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The ART of HIV therapies: dopaminergic deficits and future treatments for HIV pediatric encephalopathy

Katy M Webb, BS[†],
Behavioral Neuroscience Program, Department of Psychology, University of South Carolina, Columbia, SC 29208, USA and Department of Pharmacology, Physiology & Neuroscience, University of South Carolina School of Medicine, Columbia, SC 29208, USA

Charles F Mactutus, PhD, and
Behavioral Neuroscience Program, Department of Psychology, University of South Carolina, Columbia, SC 29208, USA

Rosemarie M Booze, PhD
Department of Pharmacology, Physiology & Neuroscience, University of South Carolina School of Medicine, SC, USA and Behavioral Neuroscience Program, Department of Psychology, University of South Carolina, Columbia, SC 29208, USA

Katy M Webb: kwebb@med.sc.edu; Charles F Mactutus: mactutus@sc.edu; Rosemarie M Booze: booze@sc.edu

Abstract

The concerted efforts of clinicians, scientists and caregivers of HIV-infected children have led to tremendous advances in our understanding of pediatric HIV/AIDS. Antiretroviral therapy (ART; formerly known as highly active antiretroviral therapy [HAART]) has significantly extended the longevity of HIV-infected children, but there are limitations to improvements in quality of life that may persist despite therapy. ART has remarkably reduced the incidence of neurologic deficits for the majority of infected children, but some patients do not experience these benefits and children living in poorer nations, who may not have access to antiretrovirals, are particularly at risk for developing neurologic deficits. This article reviews the neurologic symptoms of pediatric HIV infection that manifest as dopaminergic disruptions and explores potential future adjuvant therapies for HIV-related neurologic disorders in children.

Keywords

attention; children; dopamine; encephalopathy; HIV; language; motor deficits; treatment

HIV-1 is a highly infectious member of the lentiviral family. As such, HIV is responsible for the depletion of T-helper lymphocytes, resulting in a systemic degradation of immune function. In addition to its immunocompromising effects, HIV is neurotropic and can be detected in the CNS of infected individuals soon after initial infection [1, 2]. The widely accepted theory of HIV penetration into the brain posits that the virus stealthily crosses the

[†]Author for correspondence, Department of Pharmacology, Physiology & Neuroscience, University of South Carolina, School of Medicine, Columbia, SC 29208, USA, kwebb@med.sc.edu.

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blood–brain barrier (BBB) inside infected monocytes [3–5]. Although only microglia and macrophages are productively infected by HIV, neurons seem to bear the brunt of the damage, as is evident by the incidence of neuronal injury and apoptosis [6, 7]. A 2006 review by Kaul and Lipton provides an elegant overview of the mechanisms of HIV neuropathogenesis and the pathology of HIV-associated dementia [8], and the 2002 Belman review is a generous source of information on the pathology associated with HIV encephalopathy, as well as discussing topics such as mother-to-child transmission, antiretroviral therapy (ART) and disease management, and neurobehavioral/ neuropsychiatric problems that are associated with pediatric HIV infections [9].

Pathologic studies of HIV-infected children have revealed the accumulation of productively infected cells in many brain regions, including the white matter and basal ganglia [10], an area that is also susceptible to calcification [11, 12]. HIV-infected pediatric brains may be smaller in size and frequently show evidence of astrocytosis, myelin pallor and an inflammation of the brain vasculature [13], in addition to the detection of apoptotic neurons in the cerebral cortex and basal ganglia [3].

HIV can contribute to cognitive and motor deficits in infected children, in addition to causing structural damage. The appearance of encephalopathy in HIV-infected children is commonly the AIDS-defining symptom and can indicate a more-progressive disease course and a shorter survival time than can be expected in children without encephalopathy [14]. Signs of the neurologic consequences of an HIV infection appear sooner in the course of infection and progress more rapidly in HIV-positive children than in infected adults [15, 16]. The manifestation of cognitive and motor alterations resulting from structural pathologies can be classified by the rate of progression of neurologic impairments and the resulting effects on the infected child’s behavioral and cognitive development. The most severe form of HIV-related neurologic damage is referred to as progressive encephalopathy (PE). PE is analogous to HIV-associated dementia in adults [9], and clinically presents as impairments in brain growth (microcephaly), marked and progressive motor dysfunction and an early plateau in the attainment of developmental milestones or a loss of milestones that have already been achieved [17]. Pediatric patients affected by static encephalopathy resulting from HIV infection can also demonstrate neurodevelopmental deficits, such as motor dysfunction, a delay in milestone attainment and learning disabilities [18]. Unlike PE, however, the cognitive and motor deficits of HIV-infected children with static encephalopathy remain fixed or can even improve with time, although progression to PE can occur [15].

