

RESEARCH ARTICLE

Blood-based Alzheimer's disease biomarkers and cognitive trajectories in older people with HIV with undetectable viral loads

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Funding information

U.S. National Institutes of Health's (NIH)

Abstract

INTRODUCTION: Cognitive impairment among people with HIV (PWH) remains common, yet underlying mechanisms remain unclear. Alzheimer's disease (AD) is the leading cause of dementia, and blood-based biomarkers offer a promising diagnostic alternative. We evaluated phosphorylated-tau 217 (p-tau217), neurofilament light (NfL), and glial fibrillary acidic protein (GFAP) as predictors of cognitive decline among virologically suppressed older PWH.

METHODS: Thai PWH aged ≥ 50 years with plasma viral loads < 50 copies/mL completed the Montreal Cognitive Assessment (MoCA) at baseline (2015–2017) and a follow-up visit (2021–2024). Associations between each biomarker and cognitive trajectories were assessed using multivariate mixed-effects models.

RESULTS: Among 255 participants followed for a median of 5.9 years, those in Q4 of p-tau217 and GFAP had greater MoCA decline than Q1–3 (p-tau217: -3.3 vs. -1.4, p-interaction = 0.02; GFAP: -2.9 vs. -1.3, p-interaction = 0.03).

DISCUSSION: Elevated p-tau217 and GFAP predict cognitive decline in PWH, underscoring AD and inflammatory biomarker relevance.

KEYWORDS

aging, Alzheimer's disease, biomarkers, cognition, people with HIV

Highlights

- Higher baseline blood p-tau217 was associated with significantly greater cognitive decline in older people with HIV (PWH) with undetectable viral loads.
- Elevated glial fibrillary acidic protein (GFAP) levels also predicted greater cognitive decline, whereas neurofilament light chain (NfL) showed no significant association.

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- Phosphorylated-tau 217 (p-tau217) and GFAP highlight the relevance of Alzheimer's disease (AD) and inflammatory as the underlying mechanisms to cognitive decline in this population.

1 | BACKGROUND

With the substantial increase in life expectancy among people with HIV (PWH), HIV has transitioned into a manageable chronic condition.¹ Consequently, a growing number of PWH are now living with age-related comorbidities, including cognitive impairment. Although cognitive impairment in the modern antiretroviral therapy (ART) era appears to have shifted toward milder forms,² its overall prevalence remains common and clinically meaningful, underscoring the importance of addressing cognitive health in this population. The mechanisms underlying cognitive decline in PWH are complex and multifactorial.³ However, despite sustained virological suppression achieved through ART, the main drivers of cognitive decline in PWH remain uncertain.

In the general population, Alzheimer's disease (AD) is by far the leading cause of dementia worldwide, accounting for 60–80% of cases. AD is characterized by accumulation of neuritic plaques and neurofibrillary tangles in the brain, accompanied by synapse and neuron loss.⁴ Like many neurodegenerative diseases, AD is irreversible; however, unlike most, there are well-established biomarkers that could aid diagnosis and become abnormal up to almost two decades before clinical symptoms emerge.^{5,6} Among these, blood phosphorylated tau 217 (p-tau217) has demonstrated diagnostic performance comparable to cerebrospinal fluid and positron emission tomography measures,^{7–11} offering a more accessible diagnostic tool for future clinical application and public health implementation, particularly in resource-limited settings (RLS). Furthermore, the approval of disease-modifying therapies for AD—currently restricted to individuals with early-stage disease—underscore the urgent need for timely, accurate, and accessible diagnostic strategies.

Whether AD pathology plays the same central role in cognitive decline among PWH, however, remains unclear. HIV infects microglia and astrocytes early in the disease course, and peripheral viral suppression does not necessarily indicate central nervous system (CNS) control.^{12,13} Glial fibrillary acidic protein (GFAP), a marker of astrocytic activation,¹⁴ may therefore capture ongoing CNS inflammation even in the setting of undetectable plasma viral loads.

Other potential pathways contributing to cognitive decline in PWH variably involves neuronal and/or axonal injury. PWH who experience cognitive decline often show white matter lesions on MRI that resemble those caused by vascular injury.¹⁵ Neurofilament light chain (NfL), a biomarker of neuroaxonal injury, offers a useful measure of such processes.¹⁶ NfL levels are known to rise across diverse neurological conditions, including vascular cognitive impairment and HIV-associated dementia.^{17,18} Thus, NfL may capture contributions

from both vascular and HIV-related mechanisms underlying cognitive decline.

Recent diagnostic frameworks highlight blood phosphorylated-tau 217 (p-tau217), GFAP, and NfL, though their roles differ—p-tau217 is considered a core AD biomarker, whereas GFAP and NfL are regarded as non-core biomarkers that nonetheless provide important information on disease pathophysiology.⁵ Collectively, blood-based biomarkers may provide valuable insights into the mechanisms of cognitive decline in PWH and hold promise for predicting its course. These plasma biomarkers have important additional advantages: they are simple, inexpensive, noninvasive, and increasingly accurate. However, data on their use in PWH remain limited. We aimed to evaluate the role of p-tau217, NfL, and GFAP in predicting cognitive trajectories among older adults with chronic HIV and undetectable viral loads.

