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Depression and Apathy Among People Living with HIV: Implications for Treatment of HIV Associated Neurocognitive Disorders

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Abstract

Depression and apathy are common among people living with HIV (PLWH). However, in PLWH, it is unclear whether depression and apathy are distinct conditions, which contribute to different patterns of disruption to cognitive processing and brain systems. Understanding these conditions may enable the development of prognostic indicators for HIV associated neurocognitive disorders (HAND). The present study examined substance use behavior and cognitive deficits, associated

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with depression and apathy, in 120 PLWH, using hierarchical regression analyses. Higher levels of depression were associated with a history of alcohol dependence and greater deficits in processing speed, motor and global cognitive functioning. Higher levels of apathy were associated with a history of cocaine dependence. It is recommended that PLWH get screened appropriately for apathy and depression, in order to receive the appropriate treatment, considering the comorbidities associated with each condition. Future research should examine the neurological correlates of apathy and depression in PLWH.

Introduction

Depression and apathy are neuropsychiatric complications of human immunodeficiency virus (HIV) with distinct clinical manifestations. Depression is a prominent neuropsychiatric disorder that is more common among people living with HIV (PLWH), as compared to uninfected individuals [1, 2]. Estimates suggest that the prevalence of current depression is between 30 and 40 % in this population [3–5]. Similarly, apathy, which refers to reduced, self-initiated, cognitive, emotional, and behavioral activity, is also commonly reported among PLWH [6]. Some studies suggest that apathy is more prominent in PLWH, than in HIV negative individuals, with rates as high as 65 percent in one sample [7]. While apathy had long been regarded as a symptom of depression (e.g. diminished interest or pleasure in activities, psychomotor retardation) [8], research over the last decade suggests that the two conditions require distinct prognostic and therapeutic strategies [9, 10]. A major question regarding apathy's relationship with depression in PLWH, is whether it is simply a symptom of depression, or other psychiatric disturbance, or if it is a behavioral manifestation of a neurologic condition [11].

Distinguishing between the two conditions can often be difficult because many individuals with depression present with symptoms of anhedonia and both conditions can be accompanied by dysphoria. Additionally, both conditions frequently co-occur in PLWH [11–13]. Furthermore, depression has been associated with reduced adherence to Antiretroviral (ARV) medication [14]. Though, apathy's effect on adherence has been less studied. One study suggests that higher levels of apathy may have negative effects on ARV adherence, among younger, but not older, PLWH [15]. Both conditions have been associated with functional impairment [13]. Though, higher levels of apathy have been associated with greater functional impairment, after adjusting for other covariates, such as depression [11]. Additionally, apathy has been associated with different neurocognitive deficits than depression, which may indicate central nervous system (CNS) involvement, independent of depression [16]. For example, PLWH with higher levels of apathy, tend to have deficits in executive functioning, learning, and cognitive flexibility [7, 17]. Depression has been associated with deficits in all domains of cognitive functioning in PLWH, but particularly, processing speed, learning, and memory [18]. One study of both conditions, in a sample of PLWH, indicated that apathy was consistently related to depression, but had no relationship with neuropsychological impairment, suggesting that there may be significant overlap in constructs and/or construct measurement [11].

Predictors of depression and apathy among PLWH are also very different. Higher levels of depression among PLWH, have been associated with demographic variables (e.g., female sex, age range within adolescent years); behavioral or social indicators (e.g., men who have sex with men, low social support), and biological indicators (e.g., low antiretroviral (ARV) adherence, hepatitis C (HCV) [4, 19]. Previous literature suggests that depressed individuals with HIV are more likely to have had a history of alcohol abuse than non-depressed individuals with HIV [20]. Additionally, in a large sample of individuals in Haiti living with HIV, alcohol problems in the past year, were a significant predictor of depression [21]. Higher levels of apathy have been associated with positive HCV status, but not necessarily coinfection with HIV [22]. Additionally, lower levels of cognitive reserve, measured using a composite score which included years of education and word reading ability, was significantly associated with higher levels of apathy. Though, this relationship was moderated by CD4 nadir, in that individuals with nadir CD4 levels ≤ 200 , demonstrated a stronger association than those with nadir CD4 levels >200 [23]. Furthermore, higher levels of apathy have previously been associated with higher HIV RNA [24]. Finally, having a history of cocaine dependence has been associated with apathy, in PLWH and in HIV negative samples [7, 12, 25, 26]. Apathy has been implicated as a potential early indicator of HIV Associated Neurocognitive Disorders (HAND), a category of disorders characterized by cognitive deficits, and may be present in those with asymptomatic disease, making it important to have tools in place that assist in screening in order to promote early intervention [27].

