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## The Neuropathology of HIV/AIDS

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### Abstract

The introduction of Highly Active Anti-retroviral Therapy (HAART) has resulted in significant decreases in morbidity and mortality for subjects infected with HIV. The brain is a major target organ for HIV resulting in significant neuropathological changes in most HIV infected subjects and a wide range of clinical neurological symptoms including HIV associated dementia. In the pre-HAART era HIV associated dementia was a common complication of AIDS. However, since the introduction of HAART the incidence of HIV associated dementia has fallen, but the prevalence has actually risen due to the increasing number of infected subjects and increased life expectancy. HIV associated dementia correlates most closely with neuroinflammation rather than directly with viral load or HIV encephalitis. HIV related clinical and neuropathological disorders are more prevalent in drug abusers than in other risk groups. This review focuses on the shifting pathology observed in HIV infected subjects since the introduction of HAART, discussing the clinical manifestations of these and the influence of confounding factors such as drug abuse and Hepatitis C co-infection.

### Introduction

HIV emerged as a novel infection over 25 years ago. Early patients presented not only with systemic opportunistic infections but, very frequently, with a bewildering variety of neurological signs and symptoms pointing to involvement of the central nervous system (CNS). We now know that these dramatic disorders are only the end stage of what is at first an occult and largely asymptomatic infection. Before the development of highly effective antiretroviral therapy (HAART), infected individuals progressed almost inevitably from a pre-symptomatic stage lasting several years to the symptomatic and fatal end stages (AIDS). This review addresses some of the questions still posed by HIV infection of the brain.

### Which brain cells are infected by HIV?

The most likely route for brain invasion by HIV is across the blood-brain barrier (BBB) (Kaul, Garden, & Lipton, 2001) although the choroid plexus and CSF pathway may also be implicated (Petito, Roberts, Cantando, Rabinstein, & Duncan, 2001). The primary CNS cell types which are vulnerable to HIV infection are the parenchymal microglia and the perivascular microglia/macrophages. These monocyte lineage cells express the primary HIV receptor, CD4, albeit at a low level, together with a chemokine co-receptor CCR5 (Clapham & McKnight, 2001).

These two receptors are usually required for HIV entry to the cell. Microglia are the only indigenous CNS cell type to express both. Infection of microglia by HIV has two potential effects; firstly, production of new virions and viral proteins and secondly, induction of aberrant cytokine expression within the CNS (Anderson, Zink, Xiong, & Gendelman, 2002).

Apart from microglia, astrocytes are also a possible target but are thought to be capable of only a restricted form of HIV infection *in vivo* (Brack-Werner, 1999). The mechanism by which astrocyte infection occurs is unclear as these cells are not thought to express CD4, although they do express the chemokine receptors CCR5 and CXCR4. Regardless of whether astrocytes are infected or not, it is likely that these cells play a key role in the neuropathogenesis of HIV infection if their crucial functions in supporting neurones are disrupted. These functions include the production of neurotrophic cytokines and buffering of substances which are neurotoxic in high concentration such as glutamate. There have also been occasional reports of endothelial cells, oligodendrocytes and neurones being infected with HIV. However these reports have not been widely reproduced and the consensus opinion is that infection of these cell types is rare and unlikely to contribute significantly to HIV related CNS disorders. Given the lack of evidence for significant neuronal infection, it is assumed that neuronal damage and death in AIDS is an indirect

