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Original Research

The differential effects of integrase strand transfer inhibitors and efavirenz on neuropsychiatric conditions and brain imaging in HIV-positive men who have sex with men

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ABSTRACT

Integrase strand transfer inhibitors (INSTIs) have emerged as the first-line choice for treating human immunodeficiency virus (HIV) infection due to their superior efficacy and safety. However, the impact of INSTIs on the development of neuropsychiatric conditions in people living with HIV (PLWH) is not fully understood due to limited data. In this study, we conducted a cross-sectional examination of PLWH receiving antiretroviral therapy, with a specific focus on HIV-positive men who have sex with men (MSM) on INSTI-based regimens (n = 61) and efavirenz (EFV)-based regimens (n = 28). Participants underwent comprehensive neuropsychiatric evaluations and multimodal magnetic resonance imaging (MRI) scans, including T1-weighted images and resting-state functional MRI. Compared to the EFV group, the INSTI group exhibited primarily reduced gray matter volume (GMV) in the right superior parietal gyrus, higher regional homogeneity (ReHo) in the left postcentral gyrus, lower ReHo in the right orbital part of the inferior frontal gyrus, and increased voxel-wise functional connectivity for the seed region in the left inferior temporal gyrus with clusters in the right cuneus. Furthermore, the analysis revealed a main effect of antiretroviral drugs on GMV changes, but no main effect of neuropsychiatric disorders or their interaction. The repeated analysis of participants who did not switch regimens confirmed the GMV changes in the INSTI group, validating the initial findings. Our study demonstrated gray matter atrophy and functional brain changes in PLWH on INSTI-based regimens compared to those on EFV-based regimens. These neuroimaging results provide valuable insights into the characteristics of brain network modifications in PLWH receiving INSTI-based regimens.

1. Introduction

The introduction of antiretroviral therapy (ART) has significantly improved the health of people living with human immunodeficiency virus (HIV), allowing them to achieve HIV plasma viral loads below detectable levels [1]. However, despite the benefits of ART, people living with HIV (PLWH) may still experience a range of non-acquired

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HIGHLIGHTS

Scientific question

Integrase strand transfer inhibitors (INSTIs) are first-line drugs for treating human immunodeficiency virus (HIV) infection. However, their effects on brain structure and function have not been well addressed.

Evidence before this study

Factors related to antiviral drugs have been shown to play a significant role in the increased incidence of non-acquired immunodeficiency syndrome-related neuropsychiatric adverse events. Neuropsychiatric symptoms have also been reported in people living with human immunodeficiency virus (HIV) receiving INSTI-based regimens.

New findings

In this study, multimodal magnetic resonance imaging techniques were employed to investigate the effects of INSTIs versus efavirenz in HIV-infected men who have sex with men. The results demonstrated that the INSTI group exhibited gray matter volume atrophy and brain functional changes compared to the efavirenz group.

Significance of the study

Our study revealed significant brain imaging changes between HIV-infected individuals receiving INSTIs and those receiving efavirenz, potentially offering new insights for future antiretroviral drug selection in HIV-infected individuals.

immunodeficiency syndrome-related neuropsychiatric adverse events (NPAEs) [2–4]. Numerous factors, including age, education, socioeconomic status, disease severity, comorbidity, adverse experiences, and social support, have been implicated in the development of neuropsychiatric conditions in PLWH [5,6]. Importantly, drug treatment factors have also been shown to contribute to the increased incidence of NPAEs [7,8].

Integrase strand transfer inhibitor (INSTI)-based regimens are increasingly preferred as first-line therapy due to their superior efficacy and safety compared to regimens based on older antiretroviral drugs, such as efavirenz (EFV) [9]. Although EFV, a non-nucleoside reverse transcriptase inhibitor, has been effective in treating HIV infection, it is associated with NPAEs in 25 % - 70 % of PLWH [10]. As a result, the latest international recommendations have minimized the use of EFV [11]. Commonly used INSTIs include dolutegravir (DTG), bictegravir (BIC), and elvitegravir (EVG). Previous studies have demonstrated that these INSTIs are more effective and safer than EFV in treating HIV infection [12,13]. DTG-based regimens have shown enhanced viral suppression and $CD4^+$ T cell recovery while improving safety profiles [14]. Transitioning from EFV-based regimens to EVG-based regimens in virologically suppressed PLWH has been found to significantly reduce central nervous system (CNS) symptoms [15]. However, post-marketing analysis has reported neuropsychiatric symptoms and identified smaller volumes in the brainstem, frontal, and cerebellar regions in PLWH taking INSTIs [16]. Several studies have documented depressive and insomnia symptoms in PLWH who initiated DTG-based regimens [17–20]. Thus, antiretroviral drugs are increasingly recognized as a potential cause of neuropsychiatric disorders [21].

