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Authors

Anderson, Albert M
Croteau, David
Ellis, Ronald J
et al.

Publication Date

2018-06-01

DOI

10.1016/j.jneuroim.2018.03.007

Peer reviewed



Published in final edited form as:

J Neuroimmunol. 2018 June 15; 319: 13–18. doi:10.1016/j.jneuroim.2018.03.007.

HIV, Prospective Memory, and Cerebrospinal Fluid Concentrations of Quinolinic acid and Phosphorylated Tau

Albert M. Anderson^a, David Croteau^b, Ronald J. Ellis^b, Debra Rosario^c, Michael Potter^c, Gilles J. Guillemin^{d,e}, Bruce J. Brew^{e,f}, Steven Paul Woods^g, and Scott L. Letendre^c

^aDepartment of Medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia

^bDepartment of Neurosciences, University of California at San Diego, La Jolla, California

^cDepartments of Medicine and Psychiatry, University of California at San Diego, La Jolla, California

^dDepartment of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Australia

^ePeter Duncan Neurosciences Research Unit, St Vincent's Centre for Applied Medical Research, Sydney, Australia

^fDepartment of Neurology, St Vincent's Hospital, Sydney, Australia

^gDepartment of Psychology, University of Houston, Houston, Texas

Abstract

There is mounting evidence that prospective memory (PM) is impaired during HIV infection despite treatment. In this prospective study, 66 adults (43 HIV+ and 23 HIV negative) underwent PM assessment and cerebrospinal fluid (CSF) examination. HIV+ participants had significantly lower PM but significantly higher CSF concentrations of CXCL10 and quinolinic acid (QUIN). Higher CSF phosphorylated Tau (pTau) was associated with worse PM. In a secondary analysis excluding outliers, higher QUIN correlated with higher pTau. CSF QUIN is thus elevated during HIV infection despite antiretroviral therapy and could indirectly contribute to impaired PM by influencing the formation of pTau.

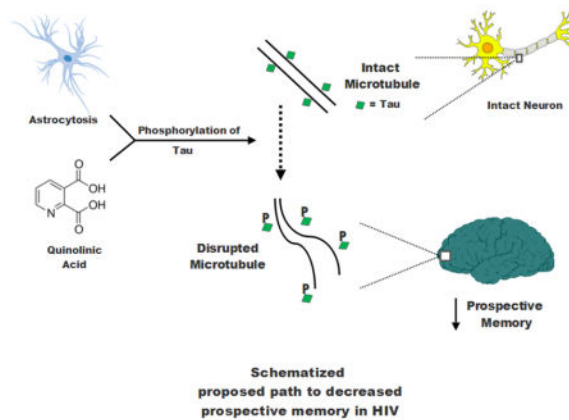
Graphical Abstract

Corresponding Author: Albert M. Anderson, MD, MHS, Emory University School of Medicine, 341 Ponce de Leon Avenue, Atlanta, GA 30308, Phone: 404-616-3147, Fax: 404-616-9702, aande2@emory.edu.

Conflicts of interest:

None

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Keywords

Human Immunodeficiency Virus; Acquired Immunodeficiency Syndrome; Neurocognitive disorder; Cerebrospinal fluid; Tau proteins; Tryptophan

1. Introduction

HIV-associated neurocognitive disorders (HAND) are persistently common in the combination antiretroviral (cART) era. Up to 40% of HIV+ adults with undetectable plasma HIV RNA levels and minimal neuropsychological comorbidities have at least mild neurocognitive impairment (Heaton et al., 2010). Biological evidence of ongoing neuronal damage during cART comes from magnetic resonance spectroscopy studies as well as studies of neuronal injury biomarkers such as neurofilament- light (Harezlak et al., 2011, Jessen Krut et al., 2014). Yet, the underlying pathogenesis of neuronal damage during cART remains poorly understood.

While inflammation persists during treated HIV and may be a cause of neuronal damage (Zayyad and Spudich, 2015), other processes could also contribute to HAND pathogenesis. Quinolinic acid (QUIN), for example, is a neurotoxin that is a product of the kynurenine pathway for tryptophan metabolism (Vecsei et al., 2013). CSF QUIN levels are elevated during HIV-associated dementia in the absence of cART (Heyes et al., 1991). The ratio of kynurenine to tryptophan (known as the K/T ratio) reflects increased activity of the kynurenine pathway and is associated with HIV-associated mortality when measured from the blood (Byakwaga et al., 2014). Similarly, the CSF Q/T ratio was found to be the earliest predictor of neurological disease in untreated simian immunodeficiency virus (SIV)-infected macaques, and kynurenine pathway metabolites in the brain do not normalize in the SIV-infected brain despite cART (Drewes et al., 2015).