Little is known about the differences in predictors of depression and apathy among PLWH. Additionally, it has not been established, if depression and apathy are predictive of cognitive deficits, and if so, which deficits. Thus, the study of depression, apathy and cognition, in this novel sample, will grant further insight into the relationship between these two conditions and HAND. If one or both of these conditions relates to HAND, it may signal that these conditions should be routinely screened for in clinical practice. This can potentially be done using the same measures used in this study. We hypothesize that: (1) a history of alcohol dependence will be associated with depression, but not apathy; and (2) a history of cocaine use will be associated with apathy but not depression. Furthermore, we hypothesize that (3) higher levels of apathy will be associated with executive functioning and learning deficits, whereas (4) higher levels of depression will be associated with deficits in processing speed, learning and memory. Finally, (5) higher levels of apathy will be associated with higher HIV RNA and lower CD4 nadir.

Methods

Participants

Methods for the current study have previously been cited [28, 29]. Participants were recruited from The Miriam Hospital Immunology Center as part of an NIH-sponsored study of HIV-associated brain dysfunction. The study was approved by the institutional review boards, and informed consent was obtained from each participant before enrollment. All participants underwent a neurological examination and thorough medical history assessment. One hundred twenty HIV infected participants were included in the analyses

(63.6 % male, 54.6 % White, age range 23–65, 81.4 % had greater than a high school education).

Measures

HIV infection was documented by enzyme linked immunosorbent assay (ELISA) and confirmed by Western blot. Active HCV infection was defined as positive anti-HCV by ELISA and positive qualitative HCV RNA by polymerase chain reaction. Participants were excluded for history of (1) head injury with loss of consciousness ≥ 10 min; (2) history of neurological conditions including dementia, seizure disorder, stroke, and opportunistic infection of the brain; (3) severe psychiatric illness that might impact brain function, for example, schizophrenia, which was screened for using the Composite International Diagnostic Interview (CIDI) [30]; and (4) current (6-month) substance dependence or positive urine toxicology screen for cocaine, opiates, or illicit stimulants or sedatives. Demographic and clinical characteristics of the participant population are presented in Table 1. Mean duration of HIV infection was 12.6 years, and the majority (82.4 %) of the sample was on stable HAART. Most participants (70.7 %) had undetectable plasma HIV RNA (75 copies/mL). Despite an average nadir CD4 of 188 cells/mL, indicating a history of being immunocompromised, participants were medically stable, with an average current CD4 count of 464 cells/mL. Forty-five (37.8 %) participants had active HCV infection.

Kreek–McHugh–Schluger–Kellogg Scale

The Kreek-McHugh-Schluger-Kellogg Scale [31] was used to assess lifetime alcohol and substance dependence. Using this classification system, respective rates of alcohol, cocaine, and opiate dependence were 49.6, 54.8, and 16.5 %, respectively.

Center for Epidemiologic Studies Depression Scale (CES-D)

Depression was assessed using the Center for Epidemiologic Studies Depression (CES-D) scale [32]. The mean CES-D score for the sample was 21.5, which exceeds the cut-off score [16], indicating considerable depressive symptomatology in the current sample. The CES-D was used to measure clinically significant symptoms of depression [32]. Developed for use with community populations, components include depressed mood, feelings of worthlessness, sense of hopelessness, sleep disturbance, loss of appetite, and concentration difficulties. Subjects rate 20 items on a 4-point scale from 0 to 3 on the basis of the past week where 0 = rarely or none of the time and 3 = most or all of the time.

Frontal Systems Behavior Scale (FrSBe)

Participants completed the 14-item apathy subscale of the self-report version of the Frontal Systems Behavioral Scale [33]. The FrSBe was used to measure behaviors associated with frontal lobe brain damage. It has demonstrated validity in the assessment of behavioral dysfunction and disturbances associated with frontal-subcortical circuitry damage and traumatic brain injury. Ratings are on a Likert-type scale that ranges from 1 (“almost never”) to 5 (“almost always”) for each question. Higher ratings indicate more abnormal behavior (e.g., neglecting personal hygiene, leaving things unfinished). Raw scores were converted into age and education corrected T scores. T scores greater than 65 were considered

clinically elevated, which is consistent with previous literature [13, 22, 34]. In the present sample, 36.6 percent met criteria for clinically significant apathy. The rate of comorbid depression and apathy was 67.3 %. The scale allows for retrospective ratings prior to the injury or illness (before) and for ratings following the injury or illness (after), creating a baseline measure with which to compare subsequent ratings. Participants were asked to provide retrospective ratings prior to the diagnosis of HIV infection (before) and current ratings (i.e., after seroconversion). The present study examined the current ratings of the apathy subscale.

