Title

Cerebrospinal fluid levels of 5-HIAA and dopamine in people with HIV and depression

Journal

Journal of NeuroVirology, 29(4)

ISSN

1355-0284

Authors

Fu, Rong

Jinnah, Hyder

Mckay, J Lucas

et al.

Publication Date

2023-08-01

DOI

10.1007/s13365-023-01142-2

Peer reviewed

HHS Public Access

Author manuscript

J Neurovirol. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:

J Neurovirol. 2023 August ; 29(4): 440–448. doi:10.1007/s13365-023-01142-2.

Cerebrospinal fluid levels of 5-HIAA and dopamine in people with HIV and depression

Rong Fu[1], **Hyder Jinnah**[2], **J. Lucas Mckay**[3], **Andrew H. Miller**[4], **Jennifer C. Felger**[4], **Eugene W. Farber**[4], **Sanjay Sharma**[4], **Neil Whicker**[4], **Raeanne C. Moore**[5], **Donald Franklin**[5], **Scott L. Letendre**[6], **Albert M. Anderson**[7]

[1]Department of Pharmacology and Chemical Biology, Emory University School of Medicine, Atlanta, GA, USA

[2]Department of Neurology, Human Genetics and Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

[3]Department of Biomedical Informatics, Emory University, Atlanta, GA, USA

[4]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

[5]Department of Psychiatry, University of California at San Diego School of Medicine, La Jolla, San Diego, CA, USA

[6]Department of Medicine, University of California at San Diego School of Medicine, La Jolla, San Diego, CA, USA

[7]Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

Abstract

Depression is a common illness in people with HIV (PWH) and is associated with substantial morbidity and mortality. The mechanisms that underpin depression in PWH remain incompletely elucidated, and more research is therefore needed to develop effective treatments. One hypothesis is that neurotransmitter levels may be altered. These levels could be influenced by the chronic inflammation and viral persistence that occurs in PWH. We examined a panel of cerebrospinal fluid (CSF) neurotransmitters in PWH on suppressive antiretroviral therapy (ART), many of whom had a current depression diagnosis. CSF monoamine neurotransmitters and their metabolites were measured from participants in studies at the Emory Center for AIDS Research (CFAR). Only participants on stable ART with suppressed HIV RNA from both plasma and CSF were analyzed. Neurotransmitter levels were measured with high-performance liquid chromatography (HPLC). Neurotransmitters and their metabolites included dopamine (DA), homovanillic acid (HVA, a major metabolite of dopamine), serotonin (5-HT), 5-hydroxyindole-3-acetic acid (5-HIAA, a major metabolite of serotonin), and 4-hydroxy-3-methoxyphenylglycol (MHPG, a major metabolite of norepinephrine). Multivariable logistic regression was used to evaluate factors

✉Albert M. Anderson, aande2@emory.edu.

Conflict of interest The authors declare no competing interests.

associated with depression. There were 79 PWH with plasma and CSF HIV RNA levels < 200 copies/mL at the time of the visit, and 25 (31.6%) carried a current diagnosis of depression. Participants with depression were significantly older (median age 53 years versus 47 years, $P = 0.014$) and were significantly less likely to be African American (48.0% versus 77.8%, $P = 0.008$). Participants with depression had significantly lower dopamine levels (median 0.49 ng/mL versus 0.62 ng/mL, $P = 0.03$) and significantly lower 5-HIAA levels (median 12.57 ng/mL versus 15.41 ng/mL, $P = 0.015$). Dopamine and 5-HIAA were highly correlated. In the multivariable logistic regression models, lower 5-HIAA was significantly associated with the depression diagnosis when accounting for other significant demographic factors. The associations between lower 5-HIAA, lower dopamine, and depression in PWH suggest that altered neurotransmission may contribute to these comorbid conditions. However, the effects of antidepressants on neurotransmitters cannot be ruled out as a factor in the 5-HIAA results.

Keywords

HIV; Depression; Cerebrospinal fluid; Serotonin; Dopamine

Introduction

Despite the effectiveness of combination antiretroviral therapy (ART) in improving health and lifespan, people living with HIV (PWH) continue to experience high rates of comorbid diseases (Gallant et al. 2017). One such disease is depression, which is associated with one of the highest rates of medical disability in the general population worldwide (Global Burden of Disease Study C 2015). The prevalence of depression in PWH far exceeds the prevalence in the general population (Vlassova et al. 2009). The Women's Interagency HIV study (WIHS), for instance, found that 20% of women with HIV have major depression based on diagnostic interview (compared to 10% nationally), and 32.4% experience major depression in their lifetime (versus 22.9% nationally) (Cook et al. 2018; Rubin and Maki 2019). The medical monitoring project also found that depression prevalence is significantly higher in men with HIV (prevalence ratio = 3.1) compared to a cohort of individuals from the general population. (Do et al. 2014)

Having untreated depression in the context of HIV is associated with significantly decreased adherence to ART and lack of virologic control (Horberg et al. 2008; Kacanek et al. 2010). With lack of HIV suppression comes increased morbidity and mortality (Strategies for Management of Antiretroviral Therapy Study et al. 2006; Group ISS et al. 2015). PWH with chronic depression symptoms are approximately twice as likely to die compared to PWH with few or no depression symptoms (Ickovics et al. 2001). Conversely, treatment of depression enhances adherence to antiretroviral therapy (Sin and DiMatteo 2014). Given the critical role of depression management for achieving favorable HIV health outcomes, the pathogenesis of depression in PWH needs to be better understood in order to inform the development of optimal treatments for depression in the setting of HIV.