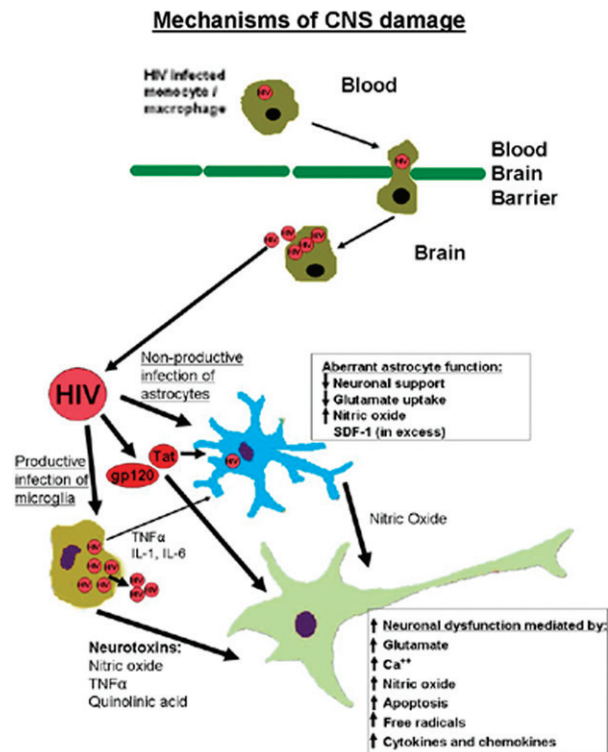


Figure 1. Basic mechanisms of CNS damage in HIV/AIDS.

result of HIV infection of other cells in the brain (Lipton, 1997). Figure 1 shows the major putative mechanisms for neuronal damage in HIV/AIDS.

### Does the brain show any pathology changes during pre-AIDS?

Examination of the brain during the pre-symptomatic phase of HIV infection has proved difficult because of the benign nature of this stage of the disease. Consequently, there are relatively few HIV related deaths before the onset of AIDS. Of the various routes of infection for HIV, which include sexual transmission, contaminated blood products and needle sharing between intravenous drug abusers, the last group has provided some opportunities for autopsy studies in the early stages of HIV because of deaths due to drug overdoses (Bell et al., 1993). It is important to note that there is an expanding literature on the neuropathological effects of drugs of abuse on the brain, and any findings in HIV positive drug abusers must be considered in the light of these findings.

The brains of pre-symptomatic HIV infected drug abusers show relatively minor changes in comparison with those seen in AIDS (Gray et al., 1996). There is no evidence at this stage of HIV encephalitis (HIVE), or of CNS opportunistic infections or lymphomas, all of which represent AIDS defining illnesses in their own right. However pre-symptomatic individuals are

likely to show a low grade lymphocytic leptomeningitis and perivascular lymphocytic cuffing particularly in the central white matter (Bell et al., 1993; Gray et al., 1996). The primary cell type found in these infiltrates is the CD8 positive lymphocyte but a significant proportion of CD20 positive B lymphocytes are also present (Anthony et al., 2003). There is also a proportionate increase in both T and B lymphocytes infiltrating the brain parenchyma. It has been suggested that these lymphoid cells may be responsible for controlling the initial viral infection in the CNS (McCrossan et al., 2006) although the role of B lymphocytes in this location is less well understood than that of CD8 cells.

Other phenomena reported in early infection include subtle gliosis and microglial activation which may represent part of an immune response to early CNS entry of the virus (An et al., 1996). Alternatively, activation of CNS microglia and astrocytes may simply be an indirect effect of the more vigorous systemic response to infection, due to systemically released cytokines. Evidence of mild axonal damage can sometimes be observed in the early stages of the disease (An et al., 1997). This is revealed by focal swellings and accumulation of normal axonal molecules such as  $\beta$  amyloid precursor protein ( $\beta$ APP) due to disrupted transport within the affected axon. Axonal damage can be caused by a number of insults including trauma, inflammation and hypoxia and is also seen in the brains of HIV negative drug abusers (Buttner, Rohrmoser, Mall, Penning, & Weis, 2006; Ramage et al., 2005).

In pre-symptomatic subjects there is no evidence of productive infection in any cell type. However, PCR studies have confirmed low levels of HIV in the brains of some pre-symptomatic subjects (Bell et al., 1993). While it is presumed that HIV is present in the microglial population based on analysis of recovered virus which is normally macrophage (CCR5) trophic, there is still no conclusive evidence as to which brain cells are harbouring the virus in the early stages of infection.

### What neuropathological differences were observed between pre-symptomatic and symptomatic subjects in the pre-HAART era?

As HIV infected subjects progress into symptomatic AIDS they become vulnerable to CNS complications which are reflected in conspicuous neuropathological changes observed at autopsy. The most significant of these are the emergence of HIVE, opportunistic infections and/or primary CNS lymphomas (Budka et al., 1987). These conditions may be found in

isolation or together but there is no convincing evidence to date of synergy between them.