2 | METHODS

2.1 | Study participants

The study utilized stored blood samples and secondary data from established cohort studies, the HIV-NAT 006 and HIV-NAT 207. The HIV-NAT 006 study is an ongoing prospective clinic-based cohort that has been enrolling adults with HIV (aged ≥ 18 years) since 1996 (NCT00411983).^{19–23} The HIV-NAT 207 (Aging) study is a sub-study of HIV-NAT 006 enrolling PWH and people living without HIV aged ≥ 50 years to assess various age-related health issues,^{24–29} including cognitive performance, using the Thai-validated paper-based Montreal Cognitive Assessment (MoCA). The Thai-validated version of the MoCA adjusted the cutoff score from 26 to 25 and added an additional point to participants with ≤ 6 years of education instead of ≤ 12 , as in the original MoCA.³⁰ PWH were enrolled from those who were already participating in the HIV-NAT 006 study. To date, the HIV-NAT 207 study has two visits: first visit occurred during 2015–2017 and second visit during 2021–2024. Participants included in this study were those with available stored blood samples collected at baseline of the HIV-NAT 006 and 207 study, aged ≥ 50 years with plasma viral loads < 50 copies/mL and completed the MoCA at baseline (2015–2017) and a follow-up visit (2021–2024).

The study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB No. 538/67), and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical guidelines.

RESEARCH IN CONTEXT

1. **Systematic review:** The authors searched PubMed for studies on blood-based, cerebrospinal fluid (CSF), and positron emission tomography (PET) biomarkers, in relation to cognitive impairment among people with HIV (PWH). While a few studies were identified, none specifically investigated phosphorylated-tau 217 (p-tau217), compared it with other biomarkers, or evaluated longitudinal outcomes.
2. **Interpretation:** Our findings demonstrated that blood p-tau217 and glial fibrillary acidic protein (GFAP) are stronger predictors of cognitive decline than neurofilament light chain (NfL) among PWH with undetectable viral loads, suggesting a role of Alzheimer's disease (AD) pathophysiology and astrogliosis and highlighting the potential utility of their blood biomarkers as predictive tools.
3. **Future directions:** Validation of blood-based biomarkers against CSF and PET imaging is essential, and longitudinal studies with repeated assessments and comprehensive neuropsychological testing are needed.

2.2 | Biomarker analysis

Plasma p-tau217 levels were measured using the Meso Scale Discovery platform with the S-PLEX Human Tau (pT217) Kit (Meso Scale Discovery) at the Department of Bacterial and Parasitic Diseases Laboratory, Armed Forces Research Institute of Medical Sciences (AFRIMS), Thailand.

NfL and GFAP levels were measured using the Simoa platform with the commercially available Neurology 2-PLEX B (Quanterix) at the Thai Red Cross Emerging Infectious Diseases Health Science Centre, King Chulalongkorn Memorial Hospital. Samples were analyzed in duplicate by technicians in a blinded fashion.

2.3 | Statistical analysis

Baseline characteristics were summarized as frequency with percentage for categorical variables and median with interquartile range (IQR) for numerical variables and categorized by the quartiles of each biomarkers of interest in a binary fashion. Pearson's chi-square, Fisher exact test, and Mann-Whitney U test were used to compare baseline characteristics between groups as appropriate. p-Tau217, NfL, and GFAP were analyzed both as continuous variables and by quartiles with a binary comparison between the highest quartile (Q4) and the lower quartiles (Q1-3) as done previously.³¹ This approach was used to facilitate clinical interpretability and visualization of potential differences between individuals with relatively higher versus lower

biomarker levels, particularly in the absence of established cut-off values for this population. Multivariable logistic regression, adjusted for confounders based on previously reported data to be associated with cognitive impairment, was used to examine the association between each biomarker and lower cognitive performance (defined by MoCA score of <25). Model I adjusted for age, sex, and education level. Model II included the same covariates as Model I, with an addition of the body mass index (BMI), diabetes mellitus, hypertension, creatinine clearance (CCr), HIV duration, nadir CD4 levels, and exposure to efavirenz. Multivariable linear regression models, built on the same covariates as Model I and II, were used to examine the differences in MoCA score between each biomarker.

