January 2014

Longitudinal Characteristics Of Depression And Mood States Beginning In Primary Hiv Infection

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LONGITUDINAL CHARACTERISTICS OF DEPRESSION AND MOOD STATES BEGINNING IN PRIMARY HIV INFECTION

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

By
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2014

LONGITUDINAL CHARACTERIZATION OF DEPRESSION AND MOOD STATES BEGINNING IN PRIMARY HIV INFECTION. Jessica A. Gold, Marie Grill, Julia Peterson, Christopher Pilcher, Evelyn Lee, Frederick M. Hecht, Dietmar Fuchs, Constantin T. Yiannoutsos, Richard W. Price, Kevin Robertson, and Serena Spudich. Department of Neurology, Yale University, School of Medicine, New Haven, CT.

Though depression is known to frequently afflict those with chronic HIV, mood during the early course of HIV is not well characterized. In a prospective study we assessed mood during primary HIV infection (PHI, <1 year duration), its association with neuropsychological performance and markers of neurological disease, and its longitudinal course including effects of highly active antiretroviral therapy (HAART). The Beck Depression Inventory (BDI) and Profile of Mood States (POMS) subscales were longitudinally administered prior to and after HAART in PHI subjects. This evaluation of mood was done concurrently with blood, cerebrospinal fluid (CSF) and neuropsychological (total z and global deficit score, GDS) evaluation at each visit. Analysis employed Spearman's rho, logistic regression, and linear mixed models. 47.7% of the 65 men recruited at a median 3.5 months HIV duration met BDI criteria for clinical depression at baseline, classified as 'mild' (n=11), 'moderate' (n=11), or 'severe' (n=9). Drug, alcohol, and depression history did not associate with BDI score. Proportional somatic-performance scores were worse than cognitive-affective scores (p=. 0045). Vigor subscore of POMS was reduced compared to norms and correlated with total z (r=0.33, p=0.013) and GDS (r=-0.32, p=0.016). BDI and POMS correlated with one another (r=0.85, p< .0001), but not with CSF or plasma HIV RNA, white blood cell (WBC) count, albumin ratio or neopterin. Improvement was not observed in BDI and POMS over 330 total follow-up visits, even after initiation of HAART. Depression was prevalent

during PHI in our subjects, associated with abnormal somatic-performance and vigor scores. Neither neuropsychological performance nor disease biomarkers correlated with depressed mood. Mood indices did not improve over time in the presence of HAART.

This work has previously been both published and presented, in part:

Gold JA, Peterson J, Lee E, Fuchs D, Price RW, Yiannoutsos CT., Roberston K, & Spudich S. (2012). Depression and Mood States and Correlations with Biomarkers of Central Nervous System Disease in Primary HIV Infection. Presented at the 2012 American Academy of Neurology Meeting in New Orleans, LA.

Gold JA, Grill M, Peterson J, Pilcher C, Lee E, Hecht FM, Fuchs D, Yiannoutsos CT, Price RW, Robertson K, Spudich S. Longitudinal characterization of depression and mood states beginning in primary HIV infection. *AIDS Behavior*. 2014, Jan 3. *Epub*

ACKNOWLEDGEMENTS

This study was funded by the following grants: National Institutes of Health (grants R01 MH081772, K23 MH074466, P30 AI027763, P01 AI071713 and M01 RR0008336)), Yale Medical School Summer Research Fellowship.

The work was made possible by collaboration between Yale University and the University of California-San Francisco, as well as other investigators at the University of North Carolina (UNC), Chapel Hill, University of Indiana, and Innsbruck Medical University (Austria). Working with this group was both valuable and educational to me, and I thank all of the co-authors for their individual contributions to this project. Without their help, this project would not be what it is today.

Additionally, I sincerely thank the participants who volunteered for these studies, the San Francisco General Hospital (SFGH)/University of California–San Francisco (UCSF) Clinical Research Center, the staff at the ARI-UCSF Laboratory of Clinical Virology, and the staff at UCSF Options and Magnet/San Francisco AIDS Foundation for their invaluable help. I also thank Drs Fauci, González-Scarano and Martín-García, for their responsiveness and permission to utilize their figures in my manuscript, the Neurology Departmental Thesis Committee and Dr. Gordon Buchanan, and the Office of Student Research and Dr. John Forrest for their continued support of research as a medical student.

On a more personal note, I thank Serena Spudich. Ben Franklin once said, *"Tell me and I forget, teach me and I may remember, involve me and I learn."* That is exactly what Serena did for me from day one, involve me and teach me. She supported my ideas, taught me how to apply them (or just plain taught me statistics), and helped me finish a paper and present at a meeting. Even still, she is more than a research mentor, but is a role model and a friend. Her life/work balance is an inspiration and knowing she exists, basically confirms to me (over and over again) that this is a career I can do, and not lose myself in the process. I am eternally grateful to have connected with her and to have known her for almost my whole time at Yale. I hope someday I can become the academic physician that she believes I can be, and that I have seen her model before me. Even if a few words aren't really enough….thank you, thank you, thank you.

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INTRODUCTION

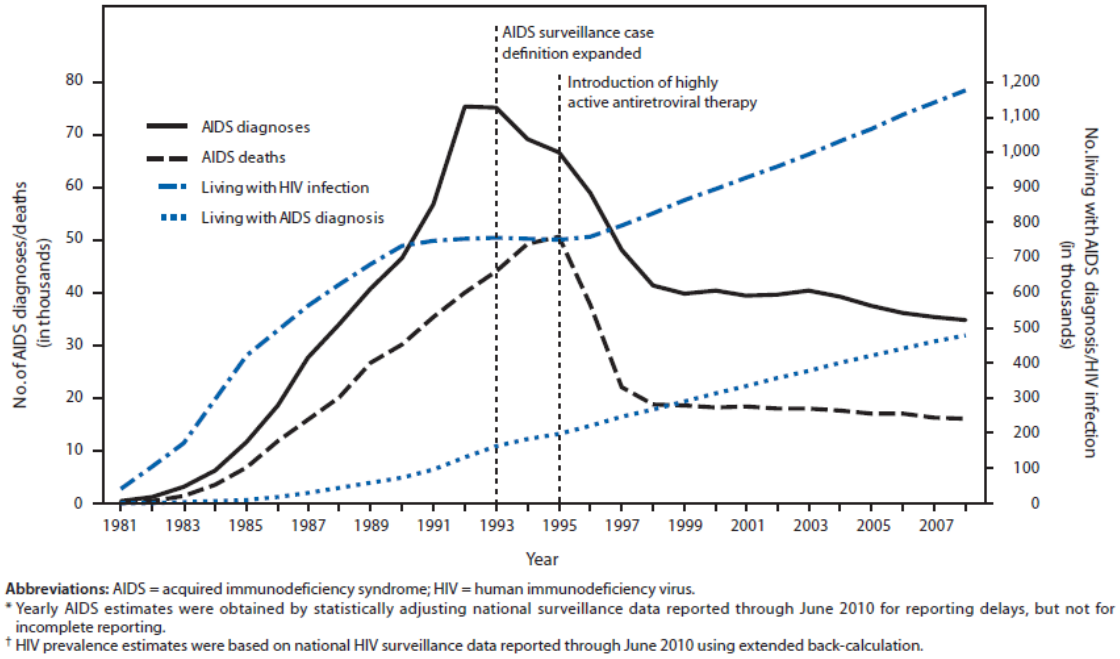
HIV/AIDS: The Problem in the U.S.

"*When I tested positive it was very clear to me that I would die"(1).*

Knowing that this quotation comes from an interview with an HIV-infected person within 2 months of diagnosis, one might expect this person to have been diagnosed in the early era of HIV infection, the 1980s. This assumption occurs because over the past few decades, the picture of HIV/AIDS in the United States has changed dramatically. Research advances have helped to: prevent vertical transmission (mother to child), improve screening blood and blood products for the virus, and develop successful treatment regimens (2). With suppressed viral replication due to highly active antiretroviral therapy (HAART), patients are also less infective to their sexual partners (3). As a result, there has been a significant decline in the HIV infection rate in the United States from 130,000 new cases a year in 1984 to 60,000 in 1991 (2) (See **Figure 1**) (4).

Beyond the decrease in new cases, HIV is also no longer unavoidably fatal. In fact, the loss of life years due to HIV (approximately 7) is equated to that due to a lifetime of cigarette smoking, or close to the levels of the uninfected population with chronic disease (5,6). Additionally, AIDS-related illnesses, such as pneumocystis pneumonia, are no longer the primary causes of death in AIDS patients, and instead, new complications of chronic disease have taken their place (7). In just a few decades, HIV has gone from a fear-inducing disease that was a death sentence, to a chronic illness that is manageable with medication (8). In response, much of our public health focus and

attention has turned to Sub-Saharan Africa where 2/3 of the cases of AIDS now reside (2).



Abbreviations: AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.
* Yearly AIDS estimates were obtained by statistically adjusting national surveillance data reported through June 2010 for reporting delays, but not for incomplete reporting.
† HIV prevalence estimates were based on national HIV surveillance data reported through June 2010 using extended back-calculation.

Figure 1. AIDS in the US from 1981 to 2008: Diagnoses, Deaths, and Living with HIV Infection or AIDS in Persons 13 or Older. Following the introduction of HAART around 1995, there has been a stable incidence of approximately 50,000 new cases/year. *Source: CDC. Morbidity and Mortality Weekly Report. HIV Survelliance-US, 1981-2008. 2011; 60(21):689-693.*

However, the initial expectation that the patient interviewed above was interviewed in the 1980s, is wrong. In fact, this study was conducted within the past year. While there have been vast scientific advances, a decrease in incidence and mortality, and a change to the cultural concept of HIV as a disease, fear about HIV persists. Why is it, then, that this patient, and 23% of the rest of the interviewed sample, still feel that HIV is a fatal diagnosis (1) ?

Perhaps this is because that while the incidence of HIV has remained stable at about 50,000 new cases of HIV a year in the US (9) (**Figure 1**), certain high risk groups, such as the 86% men who have sex with men (MSM) interviewed for the study (1), are disproportionately affected (See **Figure 2**)(10). In some urban areas, the HIV prevalence among MSM is as high as 30%, a number significantly greater than the general population prevalence of both Kenya (7.8%) and South Africa (16.9%)(2). Clearly, the burden of HIV infection today is not solely an international problem.

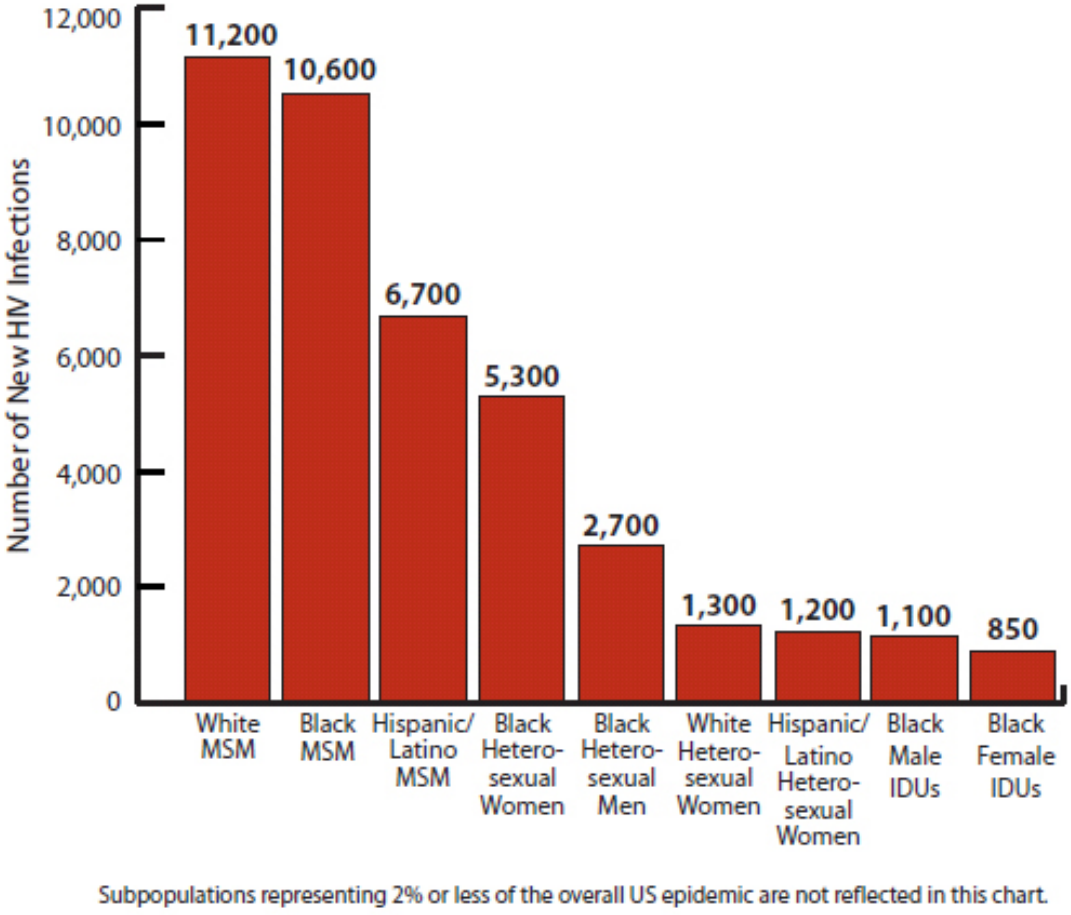


Figure 2: Rates of New HIV Infections in the US in 2010, by High-Risk Subgroup. HIV in the US disproportionally affects African Americans and Hispanics as well as MSM**.** *Source: CDC.HIV in the US: At a Glance.http://www.cdc.gov/hiv/statistics/basics/ataglance.html*

