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Brain Volumetrics Differ by Fiebig Stage in Acute HIV Infection

Jacob BOLZENIUS, PhD[1], **Carlo SACDALAN, MD**[2], **Lishomwa C. NDHLOVU, MD, PhD**[3], **Napapon SAILASUTA, PhD**[4], **Lydie TRAUTMANN, PhD**[5], **Somporn TIPSUK, MD**[2], **Trevor A. CROWELL, MD, PhD**[6,7], **Duanghathai SUTTICHOM, MD**[2], **Donn J. COLBY, MD**[6,7], **Nittaya PHANUPHAK, MD, PhD**[2], **Phillip CHAN, MBChB, PhD**[8], **Thomas PREMEAUX, PhD**[3], **Eugène KROON, MD**[2], **Sandhya VASAN, MD**[6,7], **Denise C. HSU, BSc MBBS, PhD**[6,7], **Victor VALCOUR, MD, PhD**[9], **Jintanat ANANWORANICH, MD, PhD**[10], **Merlin L. ROBB, MD**[6,7], **Julie A. AKE, MD**[5], **Kilian M. POHL, PhD**[11], **Somchai SRIPLIENCHAN, MD, MPH**[2], **Serena SPUDICH, MD**[8], **Robert PAUL, PhD**[1] **RV254/SEARCH010 and RV304/SEARCH013 Study Teams**

[1]University of Missouri, St. Louis, St. Louis, MO, USA

[2]SEARCH, Institute of HIV Research and Innovation, Bangkok, Thailand

[3]Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York City, NY, USA

[4]Department of Tropical Medicine, Medical Microbiology & Pharmacology, University of Hawaii, HI, USA

[5]Vaccine and Gene Therapy Institute, Oregon Health and Science University, Beaverton, OR, USA

[6]U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA

[7]Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA

[8]Department of Neurology, Yale University School of Medicine, New Haven, CT, USA

Corresponding Author: Jacob Bolzenius, Ph.D., University of Missouri, St. Louis Missouri Institute of Mental Health, 1 University Boulevard, St. Louis, Missouri, 63134, Phone: (314) 516-8465, Fax: (314) 516-8405, bolzeniusj@umsystem.edu.

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[9]Department of Neurology, University of California, San Francisco, CA, USA

[10]Department of Global Health, Amsterdam University Medical Centers, University of Amsterdam, and Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands

[11]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA

Abstract

Objective: People with chronic HIV exhibit lower regional brain volumes compared to people without HIV (PWOH). Whether imaging alterations observed in chronic infection occur in acute HIV infection (AHI) remains unknown.

Design: Cross-sectional study of Thai participants with AHI.

Methods: 112 Thai males with AHI (age 20-46) and 18 male Thai PWOH (age 18-40) were included. Individuals with AHI were stratified into early (Fiebig I-II; n=32) and late (Fiebig III-V; n=80) stages of acute infection using validated assays. T1-weighted scans were acquired using a 3T MRI performed within five days of antiretroviral therapy (ART) initiation. Volumes for the amygdala, caudate nucleus, hippocampus, nucleus accumbens, pallidum, putamen, and thalamus were compared across groups.

Results: Participants in late Fiebig stages exhibited larger volumes in the nucleus accumbens (8% larger; $p = .049$) and putamen (19%; $p < .001$) when compared to participants in the early Fiebig. Compared to PWOH, participants in late Fiebig exhibited larger volumes of the amygdala (9% larger; $p = .002$), caudate nucleus (11%; $p = .005$), nucleus accumbens (15%; $p = .004$), pallidum (19%; $p = .001$), and putamen (31%; $p < .001$). Brain volumes in the nucleus accumbens, pallidum, and putamen correlated modestly with stimulant use over the past four months among late Fiebig individuals (ps < .05).

Conclusions: Findings indicate that brain volume alterations occur in acute infection, with the most prominent differences evident in the later stages of AHI. Additional studies are needed to evaluate mechanisms for possible brain disruption following ART, including viral factors and markers of neuroinflammation.