Multivariate linear mixed-effects models were used to construct predictive models with each biomarker as the independent variable of interest and changes in MoCA score (the total score and each of the MoCA subdomain) as the dependent variable of interest. Model I adjusted for sex, education level, and baseline MoCA score. Model II adjusted for the same covariates as Model I with an addition of the body mass index (BMI), diabetes mellitus, hypertension, CCr, HIV duration, nadir CD4 levels, and exposure to efavirenz. An interaction term for biomarker quartiles and time-updated age were used to estimate the effect of baseline each biomarker levels on cognitive performance changes over time. Statistical significance for all models was set at $p < 0.05$ two-sided. All analyses were performed using Stata/SE 17.0 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Participant characteristics

A total of 255 participants were included. Demographic and baseline clinical characteristics are summarized in Table 1. The median age was 54.3 years (IQR: 51.8–59.1), and 94 participants (36.9%) were female. Most participants (194, 76.1%) had an education level beyond 6 years. The median BMI was 23.0 kg/m² (IQR: 20.6–25.0), and the median CCr was 73.8 ml/min (IQR: 63.0–88.7). Diabetes mellitus and hypertension were present in 41 (16.1%) and 109 (42.7%) participants, respectively. Participants had been diagnosed with HIV for a median of 18.7 years (IQR: 15.3–21.0), with a median most recent CD4 count of 624 cells/mm³ (IQR: 491–803). The majority were receiving regimens containing nucleoside reverse transcriptase inhibitor (NRTI) (94.1%) or non-NRTI (NNRTI) (65.5%). The median MoCA score was 24.0 (IQR: 21.0–26.0) at baseline and 22.0 (IQR: 19.0–25.0) at follow-up. The median interval between the two MoCA was 5.9 years (IQR: 5.6–6.8).

Baseline characteristics were comparable between PWH in Q4 and those in Q1–Q3 of plasma p-tau217 levels. In contrast, compared to those in Q1–Q3 of NfL levels, participants in Q4 were significantly older, had lower BMI and CCr, were more likely to have diabetes mellitus, hypertension, and were more likely on integrase strand transfer inhibitors (INSTIs). A similar pattern of differences in age, hypertension, and CCr was observed when comparing PWH in Q4 versus Q1–Q3 of GFAP levels.

TABLE 1 Baseline characteristics of all participants categorized by Q1–3 and Q4 of p-tau217, NFL, and GFAP.

Parameter	Overall (N = 255)	p-tau217			NFL			GFAP		
		Q1–3 (N = 191)	Q4 (N = 64)	p-Value	Q1–3 (N = 191)	Q4 (N = 64)	p-Value	Q1–3 (N = 191)	Q4 (N = 64)	p-Value
Age, y	54.3 (51.8, 59.1)	54.4 (52.2, 59.3)	54.2 (50.9, 58.6)	0.15	53.9 (51.6, 57.6)	59.0 (52.7, 62.8)	<0.001 ^{a)}	53.9 (51.6, 58.0)	56.1 (52.9, 62.0)	<0.001 ^{a)}
Sex: female	94 (36.9%)	70 (36.6%)	24 (37.5%)	0.90	74 (38.7%)	20 (31.2%)	0.28	67 (35.1%)	27 (42.2%)	0.31
Education: > 6 y	194 (76.1%)	147 (77.0%)	47 (73.4%)	0.57	147 (77.0%)	47 (73.4%)	0.57	142 (74.3%)	52 (81.2%)	0.26
BMI, kg/m ²	23.0 (20.6, 25.0)	23.0 (20.8, 24.8)	23.0 (19.7, 25.6)	0.93	23.2 (20.9, 25.4)	21.7 (19.6, 24.4)	0.01 ^{a)}	23.3 (20.8, 25.4)	21.9 (19.9, 24.5)	0.07
Current smoker	35 (13.7%)	24 (12.6%)	11 (17.2%)	0.35	25 (13.1%)	10 (15.6%)	0.61	26 (13.6%)	9 (14.1%)	0.93
Alcohol drinker	26 (10.2%)	22 (11.5%)	4 (6.2%)	0.23	17 (8.9%)	9 (14.1%)	0.24	19 (9.9%)	7 (10.9%)	0.82
DM	41 (16.1%)	30 (15.7%)	11 (17.2%)	0.78	22 (11.5%)	19 (29.7%)	<0.001 ^{a)}	29 (15.2%)	12 (18.8%)	0.50
HT	109 (42.7%)	77 (40.3%)	32 (50.0%)	0.18	67 (35.1%)	42 (65.6%)	<0.001 ^{a)}	73 (38.2%)	36 (56.2%)	0.01 ^{a)}
CCr, ml/min	73.8 (63.0, 88.7)	75.1 (63.8, 88.7)	71.1 (60.0, 87.8)	0.11	78.6 (67.3, 91.6)	60.3 (51.8, 68.2)	<0.001 ^{a)}	77.8 (65.1, 90.5)	65.2 (52.8, 76.0)	<0.001 ^{a)}
Depression	18 (7.1%)	13 (6.8%)	5 (7.8%)	0.79	14 (7.3%)	4 (6.2%)	0.77	14 (7.3%)	4 (6.2%)	0.77
MoCA score	24.0 (21.0, 26.0)	24.0 (21.0, 25.0)	24.0 (22.0, 26.0)	0.12	24.0 (21.0, 26.0)	23.0 (20.5, 25.0)	0.22	24.0 (21.0, 25.0)	24.0 (21.0, 26.0)	0.60
MoCA < 25	156 (61.2%)	121 (63.4%)	35 (54.7%)	0.22	116 (60.7%)	40 (62.5%)	0.80	120 (62.8%)	36 (56.2%)	0.35
HIV duration, y	18.7 (15.3, 21.0)	18.8 (15.4, 21.0)	18.1 (15.1, 21.3)	0.70	18.3 (15.1, 21.4)	18.7 (15.8, 20.7)	0.80	18.8 (15.4, 21.0)	17.8 (14.9, 20.8)	0.61
Current CD4, cells/mm ³	624.0 (491.0, 803.0)	655.0 (495.0, 809.0)	593.0 (487.0, 775.0)	0.13	649.0 (501.0, 814.0)	594.0 (450.0, 731.0)	0.10	644.0 (489.0, 803.0)	612.5 (500.5, 797.0)	0.84
Nadir CD4, cells/mm ³	179.0 (88.0, 261.0)	185.0 (92.0, 261.0)	172.5 (65.0, 256.5)	0.84	185.0 (81.0, 262.0)	174.5 (101.5, 236.5)	0.94	183.0 (81.0, 262.0)	171.5 (98.0, 256.0)	0.51

