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Is the History of Substance Abuse Correlated with Neuropsychiatric Disorders and Co-morbid HIV Infection? An Urban Population Study

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Abstract

Background: Human immunodeficiency virus (HIV) infection remains a serious immunological disease with new infections in the U.S. disproportionately reported in minority populations. For many years, the District of Columbia (DC) has reported the highest HIV infection rate in the nation. Drug abuse and addiction is also prevalent in DC and has traditionally been linked to HIV/AIDS because of the likelihood for opportunistic infections. Despite this data, the relationship between HIV status, drugs of abuse, and the incidence of neurological disorders are scarcely reported for minority populations.

Method: We carried out a retrospective study on the prevalence of substance abuse in HIV and their association with neuropsychiatric comorbidities in an African American subpopulation in Washington DC.

Findings: Our data suggests an 86 percent prevalence of drug use in the HIV patients with neuropsychiatric comorbidities, with cocaine use being significantly higher in patients with major depressive disorder (MDD) and bipolar disorder (BD), whereas PCP use was associated with patients with schizophrenia. The mean CD4 count was elevated in patients with neuropsychiatric disease, and specifically in MDD patients. CD8 counts were elevated as expected for HIV status but were not influenced by disease diagnosis. A majority (2/3) of patients were on HAART therapy, however the records did not account for adherence.

Conclusion: These data suggest that neuropsychiatric comorbidities are independent of HIV disease progression but are correlated with certain illicit drugs of abuse.

Keywords: Major depressive disorder, Bipolar disorder, Schizophrenia, Drugs of abuse, African American, Urban populations; Human Immunodeficiency Virus (HIV)

Introduction

Substance abuse is significantly associated with earlier progression to Acquired Immune Deficiency Syndrome (AIDS) in Human Immunodeficiency Virus (HIV)-infected people [1,2]. Furthermore, the use of recreational drugs have been found to induce CNS impairment independent of the effects of HIV infection [3]. Consequently, people living with HIV/AIDS face an additional burden of psychiatric comorbidity, where approximately 40% of patients with HIV infection will develop CNS involvement [4]. Although HIV may remain dormant in the CNS for many years, its mere presence might lead to subtle deficits in cognitive functioning. However, these deficits are not found in all patients, which has led some authors to suggest that peripheral triggers might be involved [5].

Psychopathology can occur: 1) as a risk factor for HIV infection, 2) as a psychological response to HIV complications, directly in the brain, 3) as a consequence of HIV-related opportunistic diseases, or 4) as side effects of HIV-related treatments. Despite the impressive reduction of HIV-related morbidity and mortality in places where antiretroviral therapy (ART) is available, psychiatric and neuropsychiatric repercussions of HIV disease are still expected to become more relevant in the coming years [6], especially with the recent outbreak of communicable diseases associated with opioid use disorder [7].

Interestingly, African Americans have been disproportionately affected by HIV/AIDS since the epidemic began in the United States (U.S.) in 1981, and that disparity has deepened over time [8]. Although African Americans make up only 12.3 percent of the U.S. population, they have accounted for about 40 percent of the nearly 930,000 AIDS

cases, and that proportion appears to be growing. In 2015, 17,670 African Americans were diagnosed with HIV. In addition, 48 percent (8,702) of those diagnosed with AIDS in the United States were African Americans [8].

Drug abuse and addiction is also prevalent in the District of Columbia (DC) and has traditionally been linked to HIV/AIDS because of the likelihood of opportunistic infections. In DC alone, three percent of the population have tested positive for HIV, the highest in the nation [9]. This exceeds the World Health Organization's (WHO) definition of a severe epidemic [10]. Consequently, although African Americans account for 48 percent of DC residents, they constitute 75 percent of all HIV cases, have the highest incidence of HIV infections, and account for the newest AIDS cases and AIDS-related deaths in the District [11].

Currently, no literature is available regarding the demographics and neurological manifestations in African American individuals with HIV infection. Because substances of abuse are psychoactive, and known to alter neurological function, we analyzed the relationship between various psychiatric diagnoses and specific drugs of abuse in HIV-infected African-American patients in the Washington DC metropolitan area. We investigated if specific drugs of abuse or specific mental health conditions can be predictors of CD4 and CD8 count trends and if they confer vulnerabilities to HIV.

Methodology

Study setting

This cross-sectional retrospective study was conducted using medical records of a convenient sample of African-American patients admitted into Howard University Hospital from January to December of 2010. The Institutional Review Board reviewed and approved this study protocol.

Site selection

Howard University Hospital was selected because it is the most comprehensive health care facility in the Washington DC metro area, servicing mainly minority populations, a large percentage of which are African American.

