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Original Article

Neuropathologic findings in a community-based autopsy cohort of older, virally suppressed, people with HIV

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ABSTRACT

Combination antiretroviral therapy (cART) has reduced the incidence of HIV-related mortality, leading to a growing population of older virally suppressed people with HIV (PWH). cART has also decreased the prevalence of HIV-associated dementia; however, many virally suppressed PWH still experience milder forms of cognitive impairment. It remains unclear whether aging virally suppressed PWH demonstrate distinct risks or patterns of neurodegenerative pathology. We examined brain tissue of 13 virally suppressed PWH and 13 matched HIV-negative controls from a community-based cohort and characterized β-amyloid (Aβ), tau, α-synuclein, and TDP-43 pathology. Both groups had similar demographics, medical comorbidities, and routine histologic brain findings. PWH demonstrated trends toward an increased prevalence of both Alzheimer disease (AD) and non-AD neurodegenerative pathologies, including Aβ pathology, higher stage tau pathology, aging-related tau astrogliopathy, and α-synuclein pathology. They showed similar trends toward increased severity of Aβ and tau pathology. We also identified a negative correlation between the burden of entorhinal cortical neurofibrillary tangles and end-of-life body mass index in PWH. Thus, PWH may have a greater burden of neurodegenerative pathology, including both AD and non-AD neurodegenerative pathologies; there is a need for the assessment of neurodegenerative pathology in community-based cohort studies to understand mechanisms of HIV-associated neuropathology and cognitive impairment in aging virally suppressed PWH.

KEYWORDS: aging; Alzheimer disease; HIV; neurodegeneration

INTRODUCTION

While the early HIV era was characterized by a rapid rise in the number of HIV infections and HIV-related deaths, the introduction of combination antiretroviral therapy (cART) resulted in a significant decrease in the rates of HIV-related morbidity and mortality. As a result, there is an increasing number of people living and growing older with HIV. As of 2021, the majority of the 1.2 million people with HIV (PWH) in the United States are over 50 years of age.[1,2] This growing population of older virally suppressed PWH in the United States are now at risk for aging-related comorbidities, including neurodegenerative disease. However, much remains unknown about the potential interactions between chronic HIV infection and common age-related neurodegenerative pathologies.

Prior to the introduction of cART, the prevalence of HIV-associated neurocognitive disorder was approximately 50%.[3] Of these, 10%-20% of PWH experienced HIV-associated dementia.[4,5] This was typically attributed to active viral replication in the central nervous system and associated with HIV encephalitis, which is characterized by brisk inflammation, multinucleated giant cells, microgliosis and microglial nodules, and white matter pathology.[6,7] Since the advent of cART, the prevalence of HIV-associated dementia has significantly decreased. However, 20%-50% of PWH still experience cognitive impairment, albeit milder forms.[4,8–10] The prevalence of HIV encephalitis has also significantly decreased in the cART era and the neuropathology observed in virally suppressed PWH is now, by routine neuropathologic methods, indistinguishable from any subtle pathology observed in HIV-negative contemporaries.[11–14] So, it is unclear why, despite effective cART, some virally suppressed PWH still experience cognitive deficits.

While the mechanism for cognitive impairment in PWH is likely multifactorial, one possibility is that PWH are at increased risk for age-related neurodegenerative pathology which would contribute to cognitive impairment in this aging population. Prior studies have shown variable neurodegenerative findings in the brains of PWH both before and in the cART era, primarily focusing on beta-amyloid (Aβ) plaques, tau neurofibrillary tangles (NFTs), and α-synuclein/Lewy body pathology.[12,15–24] However, these studies often included younger individuals who may have less aging-related neuropathology, have been limited to select brain regions or pathologies, and have focused on samples from individuals often from clinic- or study-based cohorts which may not represent the neuropathologic burden in the community. In some cases, studies included samples from PWH in the cART era who were not entirely virologically suppressed. Our understanding of neurodegenerative pathology has also progressed since several of these studies were published, with recent work codifying new age-related neurodegenerative pathologic diagnoses like primary age-related tauopathy (PART), aging-related tau astrogliopathy (ARTAG), and limbic-predominant age-related TDP-43 encephalopathy (LATE).[25–27] The prevalence of these non-Alzheimer's disease (AD)-related pathologies in older PWH is unknown.

Here, we present a systematic evaluation of the prevalence and severity of AD and non-AD neurodegenerative pathologies in a community-based cohort of older virally suppressed PWH compared to matched HIV-negative controls. We identified consistent trends towards more prevalent and more severe neurodegenerative pathology in PWH, with somewhat novel associations with body mass index (BMI). These findings highlight a potential increased risk of neurodegenerative pathology in virally suppressed PWH and highlight the utility of community-based studies in the characterization of the prevalence and severity of AD and non-AD neuropathology in PWH.

METHODS

Study cohort selection

A cohort of people with HIV (PWH) and HIV-negative individuals with available brain tissue was identified from the Johns Hopkins Hospital autopsy archive. Inclusion criteria for PWH included: cases performed between 2015 and 2023, individuals older than 45 years at time of death, a history of HIV infection confirmed by clinical laboratory tests, reported compliance with cART for at least 12 months preceding death, and documented plasma viral suppression (<50 to 400 viral RNA copies/mL of plasma, [depending on clinical test used] for a minimum of 12 months preceding death). A total of 32 cases of PWH were originally identified from the autopsy database, all with available tissue. Five cases were excluded due to an age at death below 45 years. Fourteen additional cases were excluded due to a lack of documented evidence of cART and/or virologic suppression for at least 12 months preceding death. This resulted in a final cohort of 13 PWH. An equal number of HIV-negative control cases (n = 13) was identified from the same autopsy archive over the same period. HIV-negative control cases were matched for age, sex, and HCV serostatus. For each pair of matched cases, an autopsy was performed within 365 days of each other (median = 61 days) to ensure similar age of archived tissue blocks. Demographic, clinical, and laboratory data were collected from each individual's electronic medical record. The work in this study was approved by the Johns Hopkins Institutional Review Board.

Histochemical and immunohistochemical staining

Formalin-fixed and paraffin-embedded (FFPE) tissue from the cerebrum (frontal, temporal, and occipital lobes), basal ganglia (at the level of the anterior commissure), medial temporal lobe (including hippocampus and entorhinal cortex), midbrain, pons, medulla, and cerebellum were stained with hematoxylin and eosin (H&E). Select tissue sections were stained with silver (Hirano method) and immunostained for Aβ, phosphorylated tau (tau), α-synuclein, and phosphorylated TDP-43, as below. All stains were performed on 10-μm-thick tissue sections. Each slide was assigned a random slide ID to blind evaluators to the diagnosis, age, and to the relationship of each pathologic slide to any other slide in the study.