(Continues)

TABLE 1 (Continued)

Parameter	Overall (N = 255)		p-tau217		NfL		GFAP		p-Value
	Q1-3 (N = 191)	Q4 (N = 64)	Q1-3 (N = 191)	Q4 (N = 64)	Q1-3 (N = 191)	Q4 (N = 64)	Q1-3 (N = 191)	Q4 (N = 64)	
Exposed to EFV	48 (25.1%)	18 (28.1%)	0.64	51 (26.7%)	15 (23.4%)	0.61	52 (27.2%)	14 (21.9%)	0.40
Current ART									
NRTI	180 (94.2%)	60 (93.8%)	0.89	180 (94.2%)	60 (93.8%)	0.89	179 (93.7%)	61 (95.3%)	0.64
NNRTI	127 (66.5%)	40 (62.5%)	0.56	132 (69.1%)	35 (54.7%)	0.04 ^{a)}	128 (67.0%)	39 (60.9%)	0.38
PI	72 (37.7%)	27 (42.2%)	0.52	73 (38.2%)	26 (40.6%)	0.73	73 (38.2%)	26 (40.6%)	0.73
INSTI	9 (4.7%)	3 (4.7%)	0.99	3 (1.6%)	9 (14.1%)	<0.001 ^{a)}	8 (4.2%)	4 (6.2%)	0.50
P-tau217, pg/mL	2.1 (1.4, 3.3)	4.1 (3.8, 4.9)	<0.001 ^{a)}	2.1 (1.3, d3.2)	2.3 (1.5, 3.8)	0.15	2.1 (1.4, 3.4)	2.2 (1.5, 3.1)	0.83
NfL, pg/mL	10.9 (8.0, 15.8)	12.6 (9.5, 17.9)	0.02 ^{a)}	9.5 (7.1, 11.7)	20.1 (18.1, 24.3)	<0.001 ^{a)}	10.1 (7.2, 13.7)	15.7 (10.8, 20.2)	<0.001 ^{a)}
GFAP, pg/mL	113.3 (80.0, 157.3)	118.7 (87.6, 155.2)	0.34	94.3 (73.2, 129.2)	154.7 (124.0, 199.1)	<0.001 ^{a)}	92.4 (71.2, 120.3)	185.8 (166.7, 228.7)	<0.001 ^{a)}

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CCr, creatinine clearance; CKD, chronic kidney disease; DM, diabetes mellitus; EFV, efavirenz; GFAP, glial fibrillary acidic protein; HT, hypertension; INSTI, integrase strand transfer inhibitor; LDL, low-density lipoprotein; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; p-tau217, phosphorylated-tau 217; y, years.

^{a)} Indicates $p < 0.05$.

There were no correlations between the log-transformed p-tau217 and the other two biomarkers ($r = 0.193$ for NfL and $r = 0.081$ for GFAP). However, there was a moderate positive correlation between NfL and GFAP ($r = 0.46$).

3.2 | Baseline blood p-tau217 and cognitive performance

There were no significant associations between p-tau217 levels and lower cognitive performance (Model I: adjusted odds ratio [aOR] 0.67, 95% confidence interval [CI] 0.36 to 1.24; Model II: aOR 0.71, 95% CI 0.37 to 1.34) or MoCA score (Model I: $\beta = 0.87$, 95% CI -0.08 to 1.81; Model II: $\beta = 0.87$, 95% CI 0.10 to 1.83) at baseline.