Data sources

Data was collected from medical records of 282 consecutive patients with an ICD-9 coded diagnosis of HIV and concurrent neurological diagnosis for demographic variables (i.e. age and sex), antiretroviral therapy, drug use history, laboratory results and neurologic diagnosis. Subsequently, neurologic diagnoses were categorized as opportunistic infections; dementia; peripheral neuropathy, seizure and epilepsy; TIA and stroke; neuropsychiatric disorders. We confirmed the accuracy of ICD-9 case acquisition by extensive manual review of medical records by investigators. Additionally, we re-categorized neurological diagnosis as necessary by this manual review. We also included individuals with multiple neurological manifestations in each of the categories. Individuals admitted more than one time during the study interval were counted only once. However, data on substance use and abuse was based on self-report.

The anonymized data were retrospectively reviewed, and laboratory and clinical variables were pooled and analyzed centrally for frequencies of comorbidities of various neurological disorders, history of substance abuse, their relation to CD4 and CD8 counts, and also in relation to HAART therapy. Any patient who reported using nicotine, alcohol, cocaine, marijuana, PCP, or heroin were considered drug users.

Data collection

Data for each patient was retrospectively recorded on a spreadsheet. Data abstracted onto a spreadsheet included age, gender, race, history of HIV related illnesses, comorbid medical or neurological conditions including current substance abuse or psychiatric illness, CD4 and CD8 cell counts, and antiretroviral medications.

Analyses

The data collected was subjected to extensive statistical analysis using the Pearson chi-squared and T tests within the SPSS 19 statistical software. Each drug (nicotine, alcohol, cocaine, marijuana, PCP and heroin) was analyzed for prevalence within a particular neuropsychiatric group (depression, schizophrenia, or bipolar disorder). CD4 and CD8 counts were also analyzed for each psychiatric group.

Results

Of the 757 admissions between January 2010 to December 2010 with a diagnosis of HIV, 282 (37.3%) had a concurrent diagnosis after excluding readmissions. The demographics of the 282 HIV-infected individuals used in the study are listed in **Table 1**. Patient age ranges were between 16 and 83, with a median age of 47 years. 54 percent of the patients were male, while the rest were female. 99 percent had their HIV diagnosis pre-admission while 1 percent had their diagnosis at the hospital. Forty-two percent (42%) met WHO CD 4 criteria for AIDS diagnosis. Of the 282 patients, 276 had record of their antiretroviral therapy status. 62 percent of these patients were observed to be on antiretroviral therapy while 39 percent were not. Also, 236 (86 percent) indicated positive for history of drug abuse (**Table 1**). **Figure 1** shows a prevalence of neurological disorders (inclusive of 16 percent more prevalence in neuropsychiatric diseases, 16 percent more prevalence in seizure/epilepsy, 28 percent more prevalence in transient ischemic attack/cerebrovascular accident (TIA/CVA), 20 percent more prevalence in peripheral neuropathy, and 28 percent more prevalence in opportunistic infections) in patients aged less than 50. As expected, dementia was twice as prevalent in patients aged more than 50 years, and twice as prevalent in females compared to males. There was, however, no gender-specific difference in the prevalence of the other neurological disorders.

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Table 1: Demographic characteristic of the patients.

Characteristics	Number	Percentage
Gender (n=282)		
Male	152	54
Female	130	46
Age	16-83	47(Mean)
HIV Diagnosis (n=282)		
Pre-admission	279	99
At Hospital	3	1
Antiretroviral therapy (n=276)		
Yes	170	62
No	106	39
Drug abuse history (n=275)		
Yes	236	86
No	39	14
Signs and symptoms of neuropsychiatric disorders		
Depression	113	50
Bipolar disorder	70	31
Schizophrenia	43	19

The number of patients who reported drug use was significantly greater when categorized by each neurological disease, ranging from 10-fold greater association for those with a neuropsychiatric disease compared to only 0.67-fold increase in drug use among patients with dementia. In the time before HAART was available, it was reported that 39-70 percent of all patients with AIDS or symptomatic HIV infection developed neurological complications. The initiation of HAART has however been shown to be useful in reducing the incidence of these disorders [12]. In our cohort, two thirds of all the patients were undergoing HAART therapy whereas one third were not (**Figure 1**).

Frequency of neuropsychiatric disease in HIV patients with neurological complications

When the frequency of psychiatric disorders in HIV-infected African American patients was analyzed, depression (MDD) was more prevalent, with a 16 percent greater frequency than bipolar disorder (BD), 26 percent greater than Schizophrenia (SCZ) patients and 18 percent more than patients with a history of seizures (**Figure 2A**). It was also observed that some of the patients were diagnosed with more than one psychiatric disorder: 29 had both MDD and BD, 11 had both MDD and SCZ, 12 had both BD and SCZ while 10 were diagnosed with all three of the disorders (**Figure 2B**). Therefore, patients reported in the BD cohort in the current study, may exhibit bipolar disorder only or have co-morbid SCZ and MDD symptoms.

