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1. Data on file (naïve), Gilead Sciences. January 2022.
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ART, Anti-retroviral therapy; HIV, Human immunodeficiency virus; TAF, tenofovir alafenamide.

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ORIGINAL ARTICLE

Correlation between CD4/CD8 ratio and neurocognitive performance during early HIV infection

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Abstract

Introduction: CD4/CD8 ratio is a marker of immune activation in HIV infection and has been associated with neurocognitive performance during chronic infection, but little is known about the early phases.

The aim of this study was to examine the relationship between blood CD4/CD8 ratio and central nervous system endpoints in primary HIV infection (PHI) before and after antiretroviral treatment (ART).

Methods: This was a retrospective analysis of the Primary Infection Stage CNS Events Study (PISCES) cohort.

We longitudinally assessed blood and cerebrospinal fluid (CSF) markers of inflammation, immune activation and neuronal injury, and neuropsychological testing performance (NPZ4, an average of three motor and one processing speed tests, and a summarized total score, NPZ11, including also executive function, learning and memory) in ART-naïve participants enrolled during PHI. Spearman correlation and linear mixed models assessed the relationships

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between the trajectory of CD4/CD8 ratio over time and neurocognitive performance, blood and CSF markers of immune activation and neuronal injury.

Results: In all, 109 PHI participants were enrolled. The mean CD4/CD8 ratio decreased with longer time from infection to starting treatment ($p < 0.001$). Every unit increase in NPZ4 score was independently associated with a 0.15 increase in CD4/CD8 ratio (95% CI: 0.002–0.29; $p = 0.047$), whereas no correlation was found between CD4/CD8 ratio and NPZ11.

Among the cognitive domains, only a change in processing speed was correlated with CD4/CD8 ratio over time ($p = 0.03$). The trajectory of the CD4/CD8 ratio was negatively correlated with change in CSF neurofilament light chain ($p = 0.04$).

Conclusions: The trajectory of CD4/CD8 ratio was independently associated with motor/psychomotor speed performance, suggesting that immune activation is involved in brain injury during the early stages of the infection.

KEYWORDS

CD4/CD8 ratio, early HIV infection, HIV-associated neurocognitive disorders, immune activation

INTRODUCTION

In the era of antiretroviral therapy (ART), individuals living with HIV who have access to ART gain a life expectancy close to that of the general population [1, 2]. Nevertheless, successfully treated subjects may still experience prolonged HIV-related neurological and cognitive symptoms. Despite the significant decline in the incidence of HIV-associated dementia due to effective ART [3–6] and the potential role of lifestyle factors and comorbid conditions, varying degrees of HIV-associated neurocognitive disorders (HAND) continue to impact the daily living and reduce the quality of life of affected individuals [7–10], as well as influencing their ability to adhere to ART regimens [11].

There are limited biomarkers associated with the risk of neurological impairment in people living with HIV. CD4 T-cell nadir is a predictor for HAND as the level of neuropsychological impairment increases among HIV-infected individuals with lower CD4 T-cell nadir [12–15]. However, accurate CD4 T-cell nadir values can be difficult to ascertain. Additionally, cerebrospinal fluid (CSF) markers of monocyte/macrophage activation, such as elevated plasma-soluble CD163 and CSF neopterin, and neuronal injury, such as CSF and plasma/serum neurofilament light (NfL), have been found in HIV-infected participants with neurological diseases and with the presence of neurocognitive impairment, suggesting their utility as additional diagnostic biomarkers of HAND [16–20].

Most of these biomarkers are not commonly included in routine laboratory evaluations for clinical indications. Additionally, none of these markers captures a combination of immune suppression and immune activation, both of which probably contribute to CNS pathogenesis. In fact, neopterin has always been considered as such a marker because its formation is induced by the activated immune system (primarily under control of interferon-gamma) and it is also associated with the development of immunodeficiency. This fact became more obvious when tryptophan breakdown by indoleamine 2,3-dioxygenase (IDO-1) was found to be associated with neopterin formation; meanwhile IDO-1 became established as a link to immunosuppressive regulatory T-cells [21, 22]

Increasing attention has been directed at the valuable information that blood CD4/CD8 ratio can provide about an individual in HIV care management, and about the pathophysiological processes underlying neurological impairment. A normal CD4/CD8 ratio is approximately 2:1 in the general population [20].