In both models, baseline p-tau217 levels were significantly associated with a decline in cognitive performance overtime (Model I: $\beta = -0.02$, 95% CI -0.03 to -0.003, p -interaction = 0.02; Model II: $\beta = -0.02$, 95% CI -0.03 to -0.003, p -interaction = 0.02). PWH in Q4 of p-tau217 levels showed significantly greater decline in cognitive performance from age 50 to 70 years, with a MoCA score decrease of -3.3 (95% CI -4.6 to -1.9) compared to -1.4 (95% CI -2.2 to -0.6) for Q1-Q3 (p -interaction = 0.02) in Model I and -3.3 (95% CI -4.8 to -1.9) for Q4 compared to -1.4 (95% CI -2.4 to -0.5) for Q1-Q3 (p -interaction = 0.02) in Model II (Figure 1a). Baseline p-tau217 levels, analyzed as both continuous variables and quartiles, were not significantly associated with trajectories of individual MoCA subdomains (Table 2).

3.3 | Baseline blood NfL and cognitive performance

NfL levels were not significantly associated with lower cognitive performance (Model I: aOR 0.83, 95% CI 0.43 to 1.61; Model II: aOR 1.04, 95% CI 0.49 to 2.20) or MoCA score (Model I: $\beta = 0.06$, 95% CI -0.94 to 1.06; Model II: $\beta = -0.03$, 95% CI -1.13 to 1.07) at baseline. In both models, there were no significant associations between baseline NfL levels and the trajectories of either total MoCA scores and individual MoCA subdomains (Figure 1b and Table 2).

3.4 | Baseline blood GFAP and cognitive performance

GFAP levels were not significantly associated with lower cognitive performance (Model I: aOR 0.60, 95% CI 0.31 to 1.15; Model II: aOR 0.70, 95% CI 0.36 to 1.38) or MoCA score (Model I: $\beta = 0.65$, 95% CI -0.33 to 1.63; Model II: $\beta = 0.69$, 95% CI -0.33 to 1.70) at baseline. There were no significant associations between baseline GFAP levels, analyzed as continuous variables, and trajectories of total MoCA score in either model. However, in Model II, PWH in Q4 of GFAP levels showed a significantly greater decline in cognitive performance from age 50 to 70 years, with a MoCA score decrease of -2.9 (95% CI -4.2 to -1.6) compared to -1.3 (95% CI -2.2 to -0.3) for Q1-Q3 (p -interaction = 0.03) (Figure 1c). Higher baseline GFAP levels was also associated with a

