, and ongoing prospective clinical studies are further addressing this critical issue [8••,9••,154••].

Conclusion

HAND pathogenesis is driven by HIV replication and the factors associated with amplifying the inflammatory milieu within the CNS. Systemic immune activation, migration of activated monocytes, drugs of abuse, and secondary effects of aging all contribute to neuronal injury associated with HAND, which persist despite effective systemic control of HIV replication by current ART. Accordingly, drugs that suppress systemic immune activation and associated inflammation, both systemically and within the CNS compartment, could represent effective adjunctive neuroprotectants [4,27•,28,29]. Investigating drugs in current clinical use that target these cellular pathways could rapidly facilitate testing and implementation of feasible adjunctive neuroprotective strategies against HAND.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 305–306).

1. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69:1789–1799. [PubMed: 17914061]
2. Grant I. Neurocognitive disturbances in HIV. Int Rev Psychiatry. 2008; 20:33–47. [PubMed: 18240061]
3. Kaul M. HIV-1 associated dementia: update on pathological mechanisms and therapeutic approaches. Curr Opin Neurol. 2009; 22:315–320. [PubMed: 19300249]
4. McArthur JC, Steiner J, Sacktor N, et al. Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. Ann Neurol. 2010; 67:699–714. [PubMed: 20517932]
5. Sacktor N, McDermott MP, Marder K, et al. HIV-associated cognitive impairment before and after the advent of combination therapy. J Neurovirol. 2002; 8:136–142. [PubMed: 11935465]
6. McArthur JC, McDermott MP, McClernon D, et al. Attenuated central nervous system infection in advanced HIV/AIDS with combination antiretroviral therapy. Arch Neurol. 2004; 61:1687–1696. [PubMed: 15534180]
7. Nath A, Schiess N, Venkatesan A, et al. Evolution of HIV dementia with HIV infection. Int Rev Psychiatry. 2008; 20:25–31. [PubMed: 18240060]
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; 75:2087–2096. This cross-sectional observational study of 1555 patients demonstrates a prevalence of HAND greater than 50% in ART-treated patients, with lowest impairment among those with suppressed viral loads and CD4 T-cell counts more than 200 cells/μl, and discusses criteria for initiating ART. [PubMed: 21135382]
9••. 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; 17:3–16. This study confirms the consistent and robust association between HAND risk and nadir CD4 cell count in the pre-ART and post-ART eras and suggests that early

ART treatment before immunosuppression may prevent neurological complications. [PubMed: 21174240]

10•. Letendre SL, Ellis RJ, Ances BM, et al. Neurologic complications of HIV disease and their treatment. Top HIV Med. 2010; 18:45–55. This update from the 2010 Conference on Retroviruses and Opportunistic Infections suggests additional HAND risk factors, including vascular disease and apoliprotein E, and discusses conflicting evidence about potential ART toxicity in the CNS. [PubMed: 20516524]

11•. Valcour V, Sithinamsuwan P, Letendre S, Ances B. Pathogenesis of HIV in the central nervous system. Curr HIV/AIDS Rep. 2011; 8:54–61. This review highlights recent studies addressing changes in the clinical, pathological, and neuroradiological findings in ART-treated patients and risk factors associated with HAND. [PubMed: 21191673]

12. Glass JD, Fedor H, Wesselingh SL, et al. Immunocytochemical quantitation of human immunodeficiency virus in the brain: correlations with dementia. Ann Neurol. 1995; 38:755–762. [PubMed: 7486867]

13. Adle-Biassette H, Chretien F, Wingertsmann L, et al. Neuronal apoptosis does not correlate with dementia in HIV infection but is related to microglial activation and axonal damage. Neuropathol Appl Neurobiol. 1999; 25:123–133. [PubMed: 10216000]

14••. Deeks SG. Immune dysfunction, inflammation, and accelerated aging in patients on antiretroviral therapy. Top HIV Med. 2009; 17:118–123. This perspective convincingly discusses the role for ongoing inflammation during ART as a treatable risk factor for disease progression, the need to aggressively manage inflammatory and vascular risk factors, and to consider early ART to prevent potentially reversible immune dysfunction. [PubMed: 19890183]

15. Calmy A, Gayet-Ageron A, Montecucco F, et al. HIV increases markers of cardiovascular risk: results from a randomized, treatment interruption trial. AIDS. 2009; 23:929–939. [PubMed: 19425222]

16. Duprez DA, Kuller LH, Tracy R, et al. Lipoprotein particle subclasses, cardiovascular disease and HIV infection. Atherosclerosis. 2009; 207:524–529. [PubMed: 19515371]

17•. Neuhaus J, Jacobs DR Jr, Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. J Infect Dis. 2010; 201:1788–1795. This study confirms the persistent activation of HIV-associated inflammatory pathways in virally suppressed ART-experienced patients among more than 5000 participants in the Strategies for Management of Anti-Retroviral Therapy (SMART) trial in comparison with age-matched participants of two large population-based studies of atherosclerosis risk in non-HIV-selected individuals. This will strongly prompt further investigations into interventions to decrease these risk factors and their effect on HIV disease progression. [PubMed: 20446848]

