Chapter 2
HIV Neuroinvasion: Early Events, Late Manifestations

Maria F. Chen, Samantha Soldan, and Dennis L. Kolson

2.1 Clinical Manifestations and Epidemiology of HIV Infection of the Nervous System

Although the widespread use of HAART has significantly improved neurological outcomes in individuals infected with HIV-1, a relatively high risk (~30%) for developing neurocognitive dysfunction caused by HIV replication within cellular reservoirs (macrophages/microglia) in the CNS remains (McArthur 2004; Roc et al. 2007; Sacktor 2002). Furthermore, damage to the peripheral nervous system (PNS) in HIV-infected individuals is probably equally prevalent, reflecting the effects of antiretroviral drug toxicity and persistent HIV replication in similar peripheral cellular reservoirs (Keswani et al. 2002; McArthur 2004). HIV-associated neurocognitive disorders (now collectively referred to as HAND) can present with a spectrum of severity: HIV-associated dementia (HAD) and less severe forms that have been categorized by selective criteria based upon both behavioral and neuropsychological test performance, minor cognitive motor disorder (MCMD), HIV-associated mild neurocognitive disorder (MND), and asymptomatic neurocognitive impairment (ANI) (Antinori et al. 2007).

Generally, HAD manifests as a subcortical dementia characterized by psychomotor slowing, behavioral changes, and deficits in memory, abstraction, information processing, verbal fluency, decision-making, and attention; also, its progression is relatively slow (years). These cognitive impairments suggest pathological involvement of the fronto-striato-thalamo-cortical circuits (Woods et al. 2004), and recent studies have demonstrated that synaptic and dendritic damage within the hippocampus and putamen is highly correlated with the degree of cognitive impairment (Moore et al. 2006). Moreover, pathological studies have demonstrated that the mere presence of antemortem neurocognitive impairment is predictive of the

M.F. Chen, S. Soldan, and D.L. Kolson (✉)
Department of Neurology, University of Pennsylvania School of Medicine,
Philadelphia, PA, USA
email: dennis.kolson@uphs.upenn.edu

pathological diagnosis of HIV encephalitis at death (positive predictive value = 95%) (Cherner et al. 2002). Despite the strong correlations between structural brain damage and the severity of neurocognitive impairment in HIV infection, these clinical deficits are not absolutely irreversible. The milder HAND disorders do not uniformly progress to HAD nor do those with HAD always present as milder disorders (Ellis et al. 2007). Furthermore, a significant number of individuals with HAD (up to 22%), irrespective of the use of HAART, can revert to normal or greatly improved cognitive function, for as yet undefined reasons (McArthur 2004; Sacktor 2002).

To date, however, the most obvious factor altering the natural history of cognitive dysfunction in HIV infected individuals is HAART. Prior to the widespread use of HAART in the United States (1996), approximately 20% of HIV-positive individuals suffered from HAD and up to 40% suffered from milder HAND disorders (McArthur 2004; Sacktor 2002; Sacktor et al. 2001). Since then, however, the incidence of HAD has decreased (~8%), while its prevalence has increased slowly, possibly due to increased survival and associated vulnerability of the aging brain to effects of even low-level HIV replication (Becker et al. 2004; Bhaskaran et al. 2008; McArthur 2004; Sacktor 2002; Sacktor et al. 2001; Valcour and Paul 2006; Valcour et al. 2004). This longer life expectancy may also partly explain the trend of increased presentation of HAD in individuals with CD4 T-cell counts greater than 200 cells/mm^3, which was rare during the pre-HAART era, when cognitive dysfunction was much more frequently associated with severe immunosuppresion (Bhaskaran et al. 2008; Ellis et al. 1997) or generally poor health associated with anemia and low weight (McArthur et al. 1993) (Sacktor et al. 2001). Within HIV infected populations of sub-Saharan Africa (Uganda), the prevalence of HAD has been estimated at 31% (72% in this cohort were HAART-naïve) (Wong et al. 2007), which is near the pre-HAART prevalence of HAD in the United States. Improvement in HAND with HAART administration has been documented in cohort studies in North America, Europe, Australia, and elsewhere (d'Arminio Monforte et al. 2004; Dore et al. 2003; Gray et al. 2001; May et al. 2007; Robertson et al. 2004; Sacktor et al. 2003; Sacktor et al. 2000; von Giesen et al. 2002), including sub-Saharan Africa (Sacktor et al. 2006).

If our experience in developed countries accurately predicts the natural history of HAND in post-HAART individuals in other such regions of the world, we can anticipate persistence of at least milder HAND syndromes throughout these regions of the world as in developed countries. It appears that the major changes in the natural history of HAND syndromes in the post-HAART era are slower and more variable progression, less predictable progression to death, and significant improvement in some subsets of patients. In addition, concern about the increasing incidence of peripheral neuropathy, because of the prolonged use of nucleoside reverse transcriptase inhibitors (NRTs) common to HAART regimens, is increasing (Cherry and Wesselingh 2003), and a concern about neurotoxicity of HAART in the brain has been raised (Schweinsburg et al. 2005). Thus, the natural history of neurological complications of HIV infection is changing in the post-HAART era (Brew 2004) and effective treatment will most likely require additional preventative adjunctive therapies to HAART and continued efforts at reducing neurotoxicity of antiretroviral compounds.

2.2 Biology of HIV Infection and Invasion of the Brain

HIV and the related simian immunodeficiency virus (SIV) are retroviruses that when introduced into non-natural hosts cause profound CD4 T-lymphocyte depletion, chronic immune activation, fatigue of T-cell responses and, eventually, immune failure. Efficient infection of cells by HIV requires surface co-expression of chemokine receptors (primarily CXCR4 and CCR5 on T-lymphocytes and CCR5 (rarely CXCR4) on macrophages) and the CD4 receptor. Binding of native HIV envelope glycoprotein (gp120) trimers to CD4 occurs first, and results in a gp120 conformational rearrangement that exposes the chemokine receptor binding site on gp120, allowing it to engage the chemokine receptor (Doms 2004). After this binding of gp120 to the chemokine receptor, the noncovalently associated fusion peptide, gp41, is exposed and inserted into the target cell membrane in the process of fusion, which delivers the infectious particle to the target cell cytoplasm for completion of the replication cycle (reverse transcription, integration, and production of new infectious virions).

