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Blood amyloid- β protein isoforms are affected by HIV-1 in a subtype-dependent pattern

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Abstract

This study aimed to compare serum amyloid processing biomarkers among HIV subtype B ($n = 25$), HIV subtype C ($n = 26$), healthy HIV-negative controls ($n = 18$), and patients with Alzheimer's disease (AD; $n = 24$). Immunoassays were used to measure main soluble A β isoforms A β 38, A β 40, A β 42, and A β -total in serum and cerebrospinal fluid (CSF). People living with HIV (PLWH) and HIV(-) samples, including AD samples, were compared for gender and age, while HIV subtypes were compared for nadir CD4 and plasma viral load suppression. CSF/serum ratios of A β 40, A β 42, and A β -total were lower in HIV-1C group than in HIV-1B group ($p = 0.020, 0.025, \text{ and } 0.050$, respectively). In serum, these biomarkers were comparable. Serum A β isoforms were significantly lower in PLWH than in AD. Serum A β 42 levels in PLWH were decreased compared to those in control group, thus similar to A β 42 alterations in CSF; these results were different from those observed in AD. Impaired cellular immunity, low CD4 cell count (nadir or current) influences serum A β metabolism in HIV-1B but not HIV-1C. However, in PLWH overall, but not in individual HIV subtype groups, greater CD4 recovery, calculated as the difference between current and nadir CD4, correlated with A β 42/A β 40 ratio in serum ($r_s 0.246; p = 0.0479$). No significant correlation was found with global deficit score (GDS), an index of neurocognitive performance, age, or duration of infection. These findings are consistent with those of subtype-dependent amyloid processing in blood in chronic HIV disease.

Keywords Neuronal injury · Aging · Biomarkers · HIV-associated neurocognitive disorders · Subtype

Introduction

The profile of amyloid processing biomarkers in HIV infection is not yet well defined. Several studies have been carried out on HIV subtype B (HIV-1B) (Brew et al., 2005; Gisslén et al. 2009; Nath and Hersh 2005; Peterson et al. 2014; Krut et al. 2013, 2014), but data on other subtypes has not been reported. Soluble amyloid- β (A β), a small ~ 4 kDa polypeptide, is the product of normal cell metabolism; it is found in various body fluids, including blood and cerebrospinal fluid (CSF) (Mehta et al. 2000). As blood can be obtained through

minimal invasive sampling methods, there is an increasing interest on the validation of blood-based neural injury biomarkers. The majority of these validation studies are on Alzheimer's disease (AD) (Wang et al. 2017).

The association between HIV infection and aging is an increasingly important topic, as the life expectancy of people with HIV has increased and quality of life has improved (Raboni et al. 2017). HIV infection is associated with the development of age-related physiological disturbances and medical co-morbidities earlier in life. HIV-associated neurocognitive disorders (HAND) are more common in older people living with HIV (PLWH). Moreover, PLWH have an epigenetic age 4.9 years older than that of healthy controls (Gross et al. 2016).

Aging is a risk factor for A β accumulation and neurocognitive impairment (High et al. 2012). PLWH may show A β deposition in the brain at younger ages. This suggests a dysregulation of amyloid processing in the setting of HIV infection. A β is the primary component of amyloid plaques (Hardy and Selkoe 2002); several studies have noted

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marked increases in the prevalence of diffuse amyloid plaques in PLWH compared to HIV(−) age-matched controls (Green et al. 2005; Rempel and Pulliam 2005; Esiri et al. 1998).

We previously reported CSF biomarkers suggesting that amyloid processing pathways are altered in a subtype-dependent manner, such that more brain A β deposits would occur in chronically infected patients with HIV-1C than in age-matched HIV-1B (de Almeida et al. 2018a, b). Additionally, over a prolonged period of time, HIV-1-induced accumulation of A β may lower the threshold for dementia (Rempel and Pulliam 2005). Based on these and previous studies of blood A β biomarkers on AD, the authors hypothesized that there is a higher level of serum A β in HIV-1C than in HIV-1B group.

This study aimed to compare serum and CSF/serum ratios of amyloid processing biomarkers between HIV-1B and HIV-1C-infected participants; additional comparisons between these and healthy HIV(−) and AD patients were done. Here, we investigated for the first time the main A β isoforms in peripheral blood of PLWH. The use of these biomarkers could influence decisions to treat neurocognitively impaired HIV+ individuals with cholinesterase inhibitors or memantine, a partial antagonist of NMDA receptors. Both drugs registered in many countries for the treatment of cognitive impairment in dementia, particularly for AD (Knight et al. 2018).

Methods

This was a cross-sectional survey of stored CSF and serum samples, which was approved by institutional review boards

(IRB) at Clínicas Hospital, University Federal of Paraná (HC-UFPR, Curitiba, Paraná, Brazil), the Brazilian National Commission of Ethics in Research (CONEP, Brasilia, Brazil), and the University of California San Diego (UCSD, San Diego, USA).

Subjects

All participants agreed and signed a consent form approved by the IRB. For AD participants, legally responsible caregivers signed the consent. CSF and serum samples were collected under a protocol funded by NIMH (R21 MH076651-01). HIV(+) and AD participants were recruited at HC-UFPR.

A total of 107 paired serum and CSF samples were analyzed. Participants were divided in groups as follows: HIV(+) ($n = 65$), HIV(−) ($n = 18$), and AD patients ($n = 24$). Demographic characteristics, HIV status, and co-infections from each group are summarized in Table 1.