While increased inflammation is associated with depression among PWH (Anderson et al. 2022; Poudel-Tandukar et al. 2014), there is also evidence that neurotransmitter levels

are perturbed (possibly as a result of this increased inflammation). For example, serotonin (5-HT) concentrations from CSF have been demonstrated to be lower in PWH compared to people without HIV (PWOH) (Kumar et al. 2001). HIV proteins such as gp120 can induce in vitro dopamine (DA) neurotoxicity (Bennett et al. 1995). In the pre-ART era, cerebrospinal fluid (CSF) concentrations of dopamine (DA) and its metabolite homovanillic acid (HVA) were found to be decreased in PWH (Berger et al. 1994; Larsson et al. 1991). In a study of postmortem brain samples, there was a significant decrease in DA levels in caudate nucleus, putamen, globus pallidus, and substantia nigra in PWH compared to brain samples from PWOH (Kumar et al. 2009). Similar findings have been shown in the non-human primate model of HIV (Scheller et al. 2005). Saloner et al. published an analysis of adult PWH on suppressive ART in which CSF concentrations of DA and HVA were investigated in relation to depression symptoms using the Beck Depression Inventory (BDI)-II (Saloner et al. 2020). Correlational analyses revealed significant associations between higher cognitive symptoms of depression and lower HVA ($r = -0.22$, $P = 0.016$) and dopamine ($r = -0.20$, $P = 0.025$) z-scores among PWH. In multivariable models, lower HVA z-scores were significantly related to higher BDI-II scores in PWH ($b = -2.14$, $r = -0.19$, $P = 0.034$). A significant interaction in the same direction was also present between HIV status and dopamine in association with BDI-II scores ($b = -3.15$, $P = 0.033$).

Due to the high frequency of depression in PWH and the need to better understand how neurotransmitters may mediate this illness, we evaluated a CSF neurotransmitter panel in PWH on ART. We then evaluated relationships between neurotransmitter levels and a current diagnosis of depression, which was common in this cohort.

Methods

We analyzed CSF samples from PWH enrolled in studies performed at the Emory Center for AIDS Research (CFAR) from 2011 to 2020. Given the known effects of uncontrolled HIV on the CNS, we limited the investigation to participants on stable ART for at least 6 months with both plasma and CSF HIV RNA < 200 copies/mL at the study visit, which meets the definition of suppression based on the latest US Department of Health and Human Services guidelines (United States Department of Health and Human Services 2022). HIV RNA levels (both plasma and CSF) were measured using the Abbott Laboratories m2000 Real Time HIV-1 assay system (reverse transcriptase polymerase chain reaction). The exclusion criteria were (1) history of neurologic diseases that could pre-dispose to depression (including stroke, malignancy involving the brain, traumatic brain injury, schizophrenia, and AIDS-related opportunistic infection of the central nervous system); (2) active substance use (cocaine, heroin, methamphetamine, or other non-marijuana illicit drug use in the last 30 days; marijuana use was permitted but participants were asked to abstain for at least 48 h prior to study visit); and (3) heavy alcohol consumption in the last 30 days (defined as > 7 drinks per week for women and > 14 drinks per week for men).

Depression was documented as a current diagnosis based on the medical record and confirmation by the participant. Bipolar depression was included in this group. A neuropsychological (NP) testing battery was administered that included nine tests used commonly in studies of cognition and HIV infection (Robertson and Yosief 2014): (1) Trail

Making Part A,(2) Trail Making Part B; (3) Hopkins Verbal Learning Test Total Learning; (4) Hopkins Verbal Learning Test Delayed Recall; (5) Grooved Pegboard (dominant); (6) Grooved Pegboard (non-dominant); (7) Stroop Color Naming; (8) Stroop Color–Word Interference; and (9) Letter Fluency (Controlled Oral Word Association Test). Scores were adjusted for demographic characteristics (including age, gender, race, and education) using published norms (Heaton et al. 2004). Score adjustment for practice effects was made with published methods for participants who had undergone testing previously (Cysique et al. 2011). A composite global mean *T* score (NPT-9) was then calculated by averaging individual *T* scores.

