Global Health & Medicine. 2024; 6(6):420-426.
BRIEF REPORT
DOI: 10.35772/ghm.2024.01039

Patient-specific brain fluorodeoxyglucose positron emission tomography can detect the first effects of combination antiretroviral therapy in patient with HIV infection

Miyako M Chikanishi[1,2,*], Junko Tanuma[3], Kenji Ishii[4], Muneyuki Sakata[4], Noritoshi Arai[5], Tomoyuki Noguchi[2], Kensuke Komatsu[3], Kimiteru Ito[6], Tetsuya Mizoue[7], Kazuo Kubota[8], Takeyuki Watadani[2], Hiroyuki Gatanaga[3], Shinichi Oka[3]

[1] Department of Neuroradiology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan;
[2] Department of Radiology, National Center for Global Health and Medicine, Tokyo, Japan;
[3] Department of AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan;
[4] Research Team for Neuroimaging, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan;
[5] Department of Neurology, National Center for Global Health and Medicine, Tokyo, Japan;
[6] Department of Diagnostic Radiology, National Cancer Center Hospital, Tokyo, Japan;
[7] Department of Epidemiology and Prevention, National Center for Global Health and Medicine, Tokyo, Japan;
[8] Department of Radiology, Southern Tohoku General Hospital, Fukushima, Japan.

Abstract: Patient-specific brain fluorodeoxyglucose-positron emission tomography (FDG PET) can detect areas with abnormal FDG uptake in patients with human immunodeficiency virus (HIV) before and after combination antiretroviral therapy (cART). There were few reports about the same patients before and shortly after cART in FDG PET. It is well known that HIV-RNA levels decrease and cognitive impairments in patients with HIV tend to improve on neurocognitive performance tests 6 months after starting cART. We conducted a quantitative imaging analysis (FDG PET and voxel-based morphometry (VBM)) of eight patients at pre- and 6 months post- cART with neurocognitive performance tests. In terms of participant-specific changes between pre- and post-cART imaging, some area showed that the size of area with abnormal FDG uptake shrunk and became a nearly physiological level at 6 months post-cART. No apparent changes in VBM were observed in this short period. FDG PET might detect the first effect of cART.

***Keywords*:** FDG, PET, VBM, HIV associated neurocognitive disorder (HAND), cART

Introduction

Mild human immunodeficiency virus (HIV) associated neurocognitive disorder (HAND) are sometimes difficult to diagnose (*1-6*). Generally, these neurocognitive symptoms are highly variable and can include the cognitive, motor, or mood domains. Clinically effective combination antiretroviral therapy (cART) shows the first effectiveness 6 months after its introduction; the HIV RNA levels decline, and neurological performance tests (NPTs) tend to improve. However, persistent inflammation despite cART can cause brain damage over a period of time (*7,8*). Our prior epidemiological study indicated that after approximately 5 years of cART, the prevalence of neurocognitive impairment in people living with HIV (PLWH) increases (*9*). This suggests that the cART effect is time-limited, and cART may act as a neurotoxin (*10*).

Imaging is expected to supplement the diagnosis and follow-up of patients with HIV-induced neurocognitive disorders. Despite several studies attempting this, a definitive imaging tool has not been confirmed. Most previous imaging studies used a single imaging modality and did not include detailed tests for assessing neurocognitive performance (*11-13*). Moreover, most studies were based on group comparisons between PLWH and HIV- participants, and the group differences were rather small with milder forms of HAND.

^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET) has been used in non-HIV-infected individuals to detect dementia, cancer, and active inflammation (*14-19*). Previous studies revealed complex FDG PET findings in PLWH (*20-26*); however, most were group studies, and the backgrounds of patients with neurocognitive disorders varied widely.

There were few studies in which the same patient was

analyzed by both FDG PET scan and NPTs with pre and shortly post cART. In this study, we analyzed whether FDG PET could detect the first cART effect in the same patient. Thus, we hypothesized that areas with abnormal FDG findings would shrink shortly after starting cART.