PLWH participants As previously mentioned, PLWH, $n = 65$, were recruited at HC-UFPR, Brazil. Individuals with opportunistic CNS infections were not selected for the study. All volunteers provided both blood and CSF samples, and underwent serological testing to confirm HIV status before enrollment, in accordance with guidelines published by the Brazilian Ministry of Health (Brasil, Ministério da Saúde 2017). For participants with clinically resistant infections, the infecting HIV strain was genotyped using *pol* sequences, while *env* sequences were used for all other participants. Genotyping indicated that 25 individuals were infected with HIV-1 subtype B, and 39 with non-B HIV-1 subtypes (C-26,

Table 1 Demographic data, clinical and HIV infection characteristics, and co-morbidities of HIV participants, uninfected volunteers, and Alzheimer's disease group

	HIV+ ($n = 65$)	HIV− ($n = 18$)	AD ($n = 24$)	<i>p</i>
Demographics				
Age, years	43 (35; 48)	40 (34; 50)	76.5 (67; 79.5)	< 0.0001
Education, years	7 (5; 11)	12 (11; 15.5)	4 (2; 6)	0.0001
Gender, <i>n</i> male (%)	32 (49)	14 (77.8)	8 (33)	0.0120
Clinical scales				
GDS	0.65 (0.3; 1.05)			
MMSE	–	–	14 (9.5; 20)	
MoCA, ($n = 8$)			11.5 (10.5; 12.5)	
FAQ	–	–	23.5 (15; 27.5)	
Geriatric Depression Scale	–	–	1 (0.5; 3)	
Co-morbidities				
HCV, <i>n</i> (%)	10 (15)	0	0	–
Log plasma HCV RNA, <i>n</i>	2.9 (1.7; 5.9)	0	0	–

Data are median (IQR) or number of cases (%)

Hepatitis C virus (HCV) status was assessed by antibody testing (Abbott-Architect). Participants co-infected with HCV were not on treatment with interferon-gamma

Mini-mental state examination (MMSE); Montreal Cognitive Assessment (MoCA); Functional Activities Questionnaire (Pfeffer's FAQ); Global deficit score (GDS) (de Almeida et al. 2013)

BF-09, BC-1, CF-1, and F-2 participants). In one participant, the HIV-1 subtype could not be determined.

HIV-uninfected controls A control group of 18 age-matched HIV(−) individuals was recruited at the HIV Neurobehavioral Research Center, University of California San Diego, USA. Inclusion criteria and characteristics were described previously (de Almeida et al. 2018b).

Alzheimer disease participants AD, $n = 24$, were clinically diagnosed by the dementia investigative team from the cognitive dysfunction outpatient clinic, Neurology Unit, HC-UFPR. They all underwent detailed clinical anamnesis and examination routine blood analyses to rule out treatable causes of dementia. All AD patients were HIV, HCV, syphilis, and neurosyphilis negatives. All AD participants met dementia criteria of the Diagnostic and Statistical Manual of Mental Disorders, DSM-V (American Psychiatric Association 2013), and criteria for probable AD according to the National Institute on Aging and Alzheimer's Association, NIA-AA (McKhann et al. 2011). Diagnostic methods used on the AD group were previously described (de Almeida et al. 2018b). Clinical diagnoses of AD were made independently of CSF AD biomarkers. AD participants were classified, at the moment of CSF and serum collection, with probable AD, with a clinical dementia rating (CDR) of 2 (2–2.5), indicating moderate dementia, severe decrease of daily instrumental activity, and no associated depression (Table 1). Neuroimaging ($n = 18$), computed tomography or magnetic resonance imaging, showed volumetric reduction of the brain, absence of expansive lesions or extra-axial collections, or pathological calcifications in the brain. The median duration of symptoms was 36 (range 24 to 60) months.

Laboratory methods

Serum and CSF biomarkers Amyloid- β isoforms (A β 38, A β 40, and A β 42) were assayed by electrochemiluminescence (MSD, Meso Scale Discovery multi-array; Rockville, MD, USA). The analytic sensitivity of these assays ranged between 0.1 and 10.1 pg/mL. All samples were assayed concurrently in duplicate according to the manufacturers' instructions. The acceptable coefficient of variation (CV) between duplicates was lower than 20%. When results were under the minimum low-detection limit determined by the manufacturer, the corresponding low-detection limit value was used for statistical analysis. A β -total was defined as the sum of all three A β isoforms quantified, which are the main A β isoforms produced. Ratios between A β 38, A β 40, A β 42, and A β -total were calculated both for CSF and serum. We calculated A β isoform CSF/serum ratios in order to evaluate the A β proportion between the compartments (blood and CSF) on the different groups studied. Not with the intend to identify the amount that crossed the blood

brain barrier (BBB); as the transport of A β isoforms across the BBB, in both directions, is carrier mediated (Deane et al. 2009; El Ali and Rivest 2013).

Sample collection and storage CSF was collected by lumbar punctures with atraumatic spinal needles under aseptic conditions by a trained neurologist. All samples were collected at the same time on sampling days to limit diurnal variations. CSF and serum were collected in parallel. Samples were collected in polypropylene tubes to avoid adherence of the proteins to the tube walls in accordance with instructions from biomarker reagent manufacturers. CSF total protein, glucose, and WBC counts were measured with standard laboratory methods. CSF and serum aliquots were frozen and stored at $-80\text{ }^{\circ}\text{C}$ at HC-UFPR facilities.

Data analyses

The demographic variables (age, gender, and education) were compared between the HIV(+), the HIV(−), and the AD groups in pair-wise using the Student t tests for continuous variables and Fisher's exact test for binary and categorical variables. Demographic and HIV disease characteristics were compared between individuals with HIV-1 subtypes B and C using similar methods. The CSF and serum biomarkers, the biomarker index, and the biomarker CSF/serum ratios were presented in terms of median (IQR), and \log_{10} -transformed prior to statistical analyses if their distributions were not approximately normal.