The inverted CD4/CD8 ratio among virally suppressed HIV-infected individuals is correlated with higher risk of early immunosenescence [23], protracted inflammation [24], age-related disease [25, 26], as well as AIDS-defining and non-AIDS-defining morbidity and mortality [25-32]. Systemic and CSF CD4 and CD8 T-cells express greater concentration of HLA-DR, a marker for T-cell activation, among chronically HIV-infected individuals with HAND as compared with those without HAND [33]. Moreover, chronically

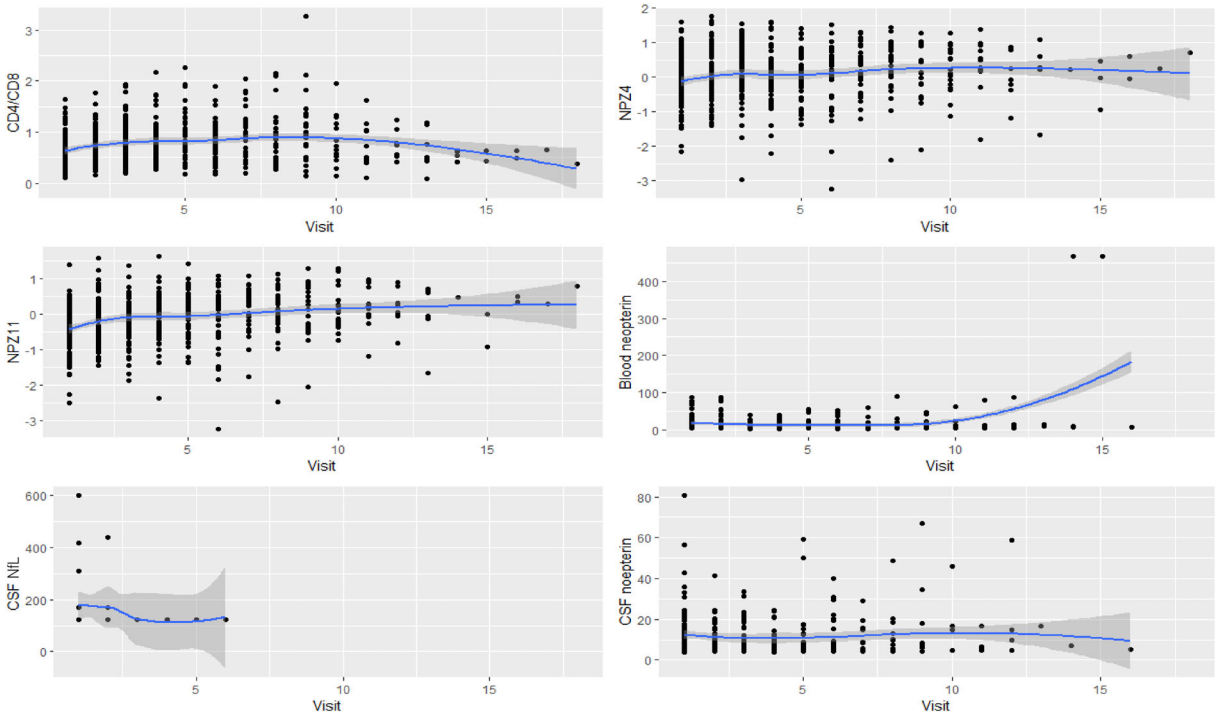

FIGURE 1 Trajectory of different markers during follow-up. CSF, cerebrospinal fluid; NfL, plasma/serum neurofilament light

HIV-infected individuals with symptomatic HAND display higher rates of inverted CD4/CD8 ratio than either unimpaired individuals or individuals with asymptomatic neurocognitive disorders, the latter defined by at least two impaired cognitive domains without any impact on daily living [34, 35]. Independent of viral replication and suppression, longitudinal decline in the ratio is associated with neurocognitive deterioration [36]. To our knowledge, there has not been any study to explore blood CD4/CD8 ratio as a potential marker of changes in neurocognitive performance or recovery after treatment in people during primary HIV infection (PHI – defined as within the first 12 months after transmission). This information may allow earlier detection of those at heightened risk of cognitive decline and provide affected individuals with greater opportunities to treat and prevent the neurological deficits due to HIV infection.

