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Developing neuroprotective strategies for treatment of HIV-associated neurocognitive dysfunction

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Abstract

Important advances have been made in recent years in identifying the molecular mechanisms of HIV neuropathogenesis. Defining the pathways leading to HIV dementia has created an opportunity to therapeutically target many steps in the pathogenic process. HIV itself rarely infects neurons, but significant neuronal damage is caused both by viral proteins and by inflammatory mediators produced by the host in response to infection. Highly active antiretroviral therapy (HAART) does not target these mediators of neuronal damage, and the prevalence of HIV-associated neurocognitive dysfunction has actually been rising in the post-HAART era. This review will briefly summarize our current understanding of the mechanisms of HIV-induced neurological disease, and emphasize translation of this basic research into potential clinical applications.

Keywords

cytokines; excitotoxicity; gp120; HAART; HIV dementia; MMP; nitrosative stress; oxidative stress; Tat

HIV-associated neurocognitive dysfunction

Neurological complications secondary to HIV infection have been recognized since the beginning of the epidemic; however, the terminology used to describe them has continued to evolve. HIV infection of the brain classically affects a triad of neurological domains – cognitive, motor and behavioral. Cognitive effects include memory loss, but are typified by psychomotor slowing. Motor effects include incoordination, parkinsonism and gait disorders. Behavioral manifestations include apathy, disinhibition, fatigue and affective distress. The clinical manifestations reflect the fact that HIV involves the basal ganglia and presents as a

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subcortical dementia. A recent working group introduced the term, HIV-associated neurocognitive dysfunction (HAND) and recommended that “the presence and degree of neurocognitive impairment constitute the fundamental criteria for establishing a diagnosis, while other criteria, for example, motor disorders and emotional or personality changes, be considered ancillary or corroborative information, possibly for defining disorder subtypes”. The interested reader is directed to excellent recent reviews [1,2].

Although highly active antiretroviral therapy (HAART) has significantly reduced the incidence of severe forms of dementia, the prevalence of HAND has risen in the post-HAART era due to the prolonged life span of HIV-infected individuals [3–7]. Severe HIV dementia typically affects patients with advanced immunosuppression; however, HAND can occur at any point during HIV infection, even as a presenting symptom, and because HIV tends to infect people in the prime working years of life, HAND has a significant socioeconomic impact.

Currently, HAART remains the main mode of treatment for HAND. Optimization of antiretroviral drugs that cross the blood–brain barrier (BBB) is the major goal [8,9]. Additionally, many of the mediators of HAND, including both viral and host factors, are not targeted by HAART. HIV does not infect neurons and yet neurons nonetheless die or are dysfunctional. Some patients with HIV infection develop dementia and others do not, despite similar viral loads and CD4 cell counts. Host susceptibility and viral virulence factors play a key role in determining which patients develop dementia [10]. HIV enters the brain within days to weeks of infection [11–13]. Although active replication of the virus in the brain is usually controlled rapidly, once the proviral DNA is formed, the reverse transcriptase inhibitors and integrase inhibitors have no effect and the protease inhibitors only target the structural proteins formed late in the course of infection. Hence, the early viral proteins such as Tat continue to be formed unchecked by HAART. Since these early viral proteins have been shown to be either directly neurotoxic or set up a cascade of events leading to glial cell activation and neurotoxicity [14], it is necessary to consider developing neuroprotective strategies for this patient population [15]. Our understanding of the neuropathogenesis of HIV infection will guide rational therapeutic developments. All of the agents discussed in this article are currently in development thanks to our understanding of the mechanisms of HIV neuropathogenesis. While we will touch upon these mechanisms, a detailed review is beyond the scope of this article, and the interested reader is directed to excellent recent reviews of this topic, such as [14].

HIV-associated peripheral neuropathy

Although most research has focused on HIV dementia, peripheral neuropathy is the most frequent neurological complaint among HIV-infected patients. Symptoms of this distal sensory polyneuropathy include predominant pain as well as numbness and paresthesias. Antiretroviral-induced toxic neuropathies are also common in patients with HIV infection and there may be synergism between the neurotoxicity of HIV infection and the neurotoxicity of the drugs [16]. Macrophage-expressed cytokines are implicated in peripheral neurotoxicity, and, although there may be differences in pathogenesis of central versus peripheral neurotoxicity in HIV infection, there are likely to be many similar mechanisms. Therefore, hopefully, similar neuroprotective strategies will be effective in both conditions.

