Clinical Infectious Diseases

RESEARCH ARTICLE

Impact of HIV and recreational drugs on cognitive functions

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***Objectives*:** This study characterizes the structural and metabolic cerebral correlates of cognitive impairments found in a preclinical setting that considers the lifestyle of young European men exposed to Human Immunodeficiency Virus (HIV), including recreational drugs.

***Design*:** Prospective inclusion of participants.

Methods: Simultaneous structural brain magnetic resonance imaging (MRI) and positron emission tomography using [18F]-fluorodeoxyglucose (FDG-PET) were acquired on a hybrid PET-MRI system in 23 asymptomatic young men having sex with men living with HIV (HIVMSN, mean age: 33.6 years, age range: 23-60 years; normal CD4+ cell count, undetectable viral load). Neuroimaging data were compared with that of 26 young seronegative men under HIV pre-exposure prophylaxis (PrEPMSN), highly well matched for age, lifestyle, and to 23 matched young seronegative men considered as "controls" (CTRL). A comprehensive neuropsychological assessment was also administered to the HIVMSN and PrEPMSN participants.

***Results*:** HIVMSN had lower performances in executive, attentional and working memory functions compared to PrEPMSN. No structural or metabolic differences were found between those two groups. Compared to CTRL, HIVMSN and PrEPMSN exhibited a common frontal hypometabolism in the right prefrontal cortex that correlated with the level of recreational drug use. No structural brain abnormality was found.

Conclusion: Abnormalities of brain metabolism in our population of young HIVMSM mainly relate to recreational drug use rather than HIV *per se*. A complex interplay between recreational drugs and HIV might nevertheless be involved in the cognitive impairments observed in this population.

Key Words: HIV-associated neurocognitive disorders, pre-exposure prophylaxis, recreative drugs, executive functions, neuroimaging.

INTRODUCTION

The combined antiretroviral therapy (cART) dramatically reduced the incidence of dementia in people living with human immunodeficiency virus (PLWH). Still, milder forms of cognitive impairments (CI) are described in 20-60% of PLWH (1). They are characterized by impairments in attention, memory and executive functions (2), and predict employment status, risky sexual behavior, and cART adherence (3).

Neuroimaging has been used to characterize the pathophysiology of CI in PLWH. Structural magnetic resonance imaging (MRI) revealed signs of cortico-subcortical atrophy (4-6). Positron emission tomography (PET) studies using [^{18}F]-fluorodeoxyglucose (FDG-PET) revealed reductions in mesial frontal/anterior cingulate cortex (ACC) (7, 8) or thalamic (9) glucose

metabolism in asymptomatic PLWH. CI in PLWH thus seems mainly associated with a dysfunction of the frontal lobe and its cortico-subcortical circuits. Such abnormalities may also be found in the context of recreational drugs use (RDU, (10)), which is highly prevalent in a subset of PLWH using chemical sex (11), i.e., men having sex with men (MSM). RDU consumption therefore represents a major confound in studies addressing CI pathophysiology in PLWH, which is frequently related to other co-morbid or lifestyle factors than to a direct effect of HIV (10). The prevalence of HIV-associated neurocognitive disorders (HAND, i.e., CI due to HIV *per se*) among PLWH appears indeed overestimated (1).

This study aims at providing novel insights into CI pathophysiology in MSM living with HIV (HIVMSM) by combining clinical, neuropsychological, and lifestyle evaluations with hybrid PET and MRI (PET-MR) investigations in highly selected and matched populations of young men living or not with HIV. To disentangle the effects of HIV, cART and lifestyle (i.e., RDU) on cognitive, structural and metabolic brain changes, we first compared data of HIVMSM with those MSM under HIV pre-exposure prophylaxis (PrEPMSN) sharing similar lifestyle. PrEP is a HIV prevention approach (12) relying on cART (tenofovir disoproxil (TDF), emtricitabine (FTC)). We then compared data of HIVMSM and PrEPMSN with those of seronegative men considered as *"controls*" (CTRL) to highlight commonalities in cognitive/brain abnormalities between HIVMSM and PrEPMSN.

MATERIAL AND METHODS

Methodological details can be found in Supplemental Digital Content (SDC). Only essential information is provided hereunder.

Participants

From December 2017 to June 2020, 25 western European, and native French-speaking HIVMSM (mean age: 38.8 years, age range: 18-60 years, >9 years of education) not declaring any CI, were prospectively included. The exact duration of HIV infection was available for all of them. All HIVMSM were taking cART with undetectable viral load for at least 6 months before inclusion and had a CD4+ cell count greater than 500/mm3. Those with a coinfection with hepatitis C, untreated syphilis, psychiatric disease, efavirenz based regimen (cART with brain side effects), or any history of brain disorder were excluded.

