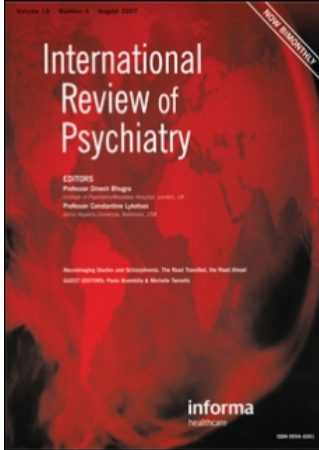


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## International Review of Psychiatry

Publication details, including instructions for authors and subscription information:  
<http://www.informaworld.com/smpp/title~content=t713427280>

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Online Publication Date: 01 February 2008

To cite this Article: Brew, Bruce James and Letendre, Scott Lee (2008) 'Biomarkers of HIV related central nervous system disease', International Review of Psychiatry, 20:1, 73 - 88

To link to this article: DOI: 10.1080/09540260701878082

URL: <http://dx.doi.org/10.1080/09540260701878082>

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## Biomarkers of HIV related central nervous system disease

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### Abstract

In this review we critically assess biomarkers of the direct effects of HIV related brain disease. This area is becoming increasingly complex because of the presence of confounds and varying degrees of activity of HIV brain disease. Sensitive and specific biomarkers are urgently needed although existing biomarkers do have some utility. The review will focus on the practical implications of the more established biomarkers. We discuss blood, cerebrospinal fluid and neurophysiological biomarkers but not neuroimaging techniques as they are beyond the scope of this review.

### Introduction

Biomarkers are important, some would say essential, for the management of patients with HIV related central nervous system (CNS) disease. However, at present there is much that still needs to be done. It would be premature to say that they have reached the point in their development at which they could, or even should, be used routinely. That said though, it should be stressed that an appreciation of the field is important: there are some areas that can be used in day-to-day clinical practice. In this review we will focus upon HIV related brain disease (HBD) in the form of dementia (HIV associated dementia – HAD) as well as its less severe manifestations namely minor cognitive motor deficit (MCMD) and asymptomatic neurocognitive impairment. Biomarkers of opportunistic HIV related brain complications are largely available, for example cryptococcal antigen. This review will be confined to biomarkers of the CNS and will focus on those relating to the blood/cerebrospinal fluid (CSF) and to a lesser extent on those related to neurophysiology.

There are several reasons for the importance and need for biomarkers in HIV CNS disease. First, an objective marker(s) that could diagnose or predict

the presence and severity of HBD has been a critically important and largely unmet clinical need since the advent of the epidemic. Several markers have been evaluated to date but they have been largely non-specific for HAD or MCMD. The acuity of this need is linked to the logistical challenges of diagnosing these conditions in resource-limited settings and to selection of the antiretroviral drugs that are most effective in the CNS. The specificity of a diagnostic marker is essential in clinical situations that are increasingly complex and diverse. For example, affected patients often have confounding conditions. In the pre-HAART era, these were opportunistic infections or tumours. In the era of HAART, increasing numbers of patients are developing more chronic conditions such as hypertension, vascular disease, and viral hepatitis that can potentially act as confounds. A marker of the severity of HBD could provide an objective measure of the quantum of the deficit that was related to HIV, as opposed to the confound. This would inform the aggressiveness of the clinical intervention, obviating the need for a wait and see approach which was used previously.

Second, recent data support the existence of different clinical phenotypes of HBD, including an

inactive form, where there is no ongoing brain damage, both at clinical and subclinical levels. The ability to identify inactive disease in real time using a marker, as opposed to serial testing over weeks, is clearly desirable. Indeed, the identification of disease activity is clinically important for two reasons: unrecognized inactive disease may mean that the patient is given new antiretroviral drugs needlessly with the consequent increased risk of toxicity. Further, the lack of recognition of disease activity in clinical trials could lead to the inclusion of a sizeable number of patients with inactive disease leading to the premature conclusion of a trial of a novel agent because of the misperception of the agent's inefficacy, when in fact the trial patients did not have active disease that would allow the agent to work.

Third, a marker(s) that can diagnose the presence and activity of HBD would be invaluable in clinical trials. It is becoming increasingly apparent that trials of investigational drugs must be set against a background of optimal HAART. In such a situation the degree and rapidity of clinical improvement is likely to be small and slow. A sensitive surrogate marker could mean faster delivery of effective new agents to the pharmaceutical armamentarium.

Fourth, a reliable marker would be helpful at the level of the individual patient in assisting assessment of response to antiretroviral drugs. While it is clear that such response can be assessed clinically, it is equally clear that clinical response can take weeks or even months. A marker that can predict clinical response would be valuable.

The approach taken in this review will deliberately be synthetic with a clear clinical practical orientation. We will not detail every study of every biomarker that has been explored. Rather we will attempt to integrate the data into a cohesive whole that will either have direct clinical practicality or will at the very least provide the clinician with an appreciation of the area that will facilitate understanding of future markers.

Many biomarkers have been described; broadly these can be divided into those related to pathogenesis and those related to the relevant cells. For example, monocyte chemotactic protein (MCP)-1 induces migration of replication-competent monocytes across the blood-brain barrier, which may increase production of neurotoxic HIV encoded proteins in the CNS. The second category contains markers reflecting the state of cells (for example, activation or injury) that play roles in these processes but not thought to be involved in pathogenesis: neurofilament light reflects injury of neurons but is not thought to reflect a mechanism of injury. We have chosen to meld the two categories using a pathogenetic framework. While it is true that the

pathogenesis of HBD is not completely understood, the general features are reasonably appreciated. In broad terms, the disorder can be divided into effectors (host cells or HIV), modulators, toxins, and target(s) and within these there are the mononuclear cells, microglia, astrocytes, neurons, endothelial cells and the blood-brain barrier. In addition to this unidirectional schema of disease causation there is also the reverse component, namely repair.