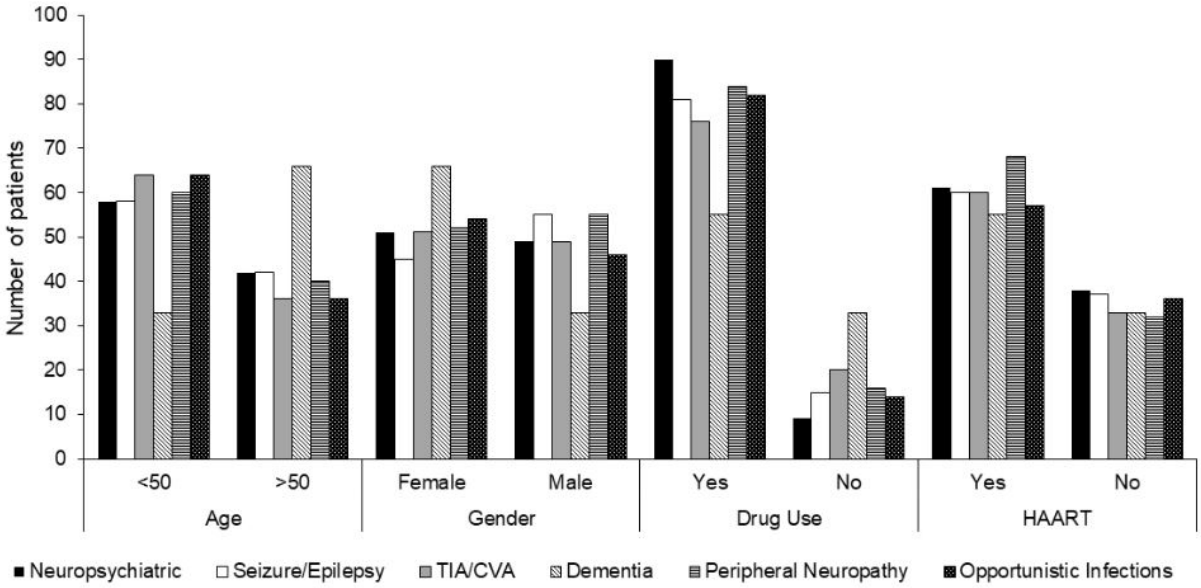

Figure 1: Prevalence of neurological disorders in relation to age, gender, drug use and HAART therapy. Patients were categorized based on history of neuropsychiatric disorders, seizure/ epilepsy, transient ischemic attack/ cardiovascular accidents, dementia, peripheral neuropathy and opportunistic infections; and were binned either into two age categories, >50 or <50 years age, or by gender, or by whether they reported drug use or if they were on HAART therapy.

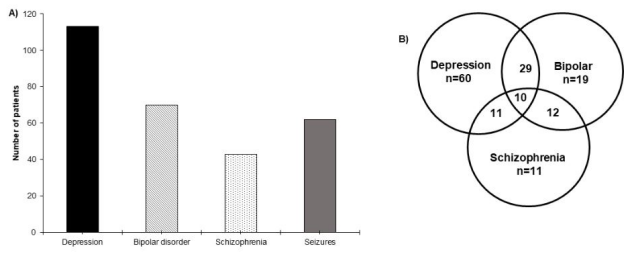

Figure 2: Frequency of psychiatric disorders among HIV-infected individuals. (A) Comparison of the number of HIV-infected patients with depression, bipolar disorder, schizophrenia and seizure co-morbidities; (B) Venn diagram of neuropsychiatric disorders showing unique or overlap of diagnoses between Major Depressive Disorder, bipolar disorder, schizophrenia.

Relationship of drugs of abuse with neuropsychiatric disease in HIV patients

To test the possibility that a specific drug class may contribute to or exacerbate mental health disease, we evaluated MDD, BD, or SCZ, in correlation with nicotine, alcohol, cocaine, cannabis, heroin, or PCP use. Since 86 percent of the patient cohort reported a history of drug use (**Table 1**), the prevalence of specific drugs of abuse in the patients was further investigated. Nicotine, alcohol, marijuana and heroin use were not significantly correlated with a specific neuropsychiatric disorder.