The aim of this study was to examine the relationship between blood CD4/CD8 ratio and central nervous system (CNS) endpoints in early infection before and after ART in order to identify an early biomarker that may affect the long-term trajectory of neurological status in HIV. We investigated the longitudinal pattern of blood CD4/CD8 ratio and its relationship with neurocognitive and motor performance as well as with CSF markers of immune activation and neuronal injury among participants identified during PHI (Figure 1).

METHODS

Study design and participants

The Primary Infection Stage CNS Events Study (PISCES) was a prospective observational study that enrolled and followed participants with PHI between 2003 and 2014 in San Francisco.

Participants with PHI had laboratory confirmation of recent HIV infection (within 12 months of viral transmission) using the Serological Testing Algorithm for Recent HIV Seroconversion [37]. The date of HIV transmission was estimated either as 14 days before the onset of seroconversion symptoms [38] or as the average date between the last negative and first positive HIV tests [39].

Participants underwent structured medical and neurological examination, detailed battery of neuropsychological testing, venipuncture and lumbar puncture at baseline, 6 weeks, 6 months, and every subsequent 6 months indefinitely. Major exclusion criteria were history of opportunistic infections and major neurological diseases, such as stroke, multiple sclerosis and seizure disorders. Although most participants were ART-naïve at baseline, over half commenced ART at various time points during follow up for reasons outside of the study. Participants were prescribed standardized ART regimens based on the decisions of the participants and their providers, which were in some, but not all, cases due to a

decline in CD4 and based on the treatment initiation criteria at the time.

All participants provided written informed consent to take part in the study, approved by the Institutional Review Board of the University of California at San Francisco and Yale University.

Specimen sampling, processing and laboratory analysis

At the San Francisco General Hospital Clinical Laboratory, routine methods measured blood CD4 and CD8 T-cell counts, as well as CSF total white blood cell (WBC) count, from fresh samples. HIV viral load was measured from frozen, paired plasma and CSF specimens using the ultrasensitive Amplicor HIVMonitor v.1.5 (Roche Molecular Diagnostic Systems, Basel, Switzerland) or the Abbott RealTime HIV-1 (Abbot Laboratories, Abbott Park, IL, USA) assays. Plasma and CSF neopterin were measured from frozen samples locally or in the laboratory of Dr Fuchs using commercial immunoassays (Brahms Aktiengesellschaft, Hennigsdorf, Germany). NfL, a sensitive marker for neuronal injury in the CNS [38, 39], was measured in CSF using a sensitive quantitative immunoassay (UmanDiagnostics, Umeå, Sweden) with a lower detection limit of 50 ng/L in the laboratory of Dr Zetterberg. Based on the analysis of 359 neurologically healthy HIV-uninfected individuals, the upper normal CSF NfL concentrations were 387 (for participants aged 20–29 years), 525 (for those aged 30–39 years), 713 (for those aged 40–49 years), 967 (for those aged 50–59 years), 1313 (for those aged 60–69 years), 1781 (for those aged 70–79 years) and 2417 ng/L (for those aged 80 years) [40].

Neuropsychological testing

Neuropsychological testing performed at every visit by a trained psychometrist employed an 11-test battery to assess five domains, including motor (timed gait, grooved pegboard and finger tapping non-dominant hand), executive function (trail making B and verbal fluency), processing speed (digit symbol and trail making A), learning (Rey Auditory Verbal Learning Test and figural memory learning) and memory (Rey Auditory Verbal Learning Test delay and figural delay). All measures, except timed gait, were normalized according to age, education, gender and ethnicity. Measures were also summarized as the total *z*-score (NPZ11) for all the 11 neuropsychological tests, as well as an abbreviated summary *z*-score (NPZ4) for psychomotor and motor speed performance (average of performance on four tests: timed gait, grooved pegboard, finger tapping and digit symbol). These domains and summarized scores were selected based on their potential involvement in neurocognitive disorders associated with HIV [41].