18. Reingold J, Wanke C, Kotler D, et al. Association of HIV infection and HIV/ HCV coinfection with C-reactive protein levels: the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study. J Acquir Immune Defic Syndr. 2008; 48:142–148. [PubMed: 18344877]

19•. Tien PC, Choi AI, Zolopa AR, et al. Inflammation and mortality in HIV-infected adults: analysis of the FRAM study cohort. J Acquir Immune Defic Syndr. 2010; 55:316–322. Plasma indicators of systemic inflammation [fibrinogen and C-reactive protein (CRP)] in 922 HIV-infected individuals followed over 5 years were found to be strong and independent predictors of mortality even when CD4 T-cell counts exceeded 500 cells/μl. Investigations are needed to determine whether reducing these inflammatory factors affects mortality and other outcomes, including HAND. [PubMed: 20581689]

20. van Vonderen MG, Hassink EA, van Agtmael MA, et al. Increase in carotid artery intima-media thickness and arterial stiffness but improvement in several markers of endothelial function after initiation of antiretroviral therapy. J Infect Dis. 2009; 199:1186–1194. [PubMed: 19275490]

21. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med. 2006; 12:1365–1371. [PubMed: 17115046]

22•. Wallet MA, Rodriguez CA, Yin L, et al. Microbial translocation induces persistent macrophage activation unrelated to HIV-1 levels or T-cell activation following therapy. AIDS. 2010; 24:1281–1290. Microbial translocation associated with elevated LPS and soluble CD14 levels persist in HIV-1-infected infants even with ART suppression of virus replication, T-cell

reconstitution, and resolution of lymphocyte activation. Thus, monocyte, macrophage activation persists in treated infants with as yet unknown consequences. [PubMed: 20559035]

23. Brenchley JM, Price DA, Douek DC. HIV disease: fallout from a mucosal catastrophe? Nat Immunol. 2006; 7:235–239. [PubMed: 16482171]
24. Brenchley JM, Schacker TW, Ruff LE, et al. $CD4^+$ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. J Exp Med. 2004; 200:749–759. [PubMed: 15365096]
25. Jiang W, Lederman MM, Hunt P, et al. Plasma levels of bacterial DNA correlate with immune activation and the magnitude of immune restoration in persons with antiretroviral-treated HIV infection. J Infect Dis. 2009; 199:1177–1185. [PubMed: 19265479]
26. Marchetti G, Bellistri GM, Borghi E, et al. Microbial translocation is associated with sustained failure in $CD4^+$ T-cell reconstitution in HIV-infected patients on long-term highly active antiretroviral therapy. AIDS. 2008; 22:2035–2038. [PubMed: 18784466]
27•. Grovit-Ferbas K, Harris-White ME. Thinking about HIV: the intersection of virus, neuroinflammation and cognitive dysfunction. Immunol Res. 2010; 48:40–58. This timely and thorough review links literature evidence for inflammation with neurocognitive dysfunction and discusses similarities with Alzheimer's disease. Important evidence from primate studies of SIV infection of natural and nonnatural hosts is clearly discussed. [PubMed: 20725864]
28. Kraft-Terry SD, Buch SJ, Fox HS, et al. A coat of many colors: neuroimmune crosstalk in human immunodeficiency virus infection. Neuron. 2009; 64:133–145. [PubMed: 19840555]
29. Kaul M, Lipton SA. Mechanisms of neuroimmunity and neurodegeneration associated with HIV-1 infection and AIDS. J Neuroimmune Pharmacol. 2006; 1:138–151. [PubMed: 18040780]
30. Boisse L, Gill MJ, Power C. HIV infection of the central nervous system: clinical features and neuropathogenesis. Neurol Clin. 2008; 26:799–819. [PubMed: 18657727]
31. Brew BJ. Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. AIDS. 2004; 18 (Suppl 1):S75–S78. [PubMed: 15075501]
32. Anthony IC, Ramage SN, Carnie FW, et al. Influence of HAART on HIV-related CNS disease and neuroinflammation. J Neuropathol Exp Neurol. 2005; 64:529–536. [PubMed: 15977645]
33. Cherner M, Masliah E, Ellis RJ, et al. Neurocognitive dysfunction predicts postmortem findings of HIV encephalitis. Neurology. 2002; 59:1563–1567. [PubMed: 12451198]
34. Bell JE. An update on the neuropathology of HIV in the HAART era. Histopathology. 2004; 45:549–559. [PubMed: 15569045]
35. Everall IP, Hansen LA, Masliah E. The shifting patterns of HIV encephalitis neuropathology. Neurotox Res. 2005; 8:51–61. [PubMed: 16260385]
36. Everall I, Vaida F, Khanlou N, et al. Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. J Neurovirol. 2009; 15:360–370. [PubMed: 20175693]
37. Gras G, Chretien F, Vallat-Decouvelaere AV, et al. Regulated expression of sodium-dependent glutamate transporters and synthetase: a neuroprotective role for activated microglia and macrophages in HIV infection? Brain Pathol. 2003; 13:211–222. [PubMed: 12744474]
38. Anthony IC, Bell JE. The neuropathology of HIV/AIDS. Int Rev Psychiatry. 2008; 20:15–24. [PubMed: 18240059]
39. McArthur JC, Haughey N, Gartner S, et al. Human immunodeficiency virus-associated dementia: an evolving disease. J Neurovirol. 2003; 9:205–221. [PubMed: 12707851]
40. Gonzalez-Scarano F, Martin-Garcia J. The neuropathogenesis of AIDS. Nat Rev Immunol. 2005; 5:69–81. [PubMed: 15630430]
41. Kolson DL, Gonzalez-Scarano F. HIV-1 and dementia. J Clin Invest. 2000; 106:11–13. [PubMed: 10880043]
42. Kaul M, Garden GA, Lipton SA. Pathways to neuronal injury and apoptosis in HIV-associated dementia. Nature. 2001; 410:988–994. [PubMed: 11309629]
43. Swindells S, Zheng J, Gendelman HE. HIV-associated dementia: new insights into disease pathogenesis and therapeutic interventions. AIDS Patient Care STDS. 1999; 13:153–163. [PubMed: 10375263]