Keywords

acute HIV infection; magnetic resonance imaging; biomarkers; neuroimaging; brain

Introduction

Research using magnetic resonance imaging (MRI) describes structural brain alterations in individuals with chronic HIV infection [1-6]. Smaller volumes are most frequently observed in basal ganglia structures and often relate to worse cognitive performance among individuals on stable antiretroviral therapy (ART) [2-5]. While these studies provide important insights related to brain integrity among people with HIV (PWH), the temporal course of structural brain changes in relation to HIV disease dynamics remains unclear.

Research among individuals with primary HIV (i.e., within one year of infection) also frequently reveal smaller brain volumes. Ragin et al. [7] reported smaller gray matter

volumes among PWH who had been infected for an average of one year. In a subsequent analysis, Ragin et al. [8] also found smaller whole brain volume and smaller gray matter volume among individuals infected with HIV for less than 100 days compared to people without HIV (PWOH). A region-of-interest examination revealed smaller putamen volumes in individuals infected for a median of 3.5 months compared to PWOH [9]. Another study reported no volumetric differences between individuals in primary infection (median duration of infection of 3.7 months) and PWOH, though basal ganglia volumes were larger among PWOH with primary infection compared to individuals with chronic HIV (median duration of infection of 90 months) [10]. These findings suggest variability among volumetric measures through the early stages of disease progression, but the chronicity of structural changes remains poorly understood, especially in earlier stages of infection.

To date, no studies have investigated structural brain changes during the acute infection period, when viral-immune mechanisms are highly dynamic (e.g., neuroinflammation) [11-14]. The acute infection period includes five distinct stages of HIV disease progression that are referred to as Fiebig stages. Fiebig staging is determined by unique patterns of HIV viremia and antibody seroconversion using viral assays [15]. HIV RNA levels exhibit marked increases during the first two weeks of infection, corresponding to Fiebig stage I and II, followed by antibody seroconversion in Fiebig stage III. Later Fiebig stages (IV and V) are characterized by decreases toward steady viral levels with increased HIV antibody presence, usually occurring 2-3 months after seroconversion.

Prior studies identify Fiebig stage II (i.e., 1-2 weeks after infection) as a critical period for cytokine induction and establishment of peak viremia [16-19]. Work from RV254/SEARCH010, a prospectively enrolled cohort of participants with acute HIV infection (AHI) followed before and after ART commenced during acute infection, reveals higher viral burden, immune activation, T-cell depletion, and incidence of acute retroviral syndrome among individuals who initiate ART after Fiebig stages I-II [17, 18, 20-22]. While some of these disease processes have been linked to variations in brain volume in primary or chronic HIV [9, 23-26], it remains unknown whether brain volumes differ by Fiebig stage (i.e., Fiebig I-II vs. Fiebig III-V) in a sample of individuals with AHI. The present study examined whether alterations in brain structure were detectable during the earliest period of infection, and whether onset of structural differences can be characterized by Fiebig stage.

Methods

Participants

A total of 112 Thai males with AHI and 18 age-matched male PWOH, enrolled between July 2015 and September 2019, were selected from the RV254/SEARCH010 and RV304/SEARCH013 biorepositories. RV254/SEARCH010 (ClinicalTrials.gov #NCT00796146) is an ongoing prospective study of the earliest biological dynamics of AHI and long-term response to ART. Individuals with AHI were recruited from the Anonymous Clinic at the Thai Red Cross Research Centre in Bangkok, Thailand as part of RV254/SEARCH010. AHI was diagnosed by sequential immunoassay (IA) or pooled nucleic acid testing (NAT) with quantitative HIV-RNA confirmation [27]. Those who were 4th generation HIV IA negative and NAT positive, and those who were 4th generation HIV IA positive, negative by less

sensitive IA and NAT positive were considered for study enrollment. PWOH comparisons were selected from archival data acquired in RV304/SEARCH013 (ClinicalTrials.gov #NCT01397669), a parallel study to RV254/SEARCH010 that enrolled demographically similar Thai males without medical or psychiatric conditions who resided in the same catchment area as the AHI participants.