Beyond greater concentrations of disease in disadvantaged populations and a greater concentration of HIV in urban areas, with 50% of persons living with HIV in the US located in only 12 cities (9) (see **Figure 3**), new cases are also found much more commonly in these groups. In fact, even though MSM represent about 4% of the male population in the US, they account for 63% of all new infections (10). This percentage, unlike the overall incidence of HIV in the US, has not remained stable. Instead, it has increased 12% in just two years (from 2008 to 2010) (10). In addition to MSM, HIV in the US also disproportionally affects African Americans and Hispanics. While African Americans represent only 12% of the US population, they account for more than 44% of the new HIV infections (10,11). Hispanic males are also disproportionally affected, infected at 2.9 times the rate of new infections in white males (10). Other risk factors such as intravenous drug use (IVDU), excessive alcohol and cocaine intake, and risky sexual behaviors continue to pose a threat for HIV acquisition (2), and as a result, HIV is found more often in populations with more risk. In these social and sexual networks, HIV remains highly concerning and even subjectively instills a sense of impending doom around the diagnosis.

Additionally troubling, despite widespread screening methods, is the fact that 1 in 6 persons living with the disease are unaware of their status (11). This means that despite effective treatment, patients will present late in the course of their infection, decreasing their life expectancy and increasing the probability of transmission to others (6). Stigma remains a serious impediment to screening and ultimately treatment (1). Given these discrepancies, it is clear that combating HIV/AIDS in the US is not finished and remains a significant public health issue, especially in populations that are “disenfranchised and

socially marginalized" (2). It is thus understandable that the patient interviewed felt HIV was still a death sentence in 2013.

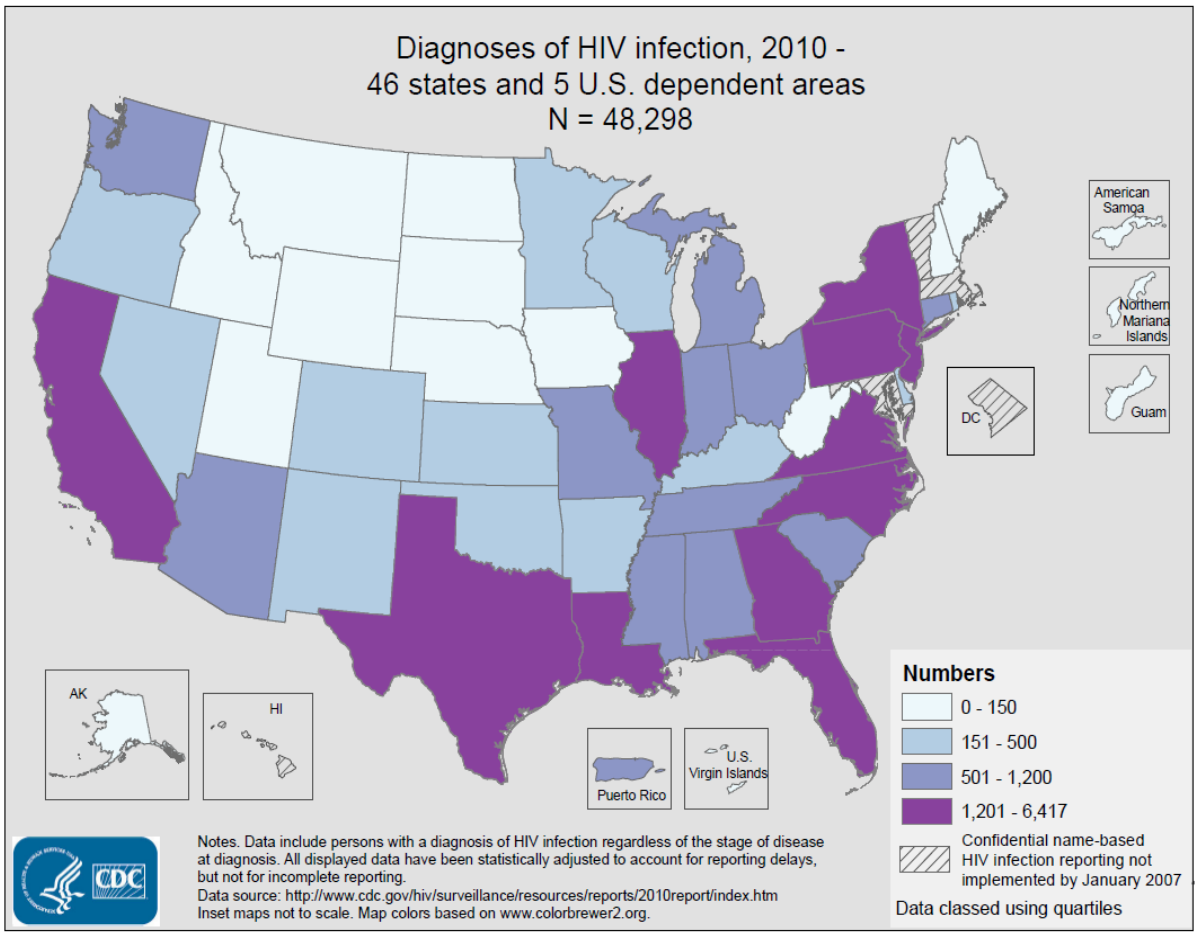


Figure 3: A Map of the Diagnoses of HIV Infection in 2010.
In 2010, the estimated number of new diagnoses of HIV infection in the US was 48,298. This rate varies widely across the US and US dependent areas: from zero in American Samoa and the Northern Mariana Islands to 6,417 in California. *Source: CDC. HIV Surveillance Report , 2011; vol. 23. http://www.cdc.gov/hiv/topics/surveillance/resources/reports/. Published February 2013.*

HIV/AIDS: The Disease and Its Treatment

Acknowledging the problem of HIV in the US, it is also important to understand the basics of the virus's time course and treatment. HIV is a retrovirus (more specifically a

lentivirus) that can be transmitted from sexual contact, IVDU, contact with infected blood products, or from mother to child (12). It infects cells in the immune system, such as helper T cells, macrophages, and dendritic cells, following the interaction of a viral surface protein known as the glycoprotein 120 (gp120) and CD (or the cluster of differentiation) receptor number 4 (CD4), which is expressed on T-lymphocytes, monocytes, macrophages, and dendritic cells (13). Once the virus enters the cell and HIV RNA is reverse transcribed to DNA, the virus can either lie dormant in the latent phase of infection or lead to a decline in CD4 (through mechanisms such as apoptosis and killing of infected cells (14)). This decline will ultimately cause a decrease in cell-mediated immunity, or, more specifically, will decrease the body's ability to fight infection (12).

The clinical presentation of HIV begins with primary HIV infection (PHI), in which a patient develops a "flu-like" syndrome approximately 14 days following transmission (see **Figure 4**). Clinically, patients may experience a fever, fatigue, sore throat, a rash, and even a headache, while biologically there is an increase in HIV RNA and a decrease in CD4 count (15,16). During this period, health care providers often miss the diagnosis of HIV, and, in one study only 25% of patients were correctly diagnosed by providers during an appointment in this time period (15). This early period, however, is a critical time for the course of infection as HIV tissue reservoirs and CD4 memory phenotype T-cells are produced, and viral and immune activation set points are determined (17). Virus can also be found in immunologically privileged areas in the CNS, such as the brain and spinal fluid, during this time (18,19)

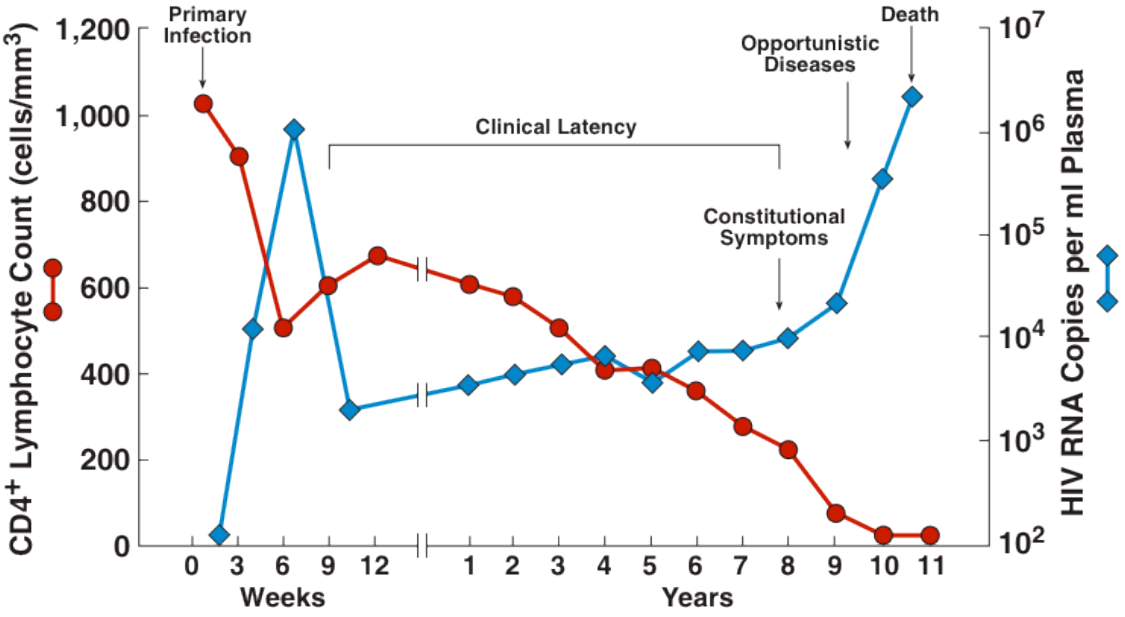


Figure 4: Typical Course of HIV Infection in an Untreated Individual. In this figure, red represents CD4 count and blue the HIV RNA copies/ml plasma. Notice how primary infection is associated with a rise in the plasma HIV RNA within the first three weeks of viral infection. Patients then develop anti-HIV cytotoxic T lymphocytes causing the CD4 count to decline. After a brief recovery of immune cells, infected individuals enter clinical latency, in which the CD4 count declines slowly over time. If HAART is not initiated, the CD4 count falls to a critically low level, the patient is susceptible to opportunistic infections, and will develop AIDS. *Re-Printed with permission courtesy of A.S. Fauci, National Institute of Allergy and Infectious Diseases, NIH*

Following primary infection, the massive peak in the plasma viral load subsides as do the clinical symptoms and the patient reaches the clinically quiescent phase. In this phase, viral particles are produced at a high rate, and CD4 cells are destroyed and replenished daily (20, 21). Over time, a patient's CD4 cell count will decrease substantially and individuals will become susceptible to severe infections and the development of AIDS. This time span ranges from less than one year to more than 20 (21).

In terms of treatment, the first antiretroviral drug was introduced in 1987, zidovudine, and for many years this drug, and others in the nucleoside reverse transcriptase inhibitors class were used as mono, and the only available, treatment.

Approximately 10 years later, protease inhibitors and non-nucleoside reverse transcriptase inhibitors were introduced. The discovery of these additional classes of drugs subsequently led to combination therapy, or the use of three drugs, from 2 different classes. This treatment modification, now known as HAART, extended survival dramatically (12). Yet, because of the blood-brain-barrier (BBB), HIV in the brain can be protected from the full effect of antiretroviral agents, especially those drugs that are large or hydrophilic. To date, studies have found choosing drugs with higher CNS-penetration-effectiveness scores (CPE) can lead to more effective viral suppression (22,23), however, this is not yet recommended practice.

Over the years, treatment guidelines for clinicians have changed with the most current recommendations suggesting that HAART be offered to all patients regardless of their CD4 count (24). However, a patient's willingness to take the treatment consistently, challenged, in part, because of significant drug side effect profiles including lipodystrophy, lactic acidosis, and insulin resistance, is a significant factor in treatment success (12). Drug resistance can occur in the setting of poor adherence secondary to the high replication rate of HIV infection and the high error rate of reverse transcriptase (12). Clinically, patients will observe a decreased susceptibility to a specific drug, and ultimately, may fail to have a beneficial response to their HIV treatment regimen.