There are also lingering questions as to whether HAND has any pathogenic similarities with Alzheimer's disease (AD), the most common dementia worldwide. The tau protein, which is critical for the stabilization of microtubules and neuronal integrity, is hyperphosphorylated in AD and other dementias (Brunden et al., 2009). Several studies have attempted to determine whether HIV is also associated with abnormal Tau levels and might represent a

“Tauopathy”. Studies in the pre-cART era focusing on total Tau (t-Tau) were small, and the results were conflicting (Andersson et al., 1999, Green et al., 2000). More recent studies have focused on phosphorylated Tau (pTau), which is more specific for Tauopathy-associated dementias. Again, some studies found a relationship between increased CSF pTau and HAND (Brew et al., 2005), while others did not (Clifford et al., 2009, Krut et al., 2016, Peterson et al., 2014).

A study published in 2006 from the HIV Neurobehavioral Research Program (HNRP) at the University of California at San Diego focused on the relationship between t-Tau and the specific cognitive domain of prospective memory (PM) (Woods et al., 2006). PM relates to the execution of a future intention, also known as “remembering to remember”. Diminished PM is common among persons with HIV disease and is strongly associated with dependence in a wide range of activities of daily living in both older adults and in HIV-infected individuals (Woods et al., 2008a, Woods et al., 2012). The earlier HRNP study demonstrated that CSF t-Tau levels correlated inversely with PM. In the current study, we examined the relationship between PM and the more specific pTau in a new cohort of HIV-infected individuals. QUIN has been shown to induce the phosphorylation of Tau in vitro and co-localizes with hyperphosphorylated Tau in cortical neurons of the brain during AD (Rahman et al., 2009). Therefore, we also measured CSF kynurenine metabolites including QUIN, as well as other selected markers that have been associated with HIV and HAND.

2. Methods

2.1 Assessment of Participants

A cohort of HIV-infected (HIV+) and HIV-uninfected (HIVnegative) adults were prospectively recruited at the HNRP. Exclusion criteria were: 1) Positive urine drug screen (except cannabis) or breath test for alcohol; 2) Current drug or alcohol dependence within the past 30 days as determined by the Composite International Diagnostic Interview (CIDI version 2.1) (WorldHealthOrganization, 1998) using DSM-IV-TR criteria (AmericanPsychiatricAssociation, 1994); 3) A diagnosis of schizophrenia, psychosis, or clinically significant neurological disease including seizures and traumatic brain injury with loss of consciousness >15 minutes; or 4) A verbal intelligence quotient (IQ) estimate ≥ 70 on the Wechsler Test of Adult Reading (WTAR; Psychological Corporation, 2001). Only HIV+ participants who had virologic control on cART with paired plasma and CSF HIV RNA levels < 50 copies/ml were included for the current study. The study was approved by the Institutional Review Board and informed consent was obtained from all participants.

The Memory for Intentions Screening Test (MIST) (Woods et al., 2008b), a standardized 30-minute assessment composed of 8 PM items, was administered to all participants. The MIST contains equally balanced PM items that use a delay of either 2 minutes or 15 minutes. Cues were either time-based (e.g., “In 2 minutes, ask me what time this session ends.”) or event-based (e.g., “When I hand you a postcard, self-address it.”) Response modalities were either verbal (e.g., “Tell me the following”) or physical (e.g., “Perform the following action”). A series of word search puzzles served as ongoing distraction tasks that separated PM trials. Raw MIST summary scores were used as the primary PM criterion in all statistical analyses (range = 0 – 48, with higher scores reflecting better PM performance).