A total of 51 men matched for age with HIVMSM were also included. They satisfied to the same age, education and ethnicity criteria. Twenty-six were selected from the PrEP outpatient clinic. Fourteen PrEPMSN were taking TDF/FTC daily (30 pills/month), while 11 were taking it on demand before having a risky sexual intercourse (mean number of 15 pills/month) (12). The other 25 seronegative men were used as CTRL based on their clinical background, heterosexual orientation, absence of RDU, and normal cognitive functioning.

Participants contributed to the study approved by the institutional Ethics Committee after written informed consent (References: P2017/541).

Clinical and neuropsychological assessment

Participants underwent an exhaustive anamnesis to collect their medical and psychiatric background. HIVMSM and PrEPMSN also underwent a comprehensive neuropsychological assessment investigating working memory, long-term episodic memory (on both verbal and visual material), gestural and visuo-constructive praxis, language (verbal fluencies and picture naming), attentional and executive functions. Questionnaires were used to assess depression, anxiety, previous night of sleep and cognitive functioning in daily living. CTRL's broad cognitive functions were assessed with the Montreal cognitive assessment (MoCA) (13). RDU was evaluated in participants through a semi-directed interview inspired by "the interview for research on addictive behavior" (14) that evaluated the frequency, the chronicity and the active/past character of the consumption of a series of drugs commonly used by MSM in the context of chemical sex (15) (SDC table 1). An operational composite score (*RDU score*) was computed and incorporated the current and past exposition to recreational drugs. RDU the day before the testing was asked to each participant (5 HIVMSM used cannabis the day before the testing, no participant reported to use recreative drugs on the testing day), but no urine drug screening was performed. Furthermore, to assess the potential toxicity of TDF/FTC on MSM brain structure and function, an index was computed based on the duration of use (Supplemental data)

Analyses of neuropsychological data

To classify participants according to HAND criteria (often referred to as the Frascati criteria (1)), HIVMSM and PrEPMSM individual performance in the different tasks was expressed as z-scores calculated by comparison with matched (age, sex, educational level) normative data issued from the literature. The z-scores for each task were computed by subtracting the mean score of the normative data from a participant raw score, and then dividing the difference by the standard deviation of the normative data. For between-group comparison, we computed composite and index scores to quantify cognitive processes and reduce the number of data and variables. Scores of HIVMSM and PrEPMSM were compared using Student's *t*-tests. Multiple comparisons were controlled using the Bonferroni correction. Relationships between cognitive scores and indexes, and TDF/FTC index or RDU score were assessed using Pearson's correlations.

PET-MR data acquisition

Cerebral FDG-PET and structural MRI data were obtained simultaneously using a 3T hybrid PET-MR scanner (SIGNA^{TM}, GE Healthcare).

MRI data preprocessing and analyses

Qualitative analyses

MRI data were reviewed by one experienced neuroradiologist (T.C.) following a systematic and comprehensive visual assessment procedure searching for signs of primary cerebral angiitis, chronic cerebral small vessel disease and other parenchymal abnormalities, including extra-axial masses.

Quantitative analyses

The Freesurfer 6 image analysis suite (http://surfer.nmr.mgh.harvard.edu/) was first used to obtain cortical volume and thickness using conventional surface-based approach (16-18) as well as to extract brain regions of interest (ROIs) based on anatomical brain parcellation (19, 20).

Student t-tests were used to search for differences in (i) maps of whole brain cortical volume and thickness and (ii) ROIs averaged volume (for cortical and subcortical ROIs) and thickness (for cortical ROIs only). These differences were tested between HIVMSM (taken individually or as a group) compared PrEPMSM taken as a group, and in HIVMSM and PrEPMSM (taken as separate or one group(s)) with that of CTRL. For whole brain surface-based analyses, statistical maps were corrected for multiple comparisons using the False Discovery Rate (FDR) as implemented in Freesurfer 6, with the significance level set to $p<0.05$. For ROIs analyses, significance was considered at $p<0.05$ Bonferroni-corrected for the number of ROIs.

PET data preprocessing and analyses

FDG-PET data were preprocessed and analyzed using the voxel-based Statistical Parametric Mapping software (SPM8, http://www. fil.ion.ucl.ac.uk/spm/, Wellcome Trust Centre for Neuroimaging, London, UK) based on conventional preprocessing, (individual and group level) subtractive and correlation analyses previously described (21-24).

Subtractive analyses identified brain areas where glucose metabolism was significantly lower or higher in HIVMSM (taken individually or as a group) compared with PrEPMSM taken as one group. Additional subtractive group-level analyses compared HIVMSM and PrEPMSM (taken as separate or one group(s)) with that of CTRL. To search for a pathophysiological link between significant hypo- and hypermetabolic brain areas found in HIVMSM and PrEPMSM compared with CTRL, we also performed pathophysiological interaction (*PPI*) analyses as previously described (25, 27). We performed separate correlations between the regional cerebral glucose metabolism of HIVMSM and PrEPMSM taken as one group and RDU score, TDF/FTC index, and neuropsychological data.