At first thought to potentially cure HIV, it is now recognized that HAART is not a cure, but is instead a life-extender. This is because HIV also infects long living cells like microglia and has latency in memory CD4 cells (25), and therefore, never entirely goes away. Though the CD4 count in treated patients will often increase (improve) over time suggesting a greater ability for the patient to fight infection, immune dysfunction,

inflammation, and coagulation disorders will persist. HIV-infected patients are then at high risk for cardiovascular, kidney, and liver disease, as well as malignancy (7). Additionally, it is believed that HIV can affect the central nervous system (CNS), in part, because HAART is systemically suppressive, allowing infection, inflammation, and brain injury to remain active and progressive over time (17).

HIV/AIDS in the Central Nervous System: Mechanism and Effects

Though reasons that HIV is able to impact the nervous system during HAART remain hypothetical, what is known is that HIV entry is associated with immune activation and inflammation in the CNS. The virus is able to traverse the BBB in infected monocytes and lymphocytes, (26) (See **Figure 5, a)**, a hidden mechanism often referred to as the "Trojan horse." Once inside, the monocytes change into perivascular macrophages and eventually release viral proteins that are known to exert toxic effects upon neurons or astrocytes (17). Microglia also become infected (27)(See **Figure 5,b)** and in some cases form large multinucleated giant cells with infected macrophages that serve as a virus production reservoir (see **Figure 5,c**). Infected cells further promote astrocytosis with the dysregulation of cytokine production. These cytokines inappropriately act to recruit activated T-cells from the periphery and activate uninfected cells. Ultimately, this will lead to a further increase in the permeability of the BBB and additional leakage of cells and inflammation products into the CNS (12,27).

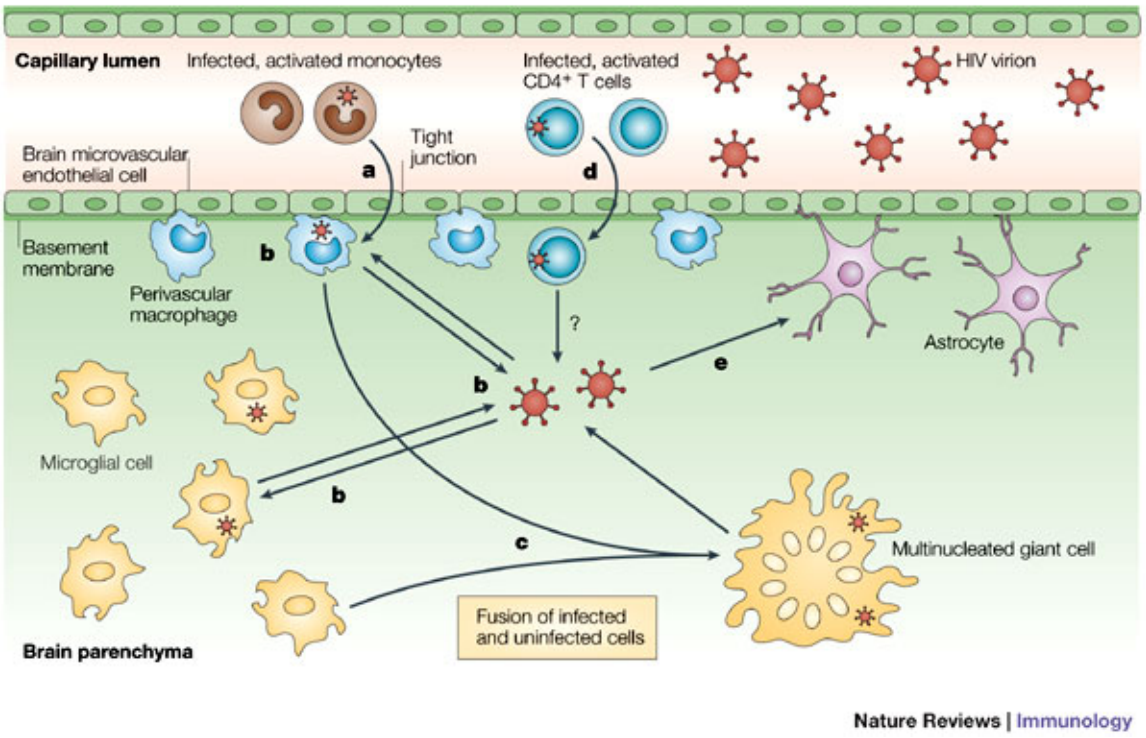


Figure 5: HIV Invasion of the CNS. HIV uses a Trojan horse mechanism to enter the BBB in infected monocytes. Inside, these become perivascular macrophages and microglia. Infected cells will induce astrocytosis and further increase permeability of the BBB. *Reprinted by permission from Macmillan Publishers Ltd:[Nature](González-Scarano, F.& Martín-García, J. (2005). The neuropathogenesis of AIDS. Nature Reviews Immunology, 5(1), 69-81), Copyright (2005), as well as Drs. González-Scarano and Julio Martín-García*

The CNS is infected very early in the course of HIV infection, during primary HIV (15). Even in the early months of infection, HIV is associated with inflammatory T-cells in the brain, an increase in cytokines, and the activation of microglia (17). The CNS reservoir for infection and inflammation is also established during this time period (17). Following the clinical picture of an acute retroviral syndrome, some infected individuals will develop neurological complaints, such as meningitis or encephalitis. As these symptoms are often self-limited, they are believed to be autoimmune in etiology (17).

Yet, the persistence of HIV associated cognitive impairment, despite the initiation and success of HAART, suggests that this early period, before even the HIV diagnosis is made, might cause irreversible damage to the CNS in infected persons (17).

In the days before HAART, one of the more common manifestations of HIV infection, occurring in up to 70% of infected individuals, was neurological disorders (28). More often associated with advanced illness and not primary infection (29,30), these disorders included opportunistic infections such as toxoplasmosis, progressive multifocal leucoencephalopathy (PML) and primary CNS lymphoma, as well as the previously-named AIDS dementia complex (31). In the latter, now called HIV-associated dementia, patients presented with cognitive, motor and behavioral symptoms, but would often only receive this diagnosis when all other causes were ruled out (32). At first these patients would have difficulty concentrating and have mental slowing, and over time, developed motor symptoms including slowing of rapid movements and hyperreflexia (33). Additionally, one large study found that in 1/3 of patients behavior change including apathy and social withdrawal was prominent (32).

With the discovery of HAART, HIV-Associated Neurocognitive Disorder (HAND) no longer manifests as HIV-associated dementia, but is instead presents as more subtle disturbances in psychomotor speed, processing speed, executive function, and/or memory (17). The disorders may be milder than in the pre-ART era, but the presence of cognitive impairment is still associated with an increased overall disease morbidity, thought due in part to low adherence to medication regimens in these patients (34). Additionally, HAND has been shown to correlate with the CD4 nadir (34), suggesting that patients with the largest immunologic ‘hit’ from HIV are most prone to develop

neurocognitive dysfunction. Ultimately, even in the presence of successful treatment with HAART, patients continue to be affected by HAND today.

HIV and Depression

Patients with chronic medical illnesses have, in general, a two-to-threefold higher rate of major depression compared with age and gender matched patients who do not have a chronic illness (35). This is particularly significant as depressed patients appear to die 5 to 10 years earlier than patients without psychiatric disorders (35). In addition, the patients who are also depressed more often report higher numbers of physical symptoms such as fatigue (even when controlling for severity of the baseline medical disorder) (35,36), have higher levels of subjective pain assessment, and contribute to a two-fold higher cost to the medical system (36). This cost is often secondary to increased functional impairment, twice as many health care visits, and a three times lower adherence to self-care regimens in this population (35). Yet, improving depression decreases somatic symptom complaints in these patients (36) and improves health care outcomes. That being said, given that HIV in the post-ART era has been transformed to a chronic illness (7), depression in this population can be presumed to be costly, both to the patient and to the health care system.

Reports of the prevalence of depression over the course of HIV infection vary widely (37-39), however, one meta-analysis found that the diagnosis of Major Depressive Disorder is nearly twice as likely in HIV-infected persons as compared to those without HIV (39). Major Depressive Disorder can be defined using the DSM IV classification, in which a patient must have depressed mood and/or loss of interest or pleasure in life activities plus 5 of the following symptoms for at least 2 weeks: depressed mood, loss of

interest, significant unintentional weight gain, insomnia, psychomotor retardation, fatigue or less of energy, feelings of worthlessness or guilt, diminished concentration, and suicidality (40). One reason for such a strong association between depression and HIV may be overlap in symptoms between depression and HIV infection itself, as appetite disturbance, fatigue, and concentration problems are all associated with HIV as well as depression (38,41-43). In fact, frequency of HIV symptoms and symptom distress were found to increase with level of depression or anxiety (44). Yet, studies suggest that depression is symptomatically different between HIV-infected and HIV-uninfected persons. The most common symptoms reported among HIV-infected subjects is sleep and appetite disturbances, while HIV-uninfected subjects more commonly endorse decreased energy and libido (38). Additionally, depressive symptoms can be caused by both the opportunistic infections associated with HIV, which alter mood and cognition, and the side effects of antiretroviral therapy, which can cause agitation, depressed mood, decreased cognition and insomnia (38). One study found that more side effects from treatment predicted depression (45). Complicating matters further, variables such as employment status, gender, history of attempted suicide, sexual orientation, history of depression, illicit drug use, drug dependence, heavy alcohol use (more than 7 drinks a week for a woman and more than 14 for a man), and social class are all independently associated with increased risks of depression and can subsequently alter the prevalence of and susceptibility to of depression in this population (37,38,46-48). Stigma in this population, which leads to isolation and lack of social support, is also correlated significantly with higher levels of depression (45,48,49). Perhaps because physicians

attribute behavioral change to the disease itself, depression in HIV infected persons often is underdiagnosed (38).

Though it is known that depression is common in HIV infection, it is not clear when depression arises during the course of infection or how this relates to other events of HIV pathogenesis. In general, cross-sectional rates of Major Depressive Disorder are similar in asymptomatic disease and in more advanced HIV disease (39). Unlike in the general population, depression rates do not seem to decline with age in HIV infected populations (47). Indeed, studies have shown no increase in the rates of depression in later stage disease even in patients more medically ill (43,50), and have found no consistent association with either CD4 cell count or HIV viral load (39,51,52). For example, some studies have found an association between low CD4 count and depression, while others found no association. Depression has also not conclusively been found to affect performance on neuropsychological testing (37,53,54). Despite an unclear association between depression and these medical and neurological aspects of HIV infection, one study did find that depressive symptoms were associated with an increased mortality in HIV-positive women (43,55).

It is often debated whether, when depressed mood and HIV infection are identified concomitantly, depression was a premorbid condition in a person who was at high risk of HIV acquisition, or whether depression followed HIV infection. There are theories, however, suggesting that there may be a biological basis to the depression seen in HIV infection. One idea is that the cytokines produced by the macrophages in the HIV infected CNS lead to depression (48,56). This concept is supported by the discovery of elevated inflammatory markers, such as cytokines, in depressed human patients, the

finding of high levels of depression in people with inflammatory illnesses, and the relation between acute inflammation in mammals and behavioral changes similar to depression known as “sickness behavior” (56). Another hypothesis suggests that gp120 inhibits the dopamine transporter, increasing dopamine levels in the synapse and promoting HIV replication. HIV then destroys the dopaminergic basal ganglia neurons leading to depression (48,56). A final theory suggests that stress from illness increases corticotropin releasing hormone and cortisol levels, leading to depression (38,48,56). On the other hand, some argue that mood changes in this population could have preceded infection with HIV, instead of secondary to the illness itself (57). This means that those with a history of a mood disorder, or those populations at high risk of having a mood disorder (MSM and IVDU), are at an increased risk for contracting HIV (58). Whether behavioral, social, or reactionary, this risk for HIV infection in populations with a high baseline risk of depression leads to higher rates of depression overall in this population (43). Developing depression may then either be a result of previous depression, or HIV’s affects on the CNS (59).

While the timing of the relationship between initiation of depression and HIV remains unproven, what is evident is that depression can impact HIV disease progression and treatment outcomes. Having depression is associated with a faster progression to AIDS and increased risk of mortality associated with HIV (59). While this may be related to an association between depression and impaired immune function (53), it may also correlate with decreased medication adherence and incomplete virologic suppression (38, 43, 52) among HIV infected individuals on HAART. In fact, in one meta-analysis, depression was consistently associated with non-adherence in all samples over time (60).

This effect (r-.19) was similar to the effect (r=.21) in meta-analyses of depression and other chronic illnesses (60). Additionally, as one study found an inverse association between depression and HAART, suggesting lower levels of depression in patients on HAART, and this association was found to increase with time on HAART, some postulate there is a protective effect of HAART on patients against depression (61). Given that non-adherence is associated with an increase risk of treatment failure and viral resistance, and, that there are potential mood benefits to using ART, diagnosing and properly treating depression in HIV infected patients becomes critical.