Participants also underwent comprehensive neuropsychological testing for the assessment of HAND according to Frascati criteria (Antinori et al., 2007). The following neurocognitive domains were assessed:

1. Retrospective memory with a) Long-delay discriminability index of the California Verbal Learning Test–Second Edition (CVLT–II; Delis, Kramer, Kaplan, and Ober, 2000) (Delis et al., 2000) and b) Logical Memory II subtest of the Wechsler Adult Intelligence Scale–Memory Scales–III (Wechsler, 1997).
2. Attention/working memory with a) Digit Span subtest of the Wechsler Adult Intelligence Scale–Third Edition and b) Trial 1 from the CVLT–II;
3. Executive function with a) total move score from the Tower of London–Drexel test (Culbertson and Zillmer, 1998) and b) Trail Making Test (TMT) Part B; (Reitan and Wolfson, 1985)
4. Speed of information processing with a) Digit Symbol subtest of the WAIS–III and b) TMT Part A;
5. Learning with a) CVLT–II Trials 1–5 total and b) Logical Memory I (LM–I);
6. Verbal fluency with the Action Fluency test (Woods et al., 2005); and
7. Motor skill with Grooved Pegboard Test (Klove, 1963).

Normative values that accounted for age, sex, race, and educational level were used to generate Z scores for each domain. A global clinical rating score was generated from results across these seven domains with a range of 1 (above average) to 9 (severely impaired). Global clinical rating scores ≥ 5 identified neurocognitive impairment and were used in HAND diagnosis (Woods et al., 2004).

2.2 Laboratory testing

HIV RNA levels from plasma and CSF were measured with a commercial assay (Roche Amplicor v.1.5 with lower limit of detection 50 copies/ml). CSF biomarkers of inflammation and astrocytosis that have been associated with HAND were also measured. These included: CXCL10, an interferon- induced chemokine shown to promote HIV replication in lymphocytes and macrophages (Liu et al., 2011); CCL2, a chemokine responsible for monocyte migration (Dhillon et al., 2008), and s100 β , a protein expressed by astrocytes that has an autocrine effect of astrocyte apoptosis (Sen and Belli, 2007). CXCL10 was measured via electrochemiluminescence (Mesoscale Discovery). pTau was measured by Luminex bead array (Invitrogen). S100 β was measured by enzyme linked immunosorbent assay (Diasorin). Tryptophan (TRP), Kynurenine (KYN), Picolinic acid (PIC), and QUIN were measured with methods previously described (Jones et al., 2015, Lim et al., 2017). Briefly, TRP and KYN were measured using ultra high performance liquid chromatography (UHPLC), while QUIN and PIC were measured using gas chromatography- mass spectrometry (GC-MS).

2.3 Statistical analyses

For the statistical analysis, variable distributions were inspected for skewness and outliers. As done in previous studies by our group and others, skewness was reduced by natural log

transformation to enable use of parametric tests (Anderson et al., 2015, Jessen Krut et al., 2014). Comparisons of HIV+ and negative subjects on continuous variables were performed using t-tests. Biomarker comparisons were made without and with adjustment for significant imbalances in demographic profiles of the two groups using linear regression. Comparisons for categorical variables were performed using chi-square tests. Transformation did not substantially improve the distribution of CSF red blood cell (RBC) count so the non-parametric Wilcoxon rank sum test was used to test differences between HIV+ and negative groups. Pearson correlation coefficients were used to test associations between CSF biomarkers and PM as well as CSF biomarkers and pTau. Linear regression was also performed to compare PM and pTau as dependent variables to independent variables that were statistically significant in univariate correlations. We hypothesized that there would be significant relationships between between QUIN, pTau, and PM. Comparisons were two-tailed and alpha for statistical significance was set at <0.05.

3. Results

3.1 Neuropsychological and biomarker results

A total of 66 participants were assessed (43 HIV+ and 23 HIV-negative, see Table 1 for demographic/disease characteristics). HIV+ participants were older and more likely to be men. HIV+ participants were infected for a median of 15 years, median current CD4+ T cell count was 559 cells/ μ L, and median nadir CD4+ T-cell count was 199 cells/ μ L. The median duration of the current cART regimen was 17 months and median central nervous system penetration (CPE) score was 7 (interquartile range 6–9). The most commonly prescribed cART regimens were: efavirenz/tenofovir/emtricitabine (n=5), ritonavir-boosted atazanavir/tenofovir/emtricitabine (n=5), and ritonavir-boosted lopinavir/tenofovir/emtricitabine (n=4). There was no significant difference in CSF RBC count between HIV+ and negative groups (median RBC 6 versus 2 respectively, $p=0.8$). The proportion of participants with neurocognitive impairment was not significantly different between groups (27.9% versus 17.4%, $p=0.34$). However, the MIST summary score was significantly lower in the HIV+ group (mean 39.8 in HIV+ versus 43.2 in HIV-negative, $p=0.039$). Mean time-based (6.07 versus 6.78, $p=0.062$) and event-based (7.21 versus 7.61, $p=0.12$) PM subscores also tended to be lower in HIV+ participants.