For immunohistochemistry, deparaffinization and heat-based antigen retrieval was performed with the Lab Vision PT Module (Thermo Fisher Scientific) using 100 mM citrate buffer, pH = 6.0, for 15 minutes at 98°C. Pretreatment with 88% formic acid for 5 min was performed for α-synuclein and Aβ immunostains. Staining was performed on the Lab Vision Autostainer 360-2D (Fisher Scientific, Waltham, MA). Endogenous peroxidases were blocked with 3% hydrogen peroxide solution. Slides were blocked with 3% normal goat serum in TBS solution for 1 hour at room temperature. Primary antibodies [anti-Aβ, 1:500, mouse, clone 6E10, 803019, BioLegend, San Diego, CA; anti-phosphorylated tau (Ser202, Thr205), 1:200, mouse, clone AT8, MN1020, Invitrogen, Waltham, MA; anti-α-synuclein, 1:100, mouse, clone 913611, MAB13381, R&D Systems, Minneapolis, MN; anti-phosphorylated TDP-43 (Ser409/410), 1:100, rat, clone 1D3, 829901, BioLegend] were applied for 1 hour at room temperature. Slides were washed with TBS and biotinylated secondary antibodies (anti-rat, 1:200, rabbit, BA-4000 Vector Laboratories, Newark, CA; anti-mouse, 1:200, horse, BA-2000 Vector Laboratories) were applied for 1 hour at room temperature. After TBS washes, ABC (Vector Laboratories) and DAB kits (Vector Laboratories) were used according to manufacturer instructions. Slides were rinsed in water, counterstained with hematoxylin (Richard-Allan Scientific, Kalamazoo, MI), dehydrated by alcohol and xylene, and cover slipped using Permount mounting medium (Fisher Chemical, Waltham, MA).

Macroscopic and histopathologic evaluation

Autopsy reports were reviewed and macroscopic findings were recorded and coded for each case. H&E-stained sections were reviewed by a neuropathologist for the presence of routine histopathologic findings, including arteriolosclerosis, metabolic/reactive astrocytes (Alzheimer type II astrocytes), infarcts, hypoxic-ischemic changes/injury, abscess, and hemorrhage.

Aβ and plaque pathologic evaluation

Cortical and mesial temporal lobe sections were examined for Aβ-immunoreactive plaques with diffuse and cored morphologies. In cases where Aβ plaque pathology was identified in the initial sections, additional Aβ immunostaining was performed on sections of the basal ganglia, midbrain, and cerebellum to determine the Thal stage for each case.[28] Cases with Aβ plaque pathology were also stained with silver (Hirano method) to evaluate for neuritic plaques. Plaque burden was scored as none (score = 0), sparse (score = 1), moderate (score = 2), or abundant (score = 3) according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria.[29] The presence of cerebral amyloid angiopathy (CAA) was assessed based on vessel wall (parenchymal or meningeal) staining for Aβ.

Tau and AD neuropathologic change evaluation

Tau immunostaining was performed on sections of the pons (including locus ceruleus), medial temporal lobe, and middle and superior temporal gyri. In cases where NFTs were identified in initial supratentorial sections, additional tau immunostaining was performed on sections of the occipital lobe to determine the Braak stage for each case.[30] NFT burden was scored as none (score = 0), sparse (score = 1), moderate (score = 2), or abundant (score = 3) and the highest score for each case was recorded. Stained sections were evaluated for ARTAG according to consensus criteria.[27] Classification and staging of Alzheimer disease neuropathologic change (ADNC) and primary age-related tauopathy were performed in accordance with consensus neuropathological criteria.[26,28]

α-Synuclein pathologic evaluation

α-Synuclein IHC was performed on sections of the midbrain and medulla. In cases where α-synuclein pathology was identified in the midbrain or medulla, additional α-synuclein IHC was performed on sections of basal forebrain to better characterize the distribution of α-synuclein pathology. α-Synuclein pathology was identified and scored in accordance with McKeith criteria.[31]

TDP-43 pathologic evaluation

TDP-43 IHC was performed on sections of the medial temporal lobe (including hippocampus and entorhinal cortex) and cases were evaluated for limbic-predominant TDP-43 encephalopathy neuropathologic change (LATE-NC).[25,32] As the amygdala is not routinely sampled in the routine autopsy cases, it was not available for LATE-NC staging studies.

Summary neuropathology score

To represent the cumulative neuropathology for each case and for both groups, we calculated a summary neuropathology score based on a previously published formula with modifications.[33] Scoring of Aβ pathology included a Thal score, which was calculated by dividing the Thal stage for each case by 2, and a neuritic plaque burden score as described above for CERAD scoring. Scoring of Tau pathology included a Braak score, which was calculated by dividing the Braak stage for each case by 2 and an ARTAG score, which was scored in a binary manner (0 = no ARTAG; 1 = ARTAG present). Scoring of α-synuclein pathology was based on the distribution of α-synuclein pathology/Lewy body disease (0 = no α-synuclein pathology, 1 = present only in brainstem, and 2 = present in brainstem and limbic region). Scoring of TDP-43 pathology was also calculated in a binary manner such that 0 = no TDP-43 pathology and 1 = TDP-43 pathology present. Finally, given the significant contribution of vascular pathology to neurodegenerative disease and cognitive impairment, we also included a chronic infarct score, which was calculated based on the burden of chronic infarcts in each individual (1 = 1 chronic infarct; 2 = 2 chronic infarcts; and 3 = 3 or more chronic infarcts). The score for each feature was calculated and plotted as an aggregate score. To compare aggregate neuropathology between the groups, we calculated the average score of the group for each neuropathologic feature and plotted as an aggregate score.

APOE genotyping

Genomic DNA was extracted from FFPE tissue using a truXTRAC FFPE DNA microTUBE Kit (Covaris; Woburn, MA) according to the manufacturers' protocol by the Johns Hopkins Genetic Resources Core Facility. One case had DNA extracted using the FastPure FFPE DNA Isolation Kit (Vazyme; Nanjing, China). APOE gene haplotypes were determined by PCR restriction-fragment length polymorphism using previously described protocols.[34] A subset of cases (n = 6) was confirmed using allele-specific real-time PCR by the Johns Hopkins Genetic Resources Core Facility with complete concordance of genotyping results.

Statistical analysis

Group differences (PWH vs HIV-negative) in demographic, genetic, and clinical characteristics as well as the prevalence and severity of neuropathologic features was determined using *t*-test for continuous variables; Chi-square and Fisher's exact tests for categorical variables; or Mann-Whitney *U* tests for ordinal variables. Kendall's Tau-b correlation was used to assess correlations of continuous [age and body mass index (BMI)] and ordinal (Braak stage; burden of NFTs in entorhinal cortex, hippocampus, and neocortex; Thal stage; and burden of diffuse, cored, and neuritic plaques) variables. Data analysis was performed using the SPSS v29 software (IBM). *P*-values less than .05 was considered statistically significant.