The pathognomonic histological feature of HIVE is the presence of giant cells (Budka, 1986; Sharer & Kapila, 1985) together with immunopositivity for HIV antigens in microglia/macrophages, signalling the presence of productive viral infection (Budka, 1990; Budka, 1991). Infection is detected predominantly in the perivascular microglia/macrophages although parenchymal microglia are also frequently immunopositive (Lambotte, Deiva, & Tardieu, 2003). In the first 15 years of the AIDS epidemic HIVE was described in 20–50% of cases, with wide variation between cohorts, and reportedly more common in drug abusers than non-drug abusers (Bell et al., 1996; Martinez et al., 1995). Productive HIV infection induces activation of surrounding microglia which show increased expression of a variety of cell surface antigens including CD14, CD16, CD68 and MHC class II (Anderson, Zink, Xiong, & Gendelman, 2002; Fischer-Smith et al., 2004; Glass, Fedor, Wesselingh, & McArthur, 1995; Swindells, Zheng & Gendelman, 1999). In addition to the microglial activation there is also a prominent CD8 T lymphocytic response, although it is unclear how effective these cytotoxic T cells are in late stage AIDS when the immune system is severely disrupted by HIV. When comparing the pre-symptomatic phase of the disease with HIVE, the microglial activation is far more pronounced in the latter group. In HIVE the CD8 response shows less perivascular cuffing and a stronger focus in the parenchyma compared with the findings in pre-AIDS. Conspicuous astrocytic hyperplasia is commonly present in HIVE (Bell et al., 1996; Budka, 1990) often with macrophage-predominant inflammation and microglial nodules.

Other generalised findings in AIDS include myelin pallor (Gray & Lescs, 1993) and dendritic (Masliah et al., 1997), synaptic (Everall et al., 1999) and axonal (Giometto et al., 1997) damage. Damage to myelin likely results from the initial viral infection or may represent an indirect effect of the immune reaction to the virus. Axonal damage is highly variable between cases, ranging from a few focal deficits to widespread disruption in the central white matter (Budka, 1991) and in general is greater than that observed in the pre-symptomatic phase of the disease.

HIVE may be present in any area of the brain, particularly the basal ganglia and central white matter, but the neocortical grey matter and to a lesser extent the brainstem and cerebellum are sometimes involved. The severity of HIVE also varies from mildly affected cases in which only a few productively infected cells and/or giant cells are

seen, to very severe states with widespread inflammation and damage and numerous giant cells. These variations are likely to contribute to the observed range of clinical symptoms. There is no consensus on how the severity of HIVE should be graded.

In the early stages of the AIDS epidemic a variety of opportunistic infections were described in the CNS (Budka et al., 1987; Jellinger et al., 2000; Mamidi, DeSimone, & Pomerantz 2002). These infections usually manifest late in the disease process when the immune system is severely impaired and the CD4 count has fallen below 200 cells/ $\mu$ l. Common opportunistic infections seen in the brain in AIDS include those resulting from cryptococcus, cytomegalovirus (CMV), toxoplasma, herpes simplex virus, JC virus and Epstein Barr virus (EBV). Their prevalence varies somewhat in different settings depending on the population and geographic exposure risk. Many of these agents commonly infect healthy humans but rarely cause disease in immune competent individuals. For instance JC virus is estimated to infect 90% while EBV is thought to infect 95% of the population. In autopsies on AIDS subjects, cryptococcal meningitis is observed in around 10%, CMV in around 9% and toxoplasmosis in 4%. JC virus is the aetiological agent responsible for progressive multifocal leukoencephalopathy (PML) which affects around 4% of subjects with AIDS. In the setting of HIV induced immunosuppression JC virus infects and destroys oligodendrocytes, the cells responsible for myelination of axons in the CNS. This may be a result of re-activation of the virus due to immunosuppression or alternatively the virus may be re-activated by HIV gene products, such as Tat, which may be able to trans-activate the JC viral promoter directly (Tada et al., 1990). PML manifests itself as demyelinating lesions which may be necrotic and which are associated with inclusion-bearing oligodendrocytes and enlarged, often bizarre astrocytes. Infection with cryptococcus gives rise to a gelatinous exudate in the subarachnoid space, made up of macrophages containing the organisms. If cryptococcal brain invasion has also occurred, the pathology is predominantly located in the basal ganglia which, on naked eye examination, are pitted with small cystic spaces. On microscopy, accumulations of infected macrophages are noted in the perivascular compartments and within the parenchyma. Cytomegalovirus infection of the central nervous system is a complication of infection elsewhere in the body, often involving the adrenal glands and the eyes. CMV is promiscuous in its cellular infective targets and viral particles may be identified in endothelial cells, in neurons and glial cells. Typically, the infected cell shows enlargement of the nucleus and/or the cytoplasm and viral inclusions may be identified in both. Two major forms of CMV encephalitis are described. These take the form of a