Statistical analyses

We performed all statistical analyses with SAS Enterprise Guide 5.1 (SAS Institute, Cary, NC, USA). Variables were described using mean, standard deviation, median and interquartile range (IQR) for quantitative variables, and frequencies and percentage for qualitative variables. Initially, Spearman's rank correlation coefficient generated correlations between variables of interest: change in CD4/CD8 ratio, time to ART initiation, neuropsychological domains, as well as blood neopterin, CSF NfL, and CSF WBC concentrations. These variables were selected based on their known relevance to the state of systemic inflammation and neuropsychological performance among HIV-infected individuals from the published literature.

In a second step, linear regressions were performed to find variables associated with the trajectory of CD4:CD8 ratio. A linear mixed model was constructed to evaluate variables associated with NPZ11 and NPZ4 scores. Age at baseline, ART treatment status, plasma viral load, recent drug use, alcohol abuse, time between each measure and duration of HIV infection at baseline were tested in univariate analysis. NPZ4 scores or CD4/CD8 ratios have also been tested according to the outcome. Variables with $p < 0.2$ in univariate analysis were used to construct a multivariate model. Variables with $p < 0.05$ were kept in the final model. Some variables of interest could be forced in the model. Multivariate regression models investigated independent associations of CD4/CD8 ratio with the aforementioned univariate variables.

RESULTS

Baseline characteristics of study cohort

From the cohort of 109 participants, 99% of whom were men a total of 550 observations were analysed for the study. In all, 103 (95%) participants were ART-naïve at enrolment, and six participants were ART-experienced for 1–4 weeks prior to joining the study. At baseline, the median age was 36 (IQR: 29–43) years, median duration of infection was 3.3 (IQR: 2.0–5.1) months, median plasma HIV viral load was 4.6 (IQR: 4.0–5.1) $\log_{10}$copies/mL, median CD4/CD8 ratio was 0.5 (IQR: 0.4–0.9), median NPZ4 score was −0.2 (IQR: −0.6–0.3) and

TABLE 1 Demographic and clinical characteristics of the study cohort

Baseline	Median (IQR)[a]
Number of participants (*n*)	109
Sex (male:female)	108:1
Age (years)	36 (29–43)
Estimated duration of HIV infection (months)	3.3 (2.0–5.1)
ART-naïve [*n* (%)]	103 (95%)
Plasma viral load (log_{10}copies/mL)	4.6 (4.0–5.1)
Viral load < 1000 copies/mL [*n* (%)]	11 (10%)
CD4 T-cell count (cells/μL)	586 (435–735)
CD4/CD8 ratio	0.5 (0.4–0.9)
NPZ4 score	−0.2 (−0.6–0.3)
NPZ11 score	−0.4 (−0.9–0.0)
Follow-up	
Total observations (% on ART)	550 (50%)
Number of follow-up visits per participant	4 (2–7)
Follow-up duration (months)	12.5 (1.6–35.0)
ART initiation during follow-up [*n* (%)]	62 (56.8%)
Delayed ART initiation after baseline (months)	3.1 (0.8–11.8)
Viral load < 1000 copies/mL after 12 months [*n* (%)]	35 (66%)
Number of visits while on treatment	2 (0–4)
Number of visits while off treatment	2 (1–3)
Median trajectory of CD4/CD8 ratio	0.30 (−0.02–0.56)
Median trajectory of CD4/CD8 ratio pre-ART	−0.07 (−0.18–0.02)
Median trajectory of CD4/CD8 ratio post-ART	0.35 (0.18–0.48)
Median trajectory of NPZ4 score	0.12 (−0.24–0.48)
Median trajectory of plasma viral load (log_{10}copies/mL)	−1.83 (−3.13–0.00)

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range.
[a]Median (IQR) unless stated otherwise.

median NPZ11 score was −0.4 (IQR: −0.9–0.0). Hepatitis coinfection was found in seven participants (6%). For the duration of the study, the median number of visits per participant was 4 (IQR: 2–7) and median duration of follow-up was 12.5 (IQR: 1.6–35.0) months. A total of 62 (56.8%) participants initiated ART treatment during follow-up with a median of 3.1 (IQR: 0.8–11.8) months after baseline; the median number of visits when participants were on treatment was 2 (IQR: 0–4), and the median when participants were off treatment was 2 (IQR: 1–3) (Table 1).