RESULTS

Cohort characteristics

We identified 13 PWH with post-mortem tissue available meeting criteria for prolonged viral suppression (Table 1). The average time of HIV infection and virologic suppression was 19.5 years (range: 4-32 years) and 92.2 months (range: 13-236 months), respectively. All individuals except one had a terminal CD4 T cell count >200 cell/μL. The one exception had persistently low CD4 T cell counts throughout the course of HIV infection but with undetectable viral titers for over 4 years prior to death. Peak plasma viral loads were available for 10 of 13 individuals and averaged 375 686 copies/mL

Table 1. HIV-related laboratory data for virally suppressed people with HIV.

Case	Years of HIV infection	CD4 (cells/μL)		Peak plasma viral load (copies/mL)	Last antiretroviral therapy regimen	Viral suppression (months)
		Last	Nadir			
1	19	424	21	>750 000	DTG/RPV/DRV/COB	64
2	32	457	Unknown	Unknown	DTG/RPV	41
3	18	488	Unknown	Unknown	DOL/ABC/3TC	216
4	23	75	3	490 202	RAL/FTC/DRV/RTV	58
5	20	309	25	323 299	DRV/DOL/RTV	28
6	17	506	164	448 416	DRV/RTV/RAL	94
7	27	524	224	619 896	DOR/DRV/COB/RAL	174
8	15	626	259	6777	DRV/RTV/EFV	60
9	28	1057	34	Unknown	BIC/FTC/TAF	236
10	18	1194	340	137 705	BIC/FTC/TAF	92
11	31	369	10	672 255	ETV/DRV/RTV/RAL	100
12	8	344	119	36 007	DTG/DRV/COB	13
13	4	1440	637	235 345	ETR/FTC/RAL	41

(range: 6777-750 000 copies/mL). CD4 T cell nadirs were available for 11 of 13 individuals and averaged 183 cells/μL (range: 3 to 637 cells/μL).

Overall, the HIV-negative and HIV+ groups were similar with respect to demographics and the prevalence of comorbid medical conditions (Table 2). The HIV-negative and HIV+ groups had identical mean age (59.3 years), an equal number of males (n = 7; 54%), a similar proportion of APOE4 carriers (38% vs 54%; $P = .70$, Fisher exact test), and were composed entirely of Black individuals. Without formal neurocognitive or neuropsychological testing information for every individual, cognitive data were limited and should be interpreted with caution. Nevertheless, cognitive signs and symptoms were noted in the medical records for 3 (23%) PWH and 1 (8%) HIV-negative individual ($P = .28$; Fisher exact test). With respect to medical comorbidities, the average BMI was similar between both groups (35.8 vs 30.5 kg/m^2; $P = .13$; 2-tailed *t*-test), and there were no differences in the prevalence of any non-HIV related medical comorbidity, including hypertension, diabetes, hyperlipidemia, chronic kidney disease, hepatitis B virus and hepatitis C virus seropositivity, liver cirrhosis, coronary artery disease or history of myocardial infarction, heart failure, chronic obstructive lung disease, psychiatric disorder, substance use disorder, non-AIDS-defining cancer, and non-HIV infectious disease. The reported causes of death for HIV-negative individuals and PWH were similar and included sudden cardiac death (8% vs 15%), myocardial infarct/coronary artery disease (15% vs 15%), complications from heart failure (8% vs 8%), pneumonia or pulmonary embolism (15% vs 15%), sepsis (15% vs 31%), metastatic carcinoma (31% vs 8%), and end-stage liver disease (8% vs 8%).

Neuropathologic findings

Overall, there were no statistically significant differences in the macroscopic or common microscopic findings for either group (Table S1). The most common routine pathologic findings were infarcts, focal hypoxic-ischemic changes/injury, arteriolosclerosis (Figure 1A and I), and atherosclerosis, which were not different between groups ($P = .43$, .68, .68, and .69, respectively, Chi-square test). Hemorrhages (subarachnoid and subdural) and abscesses were only identified in the HIV+ group, though these were rare enough findings that they were not statistically different between groups ($P = .22$ and .10, respectively, Fisher exact test). The 2 cases with brain abscesses were noted to have comorbid endocarditis as the reported etiology.

Neurodegenerative pathologic findings

We identified several forms of neurodegenerative pathology in our study cohort (Figure 2), including diffuse Aβ plaques (Figure 1B and J), neuritic plaques (Figure 1C and K), tau NFTs (Figure 1D-F and L-N), ARTAG (Figure 1G and O), Lewy body pathology (Figure 1H and P), and rare hippocampal TDP-43 pathology (not shown). Overall, we observed consistent trends towards more prevalent neurodegenerative pathology in the HIV+ group (Figure 3). The most common pathologies in this cohort were amyloid plaques (Aβ-immunoreactive plaques: HIV+ 69%, HIV-negative 54%, $P = .69$; neuritic plaques: HIV+ 29%, HIV-negative 15%, $P = .38$, Chi-square test; Figure 3A and B) and NFTs (Braak stage III+: HIV+ 62%, HIV-negative 38%, $P = .43$, Fisher exact test; Figure 3C). Non-AD neuropathology also tended to be more common in PWH, specifically ARTAG (HIV+ 23%, HIV-negative 0%, $P = .22$, Fisher exact test; Figure 3D) and Lewy body pathology (HIV+ 31%, HIV-negative 8%, $P = .32$, Fisher's exact test; Figure 3E). PWH did not show a trend toward increased cerebral amyloid angiopathy or TDP-43 hippocampal pathology; however, these pathologies were rare in this cohort and only identified in one HIV-negative case each.

We next compared the severity of Aβ and tau pathology based on established pathologic staging systems (Thal and Braak stages) and semi-quantitative measures of plaque and NFT burden. The median amyloid pathology stage for the HIV+ and HIV-negative groups were low and not significantly different (median score Thal 2 vs Thal 1; $P = .24$, Mann-Whitney *U* test). However, in PWH the Thal stage tended to be higher, with 5 of the 9 amyloid positive HIV+

Table 2. Demographic and clinical characteristics of HIV-negative and HIV-positive individuals.