microglial nodular encephalitis in which CMV inclusions may be quite hard to find. The other form is necrotising and CMV inclusion bearing cells are found relatively frequently in association with polymorph infiltration and foci of necrosis. Toxoplasma may give rise to a similar necrotising encephalitis, particularly in the periventricular regions and the acute inflammatory exudate may spread to involve the ventricular cavities. Toxoplasma is a protozoan which can exist in the brain parenchyma as numerous free organisms or as characteristic encysted forms containing numerous organisms. Both CMV and toxoplasma are immunodetectable with specific antibodies.

EBV is the aetiological agent driving proliferation of B lymphocytes and eventual neoplastic transformation (MacMahon et al., 1992). PCNSL is found in 5–10% of AIDS cases at autopsy and EBV is ubiquitously present in these high grade B cell tumours (Auperin et al., 1994; Jellinger & Paulus, 1995). In nearly all instances there is expression of two key EBV oncogenes LMP-1 and EBNA-2. Expression of LMP-1 leads to upregulation of anti-apoptotic genes such as BCL-2 in the infected B lymphocyte, while EBNA-2 is responsible for driving the infected cell into S-phase of the cell cycle (Jayachandra et al., 1999; Rowe et al., 1994). The expression of these two proteins plays a key role in the immortalisation of B lymphocytes. In most instances analysis of B lymphocyte immunoglobulin receptors shows that when these tumours occur in AIDS they are monoclonal, resulting from the outgrowth of just one infected cell. PCNSL display a predominantly perivascular distribution and can be found in almost any location in the brain including the brain stem and spinal cord.

In most subjects with CNS opportunistic infections microglial activation and focal infiltrates of CD8 lymphocytes are present particularly in the vicinity of focal pathology.

In some AIDS patients, even at advanced stages of immunosuppression, there is little evidence of significant CNS disease and HIV related disorders may not be evident in the brain at autopsy. However the brain is rarely entirely normal and at least minor, non-specific neuropathological changes are present in the vast majority of subjects with AIDS. Typical findings in these cases are mild activation of microglia above the level observed in the pre-symptomatic phase of the disease but generally not to the extent observed in HIVE or focally where opportunistic infections are present. In contrast to pre-symptomatic subjects, AIDS cases with no overt CNS pathology show minimal lymphocyte infiltration and those cells that are present are almost exclusively CD8 T lymphocytes with virtually no B lymphocytes present (Anthony et al., 2003).

### **How does the observed neuropathology correlate with psychiatric disease such as HIV-associated dementia?**

The clinical manifestations of CNS disorder in HIV/AIDS include depression and all degrees of cognitive impairment up to HIV associated dementia (HAD). Symptoms and signs of HAD include tremor, gait ataxia, loss of fine motor movement, mental slowing, forgetfulness, poor concentration and behavioural abnormalities. This subcortical dementia affects 10–20% of infected subjects. Other significant complications include peripheral neuropathies and long tract signs (Shepherd et al., 1999). The exact causes of HAD are not clearly established (Anderson et al., 2002; McArthur et al., 1997). Although recent papers have reported finding HIV DNA in neurons (Trillo-Pazos et al., 2003), the consensus is that neuronal infection is not a significant factor in the pathogenesis of AIDS dementia.

The presence of HIVE shows a degree of correlation with HAD, but this is not an absolute association. The best correlate of AIDS dementia is reportedly not viral replication or viral load but rather the degree of monocyte infiltration and the level of microglial activation in the brain (Glass et al., 1995). Both infected and non-infected activated microglia have been suggested as pathogenic factors in the development of HAD. There is a range of mechanisms through which microglia may induce neuronal damage including the release of potentially neurotoxic levels of oxidative radicals, nitric oxide and/or the cytokines TNF $\alpha$  and IL-1 (Anderson et al., 2002; Bukrinsky et al., 1995; Merrill, & Chen, 1991; Stanley et al., 1994). Aberrant cytokine release can also affect astrocyte function leading to a loss of glutamate buffering and subsequent neurotoxicity (Anderson et al., 2002).

