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CENTRAL NERVOUS SYSTEM AND COGNITION (SS SPUDICH, SECTION EDITOR)

Brain PET Imaging: Value for Understanding the Pathophysiology of HIV-associated Neurocognitive Disorder (HAND)

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Abstract

Purpose of Review The purpose of this review is to summarize recent developments in PET imaging of neuropathologies underlying HIV-associated neurocognitive dysfunction (HAND). We concentrate on the recent post antiretroviral era (ART), highlighting clinical and preclinical brain PET imaging studies.

Recent Findings In the post ART era, PET imaging has been used to better understand perturbations of glucose metabolism, neuroinflammation, the function of neurotransmitter systems, and amyloid/tau protein deposition in the brains of HIV-infected patients and HIV animal models. Preclinical and translational findings from those studies shed a new light on the complex pathophysiology underlying HAND.

Summary The molecular imaging capabilities of PET in neuro-HIV are great complements for structural imaging modalities. Recent and future PET imaging studies can improve our understanding of neuro-HIV and provide biomarkers of disease progress that could be used as surrogate endpoints in the evaluation of the effectiveness of potential neuroprotective therapies.

Keywords HIV · HIV-associated neurocognitive disorder (HAND) · Brain PET imaging · Inflammation · Neurotransmitters · Amyloid deposition

Introduction

The advent of antiretroviral therapy (ART) has decreased mortality and morbidity rates in HIV-positive (HIV+) patients and to a great extent diminished the incidence of HIV-associated dementia (HAD), the most severe form of neuro-HIV. Although the incidence of moderate or severe HAD fell from about 7% in 1989 to only 1% in 2000 [1], the frequency of milder forms of HIV-associated neurocognitive dysfunction (HAND), including mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI), remains high [2]. With the non-acute onset and relatively mild initial clinical presentation, HAND can often complicate the management of those patients and affect their quality of life. Considering the chronic nature of the disease associated with ART treatment, a change in research focus towards mild neurocognitive dysfunction is warranted [3] with a more detailed exploration of MND and ANI [4]. Understanding the pathophysiology of depression in HIV is another topic of interest considering recent reports of the role of depression in defining mortality and morbidity of HIV+ subjects [5]. Towards those goals, a better understanding of the molecular and functional neuropathologies underlying HAND becomes necessary.

Potential contributing factors to the occurrence of HAND and associated mood disorders include persistent latent HIV-1 reservoirs in the brain, irreversible CNS insult prior to ART initiation, toxicities related to antiretroviral drugs, amyloid and tau protein deposition, neuroinflammation [6, 7] as well as molecular damage of various neurotransmitter systems [8–12] (Fig. 1). Positron emission tomography (PET) is a molecular imaging modality that can non-invasively probe many of those pathologies in vivo. As such, PET can provide complementary information to conventional structural as well as novel magnetic resonance imaging (MRI) techniques such as diffusion tensor imaging (DTI) [13, 14], volumetric MRI [15–17], and magnetic resonance spectroscopy (MRS) [18, 19].