Fiebig staging was performed with a hierarchical algorithm that utilized nucleic acid testing, P24 antigen, sequential immunoassay, and Western Blot testing. AHI participants were classified into one of five stages: Fiebig I (positive HIV RNA only); Fiebig II (positive HIV RNA and p24 antigen); Fiebig III (HIV IgM positive, Western blot negative); Fiebig IV (Western blot indeterminate); and Fiebig V (Western blot positive, p31 antigen negative) [15, 28]. The distributions of individuals per Fiebig stage in this analysis reflect the population parameters of individuals seeking HIV testing at the recruitment clinic, which are skewed toward Fiebig III. HIV RNA was quantified using a COBAS AMPLICOR HIV-1 Monitor Test v1.5 or COBAS Taqman HIV-1 Test v2.0 (Roche Molecular Systems). CD4+ and CD8+ T-cell counts were quantified using standardized assays [29].

All study participants included in this analysis were between 18 and 46 years of age, spoke Thai as the primary language, had ambulatory outpatient status, and provided informed consent after receiving a thorough explanation of study procedures. For this analysis we selected only individuals who underwent MRI on the same scanner hardware. Inclusion and exclusion criteria were evaluated through interviews performed by study team personnel who had undergone extensive training in the parent protocols. Exclusion criteria for this analysis included: 1) major psychiatric disorder (e.g., schizophrenia, bipolar disorder, substance use deemed likely to interfere with compliance to study procedures and ART adherence); 2) confounding neurological disorders; 3) history of opportunistic CNS infections (e.g., toxoplasmosis, progressive multifocal leukoencephalopathy); 4) medical conditions likely to disrupt brain integrity; or 5) substance use reported at enrollment deemed to be problematic for study participation by the on-site physician. All procedures were approved by the IRBs of the participating institutions.

Behavioral Assessments

Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) [30], with total score serving as the outcome variable. Substance use questions targeted use of alcohol, inhaled nitrites (“poppers”), ecstasy, cannabis, amphetamines, methamphetamines, and opioids over the past four months. Responses to substance use surveys were coded in a binary fashion (i.e., Yes/No) for analysis. Substance use data were not collected for PWOH, as this was not the primary focus of recruitment for this group.

MRI Data Acquisition

MRI scans were acquired on the day of ART initiation for 51 participants with AHI (46% of the sample). The remaining 61 participants (54%) completed the MRI within five days (M=1.0, SD=1.9) following the start of treatment. The ART regimen was either dolutegravir- (54%) or efavirenz-based (46%). MRI scans were acquired using a single 3T Philips Ingenia (software version 5.3.1) scanner with a 15-channel head coil at Chulalongkorn Hospital

in Bangkok, Thailand. The acquisition included a high-resolution T1-weighted turbo field echo (T1W 3D TFE) scan, with a 256mm x 256mm field of view, repetition time (TR) = 8.1ms, echo time (TE) = 3.7ms, flip angle = 8°, $1mm^3$ isotropic voxels, 165 slices, and slice thickness = 1mm.

Structural MRI Preprocessing

Following visual inspection, each MRI was cropped, oriented to standard orientation, and brain extracted using tools from the FMRIB Software Library (FSL). Next, the MRI was bias field corrected using the FSL Automated Segmentation Tool (FAST) [31]. FSL FAST delineated the boundaries of gray matter, white matter, and cerebrospinal fluid, resulting in segmented data for each subject. A study-specific gray matter group template was then created using functions within FSL voxel-based morphometry (VBM) [32], an optimized VBM protocol [33] carried out with FSL tools [34]. The gray matter mask of the full sample of PWOH (n=18) was averaged together with a subset of age- and sex-matched individuals with AHI (n=18). This image was flipped along the x-axis and re-averaged to create a left-right symmetric, study-specific gray matter template.

Native gray matter MRIs for all participants were non-linearly aligned to the template [35, 36] and modulated to correct for local expansion (or contraction). As such, resulting scans were already controlled for head size prior to volumetric quantification. The data were then smoothed with an isotropic Gaussian kernel (sigma of 2mm) and quantified by registering the automated anatomical labeling atlas, version 3 (AAL3), [37] to template space with affine alignment tools in FSL using nearest neighbor interpolation. Resulting scans were visually inspected to ensure accurate registration and atlas quantification. Gray matter volumes were then calculated using the atlas mask for the amygdala, caudate nucleus, hippocampus, nucleus accumbens, pallidum, putamen, and thalamus. These brain regions were selected based on the results from prior studies [9, 10, 38]. The right and left hemisphere volumes were correlated ($r > .60$), therefore, values for each ROI were summed across hemispheres into a single volume, in line with prior work [9, 38].