Outcome measures & end points

Changes in neuropsychological scores remains the gold standard for assessment of efficacy of any neuroprotective strategy. Currently, there are no surrogate markers available for assessment of HAND; however, several biomarkers are being developed that currently serve as secondary end points that need to be validated as surrogate markers for future clinical trials. These include, magnetic resonance spectroscopy, blood oxygen level-dependent imaging,

changes in cytokine and chemokine profiles, neuronal markers such as neurofilament and markers of oxidative stress in the CSF of patients.

Neuroprotective agents in individuals with HIV infection

Several small and large Phase II trials have been conducted with neuroprotective agents in patients with HIV-associated cognitive impairment or neuropathies and in various other neurological conditions. Some have shown a small benefit, but none has found mainstream use in clinical practice. Several classes of drugs have been studied (Table 1). Reasons for failure of these trials are not clear, however, it is possible that we have targeted the wrong pathways. Alternatively, there may be sufficient redundancy in the system that we need to target multiple pathways simultaneously. Another possibility is that we may have overlooked other pathways or mechanisms of neurotoxicity. For example, in HAART-treated patients, there seems to be substantial infiltration of T cells into the brain parenchyma [17]. Mechanisms of T-cell mediated neurotoxicity may be quite different than that induced by activated macrophages [18]. Other trials are ongoing for both HIV dementia (Table 2) and HIV neuropathy (Table 3).

In our efforts to protect neurons we have often targeted pathways that lead to increases in cytokines and oxidative stress. While high concentrations of these substances can be toxic to neurons, in the setting of a viral infection it is possible that these substances may be critical mediators of an innate immune response. For example, in SIV-infected animals, if anti-inflammatory agents are given at the time of initiating infection, a more severe form of encephalitis occurs [Zink *et al.*, Pers. Comm]. Similarly, while minocycline was shown to downregulate SIV infection in macaques and show neuroprotection when administered after the acute phase of infection [19], in a rabies model, when administered at the time of inoculation, it caused worsening of the encephalitis [20].

Paradoxical responses of worsening have also been reported while targeting pathways that, in experimental systems, have shown significant benefit. For example, TNF antagonists may cause worsening of multiple sclerosis and minocycline can cause worsening of amyotrophic lateral sclerosis (ALS). A major challenge of future research will be to determine why these agents fail in patients, despite basic science that suggests they should work. Answers to this question will be widely applicable to many neurological diseases, not just HIV dementia.

Development of drugs for protection against HIV neurotoxicity

Numerous antiretroviral agents are in various stages of development [21]. This review will focus on agents that may specifically target HIV neurotoxicity. Our current understanding of the pathobiology of HIV-associated cognitive dysfunction and neuropathy is that it is initiated by HIV proteins that lead to activation of a cascade of events resulting in dysregulation of several pathways eventually resulting in neural toxicity. Several of these pathways could potentially be targeted for development of novel therapeutic approaches for these complications.

Inhibitors of cell-signaling pathways

Glycogen synthase kinase-3 β inhibitors

Tat mediates some of its neurotoxic effects through glycogen synthase kinase-3 β [22], and lithium and valproate both inhibit this enzyme. Valproate has also demonstrated a neuroprotective effect against gp120 in rat cortical neurons and in a murine model of HIV encephalitis [23]. However, high dosages of valproate may inhibit histone deaminase and lead to increased HIV replication [24]. A small observational study found cognitive decline in eight individuals with advanced HIV infection on valproate compared with 32 such individuals

without valproate [25]. On the other hand, a 12-week, open-label, single-arm study of lithium demonstrated neurocognitive improvements in all eight patients studied [26].

