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Beta amyloid levels in CSF of HIV-infected people vary by exposure to antiretroviral therapy

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Abstract

Background: HIV-associated neurocognitive disorders (HAND) persist despite the widespread implementation of combined antiretroviral therapy (ART). As people with HIV (PWH) age on ART regimens, the risk of age-related comorbidities such as Alzheimer's disease (AD) may increase. However, questions remain as to whether HIV or ART will alter such risks. Beta amyloid (A β) and phosphorylated-tau (p-tau) proteins are associated with AD and their levels are altered in the CSF of AD cases.

Methods: To better understand how these AD-related markers are affected by HIV-infection and ART, postmortem CSF collected from 70 well-characterized HIV+ decedents was analyzed for A β ₁₋₄₂, A β ₁₋₄₀, and p-tau levels.

Results: A β ₁₋₄₂ and A β ₁₋₄₀ CSF levels were higher in cases that were exposed to ART. A β ₁₋₄₂ and A β ₁₋₄₀ CSF levels were also higher in cases on protease inhibitors (PI) compared to those with no exposure to PIs. A β ₁₋₄₂ and A β ₁₋₄₀ levels in CSF were lowest in HIV+ cases with HIV-associated dementia (HAD) and levels were highest in those diagnosed with asymptomatic neurocognitive impairment (ANI) and minor neurocognitive disorder (MND). A β ₁₋₄₂ and A β ₁₋₄₀ were inversely related with p-tau levels in all cases, as previously reported.

Conclusions: These data suggest that ART exposure is associated with increased levels of A β ₁₋₄₂ and A β ₁₋₄₀ in the CSF. Also, HAD, but not ANI/MND diagnosis is associated with decreased levels of A β ₁₋₄₂ and A β ₁₋₄₀ in CSF, potentially suggesting impaired clearance. These data suggest that HIV infection and ART may impact pathogenic mechanisms involving A β ₁₋₄₂ and A β ₁₋₄₀, but not p-tau.

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Introduction

HAND affects approximately 50% of people with HIV (PWH) despite the ability to control HIV replication with antiretroviral therapy (ART)^[1, 2]. Approximately 40% of PWH in the United States (U.S.) are over the age of 55^[3], and some reports suggest that PWH experience premature aging^[4–6]. In addition to the risk of developing HAND, older PWH may also be at risk for age-associated neurodegenerative disorders including AD and its precursor, amnesic mild cognitive impairment (aMCI)^[7]. In fact, evidence of AD-related neuropathogenesis has been observed in some older PWH^[8–11], and one study showed higher risk for aMCI among PWH compared to the general population^[12] possibly due to potential compounding effects of HIV and aging on mechanisms of neural insult such as inflammation^[6, 13].

Amyloid beta (A β) and p-tau accumulation are hallmarks of AD that are used to confirm AD diagnosis in postmortem brains. Several studies have found A β and p-tau accumulation in HIV+ brains^[14, 15]. Several groups have investigated A β and p-tau levels in the CSF of HIV + cases with different levels of cognitive impairment^[10, 16–19]. However, the levels A β and p-tau in brains and CSF of PWH on ART compared to those naïve to ART have not been explored. While few of the HIV cases have lived to the age of late onset AD, it may be important to determine the levels of A β and p-tau in the CSF of people on ART because these people are expected to live normal lifespans.

In our study, the CSF from a cohort of well-characterized PWH was analyzed for A β and p-tau levels. The data were stratified by cognitive status, CD4 count, viral load (vl), age and exposure to ART. The findings illustrate a yet unreported relationship between ART and A β levels; they reveal that lowest levels of CSF A β were found in cases with the most severe forms of HAND (i.e. HAD), and demonstrate a strong inverse relationship between CSF A β and p-tau.