Previous research has demonstrated the efficacy of INSTIs in randomized clinical trials, indicating good short-term drug safety and tolerability [22,23]. In contrast, EFV has been associated with various neuropsychiatric conditions [24]. However, there is a lack of investigations examining the effects of INSTIs on brain structure and function. The use of multimodal magnetic resonance imaging (MRI) has become crucial in the early detection of HIV-related neuropathological alterations in the brain [25,26]. A previous study indicated that PLWH exhibit reduced gray matter volume (GMV) and functional brain abnormalities compared to healthy controls [27]. To address this research gap, we designed an examination of structural and functional brain imaging in PLWH receiving INSTI-based regimens, comparing them to a well-matched group of PLWH receiving an EFV-based regimen.

2. Materials and methods

2.1. Participants

This cross-sectional study was approved by the institutional ethics committee of Beijing Youan Hospital, Capital Medical University. Prior to obtaining written informed consent, participants were provided with detailed information about the entire procedure and potential risks. The inclusion criteria for our study were as follows: (1) PLWH currently undergoing antiretroviral treatment; (2) Chinese men who have sex with men (MSM); (3) Right-handed individuals; (4) Aged at least 18 years; and (5) Individuals able to provide informed consent. The exclusion criteria included: (1) Individuals with MRI contraindications or claustrophobia; (2) Individuals with a history of head injury resulting in loss of consciousness for more than 30 min; (3) Individuals with current or past opportunistic CNS infections; (4) Individuals with a history of neurological diseases such as dementia, epilepsy, Parkinson's disease, or multiple sclerosis; and (5) Individuals with a history of substance abuse.

Between May 2022 and November 2022, a total of 109 participants were enrolled in the study. Only participants who were using INSTI-based or EFV-based regimens were included in the subsequent analyses. Eight participants receiving other ART drug regimens were excluded from this study. All participants underwent clinical and MRI assessments on the same day. Three participants were excluded due to inadequate image acquisition. Additionally, nine participants were excluded from further analyses due to significant head motion, defined as more than 2.0° of maximal rotation in any direction (x, y, or z) or 2.0 mm of maximal translation throughout the scanning session. As a result, a total of 89 participants were included in the final data analysis.

2.2. Clinical assessments

2.2.1. Diagnosis of neuropsychiatric disorders

Psychiatric diagnoses were determined by a board-certified research psychiatrist based on criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* [28].

2.2.2. Neurocognitive tests

Neurocognitive function of participants was evaluated using the Montreal Cognitive Assessment (MoCA) [29].

2.2.3. Mood and sleep assessment

Levels of depression and anxiety were assessed using the Self-rating Anxiety Scale (SAS) and the Self-rating Depression Scale (SDS) [30,31]. Mental health status was evaluated using the Symptom Checklist-90 (SCL-90) [32,33], while sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) [34].

2.2.4. Other assessments

Exposure to childhood trauma and chronic alcohol abuse have been associated with altered brain structure and function [35,36]. The Childhood Trauma Questionnaire (CTQ) was used to assess the history of childhood maltreatment [37]. Alcohol craving was measured using the Alcohol Urge Questionnaire (AUQ) and the Visual Analogue Scale (VAS) [38,39].

2.3. MRI data acquisition

Imaging data were acquired using a 1.5 T MRI scanner (Philips, Amsterdam, The Netherlands) at the Second Hospital of Beijing. Foam pads were used to minimize head movements during the scanning process. Participants were instructed to assume a relaxed position, close their eyes, and avoid focusing on specific thoughts while remaining awake.

For 3D T1-weighted imaging, the following parameters were used: repetition time / echo time (TR / TE) = 2,500 / 2.98 miliseconds (ms), the field of view = 256 mm × 256 mm, flip angle = 7°, matrix = 64 × 64, slice thickness = 1 mm, slices = 192, and slice number = 48. Resting-state functional MRI (rs-fMRI) data of the entire brain were acquired using a gradient echo-planar imaging sequence with the following parameters: TR / TE = 4,019.8 / 30 ms, slices = 40, flip angle = 90°, matrix = 64 × 64, slice thickness = 2.8 mm, volumes = 102, no gap, and scanning time = 6 min and 3 s.

2.4. Image preprocessing and computation of brain MRI metrics

Image preprocessing and statistical analyses were conducted using MATLAB R2023a (The MathWorks, Natick, MA, USA). Initially, voxel-based morphometry (VBM) was utilized to calculate brain structural metrics. Subsequently, various brain functional metrics such as the amplitude of low-frequency fluctuations (ALFF), fractional ALFF (fALFF), regional homogeneity (ReHo), and seed-based whole-brain functional connectivity (FC) were computed. For a more detailed description of the methods, please refer to the Supplementary material.

2.5. Statistical analysis

Statistical analysis was performed using SPSS for Windows version 25.0 (IBM Corp., Armonk, New York, USA), with a significance threshold α set at 0.05. The normality of the data was determined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous data were reported as means with standard deviations for normally distributed variables or as medians with interquartile ranges for non-normally distributed variables. Between-group comparisons of numerical variables were conducted using a two-sample *t*-test or Mann-Whitney *U* test based on the results of the normality test. Categorical data were presented as proportions and compared between groups using the chi-square test or Fisher's exact test. Pearson's correlation analysis was used for variables with a normal distribution, while Spearman's correlation analysis was used for variables with a non-normal distribution.

An analysis was conducted to investigate whether alterations in brain function and structure were attributed to the main effects of antiretroviral drugs, neuropsychiatric disorders, or the interaction between them.