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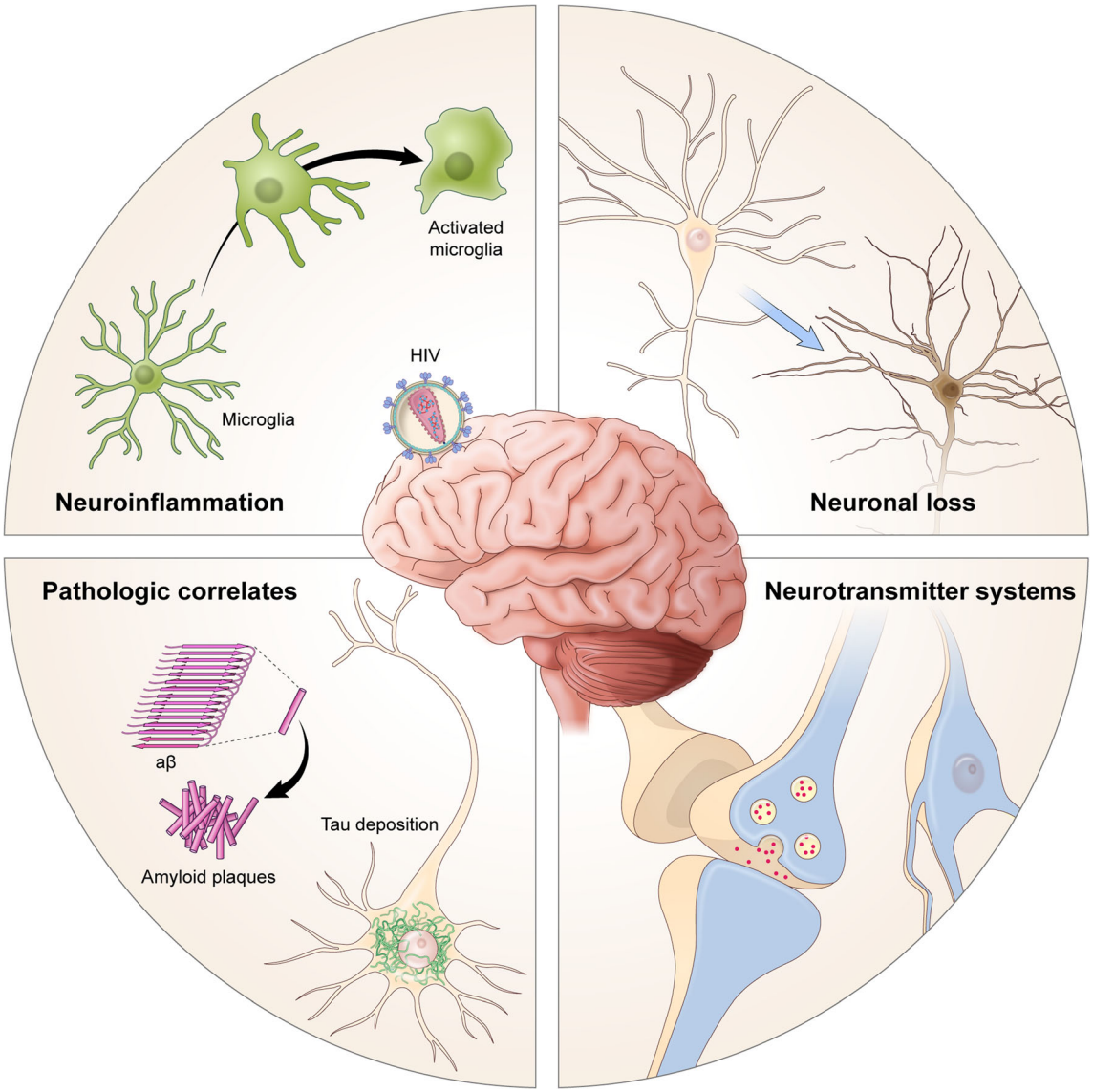

Fig. 1 PET imaging targets in the brain of HIV animal models and seropositive patients

Since preclinical studies provide a practical platform for investigation of new imaging biomarkers that can eventually be translated into clinical applications, we structured this review to briefly describe neuroimaging research in various preclinical HIV models along with relevant/related clinical studies (Table 1).

Animal Models of HIV Infection

One way of controlling for heterogeneity in patient populations and to obtain longitudinal information is to perform imaging studies in animal models [33–36]. One major challenge in developing animal models for HIV is the availability of cellular proteins in those species such as CD4 and CCR5/CXCR4 that would support viral replication. This has limited the success of original attempts to infect small animals such as mice and rats with HIV-1 [37]. A naturally occurring virus, feline immunodeficiency virus, infects domestic cats and can result in a similar disease process to HIV infection in humans. Major differences however exist, including a different primary receptor (CD134 instead of CD4) with secondary additional infection of lymphocytes, and a slow protracted course of disease, rendering this model less practical and less widely used [37]. Among rodent models, transgenic (Tg) mice and rats have been developed. The HIV-1 Tg rat model expressing seven of the nine viral proteins including gp120, nef, and tat in lymphocytes, monocytes, and in the brain was developed in 2001 [38] and was found to develop neuropathologies reminiscent of HIV infection. As such, it has been used in multiple studies evaluating the effects of HIV viral proteins on the brain and in various imaging studies [39–44]. The