Replication of HIV within the CNS appears to drive neuropathogenesis of HAND, although defining the relationships between virus replication (cellular targets, genotype/phenotype of neurotropic strains, regional distribution, level of replication) and stages of either structural damage or neurocognitive dysfunction has been difficult. Based on neuropathological studies that demonstrate predominant HIV (or SIV in macaques) expression in perivascular macrophages, entry of HIV into the CNS appears to occur via infected circulating monocytes (Budka 1991; Wiley et al. 1986; Williams et al. 2001), and this can occur early (within 1–2 weeks) after virus enters into the host (Davis et al. 1992; Gray et al. 1993). Monocytes (infected and noninfected) can pass through capillary endothelial cells via classical transendothelial migration, a process involving movement through endothelial intercellular junctions (diapedesis, reviewed in (Maslin et al. 2005)), and possibly also through transcellular migration (pinocytosis (Liu et al. 2002) (Lossinsky et al. 1991)) through the endothelial cell (although the later is controversial).

The process of monocyte recruitment and migration into the CNS during HIV infection is regulated by a complex cascade of selective induction of multiple adhesion molecules on both monocytes and endothelial cells (EC) (reviewed in (Maslin et al. 2005)). Several adhesion molecules (E-selectin on monocytes; sialomucin CD34, VCAM-1, ICAM-1, P-selectin glycoprotein ligand-1 (PSGL-1 (Marshall et al. 2003)) on EC and others) can function to promote initial monocyte adhesion (rolling, loose adhesion) to ECs and several of these are induced by proinflammatory cytokines such as TNFa and IL-8 and (Baumheter et al. 1993). Infection of monocytoid cells is associated with increased expression of VLA-4 (a4B1 integrin), which then more strongly tethers these cells to EC via binding to VCAM (Birdsall et al. 1994). Expression of each of these is induced by beta chemokine CCL-2/MCP-1 (monocyte chemoattractant protein-1). Further strengthening of monocyte adhesion is enhanced by binding of monocyte LFA-1 to EC ICAM-1 (van Buul and

Hordijk 2004), and diapedesis through EC/EC junctions is promoted by homophilic PCAM/PCAM interactions and CD99/CD99 interactions between moncocytes and EC (Mamdouh et al. 2003; Schenkel et al. 2002). Expression of each of these adhesion molecules is regulated by chemokines and/or cytokines involved in inflammatory responses in the CNS (Meager 1999).

Chemokine expression by EC (CCL2 CXCL1, IL-8, CXC3CL1) can also selectively bind monocytes through chemokine receptor binding with cytokines expressed on the EC surface (Ebnet et al. 1996; van Buul and Hordijk 2004; Weber et al. 1999). Some of these chemokines are tethered to the EC surface by heparin sulfate proteoglycans, and CX3CL1 itself is normally directly tethered to the EC surface (Goda et al. 2000). Monocytes expressing high levels of the fractalkine receptor CXC3CR1 (CD14lo/CD16hi) can preferentially bind to EC expressing fractalkine (CX3CL1), while CD14hi/CD16lo monocytes preferentially bind to EC expressing the CCR2/MCP-1 receptor (Ancuta et al. 2003; Geissmann et al. 2003; Maslin et al. 2005). Notably, Pulliam et al. (1997) have shown that increased expression of CD16 on peripheral monocytes is associated with the presence of HAD, consistent with the hypothesis that immune activation of peripheral monocytes during HIV infection is associated with increased monocyte trafficking into the CNS and an effector action of these cells in the pathogenesis of HAD (Gartner 2000). A more recent study involving a distinct patient cohort confirmed high monocyte CD16 expression in AIDS patients with and without HAD, and further demonstrated that elevated plasma levels of lipopolysaccharide (LPS) and activated monocytes are indeed associated with HAD (Ancuta et al. 2008). Infected monocytes that migrate into the brain can accumulate within the endothelial cell basement membrane to differentiate into macrophages (Nottet et al. 1996). These perivascular macrophages are generally thought to become the major CNS reservoirs for HIV replication, from which sheds virus subsequently infects other macrophages (Rempel et al. 2008).

The HIV strains that have been isolated from CSF and brain tissue, as well as functional envelope sequences amplified from these tissue compartments nearly uniformly express the characteristics of preferred use of the CCR5 chemokine coreceptor and tropism for macrophages (Gorry et al. 2001; Ohagen et al. 2003; Peters et al. 2004; Peters et al. 2007). The tropism of HIV within the CNS and throughout peripheral tissues is determined primarily by the cellular coexpression of the CD4 and CCR5 (and/or CXCR4) receptors. The published literature indicates that, for all naturally occurring primary HIV-1 envelopes, this binding of gp120 to chemokine receptors requires the initial binding of gp120 to CD4 to "uncover" the chemokine receptor binding site followed by binding of the "triggered" envelope to CCR5 or CXCR4 (discussed in (Edwards et al. 2001)). In contrast, some naturally-occurring SIV strains express gp120 that can bind directly to chemokine receptors in the absence of CD4 (Borsetti et al. 2000; Edinger et al. 1999). Furthermore, gp120 expressed by some laboratory-adapted (cell line passaged) HIV strains such as IIIB/LAI and others can *acquire* the ability to bind chemokine receptors in the absence of CD4 through mutation (LaBranche et al. 1999). For this reason, the source of gp120 proteins (naturally occurring vs. laboratory-adapted) and virions used in in vitro studies of gp120/target cell interactions is critical

for validating the biological relevance of such model systems, particularly those involving HIV neuropathogenesis.