Cognitive Assessment

The following domains of neurocognitive functioning were assessed: speed of information processing, attention/ working memory/executive functioning, learning, memory, verbal fluency, and psychomotor speed. The battery consisted of the following tests, which were chosen for their sensitivity to HAND: Hopkins Verbal Learning Test_Revised [35, 36]; Brief Visuospatial Memory Test_Revised [37]; Controlled Oral Word Association Test; and Category Fluency_Animals [38]; Stroop Color and Word Test [39]; Trail Making Test, Parts A and B [40]; Grooved Pegboard Test [41]; and the Digit Symbol_Coding, Symbol Search, and Letter-Number Sequencing tests from the Wechsler Adult Intelligence Scale_Third Edition [42]. The present tests and domains are similar to those used in the Global Deficit Score (GDS), which has shown high validity in detecting HIV-associated neurocognitive impairment [43, 44]. Demographically corrected T-scores were calculated using established norms [35, 45, 46]. Domain composite scores were calculated by averaging the T-scores of all tests in the domain. Global cognitive functioning score was calculated by averaging the T-scores of all tests in the battery. Deficit scores were calculated for all domains and domain specific tests using a range of 0–5 for each encompassing cognitive test [0 (T-score > 40), 1 (T-score<40), 2 (T-score <35), 3 (T-score <30), 4 (T-score <25), 5 (T-score <20)] and then averaging the domain test scores, in order to calculate the total domain deficit score.

Data Analysis

Demographic, HCV and Substance Use Predictors—Multiple regression analyses were conducted in order to examine the effect of demographic predictors, current HCV and substance use variables on depression and apathy. Specific demographics of age, sex and race were included because there is a paucity of literature on these factors as predictors of depression and apathy. Furthermore, higher levels of depression and apathy have previously been associated with increasing age [47, 48], so we wanted to examine if this relationship was consistent in a novel sample. HCV was included as a covariate because previous evidence suggests that it is significantly related to cognitive functioning, particularly learning and memory [29]. Raw scores for depression and apathy were used in order to examine predictive strength of demographic factors such as age, sex and race.

HIV Clinical Variables

Correlations between apathy, depression and HIV clinical variables (CD4, CD4 nadir, Viral Load (VL)) were examined.

Apathy and Depression Associations with Cognition

Hierarchical regression analyses were conducted with depression and apathy raw scores in order to examine unique and combined effects, as well as the effects after correcting for covariates. All five cognitive domains will be tested. The steps for entering into the model are as follows: Step 1—depression Step 2—apathy Step 3—HCV. Steps 1 and 2 will be tested in the reverse as well, in order to determine the unique effect of apathy and the subsequent combined effects of depression and apathy. Only models with a significant Step 1 will be analyzed further.

Results

Substance Use and Demographic Predictors

The results are presented in Table 2. The overall apathy model was significant ($r^2 = 0.169$, $F(8,100) = 2.54$, $p = 0.015$). Apathy was significantly associated with age ($B = 0.190$, $SE = 0.091$, $Beta = 0.204$, $p = 0.039$) and lifetime history of cocaine dependence ($B = 4.445$, $SE = 1.950$, $Beta = 0.254$, $p = 0.025$). In the depression model, the overall model was not significant ($r^2 = 0.187$, $F(8,106) = 1.44$, $p = 0.187$). Though, lifetime history of alcohol dependence was a significant predictor of depression ($B = 5.352$, $SE = 2.492$, $Beta = 0.212$, $p = 0.034$). None of the other predictors were significant.

HIV Clinical Variables

Correlations were run examining whether HIV clinical variables (CD4, CD4 nadir, VL and VL detectable) were related to apathy or depression and were non-significant.