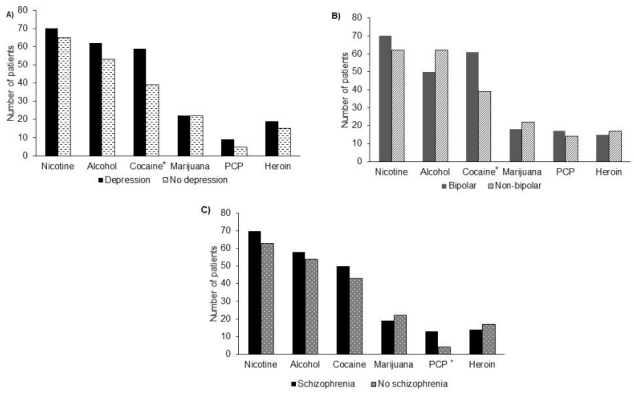

Figure 3: Prevalence of drug abuse in patients with depression, schizophrenia and bipolar disorder. (A) Comparison of nicotine, alcohol, cocaine, marijuana, PCP and heroin abuse in patients with and without (A) MDD; (B) Bipolar Disorder and (C) Schizophrenia. *denotes statistically significant correlation, p<0.05.

Compared to the other drugs evaluated, cocaine use was significantly associated with patients with an MDD diagnosis compared to the rest of the population (57.5% vs. 38.5%; p<0.01) (**Figure 3A**). BD was statistically linked to a history of drug use, in general, compared to non-bipolar patients (p<0.05). Cocaine use was more prevalent in BD patients (61.2% vs. 38.9%; p<0.01) (**Figure 3B**). Finally, PCP use was significantly associated with patients diagnosed with SCZ compared to non-SCZ patients (14% vs. 3.6%; p<0.05) (**Figure 3C**).

CD4 and CD8 counts as a function of neurological/neuropsychiatric disease in HIV patients

The CD4 clinical readout is used to measure CD4+ helper T lymphocytes in the circulation, whereas the CD8 count measures the number of cytotoxic T lymphocytes which is normally low in a non-infected, non-cancerous state. CD4+ T lymphocytes are primarily targeted for destruction by HIV viral cells and play an important role in host immune defenses against opportunistic infections [13]. With progressive HIV disease, CD4 counts drop to low levels, typically <200 (normal: 500 to 1500 cells/mm^3), resulting in AIDS–related symptoms and increased mortality.

As HIV infection progresses, there is gradual loss of CD4 T-cells and elevation of CD8 cells (normal: 150 to 1000 cells/mm^3). An elevated CD8 count may be one of the few indicators of future virologic failure. Of the 282 medical cases, only 210 had a record of their CD4/CD8 counts. 58 percent of these patients had CD4 counts >200. The most common neurological diagnosis was neuropsychiatric in nature, and within this subgroup, 57 percent of patients had CD4 count >200 while 43 percent had CD4 counts <200. In specific, patients with bipolar and schizophrenia comorbidities had a mean CD4 count that was non-statistically distinguishable from those without these neuropsychiatric comorbidities (**Figure 4A**). However, for MDD, there was a significant increase in mean CD4 counts (362.6 ± 38.6 vs. 272 ± 13.1, p<0.05).

The mean CD8 counts did not seem affected by neuropsychiatric status (**Figure 4B**). We then analyzed and compared CD4 and CD8 counts in non-neuropsychiatric neurological manifestations. Interestingly, compared to the neuropsychiatric and peripheral neuropathy categories, the seizure/epilepsy category had a significant number of patients (61%) with low CD4 counts, similar to those with opportunistic infections that show 88 percent of patients having CD4 counts <200 (**Figure 5A**). When a within group assessment of patients with MDD, BD, and SCZ was conducted as in **Figure 5B**, the data indicate a respective 61%, 63%, and 77% of patients with CD4 counts >200 (**Figure 5**).

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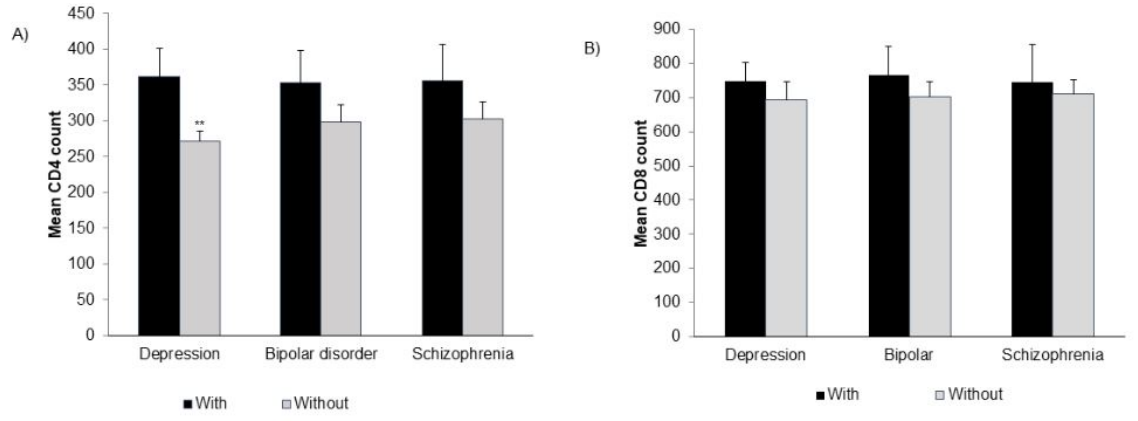