First, hierarchical comparisons were performed with AD versus HIV(+) groups as primary comparison, and HIV(−) versus AD groups and HIV(−) versus HIV(+) groups as secondary comparisons, without adjustment for multiple comparisons. Age and gender were included as covariates in multivariable linear regression models if they had a p value of < 0.2 in the adjusted model. If the effect of age was shown statistically significant non-linearity, a smooth age effect was used within a generalized additive model (Wood 2006). The p values for the biomarker effects were then corrected for multiple testing with the Benjamini-Hochberg procedure, within each class of biomarkers (serum, CSF, index, and CSF/serum ratio).

Second, the CSF and serum biomarkers, the biomarker index, and the biomarker CSF/serum ratios were compared between HIV-1 subtypes B and C. A multivariable model was applied to control for plasma HIV viral load suppression and nadir CD4 count, which has been shown in previous studies to be associated with increased soluble biomarkers of inflammation and chemotaxis in HIV (Noel et al. 2014; Mooney et al. 2015). Using similar methods as above, the p values were adjusted for multiple testing. In addition, simple linear regression was used to compare the serum biomarkers and biomarker CSF/serum ratios of controls vs. HIV subtype B, and controls vs. HIV subtype C.

Table 2 HIV(+), HIV(-), and Alzheimer's disease levels of serum amyloid-β isoforms, indexes, and cerebrospinal fluid/serum ratios

Biomarker	HIV+	AD	CTRL	Diff (95% CI) ^a	p ^a	Diff (95% CI) ^b	p ^b	Diff (95% CI) ^c	p ^c
Serum	65	24	18						
Aβ-38, pg/mL	2.48 (2.48; 21.39)	24.60 (9.00; 75.8)	7.226 (2.48; 22.50)	-0.81 (-1.33, -0.28)	0.002	0.07 (-0.45, 0.59)	0.79	0.71 (0.001, 1.41)	0.049
Aβ-40, pg/mL	93.40 (59.55; 132.0)	167.6 (145.4; 234.5)	117.9 (108.0; 141.7)	-1.06 (-1.69, -0.43)	<0.001	0.18 (-0.38, 0.73)	0.61	0.69 (0.001, 1.38)	0.049
Aβ-42, pg/mL	5.14 (2.68; 7.73)	9.95 (7.51; 14.71)	7.99 (5.24; 9.55)	-1.68 (-1.46, -0.35)	<0.001	0.73 (0.07, 1.38)	0.023	1.71 (0.006, 3.41)	0.049
Aβ-total, pg/mL	109.2 (67.65; 143.8)	213.0 (170.1; 347.9)	140.6 (121.7; 172.6)	-1.07 (-1.70, -0.44)	<0.001	0.2 (-0.36, 0.75)	0.61	0.71 (0.001, 1.42)	0.049
Indexes in serum									
Aβ-38/Aβ-40	0.0796 (0.036; 0.205)	0.158 (0.077; 0.310)	0.077 (0.0217; 0.272)	-0.33 (-0.84, 0.19)	0.19	0.021 (-0.54, 0.59)	0.94	-0.59 (-0.94, 0.39)	0.460
Aβ-38/Aβ-total	0.069 (0.032; 0.162)	0.125 (0.061; 0.221)	0.065 (0.020; 0.174)	-0.32 (-0.83, 0.19)	0.19	0.047 (-0.52, 0.62)	0.94	-0.62 (-0.95, 0.38)	0.460
Aβ-40/Aβ-total	0.866 (0.784; 0.914)	0.790 (0.692; 0.890)	0.860 (0.734; 0.918)	0.35 (-0.16, 0.86)	0.19	0.15 (-0.42, 0.72)	0.94	-0.23 (-0.89, 0.44)	0.460
Aβ-42/Aβ-38	0.876 (0.270; 1.841)	0.432 (0.148; 1.290)	1.291 (0.380; 2.821)	0.05 (-0.42, 0.52)	0.90	0.31 (-0.21, 0.83)	0.24	0.31 (-0.31, 0.92)	0.830
Aβ-42/Aβ-40	0.06 (0.04; 0.07)	0.06 (0.05; 0.07)	0.07 (0.05; 0.10)	-0.86 (-0.98, 0.05)	0.084	0.58 (0.03, 1.13)	0.045	-0.03 (-0.69, 0.64)	0.940
Aβ-42/Aβ-total	0.05 (0.03; 0.06)	0.05 (0.04; 0.06)	0.06 (0.05; 0.09)	-0.19 (-0.66, 0.28)	0.43	0.54 (0.01, 1.09)	0.045	-0.08 (-0.74, 0.59)	0.940
CSF/serum									
Aβ-38	507.9 (91.97; 918.2)	65.48 (24.11; 265.30)	322.90 (93.18; 846.60)	0.86 (0.33, 1.37)	<0.001	0.03 (-0.53, 0.59)	0.92	-0.84 (-1.61, -0.07)	0.023
Aβ-40	49.11 (27.19; 73.60)	23.42 (16.52; 32.73)	38.64 (25.75; 48.01)	1.02 (0.43, 1.59)	<0.001	0.04 (-0.52, 0.60)	0.92	-0.77 (-1.47, -0.05)	0.032
Aβ-42	83.17 (56.63; 170.2)	27.15 (16.41; 44.51)	76.71 (61.58; 132.60)	1.58 (0.86, 2.29)	<0.001	0.21 (-0.35, 0.77)	0.92	-1.31 (-2.23, -0.38)	0.001
Aβ-total	66.56 (39.50; 97.51)	25.26 (18.63; 41.64)	50.08 (38.31; 68.65)	1.09 (0.47, 1.71)	<0.001	0.06 (-0.50, 0.62)	0.92	-0.86 (-1.63, -0.08)	0.023

Values in median (IQR); Diff; group differences presented as Cohen's *d*; CI, confidence interval; *p*, *p* value; all *p* values adjusted for multiple testing with the Benjamini-Hochberg (BH) method, ^a and ^c adjusted for gender or age and BH method

Significant differences are in italic typeface

^a HIV(+) × AD

^b HIV(+) × CTRL

^c AD × CTRL

In correlation analysis, the correlation coefficients (r_s) were estimated using Spearman's rank-order method. We tested the correlation of serum biomarkers and biomarker indexes with the variables: global deficit score (GDS); HIV infection characteristics (duration of infection, age at the time of study, age at the time of the beginning of the infection, plasma and CSF HIV RNA, peripheral blood platelets cell count); cell immunity characteristics [nadir CD4, current CD4, CD4 recovery = current CD4 – nadir CD4].