44. Anderson E, Zink W, Xiong H, et al. HIV-1-associated dementia: a metabolic encephalopathy perpetrated by virus-infected and immune-competent mononuclear phagocytes. J Acquir Immune Defic Syndr. 2002; 31 (Suppl 2):S43–54. [PubMed: 12394782]
45. Fischer-Smith T, Croul S, Adeniyi A, et al. Macrophage/microglial accumulation and proliferating cell nuclear antigen expression in the central nervous system in human immunodeficiency virus encephalopathy. Am J Pathol. 2004; 164:2089–2099. [PubMed: 15161643]
46. Conant K, Garzino-Demo A, Nath A, et al. Induction of monocyte chemoattractant protein-1 in HIV-1 Tat-stimulated astrocytes and elevation in AIDS dementia. Proc Natl Acad Sci U S A. 1998; 95:3117–3121. [PubMed: 9501225]
47. Chang L, Ernst T, St Hillaire C, et al. Antiretroviral treatment alters relationship between MCP-1 and neurometabolites in HIV patients. Antivir Ther. 2004; 9:431–440. [PubMed: 15259906]
48. Brew BJ, Bhalla RB, Paul M, et al. Cerebrospinal fluid beta 2-microglobulin in patients with AIDS dementia complex: an expanded series including response to zidovudine treatment. AIDS. 1992; 6:461–465. [PubMed: 1616651]
49. Brew BJ, Dunbar N, Pemberton L, et al. Predictive markers of AIDS dementia complex: CD4 cell count and cerebrospinal fluid concentrations of beta 2-microglobulin and neopterin. J Infect Dis. 1996; 174:294–298. [PubMed: 8699058]
50. Enting RH, Foudraine NA, Lange JM, et al. Cerebrospinal fluid beta2-microglobulin, monocyte chemotactic protein-1, and soluble tumour necrosis factor alpha receptors before and after treatment with lamivudine plus zidovudine or stavudine. J Neuroimmunol. 2000; 102:216–221. [PubMed: 10636491]
51. McArthur JC, Nance-Sproson TE, Griffin DE, et al. The diagnostic utility of elevation in cerebrospinal fluid beta 2-microglobulin in HIV-1 dementia. Multicenter AIDS Cohort Study. Neurology. 1992; 42:1707–1712. [PubMed: 1355286]
52. Heyes MP, Brew BJ, Martin A, et al. Quinolinic acid in cerebrospinal fluid and serum in HIV-1 infection: relationship to clinical and neurological status. Ann Neurol. 1991; 29:202–209. [PubMed: 1826418]
53. Heyes MP, Ellis RJ, Ryan L, et al. Elevated cerebrospinal fluid quinolinic acid levels are associated with region-specific cerebral volume loss in HIV infection. Brain. 2001; 124 (Pt 5): 1033–1042. [PubMed: 11335705]
54. Brew BJ, Corbeil J, Pemberton L, et al. Quinolinic acid production is related to macrophage tropic isolates of HIV-1. J Neurovirol. 1995; 1:369–374. [PubMed: 9222379]
55. Achim CL, Heyes MP, Wiley CA. Quantitation of human immunodeficiency virus, immune activation factors, and quinolinic acid in AIDS brains. J Clin Invest. 1993; 91:2769–2775. [PubMed: 8514884]
56. Griffin DE, Wesselingh SL, McArthur JC. Elevated central nervous system prostaglandins in human immunodeficiency virus-associated dementia. Ann Neurol. 1994; 35:592–597. [PubMed: 7910004]
57. Genis P, Jett M, Bernton EW, et al. Cytokines and arachidonic metabolites produced during human immunodeficiency virus (HIV)-infected macrophage-astroglia interactions: implications for the neuropathogenesis of HIV disease. J Exp Med. 1992; 176:1703–1718. [PubMed: 1460427]
58. Haughey NJ, Cutler RG, Tamara A, et al. Perturbation of sphingolipid metabolism and ceramide production in HIV-dementia. Ann Neurol. 2004; 55:257–267. [PubMed: 14755730]
59. Schifitto G, Yiannoutsos CT, Ernst T, et al. Selegiline and oxidative stress in HIV-associated cognitive impairment. Neurology. 2009; 73:1975–1981. [PubMed: 19890073]
60. Gelbard HA, Nottet HS, Swindells S, et al. Platelet-activating factor: a candidate human immunodeficiency virus type 1-induced neurotoxin. J Virol. 1994; 68:4628–4635. [PubMed: 8207837]
61. Eden A, Price RW, Spudich S, et al. Immune activation of the central nervous system is still present after >4 years of effective highly active antiretroviral therapy. J Infect Dis. 2007; 196:1779–1783. [PubMed: 18190258]
62. Childs EA, Lyles RH, Selnes OA, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. Neurology. 1999; 52:607–613. [PubMed: 10025796]