	HIV-negative (n = 13)	HIV-positive (n = 13)	*P*-value
Demographics and cognitive symptoms			
Age at death, years, mean (SD)	59.3 (7.6)	59.3 (7.8)	.99
Sex, male	7 (54%)	7 (54%)	1
Race, Black	13 (100%)	13 (100)	1
APOE4 carriers	5 (38%)	7 (54%)	.70
Reported cognitive symptoms	3 (23%)	1 (8%)	.28
Medical comorbidities			
Body mass index, kg/m^2, mean (SD)	35.8 (8.26)	30.5 (8.38)	.13
Hypertension	10 (77%)	9 (69%)	.66
Diabetes	5 (38%)	8 (62%)	.24
Hyperlipidemia	7 (54%)	6 (46%)	.69
Chronic kidney disease	5 (38%)	8 (62%)	.24
HBV seropositive	0	1 (8%)	> .99
HCV seropositive	2 (15%)	6 (46%)	.20
Cirrhosis	2 (15%)	3 (23%)	> .99
Latent *M. tuberculosis* infection	0	2 (15%)	.48
Syphilis	0	2 (15%)	.48
Coronary artery disease	3 (23%)	1 (8%)	.28
Myocardial infarction	2 (15%)	1 (8%)	> .99
Heart failure	1 (8%)	1 (8%)	1
Endocarditis	0	3 (23%)	.22
Asthma	2 (15%)	1 (8%)	> .99
Chronic obstructive pulmonary disease	2 (15%)	1 (8%)	> .99
Interstitial lung disease	0	1 (8%)	> .99
Post-solid organ transplant immunosuppression	1 (8%)	0	> .99
Traumatic brain injury	0	1 (8%)	> .99
Seizure disorder	0	1 (8%)	> .99
Psychiatric disorder	3 (23%)	3 (23%)	1
Lifetime substance use disorder	4 (31%)	5 (38%)	> .99
Non-AIDS-defining cancer	3 (23%)	2 (15%)	> .99

P-values calculated using 2-tailed t-test, Pearson's Chi-square test, or Fisher's exact test.

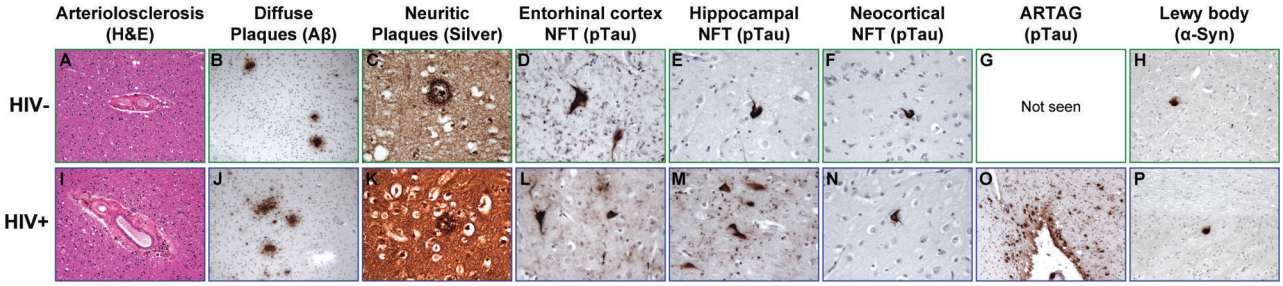

Figure 1. Representative neurodegenerative pathologic findings. Representative microscopic images from tissue sections stained with hematoxylin and eosin (H&E; A and I), Aβ immunohistochemistry (6E10; B and J), silver (Hirano method; C and K), tau immunohistochemistry (AT8; D-G, L-O), and α-synuclein immunohistochemistry (α-Syn; 913611; H and P) from HIV+ (A-H) and HIV- (I-P) individuals. Arteriolosclerosis (A and I) was a common finding in both groups. Diffuse plaques (B and J), neuritic plaques (C and K), tau-immunoreactive neurofibrillary tangles (NFTs) in the entorhinal cortex (D and L), hippocampus (E and M), and neocortex (F and N) were present to varying degrees in both groups. About one-third of HIV+ cases also demonstrated foci of aging-related tau astrogliopathy (ARTAG; H) with no evidence of ARTAG in HIV-negative cases (G). α-Synuclein pathology in the form of Lewy bodies and Lewy neurites was also present at varying proportions in both groups (H, P). Original magnification 100× (B and J), 200× (A, G-I, and P), and 400× (C-F, K-N).

cases showing a Thal score of 3-4 (55%), while only 2 of the 7 amyloid positive cases in the HIV-negative group reach a Thal score of 3 (29%) (Figure 4A). This remained true when subdividing the groups by ApoE4 carrier status; HIV+ ApoE4 carriers tended to have a higher Thal burden compared to HIV-negative ApoE4 carriers (Thal 3-4: HIV+ 43%, HIV-negative 20%). Semi-quantitative measures of the diffuse plaque burden mirrored these trends, with similar median burdens of diffuse plaque pathology in PWH and HIV-negative individuals (2 vs 1, $P = .20$, Mann-Whitney U test), but with nearly half of HIV+ individuals showing frequent plaques (6/13, 46%) compared to only a few cases in the HIV-negative group (2/