Results were considered significant at $p < .05$ corrected for multiple comparisons over the entire brain volume (Family Wise Error (FWE)) or at a more liberal threshold ($p < .001$ uncorrected, height threshold: 0.001, cluster size $k \geq 50$ voxels; or small-volume-corrected $P<0.05$ using a 10-mm radius spherical volume of interest).

RESULTS

Clinical characteristics

Table 1 describes the clinical characteristics of each participants' group.

Details on RDU can be found in SDC.

No significant difference was found between HIVMSM and PrEPMSM in age, levels of anxiety/depression/quality of sleep, RDU score, and mean number of abnormal neuropsychological fields. Based on HAND criteria, 21 HIVMSM out of 23 were classified as having asymptomatic neurocognitive impairment (ANI) as they did not report any cognitive complaints but were impaired in 2 or more cognitive domains (>1.0 standard deviation (SD) below the mean in a demographically appropriate normative mean). Using those criteria, ANI was also observed in 23/25 PrEPMSM. At the group level, performance was significantly lower in HIVMSM compared with PrEPMSM in executive functions (inhibition, p_{corr}=0.038; combined EF, p_{corr}=0.011; planification, p_{corr}=0.031), attentional functions (vigilance, p_{corr}=0.01; divided attention, p_{FWE}=0.019) and working memory (WM updating, p_{corr}=0.009), see Fig. 1. No correlation was found between RDU score and neuropsychological performance.

Structural MRI analyses

Qualitative analysis

Two HIVMSM, 1 PrEPMSM and 2 CTRL were excluded from further analyses due to incidental brain pathology or incomplete PET-MR acquisition. The final sample was therefore composed of 23 HIVMSM, 25 PrEPMSM and 23 CTRL.

Quantitative analysis

No difference (whole brain and ROI analyses) was found at individual or group levels, either with cortical volume/surface maps between HIVMSM and PrEPMSM, or between HIVMSM/PrEPMSM taken as one group and CTRL.

Regional cerebral glucose abnormalities

Figures 1-2 and Supplementary Tables 2-3 describe group-level brain metabolism abnormalities.

No group-level difference in regional cerebral glucose metabolism was found between HIVMSM and PrEPMSM (even at $p_{uncorrected}$<0.001). When HIVMSM and PrEPMSM were pooled in one group and compared with CTRL, significant (p_{FWE}<0.05) hypometabolism was found in the lateral and mesial (right > left) prefrontal cortex (T values ranged from 5.63 to 4.86) as well as significant (p_{FWE}<0.05) hypermetabolism in posterior midline cortices bilaterally (precuneus and posterior cingulate cortex (PCC)(T values ranged from 5.18 to 4.37). Similar prefrontral hypometabolism was found when comparing the brain metabolism of HIVMSM or PrEPMSM

with that of CTRL. When considering the peak voxel value in the hypometabolic right dorso-lateral prefrontal (DLPFC, MNI coordinates: [60, 14, 28]) and dorso-mesial prefrontal (DMPFC, [16, 64, 4]) cortices found in the pooled groups of HIVMSM and PrEPMSM, no significant (event at $p_{uncorrected}<0.001$) correlation was found between the level of metabolism in those brain regions and the rest of the brain, suggesting that prefrontal hypometabolism and posterior midline hypermetabolism were unrelated.

Correlation analyses were then performed between regional cerebral glucose metabolism and RDU score or TDF/FTC index in HIVMSM/PrEPMSM taken as one group. These analyses revealed a significant (p_{FWE} <0.05) negative correlation between RDU score and the level of metabolism in a right prefrontal cluster (right DLPFC, [60, 14, 28], $p_{FWE}<0.01$, r=-0.51; right DMPFC, [16, 64, 4], $p_{FWE}<0.01$, r=-0.52), Figure 3). No significant correlation was found between TDF/FTC index and prefrontal cortex metabolism. Finally, we did not find any significant correlation between regional cerebral glucose metabolism and the score of neuropsychological tests that significantly differed between HIVMSM or PrEPMSM.

Figure 4 illustrates the significant hypometabolism observed at the individual level in 6 HIVMSM compared with the group of PrEPMSM in the DLPFC or DMPFC (2 at $p_{FWE}<0.05$, voxel level; 2 $p_{FWE}<0.05$, cluster level; 2 at $p_{uncorrected}<0.001$).

DISCUSSION

Based on HAND criteria, a high proportion (90%) of ANI was observed in HIVMSM. Using those criteria, ANI was also observed in 92% of MPrEP. Compared to PrEPMSM, HIVMSM also had significant group-level alterations in executive, attentional and working memory functions in the absence of any group-level significant difference in brain structure and metabolism. Still, when each HIVMSM was compared with the group of PrEPMSM, 25% of them showed significant hypometabolism in prefrontal regions. Critically, when compared to CTRL, HIVMSM and PrEPMSM displayed a significant prefrontal hypometabolism that correlated with their RDU but not with cognitive functioning.