63. Gray F, Chretien F, Vallat-Decouvelaere AV, et al. The changing pattern of HIV neuropathology in the HAART era. J Neuropathol Exp Neurol. 2003; 62:429–440. [PubMed: 12769183]

64. 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:e2516. [PubMed: 18575590]

65. Veazey RS, DeMaria M, Chalifoux LV, et al. Gastrointestinal tract as a major site of $CD4^+$ T cell depletion and viral replication in SIV infection. Science. 1998; 280:427–431. [PubMed: 9545219]

66•. Brew BJ, Crowe SM, Landay A, et al. Neurodegeneration and ageing in the HAART era. J Neuroimmune Pharmacol. 2009; 4:163–174. This is a comprehensive yet succinct review of evidence for enhanced progression of neurodegenerative diseases in HIV-infected individuals. [PubMed: 19067177]

67. Lovell MA, Markesbery WR. Oxidative damage in mild cognitive impairment and early Alzheimer's disease. J Neurosci Res. 2007; 85:3036–3040. [PubMed: 17510979]

68. Chang L, Wong V, Nakama H, et al. Greater than age-related changes in brain diffusion of HIV patients after 1 year. J Neuroimmune Pharmacol. 2008; 3:265–274. [PubMed: 18709469]

69. Montano M, Rarick M, Sebastiani P, et al. Gene-expression profiling of HIV-1 infection and perinatal transmission in Botswana. Genes Immun. 2006; 7:298–309. [PubMed: 16691187]

70. Isaacman-Beck J, Hermann EA, Yi Y, et al. Heterosexual transmission of human immunodeficiency virus type 1 subtype C: macrophage tropism, alternative coreceptor use, and the molecular anatomy of CCR5 utilization. J Virol. 2009; 83:8208–8220. [PubMed: 19515785]

71. Vasan A, Renjifo B, Hertzmark E, et al. Different rates of disease progression of HIV type 1 infection in Tanzania based on infecting subtype. Clin Infect Dis. 2006; 42:843–852. [PubMed: 16477563]

72. Chittiprol S, Kumar AM, Satishchandra P, et al. Progressive dysregulation of autonomic and HPA axis functions in HIV-1 clade C infection in South India. Psychoneuroendocrinology. 2008; 33:30–40. [PubMed: 17993249]

73. Wester CW, Kim S, Bussmann H, et al. Initial response to highly active antiretroviral therapy in HIV-1C-infected adults in a public sector treatment program in Botswana. J Acquir Immune Defic Syndr. 2005; 40:336–343. [PubMed: 16249709]

74. Brown BK, Wieczorek L, Sanders-Buell E, et al. Cross-clade neutralization patterns among HIV-1 strains from the six major clades of the pandemic evaluated and compared in two different models. Virology. 2008; 375:529–538. [PubMed: 18433824]

75. Santra S, Korber BT, Muldoon M, et al. A centralized gene-based HIV-1 vaccine elicits broad cross-clade cellular immune responses in rhesus monkeys. Proc Natl Acad Sci U S A. 2008; 105:10489–10494. [PubMed: 18650391]

76. Brown BK, Darden JM, Tovanabutra S, et al. Biologic and genetic characterization of a panel of 60 human immunodeficiency virus type 1 isolates, representing clades A, B, C, D, CRF01_AE, and CRF02_AG, for the development and assessment of candidate vaccines. J Virol. 2005; 79:6089–6101. [PubMed: 15857994]

77. Rao VR, Sas AR, Eugenin EA, et al. HIV-1 clade-specific differences in the induction of neuropathogenesis. J Neurosci. 2008; 28:10010–10016. [PubMed: 18829958]

78. Yepthomi T, Paul R, Vallabhaneni S, et al. Neurocognitive consequences of HIV in southern India: a preliminary study of clade C virus. J Int Neuropsychol Soc. 2006; 12:424–430. [PubMed: 16903135]

79•. Robertson K, Liner J, Hakim J, et al. NeuroAIDS in Africa. J Neurovirol. 2010; 16:189–202. This comprehensive overview of published and unpublished studies of neurological complications of HIV in Africa presented at the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (Capetown, South Africa) addresses prevalence, patterns of CNS manifestations, HIV subtypes, and treatment considerations in Africa. [PubMed: 20500018]