Patients and Methods

Patients

This study was approved by the Institutional Review Board of the National Center for Global Health and Medicine (approval number: 872, 896) and was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Eight pre-cART patients underwent the study examinations before and after receiving cART for 6 months. NPTs, neurological tests, FDG PET and magnetic resonance imaging (MRI) data acquisition, image processing, and statistical analyses were performed.

Thirty-five age-matched healthy control participants without HIV infection were also enrolled.

NPTs

Four psychologists with at least 3 years of training administered the neuropsychological tests. The Mini-Mental State Examination (MMSE), International HIV Dementia Scale (IHDS), Frontal Assessment Battery (FAB), and Self-Rating Depression Scale (SDS) were used for screening. The Category Fluency (animal), Word Fluency (starting from "ka"), Rivermead Behavioral Memory Test (RBMT) Story-Immediate Recall, RBMT Story-Delayed Recall, RBMT Picture Recognition-Delayed Recall, WAIS-III Digit Span, Trail Making Test Part A, WAIS-III Digit Symbol, and WAIS-III Block Design tests were used to assess the following six cognitive domains: "sensory perceptual/motor", "abstraction-executive", "language", "memory (learning, recall)", "attention information processing", and "complex perceptual motor skills". We regarded deficits in more than two domains with −1 standard deviation (SD) as mild HAND and those with −2 SD as HAND that interfered with daily life. Some domains had 2/3 sub-categories, and we counted "1 domain deficit" even if not all sub-categories were affected. Moreover, we performed "visuospatial" assessments as the seventh cognitive domain for reference.

Neurological tests

One neurologist performed the neurological tests for all patients. Neurological examination was performed *via* assessment, which evaluated the mental status, cranial nerves, motor strength, sensation, and reflexes, as well as activities of daily living as per Antinori's criteria. One of the six domains, sensory perceptual/motor skills, was also analyzed using these results, in addition to the NPTs.

^{18}F-FDG PET data acquisition

While resting in the supine position with their eyes covered and the noise level kept to a minimum, participants received an intravenous bolus injection of ^{18}F-FDG (5 MBq/kg). Forty-five minutes after the injection, PET-CT (Biograph Siemens 16; Siemens) imaging of the head was performed in three-dimensional-acquisition mode. Attenuation-corrected PET images were reconstructed using CT data, and a full width at half maximum Gaussian post-filter of 3.0-mm, and 53 image slices, with an interslice distance of 3 mm, were obtained. The total axial field of view was 16.2 cm with an approximate in-plane resolution of 5.8 mm.

Following the head acquisition, a whole-body PET-CT scan was performed from the vertex to the mid-thigh to check for the presence of other diseases that might affect brain metabolism.

MRI data acquisition

MRI was performed using a 3.0-Tesla Tim-Trio scanner (Magnetom Verio, Siemens, Erlangen, Germany) equipped with the standard four-channel head coil. A high-resolution, three-dimensional sagittal T1-weighted magnetization-prepared rapid gradient echo scan was acquired using the following parameters: echo time (TE) = 4.24 ms, repetition time (TR) = 1,600 ms, inversion time = 800 ms, flip angle = 15°, 256 × 256 acquisition matrix, and 1 × 1 voxels.

Image processing and statistical analyses

The PET and T1-weighted MRI images were processed and analyzed for spatially normalized to the standard brain template, using the statistical parametric mapping (SPM8) application (Wellcome Trust Centre for Neuroimaging, University College London, UK, *https://www.fil.ion.ucl.ac.uk/spm/*) implemented in MATLAB® R2010b (MathWorks, Inc., Natick, MA, USA) to detect subtle changes compared with those in the normal group. Two-sample *t* tests were used to detect differences between cART- and cART+ individuals.

The values were proportionally scaled by the whole brain means. A threshold of $p < 0.001$ (uncorrected) was used with the extent threshold for contiguous voxels set at k = 100. Two radiologists and two nuclear medicine radiologists assessed the images and separately reported abnormally decreased or increased areas. In case of any disagreement, they discussed and arrived at a consensus.