Statistical Analysis

First, we examined demographics between groups and associations between regional brain volumes and demographic variables to identify potential covariates, using $\alpha = .05$. Independent t-tests first compared regional brain volumes between the AHI and PWOH groups adjusted for multiple comparisons using false discovery rate (FDR) [39]. Significant volumetric group differences were further evaluated by stratifying the AHI participants into early Fiebig (stages I-II, n=32) and late Fiebig (stages III-V, n=80). One-way ANOVAs tested for subgroup differences in regional brain volumes between the three groups (early Fiebig, late Fiebig, and PWOH), using Bonferroni post-hoc tests to identify significant group differences. Volumetric group differences and relationships with mental health indices and substance use history were examined using Mann-Whitney U tests and Spearman rank correlation coefficients. We also computed Spearman coefficients for both AHI groups and PWOH separately to examine relationships between brain volume and HIV clinical indices (i.e., CD4+ T-cell count, CD8+ T-cell count, CD4/CD8 T-cell ratio, HIV viral load (log_{10}

transformed)). Data used for analysis are available upon request and completion of the necessary data transfer agreements.

Results

Demographic and Clinical Characteristics

Participants with AHI and PWOH were of similar age (Table 1). While the AHI group had a higher proportion of individuals achieving a high school diploma or higher, educational level did not elicit differences in volumetric indices by serostatus and thus was not included as a covariate. The sample of AHI included 12 individuals in Fiebig stage I, 20 in Fiebig stage II, 66 in Fiebig stage III, 9 in Fiebig stage IV, and 5 in Fiebig stage V. Individuals with AHI had a median disease duration of 21.5 days (range 5 - 49). Neither age nor education differed between the early Fiebig (i.e., Fiebig I-II) and late Fiebig (i.e., Fiebig III-V) subgroups. Similarly, the two subgroups did not differ by ART regimen or the number of days on ART before undergoing MRI. As expected, individuals in Fiebig stages I-II had significantly higher median CD4+ T-cell count, lower median CD8+ T-cell count, and lower plasma viral load ($\log_{10}$) than individuals in Fiebig stages III-V (ps < .05). No differences in substance use were observed for Fiebig subgroups. Nineteen individuals with AHI (17%) had a positive syphilis serology test (RPR+). Sample characteristics are presented in Table 1.

Region of Interest Analysis

Participants with AHI exhibited larger volumes in the amygdala (9% larger; p = .002), caudate nucleus (11%; p = .002), nucleus accumbens (15%; p = .007), pallidum (19%; p =.002), and putamen (31%; p < .001) compared to PWOH. When stratified by Fiebig stage, individuals in late Fiebig exhibited larger volumes in the same five brain regions compared to PWOH (ps < .005, and larger volumes in the nucleus accumbens (8% larger; p = .049) and putamen (19%; p < .001) when compared to those in early Fiebig. In addition, participants in early Fiebig exhibited larger volumes in the caudate nucleus (10% larger; p = .035) compared to PWOH (see Figure 1). The hippocampus and thalamus did not differ by serostatus or AHI subgrouping.

Relationships between Brain Volumes and HIV Disease Indices

Among all AHI participants, larger putamen volumes exhibited modest associations with lower CD4+ T-cell count (r = −.273, p = .004), lower CD4/CD8 T-cell ratio (r = −.255, p = .007), and higher HIV viral load (r = .253, p = .014). When stratified by Fiebig stage, higher CD8+ T-cell count correlated with larger amygdala volume (r = .455, p = .009), and higher viral load correlated with larger caudate nucleus volume (r = .489, p = .010) for individuals in early Fiebig. Further, a lower CD4+ T-cell count correlated with larger putamen volume among individuals in the late Fiebig group, though the strength of the association was weak (r = −.232, p = .039; see Table 2).