80•. 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. Clin Infect Dis. 2009; 49:780–786. This study suggests that HIV subtype D (prevalent in Uganda) expresses greater neuropathogenic potential than subtype A, and it represents the first direct comparison of neurocognitive outcomes in populations infected with

different HIV subtypes. Although small (n=60), the study shows highly significant and marked differences (89 vs. 24%) that require further studies to identify possible viral and host genetic determinants for enhanced neurovirulence of HIV subtype D. [PubMed: 19622045]

81. Sacktor N, Nakasujja N, Skolasky R, et al. Antiretroviral therapy improves cognitive impairment in HIV+ individuals in sub-Saharan Africa. Neurology. 2006; 67:311–314. [PubMed: 16864825]

82•. Lawler K, Mosepele M, Ratcliffe S, et al. Neurocognitive impairment among HIV-positive individuals in Botswana: a pilot study. J Int AIDS Soc. 2010; 13:15. This is the first study (n=120 patients) of neurocognitive impairment prevalence in Botswana, and it demonstrates a higher than expected prevalence of HIV-associated dementia (38%), based upon the International HIV Dementia Scoring Scale. It argues for initiation of ART before severe immunosuppression occurs, as a possible prevention strategy. [PubMed: 20406460]

83•. Liner KJ 2nd, Ro MJ, Robertson KR. HIV, antiretroviral therapies, and the brain. Curr HIV/AIDS Rep. 2010; 7:85–91. This review discusses altering ART treatment guidelines for neuroprotection against HIV and reviews the evidence for ART CNS neurotoxicity. [PubMed: 20425562]

84. Hauser KF, El-Hage N, Stiene-Martin A, et al. HIV-1 neuropathogenesis: glial mechanisms revealed through substance abuse. J Neurochem. 2007; 100:567–586. [PubMed: 17173547]

85•. Nath A. Human immunodeficiency virus-associated neurocognitive disorder: pathophysiology in relation to drug addiction. Ann N Y Acad Sci. 2010; 1187:122–128. This is a balanced review of the possible effects of cocaine, METH, and opiates on several mechanisms of HIV-induced neurodegeneration: HIV replication, BBB integrity, and glial cell functions relevant to HAND. Important therapeutic considerations are presented. [PubMed: 20201849]

86. Lucas GM. Substance abuse, adherence with antiretroviral therapy, and clinical outcomes among HIV-infected individuals. Life Sci. 2010 Epub ahead of print.

87•. Beyrer C, Wirtz AL, Baral S, et al. Epidemiologic links between drug use and HIV epidemics: an international perspective. J Acquir Immune Defic Syndr. 2010; 55(Suppl 1):S10–S16. This review summarizes the international risks for HIV spread due to the expansion of intravenous drug abuse, with implications for worldwide spread of different HIV subtypes. [PubMed: 21045593]

88. Bell JE, Arango JC, Anthony IC. Neurobiology of multiple insults: HIV-1-associated brain disorders in those who use illicit drugs. J Neuroimmune Pharmacol. 2006; 1:182–191. [PubMed: 18040783]

89. Anthony IC, Arango JC, Stephens B, et al. The effects of illicit drugs on the HIV infected brain. Front Biosci. 2008; 13:1294–1307. [PubMed: 17981630]

90. Martinez AJ, Sell M, Mitrovics T, et al. The neuropathology and epidemiology of AIDS. A Berlin experience. A review of 200 cases. Pathol Res Pract. 1995; 191:427–443. [PubMed: 7479362]

91. Quan VM, Minh NL, Ha TV, et al. Mortality and HIV transmission among male Vietnamese injection drug users. Addiction. 2011; 106:583–589. [PubMed: 21054619]

92•. Jevtovic D, Vanovac V, Veselinovic M, et al. The incidence of and risk factors for HIV-associated cognitive-motor complex among patients on HAART. Biomed Pharmacother. 2009; 63:561–565. This study demonstrates, although in a small number of patients, long-term (47 months) neuroprotective effects of azidothymidine/zidovudine and NNRTIs despite persistence of neurological impairment and HAD in ART-medicated HIV-positive participants. [PubMed: 19026516]

93. Marcondes MC, Flynn C, Watry DD, et al. Methamphetamine increases brain viral load and activates natural killer cells in simian immunodeficiency virus-infected monkeys. Am J Pathol. 2010; 177:355–361. [PubMed: 20489154]

94. Rogers TJ. Immunology as it pertains to drugs of abuse, AIDS and the neuroimmune axis: mediators and traffic. J Neuroimmune Pharmacol. 2011; 6:20–27. [PubMed: 20957520]

95. Marcario JK, Riazi M, Adany I, et al. Effect of morphine on the neuropathogenesis of SIV mac infection in Indian rhesus macaques. J Neuroimmune Pharmacol. 2008; 3:12–25. [PubMed: 18247128]

96. Perez-Casanova A, Noel RJ Jr, Rivera-Amill V, et al. Morphine-mediated deterioration of oxidative stress leads to rapid disease progression in SIV/ SHIV-infected macaques. AIDS Res Hum Retroviruses. 2007; 23:1004–1007. [PubMed: 17725417]

97. Hauser KF, El-Hage N, Buch S, et al. Impact of opiate-HIV-1 interactions on neurotoxic signaling. J Neuroimmune Pharmacol. 2006; 1:98–105. [PubMed: 18040795]

98. Guo CJ, Li Y, Tian S, et al. Morphine enhances HIV infection of human blood mononuclear phagocytes through modulation of beta-chemokines and CCR5 receptor. J Investig Med. 2002; 50:435–442.