Changes in CD4/CD8 ratio during early infection

Throughout the study, the median increase in CD4/CD8 ratio trajectory was 0.30 (IQR: −0.02–0.56). During the period before participants initiated ART, the median trajectory of the CD4/CD8 ratio showed a decrease (−0.07, IQR: −0.18–0.02). During the interval after ART initiation, the median increase of the CD4/CD8 ratio was 0.35 (IQR: 0.18–0.48; Table 1). Multivariate analysis revealed that the change in CD4/CD8 ratio over the course of the study was negatively correlated with age at baseline, time since HIV infection at enrolment, and CD4/CD8 ratio at week 0 (Table 2). Therefore, the higher the CD4/CD8 ratio at inclusion, the lower was its improvement over time (adjusted coefficient = −0.35, 95% CI: −0.59 to −0.11; $p = 0.005$). Moreover, the older the participants were at enrolment, the less their CD4/CD8 ratios changed (adjusted coefficient = −0.01, 95% CI: −0.02–0.00; $p = 0.042$). Furthermore, longer delays in time to treatment initiation were associated with less improvement in the CD4/CD8 ratio (rho = −0.45, $n = 65$, $p < 0.01$) (Table 3).

Association between CD4/CD8 ratio and general neuropsychological performance

CD4/CD8 ratio was correlated with NPZ11 in univariate regression analysis (coefficient = 0.27, 95% CI: 0.15–0.39; $p < 0.001$), but not in the multivariate model (Table 4). Of the five individual domains analysed, only the change in information processing speed was significantly correlated with the trajectory of the CD4/CD8 ratio (rho = 0.26, $n = 77$, $p = 0.03$).

Association between CD4/CD8 ratio and motor/psychomotor speed performance

Multivariate analysis including all values during the follow-up and controlling for age at baseline, plasma viraemia < 1000 copies/mL and ART treatment status revealed that every unit increase in CD4/CD8 ratio corresponded with a 0.15 increase in NPZ4 score (95% CI: 0.002–0.29; $p = 0.047$; Table 5). When blood CD4/CD8

TABLE 2 Factors associated with trajectory of CD4/CD8 ratio – linear regression

	Univariate		Multivariate	
Parameter	**Spearman's rho**	***p*-value***	**AdjCoeff (95% CI)**	***p*-value**
Age at baseline	−0.13	0.234	−0.01 (−0.02–0.00)	0.042
Time between each CD4/CD8 ratio (in years)	0.21	0.047	0.00 (−0.04–0.04)	0.977
Time since infection at baseline (in months)	−0.19	0.072	−0.05 (−0.08 to −0.02)	0.003
First CD4/CD8 ratio	−0.31	0.004	−0.35 (−0.59 to −0.11)	0.005
Delta NPZ4	0.25	0.021	0.18 (0.07–0.29)	0.002
First NPZ4	0.07	0.551		
	Mean (SD)	***p*-value****	**AdjCoeff (95% CI)**	***p*-value**
Alcohol abuse		0.611		
No	0.31 (0.50)			
Yes	0.26 (0.36)			
Recent drug use		0.888		
No	0.28 (0.41)			
Yes	0.29 (0.48)			
Treated at least once during the study		< 0.001		
No	−0.12 (0.29)		1	
Yes	0.42 (0.40)		0.50 (0.31–0.68)	< 0.001
Viral load at baseline < 50 000 (log_{10}plasma viral load < 4.7)		0.002		
No	0.42 (0.45)			
Yes	0.14 (0.40)			

Abbreviation: AdjCoeff, adjusted coefficient.
Note: Trajectory = last value – first value.
*Refers to "Spearman correlation" and ** to "Student-t test"

ratio was replaced by blood CD4 T-cell count in the multivariate model analysis with NPZ4, the relationship between CD4 T-cell and NPZ4 was not significant (coefficient = 0.00, 95% CI: −0.0000–0.0005; $p = 0.092$; data not shown).