Depression and Apathy Associations with Cognition

The results of the cognitive analyses are presented as Beta values in Tables 3 and 4. Higher levels of depression ($r^2 = 0.174$, $B = 0.013$, $SE = 0.004$, $Beta = 0.329$, $p < 0.01$), but not apathy, predicted greater deficits in processing speed, even while correcting for apathy and HCV. Neither depression, nor apathy, predicted attention/working memory/executive functioning, learning, or memory or verbal deficits. Higher levels of depression, but not apathy, predicted greater deficits in motor functioning, while correcting for apathy and HCV ($r^2 = 0.074$, $B = 0.020$, $SE = 0.008$, $Beta = 0.230$, $p = 0.020$). Finally, higher levels of depression ($r^2 = 0.186$, $B = 0.012$, $SE = 0.004$, $Beta = 0.289$, $p = 0.002$) but not apathy, predicted greater deficits in global cognitive functioning, while correcting for apathy and HCV. Approximately, 58.1 percent of the sample met Frascati criteria for HAND [49]. Frascati criteria characterize HAND according to neuropsychological performance and level of functional impairment, using three levels of impairment: Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND) and HIV Associated Dementia (HAD). ANI is defined by a score of at least one standard deviation below the mean, on at least two cognitive areas of standardized neuropsychological testing, without this deficit causing an observable functional impairment. MND is defined by a score of one standard deviation below the mean, on at least two cognitive areas of standardized neuropsychological testing, with at least mild impairment of functioning. HAD is defined by a score of at least two standard deviations below the mean, on at least two cognitive areas of standardized

neuropsychological testing, with marked associated impairment in activities of daily living. In the present study, category of HAND could not be determined, due to lack of measurement of daily living functional impairment.

Post hoc Analyses

Exploratory regression analyses were performed on individual cognitive tests, within domains that were significantly associated with apathy or depression. Deficit scores for individual tests were used for analyses because these scores place less emphasis on average and above average performance, and greater emphasis on below average performance. Deficit scores were calculated by converting raw scores to T-scores using age, education, gender and race corrected norms and then converting T-scores to deficit scores using the ranges established by Carey and colleagues [43]. Higher levels of depression significantly predicted greater deficits on the digit symbol task ($r^2 = 0.176$, $B = 0.015$, $SE = 0.005$ Beta = 0.260, $p = 0.006$), and Trail Making Test Part A time ($r^2 = 0.170$, $B = 0.017$, $SE = 0.004$ Beta = 0.415, $p < 0.001$), while correcting for apathy and HCV. Additionally, higher levels of depression predicted greater deficits in the grooved pegboard task, related to drops, using the dominant hand ($r^2 = 0.081$, $B = 0.021$, $SE = 0.009$, Beta = 0.220, $p = 0.025$), while correcting for apathy and HCV.

Based on extant literature, which shows a relationship between apathy and cognitive outcomes [10, 17, 18], we decided to examine whether it was moderated by age and cocaine use variables. In order to examine moderation effects, each cocaine use variable (frequency, duration, quantity, KMSK score) was centered and multiplied by centered apathy T-scores. Centering was done in order to reduce multicollinearity. The interaction terms were entered into a multiple regression model along with apathy and depression variables, with each of the cognitive domains as outcome measures. Results suggest that cocaine duration significantly moderated the relationship between apathy corrected t scores and memory deficits ($B = 0.021$, $SE = 0.010$, Beta = 0.335, $p = 0.041$).

Discussion

Our results suggest that depression was related to previous history of alcohol dependence, whereas apathy was related to previous history of cocaine dependence and age. This suggests that participants with a previous history of alcohol dependence should be screened for depression with the consideration that earlier treatment may lead to better cognitive outcomes. Furthermore, individuals with a previous history of cocaine dependence, as well as older individuals should be screened for apathy and should receive the appropriate targeted interventions.

Regarding the relationship between depression and apathy with cognitive deficits, our findings support the findings indicated in Rabkin et al. [11], which suggest that apathy was not an independent predictor of neuropsychological test performance in PLWH. Rabkin et al., suggests that self-reported measures of apathy should be accompanied by observer reports, in order to improve measurement of this construct. Additionally, different scales of apathy were used. We examined apathy using the domain from the FrSBe, whereas the Rabkin study used the Apathy Evaluation Scale [50]. Thus, multiple scales have

demonstrated no association with cognitive deficits. Castellon [12] found that apathy was related to working memory deficits. Though, we found that period of last cocaine use (cocaine duration) moderated the relationship between self-reported apathy and memory domain deficits, which was separate from the combined attention/working memory/executive function domain. Working memory was measured using C-SPAN in the Castellon study, whereas the present study used a combination of Trails A and B, Letter Number Sequencing and Stroop to measure working memory. Thus, there is a need to standardize construct measurement for both neurocognitive measures and measures of apathy. Additionally, we must understand the underlying factors which may be predictive of HAND and those that may overlap with depression. Furthermore, diagnosing HAND in individuals with current depression, requires deferring assessment until depressive episode has remitted for at least one month. Additionally, if the individual is a current substance user, cessation of substance use for at least one month must occur, before proper diagnostic assessment of HAND [49]. Considering the high prevalence of depression and substance use in this population, as well as the overlap between depression, substance use and HAND etiology, revision of HAND diagnostic criteria should be considered, to incorporate these comorbid conditions, rather than ruling them out, before determining HAND diagnosis.