Figure 4: Mean CD4 and CD8 counts in HIV patients with neuropsychiatric involvement. (A) Mean CD4 and (B) CD8 counts of patients with depression, bipolar disorder and schizophrenia compared with patients without these disorders. ** denotes statistically significant correlation, p<0.01.

Next, patients were stratified into two groups of CD8 counts <1200 or >1200. All neurological diseases, including neuropsychiatric, were associated with multi-fold (5-50) greater number of patients with CD8 <1200, except Dementia (**Figure 6A**). Furthermore, 75% of MDD, 90% BD, and 88% of SCZ exhibited a mean CD8 count <1200 (**Figure 6B**).

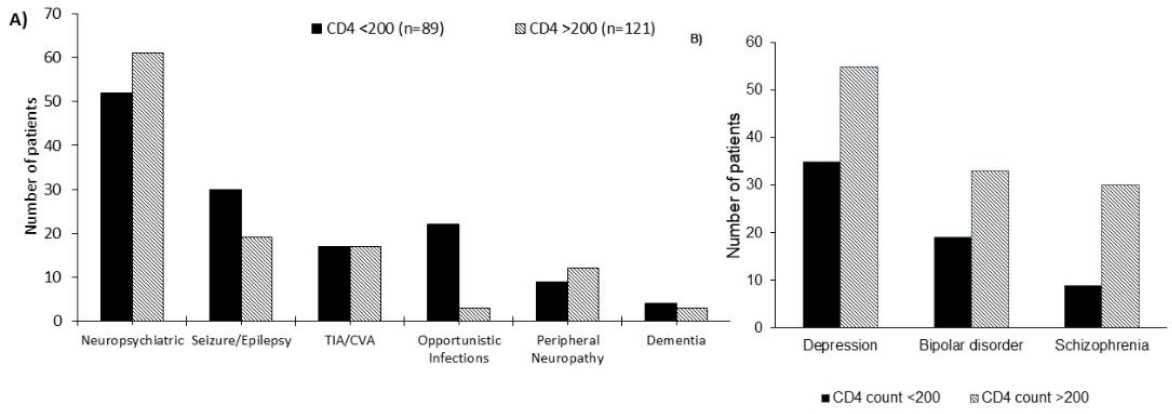

Figure 5: Neurological manifestations in HIV-infected patients in relation to CD4 counts. (A) Patients with CD4 counts <200/mm3 compared to those with CD4 counts >200 in each of 6 neurological presentations: neuropsychiatric disorders, seizure/epilepsy, transient ischemic attack/cardiovascular accidents, opportunistic infections, peripheral neuropathy and dementia that had; whereas (B) compares CD4 count stratification in patients within each neuropsychiatric mood disorder subgroup of interest.

Discussion

Even as efforts have been successful in reducing the rate of HIV infection around the world and in the District of Columbia, the rate remains at epidemic levels of 2.7 percent, nearly 10 times the nationwide values. Our results are the first to evaluate the incidence of substance abuse in HIV-infection, co-morbid with neuropsychiatric and neurological disease in an urban Washington D.C. population. Whereas much data has been published for Caucasian Americans with HIV, where psychiatric or mental disorders are common co-morbidities amongst those at risk for or infected by HIV [2,14], this unique study focuses on an African-American urban population. Here, we report a high co-morbidity of neuropsychiatric disease and drug use in HIV patients, a specific correlation of certain drug classes with MDD, BD, or SCZ, and a surprising partial protection of CD4 degradation associated with neuropsychiatric disease, and but not other neurological diagnoses, even as CD8 levels maintain their elevated levels. This effect on CD4 count was however statistically significant for MDD only.