Despite several reports of detection of HIV genomic sequences in neurons in vivo (Bagasra et al. 1996; Torres-Munoz et al. 2008; Torres-Munoz et al. 2001) and a plausible infection mechanism mediated by chemokine receptors (CXCR4 or CRR5) and independent of CD4 in neurons (Rottman et al. 1997; Sanders et al. 1998), the body of work showing lack of viral protein and RNA in neurons generally supports the absence of productive HIV infection of neurons in vivo (Achim et al. 1994; Glass et al. 1995; Takahashi et al. 1996; Williams et al. 2001). The absence of infection of neurons supports an indirect mechanism of neuronal injury through release of soluble neurotoxins from infected and/or activated macrophages/microglia and astrocytes, although released viral proteins (gp120, Tat) might also directly contribute (reviewed in (Mattson et al. 2005)).

2.3   HIV Neuropathogenesis: Human and Primate Studies

The pathological hallmark of HIV infection in the brain, termed HIV encephalitis, is characterized by the presence of myelin pallor, reactive astrocytosis, infiltration of predominantly monocytic cells, and multinucleated giant cells (MNGC), which are the unique effect of HIV-driven fusion of macrophages/microglia (Budka 1989; Navia et al. 1986; Wiley and Achim 1994). Postmortem studies have demonstrated that morphological changes in neurons (dendritic simplification and vacoulization, loss of synaptic density) and loss of neurons are commonly found in the brains of HAND patients ((Asare et al. 1996; Everall et al. 1994; Masliah et al. 1992a; Masliah et al. 1992b; Masliah et al. 1997; Sa et al. 2004; Wiley et al. 1991), reviewed in (Ellis et al. 2007)). Damage appears to occur early in the basal ganglia, thalamus, and central white matter (Navia et al. 1986; Petito 1988), where HIV antigen is commonly detected (Kure et al. 1990a; Kure et al. 1990b; Park et al. 1990) but degeneration ultimately involves the entire brain. Several of these studies have focused on specific brain regions and neuronal subtypes. The type of neuronal damage observed includes the following: loss of dendritic arborizations of the dentate granule and hilar basket cells, CA3 and CA1 hippocampal pyramidal cells (Sa et al. 2004), and frontal cortical and hippocampal interneurons (Fox et al. 1997; Masliah et al. 1992b), as well as dropout of neurons in frontal, temporal, and parietal cortex (Everall et al. 1994; Wiley et al. 1991). One study reported loss of oxytocin-producing neurons in the paraventricular hypothalamic nucleus in a study of 20 AIDS patients (4 with suspected HAD), although opportunistic brain infections were present in most of these patients, making a direct relationship between HIV replication and neurodegeneration unclear (Purba et al. 1993). Thus, neuronal damage induced by HIV infection of the brain affects multiple brain regions and neuronal subtypes, but the factors that determine neuronal vulnerability are only partially understood.

Because pathological features of HAND determined postmortem do not provide a picture of how damage is acquired over time, investigators have focused on the use

of neuroimaging analyses of infected individuals and pathological and neuroimaging analyses of SIV-infected macaques to study early effects of brain infection. Two macaque models (*Macaca mulatta*, rhesus; *Macaca nemestrina*, pigtail) of SIV infection have been effectively used for studying the virus-triggered pathways of neurodegeneration that lead to cognitive dysfunction, and for characterizing early events in pathogenesis. Several groups studying the pigtail SIVE model use an immunosuppressing viral swarm (SIV/Delta B670) either with or without co-infection with a CNS-adapted molecularly cloned SIV strain, SIV/17E-Fr to induce SIVE (Bonneh-Barkay et al. 2008; Mankowski et al. 2002). Use of the SIV/Delta B670 swarm alone results in a somewhat variable and delayed neurodegeneration, similar to the natural history of HAND in humans, while coinfection with SIV/17E-Fr typically produces SIVE in up to 90% of inoculated animals within 3 months (Mankowski et al. 2002). The rhesus model typically involves use of either SIVmac251 swarm (a dual macrophage- and T-cell line-tropic swarm) or SIVmac239 (a molecular T-cell line-tropic clone of SIVmac251), which induce SIVE in ~30% of inoculated animals in 2 years (Fuller et al. 2004; Lentz et al. 2008). These models have shown that SIV infection is associated with infection of perivascular macrophages, robust astrocytosis, multinucleated giant cell formation, infiltration of CD4+ and CD8+ T cells (CD4+ T cells predominate), and natural killer (NK) cells (Mankowski et al. 2002). An initial burst of SIV replication occurs within the CNS, followed by a period of relative quiescence, and subsequent reactivation of virus replication in the end stages of AIDS and SIVE. Furthermore, CSF/plasma ratios of CXCL2/MCP-1 are consistently higher throughout the course of infection in those animals eventually developing SIVE (Mankowski et al. 2002).

In the SIV-rhesus macaque model, similar to HIV infection in humans, entry into the brain is observed early after systemic virus inoculation (7 days for SIV entry) (Chakrabarti et al. 1991). Using calbindin as a neuronal marker specific for GABAergic neurons, and synaptophysin as a marker for presynaptic membranes, investigators showed that macaques sacrificed 14 days after infection sustained significant damage to GABAergic neuronal cell bodies and synapses in the frontal cortex (Gonzalez et al. 2000). Fragmentation and shrinkage of calbindin-immunoreactive neurons and loss of synaptophysin were even more prominent in macaques sacrificed 2 years after infection, indicating that damage to these neurons occurs early and probably throughout the chronic course of infection. In addition, reactive astrogliosis marked by enhanced GFAP expression was also noted early in infection and throughout the disease course, although at least one HIV study has shown that the degree of astrogliosis does not correlate with the presence or severity of neuronal damage (Masliah et al. 1992a).