CSF was obtained during morning visits between 8:00 AM and 12:00 AM and stored at 80 °C. The neurotransmitter analysis was performed in a single batch. One hundred μL CSF aliquots were mixed with 10 μL of 1 mol/L perchloric acid and placed on ice for 15 min. The samples were then centrifuged at 13,000 × rpm for 30 min at 4°C to remove the precipitated proteins. The analytes were measured in the supernatant by high-performance liquid chromatography with electrochemical detection as described previously (Song et al. 2012). Briefly, an ESA 5600A CoulArray detection system equipped with an ESA Model 584 pump and an ESA 542 refrigerated autosampler was used. Separations were performed using an MD-150 × 3.2 mm C18 (3 μM) column at 28°C. The mobile phase consisted of 8% acetonitrile, 75 mM NaH_2PO_4, 1.6 mM 1-octanesulfonic acid sodium, and 0.025% trimethylamine at pH 3.2. Twenty-five μL of sample was injected. The samples were eluted isocratically at 0.4 mL/minute and detected using a 6210 electrochemical cell (ESA, Bedford, MA) equipped with 5020 guard cell. Guard cell potential was set at 475 mV, while analytical cell potentials were– 175, 150, 350, and 425 mV. The analytes were identified by the matching criteria of retention time and sensor ratio measures to known standards (Sigma Chemical Co., St. Louis MO) and were quantified by comparing peak areas to those of standards on the dominant sensor. These included DA, HVA, 5-HT, 5-hydroxyindole-3-acetic acid (5-HIAA, a major metabolite of serotonin that is often measured due to the rapid metabolism of 5-HT), and 4-hydroxy-3-methoxyphenylglycol (MHPG, a major metabolite of norepinephrine). MHPG was selected as a representative of the noradrenergic pathway due to the relatively low sensitivity of norepinephrine quantification.

Distributions of data for continuous variables were assessed with the Shapiro–Wilk test. The neurotransmitter data did not meet criteria for normality. Therefore, comparisons between continuous variables were performed using the Wilcoxon rank sum test, with the exception of comparison of NPT-9 by depression category, which was performed with the *t* test. Comparisons between proportions were performed using Fisher's exact test. Spearman's rho was used for correlation testing. *P* values were two-sided and subsequently underwent adjustment for multiple comparisons using false discovery rate correction (Bejamini 1995). Multivariable logistic regression was then used to evaluate variables in relationship with the depression diagnosis. This included demographic factors and neurotransmitter levels that were associated with depression with *P* values < 0.05 in univariable analysis. In an exploratory analysis, sex (men/women) was still considered after being found non-significant in univariable analysis.

Results

Of 79 PWH analyzed, 25 (31.6%) carried a current diagnosis of depression (Table 1).Seventy-eight of 79 participants with the current depression diagnosis were on pharmacologic therapy for depression. Twenty-one of 25 (84%) were on serotonergic antidepressants (serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or tricyclic antidepressants). Two of 54 individuals (3.7%) without depression were on serotonergic antidepressants for other reasons, which was significantly less frequent ($P < 0.0001$) than individuals with depression. Nine of the 25 (36%) with depression were on antipsychotic therapy, while none of the participants without depression were on antipsychotic therapy ($P < 0.0001$). Participants with depression were significantly older (median age 53 years versus 47 years, $P = 0.014$) and were significantly less likely to be African American (48.0% versus 77.8%, $P = 0.008$).

Participants with the depression diagnosis had significantly lower dopamine levels (median 0.49 ng/mL versus 0.62 ng/mL, $P = 0.03$) (Fig. 1a and Table 2) and significantly lower 5-HIAA levels (median 12.57 ng/mL versus 15.41 ng/mL, $P = 0.015$) (Fig. 1b and Table 2). Both of these P values increased to 0.08 after FDR correction. The HVA/5-HIAA ratio was also significantly higher ($P = 0.008$) among participants with depression (median = 3.04, interquartile range (IQR) = 2.58–4.59) than those without depression (median = 2.47, IQR = 2.0–3.22). The HVA/MHPG ratio was not significantly different ($P = 0.37$) between those with depression (median = 4.42, IQR = 2.74–6.92) and those without (median = 3.79, IQR = 2.59–5.59).

There was no significant difference in NPT-9 by depression status (mean 46.9 in the group with depression versus 48.7 in the group without depression, $P = 0.29$). There were no significant associations between the neurotransmitters and NPT-9 score (all P values > 0.1). There were four significant correlations between neurotransmitters (Table 3). Specifically, 5-HIAA significantly correlated with both DA (rho = 0.76, $P < 0.0001$) and HVA (rho = 0.57, $P < 0.0001$); DA significantly correlated with HVA (rho = 0.34, $P = 0.002$); and MHPG significantly correlated with 5-HT (rho = 0.23, $P = 0.04$, which became > 0.05 after FDR).

Given the high correlation between DA and 5-HIAA, these two were not included in the same models. For models that included race as a variable, only black and white were considered ($N = 78$). As seen in the top half of Table 4, lower CSF 5-HIAA was associated with depression when age and race were considered separately. When age and race were considered together, lower CSF 5-HIAA was the only variable that was significantly associated with depression (odds ratio (OR) = 0.89, 95% confidence interval (95% CI) = 0.81–0.98). As seen in the bottom half of Table 4, lower CSF DA was significantly associated with depression in the model that included age. While the OR for CSF DA was 0.12 in the models that included age and race together, the 95% CI was 0.01–1.14. For the models in which sex (men/women) was included with age and black/white race despite being non-significant in univariable analysis, the OR and 95% CI for CSF 5-HIAA and CSF DA were 0.89 (0.81–0.99) and 0.1 (0.009–1.13), respectively.