Methods:

Study population

For the present study, we evaluated brain tissues from a total of 71 HIV+ donors (Table 1), from the National NeuroAIDS Tissue Consortium (NNTC) (Institutional Review Board [IRB] #080323). All studies adhered to the ethical guidelines of the National Institutes of Health and the University of California, San Diego. These cases had neuromedical and neuropsychological examinations within a median of 12 months before death. Subjects were excluded if they had a history of CNS opportunistic infections or non-HIV-related developmental, neurologic, psychiatric, or metabolic conditions that might affect CNS functioning (e.g., loss of consciousness exceeding 30 minutes, psychosis, etc). HAND diagnoses (neurocognitively unimpaired [NIU], asymptomatic neurocognitive impairment [ANI], minor neurocognitive dysfunction [MND], and HIV-associated dementia [HAD]) were determined from a comprehensive neuropsychological test battery administered according to standardized protocols ^[20].

Neuromedical and neuropsychological evaluation

Participants underwent a comprehensive neuromedical evaluation that included assessment of medical history, structured medical and neurological examinations, and the collection of blood, cerebrospinal fluid (CSF), and urine samples, as previously described [1, 20]. Clinical data (plasma viral load [VL], postmortem interval, CD4 count, global, learning and motor deficit scores [GDS, LDS, and MDS]) were collected for the HAND donor cohorts.

Neuropsychological evaluation was performed, and HAND diagnoses were determined via a comprehensive neuropsychological test battery, which was constructed to maximize sensitivity to neurocognitive deficits associated with HIV infection [see [20] for a list of tests]. Raw tests scores were transformed into demographically adjusted T-scores, including adjustments for age, education, gender and race. These demographically adjusted T-scores were converted to clinical ratings to determine presence and degree of neurocognitive impairment on seven neurocognitive domains, as previously described (Woods et al., 2004). As part of the neuropsychological battery, participants also completed self-report questionnaires of everyday functioning (i.e., Lawton and Brody Activities of Daily Living questionnaire; [21], and/or Patient's Assessment of Own Functioning; PAOFI [22, 23]. Participant's performance on the neuropsychological test battery and their responses to the everyday functioning questionnaires were utilized to assign HAND diagnoses following established criteria [24], i.e., HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).

Quantification of A β ₁₋₄₂ and p-tau levels in the CSF:

CSF samples were analyzed for p-tau using a solid phase enzyme immunoassay, Innostest Phospho-Tau (181P) (Fujirebio, cat. no. 81581) and phospho-tau CAL-RVC (Fujirebio, cat. no 81582) according to manufacturer's instructions. Beta amyloid peptides (1-38), (1-40) and (1-42) were measured in the CSF using V-Plex plus A β Peptide 1 (4G8) kit (Meso Scale Diagnostics, cat. no. K15199G) according to manufacturer's instructions.

Statistical analysis

Statistical significance was determined using one-way ANOVA for comparisons between more than two groups and using a T-test when there were only two groups. All results were expressed as mean \pm SEM. The differences were significant if p values were <0.05 and the actual p value was reported if near, but over the 0.05 cutoff. All sample sizes are included in figure legends.

Data Availability:

All data will be made available on-line through the National NeuroAIDS Tissue Consortium.

Results:

A β ₁₋₄₂ and A β ₁₋₄₀ concentrations are higher in the CSF of HIV+ individuals on ART compared to ART naïve, higher in those taking PIs compared to no PIs, lower in those with worse neurocognitive impairment and negatively correlated with pTau concentration.