The average time series of voxels in each seed region was extracted for each participant, and their demographic and clinical data were correlated with the imaging findings. GraphPad Prism software version 9.5.1 (GraphPad Software, San Diego, CA, USA) was used to visually represent the statistical results.

3. Results

3.1. Characteristics of study participants

A total of 89 participants completed the study, with 61 currently receiving INSTI-based regimens and 28 receiving EFV-based regimens. There were no differences in HIV infection-related clinical characteristics between the INSTI and EFV groups. The demographics and clinical assessment characteristics are summarized in Table 1.

In the INSTI group, 27 participants (44.30 %) were diagnosed with neuropsychiatric disorders, compared to 18 participants (64.30 %) in the EFV group, with depressive disorder being the most common. A lower percentage of participants in the INSTI group reported suicidal symptoms ($P = 0.025$) and insomnia symptoms ($P = 0.012$) compared to the EFV group (Table S1).

Moreover, the INSTI group exhibited significantly lower scores of SDS compared to the EFV group ($P = 0.037$), along with higher scores on the MoCA ($P = 0.012$). No notable differences were observed in the two groups in terms of SAS, PSOI, CTQ, SCL-90, AUQ, or VAS for alcohol craving (Table 1 and Table S2).

3.2. Differences in brain MRI metrics between the INSTI and EFV groups

3.2.1. GMV

The INSTI group exhibited significantly lower GMV primarily in the right superior parietal gyrus (SPG) compared to the EFV group (family-wise error corrected, voxel-level $P < 0.001$, cluster-level $P < 0.05$). Using a less strict threshold (voxel-level uncorrected $P < 0.001$), the INSTI group exhibited lower GMV in the left postcentral gyrus (PoCG), left parahippocampal gyrus (PHG), and left inferior parietal lobule (IPL), including the supramarginal and angular gyri, among other regions, compared to the EFV group. No significant differences were observed in brain volumetrics between the two groups. Detailed information is shown in Fig. 1 and Table S3 and S4.

3.2.2. ALFF/fALFF

In this final result, the largest cluster size consisted of fewer than 10 contiguous voxels, and no significant differences were found in the ALFF/fALFF comparison between the two groups.

3.2.3. ReHo

The INSTI group showed higher ReHo in the left PoCG and lower ReHo in the right orbital part of the inferior frontal gyrus (ORBinf) compared to the EFV group (voxel-level uncorrected $P < 0.001$). Detailed information is shown in Fig. 2 and Table S5.

3.2.4. Seed-based whole-brain FC

Comparative analysis of voxel-wise FC revealed that the INSTI group exhibited increased FC for the seed region in the left inferior temporal gyrus (ITG) with clusters in the right cuneus, right inferior occipital gyrus (IOG), and bilateral middle occipital gyrus, etc., compared to the EFV group. The details are summarized in Table S6 and S7.

To mitigate the possibility of result exaggeration, we included specific brain regions (frontal, striatal, thalamic, and hippocampal regions) as seed regions for further analysis, considering the early involvement of subcortical regions in HIV infection studies [26] (Table S8). Notably, the INSTI group exhibited higher FC for the seed region in the left middle frontal gyrus with clusters in the right lingual gyrus (LING). Additionally, lower FC was observed for the seed region in the left caudate nucleus with clusters in the right supramarginal gyrus, etc. (Table S9).

Table 1
Basic information of participants.