Results were considered statistically significant at the 5% alpha level. Statistical analyses were implemented using R version 3.2.3, 2015. Cohen's d effect sizes (and 95% confidence intervals) were reported for differences between groups.

Results

A β isoform levels were on average 50–1000 times higher in CSF than in serum in all three groups studied. A β isoforms were not significantly correlated between CSF and blood in the HIV(+) group or subtypes (all $p > 0.05$). A β isoform CSF/serum ratios in the three groups studied are shown in Table 2. Across all participants, the levels of serum A β -40 were higher than the levels of other A β isoforms. The concentrations of A β 38, A β 40, A β 42, and A β -total in CSF were described previously (de Almeida et al. 2018b).

Serum A β in PLWH, HIV(-), and AD patients

Figure 1 shows that serum levels of A β 38, A β 40, A β 42, and A β -total were significantly lower in the HIV(+) group than in the AD group (for A β 38 $p = 0.002$; all others $p < 0.001$). Serum levels of A β 42 were also lower in PLWH than in the HIV(-) group ($p = 0.018$). Pair-wise comparisons of A β isoforms and ratios are shown in Table 2.

The ratio of serum A β 42/A β 40 was lower in PLWH than in the HIV(-) group ($p = 0.045$; Table 2). The proportion of A β 42 to A β -total in PLWH was lower than that for HIV(-) ($p = 0.045$), but did not differ from AD participants ($p = 0.43$). However, the proportions of the other A β isoforms studied did not differ between three groups (Table 2).

HIV-1B and HIV-1C patients

Comparisons of serum A β isoforms, between HIV-1 subtypes B and C, and control group, are shown in Table 3. CSF/serum ratios of A β 40, A β 42, and A β -total were lower in HIV-1C than in HIV-1B ($p = 0.020, 0.025, \text{ and } 0.050$ respectively; Fig. 2); although comparable with the HIV(-) control group.

Higher current CD4 was significantly correlated with lower serum A β 38, A β 40, and A β -total levels in PLWH as a whole and in HIV-1B, but not in HIV-1 subtype C (for PLWH: $r_s = -0.311, p = 0.012$; $r_s = -0.266, p = 0.032$; $r_s = -0.293, p = 0.018$; for HIV-1B: $r_s = -0.465, p = 0.017$; $r_s = -0.462, p =$

Fig. 1 Serum amyloid-beta (A β) isoforms concentrations in HIV(+), AD, and HIV(-) control (CTRL) groups. **a** A β 38 (pg/mL). **b** A β 40 (pg/mL). **c** A β 42 (pg/mL). **d** A β -total (pg/mL). Comparisons between HIV(+) and AD, and AD and CTRL groups were adjusted for gender or age. All p values were adjusted for multiple testing with the Benjamini-Hochberg (BH) method. The line in the center of the box represents median; the superior and inferior borders of the box represent IQRs; the whiskers represent the least and greatest values

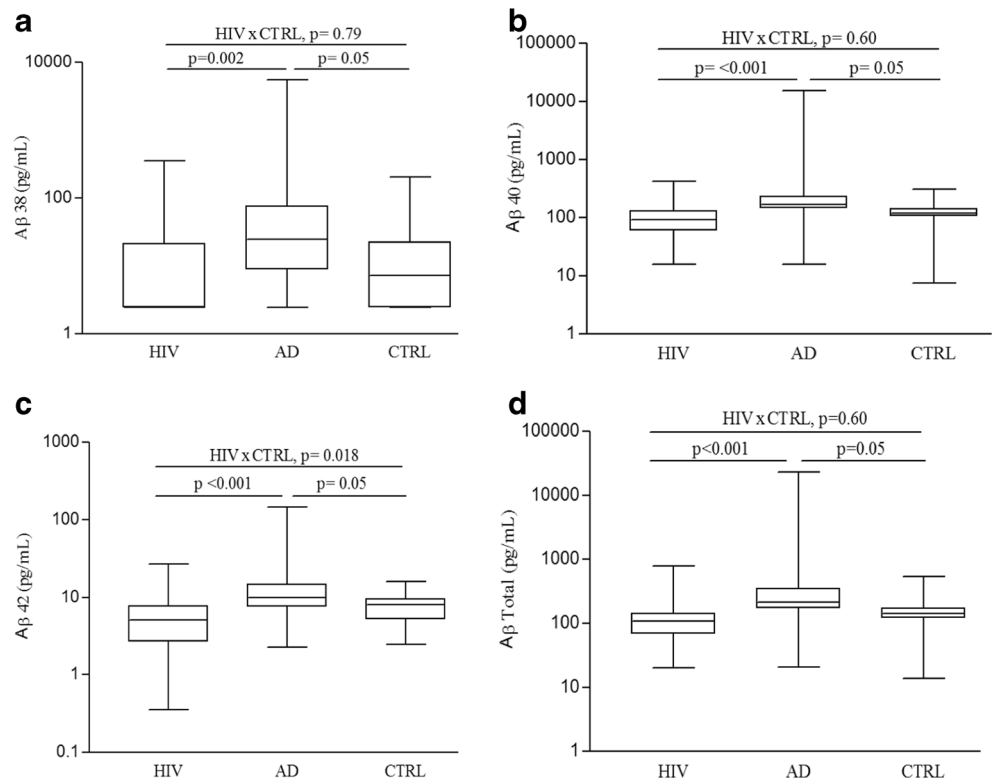


Table 3 HIV-1 subtype B and C levels of serum amyloid- β isoforms, indexes, and cerebrospinal fluid/serum ratios