$A\beta_{1-42}$ and $A\beta_{1-40}$ and pTau concentrations in the CSF were determined by electrochemiluminescent assay using Mesoscale discovery (MSD). Levels of $A\beta_{1-42}$ and $A\beta_{1-40}$ in PWH being treated with ART or not on ART were plotted. In CSF from people on ART, levels of $A\beta_{1-42}$ and $A\beta_{1-40}$ (Figure 1A and B) were increased compared to those taking no ART, $p = 0.0126$ and 0.0429 , respectively. To determine if levels of $A\beta_{1-42}$ and $A\beta_{1-40}$ differ with by PI usage, quantities were stratified by cases with history of PI and no PI in the ART regimens or ART naïve. In those last known taking PIs, levels of $A\beta_{1-42}$ and $A\beta_{1-40}$ were significantly increased compared to cases not exposed to PIs, with p values of 0.0281 and 0.0204 , respectively (Figure 1C and D). CSF $A\beta_{1-42}$ and $A\beta_{1-40}$ levels were also stratified by severity of neurocognitive impairment: NUI, ANI/MND, and HAD. In CSF, there is a trend for decrease in CSF levels of $A\beta_{1-42}$ and a decrease in $A\beta_{1-40}$ in HAD cases compared to ANI-MND or NUI (Figure 1E and F). To determine the association of p-tau and $A\beta_{1-42}$ and $A\beta_{1-40}$ in the CSF, we plotted $A\beta_{1-42}$ vs p-tau (Figure 1G) and $A\beta_{1-40}$ v. p-tau (Figure 1H). CSF $A\beta_{1-42}$ v. CSF p-tau showed a negative correlation with a Pearson r value of -0.51 and a significance value of $p < 0.0001$ (Figure 1G). CSF $A\beta_{1-40}$ vs p-tau showed a negative correlation with a Pearson r value of -0.45 and a significance value of $p < 0.0001$ (Figure 1H). These data support previous findings which have shown a negative correlation between CSF p-tau and $A\beta_{1-42}$ and $A\beta_{1-40}$. To determine if the variance in $A\beta_{1-42}$ levels between the groups was related to clinical variables (plasma viral load (VL), CSF VL, and CD4 count) the entire cohort and also the MND group alone were sub-divided into two and three groups based on $A\beta_{1-42}$ and $A\beta_{1-40}$ levels and analyzed by t-test or one-way ANOVA, respectively. The ratio of $A\beta_{1-41}:A\beta_{1-40}$ and p-tau values was compared between the groups (by HAND, ART, and PI). Finally, the differences in p-tau levels between the groups were analyzed similarly. However, no significant differences were detected between the groups.

Discussion

In this study, we report for the first time that $A\beta_{1-42}$ and $A\beta_{1-40}$ levels in CSF are significantly elevated in PWH that were exposed to ART compared to ART naïve cases. Similarly, $A\beta_{1-42}$ and $A\beta_{1-40}$ levels are significantly elevated in CSF of PWH that were exposed to PIs compared to those that were ART naïve or on ART regimens with no PIs. These analyses also revealed a trend for increased $A\beta_{1-42}$ and $A\beta_{1-40}$ in CSF from NUI, ANI and MND cases compared to those with HAD. As previously reported, a strong inverse relationship between $A\beta_{1-42}$ and $A\beta_{1-40}$ and p-tau levels in CSF was confirmed in this cohort. Interestingly, no significant differences were found in levels of p-tau when analyzed by HAND status or other clinical variables, suggesting that HIV and/or ART may more directly affect $A\beta_{1-42}$ and $A\beta_{1-40}$ levels and not p-tau.

The findings that $A\beta_{1-42}$ and $A\beta_{1-40}$ levels in the CSF are significantly higher in cases exposed to ART compared to ART-naïve cases suggest that ART may affect the clearance of $A\beta_{1-42}$ and $A\beta_{1-40}$ from the brain parenchyma. This remarkable finding may be consistent with and explain data showing that ART regimens can reduce severity of cognitive impairment [25, 26]. However, Giunta et al found that some ART drugs reduce microglial phagocytosis of $A\beta$ and increase production of $A\beta$ by neurons in murine cellular models [27]. It is possible that increased $A\beta$ levels in CSF observed in cases exposed to ART are a reflection of overall production of $A\beta$. It is also possible that ART-mediated effects on mice

is distinct from ART effects in humans. The findings presented here are inconsistent with a recent report that suggest that nucleoside reverse transcriptase inhibitors can block somatic recombination of the APP gene and subsequent generation of $A\beta_{1-42}$ [28]. Furthermore, the fact that cases with exposure to PIs also have increased $A\beta_{1-42}$ and $A\beta_{1-40}$ in the CSF may be consistent with a study suggesting that PIs result in less degradation of $A\beta$ [29]. Levels of $A\beta$ were stratified by CD4 count, viral load, and APOE4 alleles, but no significant differences were observed.