Table 1 Summary of relevant human brain PET studies

	Radioligand	Publication year	Target	Subject population	Main findings
Glucose metabolism	18F-FDG [20]	2018	Brain glucose metabolism	47 Treated HIV+ (on cART) 10 HIV− with co-morbidities 10 HC	Thalamic hypometabolism in HIV+ cohort Global hypometabolism associated with cardiovascular disease
	18F-FDG [21]	2013	Brain glucose metabolism	35 Treated HIV+ 37 Age-matched controls	Small reductions in FDG uptake in the anterior cingulate cortex (ACC) in HIV+ patients
	18F-FDG [22]	2010	Brain glucose metabolism	38 Treated HIV+ patients compared to healthy control database	Mesial frontal cortical hypometabolism in 55% pf HIV+ patients displayed hypometabolism
Neuroinflammation	11C-PBR28 [23]	2016	TSPO expression	12 Treated HIV+ 10 HIV− controls	Global and regional (occipital and parietal lobes and globus pallidus) increased binding in HIV+ patients
	11C-DPA713 [24]	2014	TSPO expression	23 Treated HIV+ patients 12 Healthy controls	Higher VT normalized to gray matter in HIV+ (white matter, cingulate cortex, and supramarginal gyrus)
	11C-PK11195 [25]	2014	TSPO expression	7 Treated HIV+ patients 9 Healthy controls	Clusters of increased TSPO expression observed in HIV+ patients within the corpus callosum, anterior and posterior cingulate, and frontal and temporal lobes
	11C-PK11195 [26]	2006	TSPO expression	12 Treated HIV+ (6/12 with HAND; 9/12 with detectable plasma viremia) 5 HIV− controls	No observed difference in TSPO binding between HIV+ and controls
	11C-PK11195 [27]	2005	TSPO expression	10 HIV+ (7/10 on cART; 3/10 with HAND) 5 HIV− controls	Significantly higher binding in HIV+ patients in five brain regions
Neurotransmitter systems	11C-cocaine 11C-raclopride [28]	2004	Dopamine transporter (DAT) Dopamine receptor (D2)	15 HIV+ (10 with HAD) 13 HIV−	Significantly decreased DAT in ventral striatum and putamen in HIV+ patients with HAD Mild, non-significant decrease in D2 receptor availability
	11C-cocaine 11C-raclopride [11]	2008	Dopamine transporter (DAT) Dopamine receptor (D2)	35 HIV+ (24 without and 11 with history of cocaine dependence) 14 HIV−	Lower levels of DAT in HIV+ in the putamen Lower levels of DAT in HIV+ with cocaine dependence in the caudate
	11C-DASB [10]	2010	Serotonin transporter	9 Depressed HIV+ (HIV-D) 9 Non-depressed HIV+ (HIV-ND) 9 Healthy controls (HC)	Lower [11C] DASB binding in HIV+ compared to HC Higher regional binding values in HIV-D compared to HIV-ND
Amyloid and tau deposition	11C-PiB [29]	2010	Aβ42	10 Treated HIV+ 20 HIV−	No increased 11C-PiB uptake in HIV+ compared to HIV−
	11C-PiB [30]	2012	Aβ42	16 HIV+ (11 asymptomatic and 5 HAND) 19 HIV− (8 asymptomatic and 9 with AD)	No increased 11C-PiB in HIV+ irrespective of the degree of impairment Increased 11C-PiB in AD
	18F-Florbetaben [31]	2016	Aβ42	1 HIV+ on cART with HAND	Increased cortical binding suggesting amyloid deposition
	18F-THK 5117 [32]	2016	Tau proteins	1 HIV+ with suggestion of HIV encephalitis on MRI	Increased tau binding in the periventricular and deep white matter regions

"humanized mouse" model, on the other hand, is generated with immunocompromised mice with transplanted humanized immune system and is also a frequently used small animal model in HIV-1 studies [45, 46]. Among the various types of humanized mice, OD/scid-IL-2Rgcnull mice have been used for imaging using MRI techniques, but not PET imaging [47–49].