Microglial activation and infiltration of monocytes into the CNS have been widely purported to be the driving force behind the development of HAD (Gartner, 2000). The mechanisms involved in recruitment of monocytes and activation of microglia in HAD are still unclear. The most obvious explanation is that this is a response to viral production in the CNS but evidence of productive infection is not always present in subjects with HAD and there are occasional cases with evidence of HIVE at autopsy who had no clinical history of dementia (Bell, Brettle, Chiswick, & Simmonds, 1998; Bell et al., 1996). These anomalies undermine the notion of a simple link between viral presence in the brain and the disturbance of higher functions.

Neuroimaging of HAD patients reveals generalized white matter reduction, with additional grey matter loss particularly in the basal ganglia and

posterior cortex (Aylward et al., 1995; Aylward et al., 1993). These findings fit with the general neuropathological findings in these cases. Neuronal loss has been described in HAD and apoptotic cells are commonly found in the basal ganglia and to a lesser extent in other regions of the brain including the hippocampus and frontal cortex (Everall, Luthert, Lantos 1991; Everall, Luthert, Lantos 1993).

The original proposals to explain the pathogenesis of HAD centred on the 'Trojan horse' model. This suggested that the virus entered the brain early in infection carried by infiltrating immune cells, either T lymphocytes or macrophages. The virus then set up a latent infection in the resident microglia cells and remained dormant in the brain until the later stages of the disease when CD4 T cell counts fell and the immune system failed leading to viral production and associated brain damage. There are several problems with this model. While there is evidence of HIV DNA in the brains of pre-symptomatic subjects, the viral load is generally extremely low and productive infection is never observed, raising questions as to how well seeded the brain becomes in the early phase of the disease. Secondly, not all subjects with clinical dementia have evidence of productive infection at autopsy. This suggests that while HIVE may contribute to the development of HAD, it is neither necessary nor probably sufficient to cause HAD. Recently a new model for the pathogenesis of HAD has been proposed which suggests that the critical events in the pathogenesis of HAD actually occur outside the CNS. The model suggests that aberrant cytokine production in late stage AIDS results in increased macrophage colony stimulating factor (M-CSF) production in the bone marrow (Gartner, 2000). Increased M-CSF results in altered monocyte production within the bone marrow with an increase in the proportion of CD14 + CD16 + monocytes produced. In healthy individuals this phenotype forms approximately 6% of total monocytes. However, in late stage AIDS this increases to around 16% and in AIDS subjects with dementia it is increased further to 37%. These cells exhibit features of tissue macrophages, are more phagocytic than CD14 + CD16- cells, express higher levels of tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1 and major histocompatibility complex (MHC) class II antigens (Thieblemont, Weiss, Sadeghi, Estcourt, & Haeffner-Cavaillon, 1995) and are perceived to be highly neuroinvasive. It is suggested that an influx of these cells into the CNS late in AIDS may cause the damage associated with HAD. It may be that these cells also carry virus into the brain causing re-seeding before the onset of HIVE, but the most likely cause of damage is through the induction of neuroinflammation. There is some neuropathological evidence to support this model.

Fischer-Smith et al., 2001, have reported an increase of CD14 + CD16+ monocytes in the brains of AIDS subjects with HIVE and dementia. It is suggested that these CD14 + CD16+ monocytes have recently entered the brain from the blood; this assumption is based on the expression of both CD14 and CD45 by these cells. CD14 and CD45 are normally detected by standard immunohistochemistry only on perivascular macrophages and not on resident microglia. This implies that any observed increase in these cells results from an influx from the blood across the BBB. Further evidence to support this concept comes from the absence of significant cell proliferation amongst cells of this phenotype in HAD. However, other studies have shown that the use of signal amplification techniques reveals low level antigen expression of CD14, CD16 and CD45 on resident parenchymal microglia, not only in HAD but also in control brains. These findings suggest that resident cells may simply upregulate expression of these particular cell surface markers in response to certain stimuli rather than CD14/16/45 positivity representing only recently imported cells. Microglia *in vitro* show the same phenomenon, which is unsurprising in that both microglia and macrophages originate from the same bone marrow progenitor cell lineage. If upregulation of CD14 and CD45 does occur on resident cells then this may inflate estimates of the influx of monocyte/macrophages in HAD. The most probable explanation is that some influx does occur and that this then stimulates resident cells, driving phenotypic and morphological change.