$A\beta$ levels in CSF have been used as a biomarker for AD severity, with increased $A\beta$ plaques being associated with reduced $A\beta$ in CSF [30]. Although conflicting reports exist regarding $A\beta$ levels in CSF of HIV+ people, Brew et al. found that CSF $A\beta_{1-42}$ levels were lower in cases with AIDS dementia complex (ADC) and therefore concluded that ADC pathogenesis may be similar to Alzheimer's disease [16]. Similarly, Clifford et al found that $A\beta_{1-42}$ levels in CSF were lower in HAND cases compared to HIV- controls and HIV+ cases that were NUI [10]. However, the HAND cases were analyzed in aggregate and not stratified by severity as reported here [10]. Gisslen et al reported that $A\beta_{1-42}$ levels in CSF from cases with AIDS dementia complex did not differ from HIV+ NUI cases, which is contrary to the findings in this report [18]. A more recent study of CSF from 25 HIV+ people with HAND showed the highest levels of $A\beta_{1-42}$ and p-tau were found in HAD cases and lowest were found in CSF of ANI cases, which is contrary to our findings when stratified by cognitive status [19]. While the differences were not significant, our findings show a trend that is consistent with the earlier studies that showed decreased $A\beta_{1-42}$ in CSF occurring in people with worse neurocognitive impairment. Given that ART is readily available to PWH, the current findings showing robust differences based on ART exposure may be most relevant moving forward.

HAND is a multifactorial disease that is likely driven partly by age, drugs of abuse, duration of infection, ART initiation, duration of ART adherence, or comorbidities. The current findings provide insight into $A\beta$ biology in the PWH. However, the findings are limited by lack of knowledge of concomitant comorbidities. The variance in $A\beta_{1-42}$ levels between and within HAND groups in this cohort, particularly within the ANI/MND group, illustrate that $A\beta_{1-42}$ levels alone are not associated neurocognitive impairment in all cases. Recent studies have shown that alterations in the ratio of $A\beta_{1-42}:A\beta_{1-40}$ may be related to the neurodegenerative process [31]. However, we found no association between $A\beta_{1-42}:A\beta_{1-40}$ ratio and HAND status or other clinical variables. Future studies that can compare multiple clinical variables with $A\beta$ levels may reveal parameters key to predicting neurocognitive impairment in PWH. Further characterization of alternative biomarkers in CSF or blood may, in conjunction with $A\beta$ levels, provide useful insight into possible mechanisms of neuropathogenesis in individual cases. Biomarkers such as triggering receptor expressed on myeloid cells 2, C-reactive protein, brain-derived neurotrophic factor, or YLK-40, which are directly or indirectly linked to $A\beta$ levels, have been associated with HAND [32-38] and may be useful markers to pair with $A\beta$ levels. A better understanding how genetics or environmental factors may interact with HIV infection to affect $A\beta_{1-42}$ levels, other biomarkers, and influence neurocognitive impairment may lead to improved prognostic and diagnostic care for PWH.

Overall, these data suggest a relationship between A β levels in CSF and exposure to ART in PWH. Furthermore, the relationship between A β levels in CSF and cognitive status deserves further study in additional cohorts. Collection of CSF from more PWH that are over the age of 55 will be helpful to better understand if A β levels are affected with age. Similarly, it will be important to determine if p-tau is affected in PWH and older ages and how it relates to cognitive status.

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Appendix 1:

Name	Location	Role	Contribution
Jerel Adam Fields, PhD	University of California, San Diego	Corresponding author	Design and conceptualization of study; drafted manuscript
Mary K. Swinton, BS	University of California, San Diego	Author	Data acquisition and manuscript revision
Benchawanna Soontornniyomkij, PhD	University of California, San Diego	Author	Data acquisition and organization
Aliyah Carson, BS	University of California, San Diego	Author	Data acquisition and manuscript revision
Cristian L. Achim	University of California, San Diego	Senior author	Data interpretation; revision of the manuscript