Volumetric Differences by Substance Use and Mental Health

Data on substance use were available for the majority of individuals with AHI (n=76). Larger pallidum (11% larger, p = .047) and putamen (16%; p = .025) volumes were observed among individuals in late Fiebig who reported methamphetamine use (19.6% and

21.6% of the subgroup, respectively) compared to late Fiebig non-users. Larger nucleus accumbens volumes (13% larger; $p = .009$) were also observed among individuals in late Fiebig reporting popper use (11.7% of the subgroup) compared to late Fiebig non-users. No volumetric differences by substance use were observed among individuals in early Fiebig stages. PHQ-9 total score did not elicit group differences or relationships with brain volume. Similarly, no relationships between substance use and CD4+ T-cell count, CD8+ T-cell count, or HIV viral load ($\log_{10}$) were noted among the AHI subgroups. Complete demographic, viral, behavioral, and volumetric statistics by individual Fiebig stage are provided in Table (Supplemental Digital Content 1).

Discussion

To our knowledge, this is the first examination of brain volumetrics in PWH who underwent high resolution MRI during AHI. We identified larger volumes among participants with AHI in the amygdala, caudate nucleus, nucleus accumbens, pallidum, and putamen when compared to PWOH. Examination of AHI subgroups by Fiebig stage revealed larger volumes in the nucleus accumbens and putamen among individuals in Fiebig III-V compared to individuals in Fiebig I-II. Participants in late Fiebig stages also exhibited larger regional brain volumes compared to PWOH, providing additional support that the larger brain volumes observed in the two AHI subgroups are not spurious. While mechanisms for these results remain unclear, this indicates that alterations in brain structure occur very early in the course of HIV infection, with the most pronounced changes evident in the later stages of acute infection window (~24 days from initial infection). Furthermore, the observation that volumes during AHI are increased, rather than decreased as seen typically in chronic infection, suggests that changes in brain structure associated with HIV infection are nonlinear in nature.

It is of interest that the caudate nucleus was among the brain regions that differed between early Fiebig participants and PWOH. The basal ganglia, which includes the caudate nucleus, is frequently implicated in neuroimaging studies of primary and chronic HIV [4, 6, 9, 10], even in the context of viral suppression [38]. Volumetric differences in the caudate nucleus between both Fiebig groups and PWOH observed in this study suggest that perturbations in this region of the brain begin during the earliest stages of infection [2]. It is also possible that the volumetric difference in the caudate nucleus represents premorbid factors that are not directly related to HIV infection (e.g., substance use). However, the observation of larger volumes during AHI, particularly among individuals in the later stages of AHI who have not or have only recently begun ART, is more consistent with mechanisms of CNS inflammation.

Research in both humans and animal models of HIV offers insight into possible explanatory mechanisms for these findings. Prior work reveals that the virus enters the brain within 8 days of initial infection [13] and triggers an inflammatory cascade that peaks in Fiebig II in the periphery and the CNS [13, 14, 40]. The natural dynamics of HIV disease pathogenesis (initial immune response to infection) may explain the observation of increased regional brain volumes among individuals who initiate ART during the later stages of acute infection. Similar dynamic changes in brain volumes have been reported in other

medical conditions. For example, studies of individuals with multiple sclerosis describe a "pseudoatrophy" effect, characterized by more pronounced volumetric decreases in the first year following diagnosis and treatment onset, with shallower rates of apparent atrophy afterwards. Intriguingly, these decreases are more likely attributable to a resolution of acute inflammatory processes underway during early untreated disease (e.g., increased permeability of the blood-brain barrier), rather than true atrophy, that begins to normalize following the onset of treatment [41, 42]. A similar effect may be operative in our sample of individuals with AHI, assessed at or just prior to the start of ART. These biomechanisms may provide an alternate explanation to previous observations of subcortical volumetric decreases in individuals with AHI following two years of ART [38]. More specifically, the volumetric reductions following early initiation of ART may reflect the resolution of inflammatory mechanisms that resulted in initial volumetric increases (rather than progressive atrophy in the context of otherwise successful ART), but this hypothesis requires further testing.