In this population, study after study has suggested the benefits of antidepressant use. Antidepressants have been shown to be an effective treatment for HIV infected patients with depression (38,41,58,62); antidepressant use in one month has been associated with a 28% increase in the odds of HAART use in the subsequent month (63). Furthermore, in a different study, the odds of adhering to HIV-treatment were 83% better if a patient was having their depression treated (64). In terms of which antidepressant is safe and effective in this population, though serotonin reuptake inhibitors (SSRIs) were found to be as effective as tricyclics, SSRIs were often the drug of choice due to their much safer side effect profile (38,43). Nonetheless, as remission of depression was associated with lower viral load or a decrease in the amount of virus (65), treating depression is crucial for medication adherence, and treating HIV.

For all of these reasons, understanding and treating depression in HIV-infected patients is of central importance in improving clinical outcomes. With new HIV clinical practice guidelines (24) recommending treating all HIV-infected patients with HAART, including those in very early HIV infection, early interventions to enhance adherence to

HAART and its effectiveness will be critical in preventing the transmission of drug resistance. Better understanding of the role of depression in the early stages of HIV has emerged as an important question in the public health approach to HIV treatment.

This study seeks to elaborate on our understanding of HIV and depression by focusing on subjects with primary HIV infection (PHI), or those infected within the past year. As mentioned previously and clarified here, during the early weeks after exposure to HIV, up to 10% of individuals develop neurological signs and symptoms of disease, and HIV can be detected in both cerebrospinal fluid (CSF) and brain tissue (18,19). PHI is also associated with impaired performance on neuropsychological testing and with neuroinflammation as measured in CSF (66,67). Yet, to date, only one study has looked at and reported on the prevalence of symptoms and signs of mood disorders during the early stages of HIV infection (68). This study measured depression in 34 individuals with PHI using qualitative methods (the Mini International Neuropsychiatric Interview) and quantitative self-report comparisons (the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory). The authors found that almost 40% of their subjects were categorized as depressed in the clinical range, though most depression was “mild”, and that subjects had a strong reliance on adaptive coping approaches (68). We aimed to further characterize depression in PHI, by assessing mood states in subjects with PHI with additional measures, and correlating mood indices with measures of CNS inflammation and infection in the CSF and with measures of cognitive performance. In addition, we longitudinally assessed mood scores in this observational study, including visits both prior to and after initiation of HAART, to evaluate the trajectory of depression

in this population over time and association of mood scores with the commencement of HAART.

HYPOTHESES

Depression and otherwise altered mood states are prevalent in the first months after HIV-1 transmission (during PHI) and will persist longitudinally despite initiation of HAART. Indices of altered mood states may correlate with CNS inflammation as measured in CSF, or with performance on neuropsychological testing.

SPECIFIC AIMS

1) To quantify and describe the extent of depression symptomatology and the range of mood states of individuals during the first six months after HIV exposure based on baseline scores on the validated Beck Depression Inventory (BDI) and Profile of Mood States (POMS) assessments obtained from a cohort of subjects with primary HIV infection.

2) To investigate whether baseline levels of depression in PHI (as measured by the BDI and POMS) correlates with known biomarkers of HIV burden and inflammation and host responses in the CNS to infection.

3) To examine whether the baseline levels of depression in PHI (as measured by the BDI and POMS) correlate with cognitive impairment based on neuropsychological testing.

4) To longitudinally assess mood states in patients with HIV, from acute infection to up to 3 years post infection, taking into account the effects of HAART initiation in this cohort.

METHODS

As lead investigator on this highly collaborative project, Jessica Gold was responsible for the key aspects of the study. Importantly, she conceived of the study concept. Though the cohort study was planned and implemented prior to her participation and relevant data to this project was in the process of collection, the specific analysis of mood features in correlation with laboratory and clinical features was an idea that she developed and pursued. After planning the study design and analysis, plan, she performed all of the key aspects of implementing the project, including reviewing the subject data and excluding inappropriate subjects, cleaning the dataset, tallying the mood inventory data from individual forms filled out by study subjects, organizing the data into spreadsheets, and performing data analysis. She performed all of the baseline cross sectional analysis and summary statistics, and worked closely with Dr. Constantin Yiannoustsos, a professor of statistics, to perform the complex analysis of longitudinal data. She also was responsible for creating figures and tables, as well as all of the writing that accompanied the research, with editing help from Dr. Serena Spudich and other collaborators. The other investigators were responsible for recruiting subjects, collecting or storing specimens, neuropsychiatric testing, conducting detailed medical histories, and performing laboratory assays. Collaborators also worked closely with the primary author in performing the complex statistics required for cofounders analysis (such as substance abuse) and the complex longitudinal data analysis and graphing as noted above, as well as assisted with normalizing the neuropsychiatric data.

Study Design and Subjects

Study subjects were enrolled in an observational longitudinal neurological study of PHI based at the University of California, San Francisco (UCSF), the Primary Infection CNS Events Study (PISCES)(66). Subjects with known or suspected HIV infection within the past year were referred to PISCES from local HIV testing centers or from a parallel systemic study of PHI, the UCSF Options Study. Subjects were over the age of 18, identified within the first twelve months after HIV-1 transmission as defined either by seroconversion on standard HIV serologic testing or by a less-sensitive HIV antibody EIA indicating early infection as previously described for this cohort (69,70). For subjects reporting classic acute retroviral symptoms within the seroconversion period, infection was estimated as having occurred 14 days prior to onset of acute retroviral symptoms (71). In the absence of such symptoms, the infection date was estimated as occurring halfway between the last negative and first positive HIV test (72).

Study visits occurred at baseline, 6 weeks, 6 months, and every 6 months thereafter indefinitely. Subjects were HAART naïve at the first visit, and some started HAART at variable times during the course of follow-up for reasons outside of the observational study. At each visit, subjects underwent a record review, a full neurological history and examination, a detailed battery of neuropsychological testing, depression screening, and lumbar puncture and phlebotomy. The Institutional Review Boards at UCSF and Yale approved study protocols, and informed consent was obtained from all subjects.

Depression Measures

The BDI-II (73) and POMS (74) measures were administered at each study visit. Study subjects completed these instruments using the standard instructions and with the help of

study staff that were available for questions and to make sure that subjects understood and properly completed the screens**.**

The BDI-II consists of 21 items. Study subjects choose a phrase that is most associated with how they are feeling ranked on a Likert Scale. The total number of points for the entire instrument is then calculated to measure the total BDI score; higher scores indicate a more severe depression. The standard cut-offs for the BDI-II indicate that a score of 0-13 is minimal depression, 14-19 is mild depression, 20-28 is moderate depression, and 29-63 is severe depression. In addition, to properly compare with the study by Atkinson et al, the only other study of depression in subjects with PHI, clinical depression was defined as a total BDI>13 (68). To calculate BDI subscale scores, items 1-13 scores were tabulated for the **cognitive/affective score**, which includes items such as self-dislike, pessimism, and worthlessness, and the points for the remaining items (14-21) were summed for the **somatic score,** which involves such symptoms as change in appetite, loss of interest in sex, irritability, and concentration difficulties (75). Proportions were calculated to compare the subscale scores to each other by dividing the raw score by the possible total score for each subscale.

The POMS consists of 65-words or brief phrases on a Likert scale. Raw scores for the mood states of depression, tension, anger, fatigue, confusion, and vigor are then calculated using standard analysis methods leading to a raw score of <60 for each mood state. Total Mood Disturbance (TMD), is calculated by the sum of the raw scores from tension, depression, anger, fatigue, and confusion, with the vigor score subtracted. This gives a TMD in the range of -24 to 177, with a lower score representing more stable

mood. In our analysis, subscale and total scores were converted to z scores for normalization.

Specimen Sampling, Processing and Laboratory Studies

CSF, blood, and general medical and neurological assessments were obtained as previously described (76,77). Briefly, this involved CSF collection via lumbar puncture, wherein subjects, after specific consent for lumbar puncture procedure, were prepped and draped, lay in a lateral supine position, and had a small amount of 1% lidocaine introduced subcutaneously and then in the slightly deeper soft tissues for local anesthesia. After accomplishment of anesthesia, a Sprotte pencil point CSF collection needle with introducer was inserted into the anesthetized space and approximately 20 cc of CSF was collected. After the procedure, subjects rested and underwent phlebotomy for blood collection for paired blood lab analysis. From CSF, total white blood cell (WBC) count, protein, and albumin were measured in the clinical laboratory on fresh samples. From blood, background labs including complete blood count and chemistries, as well as blood albumin and blood CD4+ and CD8+ T lymphocyte counts by flow cytometry were measured on fresh samples. The remainder of the samples were centrifuged and cell-free CSF and blood plasma were also aliquoted and stored within 6 hours of collection in -70 deg C freezers monitored for temperature on a daily basis using NIST-certified thermometers.

Immune Biomarker Methods

CSF and plasma concentrations of the macrophage activation marker neopterin (BRAHMS Aktiengesellschaft, Hennigsdorf, Germany) was measured in previously

frozen samples in the laboratory of Dr. Fuchs by commercial immunoassay. Neopterin is a sensitive measure for cellular immunoactivation (78) and chemokines mediate HIV-infected leukocytes through the BBB. MCP-1 recruits monocytes and macrophages, typically at low levels in asymptomatic HIV-infected individuals (79 80).

CSF chemokines interferon-inducible protein-1 (IP-10) and monocyte-chemoattractant protein-1 (MCP-1, R&D Systems, Minneapolis, MN) were also measured in previously frozen samples locally at UCSF by commercial immunoassays. IP-10 is produced by T-cells, macrophages, astrocytes, and endothelial cells, and attracts immune cells, primarily T lymphocytes, from the periphery across the blood brain barrier (81). Levels of IP-10 often correlate with CSF mononuclear and HIV RNA levels (82). MCP-1 is also produced by immune cells including resident microglial cells and macrophages within the CNS, primarily attracts monocytes across the blood brain barrier, and in advanced HIV is highly correlated with presence of HIV dementia.

Virological Methods

HIV RNA levels were measured in previously frozen cell-free CSF and plasma using the ultrasensitive (50 copies/mL lower limit of detection) Amplicor HIV Monitor (version 1.5; Roche Molecular Diagnostic Systems, Branchburg, NJ), or the Abbott RealTime HIV-1 (Abbot Laboratories, Abbot Park, IL, USA) assays. Paired blood and CSF measurements were made using the same assay, typically in the same PCR run.

Neuropsychological Testing

Neuropsychological testing performed by a trained psychometrist employed an 11 test battery encompassing five neurological/cognitive domains, including motor (timed gait, grooved pegboard, finger tapping, non-dominant hand); executive function (trailmaking B & Controlled Oral Word Association Test); processing speed (WAIS-R digit symbol, trailmaking A); memory (RAVLT delay, figure delay); and learning (average of RAVLT trials 1-5, figure memory learning). All measures except timed gait were normed according to age, education, gender, and ethnicity. Measures were summarized as a brief NPZ4 (average of performance on 4 tests: timed gait, grooved pegboard, finger tap and digit symbol), total Z (average of performance on all 11 tests), and global deficit score (uses a standardized conversion table to convert demographically corrected Z scores on individual NP measures to deficit scores ranging from 0 (no impairment) to 5 (severe impairment)).

Statistical Analysis

Baseline descriptive statistics were performed using GraphPad Prism (version 5.0, GraphPad Software, San Diego, USA). Spearman's non-parametric correlation was used for correlation between measured parameters at baseline. Cross-sectional baseline group differences were detected through the Mann-Whitney rank sum test and the Kruskal-Wallis test with post-hoc testing corrected for multiple comparisons. Longitudinal analysis was performed using SAS (version 9.0, SAS Institute, Inc., Cary, NC) and employed a mixed-effects model with covariates of weeks of infection and time-by-ART

interaction in subjects starting HAART to analyze longitudinal BDI and POMS total scores.