Early neuronal damage detected by immunohistochemistry has been confirmed by brain magnetic resonance spectroscopy (MRS) analysis of the neuronal marker N-acetylaspartate (NAA) (commonly expressed as an NAA/creatine ratio; NAA/Cr) in the acute and chronic phases of infection in SIV-infected macaques (Fuller et al. 2004; Greco et al. 2004; Lentz et al. 2005; Lentz et al. 2008; Williams et al. 2005). In a macaque model involving CD8+ T lymphocyte depletion along with SIV inoculation, Williams et al. (2005) demonstrated a reduction in NAA/Cr in the

frontal cortex within 10 weeks of infection in animals developing SIV encephalitis (SIVE). Neuronal damage was confirmed by quantitative immunohistochemical studies that showed a significant loss of synaptophysin in the frontal cortex. There was a biphasic increase in the percentage of circulating CD14+ monocytes that co-expressed CD16 as well as the CD14lo/CD16hi monocyte subset, which occurred immediately (7–14 days) after infection and again prior to or with the onset of AIDS. The early monocyte increase occurred concomitantly with the initial decrease in NAA, and the CD14lo/CD16hi monocyte subset consistently harbored SIV proviral DNA. A follow up study by Lentz et al. (2008) also showed a decrease in both GABA/Cr and Glutamate/Cr ratios in SIV-infected macaques with and without SIVE, indicating injury to inhibitory and excitatory neurons, respectively. Other studies have shown that an increase in the myoinositol (MI)/Cr ratio (marker of astrocytic activation) often occurs prior to an NAA/Cr decrease (Greco et al. 2004), indicating an early CNS inflammatory response prior to neuronal injury. Interestingly, antiretroviral drug administration had a significant effect on the NAA/Cr decrement, which was at least partially reversible by administration of non-CNS penetrating antiretroviral drugs 28 days after infection, although whether this is associated with a recovery of synaptophysin expression is unclear. In all animals studied, no structural changes were detected by conventional Magnetic resonance imaging (MRI) at any time point. These studies suggest that MRS can detect early neuronal damage in SIV infection of the CNS, similar to studies in HIV-infected individuals, and that antiretroviral therapy that reduces systemic virus replication and monocyte activation in the circulation can attenuate neuronal damage. However, the effects of long-lived SIV replication within the CNS compartment are more difficult to address in these short-term studies.

Similarly, in HIV-infected individuals, several studies using brain MRS have demonstrated changes in brain metabolites occurring early in infection that correlate with worsening neurological function. Brain NAA/Cr ratios have been found to be significantly reduced in HAD patients, indicating neuronal loss (Chang et al. 1999a; Chang et al. 1999b; Chang et al. 2003; Meyerhoff et al. 1993; Tracey et al. 1996). Increases in glial-associated metabolites such as choline and myoinositol (which are elevated during gliosis or membrane turnover that occurs with glial activation) were more sensitive in detecting clinically milder disease early in infection (Chang et al. 1999a; Yiannoutsos et al. 2004)). Increases in choline and myoinositol reverted with response to HAART (Chang et al. 1999b), indicating that virus replication, both within and outside of the CNS, contribute to glial activation. HAART is able to partially reverse neurologic impairment in HAD, and HAART regimens that express higher CNS penetration are more effective in reducing cerebrospinal fluid (CSF) viral loads and improving neurological performance (Ances and Ellis 2007; Letendre et al. 2004; Marra et al. 2003). Together with the aforementioned macaque MRS studies, these studies suggest that suppression of virus replication within the peripheral circulation and CNS compartments are necessary for maximum protection against neuronal damage, probably by decreasing virus-induced glial cell activation and trafficking. They also suggest that macaque SIV models can be very useful for testing neuroprotection treatment approaches.

In both HIV infection and SIV infection elevations of CCL2 in the cerebrospinal fluid (CSF) tend to precede the development of signs of neurological dysfunction, consistent with a proposed role for CCL2 in promoting neurodegeneration through enhancement of monocyte trafficking and establishing a resident population of infected macrophages within the CNS (Zink et al. 2001) (Williams et al. 2001).

2.4 Mechanisms of HIV-Induced Neurodegeneration: Neurotoxicity of HIV Proteins

One of the predominant hypotheses of how infected microglia and macrophages can directly mediate neurotoxicity is by the release of viral proteins such as gp120 and Tat, which then bind to receptors on neurons (Brenneman et al. 1988; Mattson et al. 2005). Neurotoxicity resulting from exposure to recombinant gp120 has been confirmed in multiple in vitro model systems (Alirezaei et al. 2007; Bennett et al. 1995; Brenneman et al. 1988; Dawson et al. 1993; Dreyer et al. 1990; Dreyer et al. 1999; Lannuzel et al. 1995; Meucci and Miller 1996), although the mechanisms by which such toxicity is induced remain controversial (Bachis and Mocchetti 2004; Gonzalez-Scarano and Martin-Garcia 2005; Kaul et al. 2001). Using Scatchard analyses, Hesselgesser et al. (1998) demonstrated binding of gp120 (HIV IIIB strain) to human neuronal CXCR4 (kD = 54 nM), which was associated with induction of apoptosis.