The FDG images were spatially normalized to the standard brain template, and the values were proportionally scaled by the whole brain means.

Results and Discussion

We analyzed eight individual changes pre- and 6 months post- cART (Table 1). After 6 months of cART, all patients showed that their HIV-RNA levels declined drastically. Two patients were diagnosed as mild HAND at pre-cART; one was also diagnosed as mild HAND at post-cART, however one changed to within normal limit (WNL) at post-cART. One patient's diagnosis changed from WNL at pre-cART to mild HAND at post-cART. In the analysis of the images, no apparent changes in voxel-based morphometry (VBM) were found after 6 months of cART, whereas the FDG PET findings differed dramatically. Some areas with abnormally decreased or increased FDG uptake at pre-cART shrunk and improved towards near-normal physiologically post-cART. After giving cART, brain glucose metabolism in some areas might revert to a near-normal physiological level, reflecting a brain function improvement.

In patient number (Pt. No.) 1, the diagnosis of mild HAND did not change pre- and post-cART. The decreased FDG uptake around the Sylvian fissure improved after cART, whereas that in the cingulate did not improve (Figure 1 and Figure 2). Abnormally increased uptake in the basal ganglia and thalamus improved dramatically after cART. The NPT score after cART indicated a mild neurocognitive disorder, similar to that before cART. However, the scores after cART differed slightly from those before cART. The patient exhibited improvement in the "visuospatial" domain, whereas the performance in the "attention information processing" and "complex perceptual (motor)" domains worsened.

NPT diagnosis of Pt. No.2 changed from mild HAND to WNL. The FDG PET images did not show any abnormal areas, even before starting cART.

Pts. No. 1 and 2 were diagnosed with mild HAND. After receiving cART, the diagnosis of Pt. No. 2 changed to WNL, and abnormal FDG PET findings could not be further detected at the pre-cART examination, suggesting that the functional disorder might not be strong. By contrast, the diagnosis of Pt. No. 1 remained as a mild HAND, and the abnormal findings in the anterior/posterior cingulate gyrus and precuneus did not improve after cART. Functional damage in these areas might be severe and not improve following cART.

The cingulate region has two main parts: the anterior cingulate and the posterior cingulate. The posterior cingulate cortex is closely related to the precuneus and hippocampus, which are associated with cognitive and visuospatial functions. The posterior cingulate and precuneus are well-known areas that have a reduced FDG uptake in patients with Alzheimer's disease (*27*). The anterior cingulate is associated with sympathy/empathy and focus maintenance during task performance. Some networks, such as the working memory, theory of mind, and saliency networks, are related to the anterior cingulate (*28,29*). The anterior cingulate adjusts networks to assigned tasks. Towgood *et al.* reported differences in FDG uptake in the anterior cingulate between patients in their 30s and those in their 50s, and these authors concluded that this change might relate to morphological shrinking and aging (*22*). Yuferov *et al.* reported neuroinflammatory changes in the anterior cingulate of postmortem brains from PLWH (*30*). In the current study, Pt. No. 1 showed improved abnormal findings without decreased FDG uptake in the anterior/posterior cingulate and precuneus after cART. Decreased function in these areas may irreversibly affect neuronal networks, which possibly relate aging and atrophy.

Abnormally decreased uptake around the Sylvian fissure (insula) improved after cART in Pt. No. 1. The insula is surrounded by the cerebral hemisphere and has several connections with the anterior brain areas, limbic system, middle and posterior cingulates, and the thalamus. Georgiou *et al.* showed that the decreased FDG uptake in areas around the Sylvian fissure area (insula) was related to drug use in HIV+ subjects (*21*). In our study, all participants were men, and most acquired HIV by having sex with other men; none of them had any apparent history of alcohol or drug abuse. The findings of Pt. No. 1 revealed decreased FDG uptake around the Sylvian fissure (insula) that diminished after cART initiation. Therefore, this abnormal uptake may be associated with factors other than drug use and might be reversible.