Neuropsychological assessment

Based on HAND criteria, the prevalence of ANI (i.e., >1.0 to <2.0 SD below mean of a matched normative population in two or more domains but no decrease in everyday functioning) in our group of HIVMSM appeared especially high compared to the 20-60% reported in PLWH (1). Surprisingly, the incidence of ANI was similar in PrEPMSM when using those criteria. Thus, current HAND criteria do not optimally distinguish HIVMSM with ANI from seronegative MSM with similar life and health habits. They result in a high frequency of false-positive diagnosis due to the use of 1.0 SD deviation below mean, leading to an overestimation of CI prevalence (1). As previously suggested (1), our data further ask to revisit HAND criteria. The

use of 2.0 SD below means of a matched normative population, as classically used in clinical neuropsychology, would be more appropriate to identify PLWH with CI. Still, group-level analyses disclosed that HIVMSM had significantly lower performances in executive, working memory and attentional functions compared with PrEPMSM, which confirmed the dysexecutive/inattentive profile of PLWH previously reported (2).

PET/MR results

Group-level analyses did not reveal any difference in regional brain structure or glucose metabolism between HIVMSM and PrEPMSM. This finding questions the pathophysiological role of HIV in the prefrontal hypometabolism found in HIVMSM when compared with CTRL. Still, individual-level analyses showed that 25% of HIVMSM exhibited lateral or mesial prefrontal hypometabolism when compared with PrEPMSM. These changes at the individual-level were in line with the localization of the relative hypometabolism previously described in PLWH (7-10). The prefrontal hypometabolism found in some HIVMSM might potentially relate to the abnormalities noted in executive functions, although prefrontal metabolism did not significantly correlate with cognitive scores. Alternatively (but not exclusively), this hypometabolism, especially in the ACC, might also play a causative role in the adoption of high-risk behaviors in a drug and sexually transmitted disease setting. Indeed, this brain area plays a pivotal role in decision making and risks/benefits balancing when emotional drive and objective reasoning come into conflict (25, 26). Under this hypothesis, that warrants further investigations, prefrontal hypometabolism might be the cause rather than the consequence of our participants' high-risk behaviors, with more blurred relationship with their CI.

The absence of group-level metabolic difference between HIVMSM and PrEPMSM suggests that their common brain hypometabolic abnormalities in comparison to CTRL might be driven by another cause than HIV. Correlation analyses pointed to the well-known vulnerability of the prefrontal areas to the effects of RDU (10, 27). In the absence of noticeable structural brain changes, hypometabolism was probably related to neural dysfunction rather than neuronal loss *per se*. RDU-induced neural dysfunction might be related to dopamine dysregulation, neuroinflammation or neurodegeneration through the accumulation of intraneuronal hyperphosphorylated TAU protein (pTAU) (28-30). In HIVMSM, RDU might exert their neural toxicity synergistically with HIV-related neuroinflammation, neurodegeneration or the reactivation of deep latency virus (29, 31). A complex interplay between RDU and HIV might thus be involved in the induction and development of the prefrontal hypometabolism and dysexecutive/inattentive profile found in our HIVMSM. Still, results obtained in PrEPMSM suggest that RDU might play a predominant pathophysiological role compared with HIV. The absence of correlation between regional brain metabolism and cognitive alterations observed in our participants might be explained by the inability of FDG to explore neuroinflammation or cerebral pTAU deposition. Other radioligands targeting neuroinflammation or pTAU proteins could thus be used and might better correlate with cognitive dysfunctions (32).

Hypermetabolism in posterior midline cortices (precuneus and PCC) belonging to the default mode network (DMN, (33)) were also found at the group level in HIVMSM and PrEPMSM compared to CTRL. Correlation analyses failed to find any relationship between the level of prefrontal hypometabolism and posterior midline cortices hypermetabolism. The posterior midline cortices hypermetabolism, which did not correlate with RDU score, could be related to attention/dysexecutive alterations (34).

Structural results

At the preclinical stage of HAND, noticeable brain atrophy is not expected. Still, our data are in relative contradiction with the literature, which supports that, even at the preclinical stage, atrophy is detectable in caudate nuclei and prefrontal cortex of patients with HAND. This discrepancy may be related to the high heterogeneity of PLWH included in previous studies, especially regarding the mix of age, comorbidities, viral loads and cognitive symptoms (13). Indeed, the impact of comorbidities in the development of CI in PLWH has already been shown (1, 35). Further studies investigating HAND pathophysiology should therefore concentrate on more homogeneous populations of PLWH in terms of age, sex, lifestyle and comorbidities, as done in the present study with our group HIVMSM.

Clinical implications

Our findings strongly support the effect of lifestyle in HIVMSM population and the importance of better screening/control strategies of RDU to limit the occurrence of CI. Development and use of an international RDU score, such as the multi-morbidity index (CCI) (36), might be of great clinical help to assess who is at higher risk of CI in PLWH. Our data also reinforces the need for future studies investigating HAND pathophysiology to include well selected HIV populations (exclusion of comorbidities and RDU) and proper control populations to address virus-driven pathogenesis in the CI observed in PLWH. Our study also describes the brain metabolic abnormalities in PrEPMSM, highlighting their vulnerability for the development of CI associated with RDU.