Contrary to hypothesis 5, neither depression nor apathy was associated with HIV clinical variables. Perhaps this was related to the sample having good viral control, or it could be due to the influence of a host of other factors that might be related to viral control, depression and apathy such as: inflammation, age, sex, race, adherence to medication, etc.

Further neurological evidence is needed to distinguish between depression and apathy, so as to better inform clinical decision making with regard to treatment of these conditions in PLWH. Studies should examine the neurological correlates of depression and apathy, as previous studies have demonstrated differences in white matter integrity [6] and corpus callosum volume associated with apathy in PLWH [27]. Furthermore, markers of inflammation such as C-reactive protein and pro-inflammatory cytokines have previously been associated with higher levels of depression in PLWH [51, 52]. Though, there is little research on the relationship between apathy and these markers among PLWH. Self-reported information along with neuroimaging analysis and serum biomarker data, may provide for targeted behavioral and pharmacological treatments. Ances et al. [53] suggests that glycogen synthase kinase-3 beta (GSK-3b) inhibitors and serotonin reuptake inhibitors (SRIs) may be beneficial pharmacological treatments for individuals with HAND. SRI's may be a more effective treatment for individuals with a long history of depressive symptomatology. Psychostimulants, dopaminergics, or cholinesterase inhibitors may be an effective pharmacological treatments for apathy, depending on the specific etiology of the disorder [54, 55]. Targeted behavioral and pharmacological treatments may be more effective at reducing the risk of HAND or slowing progression. Clinicians should be aware that depressive symptoms can interact with HAND pathology to alter the symptoms patients endorse related to the disorder [49]. Furthermore, by accumulating cognitive, neuroimaging and self-report data into a multidimensional approach toward diagnosing apathy and depression, we may inform the development of an accurate prognostic indicator, which could be utilized in a clinic setting for more efficient screening for symptoms of HAND.