Antiretroviral therapy

Since its initial identification as the virus that causes AIDS [19], HIV has contributed to the deaths of an estimated 4.2 million children globally between 1990 and 2007 [101[. Before the widespread use of ART, infected infants and children living in the USA that had progressed to AIDS had an average life expectancy of 9.4 and 19.7 months, respectively [20]. The expected longevity in sub-Saharan Africa was shorter, with nearly half of infected infants dying before their second year [21]. In addition to their remarkably decreased life expectancies, an estimated 13–35% of HIV-infected children and 35–50% of children with AIDS in the USA would develop symptoms of HIV encephalopathy [12, 22]. Until recently [23], the prevalence of HIV encephalopathy in children from less-developed nations was poorly known, even though sub-Saharan Africa contains 90% of the world’s population of HIV-infected children [101[. However, a newly published study indicates the prevalence of HIV encephalopathy in sub-Saharan Africa to be an estimated 60% [22].

Now in the post-ART era, in which antiretrovirals are readily available and more affordable in developed countries, HIV is considered a chronic illness and infected children are expected to live into their adolescent and adult years [24, 25]. Unfortunately, as the overwhelming majority of infected children are living in sub-Saharan Africa, they are largely without access to antiretrovirals and are still exceptionally vulnerable to the devastating effects of HIV on morbidity and mortality.

The current treatment options for children with either progressive or static encephalopathy are primarily limited to ART, a combination of three or more antiretrovirals that have at least two mechanisms of action by which they disrupt viral replication [26]. Many antiretrovirals, such as zidovudine and stavudine, readily penetrate the BBB, enabling them to directly reduce the damage caused by HIV in the CNS by preventing the release of neurotoxic proteins through the inhibition of viral replication [27, 28]. The ART treatment strategy has proven remarkably effective as ART has been shown to reduce the prevalence of HIV-related neurologic disorders in US children to an estimated 10% [24] and is able to delay the onset of AIDS [9]. However, the complete prevention of encephalopathy cannot be expected with any currently available treatment regimen. Despite our remarkable advances in understanding the effects of HIV on the CNS, there is still no US FDA-approved pharmaceutical compound specifically designed for the treatment of encephalopathy in children or the neurologic disorders caused by damage of the nervous system by HIV (NeuroAIDS) in adults.

Limitations of ART

As mentioned previously, an estimated 10% of children in the USA on an ART regimen will still experience the neurologic effects of HIV infection [24]. Despite the use of ART, delays in motor and language abilities first observed in early childhood may persist as infected children age [9]. While several studies have demonstrated that therapeutic intervention with antiretroviral compounds for HIV-infected children have facilitated performance within the normal range on global intelligence tests [26, 29–31], specific cognitive domains and neurobehavioral functions may remain impaired. School-age children with HIV encephalopathy frequently perform more poorly than uninfected children on tests of global intelligence and on more-detailed cognitive measurements; these children also perform poorly on tasks of fine motor skills and exhibit deficits in language and vocabulary skills [26].

Although we do know that some HIV-infected American children will still have neurologic complications, whether those deficits are the same or similar to pre-ART findings remains largely unknown. There are only a few sources of information regarding the specific natures of neurologic deficits in the post-ART era that use appropriate sample sizes and controls [31]. Nonetheless, as the majority of HIV infections are in children living in sub-Saharan Africa, these neurologic deficits are likely to remain substantial threats to their quality of life. The following section describes the neurologic deficits associated with pediatric HIV infections in the USA that were observed before the widespread use of ART, unless otherwise stated.

Cognitive & motor deficits

Assessments of cognitive performance in HIV-infected children have indicated global IQ scores in the range of low-average to mild mental retardation, visuospatial deficits, cognitive inflexibility, deficits of working and short-term memory, and learning disabilities. In addition, cognitive deficits may also manifest as language and attention difficulties and may be accompanied by motor dysfunction [9, 10, 17, 23, 32–34]. The following sections provide further information regarding two HIV-associated cognitive disturbances, attention

deficits and language disorders, as well as a discussion of HIV-associated motor dysfunction.

Attention deficits

Attention-deficit/hyperactivity disorder (ADHD) is commonly reported in HIV-positive school-age children [32] with an estimated prevalence of 29% reported in a study of infected French children [35], compared with a global prevalence of 2–14% in noninfected cohorts [36]. Clinical studies of children with HIV and ADHD have noted that infected children are more easily distracted than their noninfected counterparts, and that they seem to have difficulty in tasks of sustained attention [34]. Therapeutic options for treating attention deficits with or without corresponding hyperactivity in HIV-infected children, as with noninfected ADHD-afflicted children, typically involves the use of psychostimulant drugs, such as methylphenidate and amphetamine, inhibitors of the dopamine transporter (DAT) [15]. Given that a very large component of short-term memory is dependent upon the process of sustained attention [37], it is expected that HIV-positive children commonly present as having short-term memory impairments. However, a relationship between HIV status and ADHD is not always observed in young children and may depend upon the diagnostic assessment methods (Conners' Parent Rating Scale) and confounding variables (exposure to drugs of abuse) [38].