Several CSF biomarkers differed between HIV+ and HIV-negative groups, the majority of which persisted in adjusted analyses (Table 1). CXCL10 and QUIN were significantly higher in HIV+ participants (Figures 1a and 1b). CSF pTau was also higher in the HIV+ group in univariate analysis but this difference weakened in multivariate analysis. In contrast, CSF levels of TRP and PIC were lower in HIV+ participants. As a result, CSF KYN/TRP ratio was nearly one log higher in HIV+ participants (Figure 1c).

3.2 Outcome variable: Prospective memory

Correlations between CSF biomarkers and PM for the entire cohort are shown in Table 2. PM correlated negatively with both pTau ($r=-0.357$, $p=0.003$), and CCL2 ($r=-0.280$, $p=0.024$). Additionally, both time-based and event-based PM sub-scores correlated negatively with pTau ($r=-0.302$, $p=0.014$ and $r=-0.307$, $p=0.012$ respectively). The only significant

marker in the multiple linear regression model with PM as the outcome variable ($R^2 = 0.17$, $p=0.0032$) was pTau (T ratio= -2.61 , $p= 0.011$).

3.3 Outcome variable: pTau

Analyses comparing QUIN to pTau identified 4 substantial outliers (Figure 2). The four outliers were all HIV+ and had better PM than other HIV+ participants ($p=0.0037$) but did not differ in other demographic or disease characteristics. They did tend to be more likely to take abacavir (50.0% vs. 10.3%, $p=0.06$) but not other cART drugs, suggesting that abacavir may alter the relationship between QUIN and pTau. For this reason, stratified analyses were performed with: 1) the entire cohort ($n=66$) and 2) excluding these 4 outliers ($n=62$). For the entire cohort, pTau correlated with s100 β ($r= 0.359$, $p= 0.003$) and CXCL10 ($r= 0.307$, $p=0.012$) (Table 3). Without the 4 outliers, these two correlations remained statistically significant and the correlation between pTau and QUIN substantially strengthened ($r= 0.381$, $p= 0.002$, see Table 3 and Figures 2 and 3). For correlates of pTau, multiple linear regression for the entire cohort showed a significant association with s100 β (t ratio= 2.79 , $p= 0.007$ in Table 4) which remained significant when the outliers were excluded. This regression analysis of the subgroup also showed that the relationship between QUIN and pTau strengthened to near statistical significance (t ratio= 1.86 , $p= 0.068$).

4. Discussion and conclusions

HAND in the cART era continues to be common (Heaton et al., 2010). However, it is not clear if all markers that were associated with HAND in the pre-cART era remain pertinent in the cART era. We acknowledge that the HIV+ and HIV-negative groups were not well matched in this study (particularly with regards to sex and age). This may have influenced the finding that biomarker concentrations differed between the two groups. For example, differences in cytokine secretion have been observed based on sex in previous studies involving ex vivo models of sepsis (Asai et al., 2001). If the groups were better matched in our study, then multivariate analyses may not have been needed. The HIV-infected participants reflect the HIV clinic population at UCSD, which is mostly white and male. While some key demographics differed between the groups, CXCL10 and QUIN remained higher in the HIV+ group even after adjusting for these differences. Blood levels of CXCL10 have previously been found to be elevated during treated HIV infection (Wada et al., 2015), and the current study demonstrates that this elevation also exists in the central nervous system (CNS). The kynurenine/tryptophan (K/T) ratio, a reflection of indoleamine-2,3-dioxygenase (IDO) activity, has recently been linked to poor CD4+ recovery and mortality during cART (Byakwaga et al., 2014). The current analysis suggests that this pathway is also upregulated in the CNS during HIV infection despite virologic suppression. QUIN is a product of this pathway and is a known neurotoxin (Vecsei et al., 2013). Therefore the finding of higher QUIN levels despite complete virologic suppression is important. The contrast of higher CSF QUIN and lower CSF PIC found in this study suggests that the non-enzymatic conversion of 2-amino-3-carboxymuconate-semialdehyde, a late stage catabolite of the kynurenine pathway, predominates in the CNS during HIV. This is the likely cause of higher QUIN, which given its neurotoxic properties could contribute to neuronal injury and neuropsychological impairment. While our multivariate analyses

confirmed several biomarker concentration differences between HIV+ and negative groups, a study in which participants were matched for demographics may have been more conclusive. Future investigations should incorporate matching for age and sex.