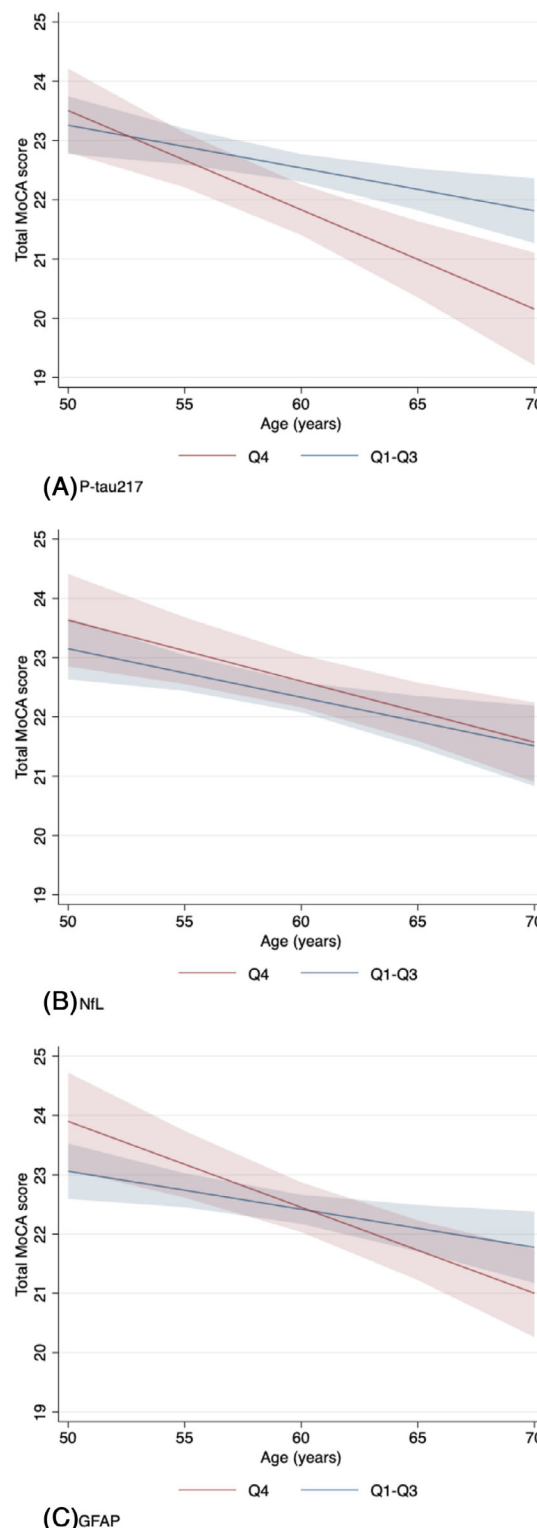


FIGURE 1 Modeled cognitive trajectories with 95% confidence intervals from age 50 to 70 years, comparing baseline blood-based biomarkers between the highest quartile (Q4) and the lower quartiles (Q1-Q3): (A) p-tau217, (B) NfL, (C) GFAP. Adjusted for sex, education level, baseline MoCA score, body mass index, diabetes mellitus, hypertension, creatinine clearance, HIV duration, nadir CD4 levels, and exposure to efavirenz. ART, antiretroviral therapy; GFAP, glial fibrillary acidic protein; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; p-tau217, phosphorylated-tau 217

TABLE 2 Coefficients and 95% confidence intervals for the interaction terms between each blood-based biomarker (Q1-3 vs. Q4) and age across MoCA subdomains.

Parameter	Model I				Model II			
	Coefficient	95% CI		p-Value	Coefficient	95% CI		p-Value
p-Tau217								
Total MoCA score	−0.092	−0.171	−0.013	0.02 ^{a)}	−0.095	−0.174	−0.017	0.02 ^{a)}
Visuospatial/executive function	−0.036	−0.072	0.001	0.06	−0.035	−0.072	0.001	0.06
Naming	0.004	−0.011	0.020	0.57	0.004	−0.011	0.019	0.60
Attention	0.006	−0.027	0.039	0.72	0.006	−0.028	0.039	0.74
Language	−0.021	−0.052	0.009	0.17	−0.021	−0.051	0.010	0.18
Abstraction	−0.010	−0.035	0.014	0.40	−0.012	−0.035	0.012	0.34
Delayed recall	−0.045	−0.095	0.005	0.08	−0.046	−0.096	0.004	0.07
Orientation	0.000	−0.016	0.016	0.99	−0.001	−0.017	0.015	0.92
NfL								
Total MoCA score	−0.020	−0.092	0.052	0.58	−0.021	−0.095	0.053	0.58
Visuospatial/executive function	−0.002	−0.036	0.031	0.89	−0.006	−0.041	0.028	0.71
Naming	0.003	−0.011	0.017	0.67	0.006	−0.008	0.020	0.40
Attention	0.000	−0.030	0.030	<0.999	0.002	−0.029	0.033	0.90
Language	−0.022	−0.050	0.005	0.11	−0.023	−0.051	0.006	0.12
Abstraction	0.006	−0.016	0.027	0.62	0.000	−0.022	0.023	0.98
Delayed recall	0.010	−0.035	0.055	0.67	0.011	−0.036	0.058	0.64
Orientation	−0.008	−0.022	0.006	0.26	−0.009	−0.024	0.006	0.21
GFAP								
Total MoCA score	−0.072	−0.146	0.003	0.06	−0.081	−0.155	−0.006	0.03 ^{a)}
Visuospatial/executive function	−0.058	−0.092	−0.024	<0.001 ^{a)}	−0.059	−0.093	−0.025	<0.001 ^{a)}
Naming	0.007	−0.008	0.021	0.35	0.007	−0.007	0.021	0.33
Attention	0.004	−0.027	0.035	0.79	0.003	−0.028	0.034	0.85
Language	−0.009	−0.038	0.020	0.54	−0.009	−0.038	0.019	0.52
Abstraction	−0.004	−0.027	0.018	0.70	−0.006	−0.028	0.017	0.61
Delayed recall	−0.012	−0.059	0.035	0.61	−0.017	−0.064	0.030	0.48
Orientation	0.001	−0.013	0.016	0.85	0.000	−0.015	0.015	0.96

Note: Model I: Adjusted for sex, education level, and baseline MoCA score. Model II: Adjusted for Model I plus body mass index, diabetes mellitus, hypertension, creatinine clearance, HIV duration, nadir CD4 levels, and exposure to efavirenz.

^{a)}Indicates $p < 0.05$.

Abbreviations: CI, confidence interval; GFAP, glial fibrillary acidic protein; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; p-tau217, phosphorylated-tau 217.

greater decline in visuospatial/executive function scores over time (Table 2).

4 | DISCUSSION

As PWH age, cognitive decline is becoming an increasingly important concern, and insights to its underlying drivers is crucial. This study is among the first to compare, blood-based AD core and non-core biomarkers with longitudinal cognitive performance in people with chronic HIV infection. By applying AD blood-based biomarkers to older

Thai PWH with undetectable viral loads, we found that baseline levels of p-tau217, a core AD biomarker, and GFAP, a biomarker for astrocytosis, levels were associated with greater cognitive decline. In contrast, NfL, a marker of neuroaxonal injury did not predict cognitive decline in this population. Notably, blood p-tau217 showed no correlation with other biomarkers.