### Principles

Several principles are critical to appreciate, not only for the understanding of the potential for a marker to be valuable in management but also in relation to the interpretation of existing tests, especially those in the CSF.

The first is that HIV disease is heterogeneous. This may seem self-evident but the concept extends beyond the issue of opportunistic conditions. HIV infected individuals differ in their likelihood of having brain disease according to several fundamental factors – the most important being CD4 cell count and HIV replication, at least in untreated patients. Disease duration may also be a factor although the evidence is less clear at present. Thus, studies must use appropriately matched controls to validate the efficacy of a particular marker.

Second, brain injury is not a universal complication of HIV infection even if patients have lived with HIV infection for an extended period. Consequently, studies must include sufficient subjects who have or who are likely to have HIV related brain disease. In the pre-HAART era, approximately 20% of patients with advanced HIV disease would be expected to develop HIV-associated dementia. The proportion of subjects who will develop HAD, at least of moderate to severe intensity, in the HAART era is much smaller. Third, it is important to appreciate that antiretroviral drugs differ in their distribution characteristics and neurologic effectiveness. For example, antivirals with better CNS penetration might be more effective in lowering CSF HIV concentration (Letendre et al., in press). Thus, accounting for inter-individual differences in antiretroviral distribution characteristics, as well as the duration of therapy, may bias the results of marker studies involving subjects on HAART. Fourth, the blood-brain barrier can be injured during HIV infection and as such may not competently exclude markers at the endothelial lumen from the central nervous system. Thus, accounting for inter-individual differences in blood-brain barrier injury is probably important when interpreting the analyses of markers in CSF, particularly if appropriate controls are not studied.

At the level of individual patient assessment, clinicians should be aware of several concepts, each of which may potentially interfere with interpretation of the significance of a particular marker (Brew, 2001b). The first concept is that of 'layering', that is to say, several abnormalities are frequently layered one upon another in HIV disease. This is especially true of CSF analyses and brain imaging. For example, a mild mononuclear pleocytosis is often found in HIV disease and may be attributable to the disease itself without any clear clinical significance. Furthermore, there is the concept of parallel tracking – several conditions occur in different parts of the neuraxis at the same time, sometimes leading to difficulties in clinical assessment as well as interpretation of test results. For example, vacuolar myelopathy co-occurred with HAD at least in the pre-HAART era thereby making the diagnostic interpretation of biomarkers associated with white matter damage potentially difficult to interpret. Finally, clinicians should be aware of the increasingly important issue of confounding conditions, especially as patients live longer. Such conditions may be difficult to diagnose and may compound existing predispositions to brain injury. New biomarkers should be cautiously applied in such patients – they may have limited utility because of the confounding conditions.

## Overview

Biomarkers associated with HBD should confirm the diagnosis and, when possible, exclude other disorders that may be playing a contributory role. This review will first discuss markers from a pathogenic perspective – categorizing markers as reflecting effector cells, modulators of pathogenesis, toxins, or target cells – and then will discuss markers that are practical for confirmation of HBD followed by those that are exclusionary. Finally, there will be a brief discussion of the probable future for biomarkers.

### *Effector cells*

#### *Lymphocytes.*

CD4 cell count. While the CD4 cell count per se is not a direct marker of the effector cells or toxins associated with HBD, it is a useful indirect marker. At least in the pre-HAART era and in untreated patients, HAD occurred most often in patients with advanced HIV disease – usually at the time of vulnerability to opportunistic conditions, namely CD4 counts below 200  $\mu$ l (Brew, 2001a). Indeed, the lower the CD4 count the greater the risk of

development of HAD (Brew, 2001a). This probably reflected impaired immune control with increased viral replication and compensatory but ineffective immune activation.

In HAART treated patients the association has changed. The CD4 count in treated patients now is much higher and indeed in some cases it is normal (Dore, McDonald, Li, Kaldor, & Brew, 2003; Valcour et al., 2006). There are several potential explanations for this change, including a greater number of survivors due to the effects of HAART, as well as the presence of inactive disease in some. Increasing evidence now points to the value of the nadir, rather than the current, CD4 cell count (Cysique, Maruff, & Brew, 2006; Tozzi et al., 2005; Valcour et al., 2006).

**Beta-2-Microglobulin.** Beta-2 microglobulin ( $\beta_2$ M) is the invariant light chain of the major histocompatibility class I. It is constitutively expressed on the surface of all nucleated cells with the exception of neurons and is particularly highly expressed on lymphocytes, thus serving as a marker of such cells. In the case of HIV disease it seems that CSF  $\beta_2$ M dominantly reflects cytotoxic T cells. Again it is not surprising that elevated concentrations are non-specific with raised concentrations being found in both inflammatory and lymphoproliferative conditions (Brew et al., 1992). CSF  $\beta_2$ M correlates well with the severity of HAD (Brew et al., 1992). A cut-off value for CSF  $\beta_2$ M at 3.8 mg/l had a sensitivity for HAD diagnosis of 44%, specificity of 90%, and a positive predictive value of 88% in the pre-HAART era (McArthur et al., 1992). CSF  $\beta_2$ M levels also fall with successful treatment of HIV (Brew et al., 1992; Enting et al., 2000) including in HAD patients. Raised CSF  $\beta_2$ M concentrations confer an increased risk of HAD in patients with advanced HIV disease (Brew, Dunbar, Pemberton, & Kaldor, 1996).