Association of CD4/CD8 ratio with CSF biomarkers

Among a small group of individuals who were treatment-naïve and who had follow-up CSF NfL available, the change in CSF NfL concentration was inversely correlated with the change in CD4/CD8 ratio (rho = −0.73, $n = 8$, $p = 0.04$). This relationship was not significant among participants on ART.

For the whole population, the change in CSF WBC (rho = −0.40, $n = 61$, $p = 0.002$) and blood neopterin (rho = −0.25, $n = 83$, $p = 0.024$) was inversely correlated with the trajectory of the CD4/CD8 ratio in univariate but not multivariate analysis (Table 2). Baseline CSF WBC was also positively correlated with the change in CD4/CD8 ratio (rho = 0.29, $n = 65$, $p = 0.02$), whereas baseline blood neopterin was not significantly correlated with the change in CD4/CD8 ratio (Table 3).

DISCUSSION

This study shows that the trajectory of blood CD4/CD8 ratio is independently associated with changes in motor/psychomotor speed performance among individuals who are diagnosed with HIV within the first 12 months after transmission. Early neuroinvasion has previously been described by Valcour et al. [42] and characterized by the increase of inflammatory biomarkers in the CSF. Besides, parenchymal inflammation could be detected early with magnetic resonance spectroscopy (MRS). These changes occur most prominently in subcortical structures, including basal ganglia, thalamus and frontal white matter and

TABLE 3 Correlations with trajectory of CD4/CD8 ratio

Variables	Spearman's rho (*n*)	*p*-value
Delayed treatment time (months)	−0.45 (65)	< 0.001
Processing speed domain	0.26 (77)	0.03
At baseline		
CSF white blood cells/mm^3	0.27 (69)	0.024
Blood neopterin	−0.03 (84)	0.813
CSF protein	−0.06 (69)	0.652
CSF IP10	0.25 (19)	0.297
CSF MCP-1	−0.14 (34)	0.431
Albumin serum:CSF ratio	0.01 (69)	0.923
Trajectory		
CSF white blood cell/mm^3	−0.40 (61)	0.002
Blood neopterin	−0.25 (83)	0.024
CSF protein	−0.06 (61)	0.635
CSF IP10	−0.08 (10)	0.829
CSF MCP-1	0.25 (13)	0.405
Albumin serum:CSF ratio	−0.10 (61)	0.464

Abbreviation: CSF, cerebrospinal fluid; IP 10, Interferon γ protein 10; MCP 1, monocyte chemoattractant protein-1.
Note: Trajectory = last value—first value.

could explain why motor findings and bradykinesia are among the most frequently described disorders during acute HIV infection [43]. Moreover, the increase in Choline/creatinine levels at MRS during the early phases of infection has been associated with higher CSF neopterin values, confirming the role of inflammation and cellular immune activation in the earliest CNS events [42].

Improvement in the NPZ4 score performance was correlated with increases in the blood CD4/CD8 ratio over time, independent of other major factors, including age at baseline, low-level plasma viremia (<1000 copies/mL) and ART treatment status.

No longitudinal association was found between the general neuropsychological performance (NPZ11) and the CD4/CD8 ratio. One explanation could be linked to the nature of the group studied, primary infection HIV, with 95% of the participants being treatment-naïve at the beginning of the study. Hence, we found a cognitive profile close to what Heaton et al. [41] observed in a pre-ART group recruited from 1988 to 1995 compared with participants recruited in the ART era from 2000 to 2007. The participants in the years without available ARV had more impairment in motor skills, cognitive speed and verbal fluency, whereas the cognitive disorders in the individuals on ARV more frequently involved memory, learning and executive function impairment. Moreover, this was a highly educated group of young subjects. Therefore, high performance in some domains could mask low performance in other domains and averaged score could be considered normal.