RESULTS

Baseline Study Subject Characteristics

65 subjects (all men) with a median age of 36 qualified to participate in this study. They also had a median of approximately 3.5 months (103.5 days) of infection at baseline, and median CD4 count of 558. One subject included in this study who met BDI criteria for severe depression committed suicide after the first visit. Other baseline features of the 65 subjects (including prior treatment for depression and substance use) are presented in **Table 1.**

	Age (*years*)	**Days post HIV exposure**	**Years of education**	**Plasma HIV RNA** *(log10 copies/ml)*	**CD4 count** (*cells/ mm3*)	**CSF HIV RNA** *(log10 copies/ml)*	**CSF WBC** (*cells/ul*)
Median/ Absolute Total	36	103.5	16	4.5	558	2.6	6
Interquartile Range	*(28.5-43.5)*	*(72.3-164.3)*	*(14-18)*	*(3.9-4.9)*	*(411-728.5)*	*(1.7-3.1)*	*(2.0-11.0)*
	Prior treatment for depression	**Prior treatment for bipolar disorder**	**No history of alcohol abuse**	**No history of drug use** *(ever)*	**No recent drug use** (*within 1 month*)		
Median/ Absolute Total	20	3	32	14	26		
Percentage of Total	*(31.7%)*	*(4.8%)*	*(50.8%)*	*(22.2%)*	*(43.3%)*		

Table 1: Baseline Characteristics of Study Participants. N = 65 subjects, 100% male, all but 3 self-identified as MSM

Baseline Analysis of BDI and POMS Scores

According to BDI definitions (total score >13), 31 (48%) of the 65 subjects met the criteria for clinical depression at baseline. Of those subjects, 11 had 'mild' depression, 11 had 'moderate', and 9 had 'severe' depression (See **Figure 6**). A comparison of somatic performance proportional scores to cognitive-affective performance proportional scores, showed somatic scores were worse than cognitive-affective scores (medians 0.29 vs 0.15, p=.0045) (**See Figure 7)**.

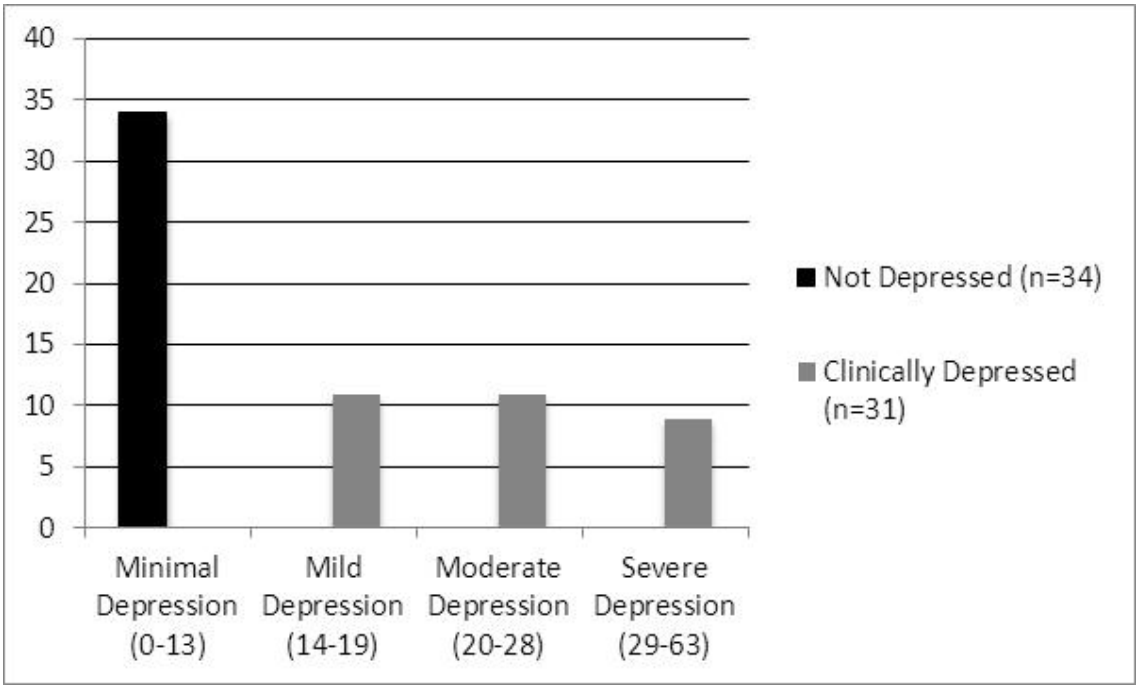


Figure 6: Depression During PHI by BDI Definition. Baseline depression severity in PHI subjects based on total BDI scores. 47.7 % met BDI criteria (total score > 13) for clinical depression.

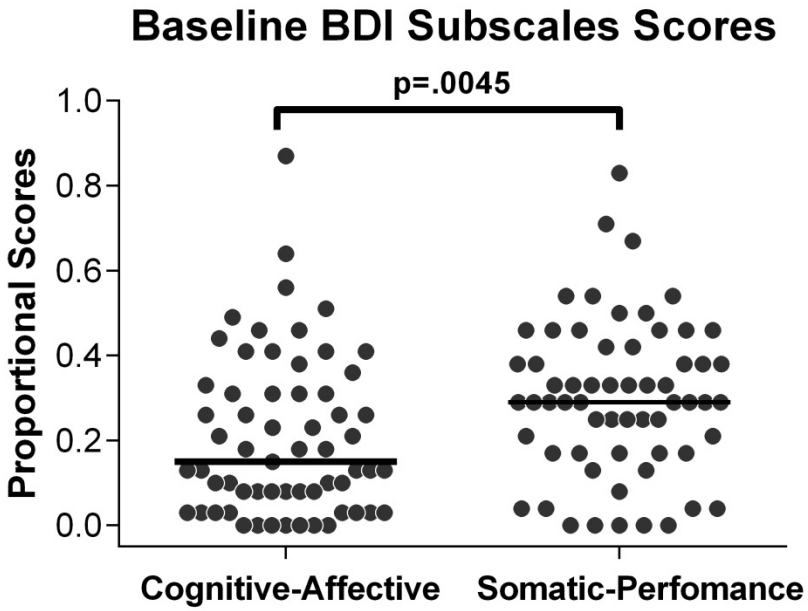


Figure 7: Baseline BDI Subscale Scores. BDI subscale scores presented as a proportion of total possible points per scale. Subjects reported greater somatic than affective symptoms. Bold lines denote median value.

Per the POMS measurement, the median Total Mood Disturbance was 44 (range -21 to 167, with standard deviation of 41.64). **Figure 8** shows the comparison between the different POMS subscales according to Z score. Vigor was the only state reduced in PHI subjects as compared to norms. The levels of tension, depression, confusion, anger and fatigue were similar. Additionally, the BDI total score and POMS Total Mood Disturbance score correlated with one another ($r = .85$, $p<.0001$) (see **Figure 9**). This suggests internal reliability between the measures in our subjects, despite self-report.

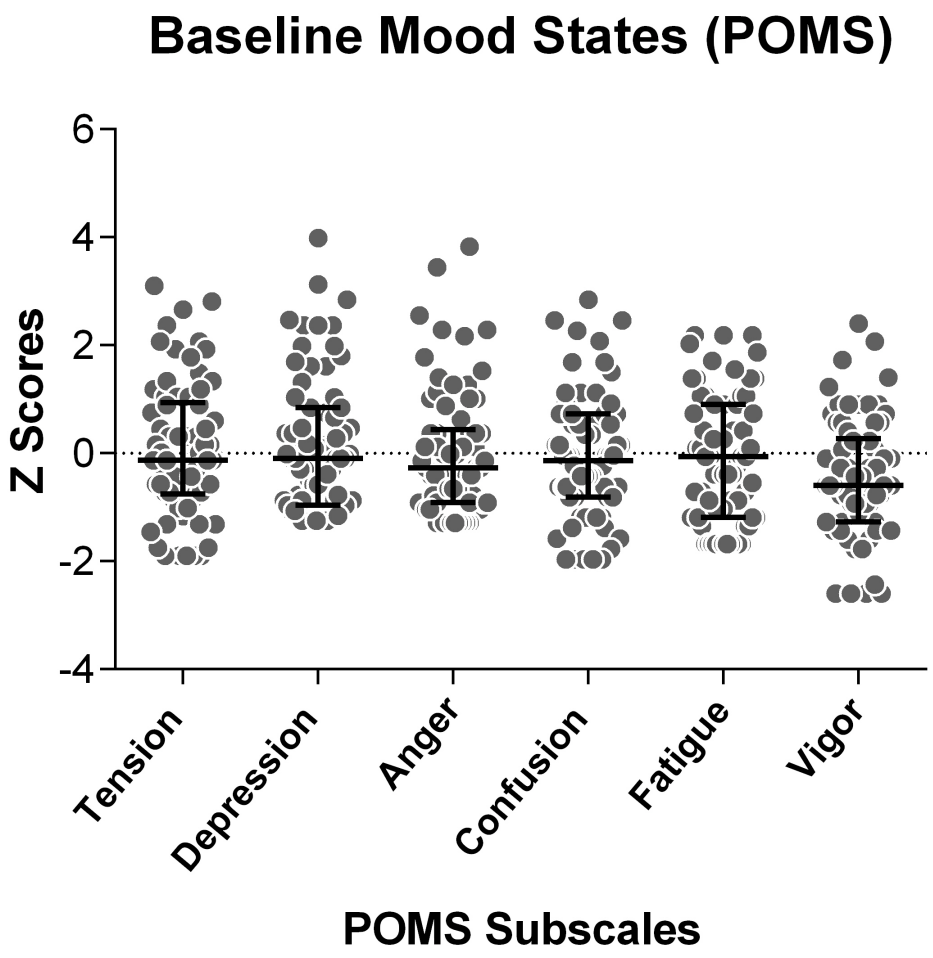


Figure 8: Baseline Mood States: POMS Subscale Scores. POMS subscale scores at baseline. Only vigor was different (reduced) in PHI subjects compared with norms (Z scores). Bars indicate median and interquartile range.

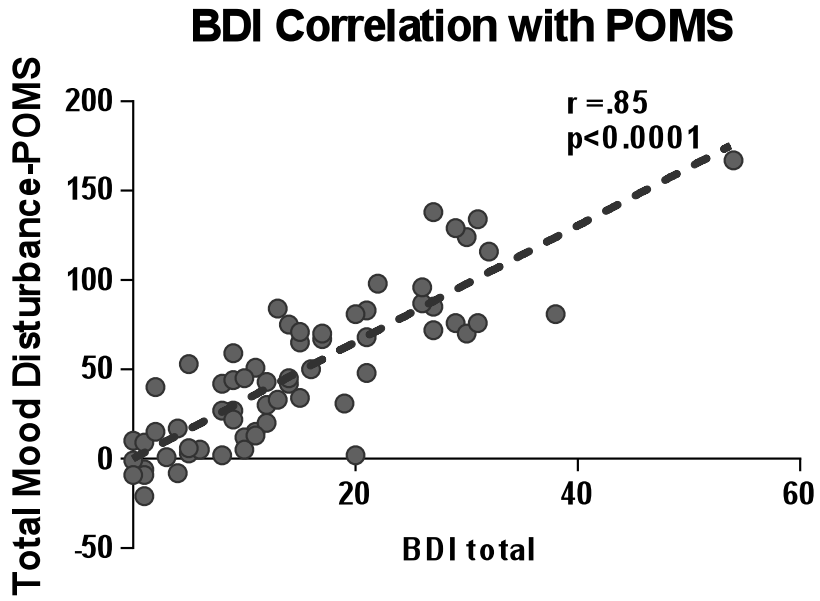


Figure 9: Correlation Between POMS Total Mood Disturbance and BDI Total Scores. Strong and significant correlation suggests internal consistency of these measures in our subject cohort.

We sought to investigate the possible effect of variables that may be associated with depression independent of HIV infection status on the mood states in our subjects. Scores on the BDI did not differ between groups defined based on the subject's history of past drug use ($p = 0.845$), recent drug use ($p = 0.885$), alcohol abuse ($p = 0.592$), or prior psychiatric history/treatment, including depression or bipolar disorder ($p = 0.875$).

Correlation of BDI and POMS Scores with Laboratory and Neuropsychological Performance Indicators

No association was found between scores on BDI or POMS measurements and laboratory measures of HIV infection or CSF markers (not shown in table) associated with blood brain barrier breakdown (CSF: serum albumin ratio), macrophage activation (neopterin) or chemoattraction of inflammatory cells into the CNS (IP-10 and MCP-1) (**Table 2**).

Similarly, scores on mood measures did not correlate with either brief or total summarized NP measures, except an association between self-reported 'vigor' and better performance. The vigor Z score (median=-0.6) was reduced and modestly correlated with total z (r=0.33, p=0.013) and GDS (r= -0.32, p=0.016).

	CD4 count (*cells/mm3*)	**Plasma HIV RNA** *(log10copies/ml)*	**CSF HIV RNA** (log10copies/ml)	**CSF WBC**	**NPZ-4**	**Total Z Score**	**Global Deficit Score**
BDI Total Score	r= -0.11	r= 0.03	r= -0.091	r= 0.053	r= -0.13	r= -0.16	r= 0.14
	p= 0.35	p= 0.80	p= 0.53	p= 0.69	p= 0.37	p= 0.24	p= 0.32
POMS Total Mood Disturbance	r= -0.13	r= -0.007	r= -0.032	r= 0.077	r= -0.055	r= -0.17	r= 0.18
	p= 0.32	p= 0.96	p= 0.83	p= 0.57	p= 0.69	p= 0.22	p= 0.20
POMS Vigor Subscore	r= 0.55	r= -0.20	r= -0.071	r= -0.13	r= 0.18	**r= 0.33**	**r= -0.32**
	p= 0.66	p= 0.10	p= 0.59	p= 0.32	p= 0.18	**p= 0.013**	**p= 0.016**

Table 2. Correlation Between Baseline BDI and POMS Scores and Laboratory Parameters and Neuropsychological (NP) Performance. Spearman r correlation value and p values are shown. Significant correlations are shown in bold. No significant correlations were identified between POMS Tension, Anger, Confusion or Fatigue subscores and lab or NP performance results.