Cognitive deterioration in PWH may result from many factors: direct effects of HIV on the central nervous system, chronic immune activation, adverse effects of ART, and/or traditional neurodegenerative processes, which themselves may be accelerated by HIV.^{3,32–34} In this study, we demonstrated that higher baseline blood p-tau217,

among other biomarkers, was associated with subsequent cognitive decline, even at the earliest stages when most individuals were asymptomatic. This suggests that AD-related pathophysiology may play a primary role in older virally suppressed PWH, similar to what is observed in PWoH. Relatively few studies have investigated AD-tau biomarkers and their association with cognitive outcomes in PWH. Positron emission tomography (PET) studies have shown no differences in tau deposition between PWH with and without cognitive impairment, while higher deposition has been observed in people without HIV (PWoH) with symptomatic AD. It should be noted; however, that there was a considerable age difference between PWH and PWoH with symptomatic AD.³⁵ Importantly, the groups also differed in recruitment: PWoH with symptomatic AD were memory clinic referrals for suspected cognitive symptoms, whereas PWH were asymptomatic individuals classified by their performance on a cognitive test. Cerebrospinal fluid (CSF) studies in younger PWH have inconsistently demonstrated that elevated total and phosphorylated tau are associated with poorer cognitive outcomes.^{36,37} Similarly, a study on plasma biomarkers of AD among women living with HIV found that a 1-year increase in p-tau231 was associated with worse cross-sectional executive function at baseline.³⁸ Our findings add to the current literature and are among the first to evaluate the potential role of baseline p-tau biomarkers in predicting longitudinal cognitive trajectories.

Given the relatively young age of our cohort, these findings should be interpreted with caution. Blood-based AD biomarkers are known to become abnormal years to decades before the onset of clinical symptoms,³⁹ which may explain their detectability in this population. However, in PWH, it remains challenging to disentangle the contribution of early neurodegenerative processes from chronic HIV-related systemic and central nervous system inflammation, even in those with sustained virological suppression. Moreover, persistent immune activation may accelerate neurodegenerative pathways, including those related to AD, although this remains a topic of ongoing research.^{40,41} Our findings suggest that AD-related pathology may contribute to cognitive decline in this population, while also highlighting important unanswered questions. Future studies incorporating more comprehensive neuropsychological phenotyping and multimodal biomarkers, including CSF and neuroimaging, will be essential to clarify the dominant underlying mechanisms. Validation studies on blood-based biomarkers are also important to support their implementation as a comparatively more accessible and feasible approach for identifying AD-related pathology, particularly in resource-limited settings. For context, an amyloid and tau PET scan in Thailand costs nearly 2000 USD, compared with roughly 200 USD for a blood p-tau217 test, while the average annual income in Thailand is around 7000 USD. However, it must be emphasized that blood-based biomarkers are not currently recommended as stand-alone diagnostic tools for AD; rather, they should be interpreted within the context of a comprehensive clinical assessment,⁴² where they enhance diagnostic accuracy.⁴³

In contrast to p-tau217, several studies have explored and demonstrated a relationship between higher levels of plasma NfL, a biomarker of neuronal injury, and cognitive impairment.^{38,44–46} One study also

showed that plasma and CSF NfL levels among PWH were highly correlated, supporting the use of plasma as a valuable tool to assess ongoing CNS injury.¹⁷ Our study, however, found no association between high NfL levels and differences in cognitive trajectories. Since our models already adjusted for comorbidities, a key confounder of NfL levels, this discrepancy with prior reports may reflect the use of the MoCA as the cognitive outcome measure, which is likely less sensitive than the comprehensive neuropsychological batteries used in previous studies.

Astrocytic activation has been increasingly recognized as a contributor to cognitive decline in PWH. Beyond serving as viral reservoirs and sources of viral proteins in the HIV-infected brain, astrocytes interact with glutamatergic, dopaminergic, and gamma-aminobutyric acid-ergic (GABAergic) pathways, thereby accelerating the progression of HIV-associated neurocognitive disorders through excitotoxicity, inflammation, and irreversible neurotoxicity.^{47,48} Previous studies have reported mixed findings regarding the association between GFAP and cognitive outcomes.^{38,44,49} For example, one study among virologically suppressed PWH of a similar age to our cohort found significantly higher GFAP levels in individuals with worse cognitive performance cross-sectionally, but no association with longitudinal cognitive decline.⁴⁶ Our study demonstrated that higher baseline GFAP levels were associated with greater cognitive decline over time, extending prior evidence and underscoring the potential role of astrocytic activation in the progression of cognitive impairment in PWH. It is important to note that astrocytes also respond to early amyloid pathology in AD and elevated GFAP has been reported as a moderate-to-good early biomarker of AD in the general population.⁵⁰ However, in our cohort, p-tau217 was not correlated with GFAP or other biomarkers, and the observed association of GFAP with cognitive decline persisted, suggesting that this effect may not be driven by AD-related tau pathology. These findings highlight GFAP as a potentially independent marker of astrocytic activation and support its promise as a prognostic biomarker for identifying PWH at risk of cognitive deterioration.