Language difficulties

Studies of the neurobehavioral and social interactions of children infected with HIV indicate that many of them have difficulties with speech and language. While it is expected that children who exhibit symptoms of encephalopathy may display speech problems, infected children that are clinically asymptomatic are also susceptible to language difficulties [10]. Some infected children may experience difficulties with receptive speech but the predominating deficit is in expressive language abilities in children living in the USA and the Democratic Republic of the Congo [23, 33], a communication disorder characterized by a limited usage of vocabulary and grammar [39]. As verbal expression reflects the coordination of language with the motor ability of producing speech, expressive speech impairments may, in part, be affected by the motor dysfunctions encephalic children typically experience [10]. The hypothesis that motor dysfunctions contribute to verbal expression deficits was reiterated and expanded with the suggestion that these communication disorders may be due specifically to difficulties in motor planning [33]. Deficits in expressive language may be treated by intensive speech therapy [36]. An interesting longitudinal study reported that, after the initial identification of expressive language deficits in HIV-infected children, 2 years of treatment with zidovudine-inclusive ART failed to prevent a further decline in expressive language abilities, although overall cognitive function remained stable [40]. Although ART may initially offer protection to vulnerable nervous tissue, it was suggested that this effectiveness may be lost over time due to therapy resistance. A CT scan of their test subjects revealed a correlation of pathologic severity with a decline in expressive language abilities, suggesting that permanent structural damage to brain tissues may result in the degradation of expressive language.

Motor dysfunction

The motor dysfunctions reflected in rigidity and dystonia that are sometimes observed in adult NeuroAIDS are rarely observed in children. Pediatric motor dysfunction typically manifests as hyper/hypotonia and spasticity, and may include hyper-reflexia in more-severe cases of encephalopathy. Motor difficulties are usually not cerebellar but rather extrapyramidal, which may present as bradykinesia, hypomimetic facies and gait disturbances that may include the loss of ambulation [17]. Five severe cases of motor dysfunction in pediatric patients that incorporated severe rigidity were successfully treated

through the administration of levodopa [41], a dopamine biosynthetic precursor able to penetrate the BBB and help restore dopaminergic neurotransmission [102[. The levodopa intervention allowed the patients in this study to achieve greater activity levels and, for one of the examined children, restored the ability to ambulate independently. In pediatric patients with less-severe encephalopathy, fine motor skill loss and clumsiness are the most commonly reported motor difficulties, which may be addressed by physical therapy [9, 17, 36]. A recent post-ART era study examined psychomotor performance in a total of 34 Thai children, 16 of whom were beginning ART at the initiation of the study, seven antiretroviral-naive children and 11 children who had been receiving ART for at least 1 year and for an average of 16 months [26]. Psychomotor performance of tracking, tapping, pursuit and simple reaction time were assessed at baseline and 4 months into the study for all children, and at 12 months for ART-naive children and children who began ART at the onset of the study (newly treated). Results indicated that, while ART did significantly improve CD4 counts in newly treated children who previously had the lowest counts at baseline, there was no improvement in their psychomotor function. At the 12-month assessment, which compared newly treated children to naive children only, there was a significant deterioration in psychomotor performance in both groups of children. The authors concluded that, in spite of immunologic reconstitution, ART was unable to benefit psychomotor performance. However, these results do not probably translate well to other HIV-infected children due to the small sample sizes and the lack of information regarding the children's socioeconomic backgrounds and other confounding factors, such as *in utero* exposure to drugs of abuse. Moderate-to-severe motor dysfunction has also been recently reported as impacting an estimated 68% of HIV-positive children living in the Democratic Republic of the Congo who were either ART naive or who had less than 1 week of ART prior to assessment of neurodevelopmental status [23].

Expert commentary

Pediatric encephalopathy & adult NeuroAIDS: the dopamine link

An interesting yet perhaps unsurprising observation of these major areas of neurocognitive problems is their common link to the neurotransmitter dopamine. Dopaminergic alterations have been described in adult NeuroAIDS [42, 43] and, given the similarities between the manifestations of pediatric and adult neurologic deficits, it may be anticipated that dopaminergic functions may also be compromised in infected children.