Furthermore, the processing speed performance was specifically correlated with the trajectory of the CD4/CD8 ratio. Cerebral processing delay remains one of the most common cognitive deficits among individuals with HIV [44, 45]. The association between processing speed and CD4/CD8 ratio is consistent with the significant inverse correlation between the CD4/CD8 ratio trajectory and CSF NfL concentration among treatment-naïve individuals. As high CSF NfL indicates axonal injury even in early infection [40, 46], the inverse relationship between blood CD4/CD8 ratio and CSF NfL reinforces the correlation between CD4/CD8 ratio and processing speed, which is associated with myelination and white matter regions in the brain [47]. As only the change in processing speed cognitive domain showed a significant association with the CD4/CD8 ratio trajectory, it is possible that myelination and white matter are either more damaged or among the first to be injured in the CNS during early HIV infection [48–52].

Taken together, these findings suggest a meaningful relationship between CD4/CD8 ratio and cognitive performance, wherein a decrease or increase in systemic CD4/CD8 ratio over time may be a valuable signal of neurocognitive status, potentially warranting an evaluation for HAND.

Interestingly, when blood CD4/CD8 ratio was replaced by blood CD4 T-cell count in the multivariate model analysis with NPZ4, the relationship between CD4 T-cell and NPZ4 was insignificant. Therefore, CD4/CD8 ratio provides unique information beyond CD4 T-cell count alone into potential mechanisms of HIV neuropathogenesis, suggesting that both levels of immune suppression (reflected in CD4 T-cell count) and immune activation (reflected in CD8 T-cell count) are needed for HAND. Additionally, change in CD4/CD8 ratio may serve as a common proxy for clinicians to identify individuals at risk of neurocognitive decline or to monitor the response of neurocognitive disease to ART.

Regarding factors affecting blood CD4/CD8 ratio in early infection, the results suggest an inverse relationship between delayed time to ART initiation and the rate of change in CD4/CD8 ratio. Hence, those who initiated ART soon after HIV transmission experience greater improvement in CD4/CD8 ratio than those who started treatment later. This inverse relationship supports previous studies that show an effect of prolonged unaddressed HIV replication in the body, depleting the systemic reserve of CD4 T-cells and causing proinflammatory responses in the body [53, 54], as well as provoking

TABLE 4 Factors associated with general neuropsychological performance (NPZ-11) – all patients/all time, mixed model ($N = 107$ patients with 525 observations)

	Univariate		Multivariate	
Parameter	**Coeff (95% CI)**	***p*-value**	**AdjCoeff (95% CI)**	***p*-value**
Age at baseline	0.01 (0.00–0.03)	0.040		
Time since infection at baseline (in years)	0.03 (−0.59–0.65)	0.922		
Time between baseline and each visit (in years)	0.08 (0.05–0.10)	< 0.001	0.05 (0.02–0.07)	0.001
CD4/CD8 ratio during follow-up	0.27 (0.15–0.39)	< 0.001	0.07 (−0.07–0.20)	0.345
Alcohol abuse				
No	Ref			
Yes	−0.18 (−0.43 to +0.6)	0.145		
Recent drug use				
No	Ref			
Yes	−0.07 (−0.33–0.19)	0.603		
Treated				
No	Ref		ref	
Yes without integrase inhibitor	0.22 (0.13–0.31)	< 0.001	0.14 (0.03–0.24)	0.009
Yes with integrase inhibitor	0.33 (0.21–0.46)	< 0.001	0.21 (0.07–0.35)	0.004
Viral load < 1000 ($\log_{10} < 3$)				
No	Ref			
Yes	0.23 (0.15–0.31)	< 0.001		

Abbreviation: AdjCoeff, adjusted coefficient; CI, confidence interval.
*Refers to "Spearman correlation" and ** to "Student-t test"

TABLE 5 Factors associated with motor/psychomotor speed performance (NPZ4) – all patients/all time, mixed model ($N = 107$ patients with 525 observations)