Several other studies have indirectly addressed gp120/chemokine receptor interactions in neurotoxicity model systems. Zhang et al. (2003) demonstrated the ability of anti-gp120 antibodies and antibodies against CCR5 and CXCR4 to reduce (20–80%) gp120 toxicity in exposed, non-differentiated human neuronal cells. Meucci et al. (1998) showed that anti-gp120 (IIIB) antibodies reduced toxicity of recombinant gp120 by 45% in purified primary rat hippocampal neurons co-cultured with an astrocyte feeder layer. Zheng et al (Zheng et al. 1999a) examined the ability of virions from laboratory-passaged X4 HIV strains (MN, IIIB, Lai) and several R5 strains (JR-FL, Bal, ADA, DJV, MS-CSF) to induce apoptosis in human fetal neurons in mixed neuronal/glial cultures. Surprisingly, virions from each strain induced neuronal apoptosis (X4 virions more so than R5 virions) in a manner that was blocked by an anti-CXCR4 antibody. These and other similar studies suggest that complex interactions between gp120 and cellular surface binding moieties in cultured cells can lead to effects that may or may not be linked to gp120/chemokine receptor binding in neurons. In support of indirect effects of gp120 on neuronal survival, Kaul and Lipton (Kaul and Lipton 1999) provided evidence that gp120 neurotoxicity in primary rat neuronal cultures depends upon the presence of macrophages/microglia, through which gp120 can induce neurotoxin release after engaging chemokine receptors (and CD4) (reviewed in (Kaul et al. 2001)). Signaling initiated by gp120/macrophage chemokine receptor interactions is thought to result in activation of the p38 MAPK proapoptotic pathway, because pharmacologic inhibition of p38 MAPK can abrogate gp120-induced apoptosis (Kaul and Lipton 1999).

There are also reports of gp120 interacting directly with the N-methyl-D-aspartate receptor (NMDAR) in neurons and activating death pathways (Fontana et al. 1997; Gemignani et al. 2000; Pattarini et al. 1998; Pittaluga et al. 1996; Xin et al. 1999). These studies indicate that gp120 and peptide-fragments of gp120 are able to bind to NMDA receptors at the glycine-binding site (on the NR1 subunit) to activate the receptor and induce release of neuropeptides or neurotransmitters. However, it is not clear whether such gp120 effects are associated with neurotoxicity (Gemignani et al. 2000). It thus seems likely that selected recombinant gp120 proteins can induce neurotoxicity by several mechanisms: direct toxic effects mediated by interactions with neuronal receptors and indirect effects mediated through interactions with glial cells.

In addition to gp120, the HIV-1 transactivating protein, Tat, is thought to be released by virus producing cells either during lysis or by active secretion (Chang et al. 1997; Ensoli et al. 1993). Similar to addition of gp120, addition of recombinant Tat protein to neuronal cultures can induce neuronal apoptosis (Kruman et al. 1998; Magnuson et al. 1995; Nath et al. 1996; New et al. 1998). Tat, (86–104 amino-acids in length in its naturally occuring two-exon form; 72 amino acids in length in the laboratory-adapted IIIB strain (one exon), has been shown to be released from HIV-infected T lymphocytic cell lines, and it can be detected in the serum of a minority of HIV-infected individuals (Ensoli et al. 1990; Westendorp et al. 1995). In our review of the literature, we found no clear evidence of the release of Tat by HIV-infected primary macrophages in vitro. A study by Tardieu et al. (1992) demonstrated Tat immunoreactivity in the human U937 monocytic cell line after infection with HIV-1 in co-cultures with primary human neuronal/glial cell populations. Although release of Tat from the infected U937 cells was not demonstrated, immunhistochemical labeling demonstrated Tat and gp120 expression associated with the extension of necrosis in neurons and astrocytes, which suggested the possibility of release of both Tat and gp120 by the infected U937 cells. In other studies, Tat transcripts and Tat protein have been identified in the brains of patients with HAD or those with HIV encephalitis (Hudson et al. 2000; Nath et al. 2000; Wesselingh et al. 1993; Wiley et al. 1996).

Soluble Tat protein has been shown to bind via its basic region (located at amino acid position 48–57) to heparan sulfate proteoglycans on cell surfaces or in extracellular matrix, where it is protected from degradation (Chang et al. 1997). Binding to heparin or heparinase results in the release of Tat from the extracellular matrix and allows it to bind to integrins (Barillari et al. 1993). Tat can also bind to the low density lipoprotein receptor-related protein (LRP) on neurons (Chang et al. 1997; Eugenin et al. 2007; Evans et al. 2007; Liu et al. 2000), and such binding prevents LPR-mediated clearance of its natural ligands, which include amyloid precursor protein, amyloid beta protein, apolipoprotein E4, and alpha-2-macroglobulin. The accumulation of these natural ligands in the extracellular space of the brain has been shown in other neurodegenerative diseases, which suggests a possible mechanism by which Tat could induce extracellular protein deposition in the brain.

Although Tat may directly interact with receptors on neurons, the major pathway for Tat-mediated neurotoxicity in vitro is thought to occur through a direct interaction

with neuronal membranes, resulting in depolarization (Nath 2002). By causing an initial release of calcium from intracellular IP_3 sensitive pools, Tat can activate non-NMDA-glutamate and NMDA receptors and induce calcium influx into neurons (Haughey et al. 1999; Kruman et al. 1998; Li et al. 2004; Magnuson et al. 1995). Tat-induced disruption of calcium homeostasis can result in the production of reactive oxygen species (ROS), leading to oxidative stress, mitochondrial dysfunction and apoptosis (Mattson et al. 2005). Thus, as for gp120, there are multiple mechanisms by which Tat could potentially induce neurotoxicity, although nearly all of the published studies have focused on direct effects on neurons. Nonetheless, indirect neuromodulating effects of Tat could be mediated through Tat modulation of glial cell cytokine and chemokine production (induction of CCL2, CXCL8, CXCL10, CCL3, CCL4 and CCL5), inhibition of astrocyte glutamate scavenging, and disruption of the blood–brain barrier (reviewed in King et al. (2006)). The ability of recombinant Tat to induce expression of multiple chemokines from glia suggests a mechanism by which HIV replication in the CNS (with release of Tat) could modulate multiple steps in neurodegeneration through effector functions of induced chemokines (monocyte transendothelial migration, glial cell activation, and direct neurotoxicity).