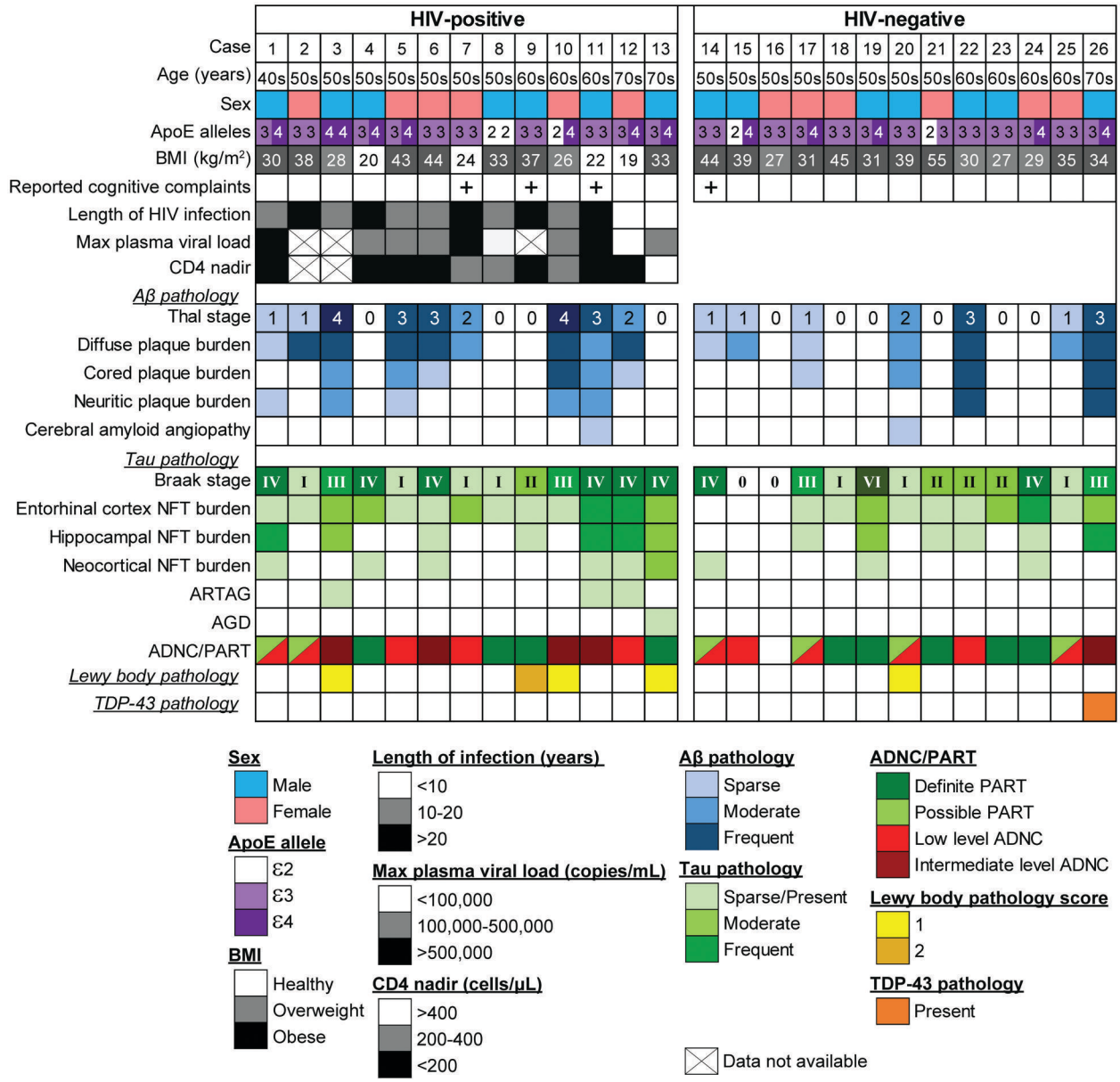

Figure 2. Graphical summary of demographic, clinical, and neurodegenerative pathologic findings of study cohort. Individuals with reported subjective or objective cognitive complaints are indicated with a "+" symbol. BMI, body mass index; NFT, neurofibrillary tangle; ARTAG, aging-related tau astrogliopathy; AGD, argyrophilic grain disease; ADNC, Alzheimer disease neuropathologic changes; PART, primary age-related tauopathy.

13, 15%) (Figure 4B). Cored and neuritic plaques for both groups were relatively infrequent in this cohort and similar between groups (Figure 4C and D).

With respect to the severity of tau pathology, Braak staging showed an interesting change in tau pathology distribution between the 2 groups. The median Braak stage of the HIV+ and HIV-negative groups were not significantly different (median score Braak III vs Braak II, $P = .31$, Mann-Whitney U test), and in the HIV- cases there was an approximately even distribution of Braak stages between 0-IV. However, HIV+ cases showed a bimodal distribution, peaking at early (stage I) and intermediate (stage IV) Braak stages. Unlike the HIV-negative group, all cases showed tau pathology in the HIV+ group and nearly half the cases (6/13, 46%) were Braak stage IV (Figure 5A). Within each of the measured regions the burden of NFT pathology was similar between HIV-negative and HIV+ individuals (Figure 5B-D).

Given the sex-specific differences in HIV pathogenesis and neurodegenerative pathology in prior studies,[35,36] we also evaluated trends in the severity of Aβ and tau pathology among males and females. Overall, plaque and NFT pathology were similar in males and females. However, when stratified by HIV status, HIV+ female individuals tended to show a higher median Thal stage (stage 2) and burden of diffuse plaque

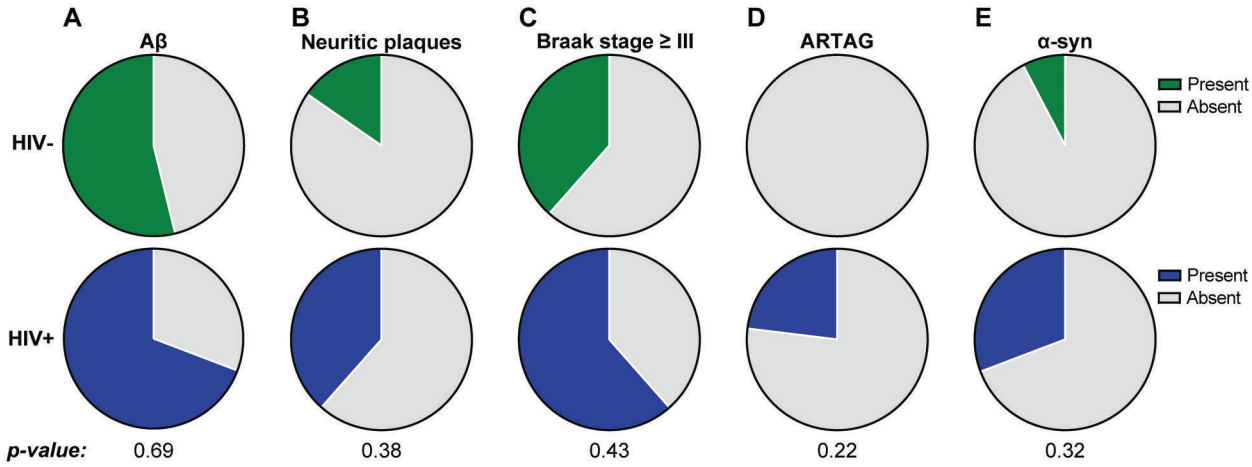

Figure 3. Prevalence of Aβ, tau, and α-synuclein pathology. The prevalence pathology in HIV-negative (green; top row) and HIV+ (blue; bottom row) individuals for (A) Aβ-immunoreactive plaques, (B) neuritic plaques (determined by Hirano silver staining), (C) intermediate-to-high stage neurofibrillary tangles (Braak stage III or greater), (D) aging-related tau astrogliopathy (ARTAG), and (E) alpha-synuclein (α-syn) pathology in the form of Lewy bodies and/or Lewy neurites. *P*-values comparing groups determined by Pearson's Chi-square or Fisher's exact tests.