Pt. No. 3 showed abnormal FDG uptake on pre-cART images, and this finding improved after cART (Figure 1 and Figure 2). The patient had not been diagnosed with a neurocognitive disorder. FDG might detect the abnormal area before the symptoms become apparent in pre-cART. The diagnosis for Pt. No. 4 changed from WNL to mild HAND after cART. The FDG PET showed no abnormalities except for the area regarded as atrophic based on the VBM results. The patient exhibited brain atrophy before the initiation of cART.

In this study, the areas with abnormal FDG uptake shrank and reached nearly normal levels shortly after cART initiation in some areas. However, the initial cART effect might only be present for a limited time because the prevalence of neurological impairment tends to increase again after 5 years of cART. Lamers *et al.* showed that HIV DNA was detected in brain autopsy tissue following cART even if the viral load was undetectable (*7*). Blood-brain barrier impairment observed in PLWH could be attributable to HIV or secondary post-cART immune activation. In the post-cART period, these areas might reflect the direct or indirect effects of HIV on brain inflammation. FDG PET might detect the initial cART effects (*e.g.*, shrunken size and normalized levels in areas of abnormal FDG uptake) after only 6 months. Follow-up of FDG findings might be used to determine cART-related treatment effects and damage in these brain regions.

This study had several limitations. First, only 8

Table 1. Eight participants' NPTs and FDG PET findings, pre and post cART

Pt. No	Age (y)	cART	CD4 Recent (/μL)	Recent HIV/RNA (copies/mL)	NPT											FDG	
					NPT diagnosis	ADL	FAB	Language		Memory			AIP	CPM		Visuospatial		
								c	w	I	D	P		TMTA	Digit		Decreased	Increased
1	41	pre	2	1,200,000	Mild HAND	WNL	↓						↓		↓	↓↓	+	+
		post	277	ND	Mild HAND	WNL	↓						↓↓	↓	↓	↓	partially improve	partially improve
2	40	pre	571	12,000	Mild HAND	WNL	↓		↓						↓↓	–	–	–
		post	807	ND	WNL	WNL	improve		improve						↓(improve)			
3	47	pre	570	22,000	WNL	WNL											+	+
		post	655	32	WNL	WNL											improve	improve
4	47	pre	380	54,000	WNL	WNL									↓		atrophy	
		post	641	28	Mild HAND	WNL	↓			↓	↓				↓		no change	
5	41	pre	550	3,400	WNL	WNL		↓										
		post	471	< 20	WNL	WNL		improve										
6	50	pre	679	20,000	WNL	WNL								↓				
		post	729	ND	WNL	WNL								improve				
7	47	pre	358	27,000	WNL	WNL												
		post	504	ND	WNL	WNL												
8	40	pre	353	35,000	WNL	WNL												
		post	467	< 20	WNL	WNL												

NPT, neurological performance test; FDG PET, fluorodeoxyglucose positron emission tomography; cART, combination antiretroviral therapy; FAB, Frontal Assessment Battery; HAND, HIV associated neurocognitive disorder; AIP, Attention Information Processing; CPM, Complex Perceptual Motor Skills; TMTA,Trail Making Test, Part A; ND: not detected; Language c: Category Fluency, w: Word fluency; Memory I: RBMT Story-Immediate Recall; D: RBMT Story-Delayed Recall; P: RBMT Picture Recognition-Delayed Recall.