Limitations

The limited number of participants included in this study, due to the strict inclusion criteria, may have impacted the statistical power of group-level subtractive and correlation FDG-PET analyses. The very homogeneous profile of our population is our main asset, but it inherently results in a limitation, i.e., our results might be inapplicable in another settings (e.g., African older comorbid women) since only Caucasian young men were investigated.

The RDU score used in this study was a coarse measure of ongoing and past RDU that was not validated. Still, this score was sufficient to evaluate the effects of RDU on brain metabolism.

CONCLUSION

This study disclosed a dysexecutive/inattentive profile and prefrontal hypometabolism in HIVMSM in the absence of noticeable brain atrophy. Prefrontal hypometabolism was similar to that observed in PrEPMSM and was related to RDU. A dynamic prevention of RDU in those populations is therefore warranted to cope with their negative impact on brain function and cognition. A complex interplay between recreational drugs and HIV might be involved in the development of CI in HIVMSM.

Notes

Author contributions:

Name	Location	Contribution
Sophie Henrard, MD	Department of Internal Medicine, HIV Reference Center, HUB Erasme, Université libre de Bruxelles (ULB), Brussels, Belgium	Study concept and design; data acquisition and analysis; interpretation of data; full access to all of the data in the study; responsible for the integrity of the data and the accuracy of the data analysis; drafting the manuscript; critical revision of the manuscript for important intellectual content. First authorship. Obtained funding.
Nicola Trotta, PhD	Laboratoire de Cartographie fonctionnelle du Cerveau, UNI — ULB Neuroscience Institute, Université libre de Bruxelles (ULB), Brussels, Belgium; Department of Nuclear Medicine, CUB Hôpital Erasme,	Analysis and interpretation of data; critical revision of the manuscript for important intellectual content
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Tim Coolen, MD	Department of Radiology, CUB Hôpital Erasme, Université libre de Bruxelles (ULB), Brussels, Belgium; Laboratoire de Cartographie fonctionnelle du Cerveau, UNI — ULB Neuroscience Institute, Université libre de Bruxelles (ULB), Brussels, Belgium	Interpretation of data; critical revision of the manuscript for important intellectual content
Hichem Slama, PhD	Head of neuropsychology department and speech, HUB	Cognitive data acquisition. Analysis and interpretation of data; critical

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Jean-Paul Van Vooren, MD, PhD	Department of Internal Medicine, HIV Reference Center, HUB Erasme, Université libre de Bruxelles (ULB), Brussels, Belgium	Critical revision of the manuscript for important intellectual content.
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Data availability statement Anonymized neuropsychological and neuroimaging data can be obtained upon reasonable request to the corresponding author and after approval of institutional (Hôpital Universitaire de Bruxelles and Université libre de Bruxelles) authorities.

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References

1. Nightingale S, Dreyer AJ, Saylor D, Gisslen M, Winston A, Joska JA. Moving on From HAND: Why We Need New Criteria for Cognitive Impairment in Persons Living With Human Immunodeficiency Virus and a Proposed Way Forward. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021;73(6):1113-8.
2. Walker KA, Brown GG. HIV-associated executive dysfunction in the era of modern antiretroviral therapy: A systematic review and meta-analysis. Journal of clinical and experimental neuropsychology. 2018;40(4):357-76.
3. Thames AD, Streiff V, Patel SM, Panos SE, Castellon SA, Hinkin CH. The role of HIV infection, cognition, and depression in risky decision-making. J Neuropsychiatry Clin Neurosci. 2012;24(3):340-8.
4. Ances BM, Hammoud DA. Neuroimaging of HIV-associated neurocognitive disorders (HAND). Curr Opin HIV AIDS. 2014;9(6):545-51.
5. Sui J, Li X, Bell RP, Towe SL, Gadde S, Chen NK, et al. Structural and Functional Brain Abnormalities in Human Immunodeficiency Virus Disease Revealed by Multimodal Magnetic Resonance Imaging Fusion: Association With Cognitive Function. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021;73(7):e2287-e93.
6. Underwood J, Cole JH, Caan M, De Francesco D, Leech R, van Zoest RA, et al. Gray and White Matter Abnormalities in Treated Human Immunodeficiency Virus Disease and Their Relationship to Cognitive Function. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;65(3):422-32.
7. Andersen AB, Law I, Krabbe KS, Bruunsgaard H, Ostrowski SR, Ullum H, et al. Cerebral FDG-PET scanning abnormalities in optimally treated HIV patients. J Neuroinflammation. 2010;7:13.
8. Towgood KJ, Pitkanen M, Kulasegaram R, Fradera A, Soni S, Sibtain N, et al. Regional cerebral blood flow and FDG uptake in asymptomatic HIV-1 men. Hum Brain Mapp. 2013;34(10):2484-93.
9. Hammoud DA, Sinharay S, Steinbach S, Wakim PG, Geannopoulos K, Traino K, et al. Global and regional brain hypometabolism on FDG-PET in treated HIV-infected individuals. Neurology. 2018;91(17):e1591-e601.
10. Georgiou MF, Gonenc A, Waldrop-Valverde D, Kuker RA, Ezuddin SH, Sfakianakis GN, et al. Analysis of the effects of injecting drug use and HIV-1 infection on 18F-FDG PET brain metabolism. J Nucl Med. 2008;49(12):1999-2005.