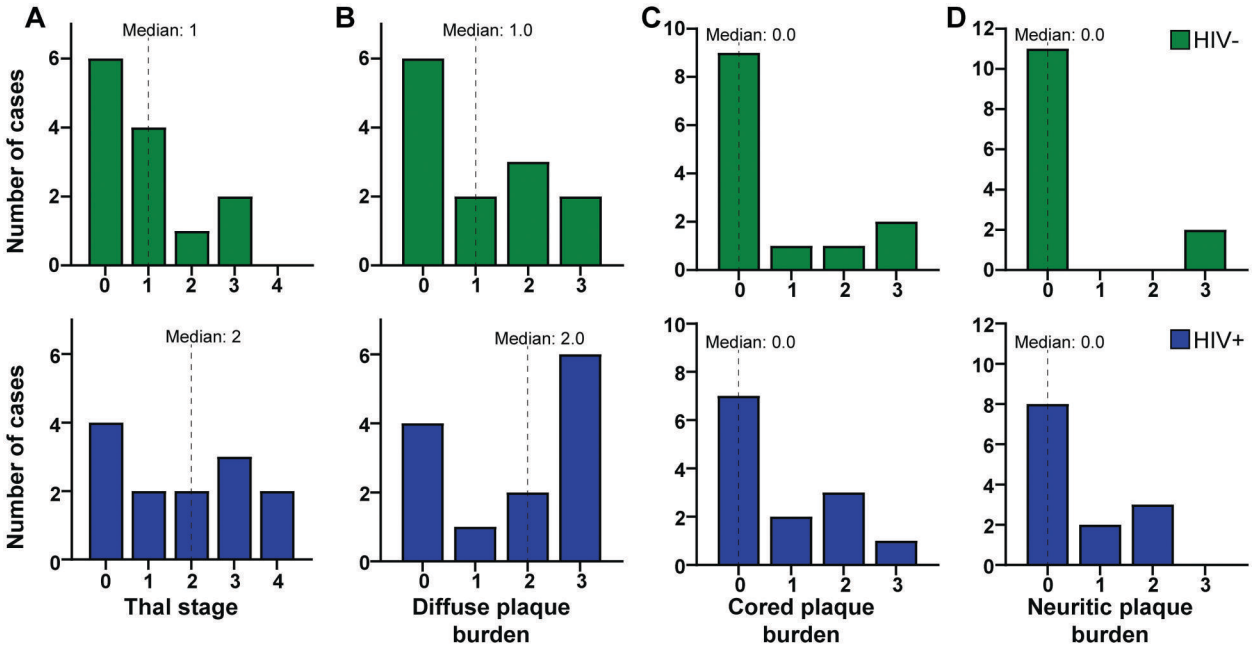

Figure 4. Severity of Aβ pathology. The number of cases with Aβ pathology in HIV-negative (green; top row) and HIV+ (blue; bottom row) individuals shown by (A) Thal stage or semi-quantitative burden of (B) diffuse, (C) cored, and (D) neuritic plaques. Dotted lines indicate median severity score.

pathology (score = 3) compared to HIV-negative females or males regardless of HIV infection status (Figure S1A and B). The burden of cored and neuritic plaques were uniformly low across groups (Figure S1C and D). By contrast, HIV+ males tended to show higher median Braak stages compared HIV+ females (II vs IV; Figure S2A), with trends toward higher NFT burdens in the entorhinal cortex (score = 1 vs 2; Figure S2B), hippocampus (score = 0 vs 2; Figure S2C), and neocortex (score = 0 vs 1; Figure S2D).

Combining the amyloid and tau staging, we assigned each case a diagnosis of PART or ADNC, as appropriate. The proportion of PART (definite and possible) and low level ADNC were similar between the 2 groups. However, there were 4-times more cases of intermediate level ADNC in the HIV+ group (4; 31%) compared to the HIV-negative group (1; 8%) ($P = .14$; Figure 2). No high level ADNC was present in this cohort.

We next evaluated the degree of total neuropathologic findings that could relate to cognitive impairment in each group. To accomplish this, we calculated a summary neuropathology score for each individual based on the presence and severity of several pathologies including Thal stage, neuritic plaque

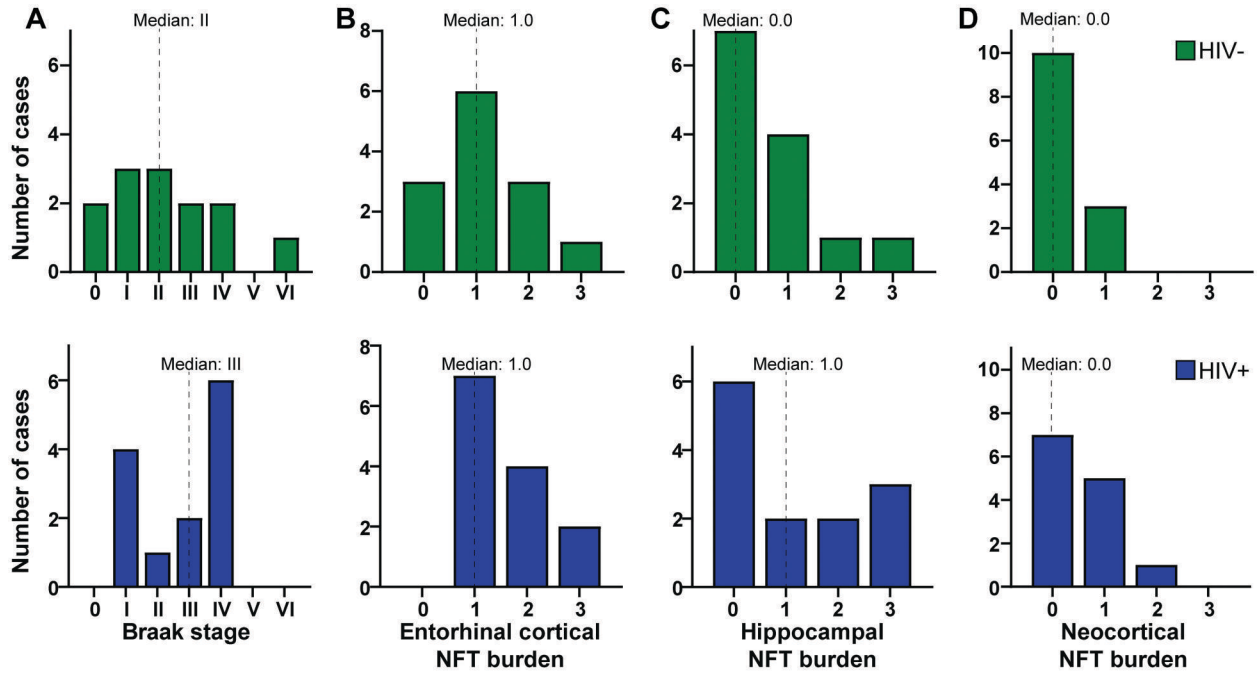

Figure 5. Severity of tau pathology. The number of cases with tau pathology in HIV-negative (green; top row) and HIV+ (blue; bottom row) individuals by (A) Braak stage or semi-quantitative burden of (B) entorhinal cortex, (C) hippocampal, and (D) neocortical neurofibrillary tangles (NFTs). Dotted lines indicate median severity score.

burden (CERAD), Braak stage, ARTAG, α-synuclein/Lewy body pathology, TDP-43 pathology, and chronic infarcts. Individually, PWH appear to have higher cumulative neuropathology scores than HIV-negative individuals (Figure 6A). This was also true when comparing between group data (Figure 6B), although not statistically significant (HIV+ 4.72; HIV-negative 2.73; $P = .41$).

Finally, examining the data for demographic or clinical correlates of Aβ and tau pathology in our cohort yielded 2 correlates of tau pathology. Across the entire cohort, age at death positively correlated with entorhinal cortical NFTs ($r_\tau = 0.46$, $P = .003$) whereas end-of-life BMI was negatively associated with entorhinal cortical NFTs ($r_\tau = -0.48$, $P = .002$; Figure 7A; Figure S3A and C). When each group was considered separately, the HIV-negative group demonstrated a significant correlation only between entorhinal cortical NFT burden and age at death ($r_\tau = 0.63$, $P = .006$; Figure 7B; Figure S3B). On the other hand, the HIV+ group demonstrated a significant negative correlation between entorhinal cortical NFT burden and end-of-life BMI ($r_\tau = -0.64$, $P = .006$; Figure 7C; Figure S3D). HIV infection clinical characteristics did not correlate with neurodegenerative pathology (Figure 7C).