	Univariate		Multivariate	
	Coeff (95% CI)	***p*-value**	**AdjCoeff (95% CI)**	***p*-value**
Age at baseline	0.02 (0.01–0.04)	0.001	0.02 (0.01–0.04)	0.001
Time since infection at baseline (in years)	0.08 (−0.62–0.77)	0.825		
Time between baseline and each visit (in years)	0.02 (−0.01–0.04)	0.136	−0.01 (−0.04–0.02)	0.561
CD4/CD8 ratio	0.20 (0.07–0.32)	0.003	0.15 (0.002–0.29)	0.047
Alcohol abuse				
No	Ref			
Yes	−0.22 (−0.50–0.05)	0.112		
Recent drug use				
No	Ref			
Yes	−0.20 (−0.49–0.09)	0.175		
Treated				
No	Ref		Ref	
Yes	0.12 (0.03–0.21–)	0.007	0.10 (−0.01–0.20)	0.062
Viral load < 1000 ($\log_{10} < 3$)				
No	Ref			
Yes	0.13 (0.05–0.21–)	0.002		

Abbreviation: AdjCoeff, adjusted coefficient; CI, confidence interval.

resistance of CD4 T-cell count restoration despite long-standing viral suppression of up to 10 years [55].

This deleterious effect of delayed treatment time on the progress of CD4/CD8 ratio normalization in early HIV infection further reinforces the importance of early ART initiation for optimal CD4/CD8 ratio improvement [56, 57].

Although delayed treatment time was correlated with change in CD4/CD8 ratio, it was not related to the rate of change in NPZ4 score. Thus, there may be other factors that can explain the link between blood CD4/CD8 ratio and motor/psychomotor speed performance in this group of participants. Inflammation and immune activation in the CNS manifest after HIV transmission during the acute stage (before seroconversion) [48, 58, 59] and even persist among individuals with long-term HIV viral suppression [60, 61]. Furthermore, elevated CSF WBC is common among HIV-infected people with neurological impairment despite the paucity of evidence of other CNS infections, as well as individuals who are neurologically asymptomatic [58, 61].

This retrospective study is limited due to the nature of the analytical approach, relying on data collected based on the criteria of the PISCES protocol. Additionally, the study cohort is composed primarily of men, which limits the generalizability of the findings to HIV-infected women in the population. Despite adjusting for time between each neuropsychological testing and baseline, there may be a risk of practice effect due to repeated test exposure. Additionally, as a quarter of participants entered the study less than 2 months after their HIV diagnosis, their systemic CD4 T-cell levels may not yet have stabilized. Therefore, potential bias of infection time may have affected the analysis of the CD4/CD8 ratio and neuropsychological performance. However, this risk of bias was reduced by the relatively long duration of infection (after 3 months) by 61% of the cohort after which viral set point is typically reached [62], as well as by adjusting for this variable of infection duration in the multivariate analysis. Moreover, a longer follow-up would have been useful in understanding the long-term relationship between the CD4/CD8 ratio and cognitive performance. Besides, we did not measure the CD4 and CD8 cell count in CSF. Lastly, although the role of cytomegalovirus (CMV) on immune activation is mainly known during chronic HIV infection, we cannot excluded an influence of CMV coinfection on the trajectory of the CD4/CD8 ratio.

In conclusion, the trajectory of CD4/CD8 ratio, but not that of CD4 cell count alone, was independently associated with motor/psychomotor speed performance, suggesting that immune activation is involved in brain injury during the early stages of the infection.

Improvements in neuropsychological test performance observed in our overall cohort after most participants started ART were correlated with improvement in CD4/CD8 ratio, suggesting that both immune suppression and immune activation are needed for HAND. Furthermore, change in CD4/CD8 ratio may serve as a common proxy for clinicians to identify individuals at risk of neurocognitive decline or to monitor the response of neurocognitive disease to ART. Longitudinal follow-up of blood CD4/CD8 ratio during early HIV infection may be able to inform healthcare providers about patients whose neurocognitive health needs closer monitoring.

AUTHOR CONTRIBUTIONS

LTL, SS, and MV wrote the manuscript. SS and RWP conceived and designed the experiments. MG, HZ, BE and SA interpreted the data. HZ performed laboratory measurements. RF and CP statistically analysed the data. All authors reviewed the manuscript and contributed to the intellectual content of the paper.

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CONFLICT OF INTEREST

HZ has served on scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens

Healthineers, Triplet Therapeutics and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures incubator programme (outside submitted work).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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