Demographic and clinical data	INSTIs (N = 61)	EFV (N = 28)	Statistic	*P* value
Age, year	33.00 (27.50–39.00)	36.50 (29.25–41.75)	$Z = -0.871$	0.384*
Height, m	1.75 ± 0.06	1.74 ± 0.05	$t = 0.769$	0.444†
Weight, kg	69.00 (63.00–76.50)	65.00 (58.25–70.00)	$Z = -1.772$	0.076*
BMI, kg/m^2	22.65 (21.09–24.00)	21.11 (19.94–23.60)	$Z = -1.816$	0.069*
Education, year	16.00 (15.00–17.00)	15.00 (12.00–16.00)	$Z = -2.486$	0.013*
Period of diagnosed HIV infection				
CD4 at diagnosis, cells/μL	377.64 ± 199.72	357.88 ± 198.40	$t = 0.434$	0.665†
CD8 at diagnosis, cells/μL	974.00 (844.50–1,259.00)	983.97 (738.41–1,252.00)	$Z = -0.579$	0.563*
CD4/CD8 ratio at diagnosis	0.36 (0.26–0.47)	0.35 (0.24–0.48)	$Z = -0.230$	0.818*
VL at diagnosis, log10 copies/mL	3.99 (3.61–4.64)	4.11 (3.82–4.71)	$Z = -0.601$	0.548*
Period of initial ART start				
CD4 at initiation of ART, cells/μL	380.26 ± 200.09	371.02 ± 219.18	$t = 0.196$	0.845†
CD8 at initiation of ART, cells/μL	984.00 (809.94–1,259.00)	1,031.00 (726.22–1,305.52)	$Z = -0.402$	0.688*
CD4/CD8 ratio at initiation of ART	0.36 (0.26–0.47)	0.36 (0.23–0.55)	$Z = -0.044$	0.965*
VL at initiation of ART, log10 copies/mL	3.93 (3.57–4.71)	4.11 (3.78–4.64)	$Z = -0.508$	0.611*
Period of clinical and MRI assessment				
Current CD4, cells/μL	626.26 ± 299.80	603.57 ± 242.57	$t = 0.351$	0.726†
Current CD8, cells/μL	857.00 (585.52–1,066.84)	775.50 (618.25–1,062.75)	$Z = -0.318$	0.750*
Current CD4/CD8 ratio	0.76 ± 0.38	0.77 ± 0.34	$t = -0.117$	0.907†
Current virus not detectable (yes/no)	61/0	28/0	NA	NA
Current ART regimen (BIC/DTG/EVG/EFV − based regimen)	44/8/9/0	0/0/0/28	NA	NA
Duration between diagnosis and initiation of ART, month	0.50 (0.40–1.40)	0.55 (0.40–1.00)	$Z = -0.450$	0.653*
Duration of ART, month	60.71 ± 40.63	73.39 ± 44.19	$t = -1.330$	0.187†
Duration of HIV diagnosis, month	65.67 ± 42.81	83.29 ± 44.85	$t = -1.776$	0.079†
Diagnosis of neuropsychiatric disorders (positive/negative)	27/34	18/10	$\chi^2 = 3.078$	0.079‡
SAS	33.46 ± 8.23	36.68 ± 7.35	$t = -1.770$	0.080†
SDS	33.00 (27.00–43.50)	39.00 (33.25–45.75)	$Z = -2.082$	0.037*
PSQI	5.00 (3.00–8.00)	6.50 (3.00–9.00)	$Z = -0.852$	0.394*
CTQ	60.00 (53.50–63.00)	58.50 (39.25–63.25)	$Z = -0.956$	0.339*
SCL-90	124.00 (99.50–168.00)	140.50 (104.50–190.75)	$Z = -0.884$	0.377*
AUQ	11.00 (8.00–14.50)	8.00 (8.00–13.50)	$Z = -1.570$	0.116*
VAS	2.00 (1.00–4.00)	2.00 (1.00–3.75)	$Z = -0.291$	0.771*
MoCA	27.00 (26.00–28.00)	25.50 (24.00–27.00)	$Z = -2.521$	0.012*

The continuous data were presented as mean ± SD or median (IQR), and the categorical data were expressed as numbers. Two-sample *t*-tests were used for continuous data with a normal distribution, while Mann-Whitney *U*-tests were used for continuous data that did not obey a normal distribution. Chi-square and Fisher's exact tests were used to compare categorical variables. *, Mann-Whitney *U* test; †, two-sample *t*-test; ‡, chi-square test. Abbreviations: NA, not available; SD, standard deviation; IQR, interquartile range; INSTIs, integrase strand transfer inhibitors; EFV, efavirenz; BMI, body mass index; HIV, human immunodeficiency virus; CD4, CD4$^+$ T cell count; CD8, CD8$^+$ T cell count; VL, viral load; ART, antiretroviral therapy; MRI, magnetic resonance imaging; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; SCL-90, Symptom Checklist 90; PSQI, Pittsburgh Sleep Quality Index; CTQ, Childhood Trauma Questionnaire; AUQ, Alcohol Urge Questionnaire; VAS, Visual Analogue Scale for alcohol craving; MoCA, Montreal Cognitive Assessment; BIC, bictegravir; DTG, dolutegravir; EVG, elvitegravir.

3.3. Results of the main effect and interaction

The brain regions showing differences in VBM analysis included the right IOG, right SPG, and left IPL as the main effects of antiretroviral drugs. Meanwhile, group differences in ReHo were observed in the left PoCG, which demonstrated a main effect of neuropsychiatric disorders. The VBM and ReHo results indicated no interaction between antiretroviral drugs and neuropsychiatric disorders (Table 2).

3.4. Correlations of the imaging alterations with basic information and clinical data

In the INSTI group, a negative correlation was found between GMV in the right SPG and age ($r = -0.282$, $P = 0.029$; Fig. 3). Additionally, there was a negative correlation between the duration of HIV diagnosis and GMV in the right PoCG ($r = -0.259$, $P = 0.046$; Fig. 3 and Table S10–S12).

3.5. Validation analyses: impact analysis of a recent regimen switch

The validity of the primary findings was largely confirmed through validation analyses. A total of 44 participants (16 PLWH on INSTI-based regimens and 28 PLWH on EFV-based regimens) who maintained a consistent drug regimen throughout the treatment period were included in the repeated analysis. The observed changes in GMV in the INSTI group were validated. These results are included in the Supplementary data.

4. Discussion

In the present study, we conducted a comparison between PLWH on INSTI-based regimens and a well-matched group on EFV-based regimens to examine their neuropsychiatric conditions, brain structure, and function. In comparison to the EFV group, the INSTI group exhibited lower GMV in the right SPG. Additionally, the INSTI group showed increased ReHo in the left PoCG and reduced ReHo in the right ORBinf compared to the EFV group. Furthermore, there was significantly higher voxel-wise FC observed for the seed region in the left ITG with clusters in the right cuneus and other regions in the INSTI group. The VBM results indicated the main effects of antiretroviral drugs, including in the right SPG. Notably, both the VBM and ReHo findings demonstrated no interaction between antiretroviral drugs and neuropsychiatric disorders.