#### **What is the influence of confounding factors such as drug abuse and the hepatitis viruses on the neuropathology of HIV infection?**

The interpretation of HIV related neuropathology is rendered difficult by a number of factors. The presence of opportunistic infections and associated conditions such as CNS lymphoma is discussed above. Other potentially confounding factors relate to the mode of viral acquisition. Many infected subjects are also co-infected with other blood-borne viruses, commonly hepatitis B and C. As these viruses share the same mode of transmission, blood to blood and sexual, it is unsurprising that they are prevalent in the HIV positive population. In the early years of the pandemic hepatitis B was more common in many cohorts. However, in recent years hepatitis B has been overtaken by hepatitis C (Khalsa, Kresina, Sherman, & Vocci, 2005). Both viruses may induce liver damage leading to hepatic encephalopathy. This condition is manifested by a change in astrocytic morphology, particularly in the basal ganglia and brain stem nuclei. The affected astrocytes show nuclear enlargement and clearing but no great

increase in glial cell-specific staining. These changes are accompanied by failure of glutamate homeostasis and accumulation of ammonia, resulting in cognitive dysfunction.

The exact contribution of hepatitis C to HIV related CNS disorders remains to be fully elucidated. Hepatitis C has been linked directly with cognitive decline and CNS disturbances both in HIV infected and uninfected subjects (Forton et al., 2001; Thomas, 2002). In HIV infected subjects it has been reported that those co-infected with hepatitis C perform worse neurocognitively than those infected with HIV only (Ryan, Morgello, Isaacs, Naseer, & Gerits, 2004). The differences in cognitive functioning were associated with positive serology but did not correlate with indices of the severity of liver disease. The HCV+ patients were also more likely to be diagnosed with HIV associated dementia (Ryan et al., 2004).

Patients with hepatitis C virus infection frequently complain of symptoms akin to chronic fatigue syndrome. Using proton magnetic resonance spectroscopy, Fortan et al. (2001) have shown elevations in basal ganglia and white matter of choline/creatine ratios in patients with histologically mild hepatitis C, compared with healthy volunteers and patients with hepatitis B. This elevation is unrelated to hepatic encephalopathy or to a history of intravenous drug abuse, and suggests that a biological process underlies the extrahepatic symptoms in chronic hepatitis C infection.

The influence of concurrent drug abuse in AIDS is important, as drug abusers are reported to have higher rates of both HIVE and HAD compared to infected non-drug abusers (Bell et al., 1996; Chiesi et al., 1996; Goodkin et al., 1998; Martinez et al., 1995; Nath, Maragos, Avison, Schmitt, & Berger, 2001). Neuropathologically drug abusers tend to show greater levels of neuroinflammation in the form of microglial activation, astrocytosis and CD8 lymphocytic infiltration (Anthony, Ramage, Carnie, Simmonds, & Bell 2005; Tomlinson, Simmonds, Busuttill, Chiswick, & Bell, 1999). Axonal damage is also associated with drug abuse, particularly opiates (Buttner et al., 2006; Ramage et al., 2005). This may be due to respiratory depression induced by opiates, often leading to episodes of hypoxia. In this respect drug abusers may be more at risk than non-drug abusers infected with HIV.

### **How has the introduction of HAART influenced the neuropathology of HIV?**

The introduction of HAART in 1996/97 in most developed countries has had a profound impact on HIV disease, both in terms of the clinical course of the disease and the neuropathology.