Biomarker	HIV-B	HIV-C	B \times C Diff (95% CI)	B \times C p^a	B \times C p^b	B \times Ctrl Diff (95% CI)	B \times Ctrl p^c	B \times Ctrl p^d	C \times Ctrl Diff (95% CI)	C \times Ctrl p^c	C \times Ctrl p^d
Serum	25	26									
A β -38, pg/mL	2.48 (2.48; 24.75)	4.58 (2.48; 17.69)	-0.01 (-0.59, 0.56)	0.93	0.93	-0.08 (-0.68, 0.53)	0.809	0.81	-0.07 (-0.67, 0.53)	0.83	0.92
A β -40, pg/mL	64.30 (43.45; 147.90)	99.55 (70.95; 133.60)	-0.46 (-1.04, 0.13)	0.11	0.34	-0.32 (-0.93, 0.29)	0.307	0.41	0.03 (-0.57, 0.63)	0.93	0.92
A β -42, pg/mL	3.24 (2.06; 6.83)	5.67 (3.11; 7.93)	-0.41 (-0.99, 0.17)	0.19	0.34	-0.93 (-1.54, -0.32)	0.004	0.018	-0.69 (-1.30, -0.09)	0.029	0.11
A β -total, pg/mL	78.59 (51.79; 162.30)	118 (78.66; 147)	-0.37 (-0.95, 0.21)	0.20	0.34	-0.32 (-0.92, 0.29)	0.309	0.41	-0.03 (-0.63, 0.57)	0.92	0.92
Indexes in serum											
A β -38/A β -40	0.114 (0.041; 0.211)	0.045 (0.031; 0.234)	0.31 (-0.28, 0.90)	0.31	0.34	0.14 (-0.46, 0.75)	0.646	0.77	-0.10 (-0.70, 0.50)	0.75	0.82
A β -38/A β -total	0.093 (0.037; 0.166)	0.042 (0.029; 0.184)	0.31 (-0.28, 0.90)	0.31	0.34	0.17 (-0.44, 0.77)	0.594	0.77	-0.07 (-0.67, 0.53)	0.82	0.82
A β -40/A β -total	0.854 (0.784; 0.912)	0.900 (0.762; 0.923)	-0.29 (-0.89, 0.30)	0.34	0.34	0.04 (-0.56, 0.65)	0.890	0.89	0.30 (-0.30, 0.90)	0.34	0.65
A β -42/A β -38	0.783 (0.206; 1.277)	0.931 (0.249; 1.951)	-0.09 (-0.63, 0.45)	0.55	0.55	-0.42 (-1.03, 0.19)	0.182	0.36	-0.24 (-0.84, 0.36)	0.43	0.65
A β -42/A β -40	0.06 (0.03; 0.08)	0.06 (0.05; 0.07)	0.15 (-0.43, 0.72)	0.60	0.75	-0.57 (-1.17, 0.04)	0.075	0.22	-0.69 (-1.29, -0.09)	0.029	0.12
A β -42/A β -total	0.05 (0.03; 0.07)	0.05 (0.04; 0.06)	0.10 (-0.48, 0.67)	0.75	0.75	-0.57 (-1.17, 0.04)	0.074	0.22	-0.65 (-1.25, -0.05)	0.039	0.12
CSF/serum											
A β -38	609.1 (70.16; 882.8)	328.6 (82.36; 918.2)	0.08 (-0.51, 0.67)	0.80	0.91	0.04 (-0.57, 0.65)	0.897	0.90	-0.05 (-0.65, 0.55)	0.87	0.87
A β -40	53.99 (29.33; 99.86)	41.88 (24.33; 55.54)	0.73 (0.14, 1.32)	0.020	0.099	0.25 (-0.36, 0.85)	0.431	0.60	-0.28 (-0.88, 0.32)	0.37	0.87
A β -42	110.3 (68.88; 230.4)	76.46 (43.43; 128.1)	0.70 (0.11, 1.29)	0.025	0.099	0.56 (-0.04, 1.17)	0.076	0.31	-0.14 (-0.74, 0.46)	0.65	0.87
A β -total	82.50 (42.61; 125.5)	57.13 (31.17; 82.76)	0.61 (0.02, 1.20)	0.050	0.13	0.24 (-0.37, 0.84)	0.450	0.60	-0.24 (-0.84, 0.36)	0.44	0.87

Values in median (IQR); significant differences are in italic typeface; *Diff.*, group differences presented as Cohen's *d*; *CI*, confidence interval; *B*, HIV-B; *C*, HIV-C; *Ctrl*, controls; *p*, *p* value