In the study, we identified specific brain regions where the INSTI group exhibited lower GMV, including the right SPG, left PoCG, right LING, and left PHG, among others. Previous neuroimaging studies across diverse human pathologies have suggested the involvement of the SPG, middle temporal gyrus, and PoCG in a range of neurocognitive processes, encompassing auditory, attentional, and sensory networks [40–45]. The right SPG is primarily located within the control

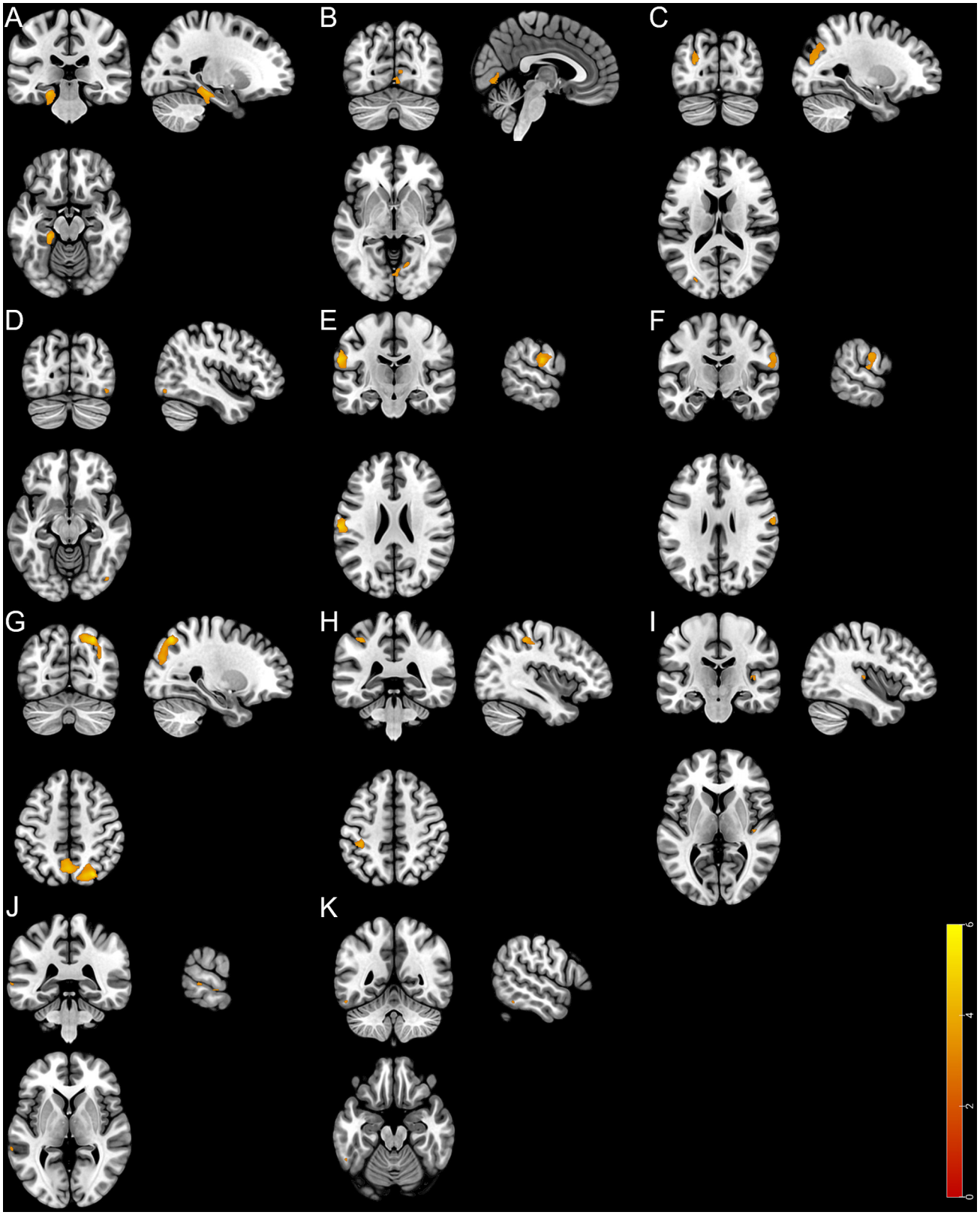

Fig. 1. Brain regions with lower gray matter volume in the INSTI group compared to the EFV group (voxel-level uncorrected $P < 0.001$). A) Left parahippocampal gyrus. B) Right lingual gyrus. C) Left middle occipital gyrus. D) Right inferior occipital gyrus. E) Left postcentral gyrus. F) Right postcentral gyrus. G) Right superior parietal gyrus. H) Left inferior parietal, but supramarginal and angular gyri. I) Right heschl gyrus. J) Left middle temporal gyrus. K) Left inferior temporal gyrus. Abbreviations: INSTI, integrase strand transfer inhibitor; EFV, efavirenz. The color bars indicate *t*-statistics (red/yellow).