Rodents, however, remain suboptimal models of HIV, especially when compared to the simian immunodeficiency virus (SIV) and simian/human immunodeficiency syndrome (SHIV) infected monkey models, which are considered to be more appropriate animal models in HIV/AIDS research. Despite the associated costs and logistical limitations, SIV and SHIV-infected monkeys continue to provide valuable in vivo experimental data complementing human studies of transmission, pathogenesis, prevention, and treatment of HIV [50–53]. This is mainly because non-human primates (NHPs) are physiologically and immunologically similar to humans. This similarity results in the development of simian AIDS in those animals that is analogous in many aspects to HIV-1 AIDS in humans [37, 54]. SIV encephalitis (SIVE) is one of the aspects of SIV infection reminiscent of HIV CNS involvement in the early days of the epidemic [55–57], while newer models of non-accelerated diseases (e.g., SHIV model) seem to better reflect milder neurologic changes currently seen in infected treated patients [58]. Models of SIVE have already been used to investigate the pathophysiology of CNS involvement as well as in the evaluation of novel therapies [50, 55, 59, 60]. PET imaging studies have mostly used rhesus macaques [61–66] infected with SIV or SHIV, although there have been suggestions that pigtail macaques progress more rapidly to SIVE [50].

PET Imaging of Glucose Metabolism Using ^{18}F-FDG

^{18}F-fluorodeoxyglucose (FDG)-PET imaging can non-invasively quantify glucose metabolism within various tissues and can help detect brain activation patterns involved in normal and abnormal brain functioning. FDG brain imaging has been used in many CNS diseases such as Alzheimer's dementia (AD) and Parkinson's disease; however, limited literature is available on its use in SIV and HIV studies, especially in the post ART era.

In the setting of SIV and SHIV infection, FDG-PET imaging has mainly concentrated on peripheral patterns of immune activation rather than brain involvement [65, 66]. In a recent study, we used brain FDG-PET imaging in a group of SIV-infected macaques to longitudinally assess the effect of ART initiation and interruption by monitoring alterations in brain glucose metabolism. We observed increased brain glucose metabolism within 1 month of treatment cessation, which may reflect neuroinflammation in the setting of viral rebound. This was significantly associated with decreased CD4+ and CD8+ T cell counts and increased plasma/CSF viral load (VL). While we cannot assert neurologic damage in association with cerebral hypermetabolism, it is a concerning outcome of non-adherence to ART, even for short periods of time [67]. We did not find significant or consistent changes in FDG uptake when ART was initiated however, suggesting that abatement of neuroinflammatory changes associated with viral replication might take a long time to occur [67].

FDG-PET has been used more extensively in HIV+ patients, however. Early studies in the pre-ART era suggested early CNS HIV involvement with high FDG uptake consistent with increased glucose metabolism seen in the basal ganglia [68–71] and thalamus [71] as well as relative increased metabolism in subcortical regions for patients with AIDS dementia complex (ADC) [72]. Hypometabolism was found to eventually occur in infected patients suggesting neuronal damage/loss [70].

Among the few studies in the recent ART era, Andersen et al. studied the prevalence of cerebral metabolic abnormalities in an HIV+ patient group on ART, with at least 3 years of fully suppressed VLs. The authors observed a substantial fraction (55%) of the optimally treated patients displaying abnormally low mesial frontal FDG uptake [22]. The observed hypometabolism correlated with shorter history of known HIV infection, fewer years on ART and higher circulating levels of TNF-α and IL-6 [22]. In another study by Towgood and colleagues, the authors reported reduced metabolic activity in frontal brain regions with no significant interaction between HIV and aging [21]. However, in both study populations [21, 22], subjects had none of the co-morbidities commonly seen in HIV+ patients. Being able to assess the contribution of those co-morbidities to neuronal dysfunction in HIV has the potential of changing the clinical approach to HAND subjects. We have recently evaluated a large group of subjects (47 treated HIV+ patients with a long history of infection, 10 HIV− with co-morbidities similar to the HIV+ group, and 19 healthy volunteers). Interestingly, we observed abnormal global glucose metabolism in HIV+ and HIV− patients with co-morbidities that was best predicted by cardiovascular disease rather than HIV status [20]. This suggests a very important role for cardiovascular disease in neuronal loss/dysfunction, as measured by FDG-PET in this vulnerable patient population. In addition, however, we did see significant focal hypometabolism in the thalamus of HIV+ patients that was best predicted by HIV serostatus suggesting an HIV-related effect [20]. The exact pathophysiology underlying thalamic hypometabolism in HIV+ patients and its association with potential executive function dysfunction is unclear and warrants further evaluation.