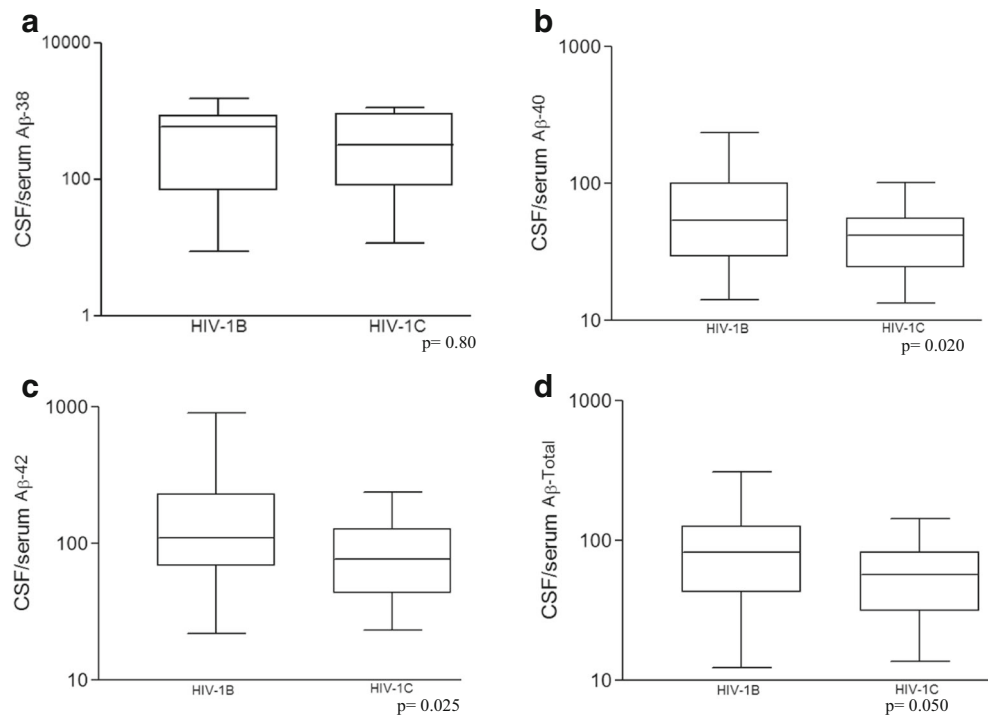
^a *p* values adjusted for plasma VL suppression and CD4 nadir count

^b *p* values adjusted for plasma VL suppression and CD4 nadir count, corrected for multiple testing with the Benjamini-Hochberg (BH) method

^c *p* values not adjusted

^d *p* values corrected for multiple testing with the BH method

Fig. 2 Cerebrospinal fluid/serum ratio of main amyloid-beta ($A\beta$) isoforms from HIV-1 subtype B and C samples. **a** CSF/serum ratio for $A\beta_{38}$. **b** CSF/serum ratio for $A\beta_{40}$. **c** CSF/serum ratio for $A\beta_{42}$. **d** CSF/serum ratio for $A\beta$ -total. p values were adjusted for plasma VL suppression and CD4 nadir count, not corrected for multiple testing with the Benjamini-Hochberg (BH) method. We calculated $A\beta$ isoform CSF/serum ratios in order to evaluate the $A\beta$ proportion between the compartments (blood and CSF) on the different groups studied. The line in the center of the box represents median; the superior and inferior borders of the box represent IQRs; the whiskers represent the least and greatest values



0.017; $r_s = -0.481$, $p = 0.013$, respectively). Nadir CD4 correlated negatively with serum $A\beta_{42}$ and $A\beta$ -total ($r_s = -0.412$, $p = 0.041$; $r_s = -0.452$, $p = 0.023$, respectively) in the HIV-1B group, but not in PLWH as a whole or HIV-1 C group. Greater CD4 recovery correlated with higher $A\beta_{42}/A\beta_{40}$ ratio in serum ($r_s = 0.244$; $p = 0.050$) in PLWH as a whole, but not when subtypes were analyzed separately (Fig. 3). There was no correlation between serum $A\beta$ isoform levels and other variables studied ($p > 0.05$).

PLWH participants' clinical characteristics From the group, 52 (80%) patients had AIDS; duration of infection, 87 (29; 135) months; current CD4, 347 (193; 534) cell/mm³; nadir CD4, 88 (28; 267) cell/mm³; Log plasma HIV RNA, 1.7 (1.7; 3.6); plasma HIV RNA < 50 copies/mL, 35 (54%); Log CSF HIV RNA, 1.7 (1.7–2.8); CSF HIV RNA < 50 copies/mL, 32 (49%); on combination antiretroviral therapy (cART), 52 (80%); antiretroviral CNS penetration effectiveness (CPE) (Letendre et al. 2010), 6 (5–9); adherence, antiretroviral treatment adherence was evaluated using AIDS clinical trial group (ACTG) adherence questionnaire (4-day recall), 51 (93%). From those on therapy, the most frequent cART regimen (33 participants; 63%) contained a ritonavir-boosted HIV protease inhibitor (PI) plus two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI and NtRTI); whereas, 18 participants (35%) received a non-nucleoside RT inhibitor (NNRTI) with 2 NRTIs, and 4 (8%) participants received other regimen types. Platelets count in the HIV+ group as a whole 223×10^3 (179×10^3 ; 256×10^3); in the group HIV-1B $227 \times$

10^3 (176×10^3 ; 259×10^3); and HIV-1C 221×10^3 (181×10^3 ; 253×10^3), $p = 0.948$.

