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RESEARCH

Accelerated cognitive aging in chronically infected HIV-1 positive individuals despite effective long-term antiretroviral therapy

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Abstract

People living with HIV (PLHIV) are known to be at a higher risk of developing an array of aging-related diseases despite well-adhered combined antiretroviral therapy (cART). The present study aimed to investigate the impact of chronic HIV infection on neurocognitive function in virally suppressed PLHIV. We enrolled HIV-positive individuals randomly from an ART Center in Chennai, South India. A similar number of HIV-uninfected individuals matched for age and gender with the HIV-infected individuals served as controls. All individuals provided a detailed clinical history and underwent neuropsychological assessment using the International HIV Dementia Scale (IHDS). Plasma proteome analysis was performed using the Proximity extension assay (PEA) with the Olink® neuroexploratory panel, and untargeted metabolomics was performed using Ultra-High-Performance Liquid Chromatography/Mass Spectrometry/Mass Spectrometry. Despite a median duration of 9 years on first-line cART and suppressed viremia, a significant proportion of PLHIV registered significant levels of asymptomatic neurocognitive impairment, with 71% of these individuals scoring ≤ 10 in the IHDS test. We also observed significant alterations in a number of proteins and metabolites that are known to be associated with neuroinflammation, neurodegeneration, cognitive impairment, and gastrointestinal cancers, in the PLHIV group. Thus the study provides clinical as well as laboratory evidence to substantiate the presence of asymptomatic neurocognitive impairment in a large proportion of PLHIV, despite adequate cART and undetectable viremia, thereby supporting the view that HIV infection potentiates the risk for accelerated and accentuated neurological aging. This observation highlights the need to devise and implement appropriate intervention strategies for better long term management of HIV-infected persons.

Keywords HIV-1 · Antiretroviral therapy · Cognitive aging · Biomarkers · Neuroinflammation · Neurodegeneration

Introduction

The availability of combined antiretroviral therapy (cART) has resulted in significantly improved life expectancies and reduced risk of death due to opportunistic infections in people living with HIV (PLHIV). The UNAIDS reported that AIDS-related deaths (ARD) worldwide declined by about 55% since the introduction of antiretroviral therapy (Deeks 2011). In India, 41.97 thousand ARDs were recorded in 2021, a 76.5% decline from the 2010 estimate (Deeks 2011). This decline in ARD has paralleled the substantial increase in longevity among PLHIV (Okonkwo et al. 2010; Deeks 2011; Petoumenos et al. 2017). As per the UNAIDS report, the number of PLHIV globally over the age of 50 years increased from 5.4 million in 2015 to 8.1 million in 2020 (The Lancet Healthy Longevity 2022). India has approximately 2.14 million PLHIV on ART (NACO 2023). This has resulted in a shift in the focus of medical care and research from the management of immunodeficiency and opportunistic infections to the management of non-communicable diseases, especially aging-related comorbidities, that are collectively termed as 'HIV-associated, non-AIDS' (HANA)

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conditions. PLHIV are known to have a higher prevalence of comorbidities and systemic geriatric syndrome (multimorbidity, polypharmacy, frailty, etc.) than the HIV-uninfected counterparts. Numerous studies have demonstrated increased levels of inflammation and immunological senescence in PLHIV (Deeks 2011; Babu et al. 2019a,), and hinted at their role in increasing the risk of development of end-organ illnesses like cardiovascular disease (Okonkwo et al. 2010), diabetes mellitus, neurological disorders and fractures (Petoumenos et al. 2017).

Accelerated cognitive decline has been reported in various metabolic diseases like Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, Type 2 diabetes mellitus and coronary artery disease (Simioni et al. 2010; Okonkwo et al. 2010; Heaton et al. 2011), as well as in certain acute and chronic infections (Lawrence et al. 2004). HIV has been detected in the cerebrospinal fluid (CSF) of infected persons as early as 8 days after infection, and is believed to enter the brain within 15 days of infection (Valcour et al. 2012). HIV infects the perivascular macrophages, microglia and astrocytes in the brain via a Trojan horse mechanism, i.e. peripheral monocytes infected with HIV cross the blood-brain barrier and differentiate into macrophages resulting in increased virus replication in the brain and seeding of local reservoirs (Valcour et al. 2012). Findings from studies conducted on virally suppressed PLHIV have shown loss of brain volume, accelerated brain aging regardless of chronological age, and aging-associated physiological alterations such as increased oxidative stress and chronic inflammation (González-Scarano and Martín-García 2005; Nir et al. 2019). The subtype of the virus, duration of HIV infection, ongoing state of viral replication, lack of drug transport to the brain, and ART toxicity have been shown to influence the extent of neurological impairment in PLHIV (Petersen et al. 2021).

HIV-associated neurocognitive disorder (HAND) encompasses a spectrum of neurological abnormalities in the central nervous system (CNS), caused by persistent CNS HIV infection, neuro-inflammation, limited ART penetration, neurodegenerative changes and comorbidities. These include HIV-associated Dementia (HAD) or AIDS dementia complex, asymptomatic neurocognitive impairment (ANI), and mild neurocognitive disorder (MND) that generally affect memory and motor functions in PLHIV (Petersen et al. 2021). Although studies have shown that the introduction of ART reduces the incidence of severe forms of dementia, milder forms of cognitive impairment do develop and exist in PLHIV that call for medical attention (Petersen et al. 2021).

The complexity of neural networks and cognitive function makes it difficult to map the relationship between brain and behaviour. However, the development of advanced methodologies like microarrays, DNA and RNA sequencing, and targeted or untargeted proteomic and metabolomic analyses have significantly aided the characterization and understanding of the mechanisms underlying the development of neurocognitive deficits and neuropathology in PLHIV. Our study aimed to assess the presence and extent of neurocognitive impairment (NCI) in HIV-1 subtype C infected individuals on ART, and to correlate the presence of NCI with alternations in levels of proteins and metabolites implicated in the pathogenesis of NCI in these individuals.

Materials and methods

Study design and population

This cross-sectional study included 32 demographically similar PLHIV on uninterrupted first-line cART comprising of two NRTIs and one NNRTI provided through the Government-sponsored free National ART program for 5 years or more with suppressed viremia (<2.14 $\log_{10}$ copies/mL), herein referred to as PLHIV, from a tertiary care ART Centre at the Government Hospital for Thoracic Medicine (GHTM), Chennai, India, during the period January 2015 to January 2018. A group of age and gender-matched HIV-uninfected individuals, herein referred to as HC ($n=29$), were included as controls. All individuals were aged between 35 and 50 years. The study excluded (1) pregnant women, (2) those with tuberculosis or hepatitis virus infection, (3) those with Immune Reconstitution Inflammatory Syndrome (IRIS), (4) those having a history of co-morbidities like diabetes mellitus, obesity, cardiovascular disease, psychiatric illness or any other chronic disease (5), those addicted to substance use like tobacco, illicit drugs or alcohol, and (6) those on anti-inflammatory drugs during the past one month as described in our previous article (Babu et al. 2019a). Demographic details (gender, education) and clinical data of HIV infected participants (viral load, CD4 cell count, ART regimen and duration of treatment) were obtained from their medical records.

Ten millilitres of whole blood was collected from each participant in EDTA tubes. The blood was centrifuged at $800\times g$ for 20 min at room temperature and plasma was separated. A small portion of the whole blood was also processed for DNA extraction using the QIAamp DNA Mini Kit (Qiagen Germany) following the manufacturers' instructions. Both plasma samples and DNA extracts were immediately aliquoted and stored at -80 °C until further use.