99. Ho WZ, Guo CJ, Yuan CS, et al. Methylnaltrexone antagonizes opioid-mediated enhancement of HIV infection of human blood mononuclear phagocytes. J Pharmacol Exp Ther. 2003; 307:1158–1162. [PubMed: 14560041]

100. Peterson PK, Gekker G, Hu S, et al. Cannabinoids and morphine differentially affect HIV-1 expression in CD4(+) lymphocyte and microglial cell cultures. J Neuroimmunol. 2004; 147:123–126. [PubMed: 14741442]

101. Dave RS, Khalili K. Morphine treatment of human monocyte-derived macrophages induces differential miRNA and protein expression: impact on inflammation and oxidative stress in the central nervous system. J Cell Biochem. 2010; 110:834–845. [PubMed: 20564181]

102. Li Y, Wang X, Tian S, et al. Methadone enhances human immunodeficiency virus infection of human immune cells. J Infect Dis. 2002; 185:118–122. [PubMed: 11756991]

103. Kumar R, Torres C, Yamamura Y, et al. Modulation by morphine of viral set point in rhesus macaques infected with simian immunodeficiency virus and simian-human immunodeficiency virus. J Virol. 2004; 78:11425–11428. [PubMed: 15452267]

104. Happel C, Kutzler M, Rogers TJ. Opioid-induced chemokine expression requires NF-{kappa}B activity: the role of PKC{zeta}. J Leukoc Biol. 2011; 89:301–309. [PubMed: 20952659]

105. Happel C, Steele AD, Finley MJ, et al. DAMGO-induced expression of chemokines and chemokine receptors: the role of TGF-beta1. J Leukoc Biol. 2008; 83:956–963. [PubMed: 18252865]

106. Gekker G, Hu S, Wentland MP, et al. Kappa-opioid receptor ligands inhibit cocaine-induced HIV-1 expression in microglial cells. J Pharmacol Exp Ther. 2004; 309:600–606. [PubMed: 14757849]

107. Peterson PK, Gekker G, Lokensgard JR, et al. Kappa-opioid receptor agonist suppression of HIV-1 expression in $CD4^+$ lymphocytes. Biochem Pharmacol. 2001; 61:1145–1151. [PubMed: 11301048]

108. Donahoe RM. Multiple ways that drug abuse might influence AIDS progression: clues from a monkey model. J Neuroimmunol. 2004; 147:28–32. [PubMed: 14741423]

109. Ferris MJ, Mactutus CF, Booze RM. Neurotoxic profiles of HIV, psychostimulant drugs of abuse, and their concerted effect on the brain: current status of dopamine system vulnerability in NeuroAIDS. Neurosci Biobehav Rev. 2008; 32:883–909. [PubMed: 18430470]

110. Dhillon NK, Williams R, Peng F, et al. Cocaine-mediated enhancement of virus replication in macrophages: implications for human immunodeficiency virus-associated dementia. J Neurovirol. 2007; 13:483–495. [PubMed: 18097880]

111. Reynolds JL, Mahajan SD, Bindukumar B, et al. Proteomic analysis of the effects of cocaine on the enhancement of HIV-1 replication in normal human astrocytes (NHA). Brain Res. 2006; 1123:226–236. [PubMed: 17034766]

112. Conant K, Tornatore C, Atwood W, et al. In vivo and in vitro infection of the astrocyte by HIV-1. Adv Neuroimmunol. 1994; 4:287–289. [PubMed: 7874397]

113. Churchill MJ, Wesselingh SL, Cowley D, et al. Extensive astrocyte infection is prominent in human immunodeficiency virus-associated dementia. Ann Neurol. 2009; 66:253–258. [PubMed: 19743454]

114. Vincendeau M, Kramer S, Hadian K, et al. Control of HIV replication in astrocytes by a family of highly conserved host proteins with a common Rev-interacting domain (Risp). AIDS. 2010; 24:2433–2442. [PubMed: 20827171]

115. Nair MP, Mahajan SD, Schwartz SA, et al. Cocaine modulates dendritic cell-specific C type intercellular adhesion molecule-3-grabbing nonintegrin expression by dendritic cells in HIV-1 patients. J Immunol. 2005; 174:6617–6626. [PubMed: 15905500]

116. Nair MP, Saiyed ZM, Nair N, et al. Methamphetamine enhances HIV-1 infectivity in monocyte derived dendritic cells. J Neuroimmune Pharmacol. 2009; 4:129–139. [PubMed: 18958626]

117. Fiala M, Eshleman AJ, Cashman J, et al. Cocaine increases human immunodeficiency virus type 1 neuroinvasion through remodeling brain microvascular endothelial cells. J Neurovirol. 2005; 11:281–291. [PubMed: 16036808]