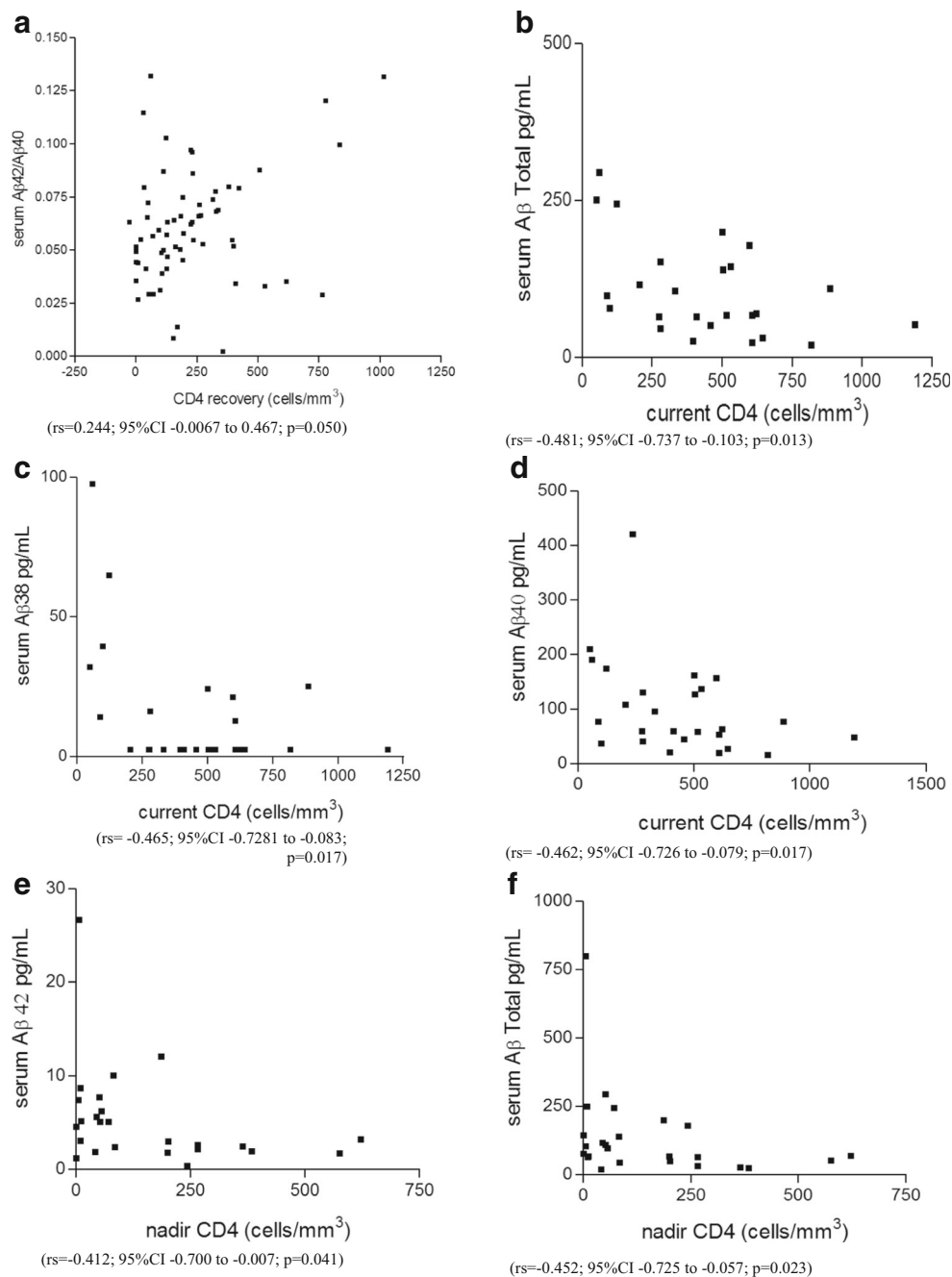
Discussion

This exploratory survey provides a broad view of the impact of HIV in the amyloidogenic pathway in blood, over the course of chronic HIV infection. Our findings suggest that impaired cellular immunity (low CD4 cell count, nadir, or current) influences serum $A\beta$ in a subtype-dependent pattern; in HIV-1B but not HIV-1C, low CD4 may increase synthesis or decrease clearance of specific $A\beta$ isoforms. However, CD4 recovery was associated with an increased serum $A\beta_{42}/A\beta_{40}$ ratio, independent of subtype. A higher ratio may indicate greater production or decreased clearance of $A\beta_{42}$ and higher probability to develop $A\beta$ deposits.

$A\beta$ accumulation in the brain is one of the pathological hallmarks in AD, and previous reports showed increased levels of blood $A\beta$ in AD participants (Wang et al. 2017). $A\beta$ overproduction is widespread in the peripheral organs and tissues in AD patients. It has been shown that β -secretase activity in the membranes of platelets is increased in patients with mild cognitive decline and AD (Liu et al. 2007; Johnston et al. 2008; Bu et al. 2017), but whether peripherally generated $A\beta$ contributes to the pathogenesis of AD is uncertain (Citron et al. 1994; Kuo et al. 2000; Deane and Zlokovic 2007; Bu et al. 2017). It has traditionally been thought that the $A\beta$ deposited in the

Fig. 3 Correlation between serum A β isoforms and cell immunity characteristics in the HIV+ group.

a CD4 recovery correlated positively with serum A β 42/A β 40 ratio in the HIV(+) group as a whole. This ratio represents the proportion between the main A β isoform constituent the amyloid plaques (A β -42) in the brain, and the main AB isoform synthesized (A β 40). In the HIV-1B group, but not on subtype C: there was moderate negative correlation between **b** current CD4 (cells/mm³) in blood and A β -Total (pg/mL) in serum; **c** current CD4 (cells/mm³) in blood and A β -38 (pg/mL) in serum; **d** current CD4 (cells/mm³) in blood and A β -40 (pg/mL) in serum; **e** nadir CD4 (cells/mm³) in blood and A β -42 (pg/mL) in serum; and **f** nadir CD4 (cells/mm³) in blood and A β -total (pg/mL) in serum



brain originates in neurons. However, investigators have shown that A β crosses the BBB; thus, A β present in plasma may contribute to the development of A β deposits in the brain and induce AD-type pathologies such as the induction and promotion of Tau hyperphosphorylation (Bu et al. 2017).

In this study, the ratio of serum A β 42/A β 40 was lower in PLWH as compared to the HIV(-) group. A previous report found that in AD patients, CSF A β 42/40 ratio was superior to quantification of A β 42 alone as a marker of amyloid positivity by PET (Lewczuk et al. 2017).

