Published in final edited form as:
Nucl Med Commun. 2014 August ; 35(8): 792–796. doi:10.1097/MNM.0000000000000139.

Role of nuclear medicine in neuroHIV – PET, SPECT and beyond

Mike Sathekge[*,#], **Alicia McFarren**[°], and **Ekaterina Dadachova**[°°,#]

[*]Department of Nuclear Medicine, University of Pretoria, Pretoria, South-Africa

[°]Department of Pediatrics, Montefiore Medical Center, Bronx, NY, USA

[°°]Department of Radiology, Albert Einstein College of Medicine, Bronx, NY, USA

The problem of neuroHIV

In 2011, an estimated 34.2 million adults and children were living with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) world-wide [1]. HIV associated neurocognitive disorders (HAND), formerly AIDS dementia complex (ADC), remain among the most common clinical disorders encountered in people infected with HIV despite widespread use of antiretroviral therapy. HAND encompasses a hierarchy of progressively more severe patterns of central nervous system (CNS) involvement, ranging from asymptomatic neurocognitive impairment (ANI), to minor neurocognitive disorder (MND), to the most severe HIV-associated dementia (HAD) [2].

HAART and neuroHIV

Since the introduction of highly active anti-retroviral therapy (HAART) in 1996, many HAART-treated patients have shown durable and complete suppression of HIV replication. The incidence of moderate or severe dementia fell from about 7% in 1989 to only 1% in 2000, and the severity of neurologic disease appears to have been attenuated [3]. Despite this remarkable effect on incidence rates, the prevalence of HAND continues at very high rates. For example, in one cohort (CHARTER), 53% of the total sample had neurocognitive impairment, with increasing rates in those with more comorbid illnesses [4]. Prevalence estimates were 33% for ANI, 12% for MND, and 2% for HAD. In fact, the recent review on the subject calls HIV-associated neurocognitive disorders “a hidden epidemic” [5]. The persistence of this high risk for HAND in individuals experiencing effective control of systemic HIV viral load is incompletely explained, and suggested factors include effects of aging on brain vulnerability, persistence of HIV replication in brain macrophages, evolution of highly neurovirulent CNS HIV strains, and even long-term CNS toxicity of ART [4,6]. Thus, there is an enormous need for further evaluation and early diagnosis of HAND. Although the primary imaging methods to enhance diagnosis of neurological complications associated with HIV-infection are MRI and CT, functional imaging may prove to be of

[#]Address correspondence and reprint requests to Prof. Mike Sathekge, University of Pretoria, Steve Biko Academic Hospital, Private Bag X169, Pretoria 0001, South-Africa. Tel: 0123541794, Fax: 0123541219 mike.sathekge@up.ac.za; or Prof. Ekaterina Dadachova, Albert Einstein College of Medicine of Yeshiva University, 1695A Eastchester Rd, Bronx NY 10461 USA. Tel: 1-718-405-8485; Fax: 1-718-405-8457; ekaterina.dadachova@einstein.yu.edu.

greater value because HAND causes functional abnormalities before structural atrophy, ventricular dilatation or focal CNS lesions are visible [7].

HAND is a subcortical dementia that is characterized by disturbances in cognition, motor performance, and behavior. Diagnosis of early HAND is important as many of its symptoms can be caused by other conditions common to people with HIV/AIDS, many of which may be treatable [8]. It is important to emphasize that presently there is no diagnostic marker or combination of markers for HAND. The diagnosis is made in HIV-positive patients with cognitive impairment after ruling out confounding conditions (CNS opportunistic infections, neurosyphilis, substance abuse, delirium, toxic-metabolic disorders, psychiatric disease, age-related dementias). An essential feature in the diagnosis of HAND is the presence of well-documented cognitive decline and the exclusion of other neurological complications of HIV infection, such as cerebral toxoplasmosis, cryptococcal meningitis, lymphoma, and progressive multifocal leukoencephalopathy [9]. Cerebrospinal fluid (CSF) examination and imaging studies of the brain are mandatory. CSF analysis should exclude infectious agents other than HIV.