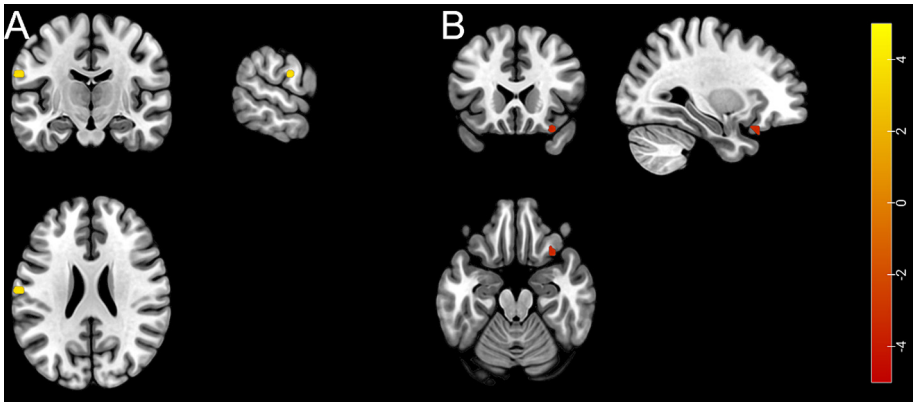

Fig. 2. Regions exhibiting different regional homogeneity (ReHo) between the INSTI group and the EFV group. Compared to the EFV group, the brain region with higher ReHo values was located at (A) left postcentral gyrus, while the brain region with lower ReHo was located at (B) right orbital part of the inferior frontal gyrus in the INSTI group (voxel-level uncorrected $P < 0.001$). Abbreviations: INSTI, integrase strand transfer inhibitor; EFV, efavirenz. The color bars indicate *t*-statistics (red/yellow).

execution network, which oversees higher cognitive functions like attention and working memory [46]. Research indicates that the right LING contributes to executive and abstract functioning [47], while abnormalities in this region have been linked to decreased cognitive function [48]. The PHG plays a crucial role in the limbic system, contributing to the regulation of motivation, memory, emotion, and the affective dimension of pain [49,50]. Furthermore, GMV in the PHG has been found to negatively correlate with symptoms of anxiety and depression [51]. Consequently, these results imply that the gray matter atrophy in the INSTI group may be related to neuropsychiatric conditions and decreased cognitive functions.

Regarding the results of the rs-fMRI analysis, the INSTI group showed a higher ReHo value in the left PoCG and a lower value in the right ORBinf compared to the EFV group. The PoCG plays a crucial role as a sensory region in the brain, responsible for integrating information from diverse somatosensory stimuli to accurately perceive objects and external signals [52]. It also receives projections related to social cooperation and emotional expression. Our investigation identified increased ReHo in the right PoCG, indicating enhanced information transmission within the broader brain network. The right ORBinf, as part of the orbitofrontal cortex within the cingulo-opercular network, contributes to decision-making, reward learning, emotional processes, and cognitive control [53,54]. Notably, a study demonstrated a negative correlation between the ReHo of the right ORBinf in the cingulo-opercular network and the severity of suicidal ideation [55]. These observed alterations in brain function may contribute to the development of neuropsychiatric conditions, as observed in our study.

We observed significant main effects of antiretroviral drugs on the alteration of GMV in the right IOG, right SPG, and left IPL in our study. Moreover, there was no interaction between antivirals and neuropsychiatric disorders in the results of the ReHo and VBM analyses. These results suggest that antiretroviral drugs have a primary impact on structural changes in the brains of PLWH, regardless of their neuropsychiatric status. In the correlation analysis between the altered MRI results and clinical variables, we observed a negative correlation between age and GMV of the right SPG in the INSTI group. It is well-documented that GMV increases during adolescence, plateaus, and then begins to decline [56,57]. Additionally, the duration of HIV diagnosis was negatively correlated with altered GMV in the right PoCG. Previous research has demonstrated that decreased GMV is correlated with longer durations of HIV infection [58]. These relationships were not observed in the EFV group, indicating differential effects of different types of antiretroviral drugs on brain volume.

In this study, we present evidence of gray matter atrophy and alterations in brain function in several regions of interest among PLWH receiving INSTI-based regimens. These changes can potentially be attributed to several factors, including the neurotoxicity associated with INSTI-based ART regimens and variations in the concentration of different ART agents in the cerebrospinal fluid. However, PLWH on EFV-based regimens exhibited worse clinical outcomes compared to those on INSTIs in various clinical manifestations. This difference could be attributed to the well-established toxicity of EFV [7]. Alternatively, it may be a result of compensatory effects from enhanced functional connections associated with INSTI-based regimens. These findings call for further investigation into the underlying mechanisms through future studies.