Larger nucleus accumbens, pallidum, and putamen volumes were observed in recent users of poppers and methamphetamine among individuals in late Fiebig stages. While problematic use of methamphetamine (i.e., methamphetamine dependence) has been associated with larger basal ganglia volumes among individuals with chronic HIV [43], this is a novel finding among individuals with AHI. Importantly, while AHI participants reported recreational use of illicit substances (including methamphetamine), often in the context of "chemsex", the substance use is not of sufficient severity to negatively impact adherence to ART (100% viral control for up to 13 years, no treatment failure, <2% study attrition) or compliance with the rigorous longitudinal assessments of the RV254/SEARCH010 protocol. We also observed no differences in recent methamphetamine use or any other illicit substance between the two Fiebig subgroups. Animal research highlights potential mechanisms by which these brain changes may occur following stimulant use, including increased dendritic branching and dendritic spine density in the nucleus accumbens [44], as well as compensatory sprouting of fibers in striatal regions [45]. Additional studies are needed to further interrogate substance use patterns and metrics of brain structure and function before and after the initiation of ART commenced during acute infection.

Several limitations of this study merit discussion. This was a cross-sectional analysis and insight about the progression of brain volume differences by Fiebig stage cannot be determined from these results. Our sample was comprised of males (consistent with the demographics of individuals who seek HIV testing at the Thai Red Cross Anonymous Clinic), and as such we cannot infer if these study findings generalize to females. Similar to prior studies by other groups, the sample of PWOH in the current study was restricted, but very well matched to the AHI sample in terms of demographics and MRI acquisition using the same system. A subset of study participants underwent MRI after initiating ART (37%) and it is unclear if early treatment effects had any impact on the study findings. However, the maximum delay between MRI and ART onset was five days, the majority (69%) completed the scan within one day, and there was no difference in the timing between Fiebig subgroups. A critical next step is to test for resolution of volumetric differences at longitudinal follow up.

Overall, volumes of subcortical brain structures are increased in the late stages of AHI, approximately three weeks post infection. Additional studies are needed to confirm whether larger volumes in individuals with AHI reflect HIV pathogenic mechanisms that resolve following the onset of suppressive ART initiated within the first month of infection. Further interrogation of specific biomarkers during each Fiebig stage (e.g., neopterin, MCP-1) represents an important next step towards identifying the causal pathways involved in alterations in brain structure and function over the course of the disease continuum and sustained use of ART.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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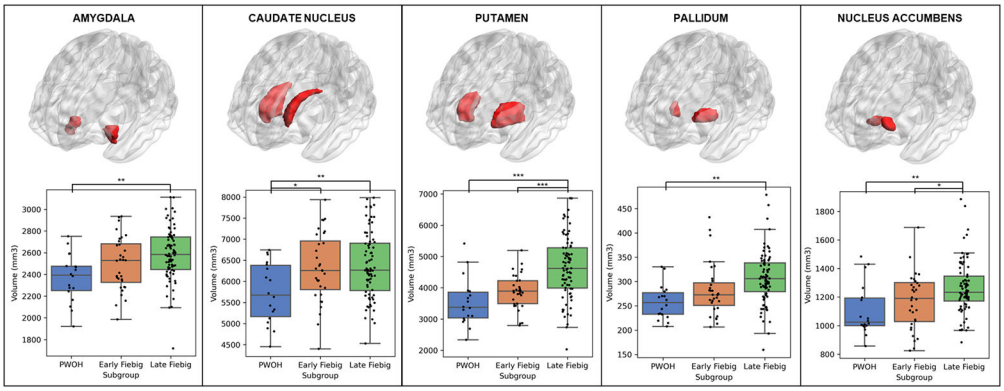

Figure 1.
Regional brain volumes exhibiting significant differences among subgroups.

Table 1.

Study participant characteristics.