118. Berger JR, Avison M. The blood brain barrier in HIV infection. Front Biosci. 2004; 9:2680–2685. [PubMed: 15358591]

119. Zhang L, Looney D, Taub D, et al. Cocaine opens the blood-brain barrier to HIV-1 invasion. J Neurovirol. 1998; 4:619–626. [PubMed: 10065903]

120. Mahajan SD, Aalinkeel R, Sykes DE, et al. Methamphetamine alters blood brain barrier permeability via the modulation of tight junction expression: implication for HIV-1 neuropathogenesis in the context of drug abuse. Brain Res. 2008; 1203:133–148. [PubMed: 18329007]

121. Gurwell JA, Nath A, Sun Q, et al. Synergistic neurotoxicity of opioids and human immunodeficiency virus-1 Tat protein in striatal neurons in vitro. Neuroscience. 2001; 102:555–563. [PubMed: 11226693]

122. Avison MJ, Nath A, Greene-Avison R, et al. Inflammatory changes and breakdown of microvascular integrity in early human immunodeficiency virus dementia. J Neurovirol. 2004; 10:223–232. [PubMed: 15371152]

123. Chang L, Alicata D, Ernst T, et al. Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. Addiction. 2007; 102 (Suppl 1):16–32. [PubMed: 17493050]

124. Chang L, Cloak C, Patterson K, et al. Enlarged striatum in abstinent methamphetamine abusers: a possible compensatory response. Biol Psychiatry. 2005; 57:967–974. [PubMed: 15860336]

125. Berger JR, Nath A. HIV dementia and the basal ganglia. Intervirology. 1997; 40:122–131. [PubMed: 9450229]

126•. Xu J, Ikezu T. The comorbidity of HIV-associated neurocognitive disorders and Alzheimer's disease: a foreseeable medical challenge in post-HAART era. J Neuroimmune Pharmacol. 2009; 4:200–212. This review summarizes the potential contribution of HIV and ART to Alzheimer's disease-like pathology in HAND patients and proposes several mechanisms for HIV-mediated intraneuronal beta-amyloid deposition. [PubMed: 19016329]

127. Ernst T, Chang L. Effect of aging on brain metabolism in antiretroviral-naive HIV patients. AIDS. 2004; 18 (Suppl 1):S61–S67. [PubMed: 15075499]

128. Cherner M, Ellis RJ, Lazzaretto D, et al. Effects of HIV-1 infection and aging on neurobehavioral functioning: preliminary findings. AIDS. 2004; 18 (Suppl 1):S27–34. [PubMed: 15075495]

129. Ances BM, Vaida F, Yeh MJ, et al. HIV infection and aging independently affect brain function as measured by functional magnetic resonance imaging. J Infect Dis. 2010; 201:336–340. [PubMed: 20047503]

130•. Anthony, IC.; Bell, J. Neuropathological findings associated with long-term HAART. In: Paul, RH.; Sacktor, NC.; Valcour, V.; Tashima, KT., editors. HIV and the brain. Edinburgh: Humana Press; 2009. p. 29-47.This book chapter details HAND neuropathology in the pre-ART and post-ART eras and proposes mechanisms for neurodegeneration, specifically relating to Tau dysregulation, via HIV and ART

131. Tisch S, Brew B. Parkinsonism in HIV-infected patients on highly active antiretroviral therapy. Neurology. 2009; 73:401–403. [PubMed: 19652146]

132. Green DA, Masliah E, Vinters HV, et al. Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. AIDS. 2005; 19:407–411. [PubMed: 15750394]

133. Anthony IC, Ramage SN, Carnie FW, et al. Accelerated Tau deposition in the brains of individuals infected with human immunodeficiency virus-1 before and after the advent of highly active antiretroviral therapy. Acta Neuropathol. 2006; 111:529–538. [PubMed: 16718349]

134. Achim CL, Adame A, Dumaop W, et al. Increased accumulation of intraneuronal amyloid beta in HIV-infected patients. J Neuroimmune Pharmacol. 2009; 4:190–199. [PubMed: 19288297]

135. Brew BJ, Pemberton L, Blennow K, et al. CSF amyloid beta42 and Tau levels correlate with AIDS dementia complex. Neurology. 2005; 65:1490–1492. [PubMed: 16275845]

136•. Brew BJ. Benefit or toxicity from neurologically targeted antiretroviral therapy? Clin Infect Dis. 2010; 50:930–932. The author presents a thoughtful discussion about potential neurotoxicity vs.

neuroprotection by ART, and they recognize the need for a prospective randomized study to investigate CNS ART toxicity. [PubMed: 20146628]

137. Vehmas A, Lieu J, Pardo CA, et al. Amyloid precursor protein expression in circulating monocytes and brain macrophages from patients with HIV-associated cognitive impairment. J Neuroimmunol. 2004; 157:99–110. [PubMed: 15579286]

138. Esiri MM, Biddolph SC, Morris CS. Prevalence of Alzheimer plaques in AIDS. J Neurol Neurosurg Psychiatry. 1998; 65:29–33. [PubMed: 9667557]