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References

1. Dew MA, Becker JT, Sanchez J, Caldararo R, Lopez OL, Wess J, et al. Prevalence and predictors of depressive, anxiety and substance use disorders in HIV-infected and uninfected men: a longitudinal evaluation. *Psychol Med*. 1997; 27(2):395–409. [PubMed: 9089832]
2. Ciesla JA, Roberts JE. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. *Am J Psychiatr*. 2001; 158(5):725–30. [PubMed: 11329393]
3. Asch SM, Kilbourne AM, Gifford AL, Burnam MA, Turner B, Shapiro MF, et al. Underdiagnosis of depression in HIV: who are we missing? *J Gen Intern Med*. 2003; 18(6):450–60. [PubMed: 12823652]
4. Wolff LC, Alvarado MR, Wolff RM. Prevalencia, factores de riesgo y manejo de la depresión en pacientes con infección por VIH: revisión de la literatura. *Revista Chilena de Infectología*. 2010; 27:65–74. [PubMed: 20140318]
5. Judd F, Komiti A, Chua P, Mijch A, Hoy J, Grech P, et al. Nature of depression in patients with HIV/AIDS. *Aust N Z J Psychiatr*. 2005; 39(9):826–32.
6. Hoare J, Fouche JP, Spottiswoode B, Joska JA, Schoeman R, Stein DJ, et al. White matter correlates of apathy in HIV-positive subjects: a diffusion tensor imaging study. *J Neuropsychiatr Clin Neurosci*. 2010; 22(3):313–20.
7. Castellon SA, Hinkin CH, Myers HF. Neuropsychiatric disturbance is associated with executive dysfunction in HIV-1 infection. *J Int Neuropsychol Soc*. 2000; 6(3):336–47. [PubMed: 10824505]
8. Association AP. Diagnostic and statistical manual of mental disorders. 5th. Arlington: American Psychiatric Publishing; 2013.
9. Marin RS. Apathy: a neuropsychiatric syndrome. *J Neuropsychiatr Clin Neurosci*. 1991; 3(3):243–54.
10. Tagariello P, Girardi P, Amore M. Depression and apathy in dementia: same syndrome or different constructs? A critical review. *Arch Gerontol Geriatr*. 2009; 49(2):246–9. [PubMed: 19022508]
11. Rabkin JG, Ferrando SJ, van Gorp W, Rieppi R, McElhiney M, Sewell M. Relationships among apathy, depression, and cognitive impairment in HIV/AIDS. *J Neuropsychiatr Clin Neurosci*. 2000; 12(4):451–7.
12. Castellon SA, Hinkin CH, Wood S, Yarema KT. Apathy, depression, and cognitive performance in HIV-1 infection. *J Neuropsychiatr Clin Neurosci*. 1998; 10(3):320–9.
13. Kamat R, Morgan E, Marcotte TD, Badiee J, Maich I, Cherner M, et al. Implications of apathy and depression for everyday functioning in HIV/AIDS in Brazil. *J Affect Disord*. 2013; 150(3):1069–75. [PubMed: 23245465]
14. Wagner GJ, Goggin K, Remien RH, Rosen MI, Simoni J, Bangsberg DR, et al. A closer look at depression and its relationship to HIV antiretroviral adherence. *Ann Behav Med*. 2011; 42(3):352–60. [PubMed: 21818528]
15. Barclay TR, Hinkin CH, Castellon SA, Mason KI, Reinhard MJ, Marion SD, et al. Age-associated predictors of medication adherence in HIV-positive adults: health beliefs, self-efficacy, and neurocognitive status. *Health Psychol*. 2007; 26(1):40–9. [PubMed: 17209696]
16. Tate D, Paul RH, Flanigan TP, Tashima K, Nash J, Adair C, et al. The impact of apathy and depression on quality of life in patients infected with HIV. *AIDS Patient Care STDs*. 2003; 17(3):115–20. [PubMed: 12724007]
17. Cole MA, Castellon SA, Perkins AC, Ureno OS, Robinet MB, Reinhard MJ, et al. Relationship between psychiatric status and frontal-subcortical systems in HIV-infected individuals. *J Int Neuropsychol Soc*. 2007; 13(3):549–54. [PubMed: 17445305]