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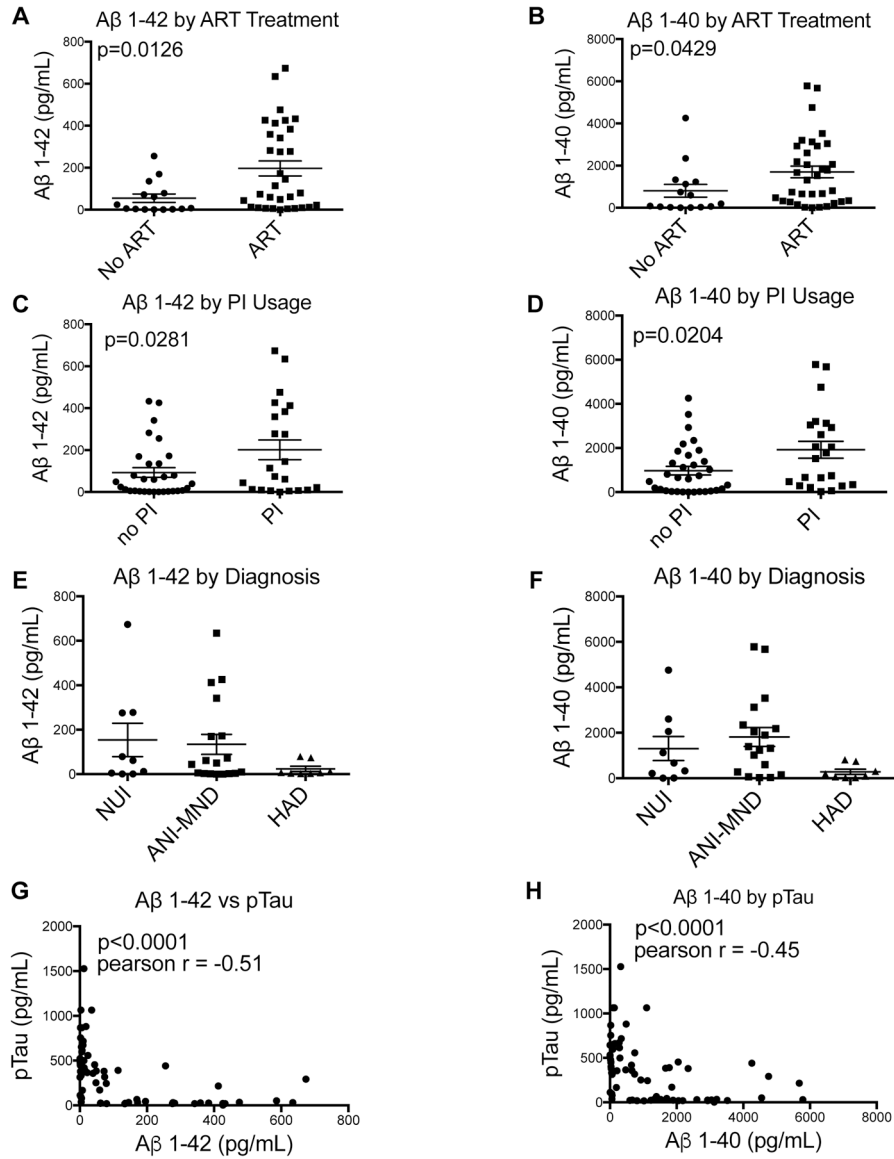


Figure 1: CSF Aβ₁₋₄₂ and Aβ₁₋₄₀ were quantified and plotted based on antiretroviral therapy regimen, HAND diagnosis and by ptau concentration. Last known ART regimen was determined, and CSF concentrations were plotted based on if donors were last known taking ART or last known taking no ART and if they were last known taking PIs or not taking PIs. Aβ₁₋₄₂ and Aβ₁₋₄₀ concentrations were plotted based on ART therapy (A and B). Aβ₁₋₄₂ and Aβ₁₋₄₀ were plotted based on PI usage or no PI usage (C and D). Significance values were determined using student’s t-test (no ART, n = 15; ART, n = 33; no PI, n = 32; PI, n = 22). CSF Aβ₁₋₄₂ and Aβ₁₋₄₀ were quantified and plotted based on neurocognitive diagnoses. Aβ₁₋₄₂ and Aβ₁₋₄₀ were plotted based on diagnoses of NUI, ANI-MND, or HAD (E and F). Significance values were determined using a one-way ANOVA (NUI, n = 9; ANI-MND, n = 18; HAD, n = 8). CSF Aβ₁₋₄₂ and Aβ₁₋₄₀ were plotted versus pTau. (G) Aβ₁₋₄₂ plotted

versus pTau. **(H)** $A\beta_{1-40}$ plotted versus p-tau. Significance and Pearson r values were determined using correlation statistics (n= 68).