Assessment of neurocognitive function using the International HIV Dementia Scale

The International HIV Dementia Scale (IHDS) was used to assess cognitive function in PLHIV, as per the National AIDS Control Organization (NACO) testing guidelines (National Guidelines for HIV testing, India 2018). This tool is popularly used for screening of HAND as it is a culturally neutral test and does not require knowledge of English language, high education levels or any special instrumentation, and can be administered by trained non-clinical personnel. The tests were also administered to the HIV-uninfected controls (National Guidelines for HIV testing, India 2018, Sacktor et al. 2005). The IHDS tool includes three categories of assessment: motor speed, psychomotor speed, and memory recall. After briefly introducing the method, participants were asked to perform the three sets of IHDS subtests. The sum of the scores for each set of tests was taken as the total IHDS score. A composite IHDS score of ≤ 10 was indicative of potential risk of cognitive impairment. To minimize assessment errors, all the study participants were assessed by the same individual, who was trained in administering the test in a collective 3-h session followed by pilot testing on healthy volunteers. Approval from the institutional ethics committee and written informed consent from each patient were obtained prior to recruitment into the study.

Profiling of circulating metabolites in plasma

Untargeted metabolomic profiling was performed on the plasma of a subset of PLHIV ($n=22$) and matched HC ($n=22$) using Ultra-High-Performance Liquid Chromatography/Mass Spectrometry/Mass Spectrometry (UHPLC/MS/MS) at Metabolon Inc. (Durham, NC, USA). Inclusion criteria for the assessment included HIV-1 positive status, stable CD4 counts for the past 24 months, and treatment adherence > 90% (Mu et al. 2019). Briefly, 100µl of plasma was mixed with methanol to recover chemically diverse metabolites after precipitating the proteins. The methanol extract was divided into four fractions: two for analysis by two separate reverse phase (RP)/UPLC-MS/MS methods with positive ion mode electrospray ionization (ESI), one for analysis by RP/UPLC-MS/MS with negative ion mode ESI, and the other for analysis by HILIC/UPLC-MS/MS with negative ion mode ESI. The MS analysis alternated between MS and data-dependent MS^n scans using dynamic exclusion (Babu et al. 2019a).

Raw data extraction, peak-identification and QC processes were performed using proprietary hardware and software (Metabolon Inc., Durham, NC, USA). The metabolites were identified using an in house proprietary library based on standards that include the retention time/index (RI), mass to charge ratio (m/z), and chromatographic data (including MS/MS spectral data) on molecules present in the library. Peaks were quantified using area-under-the-curve (Babu et al. 2019a). Among all the significantly altered metabolites identified, only those known to be associated with neurocognitive impairment were selected for further analysis.

Proteomic profiling of plasma samples

The soluble proteome was analyzed in the plasma of the above subset of PLHIV ($n=22$) and HC ($n=22$) using the Proximity extension assay (PEA) (Olink Bioscience AB, Uppsala, Sweden) with the Olink® neuroexploratory panel which comprised of 92 proteins that represented important markers of neurological processes such as axon development, neurogenesis, synapse assembly and neurological disease (Babu et al. 2019a).

APOE genotyping

Genomic DNA was extracted from whole blood using the QIAamp DNA blood mini kit (Qiagen) following the manufacturer's instructions. The DNA concentration and purity were assessed using NanoDrop1000. Apolipoprotein E (ApoE) genotype was determined using PCR based amplification of a 584 base pair fragment of the *apoE* gene using the 5'-TCTTGGGTCTCTCTGGCTCAT-3' forward primer and 5'-CTGCCCATCTCCTCCATCCG-3' reverse primer, with Kapa HIFI master mix. The amplified product was sequenced to identify two single nucleotide polymorphisms (SNPs), rs7412 and rs429358, to determine the *apoE* allelic variant present in each individual.

Statistical and bioinformatics analysis

Descriptive data including demographic profile (age, gender, education) of the PLHIV and HC groups and clinical characteristics of the PLHIV group (baseline CD4 count, duration of treatment, CD4:CD8 ratio, CD8 count, nadir CD4 count, etc.) were collected using a case report form (CRF). Categorical variables are detailed in frequency tables, and continuous measures are summarized as mean and standard deviation or median and range, as appropriate. Cognitive functions like memory recall, motor speed, and psychomotor speed were compared between the groups using Mann-Whitney U test. The relative importance of cognitive outcome, adjusted for demographic characteristics and HIV status, was assessed using logistic regression. All analyses were performed using R Studio (R Studio Team 2022) and IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp 2017).

Log-transformed and volume normalized data were used for standard statistical analyses. A heat map was constructed to study the hierarchical clustering and to visualize the correlation matrix with R function heatmap.2 in the gplots package (Version 3.0.1.1). Spearman's correlation analysis was performed using the R function corr. test to determine the correlation between the proteins and metabolites identified in the study. Random Forest (RF) analysis was performed using R package Random Forest. False discovery rate (FDR) correction was applied to obtain the corrected p-value and q-value. A p-value < 0.05 and a false discovery rate (q) < 0.10 were considered significant. Principal component analysis (PCA) was performed to reduce the dimension of the normalized data using the R package pca3d (version 0.10) and sample distribution was visualized using the R package ggplot2 (version 3.2.0).

Table 1 Demographic and clinical profile of the study groups

Parameter	Treatment Experienced PLHIV (PLHIV)	Healthy Control (HC)	*P* Values
N	32	29	ND
Gender, Female, N (%)	12 (37.5%)	16 (55.2%)	0.6734[#]
At sampling			
Age in years, median (IQR)	45 (42–49)	43(35–53)	< 0.0001[§]
CD4 count (cells/mL); median (IQR)	624 (514–738)	NA	< 0.0001[§]
CD8 count (cells/mL); median (IQR)	772(379–1711)	NA	< 0.0001[§]
CD4:CD8 ratio, median (IQR)	0.73(0.65–1.02)	NA	< 0.0001[§]
Viral Load, Log10 copies/mL	< 2.174	NA	< 0.0001[§]
Years on treatment, median (IQR)	9 (5–10)	NA	ND
Treatment Regimen, *n* (%)			
ZDV + 3TC + NVP	17 (53%)	NA	ND
TDF + 3TC + EFV	15 (47%)	NA	ND
Nadir CD4 Count at treatment initiation (cells/mL), median (IQR)	208(100–303)	NA	ND
IHDS (≤ 10), N (%)	23(71.2%)	2 (6.9%)	< 0.0001[§]
APOE, N (%)	Total = 32	Total = 29	
E2	3 (9.4%)	6 (20.7%)	NA
E3	28 (87.5%)	20 (69%)	NA
E4	1 (3.1%)	3 (10.3%)	NA

NA: Not available, ND: Not Done, [#]χ^2 test, §Mann–Whitney test, ZDV: zidovudine, 3TC: lamivudine, NVP: nevirapine, TDF: tenofovir and EFV: efavirenz, IHDS: International HIV Dementia Scale

Results

Study participants

The demographic and clinical characteristics of the study population are presented in Table 1. The median age for PLHIV was 45 years and HC was 43 years. About 38% and 55% of participants in the PLHIV and HC groups were women. The median (IQR) duration of treatment for PLHIV was 9 (5–10) years; 53% were on a zidovudine + lamivudine + nevirapine (ZDV/3TC/NVP or ZLN) regimen, and the rest were on a tenofovir + lamivudine + efavirenz (TDF/3TC/EFV or TLE) regimen.