11. Daskalopoulou M, Rodger A, Phillips AN, Sherr L, Speakman A, Collins S, et al. Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: results from the cross-sectional ASTRA study. Lancet HIV. 2014;1(1):e22-31.
12. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med. 2015;373(23):2237-46.
13. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9.
14. Verdejo-Garcia AJ, Lopez-Torrecillas F, Aguilar de Arcos F, Perez-Garcia M. Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. Addict Behav. 2005;30(1):89-101.
15. Mor Z, Turner D, Livnat Y, Levy I. Recreational drug and excessive alcohol use among HIV-infected men who have sex with men in Central Israel. BMC Public Health. 2019;19(1):1360.
16. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. NeuroImage. 1999;9(2):179-94.
17. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. NeuroImage. 1999;9(2):195-207.
18. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A. 2000;97(20):11050-5.
19. Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, et al. Automatically parcellating the human cerebral cortex. Cerebral cortex (New York, NY : 1991). 2004;14(1):11-22.
20. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage. 2006;31(3):968-80.
21. De Tiege X, Goldman S, Laureys S, Verheulpen D, Chiron C, Wetzburger C, et al. Regional cerebral glucose metabolism in epilepsies with continuous spikes and waves during sleep. Neurology. 2004;63(5):853-7.
22. Trotta N, Archambaud F, Goldman S, Baete K, Van Laere K, Wens V, et al. Functional integration changes in regional brain glucose metabolism from childhood to adulthood. Hum Brain Mapp. 2016;37(8):3017-30.
23. De Tiege X, Ligot N, Goldman S, Poznanski N, de Saint Martin A, Van Bogaert P. Metabolic evidence for remote inhibition in epilepsies with continuous spike-waves during sleep. NeuroImage. 2008;40(2):802-10.
24. Niesen M, Trotta N, Noel A, Coolen T, Fayad G, Leurkin-Sterk G, et al. Structural and metabolic brain abnormalities in COVID-19 patients with sudden loss of smell. Eur J Nucl Med Mol Imaging. 2021;48(6):1890-901.
25. Fukunaga R, Purcell JR, Brown JW. Discriminating Formal Representations of Risk in Anterior Cingulate Cortex and Inferior Frontal Gyrus. Front Neurosci. 2018;12:553.
26. Connolly CG, Bischoff-Grethe A, Jordan SJ, Woods SP, Ellis RJ, Paulus MP, et al. Altered functional response to risky choice in HIV infection. PLoS One. 2014;9(10):e111583.
27. Moreno-Lopez L, Stamatakis EA, Fernandez-Serrano MJ, Gomez-Rio M, Rodriguez-Fernandez A, Perez-Garcia M, et al. Neural correlates of the severity of cocaine, heroin, alcohol, MDMA and cannabis use in polysubstance abusers: a resting-PET brain metabolism study. PLoS One. 2012;7(6):e39830.

28. Shin EJ, Dang DK, Tran TV, Tran HQ, Jeong JH, Nah SY, et al. Current understanding of methamphetamine-associated dopaminergic neurodegeneration and psychotoxic behaviors. Arch Pharm Res. 2017;40(4):403-28.
29. Chilunda V, Calderon TM, Martinez-Aguado P, Berman JW. The impact of substance abuse on HIV-mediated neuropathogenesis in the current ART era. Brain Res. 2019;1724:146426.
30. Ramage SN, Anthony IC, Carnie FW, Busuttil A, Robertson R, Bell JE. Hyperphosphorylated tau and amyloid precursor protein deposition is increased in the brains of young drug abusers. Neuropathol Appl Neurobiol. 2005;31(4):439-48.
31. Ohene-Nyako M, Persons AL, Napier TC. Region-specific changes in markers of neuroplasticity revealed in HIV-1 transgenic rats by low-dose methamphetamine. Brain Struct Funct. 2018;223(7):3503-13.
32. Sinharay S, Hammoud DA. Brain PET Imaging: Value for Understanding the Pathophysiology of HIV-associated Neurocognitive Disorder (HAND). Current HIV/AIDS reports. 2019;16(1):66-75.
33. Raichle ME. The brain's default mode network. Annu Rev Neurosci. 2015;38:433-47.
34. Bozhilova NS, Michelini G, Kuntsi J, Asherson P. Mind wandering perspective on attention-deficit/hyperactivity disorder. Neurosci Biobehav Rev. 2018;92:464-76.
35. Ellis RJ, Paolillo E, Saloner R, Heaton RK. Higher comorbidity burden predicts worsening neurocognitive trajectories in people with HIV. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021.
36. Alemi F, Levy CR, Kheirbek RE. The Multimorbidity Index: A Tool for Assessing the Prognosis of Patients from Their History of Illness. EGEMS (Wash DC). 2016;4(1):1235.