FDG PET

A number of studies have reported on FDG PET brain findings in demented AIDS patients as well as in asymptomatic HIV-infected subjects [8–21]. In an early imaging study using FDG PET in 12 patients with dementia, Rottenberg et al. found relative increase of FDG uptake in the subcortical region in 9 patients in the early stage of AIDS related dementia [19], however, the disease progression was characterized by gradually reducing glucose uptake in cortical and subcortical gray matter. In a follow-up study by the same group, 21 HIV-infected subjects (11 with AIDS) were examined. Twelve had follow-up scans at 6 months and 4 had a third scan at 12 months. Principal component analysis of the combined (HIV-infected and controls) PET data revealed two major disease-related metabolic components: a non-specific indicator of cerebral dysfunction, which was significantly correlated with age, cerebral atrophy and HAND stage; and the striatum, which was hypermetabolic and appeared to provide a disease-specific measure of early CNS involvement [22]. Similar findings were reported by Van Gorp et al. who described regional hypermetabolism in the basal ganglia and the thalamus in 17 subjects with AIDS when compared to 14 seronegative controls [23]. The authors also found a significant relationship between temporal lobe metabolism and the severity of dementia. Hinkin et al. showed that as HIV-associated brain infection progressed, relative basal ganglia metabolism increased as well as metabolism in the parietal lobe [17]. Pascal et al. found in 10 out of 15 asymptomatic HIV-positive patients, significant asymmetries in FDG uptake which were most prominent in the frontal regions, while MR showed no abnormalities [24]. Finally, during a motor task, von Giesen et al. found frontomesial hypometabolism in 9 of 19 non-demented HIV-infected subjects. The authors indicated that frontomesial hypometabolism was associated with deteriorating motor performance [21]. In another FDG study it was shown that optimally treated HIV patients exhibit metabolic abnormalities of cerebral glucose metabolism, which may represent imminent neuronal damage. This study may confirm the notion that neuroinflammation continues to be associated with HIV CNS infection in ART-experienced individuals [25]. Furthermore, the primary sites of neuroinflammation are different; the

characteristic involvement of the basal ganglia in pre-ART specimens as demonstrated by earlier studies is less commonly seen in post-ART specimens, which display inflammation in the hippocampus and in adjacent parts of the entorhinal and temporal cortices [26]. In spite of those interesting insights into the connection between HAND and glucose metabolism in the brain – FDG cannot be recommended for the diagnosis of HAND in HIV patients.

PET with ^{11}C-labeled radiotracers

Pittsburgh compound B (PiB) is an analog of thioflavin T which when radiolabeled with ^{11}C, can be used in PET scans to image beta-amyloid plaques in neuronal tissue [27]. Pathologic similarities exist between HAND and neurodegenerative disorders such as Alzheimer disease (AD), which is characterized by the presence of extracellular deposits of amyloid-β protein 1-42 (Aβ42) in the form of plaques and aggregations of microtubule-associated, tau-forming, neurofibrillary tangles. Typically, diffuse [28, 29] rather than neuritic [30] plaques have been observed in HIV-positive individuals at autopsy compared with age-matched community participants. Observed pathologic changes within HIV-positive participants have been seen despite virologic control by HAART [31]. HAART may not provide sufficient protection to prevent the development of HAND [32]. Furthermore some HAART, particularly nucleoside reverse transcriptase inhibitors (NRTIs) are highly neurotoxic and may contribute to persistent high prevalence of HAND [33]. Multiple pathways could be responsible for increases in Aβ42 deposition in the setting of HIV. Transactivator of transcription (TAT) is an HIV protein that can inhibit the activity of neprilysin, a metalloendoprotease involved in the degradation of Aβ42 [28]. TAT can bind to lipoprotein receptor–related protein, leading to a decrease in Aβ42 clearance from the brain. TAT also attaches to the receptor for the advanced glycation end products, which may result in increased Aβ42 absorption from the blood [34]. Infected macrophages and microglia can also shed viral proteins, resulting in an upregulation of amyloido-genesis-promoting cytokines (ie, tumor necrosis factor and interleukin factor 1β) [35]. These cytokines not only directly contribute to neurodegeneration but also promote an increase in Aβ42 generation by stimulating expression of the β site amyloid precursor protein cleaving enzyme 1 [36]. HAND and AD may therefore share similar molecular mechanisms that lead to neurodegeneration [37]. What is still unclear is whether fibrillar cerebral amyloid plaques can be visualized in participants with HAND.