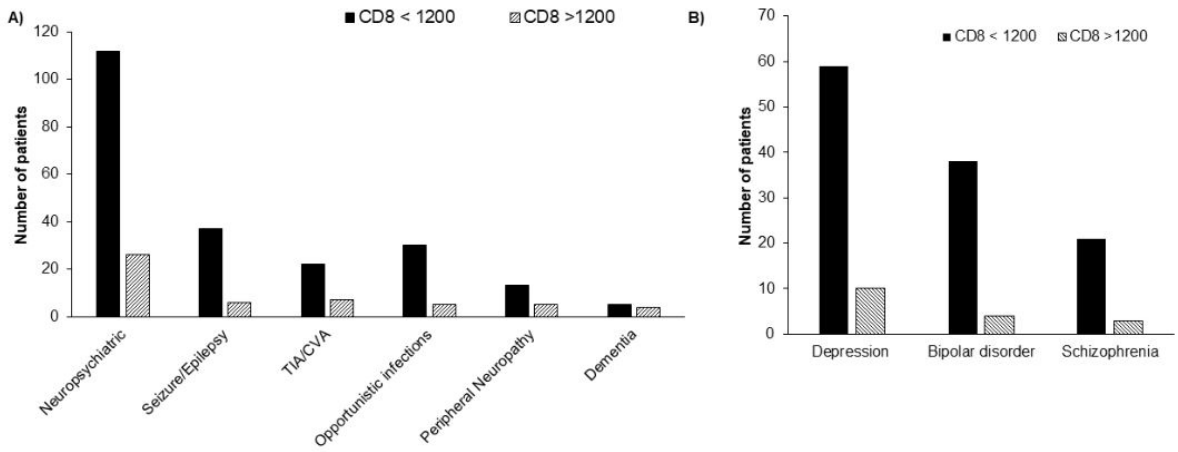

Figure 6: Neurological manifestations in HIV-infected patients in relation to CD8 counts. (A) Patients with CD8 counts <1200/mm3 compared to those with CD8 counts >1200 in each of 6 neurological presentations: neuropsychiatric disorders, seizure/epilepsy, transient ischemic attack/cardiovascular accidents, opportunistic infections, peripheral neuropathy and dementia that had; whereas (B) compares CD8 count stratification in patients within each neuropsychiatric mood disorder subgroup of interest.

Our study shows a prevalence of neurological manifestations in HIV-infected patients younger than 50, except for dementia, which occurred in patients older than 50. Studies have shown that different brain regions that interact to promote cognitive functions show less-coordinated activation with aging, suggesting a vast loss of integrative function, related in part, to disruption of neuronal connections in different cortical regions [15,16]. There was a very high percentage of drug users in our cohort. Only six percent of HIV/AIDS cases in the United States are attributed to drug use [8], but in this cohort, there seemed to be a higher correlation percentage. These data do not allow an interpretation of the cause of HIV infection, but because of the 86% prevalence of drug use in the subjects, it is likely a major contributing factor. It is well established that drugs of abuse alter judgment, induce loss-of-inhibition, and play a massive role in the spread of HIV by leading to engagement in impulsive and unsafe behaviors [17].

The use of potent antiretroviral combinations, like the highly active antiretroviral therapy (HAART), has provided unprecedented opportunities for effectively treating HIV disease and led to a dramatic decline in HIV mortality by profoundly inhibiting viral replication and delaying disease progression [18,19]. This delay in progression would require adherence to the treatment regimen, as non-adherence results in the selection of drug-resistant HIV strains [20,21]. Although our results indicate that over 60% of patients were on HAART therapy, the records did not account for adherence, and thus disease treatment could have been severely impacted in this population. Various demographic, psychosocial, and diagnostic factors affect adherence to HAART [22], and neuropsychiatric disorders often correlate with increased substance use behaviors and can interfere with cognitive functioning [23-25], which also negatively affects HAART adherence. HIV patients with increased life span due to effective therapy may develop cerebrovascular or degenerative encephalitis related to less robust HIV-associated mechanisms acting on neurons over a longer term [26]. Although it is suggested that neurocognitive complications are usually mild, and survival is not compromised [27,28], they may negatively affect quality of life [28], independence in daily activities, or treatment adherence [29-34].

Our results show that MDD was 1.6 to 2.6 times more prevalent than other neuropsychiatric disorders in the study cohort (**Figure 2**). This is consistent with reports from numerous studies in which syndromes ranging from MDD to apathetic and irritable mood disorders have been observed to be frequently present among HIV-infected individuals [35-37]. MDD is the most prevalent psychiatric disorder among HIV-infected persons [38,39], two to four times higher than those found in general populations [2,38-40]. The depressive symptoms may be either a primary consequence of the central nervous system (CNS) effects of HIV infection, or the frustrations, and stigmatization sometimes associated with living with HIV/AIDS [41]. It is well recognized that lesions in specific neural structures due to disease or insult, such as those resulting from a stroke or brain tumor, may contribute to the development of secondary depression. In HIV-positive people with MDD, morphological alterations have been identified in various neuroanatomical structures, including cortical and subcortical regions [36].