18. Fellows RP, Byrd DA, Morgello S, Manhattan HIVBB. Major depressive disorder, cognitive symptoms, and neuropsychological performance among ethnically diverse HIV+ men and women. *J Int Neuropsychol Soc.* 2013; 19(2):216–25. [PubMed: 23290446]
19. Bayon C, Ribera E, Cabrero E, Griffa L, Burgos A. Prevalence of depressive and other central nervous system symptoms in HIV-infected patients treated with HAART in Spain. *J Int Assoc Phys AIDS Care.* 2012; 11(5):321–8.
20. L'Akoa RM, Noubiap JJ, Fang Y, Ntone FE, Kuaban C. Prevalence and correlates of depressive symptoms in HIV-positive patients: a cross-sectional study among newly diagnosed patients in Yaounde, Cameroon. *BMC Psychiatr.* 2013; 13:228.
21. Malow R, Devieux JG, Stein JA, Rosenberg R, Jean-Gilles M, Attonito J, et al. Depression, substance abuse and other contextual predictors of adherence to antiretroviral therapy (ART) among Haitians. *AIDS Behav.* 2013; 17(4):1221–30. [PubMed: 23338563]
22. Posada C, Moore DJ, Woods SP, Vigil O, Ake C, Perry W, et al. Implications of hepatitis C virus infection for behavioral symptoms and activities of daily living. *J Clin Exp Neuropsychol.* 2010; 32(6):637–44. [PubMed: 20603743]
23. Shapiro ME, Mahoney JR, Peyser D, Zingman BS, Verghese J. Cognitive Reserve Protects Against Apathy in Individuals with Human Immunodeficiency Virus. *Arch Clin Neuropsychol.* 2013; 29(1):110–20. [PubMed: 24021844]
24. Shapiro ME, Mahoney JR, Zingman BS, Pogge DL, Verghese J. Apathy correlates with cognitive performance, functional disability, and HIV RNA plasma levels in HIV-positive individuals. *J Clin Exp Neuropsychol.* 2013; 35(9):934–45. [PubMed: 24090038]
25. Kalechstein AD, Newton TF, Leavengood AH. Apathy syndrome in cocaine dependence. *Psychiatry Res.* 2002; 109(1):97–100. [PubMed: 11850056]
26. Winhusen TM, Somoza EC, Lewis DF, Kropp FB, Horigian VE, Adinoff B. Frontal systems deficits in stimulant-dependent patients: evidence of pre-illness dysfunction and relationship to treatment response. *Drug Alcohol Depend.* 2013; 127(1–3):94–100. [PubMed: 22771145]
27. Paul R, Flanigan TP, Tashima K, Cohen R, Lawrence J, Alt E, et al. Apathy correlates with cognitive function but not CD4 status in patients with human immunodeficiency virus. *J Neuropsychiatr Clin Neurosci.* 2005; 17(1):114–8.
28. Devlin KN, Gongvatana A, Clark US, Chasman JD, Westbrook ML, Tashima KT, et al. Neurocognitive effects of HIV, hepatitis C, and substance use history. *J Int Neuropsychol Soc.* 2012; 18(1):68–78. [PubMed: 22132928]
29. Bryant VE, Kahler CW, Devlin KN, Monti PM, Cohen RA. The effects of cigarette smoking on learning and memory performance among people living with HIV/AIDS. *AIDS Care.* 2013; 25(10):1308–16. [PubMed: 23394125]
30. Robins LN, Wing J, Wittchen H, et al. The composite international diagnostic interview: an epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Arch Gen Psychiatr.* 1988; 45(12):1069–77. [PubMed: 2848472]
31. Kellogg SH, McHugh PF, Bell K, Schluger JH, Schluger RP, LaForge KS, et al. The Kreek-McHugh-Schluger-Kellogg scale: a new, rapid method for quantifying substance abuse and its possible applications. *Drug Alcohol Depend.* 2003; 69(2):137–50. [PubMed: 12609695]
32. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas.* 1977; 1(3):385–401.
33. Grace, J.; Malloy, P. FrSBe, Frontal Systems Behavior Scale: Professional Manual: Psychological Assessment Resources. 2001. Psychological Assessment Resources I.
34. Lane-Brown AT, Tate RL. Measuring apathy after traumatic brain injury: psychometric properties of the apathy evaluation scale and the frontal systems behavior scale. *Brain Injury.* 2009; 23(13–14):999–1007. [PubMed: 19891539]
35. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test—revised: normative data and analysis of inter-form and test-retest reliability. *Clin Neuropsychol.* 1998; 12(1):43–55.
36. Brandt, J.; Benedict, RHB. Hopkins verbal learning test-revised (HVLTR). Lutz: Psychological Assessment Resources, Inc.; 1991.

37. Benedict, RHB. Brief Visuospatial Memory Test-Revised. Odessa: Psychological Assessment Resources; 1997.
38. Benton, AL.; Hamsher, K.; Sivan, AB. Multilingual aphasia examination. Iowa City: AJA Associates; 1994.
39. Golden, CJ. Stroop color and word test. Chicago: Stoelting; 1978.
40. Reitan, RM. Trail Making Test. Tucson: Reitan Neuropsychology Laboratory; 1992.
41. Kløve, H. Grooved Pegboard. Lafayette: Lafayette Instruments; 1963.
42. Wechsler, D. Wechsler Adult Intelligence Scale-III (WAIS-III). San Antonio: The Psychological Corporation; 1997.
43. Carey CL, Woods SP, Gonzalez R, Conover E, Marcotte TD, Grant I, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *J Clin Exp Neuropsychol*. 2004; 26(3):307–19. [PubMed: 15512922]
44. 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(1):3–16. [PubMed: 21174240]
45. Benedict RHB, Schretlen D, Groninger L, Dobraski M, Shpritz B. Revision of the brief visuospatial memory test: studies of normal performance, reliability, and validity. *Psychol Assess*. 1996; 8(2):145–53.
46. Heaton, RK.; Taylor, MJ.; Grant, I. Revised comprehensive norms for an expanded Halstead-Reitan battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults. Lutz: Psychological Assessment Resources; 2004.
47. Mirowsky J, Ross CE. Age and Depression. *J Health Soc Behav*. 1992; 33(3):187–205. [PubMed: 1401846]
48. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2006; 77(1):8–11. [PubMed: 16361584]
49. 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(18):1789–99. [PubMed: 17914061]
50. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res*. 1991; 38(2):143–62. [PubMed: 1754629]
51. Poudel-Tandukar K, Bertone-Johnson ER, Palmer PH, Poudel KC. C-reactive protein and depression in persons with Human Immunodeficiency Virus infection. *Brain Behav Immun*. 2014
52. Del Guerra FB, Fonseca JL, Figueiredo VM, Ziff EB, Konkiewitz EC. Human immunodeficiency virus-associated depression: contributions of immuno-inflammatory, monoaminergic, neurodegenerative, and neurotrophic pathways. *Journal of neurovirology*. 2013; 19(4):314–27. [PubMed: 23868513]
53. Ances BM, Letendre SL, Alexander T, Ellis RJ. Role of psychiatric medications as adjunct therapy in the treatment of HIV associated neurocognitive disorders. *Int Rev Psychiatry*. 2008; 20(1):89–93. [PubMed: 18240065]
54. Ishizaki J, Mimura M. Dysthymia and apathy: diagnosis and treatment. *Depression research and treatment*. 2011; 2011:893905. [PubMed: 21747995]
55. Padala PR, Burke WJ, Bhatia SC, Petty F. Treatment of apathy with methylphenidate. *J Neuropsychiatr Clin Neurosci*. 2007; 19(1):81–3.