Mixed lineage kinase-3 inhibitors

Tat and gp120 were shown to induce autophosphorylation of mixed lineage kinase (MLK)-3 in primary rat neurons and this signaling mechanism could be attenuated by an agent known as CEP1347. CEP1347 also enhanced survival of both rat and human neurons and inhibited the activation of human monocytes after exposure to Tat and gp120. Expression of a dominant negative MLK3 mutant protected neurons from the toxic effects of Tat. Inhibition of signaling proteins downstream of MLK-3, such as p38 MAPK and JNK, may also be useful in new therapeutic approaches [27].

Protein kinase inhibitors

The protein kinase C inhibitors rottlerin and hispidin may provide neuroprotective effects against HIV-mediated neurodegeneration [28,29]. In HIV-infected patients, production of IL-10, a highly immunosuppressive cytokine, is associated with the disease progression towards AIDS. HIV-1 Tat induction of IL-10 production by human monocytes was mediated via a PKC-dependent pathway. Inhibition of either PKC- δ or PKC- β II partially inhibited IL-10 production, while the simultaneous inhibition of both PKC isoforms totally inhibited Tat-mediated IL-10 [29]. More recently, rottlerin has demonstrated significant neuroprotective effects against dopaminergic loss in both *in vitro* and *in vivo* models of Parkinson's disease [28].

Cyclin-dependent kinase inhibitors

Selective inhibitors of cyclin-dependent protein kinases (cdk) may elicit protective effects against neurodegenerative damage. Upregulation of cell cycle-dependent proteins has been associated with caspase-mediated neuronal apoptosis and glial proliferation after traumatic brain injury (TBI) in rats. Cell cycle inhibition, including by cdk inhibitors such as flavopiridol, roscovitine and olomoucine, reduced neuronal cell death, microglial activation and astroglial proliferation in primary neuronal and astrocyte cultures and after TBI in rats [30]. In other studies, flavopiridol inhibition of cdk improved CA1 survival and behavioral performance after global ischemic insult in rats [31], where flavopiridol decreased the loss of CA1 neurons and improved spatial learning behavior in the Morris water maze 7 days postlesion. In addition, through the inhibition of cdk2 and cdk9, co-factors for HIV-1 Tat transactivation, HIV-1 replication is blocked by two specific cdk inhibitors, roscovitine and flavopiridol (reviewed in [32]). Thus, these compounds may provide antiretroviral actions along with potential neuroprotective activities.

Anti-TNF therapies

Pentoxifylline blocks TNF-induced neurotoxicity *in vitro* and attenuated immune activation and serum TNF- α levels in HIV-infected patients treated for 4 weeks. Thalidomide is another currently available anti-TNF- α agent. Neither of these agents have been tested in patients with HIV dementia, and there are concerns that such agents may have intolerable adverse effects. It may be necessary to develop new anti-TNF strategies that block TNF-induced neurotoxic effects without inhibiting the beneficial effects, but separating these effects is likely to be very challenging.

Matrix metalloproteinase inhibitors

Many small-molecule matrix metalloproteinase (MMP) inhibitors have been tested, and failed to work, in patients with metastatic cancer. They have not yet been tested in patients with HIV dementia. Minocycline is currently used as an antibiotic and has shown neuroprotective

properties in various models [33]. Minocycline inhibits activation of p38 MAPK, a proapoptotic pathway in the pathogenesis of SIV encephalitis and HIV dementia [19]. Minocycline also inhibits MMPs, inflammatory cytokines and free radicals, and is promising because it crosses the BBB. It inhibits MMP cleavage at the active site, and also decreases MMP levels and reduces MMP-associated chemotaxis [34]. Statins, currently used as lipid-lowering agents, decrease levels of MMPs and other cytokines [35,36]. However, it may be necessary to develop very specific MMP inhibitors, and/or MMP agonists, to effectively target MMPs for neuroprotection.

Inhibitors of excitotoxicity

Glutamate receptor antagonists

Pentamidine, an *N*-methyl D-aspartate (NMDA) antagonist currently used for pneumocystis pneumonia prophylaxis or treatment in HIV infection, as well as various pentamidine analogs, are available for study in HIV dementia. Additional compounds, such as 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and (*E*)-2-methyl-6-(2-phenylethenyl)-pyridine (SIB-1893), which act as selective metabotropic glutamate receptor (mGluR5) antagonists, may also be considered. These compounds have demonstrated neuroprotective efficacy both *in vitro* and *in vivo* against glutamate and NMDA excitotoxicity and the effects of TBI, perhaps via antagonizing NMDA receptor signaling [37,38]. Subsequent studies with newer and more selective mGluR5 agents, such as 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP) protect neurons with treatments given more than 6 h after toxicity was initiated [39].