#### *Monocytes.*

CD14+/CD69+ Monocytes. Most investigators consider the monocyte/macrophage to be important in HBD pathogenesis. Increased numbers of the subset CD14lo/CD69hi in the peripheral blood appear to be important (Pulliam, Gascon, Stubblebine, McGuire, & McGrath, 1997) but they are non-specific as they can be elevated in the presence of co-existing infection. Pulliam et al., were the first to describe increased numbers of the subset and their correlation with HAD (Pulliam et al., 1997). The prognostic significance of an elevation of this subset in asymptomatic patients is presently unknown. Highly active antiretroviral therapy

(HAART) reduced this subset in one study (Kusdra, McGuire, & Pulliam, 2002, p. 896).

One group (Neuenburg, Furlan, Bacchetti, Price, & Grant, 2005) measured this subset in a large number of patients although none was demented. Patients who were on a HAART regimen containing a protease inhibitor were the most likely to have significant elevations in this monocyte subset in the CSF. Both the reason for this and its prognostic significance are unknown.

**Soluble CD14 (sCD14).** Soluble CD14 is found principally on human monocytes, exists in both membrane and soluble forms (Landmann, Muller, & Zimmerli, 2000), and is released by stimulated monocytes *in vitro*. Elevations in serum are associated with HIV disease progression *in vivo* (Lien et al., 1998; Nockher, Bergmann, & Scherberich, 1994). Ryan reported that sCD14 concentrations were higher in plasma in cognitively impaired compared with those from unimpaired subjects taking combination antiretroviral therapies (Ryan et al., 2001). An important distinction from other markers of macrophage activation may be that in the CNS, sCD14 may derive primarily from trafficking monocytes and perivascular macrophages, rather than native microglia (Cauwels et al., 1999). As such, sCD14 may indicate inter-individual differences in infiltration of immune cells into the CNS. If levels of sCD14 correlate with those of CD14+/CD69+, they may be a more clinically accessible indicator of CD14+/CD69+ cell numbers since they can be measured by simple ELISA rather than specialized flow cytometry. Although HAART can decrease sCD14 levels (Kusdra et al., 2002), detection of high levels may identify those at risk for subsequent neurological injury, although no validation of this concept yet exists.

**Neopterin.** Neopterin is a product of guanosine triphosphate metabolism (Hamerlinck, 1999). It is mainly produced by activated monocytes, macrophages and microglia (Brew et al., 1990), and as such serves as a marker for such cells. Consequently, it is not surprising that high CSF concentrations are found in patients with opportunistic CNS infections as well as HAD. Furthermore the CSF concentrations correlate with HAD severity (Brew et al., 1990). Elevated CSF concentrations increase the risk of HAD at least in patients with advanced HIV disease (Brew et al., 1996). CSF neopterin levels decrease with antiretroviral therapy (Brew et al., 1990). However, after two years of virologic suppression, only 55% had normal CSF neopterin levels (Abdulle, Hagberg, Svennerholm,

Fuchs, & Gisslen, 2002). What this means in terms of the risk of later development of HAD is unknown.

**Quinolinic acid.** Quinolinic acid (QUIN) is a product of the kynurenine pathway, the principal degradative pathway for tryptophan metabolism (Heyes et al., 1991). It is produced by monocytes after stimulation by a number of agents but especially interferon gamma (IFN $\gamma$ ) and HIV proteins. It is important as it not only reflects monocyte activation but it is a toxin in itself: QUIN is an agonist of N-methyl-D-aspartate receptors and so can lead to excitotoxic cell death. Furthermore, it can cause cell death through lipid peroxidation and the generation of free radicals (Behan, McDonald, Darlington, & Stone, 1999). At present, QUIN can only be measured by gas chromatography/mass spectrometry.

Increased CSF QUIN concentrations may be seen in opportunistic conditions as well as HAD (Heyes et al., 1991). CSF QUIN levels are correlated with the severity of HAD (Heyes et al., 1991). There is only one small study showing that elevated CSF concentrations confer an increased risk of HAD through increased psychomotor slowing (Martin et al., 1992). CSF QUIN is also relatively unique in that it reflects disease activity within the brain - QUIN cannot cross an intact blood-brain barrier at least in the short term, so elevated CSF concentrations usually indicate an intrathecal process (Valle, Price, Nilsson, Heyes, & Verotta, 2004). Only CSF S100b, NFL, and tau have such brain specificity. CSF QUIN levels fall rapidly with antiretroviral treatment (Heyes et al., 1991; Valle et al., 2004).

#### *Microglia*

At present there is no specific marker of microglia. The development of such a marker would be of considerable benefit given the fact that the degree of activation of microglia is the best correlate of the presence and severity of HAD in neuropathological terms (Glass, Fedor, Wesselingh, & McArthur, 1995). Thus for the moment CSF markers of microglia are inferred from those previously discussed in relation to monocytes.

#### *Astrocytes.*

**S-100 $\beta$ .** S-100 is an acidic calcium-binding protein which exists in dimer forms of  $\alpha$  and  $\beta$  subunits. S100 $\beta$  is virtually exclusively found in astrocytes (Pemberton & Brew, 2001). As such it is one of the few biomarkers that reflects brain damage. S100 $\beta$  may be more than just a marker of astrocytosis as high concentrations may lead to neuronal apoptosis

(Hu et al., 1997). Elevated CSF S100 $\beta$  concentrations occur in any condition that causes astrocytosis. Raised levels occur in patients with either moderate or severe HAD and predict rapid progression to death (Pemberton & Brew, 2001). There are no published data on response to HAART.

Glial fibrillary acid protein (GFAP). GFAP is another protein produced by astrocytes but its levels in CSF do not appear to have a role in HBD or at least HAD (Sporer et al., 2004b).

### *Modulators*

HIV primarily targets cells of the immune system so measurement of modulators of immune activation or suppression is a rational focus for biomarker investigations. Many critical interactions among cells of the immune system are controlled by soluble mediators called cytokines, a diverse group of intercellular signalling peptides and glycoproteins. Each is produced by particular cell types in response to a variety of stimuli and produces characteristic effects on the growth, mobility, differentiation, or function of target cells. Collectively, they regulate immune and inflammatory responses as well as healing, haematopoiesis, angiogenesis, and many other biological processes (Oppenheim & Ruscetti, 2001).