	Early Fiebig (n=32)	Late Fiebig (n=80)	PWOH (n=18)	*p* value
Age, M (SD)	27.47 (5.69)	27.81 (6.53)	28.50 (7.03)	.860
Male Sex; n (%)	32 (100%)	80 (100%)	18 (100%)	
Education; n (%)				**.021**
Primary School	1 (3.1%)	0 (0%)	1 (5.6%)	
Secondary School	3 (9.4%)	5 (6.3%)	6 (33.3%)	
High school/basic technical school	7 (20.6%)	20 (25.0%)	7 (38.9%)	
Advanced technical school	2 (6.3%)	7 (8.8%)	1 (5.6%)	
Bachelor's degree	17 (27.4%)	42 (52.5%)	3 (16.7%)	
Master's degree or higher	2 (6.3%)	6 (7.5%)	0 (0%)	
ART Regimen; n (%)[a]				.857
Efavirenz	17 (53.1%)	44 (55.0%)	-	
Dolutegravir	15 (46.9%)	36 (45.0%)	-	
Fiebig Stage; n (%)				
I	12 (37.5%)	-	-	
II	20 (62.5%)	-	-	
III	-	66 (82.5%)	-	
IV	-	9 (11.3%)	-	
V	-	5 (6.3%)	-	
Days of HIV Infection[a]	16 (13-21)	24 (19-30)	-	**<.001**
Viral Load (log_{10} copies/mL)[a]	5.59 (4.57-6.19)	6.67 (5.82-6.95)	-	**<.001**
CD4+ T-cell Count (cells/mm^3)[a]	326 (279-563)	319 (229-432)	902 (694-1084)	**.033**
CD8+ T-cell Count (cells/mm^3)[a]	366 (256-493)	648 (391-995)	673 (467-1028)	**<.001**
CD4/CD8 T-cell Ratio[a]	1.20 (0.37-1.35)	0.49 (0.32-0.71)	1.46 (1.00-1.74)	**<.001**
PHQ-9 Total Score[a]	8 (5-12)	8 (6-12)	-	.799
Methamphetamine Use; n (%)[a,b]	7 (28.0%)	11 (21.6%)	-	.536
Popper Use; n (%)[a,b]	6 (24.0%)	6 (11.8%)		.169
Amphetamine Use; n (%)[a,b]	1 (4.0%)	0 (0%)		.150
Erectile Dysfunction Drug Use; n (%)[a,b]	3 (12.0%)	1 (2.0%)		.066

Values are reported as median (IQR) unless otherwise noted. Early Fiebig included Fiebig stages I-II. Late Fiebig included Fiebig stages III-V. Substances were surveyed for use over the past four months. PWOH: people without HIV. PHQ-9: Patient Health Questionnaire-9 (not collected in PWOH). Statistical comparisons were performed using the non-parametric Kruskal-Wallis test for continuous variables (except age, which was compared using one-way ANOVA), and comparisons for categorical variables was performed using Pearson chi-square tests for independence.

[a]Statistical test compared Early Fiebig and Late Fiebig subgroups only.

[b] Percentages calculated from N=25 Early Fiebig and N=51 Late Fiebig

Table 2.

Relationships between brain volumes and measures of HIV disease progression.

	Early Fiebig (n=32)					Late Fiebig (n=80)				
	Amygdala	**Caudate Nucleus**	**Pallidum**	**Putamen**	**Nucleus Accumbens**	**Amygdala**	**Caudate Nucleus**	**Pallidum**	**Putamen**	**Nucleus Accumbens**
CD4+ T-cell count (cells/mm^3)	.329	−.134	.202	−.084	.164	−.211	−.177	−.080	**−.232** *	−.180
CD8+ T-cell count (cells/mm^3)	**.455** **	−.187	.252	.202	.276	−.104	−.171	−.202	−.142	−.050
CD4/CD8 T-cell ratio	−.158	.212	−.059	−.133	−.045	.009	.068	.146	.003	.001
Viral Load (log_{10} copies/mL)	−.103	**.489** **	−.244	.093	−.005	−.103	−.009	.015	.061	.079
PHQ-9 Total Score	.131	.060	.122	.120	−.103	.156	.001	.018	−.021	−.036

Values represent Spearman rho correlation coefficients. PHQ-9: Patient Health Questionnaire-9.

* $p < .05$

** $p < .01$, uncorrected