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REVIEW ARTICLE

Blood biomarkers for HIV infection with focus on neurologic complications—A review

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Although clinical examinations, neuroimaging, and cerebrospinal fluid analyses are the most important ways to evaluate the impact of HIV infection on the brain and in diagnosis of opportunistic infections, several blood biomarkers including HIV RNA concentrations, CD4 +T-cell count, and neurofilament light chain protein (NfL) concentration, along with tests for opportunistic infections can provide important information for clinical decisions.

KEYWORDS
blood biomarkers, HIV, neurology

1 | INTRODUCTION

HIV-1 infects the central nervous system (CNS) shortly after transmission during primary infection[1] and can cause risk of HIV-associated dementia during its advanced stage of the disease several years later, if left untreated.[2] In general, HIV is detected in the cerebrospinal fluid (CSF) in individuals with and without neurologic symptoms during all stages of infection, although the CSF the viral load is often higher in patients with HIV-associated dementia or CNS opportunistic infections causing meningeal inflammation.[3]

Chronic HIV infection causes progressive reduction in blood CD4+T-cell counts leading to immunosuppression and AIDS in a median of 10–11 years after primary infection. HIV-associated dementia and CNS opportunistic infections in general occur when CD4+ T cell counts fall below 200/mm^3, that is, in patients with severe immunosuppression. The introduction of combination antiretroviral treatment, by preserving or restoring immune functions, has had a major impact on the morbidity and mortality including a marked reduction of HIV-associated dementia.[4] However, milder forms of HIV-associated neurocognitive disorder appear to persist.

Mild form of neurocognitive disorder and asymptomatic cognitive impairment detected by neuropsychological tests has been reported among well-treated HIV patients ranging from 20%–50%.[5,6] More severe symptoms of cognitive slowing, poor concentration, and memory problems post-treatment are rare. How much aging, underlying diseases, life-style factor, or the impact of HIV infection play a role for the findings of mild neurocognitive disorder is unknown. In these patients, biomarkers may be helpful to analyze if there is any active ongoing inflammatory or neurotoxic process in the brain after effective antiretroviral treatment.

Neurofilament light chain protein (NfL) is a sensitive marker of neuronal injury in a variety of neurodegenerative conditions, including HIV-related neuronal injury.[7,8] Its CSF concentrations reflect leakage from injured or degenerating neurons and correlates with white-matter lesions and other injuries to subcortical brain regions.[9] Markedly elevated CSF NfL concentrations in patients without opportunistic CNS infections are associated with HIV-associated dementia and follow the grade of severity.[10] NfL concentration decreases after initiation of effective antiretroviral therapy.[11,12] In opportunistic CNS infections, CSF NfL concentrations are also usually markedly elevated.[10,13]

HIV enters the brain presumably within lymphocytes and monocyte-derived macrophages and leads to infection and activation of parenchymal macrophages and chronic inflammation. This local inflammation is likely an important pathogenetic factor both in treatment-naïve patients and probably also in a milder form after effective antiretroviral treatment.[14]

However, since CSF analyses need a lumbar puncture, which may be uncomfortable for the patient and require a more laborious invasive procedure, it would be helpful if this could be circumvented by assessment of blood biomarkers that provide similar information.

TABLE 1 Median plasma NfL concentrations in people living with HIV

Healthy controls (n = 19) 9.3 nmol/L
HIV with little risk of AIDS, CD4 >200/mm^3 (n = 26) 9.3 nmol/L
HIV with high risk of AIDS, CD4 <200/mm^3 (n = 20) 39.6 nmol/L
AIDS dementia (n = 11) 114 nmol/L
HIV treated suppressed (n = 22) 11.1 nmol/L[a]

Note: Data from Gisslén et al EBioMedicine. 2016 Jan; 3: 135–140.
[a]Antiretroviral treatment for >1 year and HIV <50 copies/ml.

2 | METHOD

We conducted a literature search in the databases PubMed using the search terms "HIV, neurology, and blood biomarker" was conducted. Two hundred and thirty-five titles were initially detected. Most were excluded by title or abstract, particularly if they only analyzed CSF markers or brain blood flow. We included only original articles that convincingly reported the analysis of blood markers and excluded review articles. The reference lists of the retrieved articles were checked for additional original articles overlooked by the search.

3 | RESULTS

Twenty-six studies of blood biomarkers other than routine analyses applied to HIV infection such as quantitative HIV RNA and CD4+ T measurement were found. For this review, we did not focus on biomarkers used in the diagnosis of CNS opportunistic infections though these are briefly discussed below. Rather our main focus was on biomarkers of CNS injury and cognitive impairment.

3.1 | Neurofilament light chain protein (NfL)

A new ultrasensitive diagnostic assay for quantification of NfL in plasma has been developed, providing a convenient way to assess CNS neuroaxonal damage without having to perform a lumbar puncture.[15] Plasma and CSF NfL concentrations were highly correlated in patients with HIV infection.[15,16] The use of blood NfL concentrations was confirmed to correspond with previous CSF data from several defined HIV-infected people in various stages of disease.[15] People living with HIV and high risk of AIDS and patients with HIV-associated dementia had much higher blood NfL concentrations than those with more preserved immune status (Table 1). Like CSF, blood NfL concentrations declined after initiation of antiretroviral treatment.[17] Plasma NfL concentration have also been used to study switches in antiretroviral treatment and estimate if the switch has a possible effect on the risk for neural injury.[18] In general, blood NfL concentrations can be used to document whether active CNS injury is present in individuals presenting with new neurological symptoms or if there is ongoing disease activity in those with more chronic deficits. It can also be used to monitor treatment effects.