Previous research has identified that PLWH on INSTI-based regimens exhibited reduced GMV in the frontal lobe, brainstem, and cerebellum compared to those on non-INSTI-based regimens [16]. Notably, the specific areas of brain atrophy observed in the previous study differed from our findings, potentially due to methodological variations between the two studies. In the previous study, 40 participants (40.00 %) were on raltegravir (RAL), 29 (29.00 %) on EVG, and 30 (30.00 %) on DTG as part of their INSTI-based regimens. In contrast, our study included 44 (72.13 %) on BIC, 8 (13.12 %) on DTG, and 9 (14.75 %) on EVG as part of their INSTI-based regimens. Furthermore, while our study focused on comparing INSTI-based regimens with EFV-based regimens, the previous study examined non-INSTI-based regimens, including EFV-based and protease inhibitor-based regimens. Moreover, there were differences in demographic and clinical characteristics between the two studies. Our participants were younger, had a longer duration of HIV infection, and reported no illicit drug use, among other variations. These discrepancies in drug types and baseline characteristics may contribute to the observed differences in gray matter atrophy across different brain regions between the two studies.

Compared to previous studies, our study offers several notable advantages. Firstly, we employed multimodal MRI data analysis at the voxel level, which allowed us to investigate both brain structure and function. By utilizing multiple MRI metrics, we gained comprehensive insights into the anatomical properties of the brain, surpassing the limitations of unimodal analyses. Secondly, our study primarily focused on the newest generation of INSTIs (BIC). There is limited available data on the effects of BIC-based regimens, making our investigation particularly valuable. Thirdly, our study included a comparative analysis of subjects who did not change their drug regimen during treatment. The final results indicate that, after excluding the potential confounding effect of changing antiretroviral therapy during the treatment period, we observed the same significant differences as in the primary analysis.

This study has several limitations that should be acknowledged. Firstly, the cross-sectional design introduces inherent bias, preventing

Table 2
Main effects and interaction of antiretroviral drugs and neuropsychiatric disorders on VBM and ReHo values of brain regions with differences.

MRI metric	Group	Negative	Positive	Main effect of antiretroviral drugs			Main effect of neuropsychiatric disorders			Interaction of antiretroviral drugs and neuropsychiatric disorders		
		mean ± SD	mean ± SD	*F*	*P* value	Partial η^2	*F*	*P* value	Partial η^2	*F*	*P* value	Partial η^2
ReHo												
R inferior frontal gyrus, orbital part	INSTIs	0.90 ± 0.06	0.89 ± 0.06	0.622	0.432	0.007	0.066	0.799	0.001	1.428	0.235	0.017
	EFV	0.90 ± 0.05	0.92 ± 0.09									
L postcentral gyrus	INSTIs	0.84 ± 0.07	0.83 ± 0.04	1.622	0.206	0.019	4.820	0.031	0.054	1.191	0.278	0.014
	EFV	0.84 ± 0.05	0.80 ± 0.04									
VBM												
L parahippocampal gyrus	INSTIs	0.46 ± 0.04	0.45 ± 0.03	2.857	0.095	0.033	0.235	0.629	0.003	0.001	0.982	< 0.001
	EFV	0.47 ± 0.02	0.47 ± 0.05									
R lingual gyrus	INSTIs	0.37 ± 0.03	0.38 ± 0.03	2.690	0.105	0.031	3.583	0.062	0.041	0.068	0.794	0.001
	EFV	0.38 ± 0.03	0.40 ± 0.04									
L middle occipital gyrus	INSTIs	0.37 ± 0.05	0.37 ± 0.03	1.496	0.225	0.018	1.033	0.312	0.012	0.799	0.374	0.010
	EFV	0.37 ± 0.04	0.39 ± 0.05									
R inferior occipital gyrus	INSTIs	0.36 ± 0.04	0.36 ± 0.04	5.120	0.026	0.058	0.004	0.951	< 0.001	< 0.001	0.992	< 0.001
	EFV	0.39 ± 0.04	0.39 ± 0.05									
L postcentral gyrus	INSTIs	0.28 ± 0.03	0.28 ± 0.03	3.192	0.078	0.037	0.184	0.669	0.002	0.225	0.637	0.003
	EFV	0.29 ± 0.03	0.30 ± 0.04									
R postcentral gyrus	INSTIs	0.29 ± 0.03	0.29 ± 0.03	0.465	0.497	0.006	0.694	0.407	0.008	0.130	0.720	0.002
	EFV	0.29 ± 0.03	0.30 ± 0.03									
R superior parietal gyrus	INSTIs	0.28 ± 0.02	0.28 ± 0.02	10.386	0.002	0.111	0.316	0.575	0.004	1.657	0.202	0.020
	EFV	0.31 ± 0.03	0.30 ± 0.03									
L inferior parietal, but supramarginal and angular gyri	INSTIs	0.39 ± 0.04	0.40 ± 0.04	4.992	0.028	0.057	0.720	0.399	0.009	0.004	0.948	< 0.001
	EFV	0.41 ± 0.03	0.42 ± 0.05									
R heschl gyrus	INSTIs	0.46 ± 0.06	0.44 ± 0.05	2.368	0.128	0.028	0.070	0.793	0.001	0.979	0.325	0.012
	EFV	0.46 ± 0.06	0.47 ± 0.07									
L middle temporal gyrus	INSTIs	0.42 ± 0.04	0.43 ± 0.04	1.301	0.257	0.015	0.491	0.485	0.006	0.040	0.841	< 0.001
	EFV	0.43 ± 0.04	0.44 ± 0.05									
L inferior temporal gyrus	INSTIs	0.43 ± 0.04	0.44 ± 0.05	1.904	0.171	0.022	0.003	0.956	< 0.001	0.154	0.696	0.002
	EFV	0.45 ± 0.03	0.45 ± 0.06									

The continuous data are presented as mean ± SD. Abbreviations: SD, standard deviation; MRI, magnetic resonance imaging; INSTIs, integrase strand transfer inhibitors; EFV, efavirenz; VBM, voxel-based morphometry; ReHo, regional homogeneity; L, left; R, right.