Discussion

PWH are significantly more likely to experience depression than PWOH (Cook et al. 2018; Do et al. 2014). The consequences of having depression and HIV are substantial. Depression is associated with decreased adherence to ART and lack of virologic control (Horberg et al. 2008; Kacanek et al. 2010). Each 25% increase in time spent with depression is associated with a 19% increase in mortality hazard among PWH (Pence et al. 2018). A better understanding of the biological underpinnings of depression in PWH is therefore needed.

Both the dopamine and serotonin systems have been linked to depression in HIV-negative general populations, but these findings have not always been consistent. Multiple studies showed a decrease in CSF 5-HIAA among people with depression and a decrease in 5-HT in postmortem brains of people with depression (Owens and Nemeroff 1994; Roy et al. 1989). However, a meta-analysis of drug-free individuals found significantly lower HVA (but not 5-HIAA or MHPG) among individuals with depression (Ogawa et al. 2018). There has been a dearth of studies in which CSF neurotransmitters have been evaluated in relation to depression in PWH. In the current study, we evaluated a panel of neurotransmitters and their metabolites representing three categories: serotonergic (5-HT and 5-HIAA), dopaminergic (DA and HVA), and noradrenergic (MHPG). We found that both DA and 5-HIAA were significantly lower among PWH with a current depression diagnosis. While the *P* values in the univariable analysis became > 0.05 with false discovery rate correction, the effect sizes between the two groups were substantial (Cohen's D = 0.55 for DA and = 0.58 for 5-HIAA). 5-HT is quickly metabolized to 5-HIAA, which appears to be more stable than 5-HT and thus may be a more reliable measure of serotonin abundance (Jayamohananan et al. 2019). This is supported by the results of the current study, in which 5-HIAA concentrations were tenfold higher than 5-HT concentrations. In multivariable logistic regression models, lower CSF 5-HIAA was associated with the depression diagnosis when accounting for age and race (as well as sex in exploratory analysis). The findings of the study support a possible relationship between the serotonin system and depression in PWH. However, an important limitation of the study is that most of the participants with depression were on serotonergic antidepressants while almost none of the participants without depression were on serotonergic antidepressants. This means that a comparison of neurotransmitters between participants on and off serotonergic therapy was similar to the comparison based on depression status. It is possible that the differences based on depression status were driven by the differences in serotonergic medication use. Specifically, while CSF 5-HIAA concentrations increase in the acute period with administration of serotonergic medication therapy (Carpenter et al. 2003), there is evidence that these levels paradoxically decrease after several weeks of use (Bellis et al. 1993; Sheline et al. 1997). We acknowledge that this is a possible factor in the study results.

Conversely, the potential confounding of medication use may be less significant on the dopamine findings in the study. Chronic serotonergic medication use does not appear to significantly change levels of dopamine metabolites (Bellis et al. 1993; Sheline et al. 1997). Meanwhile, antipsychotic medication treatment (which many of the participants with depression in the current study were taking) is associated with increased dopamine

metabolites (Scheepers et al. 2001; Kahn et al. 1993). Therefore, the association between lower dopamine level and depression in the study may have been even stronger in the absence of antipsychotic medications. It is also important to note that the magnitude of the OR for dopamine (0.12) appeared to higher than for 5-HIAA (0.89), though the 95% CI for dopamine crossed 1 in the model that included both age and race.

The only other published study evaluating the relationship between neurotransmitters and depression among PWH also used HPLC to measure DA and its metabolite HVA (serotonin-related markers were not measured) (Saloner et al. 2020). This previous study found that lower DA and HVA were associated with higher depression symptom severity in PWH, with the HVA relationship being the strongest. There are a few differences in the study populations. The participants in the current study were (1) older (mean 48 years versus 41 years; (2) more likely women (24% versus 8%; and (3) more likely African American (68% versus 11%. While all participants in the current study were on ART with suppressed blood and CSF HIV RNA, almost 50% did not have virologic suppression in the previous study. Given the relationships of HIV proteins to dopamine neurotoxicity and uncontrolled HIV to decreased DA and HVA (Bennett et al. 1995; Berger et al. 1994; Larsson et al. 1991), virologic control may attenuate the relationship between dopamine and depression in PWH. However, a smaller secondary analysis in the previous study limited to individuals with virologic control still showed a significant relationship between lower HVA and higher depression symptoms. In the previous study, current depression symptoms were assessed by Beck Depression Inventory (BDI-II) interview. In contrast, a current depression diagnosis based on medical record and participant report was used for the current study. Depression severity assessment was not performed at the time of the study visits for the current study, which we acknowledge is a limitation. Depression scales that evaluate current symptoms, such as the BDI-II, the Patient Health Questionnaire (PHQ)-9, the Center for Epidemiological Studies Depression (CES-D) assessment, and other scales, should be considered when studying PWH with depression. Another difference between the two studies is that we did not analyze inflammatory biomarkers in this study. Several markers of inflammation, including tumor necrosis factor, interleukin-6, soluble CD163, and others, have been linked to depression among PWH (Ellis et al. 2020; Musinguzi et al. 2018; Norcini Pala et al. 2016). Further research should include both markers of inflammation and neurotransmitters, which may be linked.