As noted in Table 1, memantine has generated interest and has even been used in clinical trials as a possible NMDA antagonist. A recent study [40] using SIV-infected rhesus macaques found that memantine prevented changes in dopaminergic systems, perhaps by upregulating mRNA and protein expression of brain-derived neurotrophic factor, thus suggesting the possibility of additional protective effects of memantine that are not mediated by NMDA receptor antagonism.

Stimulators of glutamate transport

Another strategy related to neuroprotection via excitotoxicity pathways is direct stimulation of the astroglial glutamate transporter, EAAT-2, which inactivates synaptic glutamate. Rothstein and colleagues identified many β -lactam antibiotics as potent stimulators of EAAT-2 expression both *in vitro* and *in vivo* [41], which may counteract the excitotoxicity of viral proteins by increasing the ability of astrocytes to inactivate synaptic glutamate. In fact, ceftriaxone was protective against both Tat and gp120 neurotoxicity in human glial-neuronal cultures *in vitro* [42].

Glutamate carboxypeptidase II inhibitors

Yet another potential neuroprotective class of compounds are the *N*-acetylated α -linked acidic dipeptidase or glutamate carboxypeptidase (GCP)II inhibitors. GCPII inhibition results in decreased extracellular excitotoxic glutamate and increased levels of extracellular *N*-acetyl-aspartylglutamate, both of which provide neuroprotection. These GCPII inhibitors have demonstrated neuroprotective effects *in vitro* and in animal models of stroke, ALS and neuropathic pain [43]. We have found that a prototypic GCPII inhibitor, 2-PMPA, protected hippocampal and cortical cultures from HIV-1 Tat toxicity in a concentration-dependent manner with 1–5 μ M potency [Steiner J, Nath A, Unpublished Data].

Neuroimmunophilin ligands

Neuroimmunophilin ligands (NILs) are compounds, such as the immunosuppressive drugs cyclosporine A and FK506, which bind with high affinity to their receptor proteins,

cyclophilins and FK506 binding proteins respectively. These drugs have demonstrated significant neuroprotective effects against NMDA⁻, 1-methyl-4-phenylpyridinium (MPP)⁺ and 6-hydroxydopamine toxicities *in vitro*, as well as protection against focal ischemia and 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) *in vivo* (reviewed in [44]) Nonimmunosuppressive derivatives of these compounds, such as GPI-1046 and timcodar displayed similar neuroprotective activities *in vitro* and *in vivo*, without the depressive effects on the immune system. Interestingly, GPI-1046 provided significant protection to hippocampal and cortical cultures against the HIV-1 proteins Tat and gp120 [45].

Inhibitors of oxidative & nitrosative stress

Several antioxidants have been shown to decrease the oxidative stress produced by treatment of neurons with CSF from patients with HIV dementia [15], including estrogens, selenium, and glutathione (GSH) analogs.

Estrogens

The use of estrogens would require development of an agent that has neuroprotective properties without feminizing and carcinogenic properties. Plant phytoestrogens, including diosgenin and resveratrol, have promise in this regard [15,46].

Glutathione modulators

Compounds that upregulate glutathione and increase glutathione synthesis would have promise as an antioxidant therapy for HIV neurodegeneration. *N*-acetylcysteine is a glutathione precursor, decreases TNF levels in the serum of HIV-infected individuals and slows the rate of decline of CD4 cell counts. It is currently in use as a mucolytic agent in respiratory diseases and could therefore proceed rapidly to trials in patients with HIV. An agent called AD-4 is being developed by Nova Pharmaceuticals, as a glutathione precursor that could have better CNS penetration than *N*-acetylcysteine.

