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# Imaging serotonergic transmission with [$^{11}$C]DASB-PET in depressed and non-depressed patients infected with HIV

Dima A. Hammoud [a], Christopher J. Endres [b], Edward Hammond [c], Ovsev Uzuner [b], Amanda Brown [d], Avindra Nath [d], Adam I. Kaplin [c], Martin G. Pomper [b,c,*]

[a] Radiology and Imaging Sciences, National Institutes of Health/Clinical Center, Bethesda, MD, USA
[b] Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins Medical Institutions, Baltimore, MD 21231, USA
[c] Department of Psychiatry, Johns Hopkins Medical Institutions, Baltimore, MD 21231, USA
[d] Department of Neurology, Johns Hopkins Medical Institutions, Baltimore, MD 21231, USA

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ABSTRACT

*Introduction:* Site-selective imaging can provide significant insight into the mechanism of HIV-associated neurological disease. The goal of this study was to evaluate the involvement of serotonergic transmission in HIV-associated depression using [$^{11}$C]DASB, a serotonin transporter (5-HTT)-specific radiopharmaceutical for positron emission tomography (PET).
*Methods:* Nine depressed HIV+ subjects (HIV-D), 9 non-depressed HIV+ subjects (HIV-ND) and 7 healthy controls (HC) underwent an MRI scan and a [$^{11}$C]DASB-PET scan. The outcome measure was 5-HTT binding potential normalized to non-displaceable tissue radioligand ($BP_{ND}$).
*Results:* HIV-ND subjects had lower mean regional 5-HTT $BP_{ND}$ estimates across regions compared to HC, while HIV-D subjects demonstrated higher mean regional binding values than HIV-ND subjects in most regions. Prior to correction for the false discovery rate, HIV-ND had significantly lower $BP_{ND}$ values compared to HC subjects in two regions (insula and anterior cingulate) and all HIV+ patients had significantly lower binding than HC in all regions except for the midbrain, thalamus and pons. After correction for the false discovery rate, only the insula showed significantly lower binding in HIV+ subjects compared to HC ($P<0.0045$). Despite a significant difference in the duration of illness between the HIV-D and HIV-ND groups, there was no definite correlation between the duration of illness and $BP_{ND}$.
*Conclusion:* Lower [$^{11}$C]DASB binding in HIV+ patients compared to HC may reflect serotonergic neuronal loss as a component of generalized HIV-associated neurodegeneration. Higher mean regional $BP_{ND}$ values in HIV-D compared to HIV-ND subjects could reflect increased density of 5-HTT, leading to increased clearance of serotonin from the synapse, which could account, in part, for symptoms of depression. The lack of correlation between duration of illness and binding argues against these findings being the result of differential neurodegeneration only. Our findings suggest a possible role for dysregulated serotonergic transmission in HIV-associated depression.



## Introduction

Neuropsychiatric symptoms, including depression, are very common and well recognized in the setting of HIV infection (Cruess et al., 2003; Repetto et al., 2003; Starace et al., 2002; Trepanier et al., 2005). In fact, a meta-analysis of the relationship between HIV infection and risk for depressive disorders found that HIV-seropositive (HIV+) individuals were twice as likely to be diagnosed with major depression as HIV-negative individuals (Ciesla and Roberts, 2001). Besides its known direct negative effects, depression in HIV+ patients is associated with increased substance abuse (Kalichman et al., 1997), poor treatment adherence (Catz et al., 2000; Safren et al., 2001) and worse HIV viral control (Horberg et al., 2007). Also, untreated depression in HIV+ individuals can promote risk-taking behavior leading to further spread of the disease (Dursun and Reveley, 1995; Kopnisky et al., 2004). Because of the abovementioned reasons, recognizing and treating depression become of utmost importance in this patient population.