Neuroinflammation PET Ligands in SIV/HIV

Despite successful control of HIV replication in the periphery and in the brain, low levels of persistent inflammation have been implicated in the pathophysiology of HAND [73]. Following HIV infection, the virus enters the brain and persists in perivascular macrophages and microglia, with the resulting cascade of viral neuropathogenesis assumed to be related to proinflammatory and cytotoxic products secreted by those cells [74–76]. PET imaging enables the in vivo quantification of microglial activation/neuroinflammation through radiolabeled ligands that target the translocator protein (TSPO), a naturally expressed receptor on the outer mitochondrial membrane of microglia, macrophages, and astrocytes. During microglial activation, TSPO is significantly upregulated [64] and as such can reflect the degree of neuroinflammation. The earliest TSPO radioligand to be used to assess neuroinflammation in various neurodegenerative diseases was ^{11}C-PK11195, an isoquinoline carboxamide [77–79]. More recently however, multiple second-generation TSPO ligands have been developed with higher TSPO affinity and generally higher specific to non-specific binding compared to ^{11}C-PK11195 [80–82].

In animal models, one of the second-generation ligands, ^{18}F-DPA714, showed higher but not statistically significant uptake in Tg rats compared to wild-type rats. This raised the concern that microglial activation might not necessarily be the key mechanism for neuropathology in the Tg rat model [42] but rather chronic exposure to HIV viral proteins [40]. Earlier work in SIV-infected monkeys using ^{11}C-PK11195, on the other hand, showed evidence of microglial activation in animals with SIVE compared to those without SIVE [64].

In humans, early studies using ^{11}C-PK11195 in HIV+ patients had conflicting results [26, 27] which could be due to the heterogeneity of HIV patient populations assessed and the inherent high non-specific binding of the ligand. In a more recent study, also using ^{11}C-PK11195, clusters of significantly increased ^{11}C-PK11195 binding suggestive of the presence of focal cortical regions of activated microglia were observed by Garvey et al. in a group of asymptomatic subjects with chronic HIV infection on suppressive ART [25]. Using second-generation TSPO ligands by two different groups also showed microglial activation in treated HIV+ patients [23, 24]. In the paper by Coughlin et al., the authors uncovered suboptimal test-retest reproducibility of TSPO distribution volume values (Vt) in healthy controls using a second-generation ligand, ^{11}C-DPA713. As a result, they resorted to a different approach in which the ratios of Vt relative to overall gray matter (VtGM) were calculated relative to overall gray matter (Vt_{GM}). Higher Vt_{GM} values were then observed in treated HIV+ patients compared to HIV-negative subjects in the white matter, cingulate cortex, and supramarginal gyrus. Increased binding in the frontal cortex was specifically seen in patients with dementia [24]. Similar positive results were found by Vera et al. using a different second-generation TSPO ligand, ^{11}C-PBR28, in a cohort of cognitively healthy treated HIV+ individuals: increased uptake was found globally as well as regionally, in the parietal and occipital lobes and in the globus pallidus [23]. The findings of both papers seem to support glial cell activation that is persistent in the course of HIV infection, despite treatment and virological suppression.

Imaging Neurotransmitter Systems in SIV/HIV

Dopaminergic System

Among the neurotransmitter systems, the vulnerability of the dopaminergic system to the effects of the virus has been well documented, with the basal ganglia being most affected, resulting in a Parkinsonian-like symptomology [83]. These findings were supported by decreased neuronal number and neuronal density in the globus pallidus and substantia nigra in SIV-infected monkeys compared to controls [84].