Acetyl L-carnitine (ALCAR) is an endogenous mitochondrial membrane compound that helps to maintain mitochondrial bioenergetics and lowers the increased oxidative stress associated with aging. GSH levels have been shown to decrease with aging, but administration of ALCAR increased cellular levels of GSH in rat astrocytes. While decreased cell survival was observed in neuronal cultures treated with Aβ1–42, which correlated with an increase in protein oxidation (protein carbonyls, 3-nitrotyrosine) and lipid peroxidation (4-hydroxy-2-nonenal) formation, pre-treatment of cortical neurons with ALCAR significantly attenuated Aβ1–42-induced cytotoxicity, protein oxidation, lipid peroxidation and apoptosis in a dose-dependent manner. ALCAR treatment of neurons also led to an elevated cellular GSH and heat shock protein 72 levels, as well as increased heme oxygenase-1 protein [47]. Treatment of mixed neuroglial cultures with the food preservative t-butylhydroquinone resulted in increased glutathione biosynthesis [48] and protection against MPTP toxicity in mice [49].

Spin trap nitrones

Nitrone-based antioxidants have recently emerged as promising therapeutic agents for pathological conditions involving free radical-driven oxidative stress [50]. Nitron spin-trap agents are important chain-breaking antioxidants in that they capture reactive paramagnetic species to form stable nitroxides. Nitrones affect the cellular oxidation state and oxidatively sensitive enzyme systems and are able to suppress gene transcription, particularly the amplification of NF-κB-regulated cytokines and inducible nitric oxide synthase [50]. Nitrones affect cellular oxidation by prevention of mitochondrial dysfunction, which is known to contribute to the death of a cell. A prototypic class of nitrones – the α-phenyl nitrones, represented by α-phenyl-N-*tert*-butyl nitron and its 2,4-bis-sodium sulfonate derivative,

NXY-059, have been widely tested as antioxidant therapeutics [51]. Second-generation azulenyl nitrones, such as stilbazulenyl nitron, demonstrated more effective antioxidant properties and better BBB permeability, and thus displayed significant neuroprotective efficacy in models of transient forebrain ischemia, MPTP toxicity and axotomy-induced retinal injury [52].

Poly (ADP-ribose) polymerase inhibitors

Poly (ADP-ribose) polymerase (PARP) is a nuclear enzyme that is activated by DNA strand breaks to participate in DNA repair. However, excessive activation of PARP results in the transfer of multiple ADP-ribose units from nicotinamide adenine dinucleotide (NAD) to substrate proteins, depleting tissue stores of NAD, with the resultant depletion of ATP leading to cell death [53]. Inhibition of PARP by specific inhibitors, such as GPI 6150 and GPI 15427, and gene deletion resulted in significant protection from tissue damage in focal cerebral ischemia, myocardial infarction and models of diabetic neuropathy (reviewed in [54]). Accordingly, PARP inhibitors with anti-inflammatory and neuroprotective properties could provide a novel therapeutic to treat HIV neurodegenerative disorders. Interestingly, the tetracycline derivatives doxycycline and minocycline are active PARP inhibitors that are neuroprotective against HIV toxicity.

Neurotransmitter antagonists

Neurokinin antagonists

Substance P (SP) and its receptor, NK-1R, are involved in the modulation of HIV infection both *in vivo* and *in vitro*. Azzari *et al.* [55] observed that HIV-positive children had higher plasma levels of SP compared with HIV-negative children. Annunziata also showed that SP plays a critical role in HIV gp120-induced increases in permeability of rat brain endothelium cultures (reviewed in [56]). The only NK-1 receptor antagonist on the market is EMEND™ (aprepitant or MK-869). Aprepitant blocks replication of different HIV subtypes (A, F and H) in human monocyte-derived macrophages, as well as enhancing the anti-HIV activity of retroviral agents, such as AZT, efavirenz and indinavir in macrophages. Perhaps this agent and other NK-1 receptor antagonists may act to spare vulnerable neuronal populations following HIV infection.