The role of phosphorylated Tau (pTau) in HAND has been the subject of controversy. A recent study found no significant difference in CSF pTau concentration between individuals with HIV on cART and HIV seronegative controls (Krut et al., 2017). CSF pTau was significantly higher in the HIV+ group in our study, but this difference became statistically non-significant after adjustment for demographics. Strict matching may be needed to more definitively determine differences in pTau between HIV+ individuals on cART and HIV-negative individuals. We found that multiple markers were associated with elevated pTau, which suggests that the formation of this abnormal protein may result from multiple processes in the CNS during HIV (see graphical abstract). In the multivariate model, s100 β (a marker of astrocytosis) was significantly associated with pTau, while there was a strong association trend between QUIN and pTau. These findings might be explained by evidence that QUIN can induce phosphorylation of Tau (Rahman et al., 2009), and that astrocytosis may contribute to tauopathies (Leyns and Holtzman, 2017). However, given that our analysis included HIV-negative participants, further research will be needed to more definitively evaluate whether s100 β and QUIN are independently associated with pTau in a cohort limited to HIV+ individuals.

Prospective memory (PM) has been consistently linked to problems with activities of daily living during HIV (Woods et al., 2008b). Previous studies by our group showed that PM is diminished in HIV+ individuals with mixed profiles of virologic control (Carey et al., 2006, Morgan et al., 2012). The current analysis shows that PM is significantly worse in HIV+ adults despite virologic suppression in both plasma and CSF during cART. However, we acknowledge that the difference between the two groups became less significant in multivariate analysis. There is a reliable effect of age on prospective memory (PM) in the general population, such that older adults show worse PM than younger adults. (Henry et al., 2004) In the setting of HIV disease, we tend to see additive effects of HIV and aging on PM as measured in the laboratory such that HIV-associated PM deficits are exaggerated in older versus younger samples. (Avci et al., 2016, Woods et al., 2010) In the current data, we see a similar effect, whereby we observe a large, significant adverse effect of HIV on our summary measure of PM in the older adults (using a median split) ($p=0.003$, Cohen's $d = -1.1$). In our younger adults, HIV is associated with a small, non-significant effect ($p=0.51$, Cohen's $d = -0.2$). There is no reliable evidence that sex affects PM in either healthy samples or in the setting of HIV disease. For example, recent data from our laboratory using a large HIV+ cohort found no significant effects of sex on the summary measure of PM used in this study. (Avci et al., 2017) Similarly, in the present study, sex was not significantly associated with PM in either the HIV- or HIV+ groups (p values > 0.05).

Larger studies are indicated to determine the overall prevalence of HIV-associated PM impairment during effective cART and to examine its relationship to other clinical outcome measures such as mortality. Lastly, the finding of a significant relationship between higher pTau and decreased PM in multivariate analysis indicates that this protein may have a detrimental role with regards to this particular cognitive domain. Again, a study limited to

HIV-infected individuals will be needed to show an HIV-specific effect. While we found that pTau was the only marker that was significantly associated with diminished PM, we did not measure all markers that have been associated with HAND. It is possible that the incorporation of other HAND-associated markers would have resulted in a weaker association between pTau and PM. While we acknowledge that the relationship between higher pTau and lower PM does not prove causation, the results justify more research into all domains of cognition during HIV and the factors that may influence them.

Acknowledgments

Funding sources:

NIH K23MH095679

NIH K24MH097673

NIH R01MH073419

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Highlights

- Study of prospective memory (PM) and cerebrospinal fluid (CSF) during HIV infection
- Prospective memory was diminished in HIV+ compared to HIV negative
- CSF levels of CXCL10 and quinolinic acid (QUIN) were higher in HIV+ participants
- Higher phosphorylated Tau was associated with worse PM
- Secondary analysis showed that higher CSF QUIN was associated with higher pTau