Cognitive impairment and HIV status

Seventy one percent of individuals in the PLHIV group obtained an IHDS score of ≤ 10 in contrast to 6.9% of HCs who had a low IHDS score (Table 1). One participant in the PLHIV group had an IHDS score of < 8. Correlation analysis revealed significant association between HIV status and higher odds of having a potential cognitive impairment (OR: 35.35, 95% CI: 6.57—190.04, $p < 0.001$) when adjusted for age. It was further observed that the scores were significantly lower specifically for memory recall ($p < 0.001$) and motor speed ($p < 0.001$), while the scores for the psychomotor speed were more or less similar between the two groups (Fig. 1). Sub-group analysis revealed no significant difference in cognitive scores between PLHIV on the two different ART regimens.

Altered levels of plasma metabolites associated with neurocognitive impairment in PLHIV

Metabolites associated with neurocognitive function and dysfunction were identified from the untargeted metabolomics data and compared between the PLHIV and HC groups. We found significant alterations in the levels of several metabolites known to be implicated in various forms of cognitive dysfunction like Mild Cognitive Impairment (MCI), Dementia, Alzheimer's disease (AD) and Parkinson's disease in the PLHIV group (Table 2). Some of the significantly dysregulated metabolites include ceramides, sphingomyelins and sterols from the lipid metabolism pathway, and tryptophan, branched-chain amino acids (BCAAs) (leucine, isoleucine, valine), phenylalanine, methionine, and cysteine from the amino acid metabolism pathway. Supervised principal component analysis (PCA) based on the metabolites grouped the PLHIV separately from the HCs (Fig. 2a). Hierarchical clustering analysis (HCA) of metabolites, revealed distinct clustering of the HCs and PLHIV (Fig. 2b). Significant contributors to the distinct separation

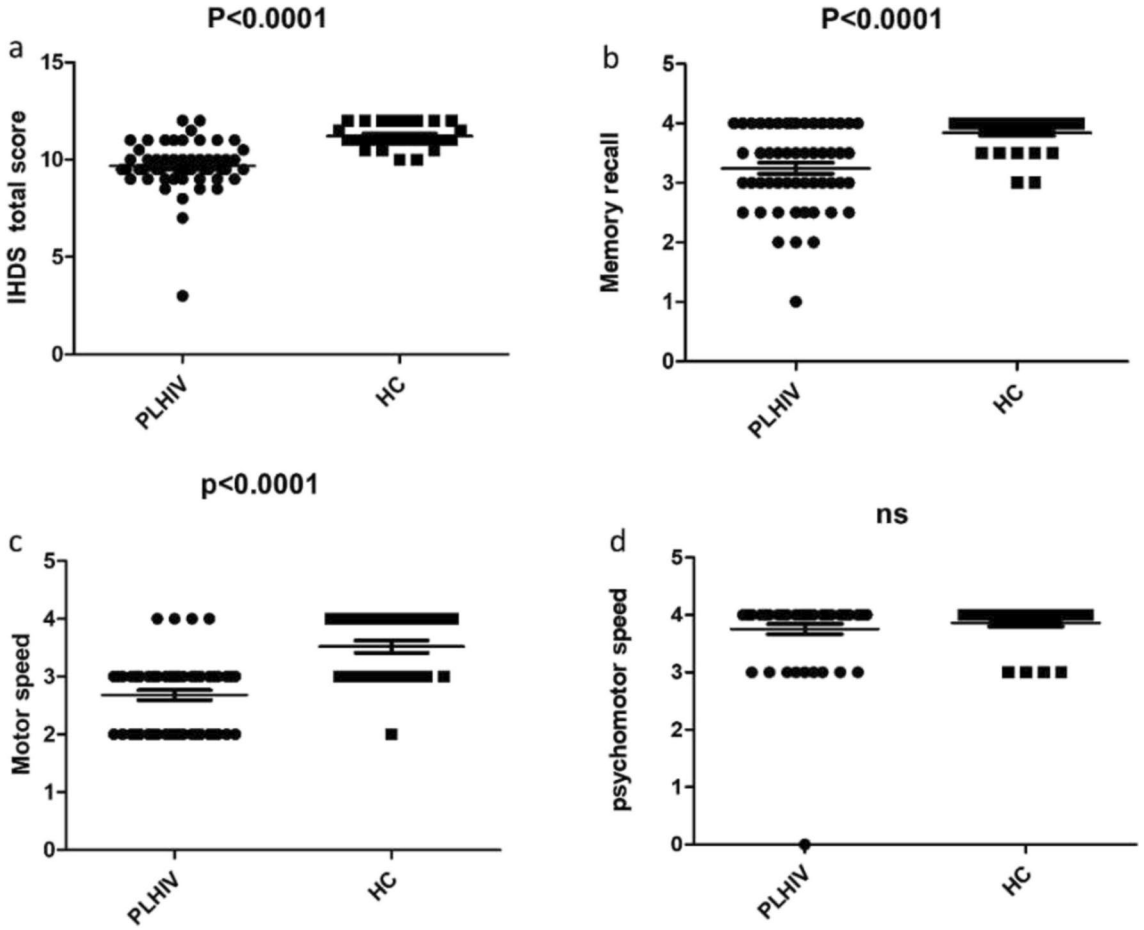

Fig. 1 Assessment of cognitive function in PLHIV and HC groups: **a**) Total IHDS score, **b**) memory recall test score **c**) motor speed test score and **d**) psychomotor speed test score (Mann-whitney U test)

between the PLHIV and HC groups were sphingomyelin (d17:2/16:0, d18:2/15:0), N-palmitoyl-sphingosine (d18:1/16:0), homoarginine, valine, isoleucine, methionine, leucine, palmitoyl arachidonoyl, uridine, urea, threonate, beta-sitosterol, bilirubin (E, Z or Z, E), nicotinamide riboside and drugs like lamivudine, nevirapine, efavirenz and zidovudine, as identified through RF analysis (Fig. 3).

Altered levels of neuroinflammatory proteins in PLHIV

We analyzed the levels of a panel of protein biomarkers well-known to be associated with various neurological disorders and pathological conditions in the plasma of PLHIV and HC. Proteins that were found to be significantly altered in PLHIV included Glycoprotein Nmb (GPNMB), Secreted Frizzled Related Protein 1 (SFRP1), Defensin Beta 4A (DEFB4A), Tubulin polymerization promoting protein family member 3 (TPPP3) and Amiloride-sensitive amine oxidase (copper-containing (AOC1), which were significantly lower in PLHIV as compared to HC, and Cadherin-17 (CDH17), Bone Marrow Stromal Cell Antigen 2 (BST2), 6-Pyruvoyltetrahydropterin synthase (PTS), Annexin A10 (ANXA10) and Interleukin 15 (IL15) which were significantly higher in PLHIV as compared to HC. Among these proteins, ANXA10, IL15, TPPP3, DEFB4A, SFRP1 and GPNMB were considered for further analysis based on their association with neuropathology as reported in earlier studies. The pathologic mechanisms involving these proteins in the gut-brain relationship and their levels in neurodegenerative diseases were also explored and listed in Table 3.