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Table:

Demographic data for human CSF samples. Quantities shown are mean +/-standard deviation. Bottom rows depict the p-values and effect sizes between the illustrated groups.

Variables	HAND (n=26)						NUI vs HAND		NUI vs ANI vs MND vs HAD	
	NUI (n=110)	ANI (n=6)	MND (n=12)	HAD (n=8)	ANI-O (n=15)	ND (n=20)	p-value (Cog. Normal vs HAND; t-test)	Effect Size - Cohen's d (Cog. Norm vs HAND)	p-value (NUI vs ANI, NUI vs MND, NUI vs HAD, ANI vs MND, ANI vs HAD, MND vs HAD; ANOVA)	Effect Size: overall (NUI vs ANI, NUI vs MND, NUI vs HAD, ANI vs MND, ANI vs HAD, MND vs HAD)
Years of Age	42.8 ± 7.21	46.83 ± 13.35	42.50 ± 4.56	43.88 ± 9.45	44.27 ± 11.97	45.0 ± 9.51	0.72	0.14	0.44, 0.91, 0.79, 0.32, 0.63, 0.67, 0.75	0.38, 0.05, 0.13, 0.43, 0.26, 0.19
Hispanic ethnicity (%)	10.00	16.67	25.00	0.00	53.33	12.50	n/a	n/a	n/a	n/a
Sex (f/m)	1/9	1/5	1/11	1/7	3/12	4/16	n/a	n/a	n/a	n/a
Years of Education	12.0 ± 1.76	15.0 ± 2.76	13.0 ± 3.07	12.83 ± 2.56	11.27 ± 3.73	12.0 ± 1.73	0.15	0.61	0.02, 0.37, 0.45, 0.20, 0.19, 0.91, 0.19	1.30, 0.40, 0.38, 0.69, 0.82, 0.06
HIV Disease Characteristics										
Plasma VL	160,625.22 ± 292965.6	169540.40 ± 332082.60	315359.55 ± 522262.50	364349.09 ± 631006.34	104554 ± 200222.65	320949 ± 275890.09	0.46	0.12	0.96, 0.44, 0.41, 0.58, 0.55, 0.87, 0.79	0.03, 0.37, 0.41, 0.33, 0.38, 0.08
CD4 count	141.9 ± 143.47	69.83 ± 93.43	109.08 ± 249.26	53.86 ± 99.75	161.53 ± 246.83	78.33 ± 72.54	0.38	0.35	0.29, 0.72, 0.18, 0.72, 0.77, 0.59, 0.74	0.60, 0.16, 0.71, 0.21, 0.17, 0.29
CSF VL (CVL)	36656.25 ± 74983.47	579.00 ± 1252.08	12320.25 ± 33307.13	376572.33 ± 578056.84	5273.14 ± 8356.89	119396.75 ± 227553.46	0.56	0.29	0.31, 0.33, 0.12, 0.45, 0.18, 0.039, 0.036	0.68, 0.42, 0.82, 0.50, 0.92, 0.89
pmi	24.56 ± 36.67	20 ± 16.78	20.75 ± 26.24	14.13 ± 8.76	19.07 ± 21.52	13.47 ± 6.47	0.54	0.2	0.78, 0.78,	0.16, 0.12,

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Variables	HAND (n=26)					NUI vs HAND		NUI vs ANI vs MND vs HAD		
	NUI (n=110)	ANI (n=6)	MND (n=12)	HAD (n=8)	ANI-O (n=15)	ND (n=20)	p-value (Cog. Normal vs HAND; t-test)	Effect Size - Cohen's d (Cog. Norm vs HAND)	p-value (NUI vs ANI, NUI vs MND, NUI vs HAD, ANI vs MND, ANI vs HAD, MND vs HAD; ANOVA)	Effect Size: overall (NUI vs ANI, NUI vs MND, NUI vs HAD, ANI vs MND, ANI vs HAD, MND vs HAD)
									0.47, 0.95, 0.41, 0.50, 0.87	0.39, 0.03, 0.44, 0.34

HIV disease characteristics for human CSF samples. Quantities shown are mean +/-standard deviation. Bottom rows depict the p-values and effect sizes between the illustrated groups.

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