3.2 | Monocyte activation and other markers of inflammation

Several studies have focused on peripheral monocyte activation and monocyte subsets[19] and found association to cognitive impairment.[20–22] Studies on chemokine receptor type 2 on monocyte subsets of CD14 and CD 16 suggested those as prognostic peripheral blood biomarkers of HIV-associated neurocognitive disorders[23] and neuronal damage,[24] while higher number of activated CD8+T lymphocytes and natural killer cells were associated with lower risk of depression.[25] In a recent study of several biomarkers, blood sCD14 and neopterin correlated strongly with CSF NfL and may be helpful in predicting CNS injury.[26] Blood C-reactive protein (CRP) has also been reported as marker for risk of cognitive impairment. In one study, variability in C-reactive protein was associated with cognitive impairment in women living with HIV.[27]

Leading theories implicate peripheral monocyte HIV DNA reservoirs as a mechanism for spread of the virus to the brain. The burden of monocyte HIV DNA was directly associated with both brain injury and glial dysfunction.[28] Another suggested inflammatory biomarker is serum levels of anti-HMGB1 IgG antibodies which was associated with early stage of neurological impairment.[29] HMGB1 is a potent proinflammatory cytokine and may also act on microglial cells.

3.3 | Additional markers

Other blood biomarkers for HIV-associated neurology disorders published are neuron-derived exosomes. Plasma neuronal exosomes have been reported to correlate with cognitive impairment in HIV infection[30] and inflammation in people with HIV on antiretroviral therapy.[31]

4 | DISCUSSION

HIV infection has pioneered the use of blood surrogate markers in therapeutics—both in their drug development and in everyday clinical practice. HIV has provided a compelling example of how blood markers can be used to efficiently evaluate treatment outcomes in a lethal disease. When antiretroviral drugs were launched during the late 1980s and their number expanded during the following years, their impact of antiretroviral treatment was easily and rapidly recorded by measuring their effect on HIV viral load by quantitative HIV PCR RNA. Within weeks to months, after initiation of antiretroviral combination treatment, it was possible to estimate the effect. HIV load decreased to low levels and was followed by clinical improvement and prevention of complications including those from the nervous system. Death because of HIV and AIDS became rare. Quantitative blood HIV RNA is a biomarker that indicate the speed of infection with high numbers generally indicating more rapid deterioration of immune functions than patients with low numbers. Thus, it can predict the risk for neurologic complications. The vast majority of patients, however, respond to antiretroviral treatment. After treatment, a high level of blood HIV RNA is therefore an indicator of bad treatment compliance or viral resistance and, in the long run, increase the risk for neurological complications.

In parallel with viral load, blood CD4+T-cell counts were important predictors of neurologic complications before effective treatment was available. This association is no longer true since CD4+T cells increase post-treatment. The lowest CD4+T-cell level experienced, that is, CD4+T-cell nadir has, however, been shown to predict risk for mild cognitive disturbance across the treatment era,[32,33] probably reflecting CNS injury before treatment initiation, the so-called legacy effect.[34]

Blood NfL concentration may be used to follow the impact of treatment regimens, the natural course of infection and identify if there is active neuronal damage in HIV patients with mild cognitive disturbances. Further studies are needed to determine if NfL could serve as a prognostic risk marker for developing mild cognitive disorder during effective treatment. Many people living with HIV has several confounding factors such as lifestyle, drug abuse, and other sexually transmitted diseases. For instance, it was reported that HIV-negative men who have sex with men and on prophylactic antiretroviral treatment had higher NfL concentrations than a control group.[35] An advantage with NfL as a marker of neurological complications is that it reflects ongoing neuronal injury. In the same way, as blood HIV RNA is a marker of systemic infection and CD4+T-cell destruction, blood NfL concentrations can be a marker for ongoing brain injury. As many other biomarkers, it cannot, however, identify the cause of injury. Biomarkers for inflammation and monocyte activation, on the other hand, reflect a more general and more unspecific condition and is not directly associated to tissues in the brain.

Several blood biomarkers may be helpful when diagnosing the cause of opportunistic CNS infection. For instance, serology has a high negative predictive value in patients with cerebral toxoplasmosis since almost all patients suffering from these complications have detectable serum antibodies.[36] However, at least a third of the world human population are infected with the parasite and thus serology positive.[37] CSF toxoplasmosis PCR test and response to treatment is therefore the definitive way to establish this diagnose. Methods for detection of cryptococcal antigen in patients with cryptococcal meningitis is highly sensitive and specific in CSF, but also in blood. Furthermore, it is possible to detect the infection prior to meningitis by cryptococcal antigen test in blood.[38] In patients with CMV encephalitis, the number of viral particles is high in CSF and blood and measured by quantitative CMV PCR.[39] There are no blood biomarkers helpful for diagnosing progressive multifocal leukoencephalopathy (PML) or Epstein-Barr virus–induced CNS lymphoma.

4.1 | In summary

Although clinical examinations, CSF analyses, and brain imaging are the most important ways to estimate the impact of CNS HIV

infection and to diagnose CNS opportunistic infections, several blood biomarkers such as viral count, CD4 cells, serology/antigen tests for opportunists, and NfL concentration may give important information for clinical decisions.

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CONFLICT OF INTEREST

HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker. MG has received research grants from Gilead Sciences and Janssen-Cilag and honoraria as speaker and/or scientific advisor from Amgen, Biogen, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV, Janssen-Cilag, MSD, Novocure, Novo Nordic, Pfizer, and Sanofi. RWP and LH have no conflicts.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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