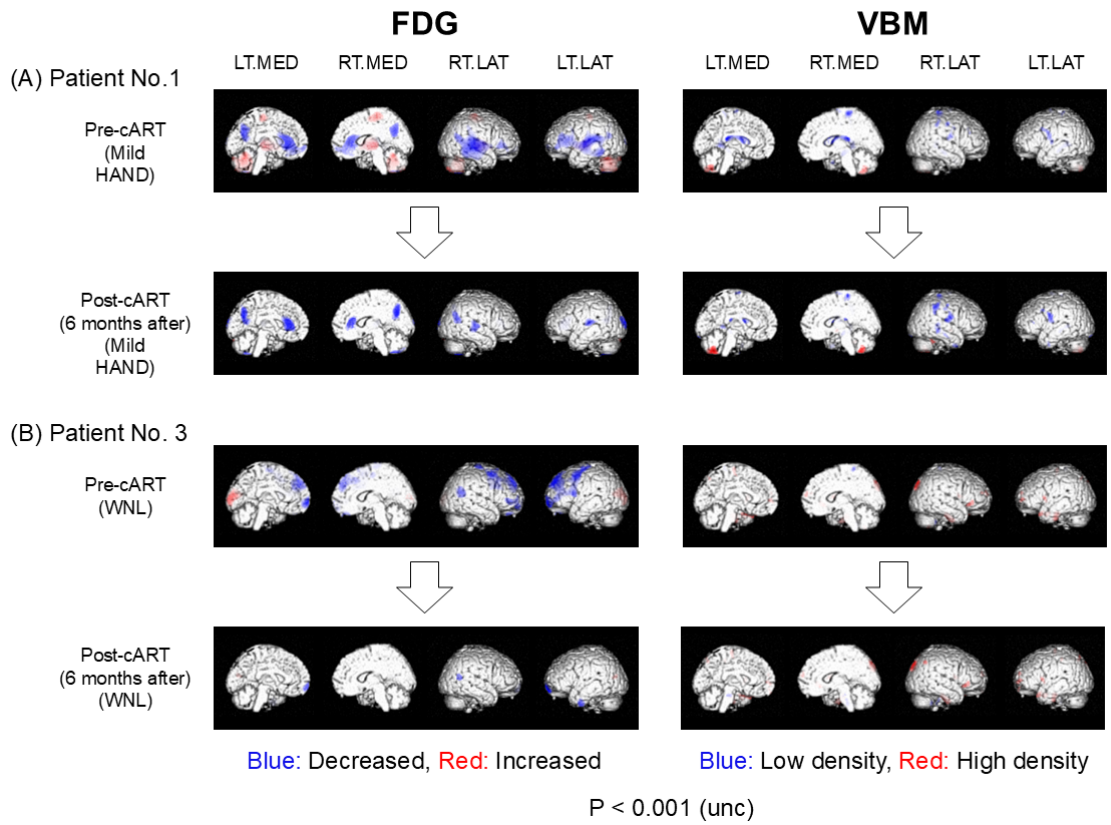

Figure 1. Comparison of FDG PET findings between pre- and post-cART images in two PLWHs. (A) Patient No. 1 shows several areas with abnormal FDG uptake in pre cART, with decreased area as blue and with increased area as red. In the post-cART images, the decreased blue area, anterior cingulate, did not improve, however, the decreased area in the left around sylvian fissure area and the increased red cerebellum and thalamus improved to normal. **(B)** Patient 3 has neurocognitive WNL and areas of abnormal FDG uptake pre-cART. The area with abnormal FDG uptake reduced in size on post-cART imaging and appeared nearly normal. cART, combination antiretroviral therapy; FDG, fluorodeoxyglucose; PET, positron emission tomography; PLWH, human immunodeficiency living with HIV; VBM, voxel-based morphometry; WNL, within normal limits.