Several reports from the basic sciences utilizing cell culture and human tissue studies have substantiated a linkage between the dopamine systems and HIV-induced neural damage. An *in vitro* project examining the effects of the neurotoxic HIV protein Tat on cells of the fetal rat midbrain has revealed that a coincubation of Tat and the dopamine Dl receptor antagonist SCH 23390 decreased cell death, as measured by cell viability [44]. Tat-exposed neuronal cultures have also shown a decrease in the binding of [^{3}H] WIN 35428, a compound known to inhibit dopamine reuptake through binding to midbrain DAT [45]. Subsequent western blotting of the Tat- and [^{3}H]WIN 35428-exposed cell cultures for DAT immunoreactivity showed no significant difference between control and Tat-treated cells, indicating that Tat has no effect on the expression of DAT. Together, these *in vitro* findings indicate that Dl-modulated pathways and the functions of DAT may contribute to the neuropathogenesis of HIV. Human case studies of HIV-infected adult male patients with AIDS dementia complex have shown that bradykinesia can be treated successfully with levodopa, but with the burden of dopaminergic side effects, such as sleep disorders and dyskinesias [42], suggesting a possible upregulation of dopamine receptors in adult HIV dementia. Pathologic studies of adult tissues have revealed a marked decrease in the expression of tyrosine hydroxylase in the substantia nigra of tissues from patients with HIV-associated dementia [46]. With the combination of findings from fetal cell cultures, clinical studies of HIV-infected children

and studies of adult tissues and neurobehavioral disturbances and tissues, it seems quite likely that, regardless of age at infection, HIV may have a substantial impact on the dopaminergic regions of the brain, particularly the basal ganglia and cortical motor and cognitive areas. All of these findings contribute to the hypothesis that the expression of some dopaminergic biomarkers and the function of DAT may be affected by the neuropathogenesis of HIV.

The dopaminergic brain regions affected by HIV arc connected by fiber pathways modulated by the dopaminergic neurons of the ventral tegmental area and the substantia nigra [43]. Frontostriatal circuits, brain regions that are modulated by dopaminergic pathways and are critical in normal cognitive functioning, connect cortical regions with the basal ganglia [47]. HIV-related alterations in the function of the basal ganglia due to HIV-related neuropathology (i.e., calcification and neuronal apoptosis) may impact the dopaminergic valence of cortical and subcortical brain regions connected by the frontostriatal circuit and the cognitive and behavioral abilities they modulate.

Neurodevelopmental effects of HIV infection

There may be areas of the developing brain, including the basal ganglia, which are more susceptible to neurotoxicity than others [9]. The developmental aspects of pediatric HIV require careful exploration due to the considerable remodeling of synapses and neuronal processes, the selective reduction in neurons, the addition of glia and an increase in myelination during the perinatal and adolescent periods of brain growth and development. The evaluation of cortical-based cognitive changes may require a careful consideration of developmental changes as the frontal cortex may be much more vulnerable in a child before myelination has been completed, potentially contributing to the language and attention deficits observed in infected children.

To the best of our knowledge, there are no reported behavioral studies in preclinical models of HIV encephalopathy that examine the developmental effects of HIV in cortical regions; however, there are more recent reports that do further our understanding of the effects of HIV on neurodevelopment. In a series of studies by Fitting *et al.* neonatal rats were injected with the toxic HIV proteins gp120 and Tat on postnatal day 1 [48]. Unilateral injections were made into the hippocampus using three different doses of HIV proteins, one of which included a combination of both gp120 and Tat (100 ng plus 25 μg, respectively). Animals were tested on measures of neurodevelopment and maintained through adulthood for behavioral and anatomical assessment. Neonatal examinations revealed that the combination of Tat and gp120 was sufficient to delay the development of the righting reflex, an indication of the achievement of developmental milestones in the young rat. In adulthood, the combined effects of postnatal Tat and gp120 in the same rats induced a significant alteration in the maximal peak inhibition in the startle reflex test, a task that assesses the pre-attentive process of sensorimotor gating. Furthermore, anatomical results obtained at 7.5 months of age demonstrated a significant decrease in overall neuron number in hippocampal regions CA2/3, and a significant increase in astrocytes and oligodendrocytes in the subiculum and an increase in astrocytes in the dentate gyrus/hilar region. Previous examinations of human tissues have revealed that the hippocampus and basal ganglia bear the highest viral loads of any brain region [49], thereby suggesting that some of these cellular composition changes noted in the hippocampus may be observed in anatomic evaluations of the basal ganglia.