### *Interleukins*

The most studied interleukins are produced by two types of cells, helper T lymphocytes, the primary targets of HIV, and macrophages, cells that play a central role in HIV neuropathogenesis. The interleukins produced by helper T lymphocytes are typically categorized as being produced by Th1 cells (for example IL-2), which generally activate macrophages, or Th2 cells (for example IL-6, IL-10), which generally activate B lymphocytes. Others, such as IL-1, are not produced by Th1 or Th2 lymphocytes but instead are produced by macrophages and other antigen presenting cells and can promote inflammation.

The interleukin family is large and diverse but most interleukin studies in neuroAIDS focused on just three members, IL-1, IL-2, or IL-6. Among six studies that measured IL-1, 4 identified a relationship with HBD, either in adults (Gallo et al., 1989a; Perrella, Carrieri, Guarnaccia, & Soscia, 1992) or in children (Gallo et al., 1991; Laverda et al., 1994). Most of the nine studies that measured IL-6 also identified associations with brain injury, in either adults (Gallo et al., 1989a; Perrella et al., 1992; Rieckmann, Albrecht, Ehrenreich, Weber, & Michel, 1995; Torre et al., 1992) or children (Gallo et al.,

1991; Laverda et al., 1994). In contrast, none of the studies of IL-2 identified associations with neurological disease. In fact, only three studies even compared IL-2 or its soluble receptor to a measure of brain injury (Gallo et al., 1989a; Griffin, McArthur, & Cornblath, 1990; Tyor et al., 1992). Of the interleukins measured in other studies (Kelder, McArthur, Nance-Sproson, McClernon, & Griffin, 1998; Kolb et al., 1999; von Giesen, Jander, Koller, & Arendt, 2004), only IL-10 was associated with HBD by one of the two largest studies in this series (Gallo et al., 1994).

As IL-1 beta, IL-6, and IL-10, but not IL-2, are produced by antigen presenting cells, such as macrophages, these findings are consistent with the central role of macrophages, but not Th1 lymphocytes, in HIV neuropathogenesis. Th2 lymphocytes can also produce IL-6 and IL-10 so the findings may also implicate these cells in HIV neuropathogenesis.

### *TNF superfamily proteins*

Tumour necrosis factor (TNF) is the prototype of a family of molecules that are involved with immune regulation and inflammation (Cosman, 1996; Gruss & Dower, 1995). Receptors for TNF and other proteins, such as soluble Fas and CD30, constitute a super-family of related proteins (Armitage, 1994; Baker & Reddy, 1996; Lotz, Terkeltaub, & Villiger, 1992; Ware, VanArsdale, & VanArsdale, 1996). The prototypical member of the super-family TNF-alpha is produced by activated macrophages and microglia and plays a central role in several pathologic processes. In HIV disease, TNF-alpha can up regulate HIV replication (Zoumpourlis, Eliopoulos, & Spandidos, 1992). Indeed, mRNA expression of TNF-alpha is elevated in the brain tissue of individuals with HAD (Achim, Heyes, & Wiley, 1993; Mastroianni et al., 1992; Wesselingh, Glass, McArthur, Griffin, & Griffin, 1994).

Most studies that measured TNF-alpha in CSF identified associations with measures of brain injury, including clinical staging, HIV RNA levels in CSF, and focal CNS damage (Calvo et al., 1995; Franciotta et al., 1992; Gendelman et al., 1998; Lafeuillade et al., 1996; Mastroianni, Paoletti, Massetti, Falciano, & Vullo, 1990; Mastroianni et al., 1992; Perrella et al., 1992; Rieckmann et al., 1995; Seigny et al., 2004). Most of the studies that reported no association with brain injury were unable to detect TNF-alpha in most or all of the specimens.

Among studies of other TNF super-family proteins, five reported that levels of soluble TNF receptors (sTNFRs) were elevated in CSF in HIV infected individuals and both studies that compared these levels to a neurological outcome identified an

association (Portegies et al., 1993; Vullo, Mastroianni, Lichtner, Mengoni, & Delia, 1995). Of interest, one study identified persistently elevated levels of sTNFR-II in CSF despite effective antiretroviral therapy, supporting persistent neuroinflammation in these individuals (Gisolf et al., 2000).

Three studies measured levels of the apoptosis associated proteins, soluble Fas (sFas)/TNFRSF6 and Fas ligand (FasL)/TNFSF6, and identified associations between higher levels of sFas HAD (Sabri et al., 2001; Sporer, Koedel, Goebel, & Pfister, 2000; Towfighi, Skolasky, St Hillaire, Conant, & McArthur, 2004). In a recent analysis, the HNRC group measured 10 biomarkers, including sFas, in 29 HIV infected, cognitively impaired subjects before and 12 weeks after a change in antiretroviral therapy (Letendre et al., 2006). In multivariate analyses, cognitive improvements were associated with reductions in sFas, even after adjusting for multiple, potentially confounding conditions.

Thus, a preponderance of the studies that have reported on TNF super-family proteins in CSF to date has identified links with HBD. The findings are most consistent for proteins other than TNF-alpha, though, perhaps because endogenous regulation of this potent pro-inflammatory cytokine makes it difficult to measure in body fluids. Strong evidence exists that TNF-alpha (Sevigny et al., 2004), sTNFRs (Gisolf et al., 2000), and sFas (Letendre et al., 2006) can be detected in body fluids despite antiretroviral therapy, supporting that these proteins might be useful biomarkers of ongoing neuroinflammation in treated individuals.