2.5 Mechanisms of HIV-Induced Neurodegeneration: Roles for Chemokines and Chemokine Receptors

Chemokines and chemokine receptors expressed within the CNS have central roles in HIV neuropathogenesis, from the function of chemokine receptors in mediating infection in the macrophage/microglial reservoir (Collman and Yi 1999; Doms 2000; Martin-Garcia et al. 2002) to other possible pathogenic effects of chemokine receptor-mediated signaling activation in neurons and glia, which are supported by a rapidly growing body of published studies. Studies of cerebrospinal fluid (CSF) in cohorts of HAND patients have revealed significant elevations of CCL2/MCP-1 and CXCL10/IP-10 (Cinque et al. 2005; Kelder et al. 1998; Mankowski et al. 2004) and elevated levels of CCL2 in SIV infected macaques that develop SIVE (Zink et al. 2001). Because neurons express multiple chemokine receptors (Coughlan et al. 2000; Horuk et al. 1997; Lavi et al. 1997; Meucci et al. 2000; Miller and Meucci 1999; Rottman et al. 1997), they are potentially functionally altered by exposure to induced chemokines during HIV/SIV infection. Alpha chemokines, which bind CXCR chemokine receptors, are normally expressed in all major cell types in the brain (macrophages/microglia, astrocytes, neurons, endothelial cells) and, upon binding to their cognate receptor, they induce signaling through a G_i protein-dependent decrease in cyclic AMP and an increase in intracellular calcium. Among those found at elevated levels in the brain or CSF of individuals with HAD are CXCL12/SDF-1 alpha and CXCL10 (Rostasy et al. 2003) (Cinque et al. 2005). On the other hand, beta chemokines (which bind CCR receptors) are expressed at relatively low levels under physiological conditions in the normal brain. CXCL12/

SDF-1 alpha, an alpha chemokine that binds CXCR4, is produced by macrophages, astrocytes, and neurons in the brain, and an increase in CXCL12 transcripts has been found in the brain tissue of individuals with HIV encephalitis (Zhang et al. 1998). Signaling in neurons via CXCL12 exposure has been shown to produce either neuroprotective or neurotoxic responses, depending upon the experimental conditions (Kaul and Lipton 1999; Khan et al. 2008; Zheng et al. 1999b). It has been shown to enhance synaptic transmission, induce AKT/protein kinase B, or activate caspase-3 under different conditions (Kaul and Lipton 1999; Zheng et al. 1999b). CXCL12 can undergo proteolytic cleavage by matrix metallic proteinases (specifically MMP-2) (McQuibban et al. 2001), which changes its coreceptor specificity from CXCR4 to CXCR3 and also enhances its neurotoxicity (Zhang et al. 2003) (Vergote et al. 2006). Activation of CXCR3 in neurons by its natural ligand CXCL10 results in elevations in intracellular calcium and activation of caspase-3 leading to neuronal apoptosis (Sui et al. 2004; Sui et al. 2006).

CNS beta chemokine expression is also altered in HIV infection and these chemokines may also result in a protective or a destructive milieu (Schmidtmayerova et al. 1996). Among the beta chemokines that are expressed at increased levels during HIV infection of the CNS are CCL2, MIP-1 alpha, MIP-1 beta, and RANTES/CCL5 (Kelder et al. 1998), although the association of MIP-1 alpha, MIP-1 beta and CCL5 with HAND is unclear (Letendre et al. 1999). In vitro studies show that MIP-1 alpha/beta can protect hippocampal neurons from gp120-induced apoptosis (Kaul and Lipton 1999; Meucci et al. 1998). CCL5 also protects neurons against gp120-induced damage, although CCL2 does not (Meucci et al. 1998). In contrast, the beta chemokine CCL2 appears to have a detrimental effect in CNS infection. Elevated CSF CCL2 expression is associated with an increased risk of HAND (Kelder et al. 1998; Ragin et al. 2006; Sevigny et al. 2004; Sevigny et al. 2007). This increased risk might reflect CCL2's role as a potent monocyte chemoattractant in the CNS (Gonzalez et al. 2002; Monteiro de Almeida et al. 2006). Its expression induced in microglia activated by interferons and in astrocytes activated by IL-1beta and TNF-alpha (Andjelkovic et al. 2000; McManus et al. 2000). Of interest, it has been suggested that the neuroprotective effects of RANTES are mediated by the induction of CCL2 (Eugenin et al. 2003). Collectively, these results suggest that the fluctuations in the ambient chemokine concentrations within the brain during the course of HIV infection have varied effects in neurons, both temporally and regionally, depending upon the local neuronal subpopulations that are exposed to activated/infected glia.

Finally, the unique chemokine, fractalkine/CX3CL1, which belongs to the Cx3C chemokine family, is also elevated in the CSF of individuals with HAND (Pereira et al. 2001). The tethering of CX3CL1 to EC cells in the brain can mediate monocyte attachment, which could promote transendothelial migration of monocytes to the CNS, suggesting a role in enhancing HIV neuropathogenesis (Ancuta et al. 2003; Geissmann et al. 2003; Maslin et al. 2005). However, several studies have demonstrated a neuroprotective function of CXCL1 against neuronal excitotoxicity (Deiva et al. 2004; Limatola et al. 2005; Mizuno et al. 2003). Thus, as for alpha and beta chemokines, CXCL3 could play a role in both neuroprotective and neurotoxic cascades induced by HIV replication in the CNS.