Table 1. Demographic and neuropsychological data

	HIVMSM (n=23)	PrEPMSM (n=25)	Controls (CTRL) (n=23)	p value
Age (years)	38 +/- 9.5	39 +/- 9.08	34 +/- 10.03	HIV+/HC: p=0.17 HIV+/PrEP; p=0.75 PrEP/HC; p=0.08
Duration of HIV infection (months)	58 +/- 46.74	/	/	/
CD4+ (cell count /mm3)	834 +/- 294.83	/	/	/
Timespan with CV>40 (rna copy/ml)	31.11 +/- 41.69	/	/	/
Recreative drug use (RDU) score	4.21 +/- 3.26	4.78 +/- 3.51	0.54 +/- 0.59	HIV+/HC: p<0.001 HIV+/PrEP; p=0.58 PrEP/HC; p<0.001
TDF/FTC index (nb of pills)	45.30 +/- 45,94	11.40 +/- 10.12	/	P<0.001
Cognitive evaluation				
Nb of altered cognitive field	1.70 +/- 1.02	1.44 +/- 0.87	/	p_{corr} =0.26
HAND status				
ANI	21	23	0	/
MND	0	0	0	/
HAD	0	0	0	/
MoCA	/	/	28 +/- 1.27	/
SRT	12.177 +/- 1.261	12.360 +/- 0.9	/	p_{corr}=0.559
Doors test	18.565 +/- 2.446	19.654 +/- 2.465	/	p_{corr} =0.128
Stroop test: Color IES	60.384 +/- 10.931	66.283 +/- 54.085	/	p_{corr} =0.480
Stroop test: Word IES	43.083 +/- 5.816	46.273 +/- 33.824	/	p_{corr} =0.613
Stroop test: Interference IES	41.660 +/- 23.852	20.912 +/- 61.350	/	**p_{corr} =0.038**
Stroop test: Flexibility IES	137.430 +/- 36.52	115.120 +/- 20.975	/	**p_{corr} =0.011**
TOL 2 IES	75.035 +/- 97.387	31.285 +/- 23.604	/	**p_{corr} =0.031**
TAP : AL_CV	0.163 +/- 0.054	0.127+/- 0.036	/	**p_{corr} =0.01**

TAP : DS3 IES	681.027 +/- 104.747	617.877 +/- 71.356	/	**p_{corr} =0.019**
TAP : WM ME3 IES	727.953 +/- 172.512	641.621 +/- 146.963	/	**p_{corr} =0.009**
cART				
Abacavir+lamivudine+dolutegravir	n=4	/	/	/
Rilpivirine+emtrictabine+tenofovir (TAF)	n=9	/	/	/
Bictegravir+emtricitabine+tenofovir (TAF)	n=4	/	/	/
Elvitegravir+cobicistat+emtricitabine+ tenofovir (TAF)	n=3	/	/	/

Figure legends

Figure 1 Subtractive analyses comparing FDG-PET data of HIVMSM and PrEPMSM taken as a group with those of CTRL. Images were thresholded at p<0.001 uncorrected for visualisation purpose. Significant relative hypometabolic areas were observed in dorso-lateral prefrontal cortex bilaterally, the right dorso-medial prefrontal cortex, as well as in the left prefrontal and insular cortices.

Fig 1

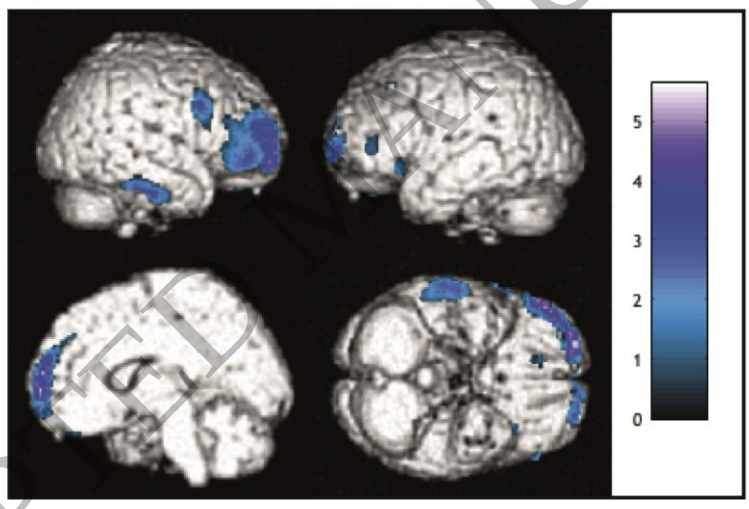


Figure 2 Subtractive analyses comparing FDG-PET data of HIVMSM and PrEPMSM users taken as a group with those of CTRL. Images were thresholded at p<0.001 uncorrected for visualization purpose. Significant relative hypermetabolic areas were observed in the precuneus and cuneus bilaterally, the right primary somatosensory and posterior cingulate cortices, as well as the left superior temporal gyrus.