DISCUSSION

There is an emerging population of older virally suppressed PWH that, due to advancing age, is at increased risk for neurodegenerative pathology and disease. Whether well-controlled HIV infection affects neurodegenerative pathogenesis in aging PWH is unclear. Here, using samples from a community-based cohort, we identified trends towards more prevalent and more severe AD and non-AD neurodegenerative pathology in PWH. We also identified a novel negative correlation in PWH between entorhinal cortical NFT burden and end-of-life BMI. These results suggest that PWH, even with well-controlled HIV, may be at increased risk for the development of both AD- and non-AD-related neurodegenerative pathology compared to their HIV-negative counterparts.

This study used several key advances to characterize neurodegenerative pathology in virally suppressed PWH. First, use of a community-based cohort affords the opportunity to study specimens from HIV+ and HIV-negative individuals with similar demographics, medical comorbidities, and exposure to community-level vulnerabilities. Previous work has predominantly relied on study- or clinic-based cohorts, which likely differ in sociodemographic, genetic, and pathologic features from the general population of PWH.[37–39] Second, while prior work has presented data from larger cohorts, most of these studies have included PWH of relatively young age or with incomplete virologic suppression, which may not be representative of the current state of the HIV epidemic in the United States where most PWH are virally-suppressed.[11,40] Here, we have selected our cohort specifically to represent individuals with well-documented virologic control and of relatively older age. We have also minimized the bias of other co-occurring medical conditions by rigorously matching medical comorbidities across the HIV+ and negative groups. Finally, while much of the previous work has focused on AD pathology, here we include the prevalence of several non-AD neurodegenerative pathologies, including ARTAG, α-synuclein, and TDP-43 pathology.

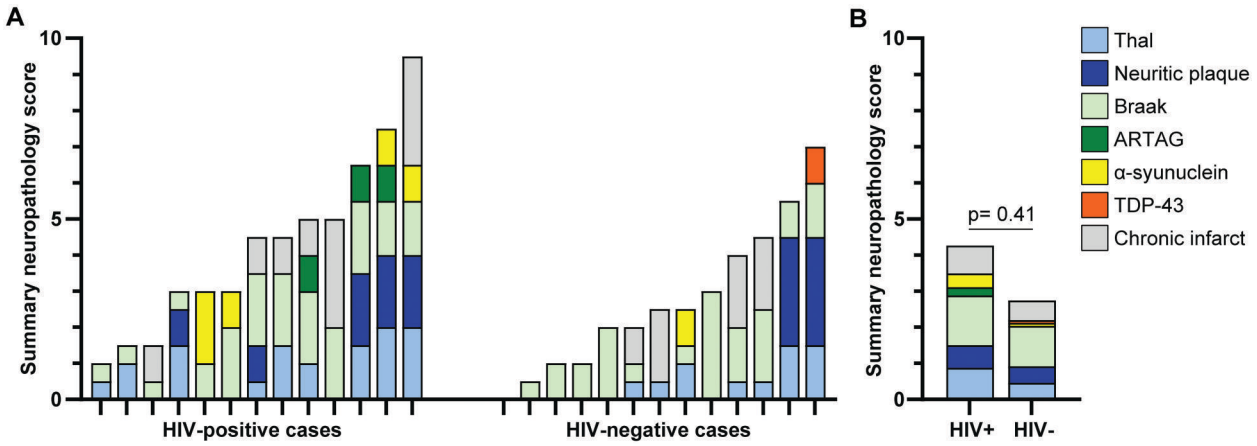

Figure 6. Summary scores of neuropathologic findings. The sums of calculated scores for the indicated neuropathologic findings for each study individual (A) and (B) HIV+ and HIV-negative groups are graphed. *P*-values calculated using 2-tailed t-test.

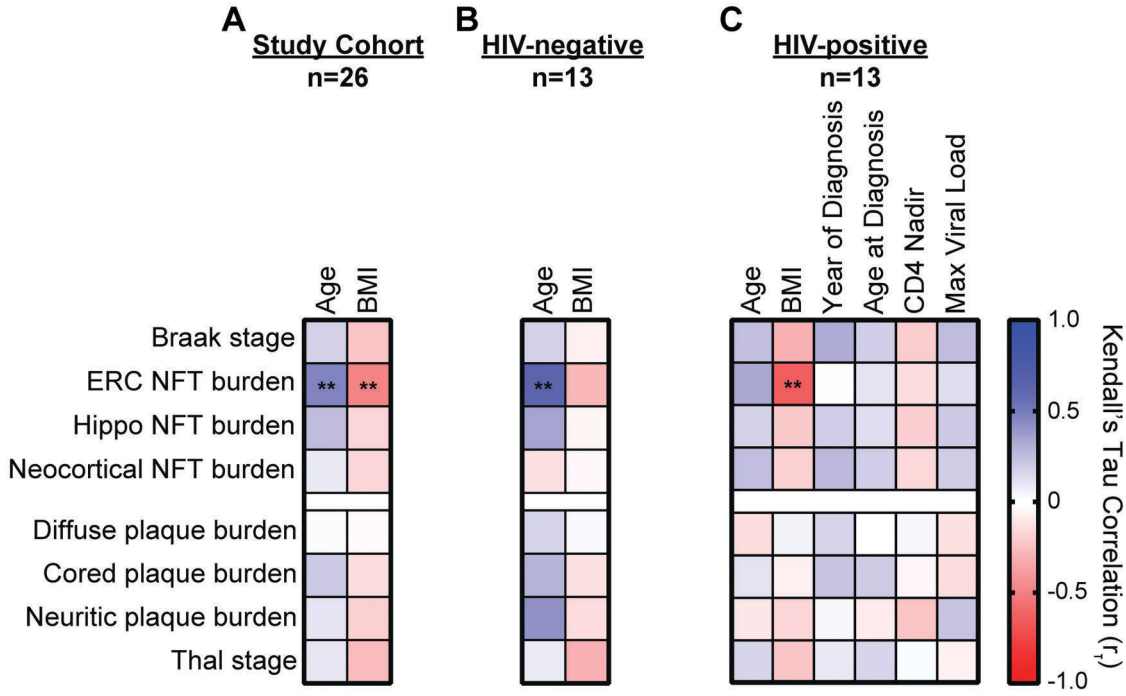

Figure 7. Correlations between demographic and clinical characteristics and neurodegenerative pathology. Heat map of the correlation coefficients for each demographic and HIV disease-related clinical data with neurodegenerative pathology. Correlations are shown for (A) the entire study cohort, (B) the HIV-negative group, and (C) the HIV+ group. ** $P < .01$. BMI, body mass index; ERC, entorhinal cortex; Hippo, hippocampus; NFT, neurofibrillary tangle.