Longitudinal Analysis of BDI and POMS Scores

Utilizing the same population of 65 subjects, we performed a longitudinal mixed-methods analysis on POMS and BDI scores. Only 60 of the 65 subjects from the baseline analysis could be used because 5 subjects did not have longitudinal follow-up. Understanding that a higher score is consistent with more depression on both the POMS and BDI measures, we did not detect a statistically significant improvement in the overall BDI either prior to

or following HAART initiation (slope of change prior to treatment over time -0.02038 change per week, p=0.1238; slope of change following ART= -0.0020, p=0.9107). The aggregate overall BDI trajectory (including pre- and post- HAART visits) also did not significantly change over the course of follow-up (slope= -.02239, p=0.0748). On the POMS, there was a small significant improvement in depression prior to initiation of HAART (slope= -0.1229, p=0.0321), but neither the slope following HAART initiation (slope=0.1005, p=0.2308) nor the aggregate trajectory of POMS over total follow-up was significant (slope=-0.2246, p=0.7136). This data is represented by the spaghetti plots in **Figures 10** (BDI) **and 11** (POMS)**.** On top of the lines, which connect each subject's trajectory, we have superimposed a Loess curve for each dataset to summarize the smooth average values of the data at each interval for visualization purposes. However, the statistical model that we used is more sophisticated than the Loess and factors in the variable duration and intervals of follow up for each subject, as well as their pre- versus post- HAART initiation status.

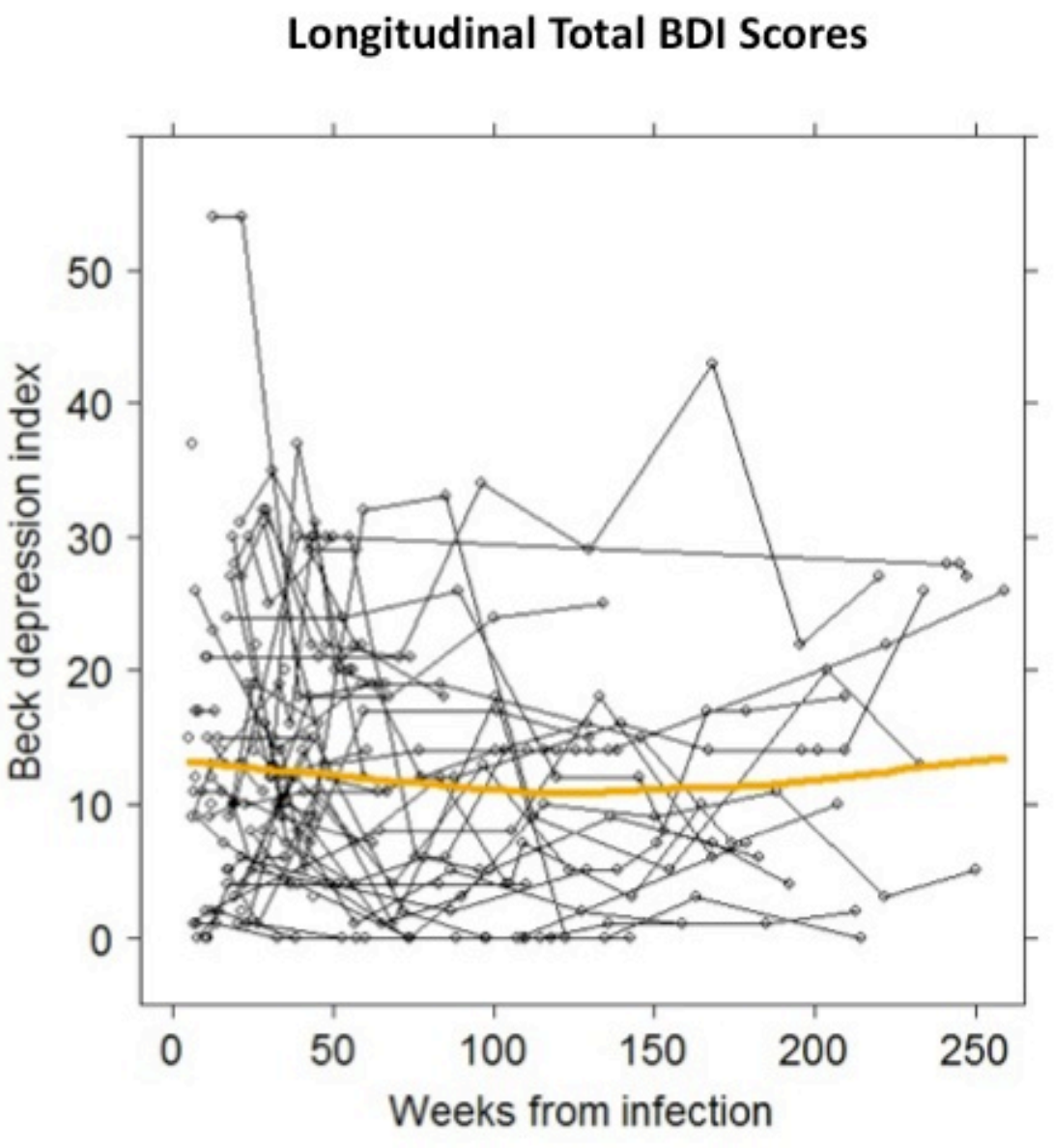


Figure 10. Longitudinal Total BDI Scores. Longitudinal BDI Total scores in those 60, of the initial 65 subjects with longitudinal follow-up, both before and after HAART initiation. Individual subject's scores are represented here as symbols connected by lines to demonstrate the BDI score trajectory. A Lowess curve is superimposed on the lines to show the average scores at each time point and to provide an overview of the trajectory, but the more complex mixed model weights number of visits per subject and duration of follow-up. In this study, subjects had a total of 330 total visits, 196 of these off of ART. There were no changes in the BDI scores over a median 54 weeks of follow-up in longitudinal mixed model analyses either prior to or following HAART initiation (slope of change prior to treatment over time -0.02038 change per week, p=0.1238; slope of change following ART= -0.0020, p=0.9107). The aggregate overall BDI trajectory (including pre- and post- HAART visits) also did not significantly change over the course of follow-up (slope= -.02239, p=0.0748).

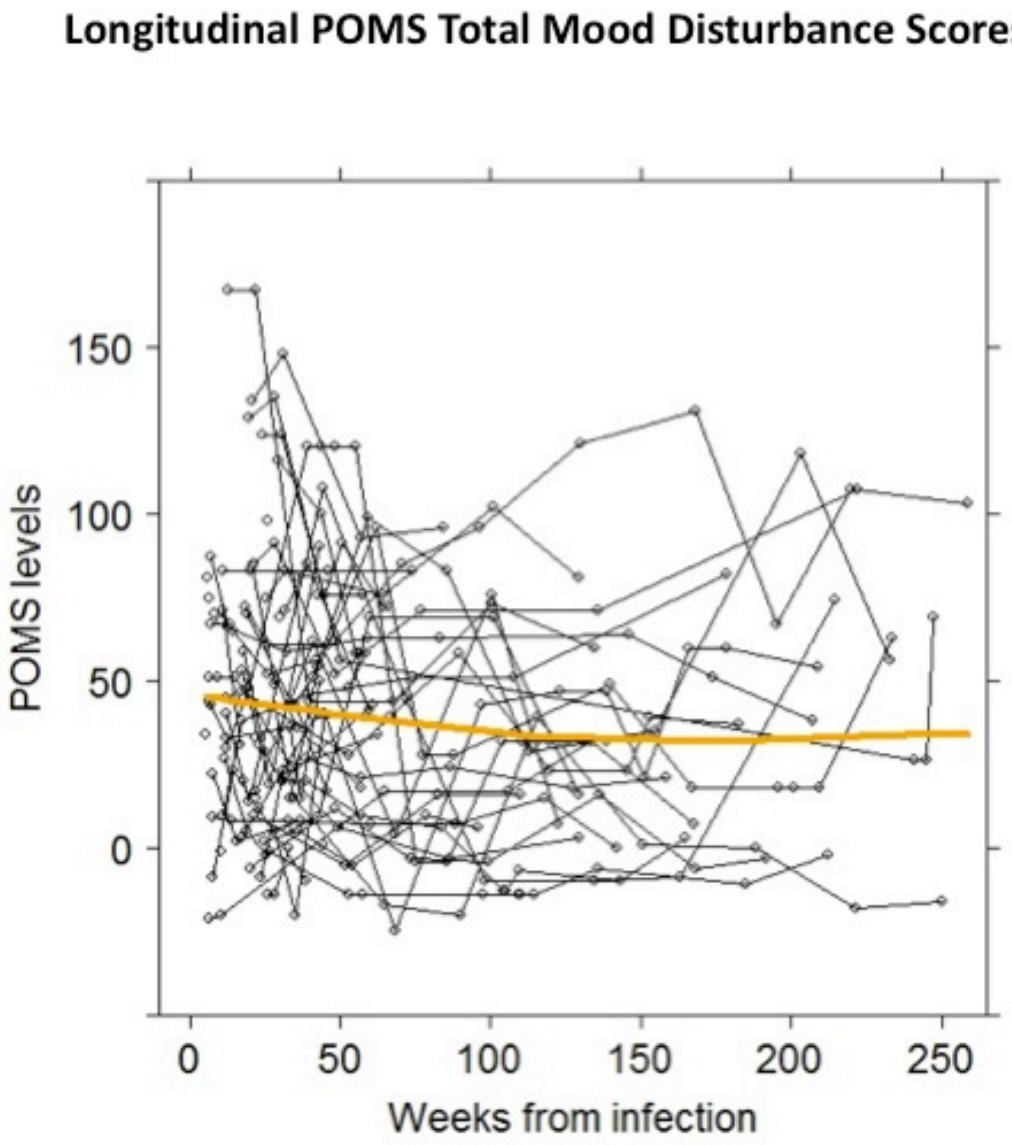


Figure 11. Longitudinal POMS Total Mood Disturbance Scores. Longitudinal POMS Total Mood Disturbance scores in those 60, of the initial 65 subjects with longitudinal follow-up, both before and after HAART initiation. Individual subject's scores are represented here as symbols connected by lines to demonstrate the BDI score trajectory. A Lowess curve is superimposed on the lines to show the average scores at each time point and to provide an overview of the trajectory, but the more complex mixed model weights number of visits per subject and duration of follow-up.

In this study, subjects had a total of 330 total visits, 196 of these off of ART. Except for a modest improvement in POMS prior to starting HAART (slope= -0.1229, p=0.0321), there was no significant change in POMS scores over a median 54 weeks of follow-up in longitudinal mixed model analyses; neither the slope following HAART initiation (slope=0.1005, p=0.2308) nor the aggregate trajectory of POMS over total follow-up was significant (slope=-0.2246, p=0.7136).

Finally, to assess potential effects of timing of HAART initiation in the outcome of mood in early HIV infection, we examined whether post-ART POMS and BDI scores correlated with number of weeks from initial infection that HAART was started. In neither all subjects who started ART, nor the 18 subjects with at least 6 months sustained treatment with ART, were any significant associations detected between timing of the start of therapy (expressed as weeks from infection, a continuous factor) and subsequent BDI or POMS levels (data not shown).

DISCUSSION

We report on depression and mood states in 65 study participants who we followed longitudinally beginning in PHI. At baseline, we explored their depression and mood states as measured by the POMS and BDI and examined whether these correlated with neurological measures of inflammation and blood-brain barrier breakdown or performance on neuropsychological testing. Over a median 54 weeks follow-up, we also examined a model for depression and mood states pre- and post-initiation of ART.

Depression is a Significant Problem in PHI

Studies have reported varying prevalence of depression over the course of HIV infection (37-39,41), though only one other study examined the population during PHI (68). Using the POMS and BDI, measures of mood that are considered valid and internally consistent (83,84) and have been used to measure depression with good validity and reliability in HIV infected patients (42,53,85), we determined that 47.7% of HIV-infected subjects at an estimated three and half months after HIV transmission experience clinical depression. While the overall prevalence of depression in our population was slightly higher (47.7 % as compared to 40 %), our findings resembled the results of the only other study, by Atkinson and colleagues (68), in that the vast majority of our PHI subjects experienced a minimal or mild depression (11 out of 65 subjects and 34 out of 65 subjects, respectively), as compared to a severe depression (9 out of 65). One subject in our study, however, did commit suicide, underscoring the potential severity of symptoms of depression that HIV-infected persons may experience. From this data, it is evident that depression is a significant and prevalent problem during PHI.