To answer this question, Ances et al. evaluated the ^{11}C-PiB localization in cognitively unimpaired HIV+ (n = 10) participants and matched community controls without dementia (n = 20) [38]. They observed that regardless of CSF Aβ42 level, none of the HIV+ participants had fibrillar amyloid plaques as assessed by increased ^{11}C-PiB mean cortical binding potential (MCBP) or binding potential within 4 cortical regions. In contrast, some community controls with low CSF Aβ42 (<500 pg/mL) had high ^{11}C-PiB MCBP with elevated binding potentials (>0.18 arbitrary units) within cortical regions. The authors concluded that cognitively unimpaired HIV+ participants, even with low CSF Aβ42 (<500 pg/mL), do not have ^{11}C-PiB parameters suggesting brain fibrillar amyloid deposition. This was a disappointing finding. The dissimilarity between unimpaired HIV+ and preclinical AD may reflect differences in Aβ42 production and/or formation of diffuse plaques. In the

follow-up study the same group put forward an objective of evaluating whether ^{11}C-PiB could differentiate AD from HAND in middle-aged HIV positive participants [39]. Sixteen HIV-positive (11 cognitively normal and 5 with HAND) and 19 HIV-negative (8 cognitively normal and 11 with symptomatic AD) participants took part in the study. Interestingly, regardless of degree of impairment, HIV-positive participants did not have increased ^{11}C-PiB levels, whereas symptomatic AD individuals have increased fibrillar Aβ42 deposition in cortical and subcortical regions. Observed dissimilarities between HAND and AD may reflect differences in Aβ42 metabolism.

PK-11195 is an isoquinoline carboxamide which binds selectively to the peripheral benzodiazepine receptor (PBR). [^{11}C]-R-PK11195 has been used in PET to visualize brain inflammation in patients with neuronal damage. Increases in [^{11}C]-R-PK11195 binding have been reported in patients with stroke, traumatic brain injury and in patients with chronic neurodegenerative conditions including Huntington's disease and Parkinson's disease [40, 41]. Glial cell activation occurs in response to brain injury and is present in a wide variety of inflammatory processes including HAND. HIV-infected glial cells release cytokines and chemokines that, along with viral neurotoxins, contribute to neuronal damage and apoptosis. Hammoud et al. undertook a small study with a purpose to determine if glial cell activation in HIV+ patients could be detected noninvasively, in vivo, using [^{11}C]-R-PK11195 PET [42]. A sub-aim was to determine if non-demented HIV+ patients could be distinguished from those with HAD on the basis of [^{11}C]-R-PK11195 binding. Five healthy volunteers and 10 HIV+ patients underwent PET with [^{11}C]-R-PK11195. Compared to controls, HIV+ patients as a group (nondemented and HAD) showed significantly higher [^{11}C]-R-PK11195 binding in the thalamus, putamen, cerebellum, frontal cortex, and occipital cortex ($P < .05$). However, again as with ^{11}C-PiB studies - HIV non-demented patients were not different from those with HAD on the basis of [^{11}C]-R-PK11195 binding. In another application of [^{11}C]-R-PK11195 PET, Garvey and colleagues set to investigate the effect of acute co-infection with hepatitis C virus (HCV) upon cerebral function and microglial cell activation in HIV-infected individuals [43]. A case-control study was conducted. Twenty-four subjects with HCV and chronic HIV coinfection (aHCV) were compared to matched controls with chronic HIV monoinfection (HIVmono). Surprisingly, in spite of poorer cognitive performance and disturbance of cerebral metabolites in subjects co-infected with HCV and HIV as compared to subjects with HIVmono - higher [^{11}C]-R-PK11195 was not observed in the co-infected subjects.

SPECT

Technetium 99m-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) is the most common radiotracer used for SPECT brain imaging (including stroke, dementia, epilepsy, trauma) it is a lipophilic radiotracer that crosses the blood brain barrier (BBB)). In a comprehensive study conducted by Samuelsson et al. 28 patients with early stage HIV infection were subjected to yearly neurologic and neurophysiologic evaluations [44]. Every other year, SPECT with ^{99m}Tc-HMPAO and brain MRI were performed. None of the patients were on HAART. The SPECT results showed some deterioration through the years when considering the patient group as a whole. No specific individual decline could be seen, nor any correlation with the clinical performance. There was no correlation between patchy pattern

(i.e. general irregular blood flow pattern) in SPECT and cortical atrophy at MRI of the brain. There were no other pathological findings at MRI corresponding to irregular blood flow in SPECT. Some minor deteriorations were noted in the SPECT but there was no corresponding clinical dysfunction. In the disappointing outcome of the study, the researchers concluded that SPECT cannot be used as a predictor for developing HIV-associated cognitive disorder.