Race was incorporated as a covariable given its association with the depression outcome in the univariable analysis. We acknowledge that the difference in depression diagnosis based on race may be due to underdiagnosis. Depression in African Americans is often diagnosed less accurately, which may be due to social determinants of health (Bailey et al. 2011). While the possibility of underdiagnosis should be acknowledged, multiple studies have shown that depression prevalence is lower in African Americans than in whites in the USA (Riolo et al. 2005; Williams et al. 2007). This difference in prevalence based on race has also been shown in some but not all analyses of HIV-infected populations (Do et al. 2014; Anderson et al. 2022). Therefore, the results of the current study may not be due strictly to underdiagnosis. Given that almost all of the participants with depression were on pharmacologic therapy, it is possible that these findings would have been different in medication-free individuals. It is possible that those with the lowest dopamine levels are the

most resistant to antidepressants and reflect a population with disease that is more severe. It is common practice in our community for people with depression to be diagnosed and managed by primary medical providers. While we can confirm through the medical record that many of the participants with depression in the current study were diagnosed and managed by mental health providers, some were not. In other cases, it was not clear. While we acknowledge that depression is sometimes falsely diagnosed in primary medical settings, a large study of over 50,000 individuals found that false-positive depression diagnosis by primary medical providers was relatively low (15% of cases). (Mitchell et al. 2009).

Overall, the results of the current study support that both the serotonin and dopamine systems should be further evaluated to better understand depression in the setting of HIV. Ideally, participants would be evaluated prior to antidepressant therapy, but this is challenging given the frequent severity of the condition, which necessitates pharmacologic therapy. Neuroimaging also suggests that the serotonin system may be perturbed during HIV. Specifically, positron emission tomography (PET) shows increased 5-HT transporter activity in the non-human primate model of HIV, which could lead to lower synaptic levels of 5-HT. (Shah et al. 2019) Future studies should also incorporate novel neuroimaging techniques when possible.

Funding

The authors gratefully acknowledge funding R01AG062387, R01MH128872, and R01MH128158, as well as P30AI050409 (Emory Center for AIDS Research).

Data availability

Study data may be provided on request.

References

Anderson AM, Bhondoekhan F, Curanovic D et al. (2022) Higher soluble CD163 in blood is associated with significant depression symptoms in men with HIV. Journal of Acquired Immune Deficiency Syndromes (JAIDS)

Bailey RK, Patel M, Barker NC, Ali S, Jabeen S (2011) Major depressive disorder in the African American population. J Natl Med Assoc 103:548–557 [PubMed: 21999029]

Bejamini YHY (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Royal Stat Soc Series B (Methodological) 257:289–300

Bennett BA, Rusyniak DE, Hollingsworth CK (1995) HIV-1 gp120-induced neurotoxicity to midbrain dopamine cultures. Brain Res 705:168–176 [PubMed: 8821747]

Berger JR, Kumar M, Kumar A, Fernandez JB, Levin B (1994) Cerebrospinal fluid dopamine in HIV-1 infection. AIDS 8:67–71 [PubMed: 8011238]

Carpenter LL, Anderson GM, Siniscalchi JM, Chappell PB, Price LH (2003) Acute changes in cerebrospinal fluid 5-HIAA following oral paroxetine challenge in healthy humans. Neuropsychopharmacology 28:339–347 [PubMed: 12589387]

Cook JA, Burke-Miller JK, Steigman PJ et al. (2018) Prevalence, comorbidity, and correlates of psychiatric and substance use disorders and associations with HIV risk behaviors in a multisite cohort of women living with HIV. AIDS Behav 22:3141–3154 [PubMed: 29460130]

Cysique LA, Franklin D Jr, Abramson I et al. (2011) Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change. J Clin Exp Neuropsychol 33:505–522 [PubMed: 21391011]

De Bellis MD, Geracioti TD Jr, Altemus M, Kling MA (1993) Cerebrospinal fluid monoamine metabolites in fluoxetine-treated patients with major depression and in healthy volunteers. Biol Psychiatry 33:636–641 [PubMed: 7687151]

Do AN, Rosenberg ES, Sullivan PS et al. (2014) Excess burden of depression among HIV-infected persons receiving medical care in the united states: data from the medical monitoring project and the behavioral risk factor surveillance system. PLoS ONE 9

Ellis RJ, Letendre SL, Atkinson JH et al. (2020) Higher levels of plasma inflammation biomarkers are associated with depressed mood and quality of life in aging, virally suppressed men, but not women, with HIV. Brain Behav Immun Health 7