As other chronic illnesses have been known to have 2-3 fold higher depression rates than the general population (35), our nearly 48% rate of depression during PHI supports the hypothesis that with HAART, HIV has features which parallel other chronic illnesses in the US population (7). Given that depressed patients who are chronically ill more frequently report physical symptoms and more pain (35,36), it is perhaps not surprising that in our study, as in other studies (42), HIV infected subjects experienced more somatic symptoms than cognitive/affective symptoms of depression. This was reflected in the increased BDI somatic-performance subscale as compared to the cognitive/affective subscale. These somatic symptoms could be associated with HIV

infection and its manifestations (38), and could be considered a confounding variable in the measurement of depression in this group. Additionally, the vigor subscale score was significantly lower than the other measured mood states, which may be expected in those experiencing a physical illness. However, given that as depression increases as physical symptoms of HIV infection increase (44), measuring depression in this population with reliable self-report tests might ideally be supplemented by psychological interviews.

What Causes Depression in HIV Infection?

Similar to the previous literature, our study is unable to definitively conclude what actually causes depression in HIV infected persons. One hypothesis suggests that depression is a premorbid condition in a person at high risk of HIV acquisition, or, in other words, a depressed person is inherently at a high risk to contract HIV (58). To support this theory, we would expect depression to be elevated in this population due to other confounding risk factors often associated with mood disorders, such as sexuality or substance use (58). However, as measured by either BDI or POMS in our study, depression was not associated with substance use, despite a high prevalence of alcohol and drug use in our cohort. In addition, though depression has been found to correlate with gender, social class, suicide attempts, and MSM in past studies (37, 38), we had a homogenous group of 100% male subjects with all but 3 self-identifying as MSM, controlling for some of these variables.

Another hypothesis postulates that depression in HIV is reactionary, and also associated with the manifestations and treatment of HIV itself. The high prevalence of clinical depression during PHI, a period characterized by dramatic systemic physiological effects, the emotional stress of recent disease diagnosis, and in some cases complex or

chaotic social settings, which led to infection, supports this theory. Additionally, as stigma in this population has been shown to correlate significantly with higher levels of depression (45,48,49), high levels of depression following diagnosis is not unexpected. However, given these social, emotional, and physical changes, one might expect the level of "severe" depression during this baseline period to be much higher than we detected ('severe' n=9). Also, both the opportunistic infections associated with HIV, and the side effects of antiretroviral therapy, are known to cause depression (38). In fact, one study found that increased side effects from treatment actually predicted depression (45). By selecting a population of treatment naive individuals, we protected against side effects causing any physical manifestations of depression. However, looking longitudinally after initiation of HAART, it becomes more difficult to assess whether symptoms such as insomnia that might manifest as high somatic performance scores and therefore higher scores on the total BDI, are a result of clinical depression or HAART.

The final hypothesis for the development of depression during HIV suggests that there is a biological basis for disease. It is believed that cytokines, stress and cortisol, and the inhibition of dopamine, could all cause depression in the HIV infected person (38 34, 48, 81). However, in our study, the lack of correlations between the BDI and POMS and any laboratory indices of disease (including blood or CSF HIV viral load or blood CD4 count), suggests that depression should be considered independently from neuropathic HIV infection. This might also suggest that the high levels of depression in our population are reactive, and despite elevated somatic performance scores on the BDI, not caused by HIV infection's influence on the physical and biological. Furthermore, our findings support the previous studies in chronic HIV indicating no association between

CD4 count, viral load, and depression, though there has been some conflicting evidence suggesting an association between these parameters and mood in HIV infected subjects at later stages of illness (38, 51). It is possible that unmeasured physiological effects contribute to mood disorders during the early stages of HIV infection, or, more likely, that the variable extent of HIV viral burden and host immune responses to early infection are independent of an individual's self-reported mood.

The lack of correlation between mood and neuropsychological testing further suggests that HIV is independent from depression, and conversely that impaired neurocognitive performance in this period is not directly caused by mood disturbance. While one might expect mood to influence cognitive performance as PHI alone is known to cause neuropsychological impairment (67), in our study, similar to the data found in additional studies that measured depression alone, or depression in those with HIV (86,87), neuropsychological performance (summarized as total Z and GDS) did not associate with BDI or POMS Total Mood Disturbance. The lack of correlation between performance and mood is important to interpretations of cognitive status during this early period of infection as poor performance in some subjects (67) might be attributed to disturbed mood during this challenging period. Our findings also suggests that the mechanisms of depression and other CNS pathology in HIV are different, as cognitive performance is impaired during PHI, but performance does not correlate with measures of depression during PHI. Therefore, early depressive symptoms are unlikely to be a predictor for early HIV-associated neurocognitive disorder (HAND), and may also be unrelated to its' later development. Though this study confirms that depression

prevalence is high in PHI, it remains uncertain whether depression is a predisposing factor to developing HIV or is, instead, an early result of the HIV infection itself.

What Happens to Depression Over Time?

Studies have suggested that depression can impact HIV disease progression and mortality (59). This is not shocking as depressed patients, even without a chronic illness, have been known to die 5 to 10 years earlier than patients without mood disorders (35). Yet, similar to effects of depression on treatment adherence in other chronic illnesses, non-adherence is high in patients with HIV and depression (60). Given that HAART has been postulated to have lowered the infection rates significantly (2) and to have increased life expectancy to close to the levels of the uninfected population with chronic disease (5), it is not surprising that HAART non-adherence is thought to contribute to the increased mortality found in depressed patients with HIV. One study even went so far as to postulate a protective effect of HAART, finding a decrease in depression with increased time on HAART (61).

Our longitudinal data, however, does not support this theory. We found that the overall group's BDI and POMS scores did not significantly change prior to or following initiation of HAART. This lack of statistically significant improvement in our results following treatment suggests that the course of HIV infection itself and its subsequent treatment with HAART might not play a role in alleviation of depression in PHI. Depression is also not changed whether the subject began HAART immediately after diagnosis, or later in the course of the disease.

Overall, depression appears at a low level throughout the course of early HIV in our subjects suggesting that depression is persistent, regardless of causation, following

infection. Our results also suggest that "watchful waiting" did not improve depression scores except for a minor improvement in the POMS (slope=-.1229, p=0.0321) prior to ART, which was not sustained over the course of the pre- and post- HAART follow-up. One might expect time to improve depression, given the expectation that after adjustment to the news of HIV diagnosis there may be a natural improvement in mood over time without intervention. Since we did not see an improvement with the natural history of early HIV, it is possible that depression in this population also is less likely to be reactive, and more likely to be either a pre-morbid or HIV-related condition.

Since depression is associated with lower adherence to HAART (62) and new treatment guidelines for HIV suggest commencing HAART at initial diagnosis (24), recognizing and treating depression in this population is important in management of HIV. Since it remains possible that depression in PHI is related to HIV infection itself, given the high somatic scores on the BDI, a synergistic approach to HAART and antidepressants might be an effective strategy in patients, especially those with early infection. Ultimately, the effects of treatment for depression, HAART adherence, HIV disease and symptom presentation in the early stages after HIV infection and diagnosis are in need of closer examination.

Limitations

The limitations of this study include a homogeneous population, primarily men who have sex with men (MSM) who live in the San Francisco area. In addition, depression is measured by self-report; however the scales correlate with each other suggesting internal consistency between our results. HAART adherence is also self-reported, though observation of persistent virological suppression this group (data not shown) suggests

excellent adherence over time in the subjects. The longitudinal correlations might be skewed by the effects of antidepressant usage, which are not included in our analysis, and the lack of randomization into ART. Also, we did not take an in depth psychological history at study visits, and merely relied on self-report of previous treatment for depression or bipolar disorder. This made it difficult to truly control for all of the psychological confounding variables that could affect depression rates in this population (e.g., previous suicidal attempts, antidepressant usage, previous treatment).

Implications of Research for the HIV Field

Our finding of 47.7% clinical depression in PHI has important implications for the management of patients with HIV. Since depression is associated with lower adherence to HAART (62) and new treatment guidelines for HIV suggest commencing HAART at initial diagnosis of HIV (24), our results would suggest that at diagnosis, it is also important to recognize and treat depression. Though the depression is more often mild or moderate, it can be severe, leading to suicide in these patients. Thus, beyond preventing non-adherence and resistance to HAART, treating depression might also save a life from self-harm.

As depression does not seem to correlate with CSF measures of inflammation or disease or with neuropsychological testing, self-assessment and psychiatric consultation will be the most effective means of screening during PHI. In order to properly diagnose these patients, physicians must understand that the physical manifestations of disease may resemble depression (38), and must learn to screen by asking more about mood, anhedonia, and decreased energy than sleep and appetite changes (38). They must also recognize that depression may have been pre-morbid, and might seek to provide support,

suggest therapy or social services, or even drug rehabilitation, for their patients to help with the additional life factors that may be contributing to their depression.

It also remains possible that depression in PHI is related to HIV infection itself, given the high somatic scores on the BDI. The literature has suggested that antidepressants are effective in this population (38,41,58,62), and in fact, substantially increase adherence to HAART (63). Therefore, a synergistic approach to HAART and antidepressants might be an effective strategy in patients, especially those with early infection. Also as our study suggests that depression remains consistent over time, despite initiation of ART, pharmacological treatment of depression may be the only way to significantly improve depression, with a significant impact of decreasing plasma viral load (65) in this population. Ultimately, the effects of treatment for depression, HAART adherence, HIV disease and symptom presentation in the early stages after HIV infection and diagnosis are in need of closer examination.

Future Directions

While we have characterized depression during PHI in our particular population, as it was only the second study of this early infection time period, it would be extremely useful to look at other populations for comparison. Given that this population was composed of only males, and studies have suggested higher rates of depression in females and increased mortality in females with HIV infection (43,55), doing a comparison study with women would be very important. Additionally, having a comparison group of matched individuals without HIV infection, or with another chronic illness, might help to better understand depression in this population as it relates to other chronic diseases and the "healthy" population.

Furthermore, though we were able to measure depression longitudinally in our population as an exploratory study, a more controlled environment would help to better describe the trajectory of depression. It would be necessary to document not only HAART initiation, but also treatment for depression, to see if antidepressant commencement or therapy initiation altered the prevalence of depression over time in any way.

Finally, as we continue to study with whether depression was concomitant or was a result of the disease itself, we need to take a better assessment of stigma and support, psychological factors (like previous psychiatric treatment, suicide, or diagnoses), and substance use at baseline and over time. As depression is often a product of the social as well as the biological, these factors might contribute significantly to the high rates of depression we are seeing in this population.

Conclusions

While HIV may no longer be a death sentence upon diagnosis, depression may shorten an HIV-infected person's life, whether by nonadherence to HAART or self-harm. This depression is highly prevalent, and though it is usually mild, it may be severe; in fact one of our 65 study subjects committed suicide during this early period. While it remains unclear whether depression is a predisposing factor to HIV infection or it is an early result of HIV infection itself, or whether it is merely persistent regardless of cause, this is an important area for future research and disease management protocols. Since HAART adherence is affected so significantly by depression, and failure to adhere leads to disease mutations and resistance to drugs as well as disease progression, screening for and properly treating depression in this population is critical. Targeted interventions for

depression in the early stages of infection may have an impact not only on psychological but also systemic outcomes in HIV.

REFERENCES

1. Moskowitz JT, Wrubel J, Hult JR, Maurer S, Acree M. Illness Appraisals and Depression in the First Year after HIV Diagnosis. *PloS One*. 2013 Oct 25; 8(10):e78904.

2. El-Sadr WM, Mayer KH, Hodder SL. AIDS in America—forgotten but not gone. *NEJM.* 2010;362:967 E

3. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *The Lancet.* 2010;375:2092-8.

4. CDC. HIV Surveillance Slide Sets. Available at: <http://www.cdc.gov/hiv/library/slideSets/index.html>.

5. Nakagawa F, May M, Phillips A. Life expectancy living with HIV: Recent estimates and future implications. *Curr Opin Infect Dis*. 2013;26:17-25

6. Nakagawa F, Lodwick RK, Smith CJ, et al. Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS.* 2012;26:335-43.

7. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *The Lancet*. 2013;382:1525-33.

8. Siegel K, Lekas H-M. AIDS as a chronic illness: psychosocial implications. AIDS. 2002;16:S69-S76.

9. CDC. *HIV Surveillance Report*, 2011; vol. 23. http://www.cdc.gov/hiv/topics/surveillance/ resources/reports/. Published February 2013.