Despite the similarities in the nature of HIV-related neurologic deficits of children and adults, it is likely that the neurotoxic effects of HIV in a developing nervous system can be far more damaging and may involve mechanisms not implicated in adult NeuroAIDS. Even within infected pediatric populations, the age at which a child becomes infected seems to

have an impact on the course of the disease. Children infected by blood transfusion products experience declines in neurologic status that follow the course of a decline in their immune status [50], whereas the onset of neurologic deficits in vertically infected children may occur even within the first year of life. Furthermore, the rate at which the disease progresses seems to be much slower in horizontally infected children and features longer latency periods, a delayed onset of symptoms and a longer course of disease advancement from the initial HIV exposure to the diagnosis of AIDS [50]. These observations may indicate that, although both infants and older children are undergoing brain growth and a fine-tuning of neural pathways, it seems likely that these separate periods of development are differentially susceptible to HIV toxicity.

As many children infected after the onset of the ART era have now reached their adolescent years, studies measuring their cognitive abilities compared with children infected during later adolescence by sexual contact or drug abuse could contribute significantly to our understanding of HIV in the developing brain.

Five-year view

Maintaining CNS ART concentrations

A newly published article has suggested that barriers exist to the sustained presence of antiretrovirals in the CNS [51]. Endothelial cells of the BBB monitor the contents of brain microvessels and permit the diffusion of lipid-soluble, low-molecular-weight molecules into the brain, while other substances either require specialized transporters or are prevented from entering the CNS [52]. Transporters constitutively expressed on the surface of endothelial cells, ATP-binding cassettes (ABC transporters) cannot only traffic antiretrovirals into the brain but can also cause their efflux, as two types of ART compounds, protease inhibitors and nucleoside reverse transcriptase inhibitors, serve as transporter substrates [53, 54]. A study by Eilers and colleagues demonstrated that the strong expression of ABC transporters in brain vasculature is correlated to an increase in the efflux of zidovudine and saquinavir [51]. Perhaps a pharmacologic blockade of ABCs may be therapeutic in HIV neurologic deficits by preventing a loss of ART compounds in the CNS.

Neuronal metabolism

A compelling facet of ART is its potential to significantly reduce and even reverse the symptoms of HIV dementia/encephalopathy. It may be that part of the etiology of HIV-associated neurologic deficits result from a reversible dysfunction of neuronal metabolism induced by soluble neurotoxins [55]. Disruptions in metabolism can contribute to neurologic deficits by eliciting many negative changes in neuronal and synaptic structure, as well as inducing neuronal apoptosis. Therefore, potential adjuvant therapeutic strategies for the treatment of HIV neurologic deficits that correct a dysregulation of neuronal metabolism may be of great importance.

The brain has inherent means of protecting itself from toxic insults, for example, the activation of nuclear factor (NF)-κB[56], which, despite its activation by HIV viral particles, is seemingly unable to provide neuroprotection in infected patients [57]. Recent findings reveal that the activity of NF-κB is inhibited by glycogen synthase kinase-3β (GSK-3β) [57], an enzyme whose activity in neurons is upregulated by Tat and platelet activating factor, which is secreted in the brain in HIV infections and acts as a neurotoxin [58, 59]. The Tat-induced activation of GSK-3β, an inhibitor of a transcription factor able to activate cell survival molecular pathways (NF-κB), may reveal how Tat contributes to the neurodegeneration associated with HIV infections of the CNS [57].

These findings lead to the observation that valproic acid, an inhibitor of GSK-3β, protected rat hippocampal and midbrain cultures from gp120-induced neurotoxicity [60]. To further this approach rat cortical cultures and severe combined immunodeficiem (SCID) mice that had been intracranially injected with HIV-infected monocyte-derived macrophages were treated with valproic acid and assessed for histologic changes indicative of neurodegeneration as well as GSK-3β activity [60]. Both cortical cultures and histologic slices from the SCID mice revealed a blockage of the reduction of neuntes, neuronal connections and dendritic nodes, neurodegenerative changes observable in gp120-exposed cultures not treated with valproic acid. Western blotting results revealed that long-term valproic acid administration was able to reduce the phosphorylation of β-catenin, a marker of GSK-3β activation, indicating a reduction in its activity. An assessment of HIV-1 viral RNA by PCR showed no significant differences between control and treated SCID mice. These findings suggest that valproic acid can protect against neurotoxicity associated with infected macrophages and promote neuronal survival both *in vitro* and *in vivo*. This research has been translated into Phase Ia and Ib clinical trials of infected adults both with and without HIV dementia [55]. The Phase Ia trial demonstrated no significant interaction of a low dose of valproic acid with the antiretroviral compounds efavirenz and lopinavir/ritonavir without any significant effect on plasma concentrations of valproic acid [61]. Phase Ib results indicated that 10 weeks of valproic acid was well tolerated and safe for patients in the trial, with no significant effects on HIV-1 RNA concentrations measured in plasma [62]. The authors were also able to report a trend suggesting an improvement in performance of neuropsychological task, such as the Rey Auditory Verbal Memory and motor Unified Parkinson Disease Rating Scale. Although these results represent effects of valproic acid in adults, this research nonetheless provides an exciting possibility for a potential adjuvant therapy for infected children and adolescents.