Table 1

Demographics

Characteristic	Participants (N = 120)
Sex, n (% Male) ^b	75 (63.6)
Age, M (SD) ^b	45.23 (9.47)
Race, n (%) ^a	
White	65 (54.6)
Black	30 (25.2)
Other	24 (20.2)
Education, n (%) ^b	
<12 years	22 (18.6)
12 years	96 (81.4)
CESD, M (SD) ^d	21.29 (12.69)
FrSBe, M (SD) ^e	
Apathy	30.43 (8.64)
Clinical apathy (n, %)	41 (36.6)
Comorbid depression (n, %)	71 (67.3)
Disinhibition	30.12 (8.56)
Executive dysfunction	36.89 (10.59)
Substance use, n (%) ^a	
Alcohol dependence	59 (49.6)
Cocaine dependence	67 (56.3)
Opiate dependence	19 [16]
Current smoking	71 (60.2)
Current HCV, n (%) ^a	45 (37.8)
HIV related, M (SD)	
VL (n = 34)	37725 (60740)
CD4 ^c	464.04 (246.6)
Nadir CD4 ^b	187.97 (163.9)
HIV duration (years) ^a	12.62 (6.86)

70.7 % (n = 82) of the sample had an undetectable viral load

^aMissing 1

^bMissing 2

^cMissing 3

^dMissing 4

^eMissing 5

Table 2
Predictors of apathy and depression

	B	SE	Beta	p
Apathy				
Age	0.190	0.091	0.204	0.039*
Sex	0.849	1.815	0.048	0.641
Race	-1.368	1.757	-0.075	0.438
Education	0.624	0.452	0.150	0.171
Alcohol	-0.189	1.709	-0.011	0.912
Cocaine	4.445	1.950	0.254	0.025*
Opiate	-0.968	2.548	-0.040	0.705
HCV	2.482	2.059	0.139	0.231
Depression				
Age	-0.178	0.135	-0.133	0.189
Sex	2.849	2.672	0.109	0.289
Race	-3.247	2.641	-0.121	0.221
Education	0.067	0.679	0.011	0.922
Alcohol	5.352	2.492	0.212	0.034*
Cocaine	2.757	2.871	0.109	0.339
Opiate	0.390	3.742	0.011	0.917
HCV	-1.206	3.066	-0.046	0.695

*
 $p < 0.05$

Table 3
Depression and apathy as predictors of cognitive domains

	Step 1	Step 2	Step 3
Processing Speed			
Depression	0.320***	0.306**	0.329**
Apathy		0.022	-0.058
HCV			0.289**
Motor			
Depression	0.296**	0.217*	0.230*
Apathy		0.038	-0.005
HCV			0.154
Global Cognitive Function			
Depression	0.263**	0.260**	0.289**
Apathy		-0.056	-0.157
HCV			0.363***

*
 $p < 0.05$;

**
 $p < 0.01$;

 $p < 0.001$

Table 4
Depression and apathy as predictors of cognitive domain specific tests

	Step 1	Step 2	Step 3
Digit Symbol			
Depression	0.256**	0.231*	0.260**
Apathy		0.028	-0.072
HCV			0.359***
Trails A			
Depression	0.395***	0.417***	0.415***
Apathy		-0.144	-0.137
HCV			-0.025
Grooved Pegboard D			
Depression	0.301**	0.210*	0.220*
Apathy		0.093	0.049
HCV			0.147

D dominant hand

*
 $p < 0.05$;

**
 $p < 0.01$;

 $p < 0.001$