^{123}I-labeled ligand N-delta-(fluoropropyl)-2-beta-carbomethoxy-3beta-(4-iodophenyl)tropene (^{123}I-FP-CIT) and ^{123}I-iodobenzamide (^{123}I-IBZM) are being used for measuring dopamine transporters (DAT) and dopamine 2 (DA2) receptors, respectively, availability by SPECT. An increasing body of clinical and experimental evidence suggests a central dysfunction of the dopaminergic (DA) pathways in HIV infection [45, 46]. Post-mortem analysis showed decreased DA concentrations in the brains of humans infected with HIV, as well as in monkeys infected with simian immunodeficiency virus (SIV) [47, 48]. Decreased DA concentrations have also been found in cerebrospinal fluid (CSF) of patients with HIV dementia [49]. Parkinsonian symptoms have been reported in late stages of infection [50]. In their prospective study, Scheller and colleagues evaluated 24 HIV-positive patients diagnosed with clinical stage 1 and 24 uninfected subjects with ^{123}I-FP-CIT and ^{123}I-IBZM SPECT and a variety of biochemical analyses [51]. They found that DA levels were increased and DA turnover was decreased in the CSF of therapy-naïve HIV patients in asymptomatic infection. Simultaneously, DA increase does not modulate the availability of DA transporters and D2-receptors in comparison with uninfected controls. The authors suggested that increases in synaptic DA in asymptomatic HIV infection may be an early finding in what eventually becomes a more dysfunctional DA system in advanced stages of HIV infection. This provides a possible explanation for the synergy between DA medication, or drugs of abuse, and the acceleration of HIV disease progression.

Future directions

The variety of PET agents such as FDG, ^{11}C-PiB and [^{11}C]-R-PK11195 as well as SPECT agents ^{99m}Tc-HMPAO, ^{123}I-FP-CIT and ^{123}I-IBZM have been investigated for the diagnosis of HAND, for distinguishing between demented and non-demented HIV patients, for differentiation between HAND and non-HIV related dementia, as well as for assessing the influence of co-infection with the other viral pathogens on the brain functionality. None of these tracers were specific for HIV disease. In spite of glimpses into the emergence of HAND, the overall results were very disappointing. The existing tracers cannot distinguish between the HIV patients with and without HAND or detect the increased glial activation in subjects with HCV and HIV co-infection. Clearly, there is a need for specialized tracers for better diagnosis and management of HAND if nuclear medicine is to play a role in solving the problem of the HAND “epidemic”. In this regard, one example of the emerging tracer could be ^{68}Ga- NOTA–UBI29-41 which is an efficient and sensitive tracer for imaging of infection with no uptake in the normal brain [52]. It remains to be seen if this tracer could be useful in the diagnosis of HAND.

Another possible and no less important application of nuclear medicine methodologies to neuroHIV is actually eliminating the HIV infected cells in the CNS which are causing

HAND. This approach will help to address evolving factors in HAND pathogenesis, which may include persistent inflammation associated with HIV replication. Our laboratories have been developing radioimmunotherapy targeting viral gp41 antigen on the infected cells as a backbone for HIV cure strategy [53, 54]. Recently we also demonstrated that the same radiolabeled antibody to gp41 was capable of penetrating the in vitro human BBB and specifically killing HIV infected PBMCs and monocytes behind the barrier [55]. Such penetration through the BBB might help to visualize the infected cells in the CNS. We are now working towards moving this promising strategy into clinical trials in HIV patients.

Acknowledgments

ED was supported by the Bill and Melinda Gates Foundation grant OPP1035945, Developmental Pilot Grant Award from the John Hopkins Center for Novel Therapeutics and by Einstein CFAR; AM was supported by CHAM Pediatric Hematology/Oncology Fellowship Training Program.