Correlation analysis was performed between the dysregulated proteins and metabolites associated with neurocognitive impairment in PLHIV. Levels of IL15, DEFB4A, SFRP1, TPPP3 and GPNMB were found to correlate positively with levels of phenylalanine, tryptophan, BCAAs and bilirubin, while levels of ceramide, sphingomyelin and cortisol were found to correlate negatively with these proteins. Interestingly, ANXA10 alone correlated negatively with phenylalanine, tryptophan, BCAAs and bilirubin and positively with ceramide, sphingomyelin and cortisol (Fig. 4),

Table 2 Summary of the altered metabolites associated with neuropathogenesis in PLHIV

Metabolite biomarkers (↑/↓) in PLHIV	PLHIV vs HC (*P*-value)	Antiretroviral therapy TLE vs ZLN (*p*-value)	Pathogenic mechanisms contributing to accelerated cognitive aging	Implication in neurocognitive impairment and neurodegenerative diseases	Supplementary References:
Nucleotide					
Beta-alanine ↓	$P=0.0452$	NS	↑Oxidative stress, ↑Protein glycation	Lower in all-cause dementia	(Wang et al. 2014; van Wijk et al. 2017)
Uridine ↓	$P=0.0055$	NS	↑Oxidative stress, ↑Neuroinflammation	Lower in plasma of MCI	(Ritchie et al. 2014)
Xenobiotics					
Ergothioneine ↓	$P=0.0012$	NS	↑Oxidative stress, ↑Inflammation	Lower in PD	(Cheah et al. 2016; Rosca et al. 2021)
Piperine ↓	$P=0.0145$	NS	↑Oxidative stress	Possesses cognition enhancing property	(Elnaggar et al. 2015)
Xenobiotics-Anti-Viral					
Efavirenz ↑	$P=0.0129$	$P=0.0176$	↑Oxidative stress	Neurotoxic properties of efavirenz,	(Ciavatta et al. 2017)
Nevirapine ↑	$P=0.0021$	$P=0.0007$	↑Oxidative stress, ↑Inflammation	ART induced cognitive decline in HIV infection	(Streck et al. 2008)
Lamivudine ↑	$P<0.000$	P= 0.0343	↑Oxidative stress	ART induced cognitive decline in HIV infection	(Giunta et al. 2011)
Zidovudine ↑	$P=0.0069$	$P=0.0043$	↑Neuro-inflammation	Higher AZT level associated perturbation of neurogenesis	(Pereda et al. 2000)
Co-factors& Vitamins					
Nicotinamide riboside ↑	$P=0.0013$	$P=0.0324$	↑Inflammation, ↓Tryptophan	Altered metabolism in the kynurenine pathway seen in neurodegenerative diseases	(Murray et al. 2001)
Threonate ↓	$P=0.0007$	$P=0.0485$	↑Inflammation, ↑Oxidative Stress	Lower level affects cognitive aging	(Billard 2011; Cuciureanu and Vink 2011; Sun et al. 2016)
Bilirubin(Z,Z) ↓	$P=0.0069$	NS	↑Oxidative stress, ↑ROS	Lower in dementia	(Kimm et al. 2009; Li et al. 2014; Hatanaka et al. 2015; Wang et al. 2018a)
Bilirubin(E,E)*↓	$P=0.0038$	NS			
Bilirubin(E,Z orZ,E)*↓	$P=0.0008$	NS			
Amino acids					
Phenylalanine ↓	$P=0.0014$	NS	↑Inflammation, ↑Immune activation	Lower in AD	(Gostner et al. 2015; Corso et al. 2017)
Tryptophan↓	$P=0.0011$	NS	↑Oxidative stress	Lower in Mild cognitive impairment and AD. Negative correlation of tryptophan with cognition	(Widner et al. 2000; Porter et al. 2003; Trushina et al. 2013a; Ramos-Chávez et al. 2018)
BCAAs ↓					

Table 2 (continued)

Metabolite biomarkers (↑/↓) in PLHIV	PLHIV vs HC (*P*-value)	Antiretroviral therapy TLE vs ZLN (*p*-value)	Pathogenic mechanisms contributing to accelerated cognitive aging	Implication in neurocognitive impairment and neurodegenerative diseases	Supplementary References:
Leucine	$P=0.0001$	$P=0.0001$	↑Inflammation	Lower level in dementia and Huntington disease (HD)	(Tynkkynen et al. 2018)
Isoleucine	P=0.0038	$P=0.0002$			
Valine	$P=0.0015$	$P=0.0495$			
Methionine ↓	$P=0.0001$	NS	↑Oxidative stress, ↑Nitric Oxide	Lower in early-stage AD	(Fekkes et al. 1998; Tan and Guiloff 1998; Ansari et al. 2014)
Cysteine ↓	$P=0.0248$	NS	↑Oxidative stress, ↑Aging, ↑Inflammation	Elevated levels in schizophrenic patients associated with cognitive preservation	(Bavarsad Shahripour et al. 2014; Wang et al. 2018b)
Lipids					
Ceramides ↑					
N-palmitoyl-sphingosine (d18:1/16:0)	$P=0.0060$	$P=0.0373$	↑Oxidative stress, ↑ROS production, ↑Inflammation	Increased in early AD	(Han et al. 2002)
N-stearoyl-sphingosine (d18:1/18:0)*	$P=0.0005$	NS			
N-palmitoyl-sphingadienine (d18:2/16:0)*	P=0.0439	NS			
N-stearoyl-sphingadienine (d18:2/18:0)*	$P=0.0049$	$P=0.0194$			
ceramide (d18:1/20:0, d16:1/22:0, d20:1/18:0)*	$P=0.0021$	NS			
ceramide (d18:2/24:1, d18:1/24:2)*	$P=0.0156$	NS			
Sphingomyelin ↓					
hydroxypalmitoyl sphingomyelin (d18:1/16:0(OH))**	$P=0.0005$	NS	↑Oxidative Stress	Lower in AD, decreases with increase ceramide levels in AD	(Han et al. 2002; He et al. 2010; Yano et al. 2013; Ellis et al. 2015)
tricosanoyl sphingomyelin (d18:1/23:0)*	$P=0.0414$	$P=0.0149$			
sphingomyelin (d18:2/18:1)*	$P=0.0208$	NS			
sphingomyelin (d18:2/23:1)*	$P=0.0418$	NS			
sphingomyelin (d18:2/24:2)*	$P=0.0186$				
sphingomyelin (d17:2/16:0, d18:2/15:0)*	$P=0.0146$				
sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0)*	$P=0.0259$				
sphingomyelin (d18:2/21:0, d16:2/23:0)*	$P=0.0332$				
sphingomyelin (d18:1/22:2, d18:2/22:1, d16:1/24:2)*	$P=0.0051$				
sphingomyelin (d18:1/25:0, d19:0/24:1, d20:1/23:0, d19:1/24:0)*	$P=0.0189$				
Cortisol↑	$P=0.0163$	$P=0.0288$	↑Neuroinflammation, ↑Oxidative stress	Higher in AD	(Meaney et al. 1995; Soares et al. 2012; Zvěřová et al. 2013; Canet et al. 2018)
Cortisone ↑	$P=0.0022$	NS	Age-related cognitive decline	Higher in MCI and AD in CSF and plasma	
Plasmalogen ↓					

Table 2 (continued)

Metabolite biomarkers (↑/↓) in PLHIV	PLHIV vs HC (*P*-value)	Antiretroviral therapy TLE vs ZLN (*p*-value)	Pathogenic mechanisms contributing to accelerated cognitive aging	Implication in neurocognitive impairment and neurodegenerative diseases	Supplementary References:
1-(1-enyl-palmitoyl)-2-linoleoyl-GPE(P-16:0/18:2)*	$P = 0.0165$	NS	↑Oxidative stress	Lower in AD	(Stenvinkel et al. 2004; Wood et al. 2010; Trushina et al. 2013b)
1-(1-enyl-palmitoyl)-2-arachidonoyl-GPE (P-16:0/20:4)*	$P = 0.0032$	NS			

(↑—indicates Up-regulation; ↓- indicates downregulation)

establishing good correlation between the significant metabolites and proteins in the PLHIV group.