Gallant J, Hsue PY, Shreay S, Meyer N (2017) Comorbidities among US patients with prevalent HIV infection-a trend analysis. J Infect Dis 216:1525–1533 [PubMed: 29253205]

Global Burden of Disease Study C (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386:743–800 [PubMed: 26063472]

Group ISS, Lundgren JD, Babiker AG et al. (2015) Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 373:795–807 [PubMed: 26192873]

Heaton RK, Miller SW, Taylor MJ, Grant I (2004) Revised comprehensive norms for an expanded Halstead-Reitan battery: demographically adjusted Europsycho-logical norms for African American and Caucasian adults scoring program

Horberg MA, Silverberg MJ, Hurley LB et al. (2008) Effects of depression and selective serotonin reuptake inhibitor use on adherence to highly active antiretroviral therapy and on clinical outcomes in HIV-infected patients. J Acquir Immune Defic Syndr 47:384–390 [PubMed: 18091609]

Ickovics JR, Hamburger ME, Vlahov D et al. (2001) Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study. JAMA, J Am Med Assoc 285:1466–1474

Jayamohananan H, Manoj Kumar MK (2019) T PA 5-HIAA as a potential biological marker for neurological and psychiatric disorders. Adv Pharm Bull 9:374–81 [PubMed: 31592064]

Kacanek D, Jacobson DL, Spiegelman D, Wanke C, Isaac R, Wilson IB (2010) Incident depression symptoms are associated with poorer HAART adherence: a longitudinal analysis from the Nutrition for Healthy Living study. J Acquir Immune Defic Syndr 53:266–272 [PubMed: 20104122]

Kahn RS, Davidson M, Knott P, Stern RG, Apter S, Davis KL (1993) Effect of neuroleptic medication on cerebrospinal fluid monoamine metabolite concentrations in schizophrenia. Serotonin-dopamine interactions as a target for treatment. Arch Gen Psych 50:599–605

Kumar AM, Berger JR, Eisdorfer C, Fernandez JB, Goodkin K, Kumar M (2001) Cerebrospinal fluid 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in HIV-1 infection. Neuropsychobiology 44:13–18 [PubMed: 11408787]

Kumar AM, Fernandez JB, Singer EJ et al. (2009) Human immunodeficiency virus type 1 in the central nervous system leads to decreased dopamine in different regions of postmortem human brains. J Neurovirol 15:257–274 [PubMed: 19499455]

Larsson M, Hagberg L, Forsman A, Norkrans G (1991) Cerebrospinal fluid catecholamine metabolites in HIV-infected patients. J Neurosci Res 28:406–409 [PubMed: 1856886]

Mitchell AJ, Vaze A, Rao S (2009) Clinical diagnosis of depression in primary care: a meta-analysis. Lancet 374:609–619 [PubMed: 19640579]

Musinguzi K, Obuku A, Nakasujja N et al. (2018) Association between major depressive disorder and pro-inflammatory cytokines and acute phase proteins among HIV-1 positive patients in Uganda. BMC Immunol 19:1 [PubMed: 29298663]

Norcini Pala A, Steca P, Bagrodia R et al. (2016) Subtypes of depressive symptoms and inflammatory biomarkers: an exploratory study on a sample of HIV-positive patients. Brain Behav Immun 56:105–113 [PubMed: 26883521]

Ogawa S, Tsuchimine S, Kunugi H (2018) Cerebrospinal fluid monoamine metabolite concentrations in depressive disorder: a meta-analysis of historic evidence. J Psychiatr Res 105:137–146 [PubMed: 30219563]

Owens MJ, Nemeroff CB (1994) Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin Chem 40:288–295 [PubMed: 7508830]

Pence BW, Mills JC, Bengtson AM et al. (2018) Association of increased chronicity of depression with HIV appointment attendance, treatment failure, and mortality among HIV-infected adults in the United States. JAMA Psychiat 75:379–385

Poudel-Tandukar K, Bertone-Johnson ER, Palmer PH, Poudel KC (2014) C-reactive protein and depression in persons with human immunodeficiency virus infection: the Positive Living with HIV (POLH) Study. Brain Behav Immun 42:89–95 [PubMed: 24929193]

Riolo SA, Nguyen TA, Greden JF, King CA (2005) Prevalence of depression by race/ethnicity: findings from the National Health and Nutrition Examination Survey III. Am J Public Health 95:998–1000 [PubMed: 15914823]

Robertson K, Yosief S (2014) Neurocognitive assessment in the diagnosis of HIV-associated neurocognitive disorders. Semin Neurol 34:21–26 [PubMed: 24715485]

Roy A, De Jong J, Linnoila M (1989) Cerebrospinal fluid monoamine metabolites and suicidal behavior in depressed patients. A 5-year follow-up study. Arch Gen Psych 46:609–12

Rubin LH, Maki PM (2019) HIV, depression, and cognitive impairment in the era of effective antiretroviral therapy. Curr HIV/AIDS Rep 16:82–95 [PubMed: 30661180]