2.6   Mechanisms of HIV-Induced Neurodegeneration: Roles for Excitotoxins and N-Methyl-D-Aspartate Receptors

In addition to the enhanced expression of chemokines, enhanced expression of other potential neurotoxic factors such as excitatory amino acids, which include glutamate, quinolinic acid (QUIN), cysteine, and the amine N-Tox is associated with macrophage/microglia activation (Brew et al. 1995; Giulian et al. 1990; Giulian et al. 1993; Giulian et al. 1996; Yeh et al. 2000). Glutamate, which is the major excitatory neurotransmitter in the CNS, has been reported to be elevated in the CSF of HIV-infected individuals (Ferrarese et al. 2001), although this has been disputed (Espey et al. 2002; Espey et al. 1999). Because the concentration of glutamate in the synaptic cleft must be kept within a physiological range to avoid sustained toxic activation of neuronal glutamate receptors and excessive calcium influx (excitotoxicity) (Hyrc et al. 1997; Rothman 1984), altered glutamate homeostasis is thought to be a major pathway of neurodegeneration in inflammatory brain diseases such as HIV infection (Kaul et al. 2001). Glutamate, QUIN, and N-Tox are all released (to varying levels) by HIV infected macrophages, and each of these has the potential to induce excitotoxicity through N-methyl-D-aspartate (NMDA) receptor activation (Giulian et al. 1990; Jiang et al. 2001; O'Donnell et al. 2006). Therefore, the distribution and function of NMDAR within CNS neuronal populations is likely a major determinant of neuronal vulnerability to HIV-induced damage.

The NMDAR, a subtype of glutamate receptor, is a voltage and ligand-gated calcium ion channel that generates excitatory postsynaptic currents through calcium influx into the neuron. Functional NMDAR are heteromeric assemblies of four subunits of at least 2 types: two NMDA-R1 (or NR1) subunits and two NMDA-R2 (or NR2) subunits. The subunit composition of NMDAR varies throughout neuronal development, and, to some degree, within different brain regions (Lynch and Guttmann 2001; Lynch and Guttmann 2002). The 8 variants of NR1 are derived from 1 gene via alternative splicing (Goebel et al. 2005) whereas 4 separate genes encode NR2 subunits (NR2A, NR2B, NR2C, and NR2D). Two variants of subtype NR3 also exist but their expression is not required for a functional NMDAR. NR1 subunits bind glycine, and NR2 subunits bind glutamate and quinolinic acid. The different NR2 subunits have different pharmacologic and biophysical properties and thus variations in the type of NR2 subunit can confer distinct properties to the receptor (Lynch and Guttmann 2001; Lynch and Guttmann 2002). For example, quinolinic acid activates NR2A- and NR2B-containing receptors but not those containing NR2C or NR2D. Furthermore, although all four NR2 subunits can bind glutamate with equal affinity, NR2A and NR2B trigger greater excitotoxicity than NR2C and NR2D. NR2 subtypes also have different specificities for pharmacologic inhibitors, which have been effectively used to distinguish which NR subunits are responsible for functional responses in NMDAR.

The distribution of NMDAR subtypes offers one explanation for regional brain vulnerability to HIV-associated injury. Neonatal brain predominantly expresses

NR2A, NR2B, and NR2D subunits and, in some regions, NR2C, over the course of development (Monyer et al. 1994). In the adult rat brain, NR2A is ubiquitously expressed, whereas NR2B is restricted to the forebrain, and NR2C is largely restricted to the cerebellum (Kohr 2006). Notably, regions such as the hippocampus, striatum, and forebrain, which have high expression of NR2B, are often the areas demonstrating neuronal death in HIV infection whereas areas such as the cerebellum with NR2C expression are relatively spared (Archibald et al. 2004; Conti et al. 1999; Everall et al. 1999). This suggests a role of specific NR2 subtypes in HIV-mediated neuronal excitotoxicity.

Our group examined the role of NMDAR subtypes in determining susceptibility to HIV-induced neurotoxicity and found that neurons become vulnerable to injury from exposure to HIV-infected macrophages only after establishing functional NMDAR expression (O'Donnell et al. 2006). We established an in vitro model utilizing embryonic rat hippocampal neuronal cultures exposed to supernatants from HIV-infected macrophages and we found that neuronal death occurred only with the appearance of NR2A and NR2B subtypes as the neurons matured. As shown previously by others (Giulian et al. 1996; Jiang et al. 2001), we confirmed that the neurotoxic factor(s) released from the infected macrophages are of low molecular weight (<3 kD), and are heat- and protease-resistant excitotoxins that act through NMDAR. Furthermore, blockade of neurotoxicity at different neuronal developmental stages could be achieved using antagonists to specific NMDAR subunits (to either NR2A or NR2B) and this protection was consistent with the NR subtype expression profile of the cultured neurons. For example, inhibitors specific for NR2B/NR2B homodimers (Ifenprodil and Ro25-6981) were most effective earlier in the maturation process when NR2A was not heavily expressed. Neuronal protection in more mature cultures (with increased expression of NR2A and NR2B) required use of inhibitors that blocked both NR2B/NR2B homomeric receptors and NR2A/NR2B heteromeric receptors.

In addition to glutamate, other amines released by activated macrophages that act at the NMDAR, such as quinolinic acid (QUIN), may also contribute to excitotoxity in HIV infection. Like glutamate, QUIN levels are shown to be elevated in CSF and brain parenchyma of HIV-infected patients and those with other CNS infections (Heyes et al. 1991; Heyes et al. 2001) (Achim et al. 1993). The accumulation of these excitatory amines points to malfunctioning glia cells since microglia are predominate producers of QUIN while both microglia and astrocytes regulate extracellular glutamate levels. QUIN and glutamate are metabolically processed by microglia and astrocytes and inflammatory mediators can alter the normal processing of these amines resulting in their accumulation in the extracellular space. QUIN is produced via the kynurenine pathway from the substrate L-tryptophan, and the key regulatory enzyme in this pathway, idoleamine 2, 3-dioxygenase (IDO), is upregulated in inflammatory states by cytokines such as IFN-gamma. In the brain, IDO is expressed by microglia, astrocytes, endothelial cells, and neurons. Macrophages/microglia are key QUIN producers because they express all enzymes of the pathway leading to QUIN production, whereas astrocytes predominantly have enzymes that shift production away from QUIN to other metabolites such as

kynurenic acid, an antagonist of QUIN, and kynurenine (Guillemin et al. 1999) (Heyes 1996). Bruce Brew and colleagues have proposed a model of QUIN metabolism in the brain where astrocytes play a neuroprotective role by minimizing production of QUIN (Guillemin et al. 2001; Guillemin et al. 2005). Thus, interactions between astrocytes and macrophages/microglia likely regulate extracellular QUIN concentrations, which, like glutamate, directly induce neuronal cell responses through NMDAR during HIV infection.

