



Commentary

Plasma Biomarkers of HIV-associated Cognitive Disease



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By controlling human immunodeficiency virus (HIV) replication and allowing recovery of immune system function, combination antiretroviral therapy (cART) has revolutionised the outlook for people-living-with-HIV (PLWH) to that of a chronic but manageable medical condition. Despite this success, other medical problems, such as hypertension and cardiovascular disease, are reported to occur more frequently and at a younger age in PLWH compared to matched control populations (Schouten et al., 2014). Another medical problem with a high prevalence and high morbidity is cognitive impairment (Robertson et al., 2007).

For many co-morbidities, surrogate markers aid diagnosis and assist in the clinical staging of a disease state. For cognitive impairment however, disease markers to date have either been unreliable or impractical to measure. For instance, clinical assessments such as formal neuropsychological testing are time consuming to perform and prone to many confounding issues such as illicit drug and alcohol use, the presence of depression and anxiety, and day to day variability in a patient's performance. Novel cerebral imaging techniques show promise in the diagnosis and assessment of HIV-associated cognitive impairment (Descamps et al., 2008). However, many of these novel imaging techniques are not widely available and may only be accessible as part of a research study, rather than in general clinical care. And lastly, although cerebrospinal fluid (CSF) markers, such as neurofilament light protein (NFL) concentration, show promise, collection of CSF is problematic. Lumbar puncture, whilst generally safe, is an invasive and resource expensive procedure which does not lend itself particularly well to repeated measure (Peterson et al., 2014).

In this issue of *EBioMedicine*, Gisslen et al. (2015) report on the measurement of plasma NFL concentrations, using a new ultrasensitive single molecule assay, and its correlations with CSF NFL concentrations in several cohorts of PLWH. Groups assessed included individuals with primary HIV-infection, neuroasymptomatic PLWH not on cART with different ranges of CD4 + lymphocyte counts (above 350 cells/uL, 200–349 cells/uL, 50–199 cells/uL and below 50 cells/uL), individuals with overt HIV-associated dementia and subjects on cART with plasma HIV RNA <50 copies/mL for greater than one year. Furthermore an HIV-uninfected control group was included in their analysis. As expected, CSF concentration of NFL was dependent on the cohorts studied with

the highest concentrations observed in those with HIV-associated dementia and higher concentrations in PLWH with untreated HIV-disease and low CD4 + lymphocyte counts. Of importance, in all groups studied, a strong correlation between plasma NFL and CSF NFL was reported.

The values of NFL plasma concentrations were 1–2 log₁₀ lower than in the CSF. However, by developing and utilising this new ultrasensitive plasma NFL assay, concentrations as low as a mean of 9.3 nmol/L were measured in the HIV-uninfected control group and every subject had a detectable and quantifiable concentration. This impressive dynamic range highlights the potential sensitivity of this biomarker to detect subtle axonal injury in a variety of patient groups.

The ability to utilise a sensitive plasma biomarker which closely correlates with active CNS axonal injury has several potential implications for future research. Within longitudinal cohorts, clinical observations and non-invasive neuroimaging observations could now be correlated with readily obtainable plasma biomarkers. Within interventional studies, a novel plasma biomarker which correlates with the effects of a drug or other interventions on cerebral function, could dramatically simplify the practical issues which are currently associated with the development of such therapeutics. Furthermore, this assay has the potential in clinical practice, as well as research studies, to discriminate between those with ongoing CNS injury in whom intervention may be more successful and those with quiescent disease in whom it may not.

In summary, these initial results described are highly promising with further work needed to assess the utility of this marker in other cohorts of PLWH, such as those with minor cognitive complaints, and other neurodegenerative diseases.

Disclosure

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