APOE allele frequencies in the study groups

To evaluate the impact of genetic factors in predisposing PLHIV to increased risk for cognitive impairment, we screened all participants for polymorphisms in the apolipoprotein E gene. The APOE allele ε3 was found to be most predominant among PLHIV, with 28/32 individuals having the ε3 allele, 3 individuals having the ε2 allele and one individual having the ε4 allele. In the healthy control group, 20, 6 and 3 individuals had the ε3, ε2 and ε4 alleles respectively. The distribution of the APOE alleles in the two groups is shown in Table 1. We found no significant correlation between *apoE* genotype and cognitive impairment, nor any difference in the plasma levels of apolipoprotein E between the PLHIV and HC groups (data not provided).

Discussion

This observational study from India found a high prevalence of reduced neurocognitive function among PLHIV infected with subtype C HIV-1, as compared to age and sex-matched HIV-negative counterparts, despite being on adequate ART and having suppressed viremia. About 71% of PLHIV in our cohort had lower than optimal IHDS scores (≤ 10), indicating the presence of unnoticed asymptomatic cognitive dysfunction in these individuals. In this study, the IHDS test was used for neurocognitive assessment due to its widespread utilization in resource-limited settings, as indicated in previous literature (Dunlop et al. 1997; Sacktor et al. 2016; Rosca et al. 2021; Namagga et al. 2023). Pooled analysis of IHDS as an assessment tool for neurocognitive function by Rosea et al. revealed good performance of this test in clinical studies conducted in various parts of the world including North and Central America, sub-Saharan Africa, South Asia and Europe, which has resulted in the inclusion of this test as a screening tool in the National HIV treatment guidelines (National Guidelines for HIV testing, India 2018; Rosca et al. 2021). The increased prevalence of asymptomatic neurological impairment (ANI) observed in our study was found to be in agreement with other studies that have also reported high ANI prevalence rates from the same as well as different population settings (Mugendi et al. 2019; Gupta and Venugopal 2020). The functions that appear to be most commonly affected in these individuals were motor speed and memory recall. However, none of these individuals had reported any clinically identifiable functional impairment.

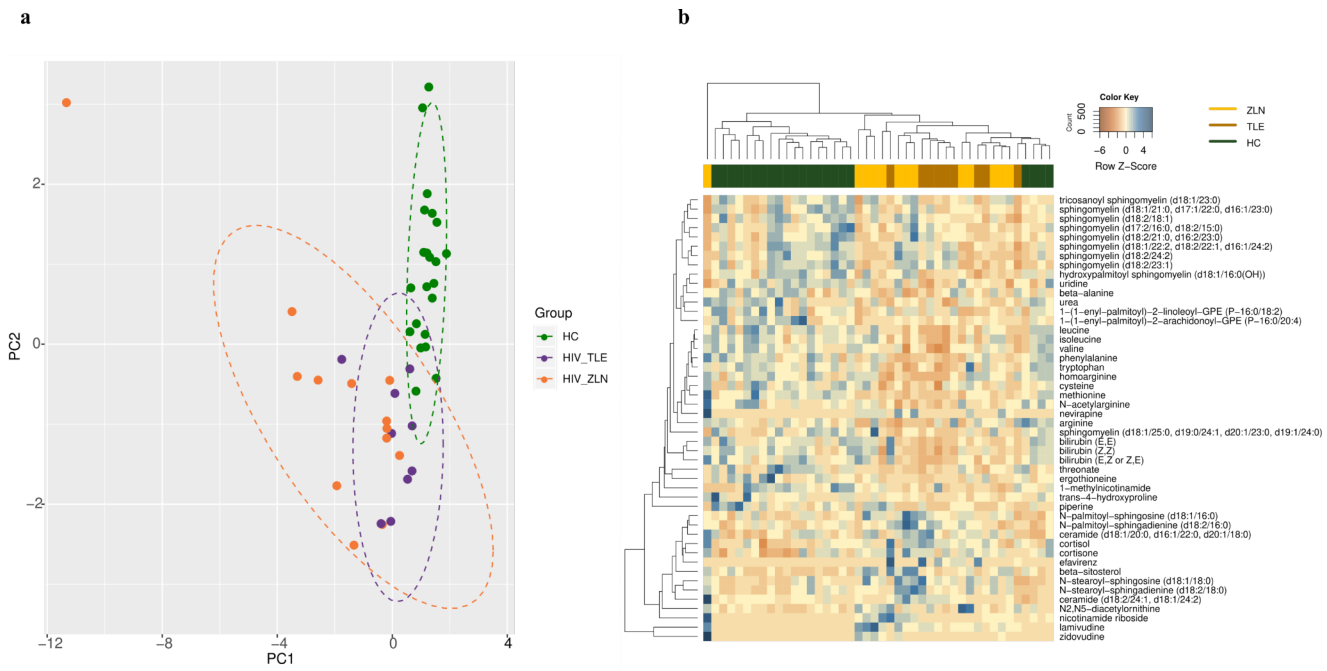

Fig. 2 (**a**) Principal component analysis indicating the grouping of individuals in PLHIV (HIV_TLE and HIV_ZLN) and HC groups based on metabolites. (**b**) Hierarchical clustering analysis of the samples indicated negative Z-scores for BCAAs, phenylalanine, tryptophan, and sphingomyelins in PLHIV indicating lower levels in PLHIV as compared to HC. On the other hand, ceramide, cortisol, cortisone, and beta-sitosterol were found at higher levels with positive Z-scores in PLHIV

Most of the previous studies related to HAND have focussed on populations from the developed countries where the most prevalent subtype of HIV in circulation is subtype B, although subtype C happens to be the subtype that dominates the global HIV-1 epidemic, besides being the most predominant HIV strain circulating in countries like India and parts of Africa which bear the brunt of the HIV epidemic (Gupta et al. 2007; Buonaguro et al. 2007). Some of the challenges in HIV-associated neurocognitive testing outside Europe and the USA have included limited access to validated tools, cultural and linguistic variations impacting test validity, co-existence of multiple HIV subtypes, presence of comorbidities affecting neurocognitive function, disparities in healthcare infrastructure hindering monitoring and treatment, and data gaps limiting comprehensive understanding and comparability of findings.