References

1. UNAIDS. Together we will end AIDS. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2012. Available from www.unaids.org/en/resources/campaigns/togetherwewillendaids/
2. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69:1789–1799. [PubMed: 17914061]
3. Sacktor N. The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. J Neurovirol. 2002; 8 (Suppl 2):115–121. [PubMed: 12491162]
4. Heaton R, Clifford D, Franklin D, Woods S, Ake C, Vaida F, et al. HIV-associated neurocognitive disorders (HAND) persist in the era of potent antiretroviral therapy: The CHARTER Study. Neurology. in press.
5. McArthur JC, Brew BJ. HIV-associated neurocognitive disorders: is there a hidden epidemic? AIDS. 2010; 24:1367–1370. [PubMed: 20559041]
6. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011; 17:3–16. [PubMed: 21174240]
7. Boska M, Mosley R, Nawab M, Nelson JA, Zelivyanskaya M, Poluektova L, et al. Advances in neuroimaging for HIV-1 associated neurological dysfunction: clues to the diagnosis, pathogenesis and therapeutic monitoring. Curr HIV Res. 2004; 2:61–78. [PubMed: 15053341]
8. Woods SP, Moore DJ, Weber E, Grant I. Cognitive neuropsychology of HIV-associated neurocognitive disorders. Neuropsychol Rev. 2009; 19:152–1568. [PubMed: 19462243]
9. Hammoud DA, Hoffmann JM, Pomper MG. Molecular Neuroimaging: From Conventional to Emerging Techniques. Radiology. 2007; 24:21–42. [PubMed: 17885179]
10. Just P, Fieschi C, Baillet G, Galicier L, Oksenhendler E, Moretti JL. 18F-fluorodeoxyglucose positron emission tomography/computed tomography in AIDS-related Burkitt lymphoma. Aids Patient Care STDS. 2008; 22:695–700. [PubMed: 18793085]
11. Martis H, Mounier N. Hodgkin Lymphoma in Patients with HIV Infection: A Review. Curr Hematologic Malignancy Reports. 2012; 7:228–234.
12. Hoffman JM, Waskin HA, Schifter T, Hanson MW, Gray L, Rosenfeld S, et al. FDG-PET in differentiating lymphoma from nonmalignant central nervous system lesions in patients with AIDS. J Nucl Med. 1993; 34:567–575. [PubMed: 8455072]
13. Villringer K, Jager H, Dichgans M, Ziegler S, Poppinger J, Herz M, et al. Differential diagnosis of CNS lesions in AIDS patients by FDG-PET. J Comput Assist Tomogr. 1995; 19:532–536. [PubMed: 7622678]