Biologics

Monoclonal antibodies

Monoclonal antibodies could be used against numerous targets in HIV infection and HIV dementia, such as CXCR4 and CCR5 to prevent cellular infection, adhesion molecules to prevent BBB penetration, TNF- α and IL-1 β to decrease inflammation, and perhaps even against viral proteins like gp120 and Tat. In fact, since it may be difficult to use monoclonal antibodies against human proteins without causing deleterious effects [57], using them to target viral proteins may be preferred.

siRNAs

siRNA designed to target sequences of the viral genome that are conserved in neurotropic strains of HIV have already demonstrated antiviral efficacy *in vitro* [58], particularly the RNA that targets gp41. While substantial progress has been made to stabilize these molecules *in vivo*, delivery of siRNA to the brain can be challenging, since they do not cross the BBB easily and even that could be overcome, they would need to cross the cell membrane of the targeted HIV-infected macrophage/microglia and astrocytes within the brain.

Vaccine strategies

In addition to their role in adaptive immunity, antibodies may also complex with foreign and host proteins, disrupting inflammatory or otherwise deleterious cascades. Antibodies can neutralize toxic or infectious processes by binding to antigenic determinants on the harmful agent, thereby hindering interaction of the agent with a receptor. This neutralizing function of antibodies, widely publicized recently with the study of neutralizing antibodies against interferons in multiple sclerosis therapeutics [59], is central to the idea of finding a vaccine against Alzheimer's disease [60] and is important in recent HIV research [61]. Recent work has found that antibodies generated against a modified Tat protein suppressed Tat-induced viral replication and HIV-associated cytopathic effects in human monocytes [62]. Antibodies against HIV proteins can be found in the spinal fluid, and immune complexes have been identified in the spinal fluid of many neurological diseases, such as multiple sclerosis and lupus [63]. Recent unpublished data from our laboratory suggests that antibodies against Tat are protective against Tat- and NMDA-mediated excitotoxicity at NMDA receptors, and that individuals with HIV but without HAND are likely to have higher anti-Tat antibody levels in their spinal fluid. Antibodies against viral proteins may therefore partially explain differences in host susceptibility to HIV dementia, and a better understanding may also lead to new approaches for treatment or prevention of HIV dementia, through development of vaccine therapies.

Executive summary

Introduction

- HIV-associated neurocognitive disorders continue to be highly prevalent amongst individuals infected with HIV and have a large socioeconomic impact.
- Current highly active antiretroviral therapy is insufficient to prevent neurocognitive deficits caused by HIV.
- Additional neuroprotective strategies are required and research into the neuropathogenic mechanisms of HIV is providing targets for such therapies.

Neuroprotective agents in individuals with HIV infection

- Several clinical trials have been conducted for putative neuroprotective agents for HIV dementia and other neurological conditions, but have uniformly shown little or no benefit. The question of why these therapies fail when the basic science suggests they should work must be addressed.
- Future, successful therapies may require combination approaches, protection of neuroprecursor cells and targeting DNA and RNA levels rather than protein levels.

Development of drugs for protection against HIV neurotoxicity

- Several new classes of drugs promise to disrupt the neurotoxic mechanisms of viral proteins. These include glycogen synthase kinase-3 β inhibitors, mixed lineage kinase-3 inhibitors, protein kinase inhibitors, cyclin-dependent kinase inhibitors and antagonists of excitotoxicity.
- Neuroimmunophilin ligands, anti-TNF- α agents, antioxidants, spin trap nitrones, poly (ADP-ribose) polymerase inhibitors, neurokinin antagonists and matrix metalloproteinase inhibitors will also likely play a role in future neuroprotective strategies for HIV dementia.
- Other exciting future therapies for HIV dementia include vaccine strategies, siRNA and monoclonal antibodies.

Erythropoietin

Erythropoietin has been demonstrated to prevent gp120-associated sensory axonal degeneration and dorsal root ganglion neuronal death [64] and cerebrocortical neuronal toxicity [65]. This result suggests that gp120-induced damage to central and peripheral nervous systems are mediated by overlapping mechanisms and therefore some of the potential therapies discussed for CNS neuroprotection could also be effective for PNS neuroprotection.

Conclusion

HIV-associated dementia results from neuronal dysfunction and death caused by both viral proteins and host inflammatory mediators via numerous mechanisms. Current HAART is inadequate to control this neurotoxicity but numerous targets are available for focused development of neuroprotective strategies.