Saloner R, Cherner M, Grelotti DJ et al. (2020) Lower CSF homovanillic acid relates to higher burden of neuroinflammation and depression in people with HIV disease. Brain Behav Immun 90:353–363 [PubMed: 32966871]

Scheepers FE, Gispen-de Wied CC, Westenberg HG, Kahn RS (2001) The effect of olanzapine treatment on monoamine metabolite concentrations in the cerebrospinal fluid of schizophrenic patients. Neuropsychopharmacology 25:468–475 [PubMed: 11557160]

Scheller C, Sopper S, Jenuwein M et al. (2005) Early impairment in dopaminergic neurotransmission in brains of SIV-infected rhesus monkeys due to microglia activation. J Neurochem 95:377–387 [PubMed: 16190867]

Shah S, Sinharay S, Matsuda K et al. (2019) Potential mechanism for HIV-associated depression: upregulation of serotonin transporters in SIV-infected macaques detected by 11C-DASB PET. Front Psych 10:362

Sheline Y, Bardgett ME, Csernansky JG (1997) Correlated reductions in cerebrospinal fluid 5-HIAA and MHPG concentrations after treatment with selective serotonin reuptake inhibitors. J Clin Psychopharmacol 17:11–14 [PubMed: 9004051]

Sin NL, DiMatteo MR (2014) Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. Ann Behav Med 47:259–269 [PubMed: 24234601]

Song CH, Fan X, Exeter CJ, Hess EJ, Jinnah HA (2012) Functional analysis of dopaminergic systems in a DYT1 knock-in mouse model of dystonia. Neurobiol Dis 48:66–78 [PubMed: 22659308]

Strategies for Management of Antiretroviral Therapy Study G, El-Sadr WM, Lundgren J et al. (2006) CD4+ count-guided interruption of antiretroviral treatment. The New England J Med 355:2283–96 [PubMed: 17135583]

United States Department of Health and Human Services (2022) Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. https://clinicalinfo.hiv.gov/en/guidelines. Accessed 30 Nov 2022

Vlassova N, Angelino AF, Treisman GJ (2009) Update on mental health issues in patients with HIV infection. Curr Infect Dis Rep 11:163–169 [PubMed: 19239808]

Williams DR, Gonzalez HM, Neighbors H et al. (2007) Prevalence and distribution of major depressive disorder in African Americans, Caribbean blacks, and non-Hispanic whites: results from the National Survey of American Life. Arch Gen Psychiatry 64:305–315 [PubMed: 17339519]

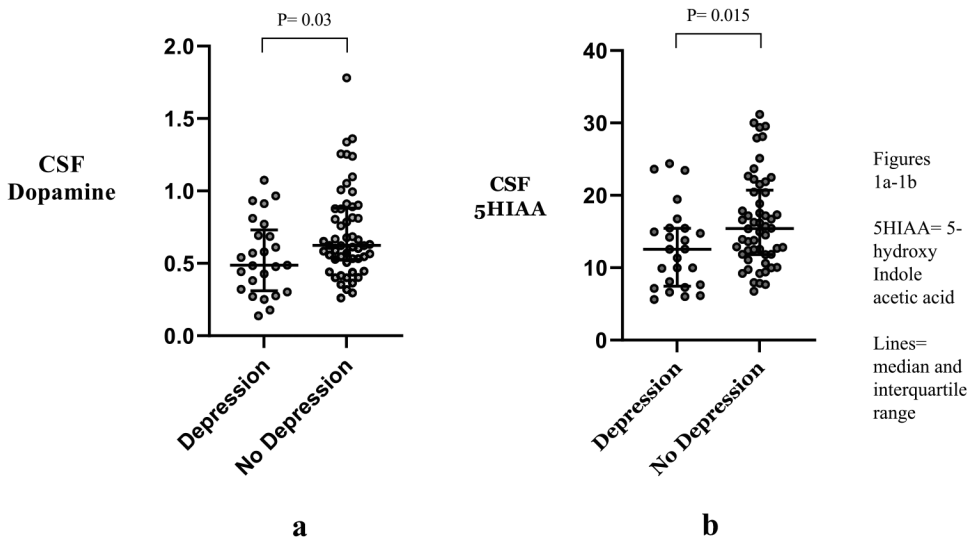

Fig. 1.

a Participants with the depression diagnosis had significantly lower dopamine levels and **b** significantly lower 5-HIAA levels. 5HIAA, 5-hydroxyindole acetic acid; lines, median and interquartile range