The prevalence and severity of multiple age-related neurodegenerative pathologies tended to be increased in older PWH for both AD and non-AD pathologies. The overall pathologic levels were low to intermediate for most pathologies in this study, due to the younger age of this cohort (average age 59.3 years) compared to typical neurodegenerative cohorts. However, even in this younger group there is a trend toward more amyloid diffuse plaques, more spread of NFTs, more Lewy body pathology, and more ARTAG. As the trends are present across different age-related neuropathologies, the findings in this study could be consistent with the observation that blood and brain tissue from PWH demonstrate accelerated epigenetic aging by 5-7 years.[41]

The role of HIV and other viral infections in neurodegenerative disease is controversial. Several infections have already been associated with specific neuropathologies, including Epstein-Barr virus with multiple sclerosis and measles virus with subacute sclerosing panencephalitis. Some studies have raised the possibility of a potential relationship between herpes simplex virus type 1 and AD.[42–45] The recent SARS-CoV-2 pandemic has also raised concerns for post-infectious neurologic dysfunction and whether infection confers an increased

risk of neurodegenerative disease is under investigation.[46] In the case of HIV, it is unclear if any association with neurodegenerative pathology would be due to direct toxicity of cells and tissue in the central nervous system or indirectly, via inflammation and accelerated aging. If HIV is acting directly in the brain, it may be through mechanisms similar to human endogenous retroviruses (HERVs), which are members of the *Retroviridae* family like HIV and make up approximately 8% of the human genome; these have been linked to a variety of neuropathologies including multiple sclerosis, amyotrophic lateral sclerosis, frontotemporal dementia, Parkinson disease, and AD.[47,48] Alternatively, chronic low-level systemic inflammation, including neuroinflammation, associated even with well-controlled HIV infection, may provide some explanation for the spectrum of clinical and pathologic features in PWH. However, to date, studies that have examined astroglial and microglial pathology by standard histologic techniques have not identified a significant difference in PWH and HIV-negative controls.[11–13] Future work leveraging modern immunologic techniques could provide additional insight. As molecular virology and immunology techniques continue to improve and emerge, the role of viruses in neuroinflammation and neurodegenerative disease should become clearer.

Previous work on HIV-associated neurodegenerative pathology has focused on Aβ pathology. These studies have evaluated Aβ pathology in over 600 PWH, mostly from study- or clinic-based cohorts, with average cohort ages between 45 and 81 years, and of varying degrees of virologic suppression. From these, a range of prevalence of Aβ pathology has been reported, from 6% to 44%.[11–13,17,20–24] Our findings suggest a slightly greater prevalence of Aβ in our cohort of PWH (69%) and one that appears higher than that of HIV-negative controls. A recent study also found that the duration of HIV infection but not age was predictive of Aβ pathology in PWH.[49] While we did not observe this same correlation in our relatively small cohort, this raises the intriguing possibility of a direct effect of either HIV itself or its treatment.

Compared to Aβ, modern studies on the prevalence and severity of tau and NFT pathology in virally suppressed PWH are sparse. Two studies that examined the neocortex of virally suppressed PWH detected NFTs in 24%-56% of cases,[11,12] similar to what we report here. Another study of 2 well-characterized and virally suppressed PWH were shown to have intermediate to high levels of ADNC.[24] Finally, one study showed elevated levels of hippocampal hyperphosphorylated tau in PWH compared to age-matched HIV-negative controls, especially in the subset of PWH on cART.[18] The trends observed in this work are consistent with the prior findings but provide a more comprehensive view of the NFT pathology burden compared to prior studies pointing toward more prevalent and severe NFT pathology in this group.

There is a paucity of studies on the prevalence of non-AD neurodegenerative pathology in virally suppressed PWH. Prior to this work, only 2 groups had investigated the prevalence of non-AD pathology in PWH. Morgello et al reported the presence of ARTAG in a case series of 2 virally suppressed PWH.[24] Our findings confirm ARTAG in PWH, with a prevalence in this larger group of 23% in virally suppressed PWH compared to 0% ARTAG in HIV-negative individuals. For Lewy body pathology, Khanlou et al reported a 16% prevalence of incidental Lewy body pathology in a larger cohort of 75 PWH, though only 85% of individuals were virally suppressed.[15] Our prevalence of incidental Lewy body pathology is similar at 31% in PWH, compared to only 8% in HIV-negative individuals. Importantly, the prevalence of incidental Lewy body pathology in our HIV-negative group is consistent with previously reported rates in a similar age group.[50] Due to the small number of cases in our study, differences identified in ARTAG and Lewy body pathology were not significant. Retrospective power analysis suggests that future studies will need to evaluate 2.2-3.5 times more cases (29-46 cases) to more definitively determine whether ARTAG and Lewy body pathology are more prevalent in in PWH.

We identified a negative correlation between end-of-life BMI and entorhinal cortical NFTs, specifically in PWH. The relationship between age-dependent BMI and neurodegenerative disease is complex. High mid-life BMI and low late-life BMI are associated with increased risk of dementia and ADNC in the general population.[51–53] However, its relationship with burden of entorhinal NFT pathology and PWH has not been previously described. This finding is unlikely to be attributable to survival bias, as we did not observe a significant correlation between age at death and end-of-life BMI (r_τ = -0.27; $P = .19$).

While our study shows interesting trends toward increased AD and non-AD neurodegenerative pathology in a community-based cohort, it is limited by the lack of cognitive data and by the relatively small number of cases. As with many community-based autopsy cohorts, detailed information on neurologic status was not available, precluding the correlation of our pathologic findings with cognitive changes. However, this study does add to the growing literature of increased neurodegenerative pathology in aging PWH spanning both AD and non-AD related pathology. Our study was also limited by a relatively small cohort size and includes only Black individuals, which was not intentional and may reflect the high percentage of PWH who are Black (73.7%) in the Baltimore metro area.[54] However, these early findings support the need for studies in a larger community-based cohort with assessment of both AD and non-AD neurodegenerative pathology.

In summary, the emergence of an aging population of virally suppressed PWH raises the concern of neurodegenerative pathology contributing to subtle HIV-associated neurocognitive deficits. The results from this study raise the intriguing possibility that even well-controlled, long-term HIV infection may increase the risk for both AD and non-AD related neurodegenerative processes. Further work will be required to better characterize the neurodegenerative pathology in this group and to determine the shared or unique mechanisms of neurodegeneration by which HIV infection affects cognitive dysfunction.

SUPPLEMENTARY MATERIAL

Supplementary material is available at academic.oup.com/jnen.

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CONFLICTS OF INTEREST

The authors have no duality or conflicts of interest to declare.

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