#### *Interferons and interferon inducible proteins*

The interferons (IFNs) are a family of cytokines that can be categorized into two major subgroups, type I (IFN- $\alpha$ ,  $\beta$ ,  $\omega$  and  $\kappa$ ) and type II (IFN- $\gamma$ ), based on their properties and cellular receptors. In the brain, astrocytes and microglia in particular can produce IFN-alpha. This endogenous IFN- $\alpha$  may help protect the brain from viral infections but, with prolonged exposure and/or high concentrations, may injure it. For example, transgenic mice that overproduce IFN- $\alpha$  in astrocytes have a high incidence of severe neuropathology, manifesting as intractable seizures and early death (Campbell et al., 1999). The expression of IFN- $\alpha$  is also elevated in the brains of patients with HIV encephalitis and correlates with the severity of ante-mortem cognitive impairment. IFNs can induce the expression of over 300 different genes, some of which may be the actual mediators of the antiviral and antitumour effects of IFNs (Stark, Kerr, Williams, Silverman, & Schreiber, 1998). Some, however, may also

promote pro-apoptotic actions (Chawla-Sarkar et al., 2003) that could lead to neurodegeneration.

Three studies have measured IFN- $\alpha$  and three others have measured IFN- $\gamma$  in CSF. All three studies of IFN- $\alpha$  in CSF identified that higher levels were associated with HAD (Krivine et al., 1999; Perrella et al., 2001; Rho et al., 1995). Two of these also linked higher IFN- $\alpha$  levels to higher HIV RNA levels in CSF (Krivine et al., 1999; Perrella et al., 2001), indicating ineffectual antiviral activity. Two of the three studies of IFN- $\gamma$  identified higher levels in HIV infected individuals (Fuchs et al., 1990; Griffin, McArthur, & Cornblath, 1991), although a third was unable to detect IFN- $\gamma$  in CSF (Gallo et al., 1989b) and none of the studies identified links to HBD.

Four studies reported levels of the interferon-inducible protein, IP-10. Two compared IP-10 levels to HIV RNA levels in CSF and identified statistically significant correlations (Gisolf et al., 2000; Shacklett et al., 2004). Gisolf et al. again identified that IP-10 was also elevated in some subjects despite apparent control of HIV replication in CSF, similar to their findings with sTNFR-II, (Gisolf et al., 2000). The two studies that compared IP-10 to brain injury both identified links between higher levels and adverse neurologic outcomes (Cinque et al., 2005; Kolb et al., 1999).

These studies implicate IFN- $\alpha$  and IP-10 more than IFN- $\gamma$  in HIV neuropathogenesis. Notably, all three studies that measured IFN- $\gamma$  were published prior to 1992, whereas nearly all of the studies IFN- $\alpha$  and IP-10 were performed after 1996. Thus, the advent of HAART in 1996 and its resulting impact on the neurologic complications of HIV could account for important differences in the findings of these studies.

#### *Chemokines*

Multiple lines of evidence support the role of chemokine receptors and chemokines in HIV neuropathogenesis. For example, *in vitro* studies first recognized that HIV could induce expression of MCP-1/CCL2 from astrocytes (Conant et al., 1998) and that MCP-1 can potently induce chemotaxis of monocytes across endothelial barriers (Weiss, Nath, Major, & Berman, 1999). Human studies corroborated these observations, identifying MCP-1 on brain macrophages of subjects dying with HIV encephalitis (Sanders et al., 1998) and genetic associations with HAD (Gonzalez et al., 2002). Fifteen published studies have reported levels of MCP-1 in CSF in HIV infected individuals, making it one of the most studied of the HAART era biomarkers. Of the nine studies that compared levels to a neurologic outcome, eight identified associations

between higher MCP-1 levels and worse outcomes (Avison et al., 2004; Bernasconi et al., 1996; Cinque et al., 1998; Conant et al., 1998; Kelder et al., 1998; Monteiro de Almeida et al., 2005; Sevigny et al., 2004; Sozzani et al., 1997).

A smaller number of studies compared levels of the CC chemokines, MIP-1 alpha, MIP-1 beta, and RANTES, to neurologic outcomes. These chemokines bind to CCR-5, the most commonly used receptor by HIV for entry into lymphocytes and microglia (He et al., 1997). These chemokines have been implicated in HIV neuropathogenesis by the identification that their mRNA levels are high in brain tissue from subjects with HIV or SIV-encephalitis (Hesselgesser & Horuk, 1999; Sasseville et al., 1996; Schmidtmayerova et al., 1996; Westmoreland, Rottman, Williams, Lackner, & Sasseville, 1998). The findings of the four published CSF studies, however, are inconsistent, identifying only that levels of RANTES/CCL5 (Kelder et al., 1998) and perhaps MIP-1 alpha/CCL3 (Letendre, Lanier, & McCutchan, 1999) were elevated in subjects with ADC, although others have had difficulty detecting these three chemokines in CSF (Kolb et al., 1999), particularly in treated individuals.

Fractalkine, a chemokine that binds to CX3CR1, appears to be important in reducing the neurotoxicity associated with activated microglia (Re & Przedborski, 2006). Two published studies measured fractalkine in CSF in HIV infected individuals, demonstrating non-specific elevations in those with neurologic complications, including HAD (Erichsen et al., 2003; Sporer, Kastenbauer, Koedel, Arendt, & Pfister, 2003). These findings seem contrary to the *in vitro* data as a neuroprotective chemokine would be expected to be lower in HBD, not higher. Perhaps the elevated levels reflect the host's attempt at neuroprotection, but the levels are not high enough. Indeed, the MRS Consortium Group demonstrated that lower fractalkine levels in CSF were associated with lower neuronal pattern scores on proton magnetic resonance spectroscopy, arguing for a loss of neuroprotection in subjects with evidence of neurodegeneration (Letendre et al., 2004).