The involvement of the serotonergic system in the pathophysiology of HIV-associated mood disorders, namely depression, has long been suspected (Dube et al., 2005; Dursun and Reveley, 1995). HIV+ depressed patients respond to antidepressant therapy, including selective serotonin reuptake inhibitors (SSRIs) (Elliott et al., 1998; Rabkin et al., 1999; Schwartz and McDaniel, 1999). However, neither the mechanism by which depression arises in those patients nor exploration of appropriate diagnostic and treatment regimens has

* Corresponding author. Johns Hopkins Medical Institutions, 1550 Orleans Street, 492 CRB II, Baltimore, MD 21231, USA. Fax: +1 443 817 0990.
*E-mail address:* mpomper@jhmi.edu (M.G. Pomper).

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been adequately addressed. There have been no neuroreceptor or neurotransmitter imaging studies targeting the serotonergic system in the setting of neuroAIDS (neurologic disorders that result primarily from damage to the central and peripheral nervous system by HIV).

One way of evaluating the serotonergic system is through evaluation of serotonin transporter (5-hydroxytryptamine transporter or 5-HTT) integrity, especially in view of the successful treatment of depressed patients with SSRIs (Elliott et al., 1998; Rabkin et al., 1999; Schwartz and McDaniel, 1999). That is especially true in the case of HIV+ individuals since SSRIs are recommended as first line treatment for depression due to their superior side effect profile (Caballero and Nahata, 2005; Elliott et al., 1999). One way to evaluate serotonergic transmission non-invasively in human subjects is through imaging with positron emission tomography (PET).

[$^{11}$C]DASB (3-$^{11}$C-amino-4-(2-dimethylaminomethylphenylsulfanyl) benzonitrile), a newer radiopharmaceutical for 5-HTT, was found to be superior to other radioligands such as [$^{11}$C]McN5652 and [$^{123}$I]β-CIT due to its fast kinetics, reversibility, higher selectivity and greater specific binding (Ginovart et al., 2001; Ichise et al., 2003; Wilson et al., 2002) as well as higher reproducibility (Frankle et al., 2006; Kim et al., 2006). Unlike the previously described radioligands, [$^{11}$C]DASB shows 1200-fold selectivity in its affinity for 5-HTT versus norepinephrine transporter or dopamine transporter sites. Currently, [$^{11}$C]DASB represents the best option among radiopharmaceuticals for imaging 5-HTT (Meyer, 2007). [$^{11}$C]DASB has been used by several groups in the setting of major depression (Bhagwagar et al., 2007; Cannon et al., 2007; Meyer, 2007; Meyer et al., 2004), bipolar disorder (Cannon et al., 2006), alcoholism (Brown et al., 2007) and tryptophan depletion (Praschak-Rieder et al., 2005) as well as in occupancy studies of different SSRIs (Voineskos et al., 2007; Parsey et al., 2006b,a; Takano et al., 2006b). However, serotonergic transmission has not been imaged with [$^{11}$C]DASB, or any other radiopharmaceutical, in the context of HIV-associated mood disorders.

In an effort to gain further understanding of the mechanism of depression in HIV, specifically to study the potential contribution of serotonergic disruption, we used [$^{11}$C]DASB-PET to compare three different groups of subjects: HIV+ depressed patients (HIV-D), HIV+ non-depressed patients (HIV-ND) and healthy non-depressed controls (HC). Our underlying hypothesis was that HIV-D subjects will demonstrate higher binding of [$^{11}$C]DASB compared to HIV-ND, similar to what has been shown in most [$^{11}$C]DASB-PET studies in the literature, which have evaluated a variety of depressive psychiatric diseases (Bhagwagar et al., 2007; Cannon et al., 2006, 2007; Meyer et al., 2004; Takano et al., 2007). We thought the depressive symptoms could possibly be related to higher 5-HTT density/activity resulting in lower intrasynaptic serotonin levels, as has been previously suggested in the literature (Meyer, 2007). We also wanted to assess whether there was any correlation between [$^{11}$C]DASB binding and the 5-HTT-linked polymorphic region (5-HTTLPR) genotype, according to the suggested genetic theory of depression (Pezawas et al., 2005).

## Methods

### *Human subjects*

HIV+ patients were recruited from the Johns Hopkins Hospital HIV/AIDS Service (Moore Clinic) Psychiatric Clinic. The control population was recruited from the general population through advertisement approved by our institutional review board (IRB).