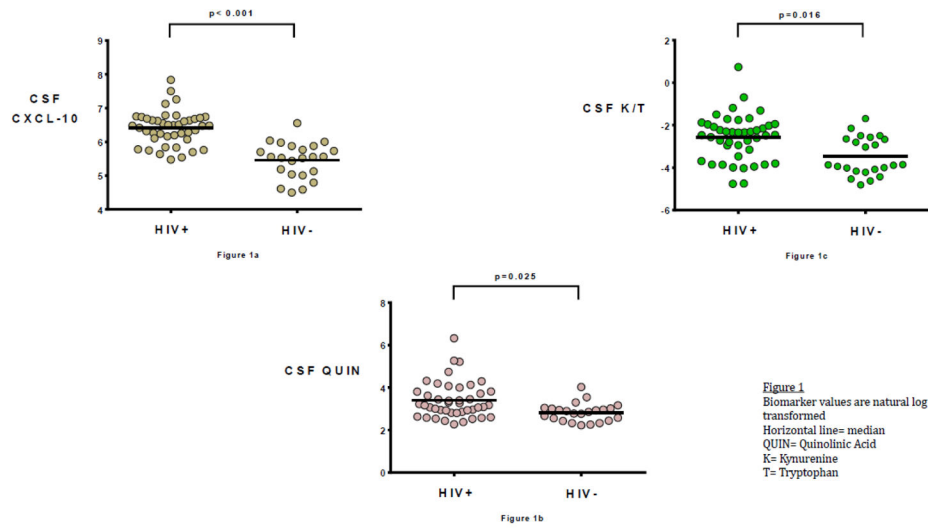


Figure 1. Biomarker values are natural log transformed. Horizontal line= median. Q=Quinolinic Acid. U=Kynurenine. I=Tryptophan

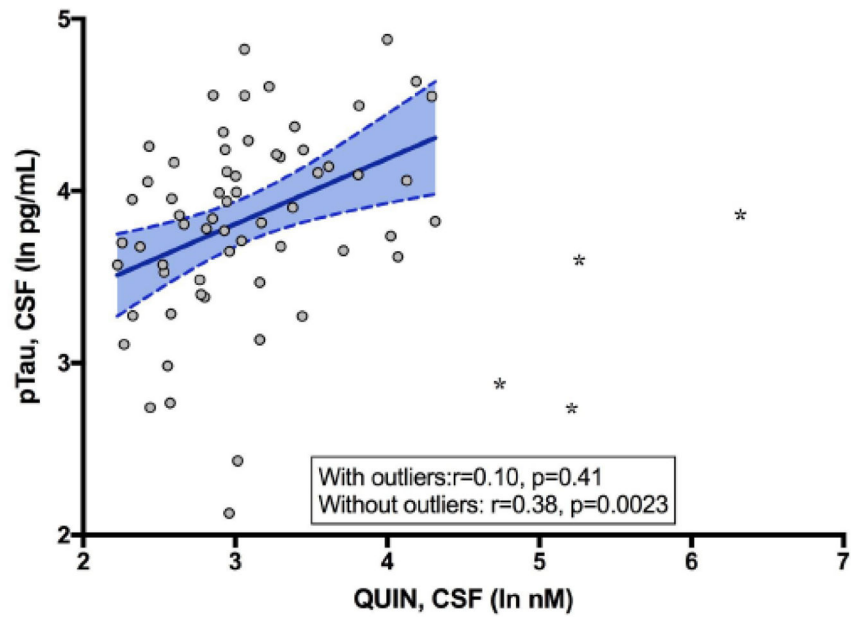


Figure 2. Positive correlation between QUIN and pTau, with and without QUIN outliers. Asterisks represent the four outliers. Blue area represents regression line and 95% confidence interval without QUIN outliers.