Minocycline therapy

A summary of presentations from the May 2006 Proceedings of the National Institute of Mental Health HIV Preclinical–Clinical Therapeutics Research Meeting [63] highlighted a fascinating development in HIV adjuvant therapeutic approaches. One of the presentations summarized the effects of the tetracycline analog minocycline in the development of encephalitis in the simian immunodeficiency virus (SIV) animal model. In the 2005 original research article, the authors administered a total of 8 mg/kg (4 mg/kg twice daily) of minocycline to pig-tailed macaques beginning 21 days after inoculation with SIV/DeltaB670 and SIV/17E-Fr [64], an immunosuppressive virus and neurovirulent viral clone, respectively [65]. The SIV model is valued for its similarities to the human condition: SIV causes encephalitis in infected primates, while inducing the common pathologic alterations and psychomotor slowing that are so prominent among HIV-infected humans [66]. Cerebrospinal fluid was collected from test subjects on 11 occasions for the purposes of determining concentrations of SIV RNA and monocyte chemoattractant protein (MCP)-l. Following 84 days of minocycline administration, animals were saline perfused for histopathologic assessment. Tissue analysis revealed significant reductions in axonal degeneration, cytotoxic T lymphocyte infiltration, macrophage infiltration and activation, as well as reductions in MCP-1 and SIV RNA concentrations in cerebrospinal fluid. Of the five macaques in their study that received minocycline, two developed mild encephalitis while three failed to develop any signs of SIV encephalitis. These results indicate that minocycline may be effective for infected patients to prevent the development of HIV encephalitis through the suppression of viral replication. Minocycline is effective against many infectious diseases and, therefore, has potential in treating infected individuals with multiple infections. It is also an inexpensive drug that readily crosses the BBB and has been demonstrated to be safe for use. These findings are remarkable in that they not only have the potential to greatly affect the prognosis in adults within developed nations but also those in

poorer nations where very few can afford antiretroviral drug therapies. In terms of treating pediatric patients, minocycline is indicated for use in children over the age of 8 years and younger children when warranted [103[. At the time of the preparation of this manuscript, there were no articles available detailing the use of minocycline in HIV-infected pediatric patients, although other manuscripts have speculated as to whether minocycline may be effective in preventing neurologic disease in children [67].

Zinc-binding proteins

The potential importance of the aforementioned studies in developing new treatments for HIV encephalopathy is readily observed. Each of those studies have in some way advanced our understanding of the potential mechanisms by which HIV contributes to the pathology of the CNS or identifies inherent roadblocks to the effectiveness of ART, and the next step towards improving the therapeutic strategies for treating HIV encephalopathy begins with an enhanced understanding of HIV neuropathogenesis.

These next studies give insights into how zinc-binding proteins may contribute to the progression or prevention of HIV neuropathogenesis. Although the connection between correcting dysregulations in neuronal metabolism, improving ART penetration into the CNS and decreasing viral replication can potentially improve the dopaminergic deficits observed in infected children, the relationship between zinc and dopamine may not be so clear. However, *in vitro* studies have shown that zinc is a high-affinity ligand of DAT and suggest that zinc can enhance the excitability of dopaminergic neurons following the binding of dopamine to its receptors [68]. In addition, many transcription factors that regulate dopamine receptor and tyrosine hydroxylase gene transcription are critically dependent upon zinc for their function [69, 70]. As zinc appears to influence the expression of dopamine biomarkers that affect dopamine biosynthesis and receptor expression, as well as the function of dopamine transporters, we feel that potential dysregulations in zinc-binding proteins may provide a greater understanding of HIV neuropathogenesis and suggest additional therapeutic targets.

The first of these studies explores the relationship between astrocytic expression of tissue inhibitors of metalloproteinase (TIMP)-1 and the neuropathology of HIV infection in an *in vitro* model of HIV dementia, as well as in brain tissues from HIV-infected adults [71]. TIMP-1 is responsible for regulating the activity of matrix metalloproteinases (MMPs), zinc-binding enzymes that can participate in neurodegeneration by excessively breaking down the extracellular matrix of cells. This action can potentially contribute to HIV neuropathology by structurally weakening neurons already compromised by other soluble factors. ELISA results obtained from the *in vitro* model indicate a significant increase in TIMP-1 production that did not parallel results from HIV-infected patients, in whom CSF levels of TIMP-1 were found to be reduced. Currently available antiretrovirals are able to decrease expression of MMP-9, as well as prevent its activity, probably through MMP-9 binding to TIMP-1 [72]. The effects of antiretrovirals on MMP-9 activity are encouraging, and it may be that methods of increasing TIMP-1 expression could yield another treatment strategy for HIV encephalopathy.