139. Cardenas VA, Meyerhoff DJ, Studholme C, et al. Evidence for ongoing brain injury in human immunodeficiency virus-positive patients treated with antiretroviral therapy. J Neurovirol. 2009; 15:324–333. [PubMed: 19499454]

140•. Marra CM, Zhao Y, Clifford DB, et al. Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. AIDS. 2009; 23:1359–1366. This prospective study demonstrates, in a small HIV-positive cohort, a significant association between highly CNS-penetrant ART regimens and impaired long-term neuropsychological and motor performance, despite decreased CSF HIV RNA. [PubMed: 19424052]

141. Schweinsburg BC, Taylor MJ, Alhassoon OM, et al. Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors. J Neurovirol. 2005; 11:356–364. [PubMed: 16206458]

142. Zhou H, Gurley EC, Jarujaron S, et al. HIV protease inhibitors activate the unfolded protein response and disrupt lipid metabolism in primary hepatocytes. Am J Physiol Gastrointest Liver Physiol. 2006; 291:G1071–G1080. [PubMed: 16861219]

143. Zhou H, Pandak WM Jr, Lyall V, et al. HIV protease inhibitors activate the unfolded protein response in macrophages: implication for atherosclerosis and cardiovascular disease. Mol Pharmacol. 2005; 68:690–700. [PubMed: 15976036]

144. Dufer M, Neye Y, Krippeit-Drews P, et al. Direct interference of HIV protease inhibitors with pancreatic beta-cell function. Naunyn Schmiedebergs Arch Pharmacol. 2004; 369:583–590. [PubMed: 15197535]

145. Schutt M, Zhou J, Meier M, et al. Long-term effects of HIV-1 protease inhibitors on insulin secretion and insulin signaling in INS-1 beta cells. J Endocrinol. 2004; 183:445–454. [PubMed: 15590971]

146. Liang JS, Distler O, Cooper DA, et al. HIV protease inhibitors protect apolipoprotein B from degradation by the proteasome: a potential mechanism for protease inhibitor-induced hyperlipidemia. Nat Med. 2001; 7:1327–1331. [PubMed: 11726973]

147. Steen E, Terry BM, Rivera EJ, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease: is this type 3 diabetes? J Alzheimers Dis. 2005; 7:63–80. [PubMed: 15750215]

148. Kroner Z. The relationship between Alzheimer's disease and diabetes: type 3 diabetes? Altern Med Rev. 2009; 14:373–379. [PubMed: 20030463]

149. Vidal F, Gutierrez F, Gutierrez M, et al. Pharmacogenetics of adverse effects due to antiretroviral drugs. AIDS Rev. 2010; 12:15–30. [PubMed: 20216907]

150•. Smurzynski M, Wu K, Letendre S, et al. Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. AIDS. 2011; 28:357–365. This study provides clear evidence for the neuroprotective effects of highly CNS-penetrant antiretroviral drug regimens in a large cohort of HIV-positive patients. [PubMed: 21124201]

151. Letendre SL, McCutchan JA, Childers ME, et al. Enhancing antiretroviral therapy for human immunodeficiency virus cognitive disorders. Ann Neurol. 2004; 56:416–423. [PubMed: 15349869]

152. 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. Arch Neurol. 2008; 65:65–70. [PubMed: 18195140]

153••. Patel K, Ming X, Williams PL, et al. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. AIDS. 2009; 23:1893–1901. This study demonstrates the effectiveness of CNS-penetrant ART in

prolonging survival in perinatally infected children and adolescents, over a greater than 6 year follow up. [PubMed: 19644348]

154••. Joska JA, Gouse H, Paul RH, et al. Does highly active antiretroviral therapy improve neurocognitive function? A systematic review. J Neurovirol. 2010; 16:101–114. The first systemic review examining the effect of ART on neurocognitive functioning in HIV-positive patients across 15 different studies that details the use of neuropsychological examinations, ART regimens and duration of use, as well as the quality of each of the studies examined. [PubMed: 20345318]

155•. Winston A, Duncombe C, Li PC, et al. Does choice of combination antiretroviral therapy (cART) alter changes in cerebral function testing after 48 weeks in treatment-naive, HIV-1-infected individuals commencing cART? A randomized, controlled study. Clin Infect Dis. 2010; 50:920–929. Different ART treatment regimens applied up to 48 weeks are demonstrated to partially reverse neuronal metabolic abnormalities by neuroimaging, and improve neurocognitive outcomes, possibly due to different CNS penetration effects. This study is discussed in reference [136•]. [PubMed: 20146627]

Key points

- Persistent inflammation in antiretroviral therapy (ART)-treated and ART-naive HIV patients drives systemic and central nervous system (CNS) disease progression.
- HIV genetic subtypes may vary in their potential to induce HIV-associated neurocognitive disorders (HAND).
- Methamphetamine and cocaine strongly increase the risk for neurocognitive dysfunction in HIV infected individuals.
- HAND risk is increased by patient age and associated aging comorbidity factors.
- Chronic antiretroviral drug therapy poses a potential risk for CNS neurotoxicity.