Previous work has demonstrated a great impact of HIV infection on A β metabolisms (Green et al. 2005; Rempel and Pulliam 2005; Aksenov et al. 2010). Impaired cellular immunity (CD4, CD4/CD8 ratio) is a hallmark of HIV infection. In this study, poorer cell-mediated immunity characteristics (current or nadir CD4) were associated with higher levels of A β isoforms in PLWH as a whole and among HIV-1B, but not HIV-1 subtype C. These findings are consistent with greater disturbance of amyloid processing as HIV-related immunosuppression worsens. The positive correlation between CD4 recovery, and the serum A β -42/A β -40 ratio, as well as the

negative correlation of A β isoforms and nadir CD4, can be result of immunological disbalance, due to an impaired cell immunity recovery with less effective CD4 cells, mainly on those cases on which there was very low CD4 nadir. This was the first study to show the impact of HIV infection on serum A β metabolism, future studies examining the mechanism by which improved immunity influences it are necessary.

Our results add to previously published studies, investigating differences between HIV-1 subtypes B and C, in which CSF A β 42 levels decreased in HIV-1C compared to HIV-1B (de Almeida et al. 2018b). We previously reported that CSF A β 42 levels in PLWH were lower than HIV- controls (de Almeida et al. 2018b); here, we found that serum A β 42 levels showed a similar pattern. These results were different from reported patterns of A β isoforms in AD, where CSF levels are decreased, but serum levels are increased. The majority of AD studies describe increased blood A β levels (Mehta et al. 2000; van Oijen et al. 2006; Graff-Radford et al. 2007; Wang et al. 2017); although these results are not uniform (Lopez et al. 2008; Toledo et al. 2013).

In the present study, there was no correlation between A β isoforms in serum and CSF. The brain is the main source of A β isoforms in blood. In addition to the brain, A β is produced in peripheral tissues or cells and secreted into blood circulation, contributing to the pool of circulating A β (Bu et al. 2017). A β is generated by the proteolytic cleavage of the amyloid precursor protein (APP). APP and the enzymes required for A β generation from APP are expressed in many tissues (Deane and Zlokovic 2007; Bu et al. 2017). In the brain, APP is ubiquitously expressed in neurons, which are believed to be its primary source (Peterson et al. 2014). In peripheral tissues, besides the brain, platelets are the primary source and can generate A β by a mechanism similar to that in neurons (Chen et al. 1995; Evin et al. 2003; Liu et al. 2007; Johnston et al. 2008; Bu et al. 2017). Other possible sources for the production of peripheral A β are skin fibroblasts, skeletal muscles, and cerebrovascular smooth muscle cells (Citron et al. 1994; Kuo et al. 2000; Van Nostrand and Melchor 2001).

One possibility to explain the lower blood A β levels in HIV is thrombocytopenia (Marks et al. 2009). This would be expected to lead to less APP and A β production, accounting for our observation that A β levels in HIV were lower than controls. Thrombocytopenia is a common feature among HIV-positive patients; it is considered a multifactorial disorder, commonly due to immune mechanisms (Marks et al. 2009). However, we found no correlation between platelet counts in peripheral blood and blood A β isoform levels and ratios. Other mechanisms must be considered to explain the blood A β isoform levels in HIV.

Both animal and human studies suggest that HIV can disrupt several steps in the amyloid cascade, from A β biogenesis to clearance (Pulliam 2009; Xu and Izeku 2009; Andras and Toborek 2013). The main HIV amyloidogenic protein is Tat

(Rempel and Pulliam 2005; Aksenov et al. 2010; Daily et al. 2006; Lan et al. 2011; Giunta et al. 2008; Kim et al. 2013); although several other proteins as NEF (White et al. 2005); gp41 (Mankowski et al. 2002); and Gp120 (Aksenov et al. 2010; Zhang et al. 2011) are amyloidogenic as well. HAART interferes with amyloidogenesis by reducing LRP (Tran et al. 2003), inhibiting A β degradation (Hamel 2007; Lan et al. 2012), increasing production, and decreasing clearance of A β peptides (Brown et al. 2014).

In this study, we found that the main A β product in blood was A β 40 as well as in CSF, which are consistent with other research's results; although we found a higher percentage in serum (~90%) than in CSF (~70%) (de Almeida et al. 2018b; van der Kant and Goldstein 2015).

The present cross-sectional study is not free of limitations. It does not include a substantial number of older (>60 years) PLWH, who are hypothetically more vulnerable to AD than young PLWH. We did not assess HIV(+) patients with known AD, though this combination of conditions is rare. The HIV(-) group was age and gender matched with the HIV(+) group, in consequence, individuals were younger than those from the AD group. Samples from the control group were collected in a different site than those from the diseased groups (HIV+ and AD). In addition, there are several difficulties in the measurement of A β levels in body fluids. Low A β concentrations in blood, for example, require sensitive and reliable laboratory assays. A β measurements are sometimes variable and imprecise measurements vary between studies and laboratories, indicating that standardization of both preanalytical and analytical procedures is essential (Molinuevo et al. 2013). In regard to blood A β measurements, contradicting results have been reached by using different detection methods or research designs (Toledo et al. 2013). The positive points of this study are that, to our knowledge, this is the first study on blood A β isoforms in PLWH. Also, most published studies on aging biomarkers from HIV populations only involve HIV-1 subtype B; this is the first study including participants with HIV-1 subtype C. Consequently, this study will contribute to the understanding of the pathophysiology of HIV infection in blood and the CNS, and the impact of HIV-1 genetic diversity in HIV-related metabolic changes.

We conclude that there was impact of HIV infection on blood amyloid metabolism in a subtype-dependent way, with differences between subtypes B and C. However, it does not appear that measurement of blood A β isoforms will be useful as a biomarker of HIV-associated dementia, as no correlation between GDS and serum A β biomarkers was found. The differences between HIV and AD in the patterns of serum A β isoforms suggested that HIV infection and AD may not share some of same mechanisms of impairment; corroborating the findings in CSF (de Almeida et al. 2018b). More studies are necessary, to test the usefulness of blood A β biomarkers to predict the development of HAND or the differential diagnosis with AD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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