10. CDC. Estimated HIV incidence in the United States, 2007–2010. *HIV Surveillance Supplemental Report* 2012;17(No. 4). http://www.cdc.gov/hiv/topics/surveillance/resources/reports/ #supplemental. Published December 2012.

11. CDC. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 U.S. dependent areas—2011. *HIV Surveillance Supplemental Report* 2013;18(No. 5). Available at http://www.cdc.gov/hiv/library/reports/surveillance/. Published October 2013.

12. Yilmaz A. Antiretroviral Treatment of HIV-1 in the Central Nervous System. Vasastadens Bokbinderi AB: The Sahlgrenska Academy at Göteborg University, Sweden; 2007.

13.Wyatt R, Sodroski J. The HIV-1 envelope glycoproteins: fusogens, antigens, and immunogens. *Science*. 1998;280:1884-8.

14. Garg H, Mohl J, Joshi A. HIV-1 induced bystander apoptosis. *Viruses.* 2012;4:3020-43.

15. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med. 1*996;125:257-64.

16. Picker LJ. Immunopathogenesis of acute AIDS virus infection. *Curr Opin Immunol.* 2006;18:399-405.

17.Spudich S. HIV and Neurocognitive Dysfunction. *Curr HIV/AIDS Rep.* 2013;10:235-43.

18. Pilcher CD, Shugars DC, Fiscus SA, et al. HIV in body fluids during primary HIV infection: implications for pathogenesis, treatment and public health. *AIDS.* 2001;15:837-45.

19. Davis LE, Hjelle BL, Miller VE, et al. Early viral brain invasion in iatrogenic human immunodeficiency virus infection. *Neurology.* 1992;42:1736-9.

20. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature.* 1995;373:123-6.

21. Fauci AS. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. *Nature.* 1993;362:25.

22. Letendre S ER, Deutsch R, Clifford DB, Marra C, McCutchan A, Morgello S, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER cohort. In program and abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA; 2010.

23. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol.* 2008;65:65-70.

24. Thompson MA, et al. Antiretroviral treatment of adult hiv infection: 2012 recommendations of the international antiviral society–usa panel. *JAMA*. 2012;308:387-402.

25. Wong JK, Hezareh M, Günthard HF, et al. Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. *Science.* 1997;278:1291-5.

26. Albright AV, Soldan SS, González-Scarano F. Pathogenesis of human immunodeficiency virus-induced neurological disease. *J Neurovirol.* 2003;9:222-7.

27. González-Scarano F, Martín-García J. The neuropathogenesis of AIDS. *Nat Rev Immunol*. 2005;5:69-81.

28. Simpson DM, Tagliati M. Neurologic manifestations of HIV infection. *Ann Intern Med.* 1994;121:769-85.

29. Price R, Brew B. Management of the neurologic complications of HIV infection and AIDS. *Infect Dis Clin North Am.* 1988;2:359.

30.Mamidi A, DeSimone JA, Pomerantz RJ. Central nervous system infections in individuals with HIV-1 infection. *J Neurovirol.* 2002;8:158-67.

31. Price RW. Neurological complications of HIV infection. *The Lancet*. 1996;348:445-52.

32. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. *Ann Neurol*. 1986;19:517-24.

33. Bouwman F, Skolasky R, Hes D, et al. Variable progression of HIV-associated dementia. *Neurology.* 1998;50:1814-20.

34. Kranick SM, Nath A. Neurologic complications of HIV-1 infection and its treatment in the era of antiretroviral therapy. *Continuum: Lifelong Learning in Neurology*. 2012;18:1319-37.

35. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues Clin Neurosci.* 2011;13:7.

36. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry*. 2007;29:147-55.

37. Braganca M, Palha A. Depression and neurocognitive performance in Portuguese patients infected with HIV. *AIDS Behav*. 2011;15:1879-87.

38. Penzak SR, Reddy YS, Grimsley SR. Depression in patients with HIV infection. *Am J Health Syst Pharm*. 2000;57:376-86.

39.Ciesla JA, Roberts JE. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. *Am J Psychiatry.* 2001;158:725-30.

40. American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed, text rev.) doi:10.1176/appi.books.9780890423349.

41. Rabkin J. HIV and depression: 2008 review and update. *Curr HIV/AIDS Rep.* 2008;5:163-71.

42. Kalichman SC, Sikkema KJ, Somlai A. Assessing persons with human immunodeficiency virus (HIV) infection using the Beck Depression Inventory: disease processes and other potential confounds. *J Pers Assess.* 1995;64:86-100.

43.Cruess DG, Evans DL, Repetto MJ, Gettes D, Douglas SD, Petitto JM. Prevalence, diagnosis, and pharmacological treatment of mood disorders in HIV disease. *Biol Psychiatry.* 2003;54:307-16.

44.Jaggers JR, Dudgeon WD, Burgess S, Phillips KD, Blair SN, Hand GA. Psychological Correlates of HIV-Related Symptom Distress. *J Assoc Nurses AIDS Care*. 2013.

45. Onyebuchi-Iwudibia O, Brown A. HIV and depression in Eastern Nigeria: The role of HIV-related stigma. *AIDS care*. 2013:1-5.

46. Bing EG, Burnam MA, Longshore D, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Arch Gen Psychiatry.* 2001;58:721.

47. Blank MB, Himelhoch S, Walkup J, Eisenberg MM. Treatment Considerations for HIV-Infected Individuals with Severe Mental Illness. *Curr HIV/AIDS Rep.* 2013;10:371-9.

48.Del Guerra F, Fonseca J, Figueiredo V, Ziff E, Konkiewitz EC. Human immunodeficiency virus-associated depression: contributions of immuno-inflammatory, monoaminergic, neurodegenerative, and neurotrophic pathways. *J Neurovirol.* 2013;19:314-27.

49. Grov C, Golub SA, Parsons JT, Brennan M, Karpiak SE. Loneliness and HIV-related stigma explain depression among older HIV-positive adults. *AIDS Care* .2010;22:630-9.

50. Rabkin JG, Goetz RR, Remien RH, Williams JB, Todak G, Gorman JM. Stability of mood despite HIV illness progression in a group of homosexual men. *Am J Psychiatry.* 1997;154:231-8.

51. Burack JH, Barrett DC, Stall RD, Chesney MA, Ekstrand ML, Coates TJ. Depressive symptoms and CD4 lymphocyte decline among HIV-infected men. *JAMA*. 1993;270:2568-73.

52.Evans D, Ten Have T, Douglas S, et al. Association of depression with viral load, CD8 T lymphocytes, and natural killer cells in women with HIV infection. *Am J Psychiatry*. 2002;159:1752-9.

53. Bornstein RA, Pace P, Rosenberger P, et al. Depression and neuropsychological performance in asymptomatic HIV infection. *Am J Psychiatry*. 1993;150:922-7.

54. Gibbie T, Mijch A, Ellen S, et al. Depression and neurocognitive performance in individuals with HIV/AIDS: 2-year follow-up. *HIV Med*. 2006;7:112-21.

55. Ickovics JR, Hamburger ME, Vlahov D, et al. Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women. *JAMA*. 2001;285:1466-74.

56. Barreto I, Viegas P, Ziff EB, Konkiewitz EC. Animal Models for Depression Associated with HIV-1 Infection.*J Neuroimmune Pharmacol.* 2013.

57.Judd F, Komiti A, Chua P, et al. Nature of depression in patients with HIV/AIDS. *Aust N Z J Psyhiatry.* 2005;39:826-32.

58.Treisman G, Fishman M, Schwartz J, Hutton H, Lyketsos C. Mood disorders in HIV infection. *Depress Anxiety*. 1998;7:178-87.

59.Leserman J. Role of depression, stress, and trauma in HIV disease progression. *Psychosom Med.* 2008;70:539-45.

60.Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. *J Acquir Immune Defic Syndr.* 2011;58:181-7.

61.Gutiérrez F, García L, Padilla S, et al. Risk of clinically significant depression in HIV‐infected patients: effect of antiretroviral drugs. *HIV Med.* 2013.

62.Akincigil A, Wilson I, Walkup J, Siegel M, Huang C, Crystal S. Antidepressant treatment and adherence to antiretroviral medications among privately insured persons with HIV/AIDS. *AIDS Behav*. 2011;15:1819-28.

63. Walkup J, Wei W, Sambamoorthi U, Crystal S. Antidepressant treatment and adherence to combination antiretroviral therapy among patients with AIDS and diagnosed depression. *Psychiatr Q.* 2008;79:43-53.

64.Sin NL, DiMatteo MR. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. *Ann Behav Med.* 2013:1-11.

65. Primeau MM, Avellaneda V, Musselman D, Jean GS, Illa L. Treatment of Depression in Individuals Living with HIV/AIDS. *Psychosomatics*. 2013.

66.Spudich S, Gisslen M, Hagberg L, et al. Central nervous system immune activation characterizes primary human immunodeficiency virus 1 infection even in participants with minimal cerebrospinal fluid viral burden. *J Infect Dis.* 2011;204:753-60.

67.Peterson J HF, Pilcher C et al. Changes in Neurocognitive Performance from Early HIV-1 Infection to Initiation of Antiretroviral Therapy. 19th CROI. Seattle, WA.

68. Atkinson JH, Higgins J, Vigil O, et al. Psychiatric context of acute/early HIV infection. The NIMH Multisite Acute HIV Infection Study: IV. *AIDS Behav*. 2009;13:1061-7.

69. Zetola N, Pilcher C. Diagnosis and management of acute HIV infection. *Infect Dis Clin North Am.* 2007;21:19-48, vii.

70.Hecht FM, Wellman R, Busch MP, et al. Identifying the early post-HIV antibody seroconversion period. *J Infect Dis.* 2011;204:526-33.

71.Lindback S, Thorstensson R, Karlsson AC, et al. Diagnosis of primary HIV-1 infection and duration of follow-up after HIV exposure. Karolinska Institute Primary HIV Infection Study Group. *AIDS.* 2000;14:2333-9.

72.Little S, Frost SDW, Wong J, et al. Persistence of transmitted drug resistance among subjects with primary human immunodeficiency virus infection. *J Virol.* 2008;82:5510-8.

73.Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;4:561.

74.McNair D, Lorr M, Droppleman L. Revised manual for the Profile of Mood States. San Diego, CA: Educational and Industrial Testing Service 1992.

75.Beck AT, Steer RA. BDI, Beck depression inventory : manual. San Antonio, Tex.; [New York]: Psychological Corp. ; Harcourt Brace & Company; 1993.

76.Spudich SS, Nilsson AC, Lollo ND, et al. Cerebrospinal fluid HIV infection and pleocytosis: relation to systemic infection and antiretroviral treatment. *BMC Infect Dis*. 2005;5:98.

77.Gisslen M, Hagberg L, Brew B, Cinque P, Price R, Rosengren L. Elevated cerebrospinal fluid neurofilament light protein concentrations predict the development of AIDS dementia complex. *J Infect Dis.* 2007;195:1774-8.

78.Schennach H, Murr C, Gachter E, Mayersbach P, Schonitzer D, Fuchs D. Association between neopterin production and other parameters in a population of blood donors. *Pteridines.* 2002;13:133-9.

79. Gu L, Tseng SC, Rollins BJ. Monocyte chemoattractant protein-1.*Chem Immunol.* 1999;72:7-29.

80.Cinque P, Vago L, Mengozzi M, et al. Elevated cerebrospinal fluid levels of monocyte chemotactic protein-1 correlate with HIV-1 encephalitis and local viral replication. *AIDS.* 1998;12:1327-32.

81. Bajetto A, Bonavia R, Barbero S, Schettini G. Characterization of chemokines and their receptors in the central nervous system: physiopathological implications. *J Neurochem.* 2002;82:1311-29.

82.Cinque P, Bestetti A, Marenzi R, et al. Cerebrospinal fluid interferon-γ-inducible protein 10 (IP-10, CXCL10) in HIV-1 infection. *J Neuroimmunol.* 2005;168:154-63.

83. Richter P, Werner J, Heerlein A, Kraus A, Sauer H. On the validity of the Beck Depression Inventory: A review. *Psychopathology. 1*998;31:160-8.

84. Nyenhuis DL, Yamamoto C, Luchetta T, Terrien A, Parmentier A. Adult and geriatric normative data and validation of the profile of mood states. *J Clin Psychol.* 1999;55:79-86.

85. Lipps G, Lowe G, De La Haye W, et al. Validation of the Beck Depression Inventory II in HIV-positive patients. *W Indian Med J.* 2010;59:374-9.

86. von Giesen H-J, Bäcker R, Hefter H, Arendt G. Depression Does Not Influence Basal Ganglia–Mediated Psychomotor Speed in HIV-1 Infection. *J Neuropsychiatry Clin Neurosci.* 2001;13:88-94.

87.Cysique LA, Deutsch R, Atkinson JH, et al. Incident major depression does not affect neuropsychological functioning in HIV-infected men. *J Int Neuropsychol Soc.* 2007;13:1-11.