The combination of two or more classes of antiretroviral drugs is highly effective in suppressing viral production allowing for at least partial recovery of the immune system to an effective and functional level. The benefits of this immune recovery are apparent in the significantly reduced morbidity and mortality. The improved immune system protects against the previously common and fatal opportunistic infections. Since the introduction of HAART the incidence of most CNS opportunistic infections has fallen. Data from the Edinburgh cohort has shown a 50% decrease in the incidence of CMV in the CNS at autopsy, 68% decrease in HIVE and an eradication of toxoplasmosis, although the incidence of both PML and lymphoma has actually risen slightly, findings which are reflected in other post-HAART studies (Anthony & Bell, 2005; Gray & Keohane, 2003; Langford, Letendre, Larrea & Masliah, 2003; Maschke et al., 2000; Masliah, De Teresa, Mallory, & Hansen, 2000). The incidence of HAD has decreased in most cohorts, though paradoxically the prevalence has risen as a result of increased life expectancy in treated subjects.

HAART is not a cure for HIV and the virus persists in sanctuary sites within the body, even in well treated individuals. The brain is proposed to be one of the key sanctuary sites for HIV due to limited immune surveillance and the presence of HIV permissive, long lived microglial cells. Failure to clear the virus completely from the body has obvious consequences for patients. Drug resistant strains of the virus may evolve causing treatment complications. In addition the cocktail of drugs used in HAART has toxic side effects. If these cannot be tolerated long term the viral load rises resulting in disease progression.

The success of HAART therapy has limited the opportunities for re-evaluating neuropathological findings in this new phase of the epidemic. The number of fatalities among well treated subjects on HAART is relatively limited and generally confined to subjects who have died from causes not directly related to HIV, such as drug overdoses or liver failure due to co-infection with hepatitis B or C. Neuropathological studies in such cases reveal ongoing neuroinflammation and increased presence of neurodegenerative proteins, even in the absence of productive HIV infection and of opportunistic conditions.

Neuroinflammation has long been recognised as a common pathological finding in HIV positive individuals and has been linked with CNS dysfunction (Anderson et al., 2002; Glass et al., 1995). In the pre-HAART era the severity of neuroinflammation generally increased as subjects moved from the pre-symptomatic phase of disease into symptomatic AIDS. It might be assumed that because HAART

effectively arrests infected subjects in the pre-symptomatic phase of the disease, the CNS of such subjects would also mirror findings in pre-HAART pre-symptomatic subjects. This is patently not the case. The level of neuroinflammation, in the form of microglial activation, is unexpectedly high and actually resembles that seen in subjects in AIDS or even in HIVE. Interestingly these studies reveal that the major site of inflammation appears to have shifted, from the basal ganglia pre-HAART to the hippocampus and surrounding entorhinal and temporal cortex post-HAART. This finding may well correlate with clinical observations in HAART treated subjects. Reports by Brew and Cysique et al., utilising PET scans and neurocognitive assessment, suggest an increasing involvement of the hippocampus in cognitive dysfunction in HAART treated subjects (Brew, 2004; Cysique, Maruff, Brew 2004), which contrasts with earlier reports in the pre-HAART era which linked HAD to basal ganglia dysfunction (i.e. a subcortical dementia). While there is evidence of significant microglial activation, lymphocytic infiltration in general is less marked. The perivascular lymphocytic cuffing associated in pre-symptomatic subjects in the pre-HAART era is not commonly observed. However, there are exceptional cases with florid cerebral lymphocytosis associated with the introduction of HAART, a condition which has become known as the immune reconstitution inflammatory syndrome (IRIS) (Miller et al., 2004). IRIS is characterised by extensive demyelination and white matter damage probably induced immunologically as a result of a HAART-induced lymphocytic influx to the brain.

Other neuropathological findings described in HAART treated subjects include the presence of neurodegenerative proteins normally associated with Alzheimer's disease both in CSF and in the brain (Anthony, Ramage, Carnie, Simmonds & Bell 2006; Brew, Pemberton, Blennow, Wallin & Hagberg, 2005). Elevated levels of both hyperphosphorylated paired helical filament (PHF) Tau and beta amyloid have been described in HAART treated subjects. Curiously, no study has yet reported finding both aberrant proteins in the same cases. Both proteins accumulate progressively in the brain with normal ageing though never to the level observed in Alzheimer's disease. Green et al. have described immunoreactivity for beta amyloid intracellularly in the neuronal soma and in dystrophic axonal processes and extracellularly in perivascular plaques. We have previously described increased deposition of hyperphosphorylated Tau in the form of neurofibrillary tangles and neuritic threads in the hippocampus of long term (4–5 years) HAART treated subjects (Anthony et al., 2006). The presence of either or both of these proteins in excess compared to age