However, in the recent years, few studies have been undertaken in individuals with non-subtype B infections to examine the influence of subtype variation on the incidence and severity of neurocognitive impairment. A study carried out in Uganda to quantify the burden of HAD among PLHIV with different HIV-1 subtypes found that HAD was more common in individuals with subtype D infection than in those with subtype A infection (Mugendi et al. 2019). Similarly, studies comparing the prevalence of HAD in populations with HIV-1 subtype B infections versus those with predominantly subtype C infections found a lower incidence of HAD in subtype C prevalent regions. An elegant study undertaken by Ranga et al. to explore viral determinants associated with this difference, identified a genetic difference in the subtype C Tat protein which compromised its monocyte chemotactic function resulting in reduced neuroinvasiveness and decreased levels of neuroinflammation (Ranga et al. 2004). The authors speculated that this could be one of the attributable causes for the differential levels of HAD seen among individuals infected with different subtypes of the virus. A subsequent study by Mishra et al. demonstrated that the di-cysteine motif at positions 30 and 31 in the subtype B Tat protein played a crucial role in mediating persistent excitation of the N-methyl-D-aspartate receptor (NMDAR) by disrupting the disulfide bond on the NMDA receptor1 (NR1) leading to increased neurotoxicity (Mishra et al. 2008). The investigators further demonstrated that substitution of cysteine at position 31 with serine as seen in subtype C Tat resulted in reduced ability of the protein as well as the virus to cross the blood-brain barrier and produce neuroinflammation or seed HIV reservoirs in the neuronal compartment. Furthermore, HIV-1 subtype C exhibits lower rates of viral replication in glial cells (Santerre et al. 2019). Other studies have associated mutations in viral proteins such as gp120 and Vpr of HIV-1 subtype C with reduced levels of neurotoxicity as compared to the other subtypes (Li et al. 2008; Samikkannu et al. 2011). Tissue-specific chronic inflammation via extracellular vesicles has

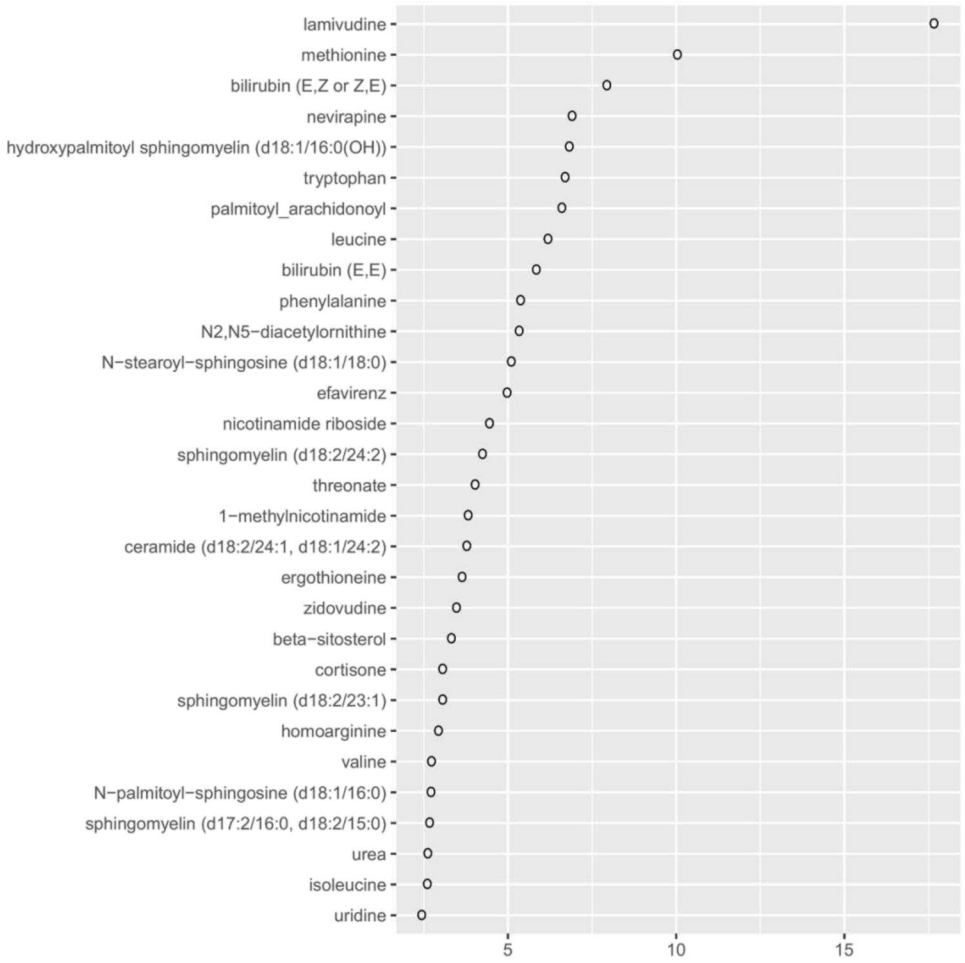

Fig. 3 Random Forest (RF) analysis displaying the top metabolites separating the PLHIV group from the HC

also been implicated in the development and progression of cognitive decline (Edén et al. 2010; Dahl et al. 2014; Tso et al. 2018; Ko et al. 2019; Buckley et al. 2021; Ramirez et al. 2021; Johnston et al. 2023).

In contrast, other studies have reported conflicting results. A study from India by Gupta et al. found similar prevalence of cognitive deficits in antiretroviral treatment naïve individuals infected with subtype C virus as seen in the Western countries where subtype B is widely prevalent. Besides finding high levels of cognitive impairment in individuals with clade C HIV infection, the study reported differences in the prevalence of mild to moderate cognitive deficit in PLHIV from different geographically/linguistically distinct regions of India (Gupta et al. 2007). However, more recent studies from India have reported a higher prevalence of HIV associated neurocognitive impairment in 59%-90% of PLHIV (Shaik et al. 2021). Our findings are in agreement with the recent studies that have reported high levels of HIV-related cognitive impairment in subtype C HIV-infected cohorts. Few interesting studies (Simioni et al. 2010; Heaton et al. 2011) had analyzed neurocognitive function in PLHIV on cART and found that these individuals also exhibited signs of impaired memory and executive function despite being on treatment, similar to the observations also made in our study.

In the recent years, omics approaches have been employed for in depth characterization of the underlying defects and causes for various metabolic disorders and diseases. Proteomic and metabolomic analyses were performed in this study to characterize the mechanisms associated with the high risk for neurocognitive impairment seen in PLHIV. Our analysis revealed significant alterations in several soluble proteins and metabolites known to be associated with neuroinflammation, neurodegeneration and gastrointestinal cancers in PLHIV as compared to HC, reflecting subtle damage to neurological function and disruption of the gut-brain relationship. Some of the key altered proteins include TPPP3, DEFB4A, IL-15, BST2, PTS and AOC1. The Tubulin polymerization-promoting protein family member 3 (TPPP3) protein is necessary for the bundling and stabilization of microtubules, a tubulin polymer that regulates the distribution of mitochondria and other cellular organelles within the cell. It plays an important role in synaptic organization and plasticity of neurons under normal conditions