A recently published review paper that highlights the role of metallothioneins (MTs) in the astrocytic response to brain injury also raises some interesting possibilities [73]. The astrocytic MTs are one example of protective intracellular proteins released following brain injury. They are thought to act as intracellular free radical scavengers and regulators of heavy metals by binding to divalent transition metals, with a pronounced affinity for zinc [73]. It has previously been established that astrocytic MTs are required for successful brain healing following traumatic injuries and biologic and chemical insults [74]. The healing and defense properties of MTs are very interesting given the emphasis in the HIV literature on

the possible involvement of oxygen radicals in the pathogenesis of HIV dementia. The effects of oxygen radicals have been demonstrated in many studies of both animal and human tissues. A 2003 paper described observations made by Aksenov *et al.* that the degeneration of neurons in Tat-injected rats was accompanied by an increase in protein oxidation, as evident by protein carbonyl immunostaining [75]. These results, combined with the known activities of MTs in response to other sources of neuronal damage, may indicate a role for MTs in the treatment of HIV dementia and encephalopathy. MTs have been implicated in a number of neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases, and amyotrophic lateral sclerosis [76]; however, to date, there are no published reports exploring MT activity in HIV neuropathogenesis. As the brain possesses numerous mechanisms of preventing and reversing the effects of damage from various sources, it could be that a brain overtaxed by the presence of a consistently toxic environment may need a boost to its natural defenses. As several of these newer areas of HIV-related research are dependent upon protein expression it may be that, in part, the future of HIV treatment could rely upon gene therapy strategies.

Table 1 provides a brief summary of the potential therapeutic approaches described in this section.

Future research directions

Assessing potential microstructural changes

Earlier in this review, a summary was presented of the behavioral and histologic findings in rats that had been exposed to HIV proteins as postnatal day 1 pups. Perhaps the most interesting aspect of these data was the report of decreases in neuron number accompanied by increases in astrocytes and oligodendrocytes in regions of the hippocampus. These findings suggest that early exposure to HIV neurotoxins can significantly alter the cellular composition of the developing brain. HIV-1-infected neural progenitors have been detected in archived tissue from pediatric patients of the pre-ART era [77], leading us to wonder whether an examination of those tissues for cell numbers would reveal any significant changes. Similar findings have recently been reported in studies of adult progenitors. The viral envelope protein gp120 has been shown to halt cell cycle progression and cell proliferation in a model of adult NeuroAIDS [78], and chemokines induced by HIV are able to promote quiescence in adult progenitors [79]. Literature on neural progenitors reveals that two, or potentially three, areas of the developing brain are capable of producing progenitor cells: the subventricular zone and the subgranular layer of the dentate gyrus, and either the external granular layer of the cerebellum or the olfactory bulb [80, 81]. The subventricular zone and dentate gyrus can generate both neurons and glia throughout development and even into adulthood [80–82], where they likely participate in neural plasticity and in new memory formation [81]. As the hippocampus is an area of high viral load, it is not surprising that such remarkable changes were detected in hippocampal subregions in the 2008 Fitting *et al.* study [48]. However, as progenitors migrate from the sites of their origin in order to complete neural circuits and cytoarchitecture [82], it may be possible for other areas of the brain still developing in later childhood or adolescence to be adversely affected by damage to neural progenitors. It may be that in the still-developing brain the quiescence of progenitors could result in the incomplete formation of some brain regions, whereas in the adult brain the consequences would likely relate primarily to new memory formation. It would appear necessary to examine other regions of the brain for changes in the number of glia, astrocytes and neurons, especially those areas that are more greatly impacted by HIV, such as the basal ganglia. As childhood and adolescence are periods during which many neuronal connections are being refined, it may be that synaptic connections and dendritic arborizations are worthy of examination, in addition to the assessment of the cellular composition of HIV-vulnerable regions.

Dopaminergic markers in children

As many of the cognitive changes observed in children are dependent upon the function of dopamine pathways between subcortical and cortical regions [47], a crucial step that must be taken is to establish whether pediatric patients have functional, structural or expression-based changes of dopaminergic markers. While there is evidence of calcification of the basal ganglia in encephalopic children [11, 12], to the best of our knowledge, there are no studies that have demonstrated any changes in dopaminergic markers in any dopaminergic brain region or in any model of pediatric HIV infection.