#### *Other modulators.*

Transforming growth factor (TGF)-beta. TGF $\beta$  is involved in down regulation of T cell and macrophage activation, modulation of pro-inflammatory cytokines and protection against HIV mediated excitotoxicity (Scorziello, Florio, Bajetto, Thellung, & Schettini, 1997). As such it may not only set the stage for reparative processes to

begin but also participate in such processes. In HIV disease, TGF $\beta$  is produced by CD8 cells, microglia and astrocytes. CSF TGF $\beta$  concentrations are elevated in mild HAD and undetectable in more severe disease (Johnson, Kim, Tourtellotte, & Federspiel, 2004; Perrella et al., 2001). The effect of HAART and the prognostic significance are not known.

Urokinase plasminogen activator receptor (uPAR). Soluble urokinase plasminogen activator receptor (suPAR) is the receptor for the urokinase plasminogen activator (uPA), or urokinase. These two molecules are main components of the uPA system, which regulates extracellular proteolysis and intracellular signaling for chemotaxis. Raised CSF suPAR levels are seen in HAD (Cinque et al., 2004) and decline significantly with HAART. The prognostic significance is unknown.

#### *Toxins*

##### *Viral toxins.*

HIV RNA. Quantitative measurement of HIV RNA reflects productive viral replication. Plasma HIV RNA levels are generally of limited use as a biomarker for HBD. Plasma HIV RNA levels are not specific or sensitive to HBD. That said, there is some clinical utility in the significance of a plasma HIV RNA which is below detection – HAD is unlikely to be present at least as an active process in HAART naïve patients. However, in HAART treated patients an undetectable plasma RNA level seems to occur more often in HAD for reasons that are unclear (McArthur et al., 1997).

CSF HIV RNA is also non-specific, with elevated levels in asymptomatic patients and those with opportunistic infections as well as HAD (Brew, Pemberton, Cunningham, & Law, 1997; Ellis et al., 1997). But CSF HIV RNA levels do correlate well with the severity of HAD in HAART naïve patients (Brew et al., 1997; McArthur et al., 1997) and fall with HAART (Ellis et al., 2000). HAD developing in the context of HAART is not related to CSF HIV RNA (Sevigny et al., 2004). Also, elevated CSF viral loads ( $\geq 200$  copies/mL) in HAART treated patients may predict progression to neuropsychological impairment after a median follow-up of approximately one year (Ellis et al., 2002).

HAD can occur in the absence of an elevated HIV RNA in CSF (Cysique et al., 2006; Sevigny et al., 2004; Shiramizu, Lau, Tamamoto, Uniatowski, & Troelstrup, 2006) but is uncommon. One explanation for this is the occurrence of HAD that has not fully responded to HAART so that there is a residual

deficit that reflects permanently damaged tissue (inactive HAD) (Cysique et al., 2006). A second explanation is that the clinical expression of the deficit may be driven not by HIV but by a confounding condition, such as hepatitis C disease (Cherner et al., 2005; Letendre et al., 2005). Third, the disorder may have been initiated by HIV but subsequently have become independent – autonomous unchecked immune activation (Sevigny et al., 2004). Fourth, the virologic response in the CSF may occur sooner than the neurologic response in some patients, although there is little evidence at present to support this. Finally, some patients may experience an immune restoration disorder after initiation of HAART (Riedel, Pardo, McArthur, & Nath, 2006), which may mitigate the beneficial effects of treatment.

**HIV DNA.** HIV DNA levels can be measured and reflect latent infection. Not unexpectedly, plasma HIV DNA is non-specific but it does appear to have some sensitivity to the presence of HAD. Interestingly, HIV DNA levels are still elevated significantly in HAD patients (Shiramizu et al., 2005). Thus far, there are no published data on CSF HIV DNA.

**HIV encoded proteins.** The HIV encoded proteins gp120, Nef, Tat, gp41, and Vpr are all neurotoxic *in vitro*. Their measurement in blood or CSF has been problematic due to the very low concentrations that appear to be present. Vpr has been assayed in the CSF but it is not clear whether the results reflected cell free or cell associated Vpr (Tungaturthi et al., 2003). More sensitive techniques are in development that will hopefully allow more accurate measurement of Vpr as well as the other HIV neurotoxins.

#### *Host toxins*

Host toxins include arachidonic acid metabolites/prostaglandins, nitric oxide, and platelet activating factor (PAF). Other host neurotoxins, including QUIN, S100-beta, interferons, interleukins, and TNF-alpha, have been discussed in previous sections.

Arachidonic acid metabolites and prostaglandins. The lipids in macrophages are highly enriched in arachidonic acid, which can be metabolized to prostaglandin products (prostaglandin E<sub>2</sub>, F<sub>2</sub> $\alpha$ , and thromboxane B<sub>2</sub>) by the cyclooxygenase pathway. These are highly correlated with the presence and severity of HAD, as well as with  $\beta$ 2M and neopterin. Studies were performed before the introduction of HAART but nonetheless,

there was no appreciable decrease in patients treated with antiretroviral drugs. The prognostic significance of elevated concentrations is unknown (Griffin, Wesselingh, & McArthur, 1994).

**Nitric oxide.** Nitric oxide is considered to be an important neurotoxin in HAD, where it is dominantly produced by macrophages and microglia. CSF levels of nitric oxide and its metabolites are, however, not raised in HAD despite the presence of increased activity of its associated enzyme in HAD brain tissue (Milstien et al., 1994). CSF concentrations are raised in opportunistic complications of HIV disease that affect the CNS (Giovannoni et al., 1998) and indeed there is some evidence that they reflect damage to the blood-brain barrier (Giovannoni et al., 1997). Its role as a CSF biomarker of HAD therefore seems doubtful.