Exclusion criteria included a history of SSRI use within 1 year prior to entry, history of current or past opportunistic central nervous system (CNS) infection at the start of the study, history or concurrent clinical evidence of a psychotic disorder (e.g., schizophrenia), history of chronic neurological disorder such as multiple sclerosis or epilepsy or structural CNS abnormalities such as stroke or arteriovenous malformation and history of present or recent (within the last year prior to the study) drug dependence, including cocaine, methamphetamine, opiates, barbiturates or alcohol. All subjects provided written consent as approved by the Johns Hopkins Hospital IRB.

Our final study population consisted of seven HC (age range = 23–53 years, mean = 39.9 ± 7.8 years), nine HIV-ND subjects (age range = 36–55 years, mean = 47.2 ± 4 years) and nine HIV-D subjects (age range = 29–54 years, mean = 42.4 ± 5.6 years). There was no significant difference in the age range between the three groups of patients [$P = 0.18$, one-way analysis of variance (ANOVA)].

All of our HIV+ patients were being treated with highly active antiretroviral therapy (HAART) at the time of recruitment except for two subjects in each group. The four patients who were not treated with HAART at the time of the study, however, had received HAART in the recent past. The CD4 counts of the patients at the time of recruitment varied from 270 to 467. There were no significant differences in the CD4 counts between the HIV-D and HIV-ND groups ($P > 0.05$, unpaired, two-tailed $t$-test). Four patients in the HIV-D group and four patients in the HIV-ND group admitted to prior drug abuse; however, all were free of drug use for at least 1 year prior to the study. Three patients in the HIV-D group admitted to past use of alcohol, with no alcohol use for at least 1 year prior to the study.

### *Psychiatric evaluation*

Written informed consent was obtained from each participant by trained study members. Participants (HIV+ and healthy controls) who fulfilled all inclusion criteria were required to complete the symptom checklist-90-R (SCL-90-R), a self-reported 90-item assessment of psychological distress and symptoms in nine areas: somatization, obsessive–compulsive personality, interpersonal sensitivity, depression, anxiety, aggression, phobia, paranoid ideation and psychoticism (Derogatis, 1992). Each item is rated on a Likert scale indicating level of distress ranging from (0) "not at all" to (4) "extremely." The depression assessment on the SCL-90-R is comprised of 10 items. The SCL-90-R serves as an effective tool for initial evaluation of symptoms and as a method of tracking changes in symptoms in response to treatment (Derogatis, 1997; Holi et al., 1998; Knekt et al., 2008; Schmitz et al., 2001; Skydsbjerg et al., 2001). The diagnosis of current depressed state was further determined by the administration of a Structured Clinical Interview for DSM IV diagnosis (SCID) by a clinician (Spitzer et al., 1992). The SCID has been used in clinical and research settings and has been found to be reliable in several research studies (Williams et al., 1992). Where there was disagreement between depression status as determined by the SCID and the SCL-90-R, depression status as determined by the SCID was used.

We recruited 19 HIV+ subjects and seven HC subjects for this study. One HIV+ patient had inconsistent psychiatric test results and markedly decreased uptake of [$^{11}$C]DASB in the brain, comparable to reported levels seen in patients treated with SSRIs (~15–20% of normal uptake) (Meyer, 2007; Takano et al., 2006a,b; Voineskos et al., 2007), despite denial of their use. When we compared the $BP_{ND}$ values of that patient to all HIV+ patients, these were at least two standard deviations lower than the mean values, in all high binding areas. Therefore, we considered this patient an outlier and excluded those $BP_{ND}$ results from the final analysis.

Among the other seven HC and 18 HIV+ patients, there was a 96% concordance rate in the diagnosis of depression between the SCID and SCL-90R. One out of 25 participants (4%) had a positive diagnosis of depression on the SCID but was not depressed as assessed by the SCL-90. In that case, a diagnosis of depression assessed by the SCID was upheld and the patient was placed in the depressed category. In total, out of 18 HIV+ subjects, nine were classified as depressed. Thus, our group included seven HC, nine HIV-D and nine HIV-ND subjects.

No one in either the patient or control population was being treated for depression at the time of the PET scan. Once a patient