Our laboratory is an eager participant in the attempt to better understand the developmental effects of HIV as well as its impact on the dopaminergic system. We have been conducting explorations into the alterations in dopaminergic molecular markers in cortical and subcortical brain regions, as well as investigating the possible role of a dysregulation of zinc metabolism in HIV encephalopathy. One research model, the HIV-1 transgenic rat, offers a unique investigative tool for these studies as these animals possess a nearly intact HIV genome (a *Gag–Pol* deletion renders them noninfectious) from the zygotic stage [83]. Not only do these animals allow us to examine the concerted effects of almost all of the HIV proteins within the neural environment, but they may be a highly useful developmental model as the animals are designed to contain the transgene from the time of their conception. Thus far, our initial findings have supported the theories set forth in this review, namely that there is evidence for pronounced changes in dopaminergic markers in postweanling transgenic rats (WEBB KM*et al.*, UNPUBLISHED DATA). In addition, a cocaine-sensitization study with adult transgenics has revealed that the locomotor response to repeated cocaine administration in the transgenic animals is significantly less than that of control animals, suggesting an alteration in subcortical dopaminergic systems [84].

Conclusion

The first pediatric case of HIV infection reported to the US CDC occurred in November of 1982 [20]. Over the past quarter of a century, we have made remarkable advances in our understanding of the methods of HIV transmission, the pathogenesis of the disease and in the development of treatments that have, without a doubt, significantly contributed to the longevity and quality of life of HIV-infected patients. However, it seems obvious that we still have a tremendous amount of work ahead of us. HIV/AIDS researchers are beginning to unravel the unique consequences of the pathogenesis of HIV in the pediatric CNS and recognize that these patients experience a different disease course than adults. In light of the challenges that lie ahead, we hope that, in 5 years time, this review will seem a quaint reminder of the progress made in treating HIV-infected children.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

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Key issues

- HIV enters the brain early after initial infection and may cause structural damage, as well as contribute to cognitive deficits.
- HIV encephalopathy is commonly the AIDS-defining condition in children, characterized by delays in attaining developmental milestones. Current therapies are primarily limited to antiretroviral therapy (ART) and there is no pharmaceutical compound specifically for the treatment of HIV neurologic alterations.
- Many antiretroviral can readily penetrate the blood–brain barrier, but neurologic deficits may still develop in some children, especially those in less-developed nations, and may significantly impair quality of life.
- As HIV-infected children age, they may demonstrate attention deficits, language difficulties and motor disorders that may be incompletely addressed by ART intervention.
- Common cognitive and motor deficits of infected children may be dopaminergic in nature, corresponding to data from animal and human studies, implicating the dopaminergic system as a target of the neuropathogenesis of HIV.
- Recent research highlights the roles of tissue inhibitors of metalloproteinase-1 expression, metallothioneins, the antibiotic minocycline and glycogen synthase kinase-3β inhibition by valproic acid as promising adjuvant therapies. Some of these approaches have been assessed in adults, but none have been examined for efficacy and safety in children.
- The extent of the effects of HIV on the developing brain are poorly understood; however, basic science studies indicate that a restructuring in the cellular content of brain regions affected by HIV may occur.
- There is a considerable need for data that help expand our understanding of HIV encephalopathy. Clinical studies that carefully dissect cognitive effects are greatly needed, as are studies that describe dopamine-based changes in pediatric models. In addition, there are alarmingly few ongoing clinical trials that are examining adjuvant therapies for CNS symptoms of HIV infection.

Table 1

Summary of potential adjuvant therapy approaches for HIV pediatric encephalopathy.

Approach	Mechanism	Findings	Ref.
ABC inhibitors	Prevent/reduce highly active antiretroviral therapy efflux	Antiretrovirals serve as substrates; can be actively pumped out of brain microvasculature	[51]
GSK-3β	Rebalance neuronal metabolism	Inhibition of GSK-3β decreased morphologic changes associated with neurodegeneration	[55, 60]
MMPs	Can cause excessive neuronal extracellular matrix degradation	Tissue inhibitors of metalloproteinase can inhibit MMPs; some antiretrovirals can decrease MMP expression	[71, 72]
Metallothioneins	Free radical scavengers	Established roles in some neurodegenerative diseases and following neuronal injury; not yet assessed in models of HIV encephalopathy	[73, 74]
Minocycline	Tetracycline analog antibiotic	Can inhibit HIV replication; reduces severity of encephalitis in SIV	[64]

ABC: ATP-binding cassette; GSK: Glycogen synthase kinase; MMP: Matrix metalloproteinase.