Table 3 Summary of altered neurogenic and neuro-inflammatory proteins

Protein biomarkers	PLHIV/HC	Significance ($p < 0.05$)	Pathology associated with neurodegeneration	*Expression level in gastro-intestinal cancers	Related article DOI:
CDH17	Up-regulated	$P = 0.030$	Unknown	Diagnostic marker of GI tract carcinoma	(Panarelli et al. 2012; Lin et al. 2014)
GPNMB	Down-regulated	$P = 0.047$	Exerts its neuroprotective effect through reduction of astrocyte-mediated neuro-inflammation,	Hypermethylation and lower expression in CRC	(Neal et al. 2018; Ashktorab et al. 2018)
BST2	Up-regulated	$p < 0.001$	Antiretroviral restriction property of BST2, and influence on the risk of MS	High expression in gastric cancer	(Nexø et al. 2013; Leal et al. 2018; Liu et al. 2018)
ANXA10	Up-regulated	$P = 0.002$	Co-localized with neuronal markers, elevated in neuropathic pain	Expressed in gastric mucosa and upregulated in colorectal cancer	(Quiskamp et al. 2014; Liu et al. 2018)
IL15	Up-regulated	$P = 0.020$	Interacts with BBB, high serum concentration in neurodegenerative diseases, and correlates with ROS level	Has anti-tumor immune response against CRC	(Rentzos et al. 2006; Pan et al. 2008; Pagliari et al. 2013; Bahri et al. 2015; Bishnoi et al. 2015; Pangrazzi et al. 2017)
SFRP1	Down-regulated	$P = 0.014$ 56	Protective against H2O2 induced oxidative damage, Neuropathic pain	Hypermethylation of SFRP1 in gastric and colorectal cancers	(Suzuki et al. 2002; Tao et al. 2015; Tang et al. 2018)
PTS	Up-regulated	$P = 0.003$	Increases nitric oxide production Costigan and mediates neurodegeneration	Unknown	(Linscheid et al. 1998; Parathath et al. 2006; Costigan et al. 2009)
TPPP3	Down-regulated	$P = 0.001$	Involved in synaptic organization and neuronal plasticity, controls amyloid β-peptide (Aβ) production	Increased during CRC	(Frykman et al. 2012; Ye et al. 2017; Shi et al. 2019)
DEFB4A	Down-regulated	$P = 0.016$	Regulates neuroimmune response and neuroinflammation	Hypermethylation and downregulation in oral carcinoma, high expression seen in gastric and colon cancer	(Williams et al. 2012; Kamino et al. 2014; Zhang et al. 2014; Maeda et al. 2019)
AOC1	Down-regulated	$P < 0.001$	Neurotransmitters regulation	Marker of mucosal lesions	(D'Agostino et al. 1991; Schlicker et al. 1994)

* The table explains the role of these proteins in neuropathogenesis and their association with gastrointestinal cancers in PLHIV

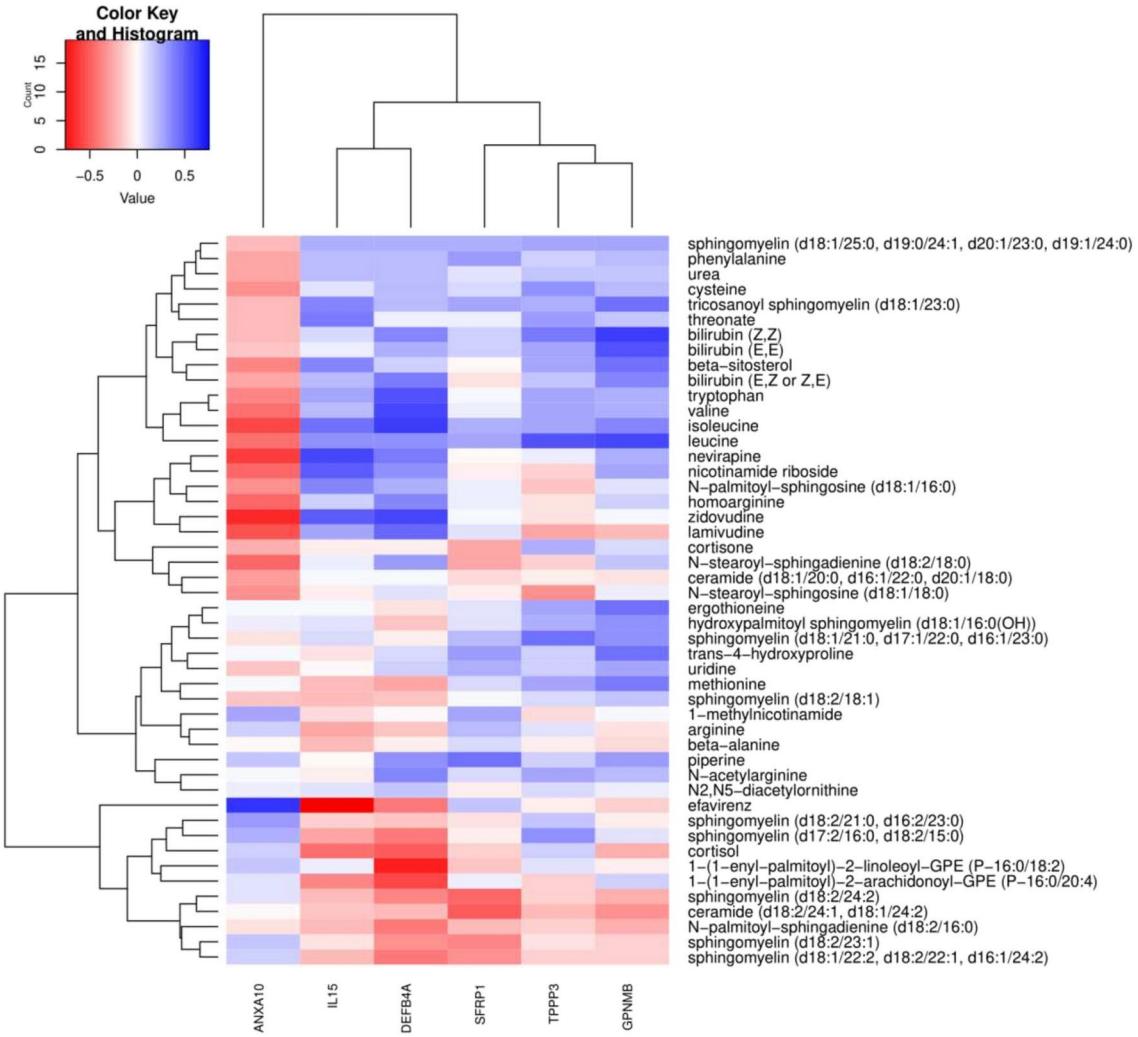

Fig. 4 Pearson correlation coefficient visualization and hierarchical clustering of proteins and metabolites in PLHIV. Metabolites from different pathways are plotted in rows and neuro exploratory proteins in columns

and controls the production of amyloid β-peptide (Aβ) by interacting with its precursor protein cleavage enzyme, γ-secretase. It could be inferred that the synaptic simplification described by O'Brien and Wong (2011) in HIV patients could be due to decreased levels of TPPP3 resulting in dysregulated synaptic organization in these individuals. The β-defensin 2 (DEFB4A) protein is a known regulator of the neuroimmune response in the central nervous system. Decreased levels of this protein has been shown to induce an inflammatory process in the brain (Williams et al. 2012). We also found significantly lower levels of DEFB4A in the PLHIV group. IL-15, GPNMB and other proteins like BST2, PTS and AOC1 that have been implicated in neurodegeneration and neuronal dysfunction, as well as in certain types of gastrointestinal cancers, particularly colorectal cancer were also found to be dysregulated in these individuals. The functions of each of these proteins are listed in Table 3.