Drug use, especially cocaine and PCP use, was observed to be higher in the HIV-infected patients with MDD, BD and SCZ, compared to patients without these comorbidities (**Figure 3**). These provocative data suggest a possible relationship between certain psychostimulants and the presentation of psychiatric disorder in HIV-infected individuals. The

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neurocognitive effects of cocaine, PCP or other drugs of abuse may influence the development and persistence of psychiatric disease in immunocompromised individuals. Additionally, the medications used to treat HIV infection could have additive or synergistic effects on the comorbid incidence of psychiatric disease and HIV when combined with drugs of abuse. Substance abuse disorders are three to five times more prevalent in patients with SCZ compared to healthy controls [42,43]. The core pathophysiologic feature of SCZ involves hypofunction of N-methyl-D-aspartate receptors (NMDARs) [44-47], implicated in the aberrant regulation of synaptic plasticity which may promote substance abuse and addiction. Specifically, modulation of the mesocorticolimbic dopamine system by glutamatergic inputs from cortical and subcortical regions appears to regulate aspects of maladaptive drug seeking [48].

The finding that mean CD4 counts in HIV-positive patients with comorbid depression was statistically higher compared to non-MDD patients (Figure 4A) but that CD8 counts were not statistically more or less elevated, implicates a possible interaction with MDD-mediated protective mechanisms against degradation of CD4+ helper T lymphocytes (**Figure 4B**). Indeed, among patients with CD4>200, the category of neuropsychiatric disorders was prominent (**Figure 5**). This could indicate a paradigm shift of neurological diseases from opportunistic infections to neuropsychiatric manifestations. CD4 count decline is linked to HIV disease progression, and previous work has shown that depression can significantly increase plasma viral load, accelerating the decline of CD4 cell counts [49]. In addition, MDD in HIV accelerates the rate of decline of cognitive symptoms, and is associated with higher deficits in comprehension, attention, and memory [41,50]. Manic symptoms in the early stages of HIV and a CD4 count >200 is indicative of BD [51,52]. A neurological symptom of late-stage HIV/AIDS, when the CD4 counts are <200 is the onset of psychosis in patients, which is postulated to be due to CNS infection, tumors, HIV invasion into the brain, and cognitive impairment [53]. In our study, the CD counts were not specifically correlated with stage of disease or delay-to-onset of comorbidities. Nonetheless, untreated neuropsychiatric manifestations in HIV-infected patients may lead to further spread of the disease, due to the pervasiveness of risk-taking behavior [54,55]. Along with MDD, other conditions including dementia, anxiety, psychosis, substance abuse, are all psychiatric factors associated with non-adherence to HIV treatment [34,56-58]. CD8 cells have an important role in fighting untreated HIV infection. However, an overstimulation of the CD8 response and an elevated CD8 cell count has been associated with accelerated HIV disease progression. Elevated CD8+ cells have also been associated with greater risk of future antiretroviral treatment failure. Our data concerning CD8 cell count (**Figure 6**) supports previous studies' conclusion that drug use is not a major predictor of disease progression as CD8 values were not altered [36].