**Platelet activating factor.** Platelet activating factor (PAF) is a product of infected or activated monocytes. While it is pleiotropic in its actions there is convincing evidence of its neurotoxicity which at least in part is mediated by N methyl D aspartate receptor activation (Bazan, Packard, Teather, & Allan, 1997; Bito et al., 1992; Epstein & Gelbard, 1999; Franconi et al., 1996). PAF levels are found non-specifically elevated in HAD but they do not appear to correlate with severity. The prognostic significance and the response to HAART are unknown (Gelbard et al., 1994).

#### *Target cell*

##### *Neuron.*

**Neurofilament light (NFL).** The neurofilament is a major structural element of neurons, mainly found in large myelinated neurons. It is composed of a triplet protein, of which the light subunit (NFL) is the essential component of the neurofilament core (Norgren, Rosengren, & Stigbrand, 2003). Its main function is to maintain the axonal calibre. CSF NFL levels are significantly but non-specifically raised in HAD and rise with HAART interruption (Abdulle et al., 2007; Gisslen, Rosengren, Hagberg, Deeks, & Price, 2005). Recent data also show that levels fall to normal in the majority of patients commenced on HAART (M. Gisslen, personal communication). CSF neurofilament heavy chain concentrations may be elevated in the context of significant neuropathies such as Guillain-Barré syndrome (Petzold et al., 2006) but thus far this does not seem to be the case for NFL in HIV neuropathy. Some asymptomatic patients with

advanced HIV disease have raised CSF NFL concentrations; this seems to carry a significant risk of HAD over the next two years (M. Gisslen, personal communication).

**Tau.** Tau is a structural neuronal protein. There are two dominant forms that can be measured: total tau (t-tau) and phosphorylated tau (p-tau). Both reflect neuronal damage non-specifically, though p-tau is more often elevated in patients with Alzheimer's disease (Andreasen, Sjogren, & Blennow, 2003). In HIV disease, however, both are elevated in the CSF even in a proportion of otherwise normal patients (Brew, Pemberton, Blennow, Wallin, & Hagberg, 2005). There is no relationship to HAD severity. Other studies have found varied results, possibly because of the effect of age. The precise relationship between tau and NFL in HBD is yet to be determined, but broadly the two neuronal markers reflect damage to different types of neurons with NFL dominantly indicating damage to large myelinated axons.

#### *Endothelial cells/blood-brain barrier.*

Albumin, immunoglobulin G, and total protein. Albumin, immunoglobulin G (IgG), and other large proteins are normally excluded from the CNS by an intact blood-brain barrier. When the BBB is injured, however, its permeability to large molecules may increase. Thus, levels of these proteins in CSF may reflect the severity of BBB injury and exposure of normally protected brain tissues to extraneural toxins. Elovaara et al., for example, reported that the albumin ratio was increased in patients with neurological 'deficits' (Elovaara et al., 1987), although Marshall et al. reported that the albumin ratio increased over time even in neuroasymptomatic individuals (Marshall et al., 1991). Hall et al. reported that 'disturbances' in the albumin ratio in 30% of 59 subjects were greater in those with more advanced HIV disease (Hall et al., 1992) and Singer et al. (1994) confirmed this finding in 139 subjects. In 2001, Andersson, Hagberg, Fuchs, Svennerholm and Gisslen (2001) reported increased albumin ratios in only 15% of 110 neuroasymptomatic, HIV infected subjects. More recently, elevations were identified in just 5% of asymptomatic individuals, although 56% still had an abnormal IgG index that persisted in 41% even after antiretroviral treatment (Abdulle, Hagberg, & Gisslen, 2005). Few, if any, studies have identified correlations between total protein levels and HBD. Somewhat unexpectedly then, the HNRC Group identified strong associations between changes in total protein levels in CSF and cognitive

improvements before and 12 weeks after changes in antiretroviral therapy (Letendre et al., 2006). Until others confirm this finding, however, total protein levels in CSF should not be considered a reliable marker of HBD.

**Serum vascular endothelial growth factor (VEGF).** Vascular endothelial growth factor (VEGF) is a potent angiogenic and mitogenic peptide. Thus far, there is one report of CSF and serum levels in HIV disease. Serum but not CSF levels were increased in HIV infection especially in HAD and decreased with HAART, although the numbers were small. Interestingly, even with effective viral suppression, serum VEGF levels were increased (Sporer et al., 2004a).

**Intercellular adhesion molecules.** HIV gp120 and pro-inflammatory cytokines can up regulate adhesion molecules, including intercellular adhesion molecule (ICAM)-1, on the luminal surface of brain microvascular endothelial cells (Huang & Jong, 2001). Rieckmann et al. measured a soluble form of ICAM-1 (sICAM-1) in CSF, finding that levels were higher in individuals with meningeal inflammation than in HIV seropositive subjects and were associated with BBB damage (Rieckmann et al., 1993). Heidenreich et al. compared sICAM-1 levels in HIV seropositive patients to a different group (HIV seronegative patients without neuroinflammatory disorders) and found that CSF levels were, in fact, higher among HIV seropositive patients. The highest levels were found in individuals who had 'HIV encephalopathy' (Heidenreich, Arendt, Jander, Jablonowski, & Stoll, 1994).

**Matrix metalloproteinases.** Matrix metalloproteinases (MMPs) are a family of neutral proteases that are important in normal development and have been implicated in many pathological processes, including neuroinflammation. In the CNS, MMPs can degrade components of the basal lamina, leading to disruption of the BBB (Rosenberg, 2002). Sporer et al. (1998) found that active MMP-9 was detected more frequently in HIV infected subjects with neurological deficits or CNS opportunistic infections and was associated with higher CSF-to-serum albumin ratios. Conant et al. (1999) confirmed that MMP-9 (along with MMP-2) activity was more frequently detectable in the CSF of subjects with HIV dementia (9/16), compared with non-demented sero-positive (2/11) or sero-negative (0/11) controls. Liuzzi et al. (2000) re-confirmed this finding more recently in 138 HIV infected individuals.