Fig 2

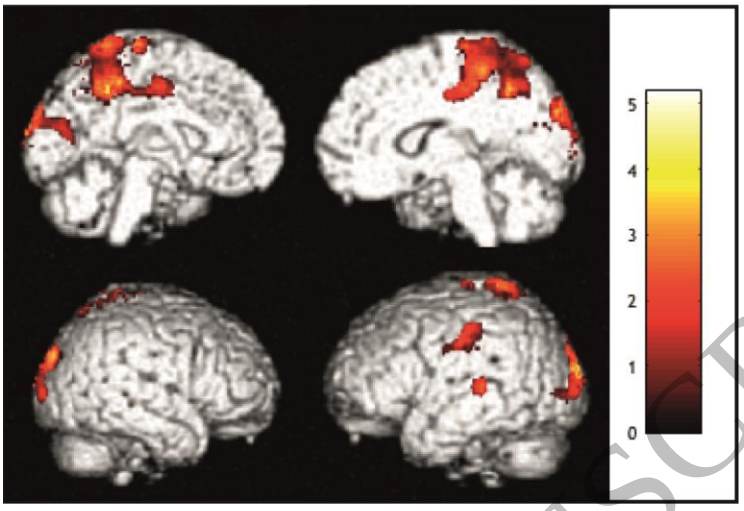


Figure 3 Results of the correlations analyses performed between the PET data of the PrEPMSM and HIVMSM and the recreational drug scores (RDU score). Regression plots of RDU scores and adjusted metabolic responses were obtained by considering the peak voxel in (A) the right dorso-lateral prefrontal cortex [60, 14, 28] (Pearson's correlation: $r = -0.48$ $p < 0.001$) and (B) the right dorso-medial prefrontal cortex [16, 64, 4] (Pearson's correlation: $r = -0.54$, $p < 0.001$). These plots showed significant positive correlation between RDU scores and cerebral glucose metabolism in the considered voxels.

Fig 3

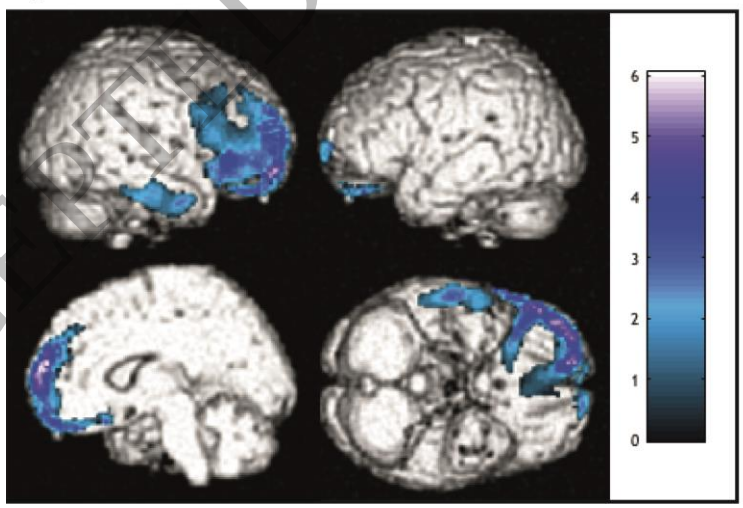
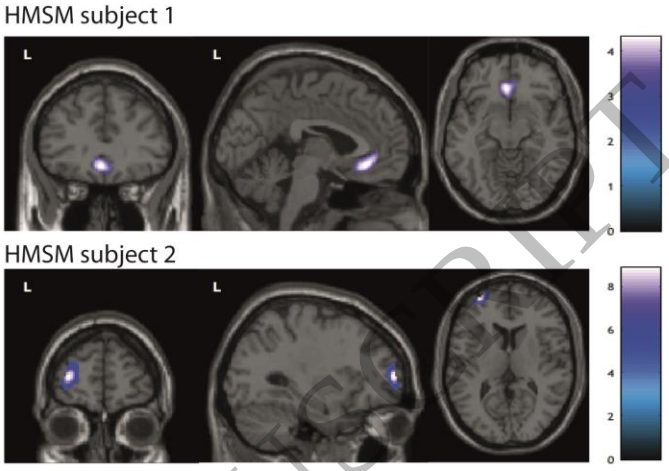


Figure 4 Subtractive analyses comparing FDG-PET data of HIVMSM taken individually with those of the group of PrEPMSM. Images were thresholded at $p<.001$ uncorrected for visualization purpose. Significant relative hypometabolic areas were observed in lateral or mesial prefrontal cortices of 25% of the HIVMSM. The figure shows for illustrative purposes two of these participants exhibiting the aforementioned metabolic abnormalities.



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