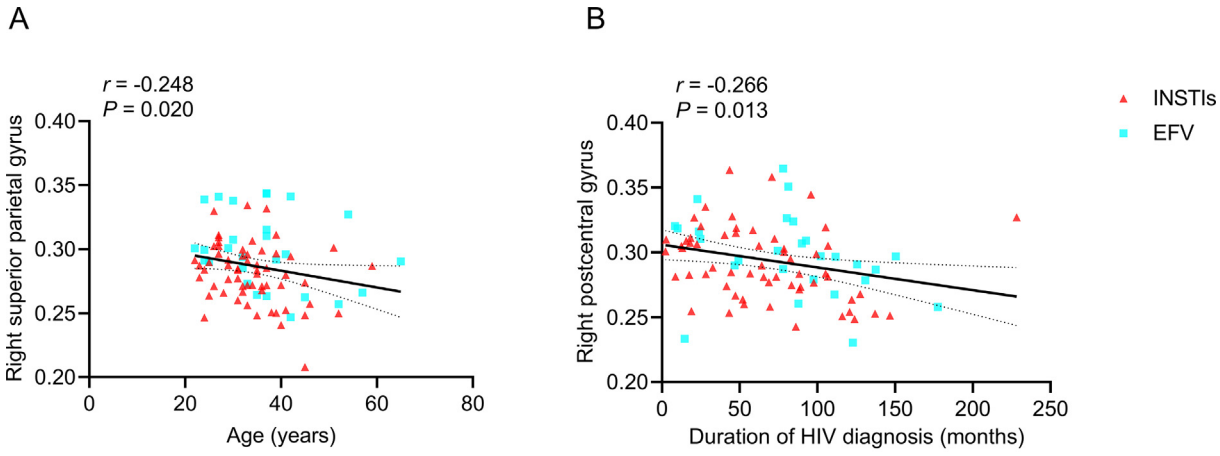

Fig. 3. The results of the correlation analysis between basic information, clinical data, and imaging results. The areas between two dotted curves represent the 95 % confidence interval. A) Across all participants, the gray matter volume of the right superior parietal gyrus was negatively correlated with age ($r = -0.248$, $P = 0.020$). In the INSTI group, the correlation was ($r = -0.282$, $P = 0.029$); and in the EFV group, the correlation was ($r = -0.273$, $P = 0.169$). B) Across all participants, the gray matter volume in the right postcentral gyrus was negatively correlated with the duration of HIV diagnosis ($r = -0.266$, $P = 0.013$). In the INSTI group, the correlation was ($r = -0.259$, $P = 0.046$); and in the EFV group, the correlation was ($r = -0.343$, $P = 0.080$). Abbreviations: INSTIs, integrase strand transfer inhibitors; EFV, efavirenz; HIV, human immunodeficiency virus.

the tracking of brain functional and structural changes during disease progression. Secondly, our study included only MSM participants, limiting the generalizability of our findings to other populations. Thirdly, the use of a 1.5 T MRI scanner for image acquisition may result in reduced sensitivity for detecting abnormalities in the brain. Furthermore, our analysis of gray matter focused solely on changes in GMV, whereas other investigations often incorporate a broader range of analytical tools and techniques. For instance, previous research has suggested that measures such as fractal dimensionality may serve as more sensitive markers of neuronal impairment compared to volumetric and cortical thickness measures, as stronger correlations with cognition have been observed [59]. Future research should aim to

incorporate a wider array of multidimensional MRI data and utilize widely adopted analytical tools such as Freesurfer, functional MRI of the brain (FMRIB) software library-FMRIB's automated segmentation tool, and advanced normalization tools. This comprehensive approach will contribute to a more thorough characterization of the brain structure and function of PLWH.

In conclusion, this study provides evidence that PLWH using INSTI-based regimens exhibit decreased GMV in multiple brain regions compared to those using EFV-based regimens. Additionally, differences in ReHo and FC were observed between the two groups in rs-fMRI. Further examination revealed that changes in GMV were primarily influenced by factors related to drug administration. Ultimately, our findings contribute to a deeper understanding of the underlying mechanisms by which INSTIs impact brain structure and function.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Boards of Beijing Youan Hospital, Capital Medical University (No. LL-2023-067-K). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and / or national research committee and with the revised version of the Helsinki Declaration from 2013. Written informed consent was obtained from all participants prior to their participation in this study.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Supplementary data

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