*Biomarkers of repair*

At present almost no studies have addressed this area, yet it is important and clinically relevant. As previously discussed, clinical evidence of improvement can take weeks or even months. A biomarker that predicted improvement would be valuable. Imaging unfortunately does not appear to be particularly helpful in this regard at least in relation to magnetic resonance spectroscopy.

The recent study by Albrecht et al. (2006) is interesting. It did show that CSF levels of nerve growth factor were raised in HAD patients, while brain derived nerve growth factor levels were low. However, more data are needed on the relationship to HAD severity, prognostic significance and the effect of HAART.

*What biomarkers should be measured to confirm HBD?*

The diagnosis of HAD and its less severe forms is still primarily a clinical diagnosis. Nonetheless, there are three biomarkers in current clinical practice that can be of confirmatory value: CD4 cell count, CSF HIV RNA, and CSF protein.

In untreated patients, the CD4 cell count can be helpful in determining the likelihood of HAD. If the CD4 cell count is above 200 cells/ $\mu$ l, a diagnosis of HAD is unlikely. In resource-poor countries, the lymphocyte count derived from the full blood count may be used – a normal lymphocyte count is unusual for HAD. On the other hand if the patient is on HAART or has failed therapy, the nadir CD4 cell count is probably more useful than the current value, indeed in a sizeable number of patients it may be normal or only mildly lowered. The same can be said for the lymphocyte count in resource limited settings.

The second biomarker that is potentially helpful is the CSF HIV RNA level. Again its utility is chiefly in those with untreated HIV disease or in those who have failed HAART. In such patients the CSF HIV RNA is almost always elevated above 50 copies/mL. In HAART treated patients the CSF HIV RNA load is much less reliable and just as is the case with CD4 cell count, a sizeable number of patients may have undetectable or minimally raised concentrations.

The third biomarker that can be clinically helpful is the CSF protein. Almost all HAD patients have a raised CSF protein.

*Is there a biomarker to indicate inactive HAD?*

Intuitively, one would consider that HAD was inactive if markers of activity were absent. However, given that there are so many markers it is not clear at present which is most sensitive. Furthermore, it is unknown whether there may

be an effect that we have termed ‘stunning’. A biomarker such as NFL or t-tau may reflect neuronal damage the cause of which is no longer operative – a ‘hit and run’ phenomenon. If this is the case then therapy directed at the presumed inciting agent would be inappropriate.

Recent data from Sacktor et al. (2004) have raised the possibility that raised CSF concentrations of sphingomyelin may serve as markers of inactive HAD. However, it is not clear yet how long sphingomyelin concentrations remain elevated.

*What biomarkers should be measured to exclude HBD?*

There are several simple biomarkers in the blood and CSF that should be measured to exclude other diseases that may mimic HAD and its more minor forms.

*B12, red cell folate, and thyroid function*

These are commonly used tests in the screening of patients with dementia. They are also entirely appropriate for HAD. Some of the symptoms associated with B12 and red cell folate deficiency can mimic those associated with HAD, especially the combined involvement of cognitive deficit and myelopathy, sometimes with neuropathy. Similarly, hypothyroidism on occasion can have symptoms and signs not dissimilar from those of HAD, especially the psychomotor slowing.

*CSF leukocyte count*

This simple biomarker has considerable utility in an exclusionary sense. A CSF white cell count in excess of 50 cells/ $\mu$ l is unlikely to be due to HIV alone, especially when the CD4 count declines below 200  $\mu$ L (Marshall et al., 1988) and suggests another disease process, for example cryptococcal meningitis. In addition to the total count being helpful, the differential is also useful. For example, a polymorphonuclear pleocytosis is unlikely with HAD and raises the possibility of cytomegalovirus encephalitis.

*What biomarkers are likely in the near future?*

There are two clear developments in the field of biomarkers. First, since HBD is multi-faceted and unlikely to be diagnosed by a single biomarker, a combination of markers will likely be required to address specific questions. Such a combination would ideally incorporate representative biomarkers of the pathogenic schema presented in this review. One such combination that has been forwarded is CSF HIV RNA, CSF neopterin, and NFL (Gisslen et al., 2007). This combination, however,

is not readily available in the clinic and its utility has yet to be tested. Furthermore, this combination does not assess an important arm of pathogenesis, namely regenerative/repairative markers.

Second, the application of proteomics to the CSF is an important development. This is a powerful tool to uncover a more specific marker or combination of markers of HBD (Berger, Avison, Mootoor, & Beach, 2005; Luo et al., 2003; Wojna et al., 2004). However, it must be judiciously applied. Approximately 50% of patients with minor and mild cognitive deficits remain unchanged over the subsequent months (Cysique et al., 2006). Studying large numbers of patients with HAD and HBD to ensure that there are sufficient numbers with active disease may, however, be practically difficult. Despite this challenge, the development of a biomarker of inactive disease is critical for the advancement of the field.

## Conclusions

The field of biomarkers is rapidly maturing especially in relation to HBD. However, the process of validating the clinical utility of pathogenesis focused biomarkers has been complicated by the multitude of biomarkers implicated in HIV neuropathogenesis and the dramatic shifts in disease that followed the introduction of HAART. Despite this, we consider it best to continue to approach this challenge from a pathogenic perspective as this ultimately facilitates the clinical application of these markers. Furthermore, this approach fosters the development of new markers and encourages the use of combinations of markers appropriate to the diagnosis of current HBD and the prediction of the risk for its development in the future.

## Acknowledgements

Dr Letendre gratefully acknowledges support from the National Institute of Mental Health (P30 MH62512, R01 MH58076, N01 MH22005) and the National Institute on Drug Abuse (R01 DA16015, P01 DA12065).

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