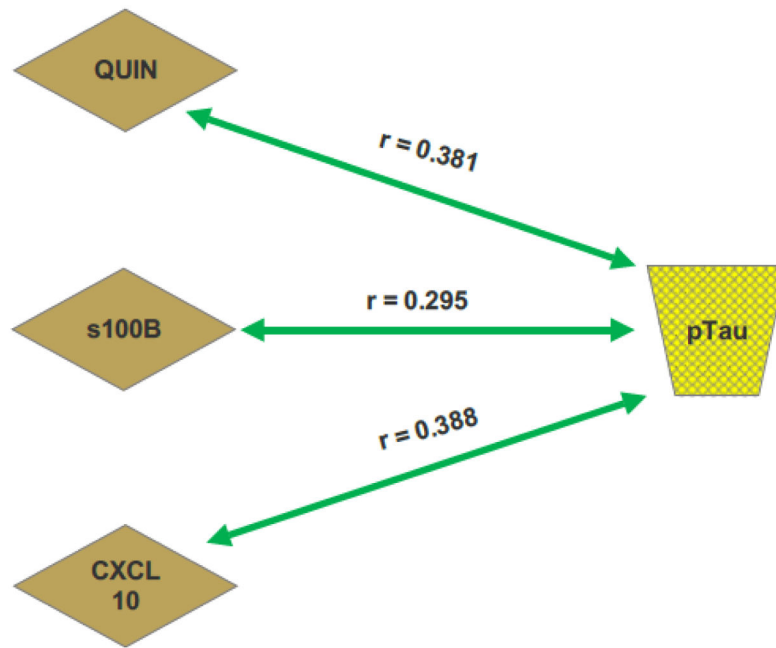


Figure 3. Significant univariate correlations between CSF biomarkers and phosphorylated Tau (pTau) in group (n=62) that excludes QUIN outliers. Green arrows denote positive relationships QUIN= quinolinic acid

Table 1

Results are reported as either mean (standard deviation) or number (percent), NA= Not applicable; PM= Prospective Memory; K= Kynurenine; T= Tryptophan Biomarkers are reported as natural log transformed values

Variable	HIV + (n=43)	HIV- (n=23)	2 group p-value	Adjusted p-value *
Age (Years)	46.1 (9.1)	37.1 (12.0)	0.003	NA
Sex (Male)	37 (86.0%)	11 (47.8%)	0.001	NA
Race (White)	31 (72.1%)	11 (47.8%)	0.051	NA
PM summary score	39.8 (6.2)	43.2 (6.1)	0.039	0.412
CSF biomarkers				
CXCL10	6.41 (0.50)	5.46 (0.53)	< 0.001	< 0.001
S100 β	-0.09 (0.60)	-0.12 (0.41)	0.859	0.781
CCL2	6.31 (0.36)	6.21 (0.31)	0.290	0.582
pTau	3.93 (0.53)	3.53 (0.55)	0.004	0.086
Tryptophan	0.52 (0.40)	0.69 (0.24)	0.070	0.041
Kynurenine	-2.07 (0.95)	-2.79(0.89)	0.004	0.058
Picolinic Acid	3.96 (0.86)	4.43 (0.44)	0.004	0.039
Quinolinic Acid	3.40 (0.86)	2.83 (0.43)	0.001	0.025
K/T ratio	-2.58 (1.07)	-3.48 (0.90)	0.001	0.016

* Denotes linear regression adjusted values based on imbalances in age, gender, and race.

Table 2

Correlations between CSF markers and prospective memory (PM) Sorted in descending order of correlation strength

Domain	Biomarker	Correlation(r) for n=66	P value
PM	pTau	-0.357	0.003*
PM	CCL2	-0.280	0.024*
PM	CXCL10	-0.175	0.160
PM	s100B	-0.156	0.210
PM	QUIN	0.072	0.568

Correlations with p value < 0.05 denoted by *

Quin= quinolinic acid; pTau= phosphorylated Tau

(See text for multivariate model results for PM)

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Correlations between CSF markers and phosphorylated Tau (pTau) Groups are n=66 (includes QUIN outliers) and n=62 (excludes QUIN outliers) Sorted in descending order of correlation strength

Table 3

Biomarker	Biomarker	Correlation(r) for n=66	P value	Correlation(r) for n=62	P value
pTau	s100B	0.359	0.003*	0.295	0.020*
pTau	CXCL-10	0.307	0.012*	0.388	0.002*
pTau	CCL-2	0.223	0.074	0.226	0.080
pTau	QUIN	0.104	0.41	0.381	0.0023*

QUIN= quinolinic acid

Correlations with p value < 0.05 denoted by *; Correlation in **bold** becomes <0.05 after exclusion of QUIN outliers

Linear regression table for best model explaining phosphorylated (pTau) for n=66 and n=62 groups when including biomarkers from table 3 with $p < 0.05$

Table 4

Biomarker (n=66)	T ratio	P Value	Biomarker (n=62)	T ratio	P Value
S100β	2.79	0.007	S100β	2.06	0.044
CXCL10	1.92	0.060	QUIN	1.86	0.068
QUIN	0.06	0.822	CXCL10	1.52	0.134

QUIN= quinolinic acid

$R^2 = 0.20$, $p = 0.0034$ for $n=66$ and $R^2 = 0.21$, $p = 0.0008$ for $n=62$