Although it is as yet unclear whether chemokines have a direct effect on glutamate or QUIN metabolism, NMDAR expression, or NMDAR function, several studies have demonstrated that NMDAR-dependent excitotoxic neuronal injury results in a rapid and robust increase in CCL2 expression, in rat brain, and peripheral nerve (Galasso et al. 2000) (Kleinschnitz et al. 2004). A concomitant increase in CCR2 expression also occurs, suggesting a mechanism for recruitment of monocyte/macrophages to areas of exicitotoxic injury, such as that seen in HIV infection. Along these lines, QUIN also up-regulates chemokine (CCL2, CXCL12, CCR5, CXCL8) and chemokine receptor expression (CXCR3, CCR5, CCR3) in astrocytes (Croitoru-Lamoury et al. 2003). This also supports the hypothesis that excitotoxic injury induced by HIV promotes activation of multiple chemokine-mediated pathways that promote either further injury or that initiate protective responses to such injury. Further studies of the ability of chemokines and NMDAR ligands (glutamate, QUIN) expressed within the CNS to cross-modulate each other's receptor expression and function could yield novel information about how chemokines influence the progression of excitotoxic injury in HAND and other neurodegenerative diseases.

The potential for NMDAR antagonists to protect the CNS against HAND has recently been investigated in a multicenter therapeutic trial (ACTG) of Namenda (memantine), which is currently FDA-approved for use in Alzheimer's disease (Schifitto et al. 2007). Although no clinically beneficial effect in neuropsychological test performance was observed during the 16-week treatment phase, there was a significant increase in the NAA/Cr ratio in the frontal white matter and parietal cortex in treated individuals, suggesting a potential neuroprotective effect. Further investigations of agents that block pathways (e.g., oxidative stress, glutamate and QUIN production) to neuronal excitotoxic injury and therapeutic trial designs that include longer duration trials (6 months or greater) are likely to follow (Bandaru et al. 2007; Brew et al. 2007; Clifford 2008; Evans et al. 2007).

2.7 Other Links Between Chemokines and Excitotoxic Injury: Glutamate Release

Besides the clear role for chemokines in modulating recruitment of cells into the CNS in HIV infection, and the potential role for chemokines to directly modulate neuronal signaling, recent evidence has suggested a link between CNS chemokine expression and enhancement of excitotoxic injury through enhancement of glutamate

release. Bezzi et al. (2001) demonstrated that CXCL12 rapidly (seconds) induces the release of glutamate from astrocytes in rat hippocampal brain slices in a calcium-dependent manner. Detailed characterization of this release process revealed that it most likely occurs by inhibition of quantal-like glutamate exocytosis, which is independent of glutamate transporter (EAAT) reversal or osmotic damage, but which is dependent upon TNFa. Other studies have confirmed that CXCL12 can induce glutamate release in hypothalamic and substantia nigra neurons (Guyon and Nahon 2007; Guyon et al. 2006), and modulate neuronal GABA release (Guyon et al. 2006). These interesting studies are the first reports of a direct link between neuronal chemokine production and enhancement of glutamate-mediated excitotoxicity, and they clearly extend previous observations of neuronal toxicity mediated by direct chemokine/neuronal signaling by CXCL10 (Sui et al. 2004; Sui et al. 2006) and CXCL12 (Kaul and Lipton 1999; Vergote et al. 2006; Zheng et al. 1999a; Zheng et al. 1999b). Additional studies are needed to more thoroughly define the abilities of chemokines to alter neurotransmitter metabolism in the CNS to better understand the mechanisms by which chemokines can modulate excitotoxic injury in HAND.

2.8 Therapeutic Considerations

There is no doubt that HAART has changed the nature of HIV-infection and altered it from a uniformly fatal disease to a chronic, and often disabling, infection. Likewise, CNS manifestations of HIV-infection have also been modified by HAART. The severity of neurocognitive impairment has been lessened but not to a point where it has no impact on the quality of life, as even minor impairment can negatively affect survival. As systemic eradication of the virus is likely not possible in the near future, we are faced with addressing when and what types of therapies to initiate. The current guidelines for administering HAART recommend deferring therapy for asymptomatic patients until CD4 T+cell counts drop below 350. HAART is recommended for patients with symptoms or a history of an AIDS-defining illness (which includes HAD) and asymptomatic patients with CD4 T+ cell counts less than 200. These recommendations for deferred therapy are in contrast to early treatment recommendations to begin therapy soon after diagnosis. These newer recommendations take into consideration the increased likelihood of resistance with longer periods of unnecessary treatment, the negative side effects of HAART, many of which are not minor, offset with the longer life expectancy imparted by HAART. Because the virus enters into the CNS early in infection, this deferred therapy allows for virus replication in the CNS undoubtedly with concomitant neuronal damage that occurs with inflammation. It is unclear whether damage incurred during this period is a contributory reason/factor to why despite the HAART therapy, less severe HAND syndromes are still pervasive among those individuals receiving HAART. Perhaps there exists a threshold level of tolerable damage that may be reversible, and beyond this damage may result in neurological

symptoms. If so, is there a role for adjunctive neuroprotective agents (NMDAR antagonists, chemokine modulators, antioxidants, others) before or after initiation of HAART?

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