14. Heald A, Hoffman JM, Bartlett J, Waskin H. Differentiation of central nervous system lesions in AIDS patients using positron emission tomography (PET). Int J STD AIDS. 1996; 7:337–346. [PubMed: 8894823]
15. O'Doherty M, Barrington S, Campbell M, Lowe J, Bradbeer C. PET scanning and the human immunodeficiency virus-positive patient. J Nucl Med. 1997; 38:1575–1583. [PubMed: 9379195]
16. Depas G, Chiron C, Tardieu M, Nuttin C, Blanche S, Raynaud C, et al. Functional brain imaging in HIV-1-infected children born to seropositive mothers. J Nucl Med. 1995; 36:2169–2174. [PubMed: 8523099]
17. Hinkin C, Van Gorp W, Mandelkern M, Gee M, Satz P, Holston S, et al. Cerebral metabolic change in patients with AIDS: report of a six-month follow-up using positron-emission tomography. J Neuropsychiatry Clin Neurosci. 1995; 7:180–187. [PubMed: 7626961]
18. Newton T, Leuchter A, Walter D, Van Gorp WC, Stern CE, Mandelkern M, et al. EEG coherence in men with AIDS: association with subcortical metabolic activity. J Neuropsychiatry Clin Neurosci. 1993; 5:316–321. [PubMed: 8369642]
19. Rottenberg D, Moeller J, Strother S, Sidtis JJ, Navia BA, Dhawan V, et al. The metabolic pathology of the AIDS dementia complex. Ann Neurol. 1987; 22:700–706. [PubMed: 3501695]
20. Villemagne V, Phillips R, Liu X, Gilson SF, Dannals RF, Wong DF, et al. Peptide T and glucose metabolism in AIDS dementia complex. J Nucl Med. 1996; 37:1177–1180. [PubMed: 8965193]
21. von Giesen H, Antke C, Hefter H, Wenserski F, Seitz RJ, Arendt G. Potential time course of human immunodeficiency virus type 1-associated minor motor deficits: electrophysiologic and positron emission tomography findings. Arch Neurol. 2000; 57:1601–1607. [PubMed: 11074792]
22. Rottenberg D, Sidtis JJ, Strother S, Schaper KA, Anderson JR, Nelson MJ, et al. Abnormal cerebral glucose metabolism in HIV-1 seropositive subjects with and without dementia. J Nucl Med. 1996; 37:1133–1141. [PubMed: 8965184]
23. Van Gorp W, Mandelkern M, Gee M, Hinkin CH, Stern CE, Paz DK, et al. Cerebral metabolic dysfunction in AIDS: findings in a sample with and without dementia. J Neuropsychiatry Clin Neurosci. 1992; 4:280–287. [PubMed: 1498579]
24. Pascal S, Resnick L, Barker WW, Loewenstein D, Yoshii F, Chang JY, et al. Metabolic asymmetries in asymptomatic HIV-1 seropositive subjects: relationship to disease onset and MRI findings. J Nucl Med. 1991; 32:1725–1729. [PubMed: 1880574]
25. Gray F, Chretien F, Vallat-Decouvelaere AV, Scaravilli F. The changing pattern of HIV neuropathology in the HAART era. J Neuropathol Exp Neurol. 2003; 62:429–440. [PubMed: 12769183]
26. Childs EA, Lyles RH, Selnes OA, Chen B, Miller EN, Cohen BA, et al. Plasma viral load and CD4 lymphocytes predict HIV- associated dementia and sensory neuropathy. Neurology. 1999; 52:607–613. [PubMed: 10025796]
27. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004; 55:306–319. [PubMed: 14991808]
28. Rempel HC, Pulliam L. HIV-1 TAT inhibits neprilysin and elevates amyloid beta. AIDS. 2005; 19:127–135. [PubMed: 15668537]
29. Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, Achim CL. Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. AIDS. 2005; 19:407–411. [PubMed: 15750394]
30. Esiri MM, Biddolph SC, Morris CS. Prevalence of Alzheimer plaques in AIDS. J Neurol Neurosurg Psychiatry. 1998; 65:29–33. [PubMed: 9667557]
31. Gisslen M, Hagberg L, Rosengren L, Brew BJ, Cinque P, Spudich S, et al. Defining and evaluating HIV-related neurodegenerative disease and its treatment targets: a combinatorial approach to use of cerebrospinal fluid molecular biomarkers. J Neuroimmune Pharmacol. 2007; 2:112–119. [PubMed: 18040834]
32. Shanbhag MC, Rutstein RM, Zaoutis T, Zhao H, Chao D, Radcliffe J. Neurocognitive functioning in pediatric human immunodeficiency virus infection: effects of combined therapy. Arch Pediatr Adolesc Med. 2005; 159:651–656. [PubMed: 15996999]