Table 1

Demographic and disease characteristics

Variable	Overall (*N* = 79)	Depression (*N* = 25)	No depression (*N* = 54)	*P* value	FDR *P* value
Age in years	48 (42–55)	53 (45–57.5)	47 (38–52)	0.014 *	0.08
Sex	19 (24.1%)	6 (24.0%)	13 (24.1%)	1.0	1
Women	57 (72.2%)	18 (72.0%)	39 (72.2%)		
Men	3 (3.8%)	1 (4.0%)	2 (3.7%)		
Transgender woman					
Race	54 (68.4%)	12 (48.0%)	42 (77.8%)	0.008 *	0.08
African American	24 (30.4%)	13 (52.0%)	11 (20.4%)		
White	1 (1.3%)	0 (0.0%)	1 (1.9%)		
Native American					
Duration HIV in months	157 (68–278)	240 (51.5–324)	146.5 (72–230)	0.09	0.27
Hypertension	27 (34.2%)	11 (44.0%)	16 (29.6%)	0.31	0.46
Diabetes mellitus	7 (8.9%)	4 (16.0%)	3 (5.6%)	0.2	0.46
Current CD4 +	432 (288–608)	423 (346–646)	473 (300.5–636.5)	0.98	1
On efavirenz	9 (11.4%)	0 (0%)	9 (16.7%)	0.05	0.20
CSF WBC	1 (0–3)	2 (0–4)	0 (0–2)	0.35	0.46
CSF RBC	0 (0–3)	1 (0–4.5)	0 (0–3)	0.30	0.46
CSF protein	39 (32–51)	41.5 (31–52)	37.5 (32–47.5)	0.38	0.46
NPT-9	48.1 (7.2)	46.9 (6.6)	48.7 (7.4)	0.29	0.46

CSF Cerebrospinal Fluid, *FDR* False Discovery Rate. Continuous variables are reported as median (interquartile range) except for NPT-9 which is reported as mean (standard deviation); categorical variables are reported as number (percentage).

*denotes P value < 0.05.

Continuous variables compared by Wilcoxon ran sum or t test in the case of NPT-9; categorical variables compared by Fisher's exact test

Table 2

Cerebrospinal fluid (CSF) neurotransmitter levels

Variable	Overall (*N* = 79)	Depression (*N* = 25)	No depression (*N* = 54)	*P* value	FDR *P* value
Dopamine	0.60 (0.44–0.82)	0.49 (0.31–0.73)	0.62 (0.52–0.88)	0.03 *	0.075
HVA	39.14 (29.52–49.06)	39.28 (29.12–48.20)	38.97 (29.67–49.40)	0.99	0.99
5-HT	0.36 (0.27–0.43)	0.38 (0.27–0.44)	0.36 (0.26–0.43)	0.86	0.99
5-HIAA	14.22 (9.99–18.86)	12.57 (7.46–15.47)	15.41 (11.83–20.73)	0.015 *	0.075
MHPG	9.06 (6.97–13.32)	9.30 (6.29–12.87)	8.88 (7.32–13.62)	0.59	0.98

HVA Homovanillic Acid, *5-HT* serotonin, *5-HIAA* 5-hydroxyindoleacetic acid, *MHPG* 3-methoxy-4-hydroxyphenylglycol, *FDR* False Discovery Rate. Values are nanograms/milliliter, reported as median (interquartile range);

* denotes *P* value < 0.05.

Continuous variables compared by Wilcoxon rank sum test

Table 3

Correlations between cerebrospinal fluid (CSF) neurotransmitters by descending strength

CSF neurotransmitter	By CSF neurotransmitter	Spearman ρ	*P* value	FDR *P* value
5-HIAA	Dopamine	0.7602	< 0.0001*	< 0.0001*
5-HIAA	HVA	0.5733	< 0.0001*	< 0.0001*
Dopamine	HVA	0.3372	0.0024*	0.008*
MHPG	5-HT	0.2299	0.0415*	0.10
MHPG	HVA	0.1545	0.1741	0.35
5-HT	HVA	0.0409	0.7204	0.90
MHPG	5-HIAA	0.0245	0.8306	0.91
MHPG	Dopamine	0.0131	0.9085	0.91
5-HIAA	5-HT	−0.0422	0.7117	0.9
5-HT	Dopamine	−0.1034	0.3643	0.61

FDR False Discovery Rate

Table 4

Logistic regression models for the depression diagnosis

Logistic regression models (5-HIAA)		
Model 1		
Variable	**Odds ratio**	**95% confidence interval**
Age	1.08	1.02–1.15 *
CSF 5-HIAA	0.89	0.80–0.98 *
Model 2		
Variable	**Odds ratio**	**95% confidence interval**
African American	0.26	0.09–0.75 *
CSF 5-HIAA	0.90	0.82–0.99 *
Model 3		
Variable	**Odds ratio**	**95% confidence interval**
Age	1.06	0.99–1.13
African American	0.35	0.12–1.07
CSF 5-HIAA	0.89	0.81–0.98 *
Logistic regression models (dopamine)		
Model 1		
Variable	**Odds ratio**	**95% confidence interval**
Age	1.07	1.0–1.14
CSF dopamine	0.10	0.01–0.86 *
Model 2		
Variable	**Odds ratio**	**95% confidence interval**
African American	0.29	0.1–0.83 *
CSF dopamine	0.14	0.02–1.15
Model 3		
Variable	**Odds ratio**	**95% confidence interval**
Age	1.06	0.99–1.13
African American	0.38	0.13–1.13
CSF dopamine	0.12	0.01–1.14

CSF Cerebrospinal Fluid, *5-HIAA* 5-hydroxyindoleacetic acid.

* denotes confidence intervals that do not cross 1