In animal models, we evaluated the dopaminergic system in the Tg rat [44, 85], based on reports of dopaminergic dysfunction in this model [86, 87]. Using two different radioligands, ^{18}F-FPCMT for presynaptic dopaminergic transporter (DAT) and ^{18}F-fallypride for postsynaptic D2/D3 receptors, we observed significant loss of both DAT and D2/D3 receptors in older (15–18 months) Tg rats compared to controls [85]. Dopaminergic dysfunction observed with this Tg rat model is probably related to viral protein exposure, considering that rats with higher serum gp120 had lower mean binding potential values for both ligands [85]. No similar reported work has been published in SIV-infected animals however.

A few human PET studies targeted the dopaminergic system in the setting of HIV infection. In an early study with ^{11}C-cocaine targeting DAT and ^{11}C-raclopride targeting D2 receptors, a significant decrease in DAT was seen in HIV+ patients with HAD compared to HIV− controls especially in the putamen and ventral striatum. Mild but non-significant decreases in D2 receptor availability were observed within the same subject groups [28]. A subsequent study using the same PET ligands with a larger cohort of HIV+ patients ($n = 35$) including a subcohort of HIV+ patients with continued cocaine abuse (11 out of 35) again found significantly decreased DAT in the putamen, compared to HIV seronegative controls [11]. In the same study, only the HIV + Coc subgroup had significantly lower DAT in the caudate compared to controls. The authors concluded that reduced dopaminergic function may contribute to cognitive dysfunction in HIV+ patients with or without additional cocaine abuse [11]. There have been no additional clinical PET studies targeting the dopaminergic system in HIV+ patients published since those two papers.

Serotonergic System

More recently, there has been a renewed interest in mood disorders, mainly depression, in HIV+ patients, mainly due to the associated deleterious effects on treatment adherence with secondary increased mortality and morbidity [5, 88, 89]. One related neurotransmitter system, the serotonergic system, is thus of interest, especially considering prior reports suggesting involvement in the pathophysiology of neuro-HIV [8, 9, 90]. Similar to the dopaminergic system, multiple ligands have been developed targeting various components of the serotonergic system. However, one of the most common targets remains the serotonin transporter (SERT) with ^{11}C-DASB, a specific PET SERT ligand, being used to assess SERT changes in the setting of depression in multiple previous studies [91–93].

In the only clinical study where ^{11}C-DASB was used to image serotonin dysfunction in a cohort of HIV+ patients with depression, HIV+ patients had generally lower ^{11}C-DASB binding than HIV− controls. Depressed HIV+ patients however had higher ^{11}C-DASB binding compared to non-depressed subjects, suggesting a role of the serotonergic system in depression associated with HIV [10]. More recently, we used ^{11}C-DASB PET to longitudinally image NHPs (rhesus macaques) infected with the neurotropic SIV strain (SIVsm804E) [94]. Interestingly, we found higher ^{11}C-DASB binding in 85% of the infected animals compared to baseline. Increased ^{11}C-DASB binding reflective of serotonergic upregulation in the midbrain in infected animals correlated significantly with the duration of infection and DASB binding in the thalamus correlated significantly with CSF cytokines [94]. Our findings suggest inherent involvement of the serotonergic system in SIV pathophysiology. Whether these results can be reproduced and correlated to depressive symptomatology in optimally treated HIV+ patients remains to be seen.

Imaging Amyloid and Tau Deposition in HIV

Histopathological similarities between AD and HIV brain involvement were suggested more than two decades ago, with deposition of amyloid-β plaques and tau proteins shown in postmortem brain tissues of HIV+ patients [95–99]. This issue became more relevant after the advent of ART and secondary prolonged survival of infected patients with increased concerns that the aging HIV population could be more prone to the risk of developing AD. Similar to what has been described in AD patients, decreased levels of CSF amyloid beta 42 (Aβ42) have been described in HIV+ patients with neurocognitive dysfunction by a few groups, potentially reflecting increased Aβ42 deposition in brain parenchyma [100–102]. Other studies however did not support the findings [30, 103, 104].