matched controls may indicate accelerated neuroageing in this population. Extrapolating the findings to 20 or 30 years on HAART raises concern for long term cognitive functioning. It has recently been reported that older subjects with HIV show signs of cognitive decline which are not present in younger infected individuals (Valcour et al., 2004). The cause of these findings is unclear; given the toxicity of many drugs used in combination therapy it is plausible HAART itself may be driving this process or alternatively it could be linked to the presence of co-factors such as hepatitis C. It is unlikely that simple ageing with HIV infection is the cause since many pre-HAART subjects lived around 15 years with HIV and did not display elevated levels of these proteins. Neither of these proteins was observed in excess pre-HAART; nor were they associated with HAD. This appears to be a phenomenon of the HAART era.

There have been a number of clinical descriptions of minor cognitive disorders in HAART treated subjects (Sacktor et al., 2002). These disorders were likely present in the pre-HAART era before progression to HAD, but are increasingly common post-HAART. As yet the neuropathological correlate of these symptoms remains to be established, though it is possible that Tau and beta amyloid deposition may play a role.

### **Are the neurological effects of HIV confined to the brain?**

Although this review has concentrated on the effects of HIV within the central nervous system, peripheral neuropathies are amongst the most common HIV associated neurological disorders. These painful neuropathies have been linked both to HIV directly and to the effect of the drugs used in HIV therapy. HIV associated neuropathies are usually distal and give rise to unpleasant symptoms in the feet but motor weakness is an unusual complication. The basis of these findings appears to be axonal degeneration of both large and small sensory fibres with focal infiltrates of lymphocytes and macrophages (McArthur et al., 2005). Degeneration of sensory ganglionic neurons is also present.

Although rarely a major problem in the HAART era, degeneration of the long white matter tracts was a significant complication in untreated AIDS patients. This presented as a spastic paraparesis with bowel and bladder dysfunction. The pathological substrate was demyelination and axonal degeneration in the corticospinal and ascending dorsal tracts, where accumulations of macrophages were often present. The cause of vacuolar myelopathy has never been established with certainty and has not been clearly linked to the presence of HIV

in spinal cord tissue (McArthur et al., 2005; Shepherd et al., 1999).

### What are the emerging issues from recent neuropathological studies?

The two most significant issues that require to be addressed in the post-HAART era are the causes and consequences first of the ongoing neuroinflammation and second of the increased presence of neurodegenerative proteins in the brains of HAART treated subjects. The major concern is that subjects living longer on HAART will go on to develop premature neuroageing or overt dementia with increasing age and treatment duration.

It is also important that the exact contribution of hepatitis C to HIV neuropathology is fully elucidated. The high prevalence of hepatitis C and its links to cognitive dysfunction are causes for concern in the setting of chronic HIV. Finally, intravenous drug abuse is an increasingly common mode of transmission for HIV in many countries. In eastern Europe, particularly in countries of the former Soviet Union, this is the major risk factor for new infections. In 2001 54% of the 100,815 individuals in eastern Europe who were newly diagnosed with HIV acquired their infection through injecting drug abuse. In some countries such as Estonia and Tajikistan over 85% of new transmissions are through intravenous drug use. The rate is similarly high in larger countries such as Ukraine (71%) and Russia (56%) (Hamers & Downs, 2003). HIV infection acquired through intravenous drug abuse is also an expanding problem in other regions of the world. Reports from China suggest that almost half of the country's estimated 650,000 HIV infections were acquired through sharing of needles. Drug abuse is also a significant factor in the USA where 26% of new infections are acquired through intravenous means and even in east Africa 53% of intravenous drug abusers tested positive for HIV (Beckerleg, Telfer, & Hundt, 2005). Clearly HIV infection and concurrent drug abuse is not confined to the more affluent countries of the world but is a global problem. As HAART becomes more readily available worldwide the global population of HIV infected drug abusers taking HAART will increase. The interaction of drugs of abuse with both HIV and HAART requires further study in order to provide better prognostic models and improved treatment.

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