Certain limitations of our study should be noted. First, cognitive outcomes were based solely on the MoCA. While MoCA is a validated and practical screening tool for MCI and mild dementia due to AD, its performance in PWH has generally been inconsistent.⁵¹ The interpretation of MoCA subdomain scores should also be approached with caution, as they were not designed to directly represent the performance of individual cognitive domains; more detailed neuropsychological assessments are needed. Second, without additional data on symptoms or comprehensive neuropsychological testing, we were unable to classify participants into clinical categories of cognitively unimpaired, MCI, or dementia. Third, all participants had only one follow-up visit, limiting our ability to characterize cognitive trajectories over time in more detail. Fourth, we did not measure APOE genotype, a strong genetic risk factor for AD. Fifth, we did not have PWoH comparison group, limiting our ability to isolate the effect of HIV itself. Finally, our cohort would be considered relatively young in most AD research contexts. This reflects the historical reality that ART only became widely available in Thailand in the early 2000s, meaning that most aging PWH are currently in their 50s or early 60s. Despite these limitations, our study provides valuable insights given the scarcity of

longitudinal data and the opportunity to investigate all three recommended AD biomarkers in a PWH population in a resource limited country.

Future studies are needed to validate blood-based biomarkers against traditional methods, that is, CSF analysis and PET imaging, especially given the complex pathophysiology of chronic HIV and the potential influence of multiple confounders. Studies with multiple follow-up assessments and more comprehensive neuropsychological testing are required to confirm and expand upon our findings, with the ultimate goal of informing integration into routine clinical care. Lastly, more diverse cohorts of PWH are also necessary, as social determinants of health and genetic factors may play an important role in both AD and non-AD related cognitive decline.

In conclusion, older Thai PWH with higher baseline blood p-tau217 and GFAP levels in our cohort experienced greater cognitive decline during follow-up. Our findings suggest that AD-related process and astrocyte reactivity may be primary drivers of cognitive decline in this special population, and that blood p-tau217 and GFAP provide a promising, minimally invasive predictive tool. While NfL did not show overall predictive value for cognitive decline, their potential roles in specific cognitive domains warrant further investigation. Validation of these results in larger, more diverse cohorts, combined with more comprehensive neuropsychological testing, will be critical for understanding the clinical applicability of these blood-based biomarkers in this population.

AUTHOR CONTRIBUTION

Akarin Hiransuthikul drafted the manuscript and study protocol, initiated the study concept, and conducted all statistical analyses. Poosanu Thanapornsanguth provided support for the study protocol and concept, statistical analyses, and logistics of biomarker measurements. Watayuth Luechaipanit and Thanaporn Haethaisong performed the biomarker measurements. Sasiwimol Ubolyam facilitated sample transportation and management. Tanakorn Apornpong contributed to data management. Win Min Han and Stephen Kerr supported data interpretation and statistical analyses. Akarin Hiransuthikul and Anchalee Avihingsanon led the study. All authors critically reviewed and approved the final manuscript.

ACKNOWLEDGMENTS

The authors thank all participants for their dedication to the study and for placing their trust in us. The authors are grateful to all HIV-NAT 006 and 207 study staff for their efforts in caring for our participants. This work was supported by TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with funding support from the U.S. National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Fogarty International Center, as part of the International Epidemiology Databases to

Evaluate AIDS (IeDEA; U01AI069907). This publication is the result of funding in whole or in part by the NIH. It is subject to the NIH Public Access Policy. Through acceptance of this federal funding, NIH has been given a right to make this manuscript publicly available in PubMed Central upon the Official Date of Publication, as defined by NIH. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the governments or institutions mentioned above. The results have been presented in part at the 2025 Conference on Retroviruses and Opportunistic Infections (CROI), held March 9-12, 2025, in San Francisco, CA, USA.

CONFLICT OF INTEREST STATEMENT

All authors declare no competing interests related to this work. Author disclosures are available in the [supporting information](#)

CONSENT STATEMENT

The study was approved by the IRB of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB No. 538/67), and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical guidelines. All participants provided their consent prior to entering the HIV-NAT 207 study.

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How to cite this article: Hiransuthikul A, Thanapornsanguth P, Luechaipanit W, et al. Blood-based Alzheimer's disease biomarkers and cognitive trajectories in older people with HIV with undetectable viral loads. *Alzheimer's Dement*. 2026;22:e71101. <https://doi.org/10.1002/alz.71101>