Although imaging of Aβ42 in AD patients has been very successful using ligands such as ^{11}C-labeled Pittsburg compound B (PIB), ^{18}F-florbetaben, and ^{18}F-florbetapir [105], clinical Aβ42 imaging studies in HIV+ subjects have not shown increased amyloid accumulation regardless of the degree of neurocognitive impairment and despite lower levels of CSF Aβ42 in some HIV+ subjects [29, 30, 106]. The exact reasons for negative imaging results in view of documented amyloid deposition in HIV by pathology are unclear. One possible explanation is a difference in structural composition/location of amyloid plaques between HIV and AD patients: while amyloid plaques are generally extracellular in AD, they are more likely to be intracellular in HIV [98, 107]. Also, extracellular amyloid plaques sometimes seen in HAND are more diffuse [107, 108], while in AD, they tend to be fibrillar [109]. Since amyloid radiotracers have generally high affinity and selectivity for fibrillar Aβ in plaques [105], this could account for lower binding in HIV+ subjects. Another possible difference in amyloid pathology between AD and HIV could be related to amyloid metabolism with downregulation of upstream pathways involved in amyloid precursor protein production [106]. Interestingly, a case report by Turner et al. recently demonstrated increased ^{18}F-florbetaben reflecting amyloid deposition in an older (71-year old) HIV+ individual [31]. It is unclear however, in the absence of post mortem tissues, whether this patient's dementia is due to HIV, co-incidental AD, or a combination of both. Additional studies are thus needed to better evaluate amyloid deposition in an older HIV population. Another issue that needs better investigation is the potential interaction between ART and amyloid clearance from the brain which could possibly increase the risk of developing AD in the treated aging HIV patient population [98, 107].

Tau protein deposition is another pathological hallmark of AD that has been seen in HIV brains [110] with the highest levels of phosphorylated tau (p-tau) deposition seen in HAART-treated patients [97]. Multiple groups have attempted to measure total tau (t-tau) and p-tau protein levels in the CSF; however, the findings have not always been in agreement: while some groups showed no changes in p- or t-tau levels, others found changes in t-tau [111]. Despite the uncertainty, there is increased interest in utilizing tau-specific PET ligands to image HIV+ patients. In one case report, a 70-year-old subject presenting with HIV encephalitis had increased binding of 18F-THK 5117 (tau ligand) in the periventricular and deep white matter regions [32]. More recently, however, PET imaging with another Tau ligand (18F-AV-1451) showed similar binding for HIV+ and HIV-negative control individuals [112]. This raises the possibility that PET with tau ligands could be used in older HIV+ individuals to differentiate AD from cognitive impairment due to HIV.

Conclusions and Future Directions

In conclusion, PET imaging remains underutilized in the evaluation of neuro-HIV, especially in the post-ART era. PET imaging targeting novel neuroinflammation biomarkers besides TSPO, such as cannabinoid receptors or cyclooxygenases 1 and 2, might be helpful in better assessing the exact role of neuroinflammation in the pathophysiology of HAND in treated subjects. In addition to the dopaminergic and serotonergic systems, other neurotransmitter systems such as the cholinergic and GABAergic systems could be assessed in HIV for possible system-specific effects of the virus. PET imaging of amyloid and tau deposition in older HIV+ subjects might provide new insights into the exact connection/interaction between HIV and AD and the role of ART in amyloid and tau deposition. Finally, in a recent immunoPET study using a ^{64}Cu-labeled SIV Gp120-specific antibody, the authors were able to detect viral dynamics and localization in the lymphoid tissues, gastrointestinal, and respiratory tracts in SIV monkeys, before and after treatment [62]. Although such ligands could be potentially useful in the detection of latent viral reservoirs in the whole body of treated HIV+ subjects, there is still the caveat of the labeled antibodies not crossing the blood brain barrier (BBB) to reveal potential sites of HIV persistence in the CNS. Developing radiolabeled ligands that can target SIV/HIV and cross the BBB would help us measure CNS reservoirs in HIV animal models and eventually in HIV+ subjects.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies with human subjects performed by the authors have been previously published and complied with all applicable ethical standards. All reported studies with animal subjects performed by the authors were approved by the Institutional Animal Care and Use Committee of the National Institutes of Health and were performed in accordance with the guide for the Care and Use of Laboratory Animals.

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