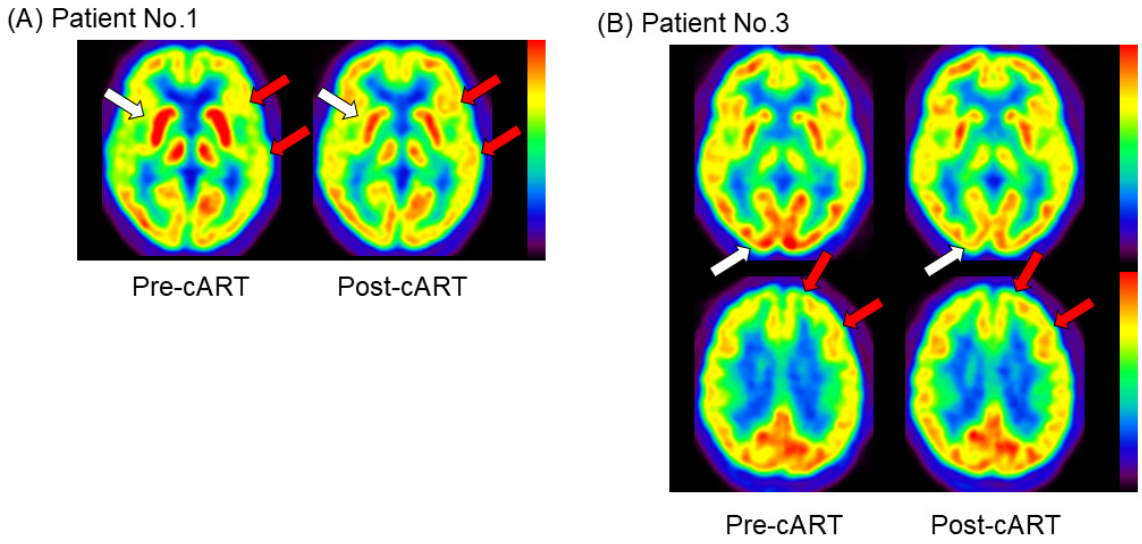

Figure 2. Decreased areas in pre-cART / improved in post-cART are shown in red arrow and increased areas in pre-cART / improved in post-cART are in white arrow. (A) Patient No. 1 showed the FDG uptake in the left around sylvian fissure areas were decreased in pre cART, however, that improved to normal after cART. The apparent increased uptake was seen in basal ganglia and thalamus in pre cART, and improved to normal in post cART. **(B)** Patient No. 3 showed decreased uptake in left frontal grey matter in pre cART and improved to normal in post cART. Uptake in the occipital areas were increased in pre cART and improved after cART. Images were spatially normalized and values were proportionally scaled by the whole brain means.

patients were analyzed with pre and 6 months post cART. Studies with larger sample sizes and longitudinal research are desirable. Second, we used Antinori's 3-HAND categories (*1*), sometimes affected by the effects of race/ethnicity, age, education, or sex. However, in this study, all PLWH and controls were age-matched Japanese men and the impact of these factors is considered to be minimal. Despite these limitations, our FDG PET data are illustrative between before and shortly after cART. More longitudinal data might be expected in the future.

In conclusion, in this study, we examined metabolic changes following cART administration in PLWH. The administration of cART tends to normalize brain metabolism in the short term; thus, FDG-PET might detect the effects of the first cART treatment.

Acknowledgements

The authors thank the following individuals: *i*) Clinical data collection: Kikuchi Y, Tsukada K, Watanabe A, Nakasato A, Ogata M; *ii*) Imaging section: Hasuo K, Tajima T, Minamimoto R; *iii*) Technical assistance: Mitsumoto T, Sunaoka F, Kajiwara H, Sato S; *iv*) SPM analysis and technical support: Tanaka M, Onishi A.

Funding: Grant for International Health Research, National Center for Global Health and Medicine (22-Shi-113, 120).

Conflict of Interest: Shinichi Oka: MSD (grant/personal fees), ViiV Healthcare (grant/personal fees), Gilead Sciences (personal fees), Torii Pharmaceutical (personal fees), Janssen Pharmaceutical (personal fees), and Japan Tobacco/Torii Pharmaceutical (nonfinancial support). The other authors declare no conflict of interest.

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Received June 11, 2024; Revised September 10, 2024; Accepted September 26, 2024.

Released online in J-STAGE as advance publication October 12, 2024.

Address correspondence to:
Miyako M Chikanishi, Department of Neuroradiology, Tokyo Metropolitan Neurological Hospital, 2-6-1, Musashidai, Fuchu-shi, Tokyo 183-0042, Japan.
E-mail: minatochan777@gmail.com