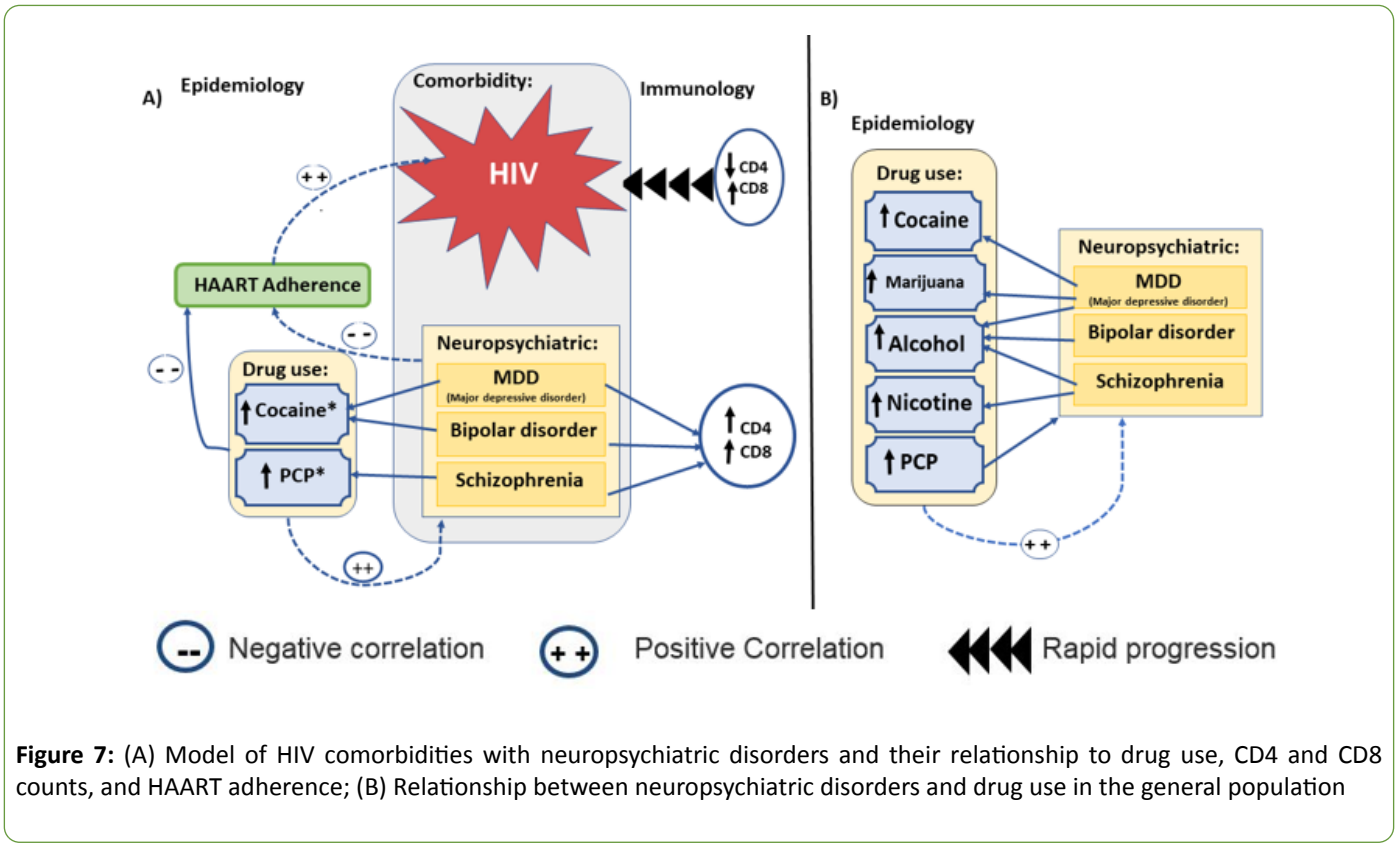

Figure 7: (A) Model of HIV comorbidities with neuropsychiatric disorders and their relationship to drug use, CD4 and CD8 counts, and HAART adherence; (B) Relationship between neuropsychiatric disorders and drug use in the general population

Adherence to HIV treatment regimens is sometimes markedly compromised when a person has serious mental illness [2]. Drug abuse and addiction can cause a greater neurocognitive impairment and poorer HAART adherence compared to non-drug users [3,27,38]. Indeed, HAART slows down the progression of HIV to AIDS, and so incomplete adherence can lead to immunosuppression and drug resistant HIV [34], while non-adherence increases HIV-related morbidity and mortality.

We propose a model (**Figure 7**) based on the findings from our study of an HIV+ urban cohort. This model, a schematic of the feedback loop between neuropsychiatric disease, drug abuse, and HIV progression, supports that the comorbidity of HIV with MDD and BD was correlated with a statistically significant increase in cocaine use (**Figure 7A**). A statistically significant increase in PCP use was observed in correlation with SCZ. An increased CD4 and CD8 cell counts was seen with MDD, BD and SCZ. Neuropsychiatric disorders and drug use correlate negatively with HAART adherence, which increases HIV progression. In the general, non-HIV-infected population, drug abuse is closely correlated with neuropsychiatric disorders (**Figure 7B**). The literature supports the following MDD is prevalent in cocaine [59-61], marijuana [62] and alcohol abusers [63-66]. BD is significantly associated with alcohol abuse [25,67,68], and nicotine and alcohol dependence is more common with SCZ patients than with the general population [69-72]. PCP use is correlated with most neuropsychiatric disorders, especially in individuals with genetic predisposition to SCZ [73,74].

Conclusion

In summary, it is important to study the variation of disease progression in different populations for a more comprehensive understanding of the pathology associated with various co-morbidities and behaviors. We have presented data from a mostly African-American urban population set, and although we found many similarities to other studies of HIV, neurological disease, and drugs of abuse already reported in the literature, we also found a high prevalence of drug abuse and neuropsychiatric complications, with specific correlations with certain drugs of abuse. We focused on mood disorders/ neuropsychiatric disease and found a relative protection of CD4 T lymphocyte degradation, which did not seem to influence progression of disease; however, illicit drugs may have a direct correlation with neuropsychiatric disease incidence. In the future, it will be important to study length of time with HIV status, adherence to HAART therapy, and extent of drug use on HIV pathology.

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