33. Letendre SL, Ellis RJ, Ances BM, McCutchan JA. Neurologic complications of HIV disease and their treatment. Top HIV Med. 2010; 18:45–55. [PubMed: 20516524]
34. Xu J, Ikezu T. The comorbidity of HIV-associated neurocognitive disorders and Alzheimer's disease: a foreseeable medical challenge in post-HAART era. J Neuroimmune Pharmacol. 2009; 4:200–212. [PubMed: 19016329]
35. Pulliam L. HIV regulation of amyloid beta production. J Neuroimmune Pharmacol. 2009; 4:213–217. [PubMed: 19288202]
36. Haughey NJ, Bandaru VV, Bae M, Mattson MP. Roles for dysfunctional sphingolipid metabolism in Alzheimer's disease neuropathogenesis. Biochim Biophys Acta. 2010; 1801:878–886. [PubMed: 20452460]
37. Giunta B, Hou H, Zhu Y, Rrapo E, Tian J, Takashi M, et al. HIV-1 TAT contributes to Alzheimer's disease-like pathology in PSAPP mice. Int J Clin Exp Pathol. 2009; 2:433–443. [PubMed: 19294002]
38. Ances BM, Christensen JJ, Teshome M, Taylor J, Xiong C, Aldea P, et al. Cognitively unimpaired HIV-positive subjects do not have increased 11C-PiB: a case-control study. Neurology. 2010; 75:111–5. [PubMed: 20534887]
39. Ances BM, Benzinger TL, Christensen JJ, Thomas J, Venkat R, Teshome M, et al. 11C-PiB imaging of human immunodeficiency virus-associated neurocognitive disorder. Arch Neurol. 2012; 69:72–7. [PubMed: 22232345]
40. Tai YF, Pavese N, Gerhard A, Tabrizi SJ, Barker RA, Brooks DJ, et al. Imaging microglial activation in Huntington's disease. Brain Res Bull. 2007; 72:148–151. [PubMed: 17352938]
41. Bartels AL, Leenders KL. Neuroinflammation in the pathophysiology of Parkinson's disease: evidence from animal models to human in vivo studies with [11C]-PK11195 PET. Mov Disord. 2007; 22:1852–1856. [PubMed: 17592621]
42. Hammoud DA, Endres CJ, Chander AR, Guilarte TR, Wong DF, Sacktor NC, et al. Imaging glial cell activation with [11C]-R-PK11195 in patients with AIDS. J Neurovirol. 2005; 11:346–355. [PubMed: 16162478]
43. Garvey LJ, Pavese N, Ramlackhansingh A, Thomson E, Allsop JM, Politis M, et al. Acute HCV/HIV coinfection is associated with cognitive dysfunction and cerebral metabolite disturbance, but not increased microglial cell activation. PLoS One. 2012; 7:e38980. [PubMed: 22808022]
44. Samuelsson K, Pirskanen-Matell R, Bremmer S, Hindmarsh T, Nilsson BY, Persson HE. The nervous system in early HIV infection: a prospective study through 7 years. Eur J Neurol. 2006; 13:283–291. [PubMed: 16618347]
45. Meisner F, Scheller C, Kneitz S, Sopper S, Neuen-Jacob E, Riederer P, et al. Memantine upregulates BDNF and prevents dopamine deficits in SIV-infected macaques: a novel pharmacological action of memantine. Neuropsychopharmacology. 2008; 33:2228–2236. [PubMed: 17971830]
46. Obermann M, Kuper M, Kastrup O, Yaldizli O, Esser S, Thiermann J, et al. Substantia nigra hyperechogenicity and CSF dopamine depletion in HIV. J Neurol. 2009; 256:948–953. [PubMed: 19240951]
47. Jenuwein M, Scheller C, Neuen-Jacob E, Sopper S, Tatschner T, ter Meulen V, et al. Dopamine deficits and regulation of the cAMP second messenger system in brains of simian immunodeficiency virus-infected rhesus monkeys. J Neurovirol. 2004; 10:163–170. [PubMed: 15204921]
48. Kumar AM, Fernandez J, Singer EJ, Commins D, Waldrop-Valverde D, Ownby RL, et al. Human immunodeficiency virus type 1 in the central nervous system leads to decreased dopamine in different regions of postmortem human brains. J Neurovirol. 2009; 15:257–274. [PubMed: 19499455]
49. Koutsilieri E, ter-Meulen V, Riederer P. Neurotransmission in HIV associated dementia: a short review. J Neural Transm. 2001; 108:767–775. [PubMed: 11478426]
50. Berger JR, Nath A. HIV dementia and the basal ganglia. Intervirology. 1997; 40:122–131. [PubMed: 9450229]

51. Scheller C, Arendt G, Nolting T, Antke C, Sopper S, Maschke M, et al. Increased dopaminergic neurotransmission in therapy-naïve asymptomatic HIV patients is not associated with adaptive changes at the dopaminergic synapses. J Neural Transm. 2010; 117:699–705. [PubMed: 20454983]

52. Ebenhan T, Zeevaart JR, Venter JD, Govender T, Kruger GH, Jarvis NV, et al. Preclinical Evaluation of ^{68}Ga-Labeled 1,4,7-triazacyclononane-1,4,7-triacetic Acid-ubiquicidin as a Radioligand for PET Infection Imaging. J Nucl Med. in print.

53. Dadachova E, Patel MC, Toussi S, Apostolidis C, Morgenstern A, Brechbiel MW, et al. Targeted Killing of Virally Infected Cells by Radiolabeled Antibodies to Viral Proteins. PLoS Medicine. 2006; 3:e427. [PubMed: 17090209]

54. Dadachova E, Kitchen SG, Bristol G, Baldwin GC, Revskaya E, Empig C, et al. Pre-clinical evaluation of a 213Bi-labeled 2556 antibody to HIV-1 gp41 glycoprotein in HIV-1 mouse models as a reagent for HIV eradication. PloS One. 2012; 7:e31866. [PubMed: 22427811]

55. McFarren, A.; Tsukrov, D.; Williams, D.; Lopez, L.; Kitchen, S.; Gorny, MK., et al. Elimination of HIV-1 Infected Cells by Radiolabeled Antibody to gp41 in a Human Blood Brain Barrier Model, H-1570d ICAAC; 2012; San Francisco, CA.