A recent systematic review published by Williams et al. reported an association between increased levels of sphingomyelin and ceramides with cognitive impairment in PLHIV in CSF and brain tissue (Williams et al. 2021). Similar to this report, our study also found increased levels of ceramides and sphingomyelins, besides other metabolites like nicotinamide riboside, cortisol, cortisone and β-sitosterol, and decreased levels of β-alanine, uridine, ergothioneine, piperine, 1-methyl nicotinamide, threonate, bilirubin, phenylalanine, tryptophan, BCAAs, methionine, cysteine, and plasmalogen, which are also known to be associated with neurocognitive impairment in the PLHIV group (Table 2). Most of the metabolites that were significantly altered in PLHIV were found at levels usually seen in individuals with mild cognitive impairment or early-stage neurodegenerative disease. For example, lower plasma uridine levels are known to be associated with poor cognitive outcome (van Wijk et al. 2017). Similarly, lower levels of ergothioneine have been

reported in NCI (Cheah et al. 2016). Low plasma levels of bilirubin have been associated with AD associated cognitive decline (Vasantharekha et al. 2017), and silent cerebral infarction (SCI) (Li et al. 2014), highlighting its importance as a potential biomarker for assessing the risk of development of neurodegenerative disease. The present study also found significantly lower levels of bilirubin in PLHIV as compared to healthy controls, clearly indicating a higher risk for cognitive impairment in these individuals. Higher levels of cortisol have been reported in individuals with early AD (Peña-Bautista et al. 2019). Significantly higher levels of cortisol were also found in the PLHIV group in our study, again pointing to a higher risk of cognitive impairment. Furthermore, several metabolites associated with neuroprotective ability were found to be negatively regulated in PLHIV. For example, 1-methylnicotinamide, a metabolite of nicotinamide with a neuroprotective property that suppresses neuronal apoptosis (Mu et al. 2019), threonate that has been demonstrated to improve synapse density (Sun et al. 2016) in animal studies, and beta-sitosterol that exhibits anti-oxidant activity through estrogen receptor (ER)-mediated PI3K signalling (Shi et al. 2019), were all found to be significantly lower in PLHIV as compared to healthy controls, providing clear evidence for higher risk of neurological impairment in PLHIV, in spite of adequate ART and suppressed viremia.

Alterations in metabolites of the kynurenine pathway like tryptophan are known to be associated with increased oxidative stress and mitochondrial dysfunction and play an important role in aging and neurodegeneration (Sas et al. 2018). A negative correlation has been reported between tryptophan levels and cognitive decline indicating its role in AD and aging-related cognitive impairment (Fuchs et al. 1990; Porter et al. 2003). Lower tryptophan levels with unaltered kynurenine levels and a high KYN/TRP ratio were observed among PLHIV in one of our earlier studies (Babu et al. 2019b). Levels of branched chain amino acids (BCAAs) are known to exhibit a negative association with dementia and other cognitive diseases (Tynkkynen et al. 2018) and have therefore been reported to be potential biomarkers of neurological pathology. Our study also found significantly lower levels of BCAAs such as valine, isoleucine and leucine in PLHIV. Lower levels of the antioxidant precursor, cysteine, and other metabolites such as citrate, serine, phenylalanine, tyrosine and urea have been reported to be associated with cognitive dysfunction in PLHIV and post Traumatic Brain Injury (TBI) patients (Lin et al. 2011).

Finally, we evaluated the impact of a key host genetic factor in predisposing PLHIV to increased risk for cognitive impairment, by screening the participants for polymorphisms in the apolipoprotein E gene. Apolipoproteins play a crucial role in blood lipid metabolism. The human apolipoprotein E gene is located on chromosome 19. The major allelic forms of *ApoE*, namely, ε2, ε3 and ε4 with amino acid differences at positions 112 and 158 (ε2—cys112, cys158; ε3—cys112, arg158; ε4—arg112, arg158) encode multifunctional apolipoprotein E isoforms. The central role played by the APOE protein in lipid metabolism and neurodegenerative diseases, particularly AD, has been studied extensively (Farrer et al. 1997; Ward et al. 2012). Lower plasma levels of the protein is reported to be associated with progression to mild cognitive impairment in ε4 carriers (Farrer et al. 1997). A study by Ward et al. (2012) reported the presence of the ε4 allele in > 50% of patients with AD (Ward et al. 2012). The combination of other alleles (ε2 or ε3) with ε4 is also believed to be associated with an increased risk for AD (Farrer et al. 1997). While the association between APOE ε4 genotype and neurocognitive decline is well established in AD, conflicting results have been published on the influence of the APOE genotype on the pathogenesis of HAND in PLHIV (Dunlop et al. 1997; Joska et al. 2010). Observations from the present study revealed no significant association between the ApoE genotype and prevalence of neurocognitive dysfunction.

Thus, the present study made several important observations of a high prevalence of neurocognitive impairment among PLHIV with HIV-1 subtype C infection, despite being covered with effective antiretroviral therapy, as evidenced by both clinical assessment as well as high throughput proteomic and metabolomics analyses. While highlighting the significant observations of the study, we propose that the high prevalence of neurocognitive impairment observed in this study must be interpreted with caution due to the following reasons. Firstly, the results were solely based on IHDS scores; secondly, the cohort under evaluation was initiated on ART during the later stages of the disease (nadir CD4 count < 350 cells/mL) as per the existing National ART guidelines at the time of the study; and thirdly, the levels of metabolites and proteins reported in our study are from plasma rather than CSF. Yet the findings of the study hold relevance and therefore need to be validated through a more comprehensive analysis using a combination of assessment tools and neuroimaging techniques. Including risk factors like opportunistic infections, perinatal injury, alcohol use, substance abuse, depression and cerebrovascular disease in future studies would allow us to analyse the big picture of neurocognitive impairment in PLHIV.

Conclusion

Overall, the study demonstrates a significantly high risk for neurocognitive impairment in PLHIV despite well-adhered suppressive cART, as also evidenced by altered levels of several proteins and metabolite markers associated

with neuroinflammation, neurodegeneration, oxidative stress, and gut-brain association. The persistence of cognitive impairment and risk for neurological complications in virally suppressed PLHIV could be attributed to the establishment of long-lived reservoir cells in the brain such as macrophages and microglial cells, lack of access to therapeutic concentrations of drugs in the brain, antiretroviral drug-driven neurotoxicity or infection-driven risk factors such as chronic inflammation and immune activation. The preliminary observations made in this study on accelerated cognitive aging and the identified protein biomarkers in PLHIV on long term ART warrant further elucidation in a larger cohort as the findings appear to have important implications for devising effective strategies to prevent neurocognitive decline in PLHIV and improve the quality of life of persons with chronic HIV infection.

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Author contributions Luke Elizabeth Hanna, Hemalatha Babu, and Ujjwal Neogi conceived and designed the experiments. Hemalatha Babu, Alangudi Natarajan Palaniappan, and Gladys Rachel analyzed the data. Hemalatha Babu, Luke Elizabeth Hanna, and Alangudi Natarajan Palaniappan drafted the manuscript. Gladys Rachel, Ujjwal Neogi and Girish Kumar edited the manuscript. Chinnaiyan Ponnuraja and Aswathy Narayanan curated the data. Luke Elizabeth Hanna and Srikanth P Tripathy administered the project. Vijila Sundar and Vinod Kumar provided the blood samples. Hemalatha Babu obtained the informed consent from the study participants. All authors reviewed the final manuscript and approved the submission.

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Data availability Data is provided within manuscript. For further assistance on the data availability kindly contact the corresponding author.

Declarations

Ethics approval The study was approved by the institutional ethics committees of ICMR-National Institute for Research in Tuberculosis and Government Hospital of Thoracic Medicine, Tambaram, Chennai.

Competing interests The authors declare no competing interests.

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