Future perspective

Over the next 5–10 years, many of the agents discussed in this review will undergo clinical trials for patients with HIV dementia. It is important to recognize the limitations of these trials, such as study size and duration, so that effective therapies are not discarded. Agents may be more effective in preventing HIV dementia or slowing its progression than in treating HIV dementia and reversing damage that has already occurred. However, because HAART has already slowed the progression of HAND, large numbers of patients may be required to provide adequate power to detect an effect on typical neurocognitive test parameters. Development of standardized and validated biomarkers, such as CSF profiles or new radiological techniques, will assist in the development of new therapies by providing more sensitive outcome measures. It may be necessary to combine neuroprotective therapies in order to see a benefit by targeting redundant pathways of neuronal damage. New therapies will be developed that attempt to protect neuroprecursor cells from damage. Strategies that target proteins may be ineffective because of rapid protein turnover. Strategies that target DNA or RNA levels will be explored.

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Table 1

Clinical trials of putative neuroprotective agents in HIV dementia.

Agent	Dosage	Number enrolled/completed	Concomitant antiretroviral therapy	Duration of study	Conclusions
Antioxidants					
OPC-14117	240 mg/day	P = 15/9 D = 15/7	NRTI	12 weeks	Trend for improvement in memory and timed gait
Selegiline	Selegiline 2.5 mg three-times per week thioctate 1200 mg/day	P = 9 Selegiline = 9 Thioctate = 9 Both = 9	NRTI	10 weeks	Improvement in verbal learning; trend in recall and psychomotor speed
Transdermal selegiline	6 mg/24 h patch 3 mg/24 h patch	P = 43/32 D(high) = 43/30 D(low) = 42/28	HAART	24 weeks	No benefit
Transdermal selegiline	1 mg/cm ² × 15 cm ² patch	P = 5/4 D = 9/8	NRTI	10 weeks	Positive effect on neurocognition
Calcium channel blockers					
Nimodipine	60 mg five-times daily 30 mg five-times daily	P = 11/7 D(high) = 13/10 D(low) = 14/11	NRTI	16 weeks	Trend for neurocognitive improvement on high dose
CCR5 antagonists					
Intranasal peptide T	2 mg three-times daily	P = 109/77 D = 106/66	NRTI	6 months	No benefit
NMDA antagonists					
Memantine	40 mg/day by week 4	P = 70/54 D = 70/56	HAART	16 weeks	No neurocognitive benefit at 16 weeks; positive effect at week 20; improvements on MRS measures
PAF antagonists					
Lexipafant	500 mg/day	P = 14/13 D = 16/14	HAART	10 weeks	Trend in verbal learning and timed gait
TNF antagonists					
CPI-1189	100 mg/day 50 mg/day	P = 21/16 D(high) = 22/20 D(low) = 22/20	HAART	10 weeks	Trend in peg board test on high dose

D: Study drug; MRS: Magnetic resonance spectroscopy; NMDA: N-methyl D-aspartate; NRTI: Nucleoside analogue reverse transcriptase inhibitor;

P: Placebo; PAF: Platelet activating factor.

Table 2

Ongoing/planned clinical trials in HIV dementia.

Drug	Mechanism of action	Number of patients to be enrolled	Double blind/placebo controlled	Primary end points	Estimated completion date
Minocycline	Anti-inflammatory	100	Yes	Neuropsychological test summary measure	2010
Valproic acid	Anti-inflammatory	60	Yes	Magnetic resonance spectroscopy metabolite	2012
CNS vs non-CNS penetrating HAART	Antiviral	120	No	Global neurocognitive measure	2012

HAART: Highly active antiretroviral therapy.

Table 3
Ongoing/planned clinical trials in HIV-peripheral neuropathy.

Drug	Mechanism of action	Number of patients to be enrolled	Double blind/placebo controlled	Primary end points	Estimated completion date
Erythropoietin	Neuroregenerative	46	No	Nerve fiber density on skin biopsy	2010
Duloxetine/methadone	Symptomatic pain relief	100	Yes	Pain intensity score	2012
Cannaboid/methadone	Symptomatic	84	Yes	Pain intensity score	2011